SOCI 40258

Causal Mediation Analysis

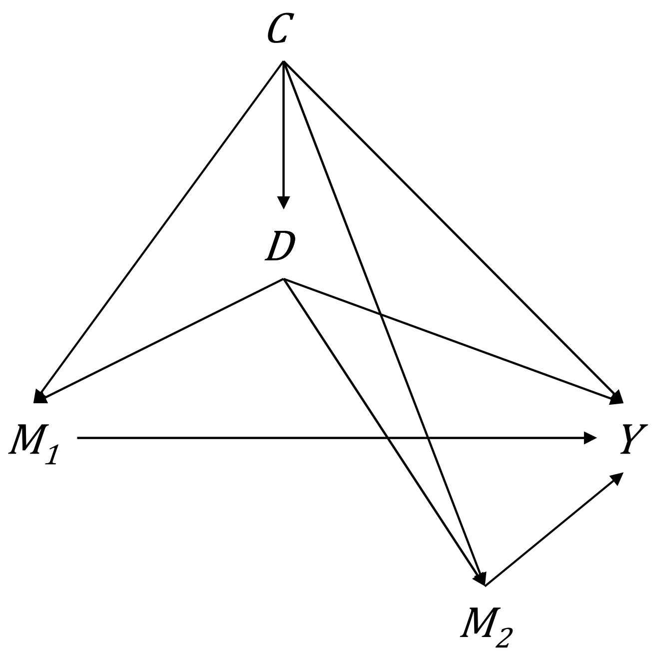
Week 7: Multiple Mediators

Outline

- Graphical mediation models
- Natural effects through multiple mediators
- Nonparametric identification and estimation
- Parametric estimation strategies

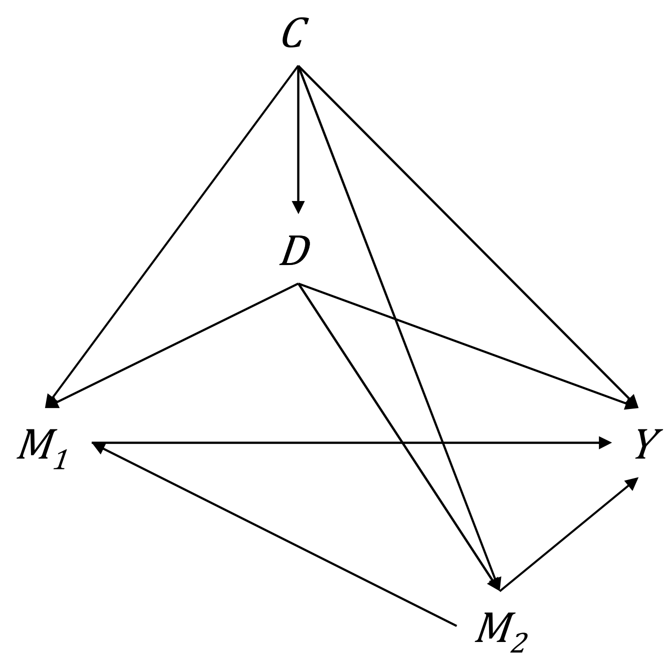
Models with multiple mediators

- In this model, the exposure D affects two mediators, M_1 and M_2, which both affect the outcome Y
- M_1 does not affect M_2, nor does M_2 affect M_1—that is, the two mediators are causally independent



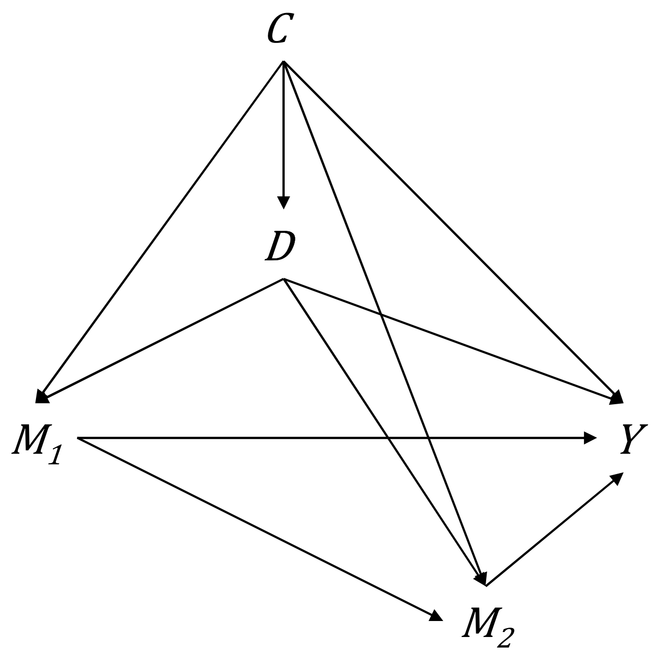
Models with multiple mediators

- In this model, the exposure D affects two mediators, M_1 and M_2, which both affect the outcome Y
- M_2 now affects M_1, such that the mediators are causally dependent
- M_2 is an exposure-induced confounder with respect to the effect of M_1 on Y



