Counterfactual-based mediation analysis
Workshop 2

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CIMPOD
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Outline

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1. Setting the scene
   - Quick summary of yesterday
   - Today's case study
   - Mediation analysis with multiple mediators
   - Sequential mediation analysis
   - Interventional effects for multiple mediators
2. Case study
3. Q&A
4. References

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- Traditional mediation methods are also limited to simple linear models.
- The causal inference literature, using counterfactuals, has clarified what we might mean by 'direct' and 'indirect' effects, but there isn't just one possibility.
- It has led to clear assumptions under which these can be identified, and a myriad methods for estimation, reaching far beyond two simple linear models.

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- We focussed only on the setting with a continuous outcome and mediator, and with a single mediator of interest.
- In today's workshop, we turn to mediation analysis with multiple mediators, and we'll look at a setting with a binary outcome/mediators.

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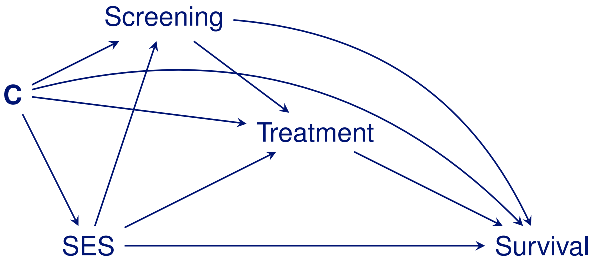
- Survival to 1 year: 95.9% in higher SES women vs. 93.2% in lower SES women
- Survival to 5 years: 64.7% vs. 54.1%
- Question: what explains this? Screening? Treatment?

Causal diagram



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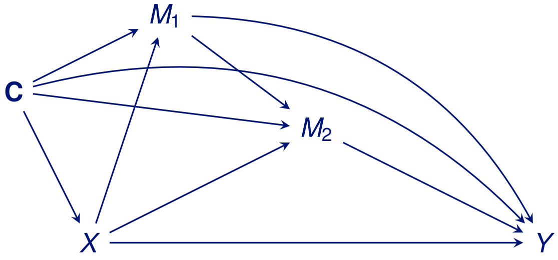

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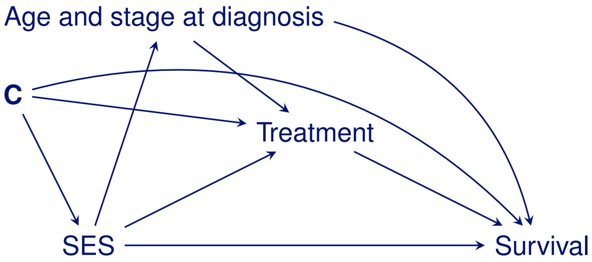

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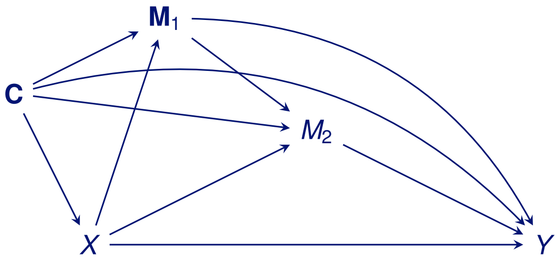

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— The third argument changes and all other arguments stay the same, making it an indirect effect through M_2 only.
— There are 8 choices for how to fix x, x', x'''.
— We can choose $(x, x', x''') = (0, 0, 0)$. We call this NIE_2-000.
— Similarly, can choose $(x, x', x''') = (1, 1, 0)$. We call this NIE_2-110.

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Indirect effect through both M_1 and M_2

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

— 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.

Indirect effect through both M_1 and M_2

— A natural indirect effect through both M_1 and M_2 is of the form:

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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:

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

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— Similarly, can choose $(x, x', x'') = (1, 0, 0)$. We call this NIE_{12}-100.

Indirect effect through both M_1 and M_2

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Indirect effect through both M_1 and M_2

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Outline

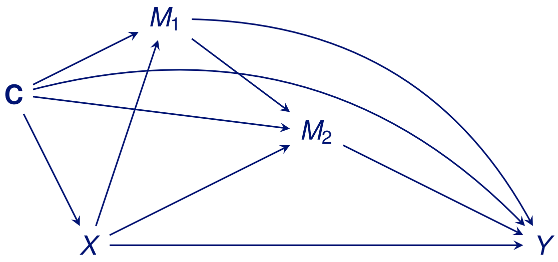
Sequential mediation analysis

- For more about the different possible decompositions of the TCE into the many path-specific effects defined above, and assumptions under which this can be achieved, see Daniel et al, Biometrics (2015).