Models with multiple mediators

- In this model, the exposure D affects two mediators, M_1 and M_2, which both affect the outcome Y
- M_1 now affects M_2, such that the mediators are again causally dependent
- M_1 is an exposure-induced confounder with respect to the effect of M_2 on Y



Graphical mediation models

- The methods covered today are appropriate for data arising from a causal process resembling any of the graphical models depicted previously
- My presentation of these methods is tailored for models that allow general patterns of baseline confounding and causal dependence among the mediators
- These methods are also appropriate for settings without any baseline confounding and/or where the mediators are independent

Natural effects with multiple mediators

- Natural effects with multiple mediators are very similar to the natural effects we have discussed previously, except they are defined in terms of a vector of K mediators, denoted by $\mathbf{M} = \{M_1, M_2, \dots, M_K\}$

- Specifically, with multiple mediators, the average total effect of the exposure on the outcome can be decomposed into direct and indirect components as follows:

$$
\begin{aligned}
ATE(d, d^*) &= E\big(Y(d) - Y(d^*)\big) \\
&= E\left(Y\big(d, \mathbf{M}(d)\big) - Y\big(d^*, \mathbf{M}(d^*)\big)\right) \\
&= E\left(Y\big(d, \mathbf{M}(d^*)\big) - Y\big(d^*, \mathbf{M}(d^*)\big)\right) + E\left(Y\big(d, \mathbf{M}(d)\big) - Y\big(d, \mathbf{M}(d^*)\big)\right)
\end{aligned}
$$

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ATE(d, d^*) &= E\big(Y(d) - Y(d^*)\big) \\
&= E\Big(Y\big(d, \mathbf{M}(d)\big) - Y\big(d^*, \mathbf{M}(d^*)\big)\Big) \\
&= \underbrace{E\Big(Y\big(d, \mathbf{M}(d^*)\big) - Y\big(d^*, \mathbf{M}(d^*)\big)\Big)}_{\text{natural direct effect}} + \underbrace{E\Big(Y\big(d, \mathbf{M}(d)\big) - Y\big(d, \mathbf{M}(d^*)\big)\Big)}_{\text{natural indirect effect}}
\end{aligned}
$$

The multivariate natural direct effect

- The multivariate natural direct effect:

$$MNDE(d, d^*) = E\left(Y\big(d, \mathbf{M}(d^*)\big) - Y\big(d^*, \mathbf{M}(d^*)\big)\right)$$

$$= E\left(Y\big(d, M_1(d^*), \ldots, M_K(d^*)\big) - Y\big(d^*, M_1(d^*), \ldots, M_K(d^*)\big)\right)$$

- The $MNDE(d, d^*)$ is the expected difference in the outcome if individuals had been exposed to d rather than d^* and if they had experienced the levels of all K mediators that would have arisen naturally for them under exposure d^*

- It captures an effect of the exposure D on the outcome Y that operates through all mechanisms other than those involving the vector of mediators $\mathbf{M} = \{M_1, M_2, \ldots, M_K\}$

The multivariate natural direct effect

- The multivariate natural direct effect:

$$MNDE(d, d^*) = E\left(Y\big(d, \mathbf{M}(d^*)\big) - Y\big(d^*, \mathbf{M}(d^*)\big)\right)$$

$$= E\left(Y\big(d, M_1(d^*), \dots, M_K(d^*)\big) - Y\big(d^*, M_1(d^*), \dots, M_K(d^*)\big)\right)$$

- The $MNDE(d, d^*)$ isolates an effect not involving the mediators by…
  - comparing outcomes across different levels of the exposure (d versus d^*)…
  - while holding all the mediators constant at their values under only one level of the exposure $\mathbf{M}(d^*) = \{M_1(d^*), M_2(d^*), \dots, M_K(d^*)\}$

- This comparison deactivates the component of the total effect that is transmitted through all causal chains from exposure to the outcome operating through any of the mediators in $\mathbf{M}$

The multivariate natural indirect effect

- The multivariate natural indirect effect:

$$MNIE(d, d^*) = E\left(Y\big(d, \mathbf{M}(d)\big) - Y\big(d, \mathbf{M}(d^*)\big)\right)$$

$$= E\left(Y\big(d, M_1(d), \dots, M_K(d)\big) - Y\big(d, M_1(d^*), \dots, M_K(d^*)\big)\right)$$

- The $MNIE(d, d^*)$ is the expected difference in the outcome if individuals had been exposed to d and then…
  - experienced the levels of all mediators that would have arisen naturally for them under exposure d rather than the levels that would have arisen naturally under exposure d^*

- It captures an effect of the exposure D on the outcome Y that operates through all mechanisms involving any of the mediators in $\mathbf{M}$

The multivariate natural indirect effect

- The multivariate natural indirect effect:

$$MNIE(d, d^*) = E\left(Y\big(d, \mathbf{M}(d)\big) - Y\big(d, \mathbf{M}(d^*)\big)\right)$$

$$= E\left(Y\big(d, M_1(d), \dots, M_K(d)\big) - Y\big(d, M_1(d^*), \dots, M_K(d^*)\big)\right)$$

- The $MNIE(d, d^*)$ isolates an effect operating through all the mediators jointly by holding the exposure for each individual constant at d…
  - while comparing outcomes across differences in all the mediators that would have arisen under different exposures, $\mathbf{M}(d)$ versus $\mathbf{M}(d^*)$

- This comparison deactivates all mechanisms from exposure to the outcome except for the causal chains operating through the vector of mediators

Nonparametric identification

- Multivariate natural direct and indirect effects can be nonparametrically identified if the following conditions are met:

Assumption MNE.1: $Y(d, \mathbf{m}) \perp D|C$

Assumption MNE.2: $Y(d, \mathbf{m}) \perp \mathbf{M}|C, D = d$

Assumption MNE.3: $\mathbf{M}(d) \perp D|C$

Assumption MNE.4: $Y(d, \mathbf{m}) \perp \mathbf{M}(d^*)|C$

Assumption MNE.5: $P(d, \mathbf{m}|c) > 0$

Assumption MNE.6: $Y = Y(D) = Y\big(D, \mathbf{M}(D)\big) = Y(D, \mathbf{M})$

No unobserved exposure-outcome confounding

- Assumption MNE.1:

$$Y(d, \mathbf{m}) \perp D | C$$

where $Y(d, \mathbf{m}) = Y(d, m_1, \ldots, m_K)$

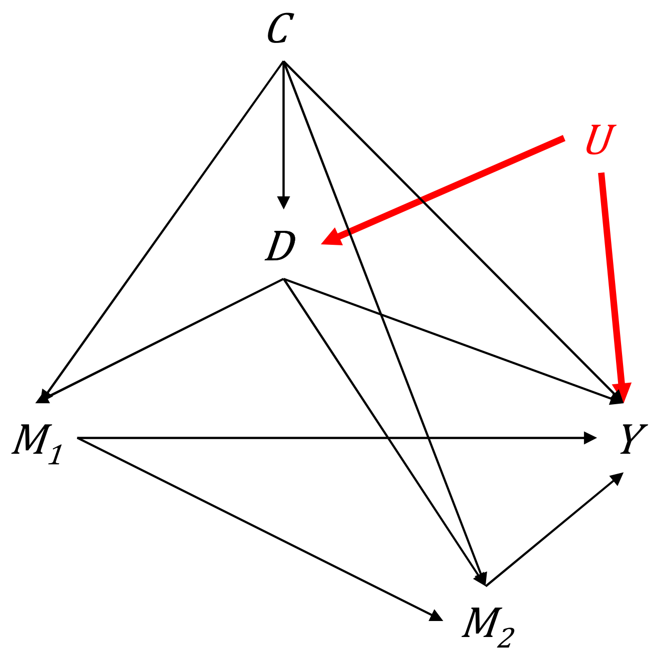
- This assumption requires that the exposure D must be statistically independent of the joint potential outcomes $Y(d, \mathbf{m})$, conditional on the baseline confounders C

- Substantively, this assumption requires that there must not be any unobserved factors that confound the exposure-outcome relationship

No unobserved exposure-outcome confounding

- Assumption MNE.1 would be violated if an unobserved variable jointly affects the exposure and outcome

- In this graph, U is an unobserved confounder for the $D \to Y$ relationship



No unobserved mediator-outcome confounding

- Assumption MNE.2:

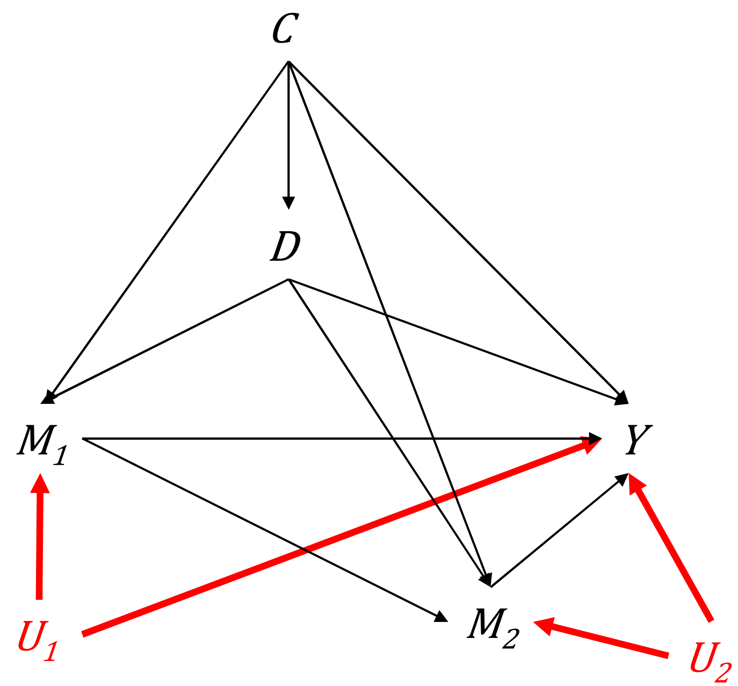
$$Y(d, \mathbf{m}) \perp \mathbf{M} | C, D = d$$