Sequential mediation analysis

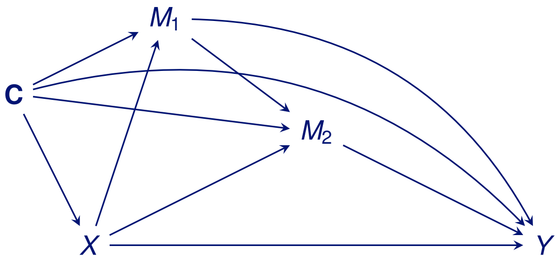
- For more about the different possible decompositions of the TCE into the many path-specific effects defined above, and assumptions under which this can be achieved, see Daniel et al, Biometrics (2015).
- But for today, we'll focus on a simpler, more practical and intuitive idea presented by VanderWeele et al (2014), known as sequential mediation analysis.

The idea



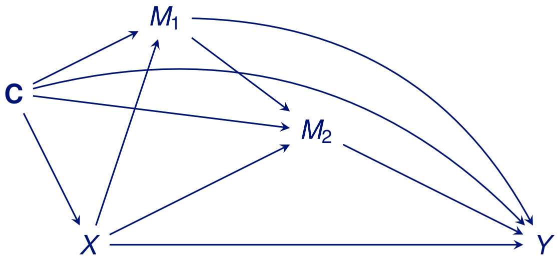
- First we consider M_1 and M_2 to be joint mediators.

The idea



- First we consider M_1 and M_2 to be joint mediators.
- This allows us to use single mediator analysis, with (M_1, M_2) as the mediator.

The idea



- We thus estimate

$$\text{NDE}_{\text{joint}} = E\left\{Y(1, M_1(0), M_2(0, M_1(0))) - Y(0, M_1(0), M_2(0, M_1(0)))\right\}$$

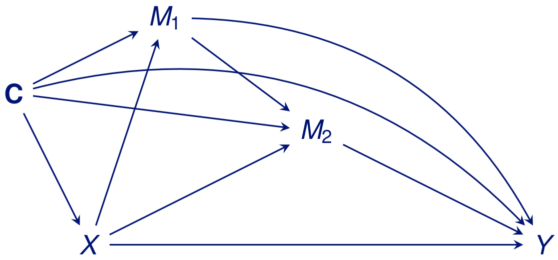
and

$$\text{NIE}_{\text{joint}} = E\left\{Y(1, M_1(1), M_2(1, M_1(1))) - Y(1, M_1(0), M_2(0, M_1(0)))\right\}$$

with

$$\text{TCE} = \text{NDE}_{\text{joint}} + \text{NIE}_{\text{joint}}$$

The idea



- Next we consider M_1 to be the only mediator of interest, and we ignore M_2.

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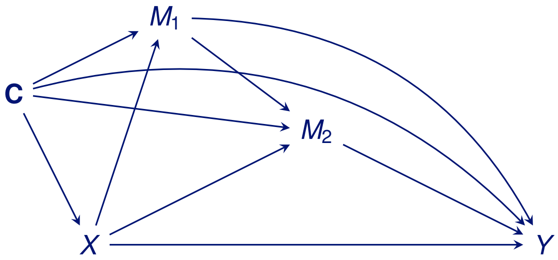

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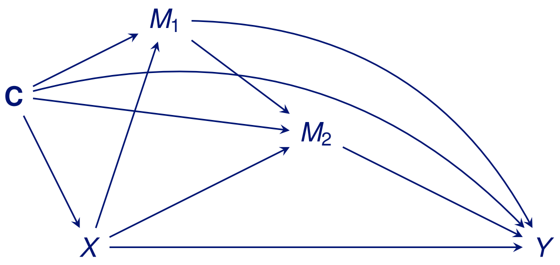

- Next we consider M_1 to be the only mediator of interest, and we ignore M_2.
- This allows us to use single mediator analysis, with M_1 as the mediator.
- The direct effect then includes the effect via neither M_1 nor M_2 and the effect through M_2 alone, whereas the indirect effect includes the effect via M_1 alone and the effect via both M_1 and M_2.