- This assumption requires that the vector of mediators $\mathbf{M}$ must be statistically independent of the joint potential outcomes $Y(d, \mathbf{m})$, conditional on the baseline confounders C in the group exposed to d

- Substantively, this assumption requires that there must not be any unobserved factors that confound the relationship between any one of the mediators and the outcome

No unobserved mediator-outcome confounding

- Assumption MNE.2 would be violated if an unobserved variable jointly affects any one of the mediators and the outcome
- In this graph, U_1 is an unobserved confounder for the $M_1 \rightarrow Y$ relationship
- And U_2 is an unobserved confounder for the $M_2 \rightarrow Y$ relationship



No unobserved exposure-mediator confounding

- Assumption MNE.3:

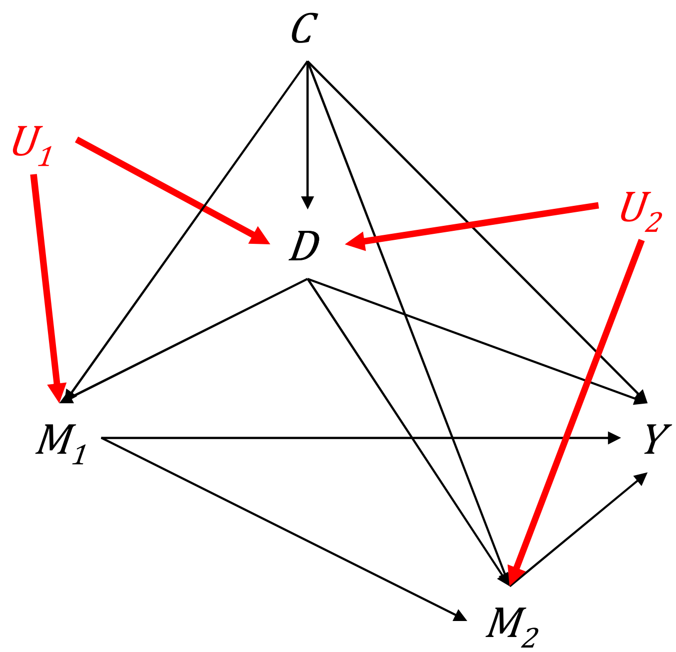
$$\mathbf{M}(d) \perp D|C$$

- This assumption requires that the exposure D must be statistically independent of the potential values of all the mediators in $\boldsymbol{M}(d)$, conditional on the baseline confounders $\boldsymbol{C}$

- Substantively, this assumption requires that there must not be any unobserved factors that confound the relationship between the exposure and any one of the mediators

No unobserved exposure-mediator confounding

- Assumption MNE.3 would be violated if an unobserved variable jointly affects the exposure and any of the mediators
- In this graph, U_1 is an unobserved confounder for the $D \rightarrow M_1$ relationship
- And U_2 is an unobserved confounder for the $D \rightarrow M_2$ relationship



No exposure-induced confounding

- Assumption MNE.4:

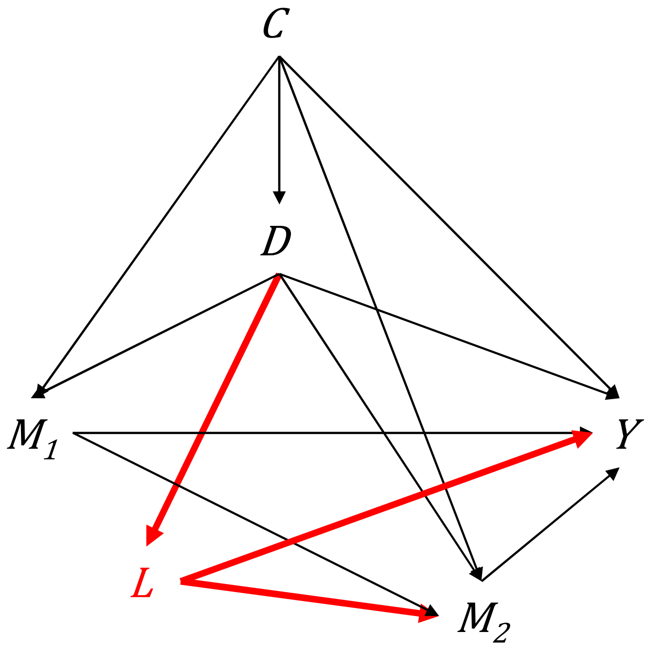
$$Y(d, \mathbf{m}) \perp \mathbf{M}(d^*)|C$$

- This assumption requires that the potential values of the mediators under exposure d must be independent of the joint potential outcomes under exposure d^*, conditional on the baseline confounders C

- Known as a cross-world independence assumption, it requires that there must not be any exposure-induced confounders for any of the mediator-outcome relationships, whether they are observed or not

No exposure-induced confounding

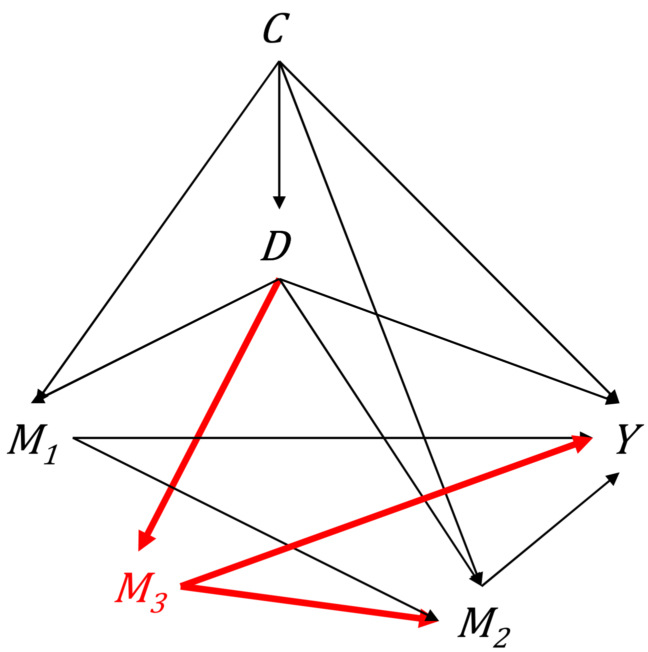
- Assumption MNE.4 would be violated if any variable, observed or not, jointly affects any of the mediators and the outcome…
  - …and is also affected by the exposure
- In this graph, L is a confounder for the $M_2 \rightarrow Y$ relationship that is affected by D



No exposure-induced confounding

- If L is observed, it can be included in the vector of other mediators $\boldsymbol{M}$ and analyzed concurrently with them

- Including any exposure-induced confounders in $\boldsymbol{M}$ as additional mediators obviates violations of MNE.4



Nonparametric identification

- Under assumptions MNE.1 to MNE.6, the multivariate natural direct effect can be equated with a function of observable data rather than nested and cross-world potential outcomes
- Nonparametric identification formula for the multivariate natural direct effect:

$$MNDE(d, d^*) = E\left(Y\left(d, \mathbf{M}(d^*)\right) - Y\left(d^*, \mathbf{M}(d^*)\right)\right)$$

$$= \sum_c \sum_{\mathbf{m}} [E(Y|c, d, \mathbf{m}) - E(Y|c, d^*, \mathbf{m})] P(\mathbf{m}|c, d^*) P(c)$$

$$= \sum_c \sum_{\mathbf{m}} [E(Y|c, d, \mathbf{m}) - E(Y|c, d^*, \mathbf{m})] \prod_{k=1}^{K} P(m_k|c, d^*, \mathbf{m}_{k-1})\, P(c)$$

where $\mathbf{m}_{k-1} = \{m_1, \ldots, m_{k-1}\}$

Nonparametric identification

- Under assumptions MNE.1 to MNE.6, the multivariate natural indirect effect can also be equated with a function of observable data rather than nested and cross-world potential outcomes

- Nonparametric identification formula for the multivariate natural indirect effect:

$$MNIE(d, d^*) = E\left(Y\big(d, \mathbf{M}(d)\big) - Y\big(d, \mathbf{M}(d^*)\big)\right)$$

$$= \sum_c \sum_{\mathbf{m}} E(Y|c, d, \mathbf{m})[P(\mathbf{m}|c, d) - P(\mathbf{m}|c, d^*)]P(c)$$

$$= \sum_c \sum_{\mathbf{m}} E(Y|c, d, \mathbf{m})\left[\prod_{k=1}^{K} P(m_k|c, d, \mathbf{m}_{k-1}) - \prod_{k=1}^{K} P(m_k|c, d^*, \mathbf{m}_{k-1})\right]P(c)$$

where $\mathbf{m}_{k-1} = \{m_1, \ldots, m_{k-1}\}$

Nonparametric estimation

- Nonparametric identification involves equating causal effects defined in terms of counterfactuals with empirical quantities defined in terms of observable data, while ignoring random variability due to sampling
- In practice, however, we rarely have data from an entire target population and thus cannot simply ignore random variability due to sampling from this population
- Nonparametric estimation just involves plugging in sample analogs for the population quantities in the nonparametric identification formulas outlined previously

Limitations of nonparametric estimation

- Limitations of nonparametric estimation
  - Sparsity
  - Curse of dimensionality
  - Excessive sampling variability
- With multiple mediators, these challenges will typically preclude nonparametric estimation as a feasible strategy
- Thus, we will focus exclusively on parametric approaches to estimation