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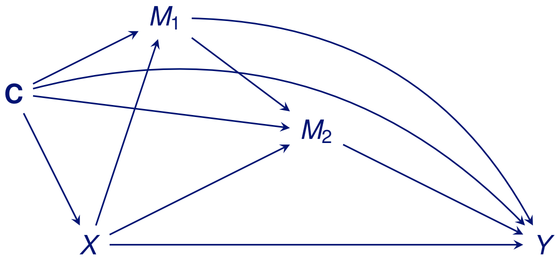


- In other words, we estimate

$$\text{NDE}_{\text{not } M_1} = E\{Y(1, M_1(0), M_2(1, M_1(0))) - Y(0, M_1(0), M_2(0, M_1(0)))\}$$

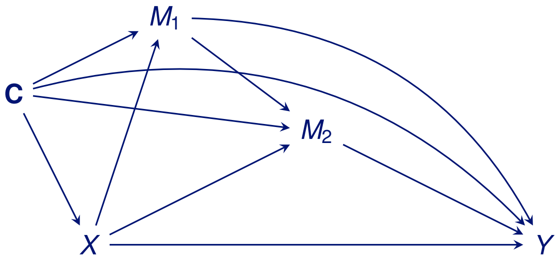
and

$$\text{NIE}_{M_1} = E\{Y(1, M_1(1), M_2(1, M_1(1))) - Y(1, M_1(0), M_2(1, M_1(0)))\}$$

with

$$\text{TCE} = \text{NDE}_{M_1} + \text{NIE}_{M_1}$$

The idea



- We then note that we can obtain (one of) the indirect effect(s) through M_2 alone by taking the difference between $\text{NIE}_{\text{joint}}$ and NIE_{M_1}:

$$\begin{aligned}\text{NIE}_{\text{joint}} - \text{NIE}_{M_1} &= E\{Y(1, M_1(0), M_2(1, M_1(0))) - Y(1, M_1(0), M_2(0, M_1(0)))\\ &= \text{NIE}_{M_2} - 100\end{aligned}$$

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- Sequential mediation analysis doesn't require any further results on identification nor any new methods for estimation, since it is simply an application of single mediator analysis twice: once with M_1 and M_2 as joint mediators, and then with M_1 as the only mediator.

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- Writing $\mathbf{M}$ for (M_1, M_2), the assumptions for identification therefore include that there should be no unmeasured confounders of X and $\mathbf{M}$, X and Y, $\mathbf{M}$ and Y, X and M_1, M_1 and Y, and no confounders (measured or unmeasured) of $\mathbf{M}$ and Y or of M_1 and Y that are affected by X.

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- This means that in order to apply sequential mediation analysis, we need to know the order of the mediators (i.e. M_1 affects M_2 but not vice versa) and the mediators cannot share any unmeasured common causes (since this would violate the no unmeasured confounding assumption for M_1 and Y).

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- In many practical applications, these assumptions are implausible.
- So we now turn to an alternative, based on interventional effects.

Outline

LONDON SCHOOL of HYGIENE & TROPICAL MEDICINE

1. Setting the scene
   - Quick summary of yesterday
   - Today's case study
   - Mediation analysis with multiple mediators
   - Sequential mediation analysis
   - Interventional effects for multiple mediators
2. Case study
3. Q&A
4. References

Our proposal

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- We will not need to assume no unmeasured confounding between different mediators, and we won't require knowledge of the order of the mediators.
- For simplicity, we again describe our approach for two mediators.

Interventional direct effect through neither M_1 nor M_2

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

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

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$$P\{M_1(0) = m_1, M_2(0) = m_2 | \mathbf{C} = \mathbf{c}\} P(\mathbf{C} = \mathbf{c})$$

- 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 **C**).

Interventional indirect effect through M_1

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

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

Interventional indirect effect through M_2

We propose the following definition of an interventional indirect effect throught M_2:

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

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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:

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

$$\Big[P\{M_1(1) = m_1, M_2(1) = m_2|\mathbf{C} = \mathbf{c}\}$$

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- This can be interpreted as the indirect effect of X on Y mediated through the dependence between M_1 and M_2 (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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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}.

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

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

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

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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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}.

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

$$E(M_1|X=x, \mathbf{C}=\mathbf{c})=\beta_{01}+\beta_{11} x+\beta_{21}^T \mathbf{c}$$
$$E(M_2|M_1=m_1, X=x, \mathbf{C}=\mathbf{c})=\beta_{02}+\beta_{12} x+\beta_{22}^T \mathbf{c}+\beta_{32} m_1+\beta_{42} x m_1$$

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 regression approach has the drawback that it requires a new derivation each time a different outcome or mediator model is considered.
- 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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- then take a random draw $M_{1,i}(1)$ for each subject i from the (fitted) distribution $P(M_1 | X = 1, \mathbf{C}_i)$
- 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 $\mathbf{C}_i$.

For instance, to evaluate the first component

$$\sum_{\mathbf{c}}\sum_{m_1}\sum_{m_2} E\left\{Y(1,m_1,m_2)|\mathbf{C}=\mathbf{c}\right\} P\{M_1(1)=m_1|\mathbf{C}=\mathbf{c}\}$$
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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 $\mathbf{C}_i$.
- The average of these fitted values across subjects then estimates the above component.

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- Its performance can be improved by repeating the random sampling many times and averaging the results across the different Monte-Carlo runs.
- In practice, we recommend the bootstrap for inference.

Outline

NYCRIS data: reminder

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- Survival to 1 year: 95.9% in higher SES women vs. 93.2% in lower SES women
- Survival to 5 years: 64.7% vs. 54.1%
- Question: what explains this? Screening? Treatment?

Pseudo NYCRIS data

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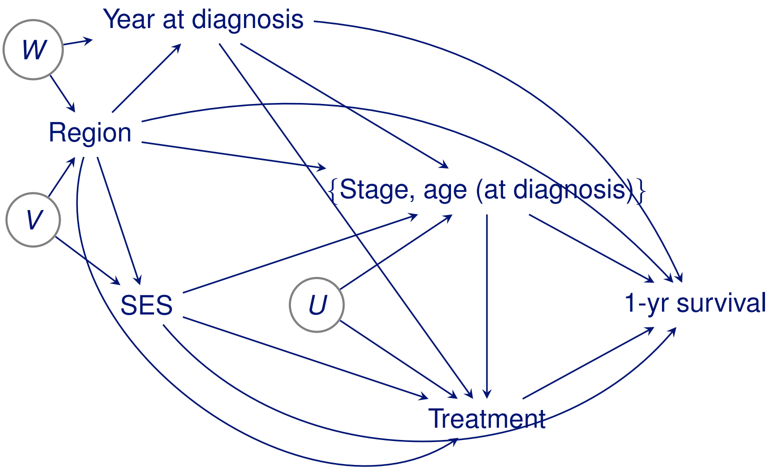
- Y: Survival to 1-year post diagnosis
- $\mathbf{C}$: Region (`c1`), year of diagnosis (`c2`)

Causal diagram



Tasks

Question 1

Familiarise yourselves with the dataset and start by exploring mediation using a traditional approach.

For example, you could fit a logistic regression to the outcome given exposure and confounders, and then add in treatment and age/stage at diagnosis, one at a time, looking at how the exposure coefficient changes.

In addition to the problems we identified yesterday, do you now see a new problem with using logistic regression for traditional mediation analysis in this way?

For help with Stata syntax, see `CaseStudy2_Q1.do`.

Tasks

Question 2

Now investigate more formally using the sequential mediation analysis approach described at the beginning of the workshop.

I suggest that you use the same approach as we used at the end of yesterday's workshop, i.e. using Monte Carlo simulation. It's probably best to start without including interactions in the models, and then to add these in a second analysis. The interactions are in fact strong in this example, and so it is important that you include them eventually.

For more help with the Stata syntax, see `CaseStudy2_Q2.do`.

Tasks

Question 3

Finally, again using MC simulation, estimate the interventional multiple mediator effects.

How large is the remainder (mediated dependence) term? Can you interpret it in terms of public health?

For more help with the Stata syntax, see `CaseStudy2_Q3.do`.

Outline

Results

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Total causal effect	0.028	0.0028	0.023	0.034
Int DE	0.013	0.0027	0.008	0.018
Int IE through $\mathbf{M}_1$	0.007	0.0008	0.005	0.008
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Results: explaining the remainder term

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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 $\times$ Agediag	1.033	0.003	1.027	1.038
SES $\times$ Stage	1.799	0.152	1.525	2.123
Agediag $\times$ Stage	1.014	0.004	1.007	1.021
SES $\times$ Agediag $\times$ 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)

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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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- Recall that we expected this effect to be small, except when there are particular interactions present, as is the case here.
- There is a negative association between age/stage and treatment: those who are older and/or 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 older patients and/or those 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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- There is little evidence of further mediation through the treatment variable (estimated effect 0.02%, 95% CI: –0.05, 0.08%), and evidence of an effect through age and stage at diagnosis (estimated effect 0.7%, 95%CI 0.5%–0.8%).

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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.
- Currently we are working on scaling this up to problems with (many) more than 2 mediators, including the incorporation of machine learning methods (via TMLE).

Outline

1. Setting the scene
   - Quick summary of yesterday
   - Today's case study
   - Mediation analysis with multiple mediators
   - Sequential mediation analysis
   - Interventional effects for multiple mediators
2. Case study
3. Q&A
4. References

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