Estimation with linear models

- Consider the following set of linear and additive models, where $c^{\perp} = c - \bar{C}$:

$$E(M_k|c,d) = \beta_{0k} + \beta_{1k}^T c^{\perp} + \beta_{2k} d \qquad \text{for } k = 1, \ldots, K$$

$$E(Y|c,d,\mathbf{m}) = \gamma_0 + \gamma_1^T c^{\perp} + \gamma_2 d + \sum_{k=1}^{K} \gamma_{3k} m_k$$

- Under these models, the natural effects of interest are given by:

$$MNDE(d,d^*) = \gamma_2(d - d^*)$$

$$MNIE(d,d^*) = \left(\sum_{k=1}^{K} \beta_{2k}\gamma_{3k}\right)(d - d^*)$$

- To compute effect estimates, fit these models by OLS and plug the parameter estimates into the expressions above

Estimation with linear models

- Now consider the following set of linear models with $D \times M_k$ interactions:

$$E(M_k|c,d) = \beta_{0k} + \beta_{1k}^T c^{\perp} + \beta_{2k} d \qquad \text{for } k = 1, \dots, K$$

$$E(Y|c,d,\mathbf{m}) = \gamma_0 + \gamma_1^T c^{\perp} + \gamma_2 d + \sum_{k=1}^{K} m_k (\gamma_{3k} + \gamma_{4k} d)$$

- Under these models, the natural effects of interest are given by:

$$MNDE(d,d^*) = \left(\gamma_2 + \sum_{k=1}^{K} \gamma_{4k} (\beta_{0k} + \beta_{2k} d^*)\right)(d - d^*)$$

$$MNIE(d,d^*) = \left(\sum_{k=1}^{K} \beta_{2k} \left(\gamma_{3k} + \gamma_{4k} d\right)\right)(d - d^*)$$

- To compute effect estimates, fit these models by OLS and plug the parameter estimates into the expressions above

Estimation with linear models

- Lastly, consider the following set of linear models with covariate interactions:

$$E(M_k|c,d) = \beta_{0k} + \beta_{1k}^T c^{\perp} + d\left(\beta_{2k} + \beta_{3k}^T c^{\perp}\right) \qquad \text{for } k = 1, \dots, K$$

$$E(Y|c,d,\mathbf{m}) = \gamma_0 + \gamma_1^T c^{\perp} + \gamma_2 d + \sum_{k=1}^{K} m_k(\gamma_{3k} + \gamma_{4k} d) + c^{\perp} \sum_{k=1}^{K} \left(\gamma_{5k}^T d + m_k\left(\gamma_{6k}^T + \gamma_{7k}^T d\right)\right)$$

- Under these models, the natural effects of interest are given by the same expressions as before, provided that the baseline confounders have been mean centered:

$$MNDE(d,d^*) = \left(\gamma_2 + \sum_{k=1}^{K} \gamma_{4k}(\beta_{0k} + \beta_{2k} d^*)\right)(d - d^*)$$

$$MNIE(d,d^*) = \left(\sum_{k=1}^{K} \beta_{2k}\,(\gamma_{3k} + \gamma_{4k} d)\right)(d - d^*)$$

Summary

- Natural direct and indirect effects through multiple mediators can be estimated using linear models for the mediators and outcome fit to sample data by the method of least squares

- These estimators are consistent provided that the assumptions required for identification are satisfied and provided that all the models used for estimation are correctly specified

- They can easily accommodate exposure-mediator interactions and effect moderation across levels of the baseline confounders

Limitations

- Models that are linear in the parameters may not perform very well when any of the mediators or the outcome is binary, ordinal, nominal, or a count
    - This approach is best suited for applications in which the mediators and outcome are unbounded and possess equal-interval scaling
    - Nevertheless, there are some situations where a linear model can provide a reasonable approximation for the conditional expected value of a binary, ordinal, or count variable, in which case this approach to estimation remains defensible
- Although this approach easily accommodates exposure-mediator and covariate interactions, it is much more difficult to incorporate interactions among the different mediators, and naïve attempts to do so can lead to uncongenial models

Estimation via simulation

- Multivariate natural direct and indirect effects can also be estimated using a simulation approach that is implemented with generalized linear models (GLMs)

- The class of GLMs is broad and subsumes normal linear regression as a special case; it also includes a number of nonlinear models, such as logit, probit, and Poisson regression, among others

- This approach to estimation is therefore very general and can be used in a wide variety of different applications (i.e., with continuous, binary, ordinal, nominal, or count variables)

Estimation via simulation

- The simulation estimator is implemented through a series of steps:
  1. Fit models for each of the mediators
  2. Simulate potential values for each of the mediators
  3. Fit a model for the outcome
  4. Simulate potential outcomes using the simulated values of the mediators
  5. Compute effect estimates using the simulated outcomes

Estimation via simulation

- Step 1: fit models for each of the mediators
  - Fit a GLM for each mediator, given the baseline confounders, the exposure, and all preceding mediators, denoted by $g_k(M_k|C, D, \mathbf{M}_{k-1})$ where $\mathbf{M}_{k-1} = \{M_1, \ldots, M_{k-1}\}$
    - For example:

$$g_1(M_1|c, d) = Bern\left(p = \text{logit}^{-1}(\beta_{01} + \beta_{11}^T c + \beta_{21} d)\right)$$

$$g_2(M_2|c, d, m_1) = Normal(\mu = (\beta_{02} + \beta_{12}^T c + \beta_{22} d + \beta_{32} m_1), \sigma^2)$$

  - Let $\hat{g}_k(M_k|C, D, \mathbf{M}_{k-1})$ denote these models with their parameters estimated by maximum likelihood

Estimation via simulation

- Step 2: simulate potential values for the mediator
  - For every individual in the sample…
    - First, simulate one copy of $M_1(d^*)$ from $\hat{g}_1(M_1|C, d^*)$, and then simulate one copy of $M_1(d)$ from $\hat{g}_1(M_1|C, d)$; let $\widetilde{M}_1(d^*)$ and $\widetilde{M}_1(d)$ denote these simulated values
    - Next, for all $k > 1$ mediators, simulate one copy of $M_k(d^*)$ from $\hat{g}_k\big(M_k\big|C, d^*, \widetilde{\mathbf{M}}_{k-1}(d^*)\big)$ and one copy of $M_k(d)$ from $\hat{g}_k\big(M_k\big|C, d, \widetilde{\mathbf{M}}_{k-1}(d)\big)$, where $\widetilde{\mathbf{M}}_{k-1}(d) = \{\widetilde{M}_1(d), \ldots, \widetilde{M}_{k-1}(d)\}$ and $\widetilde{\mathbf{M}}_{k-1}(d^*)$ is defined analogously
    - Repeat these steps $10^3 \leq J \leq 10^4$ times
  - Let $\widetilde{M}_{jk}(d^*)$ and $\widetilde{M}_{jk}(d)$ denote the simulated values for each mediator $k = 1, \ldots, K$ and for each simulation $j = 1, 2, \ldots, J$, and let $\widetilde{\mathbf{M}}_j(d) = \{\widetilde{M}_{j1}(d), \ldots, \widetilde{M}_{jK}(d)\}$ denote a vector of simulated mediators, with $\widetilde{\mathbf{M}}_j(d^*)$ defined analogously

Estimation via simulation

- Step 3: fit a model for the outcome
  - Fit a GLM for the outcome given the baseline confounders, the exposure, and the vector of mediators, denoted by $h(Y|C, D, \mathbf{M})$, where $\mathbf{M} = \{M_1, \dots, M_K\}$
    - For example:

$$h(Y|c, d, \mathbf{m}) = Pois\left(\lambda = \exp\left(\gamma_0 + \gamma_1^T c^{\perp} + \gamma_2 d + \sum_{k=1}^{K} m_k(\gamma_{3k} + \gamma_{4k} d)\right)\right)$$

  - Let $\hat{h}(Y|C, D, \mathbf{M})$ denote this model with its parameters estimated by maximum likelihood

Estimation via simulation

- Step 4: simulate potential outcomes
  - For every sample member and each simulated vector of mediators…
    - simulate one copy of $Y\big(d, \mathbf{M}(d)\big)$ from $\hat{h}\big(Y \big| C, d, \widetilde{\mathbf{M}}_j(d)\big)$ and then…
    - simulate one copy of $Y\big(d^*, \mathbf{M}(d^*)\big)$ from $\hat{h}\big(Y \big| C, d^*, \widetilde{\mathbf{M}}_j(d^*)\big)$ and then…
    - simulate one copy of $Y\big(d, \mathbf{M}(d^*)\big)$ from $\hat{h}\big(Y \big| C, d, \widetilde{\mathbf{M}}_j(d^*)\big)$
  - Let $\tilde{Y}_j\big(d, \mathbf{M}(d)\big)$, $\tilde{Y}_j\big(d^*, \mathbf{M}(d^*)\big)$, and $\tilde{Y}_j\big(d, \mathbf{M}(d^*)\big)$ denote the simulated values of the outcome for each simulation $j = 1, 2, \ldots, J$

Estimation via simulation

- Step 4: compute effect estimates
  - Average the differences between simulated outcomes over simulations and over sample members as follows…

$$\widehat{MNDE}(d, d^*) = \frac{1}{nJ}\sum\sum_j\left[\tilde{Y}_j\big(d, \mathbf{M}(d^*)\big) - \tilde{Y}_j\big(d^*, \mathbf{M}(d^*)\big)\right]$$

$$\widehat{MNIE}(d, d^*) = \frac{1}{nJ}\sum\sum_j\left[\tilde{Y}_j\big(d, \mathbf{M}(d)\big) - \tilde{Y}_j\big(d, \mathbf{M}(d^*)\big)\right]$$

$$\widehat{ATE}(d, d^*) = \frac{1}{nJ}\sum\sum_j\left[\tilde{Y}_j\big(d, \mathbf{M}(d)\big) - \tilde{Y}_j\big(d^*, \mathbf{M}(d^*)\big)\right]$$

Model specification

- This approach can easily accommodate exposure-mediator interactions, mediator-mediator interactions, covariate interactions, and nonlinear terms, as well as many different link functions and distribution models
- The steps outlined previously proceed exactly the same, regardless of the particular form of the GLMs used for the mediators and outcome

Summary

- Multivariate natural direct and indirect effects can be estimated via simulation with a broad class of GLMs fit to sample data by the method of maximum likelihood

- These estimators are consistent provided that the assumptions required for identification are satisfied and provided that all the models used for estimation are correctly specified

- Limitations
  - The method requires correctly specified models for all the mediators and the outcome, which may be difficult to achieve in practice, especially in applications with many mediators

Estimation via weighting

- In contrast to linear models and the simulation approach, which both require models for all the mediators and the outcome, weighting estimators are implemented only with models for the exposure

- These models are used to construct a set of weights that transform the empirical distribution of the sample data in ways that emulate different hypothetical experiments

- The effects of interest are estimated by comparing the mean of the outcome across differently weighted samples

Estimation via weighting

- The weighting estimator is implemented through a series of steps:
  1. Fit two different models for the exposure
  2. Compute predicted probabilities of exposure from each model
  3. Use the exposure probabilities to construct a set of weights
  4. Compute effect estimates by comparing weighted means of the outcome

Estimation via weighting

- Step 1: fit models for the exposure
  - Fit a GLM for the exposure given the baseline confounders, denoted by $f(D|C)$
  - Next, fit another GLM for the exposure given the baseline confounders and the vector of mediators, denoted by $s(D|C, \mathbf{M})$, where $\mathbf{M} = \{M_1, \dots, M_K\}$
    - If, for example, the exposure is binary, then $f(D|C)$ and $s(D|C, \mathbf{M})$ might be logit or probit models
  - Let $\hat{f}(D|C)$ and $\hat{s}(D|C, \mathbf{M})$ denote these models with their parameters estimated by maximum likelihood

Estimation via weighting

- Step 2: compute predicted probabilities of exposure
  - For each sample member, use $\hat{f}(D|C)$ to predict…
    - the probability of exposure to d given their baseline confounders, denoted by $\hat{P}(d|C)$
    - the probability of exposure to d^* given their baseline confounders, denoted by $\hat{P}(d^*|C)$
  - Next, for each sample member, use $\hat{s}(D|C, \mathbf{M})$ to predict…
    - the probability of exposure to d given their baseline confounders and values on all the mediators, denoted by $\hat{P}(d|C, \mathbf{M})$
    - the probability of exposure to d^* given their baseline confounders and values on all the mediators, denoted by $\hat{P}(d^*|C, \mathbf{M})$

Estimation via weighting

- Step 3: construct IPWs
  - Among sample members with $D = d^*$, compute…
    - $\widehat{wm}_1 = \frac{1}{\hat{P}(d^*|C)}$
  - Among sample members with $D = d$, compute…
    - $\widehat{wm}_2 = \frac{1}{\hat{P}(d|C)}$
    - $\widehat{wm}_3 = \frac{\hat{P}(d^*|C, \mathbf{M})}{\hat{P}(d|C, \mathbf{M})\hat{P}(d^*|C)}$

Estimation via weighting

- Step 4: compute effect estimates
  - Compute differences between weighted means of the observed outcome as follows…

$$\widehat{MNDE}(d, d^*) = \frac{\sum I(D=d)\widehat{wm}_3 Y}{\sum I(D=d)\widehat{wm}_3} - \frac{\sum I(D=d^*)\widehat{wm}_1 Y}{\sum I(D=d^*)\widehat{wm}_1}$$

$$\widehat{MNIE}(d, d^*) = \frac{\sum I(D=d)\widehat{wm}_2 Y}{\sum I(D=d)\widehat{wm}_2} - \frac{\sum I(D=d)\widehat{wm}_3 Y}{\sum I(D=d)\widehat{wm}_3}$$

$$\widehat{ATE}(d, d^*) = \frac{\sum I(D=d)\widehat{wm}_2 Y}{\sum I(D=d)\widehat{wm}_2} - \frac{\sum I(D=d^*)\widehat{wm}_1 Y}{\sum I(D=d^*)\widehat{wm}_1}$$

Stabilized and censored weights

- Stabilized versions of the inverse probability weights can be expressed as follows:
  - $\widehat{swm}_1 = \frac{\hat{P}(d^*)}{\hat{P}(d^*|C)}$
  - $\widehat{swm}_2 = \frac{\hat{P}(d)}{\hat{P}(d|C)}$
  - $\widehat{swm}_3 = \frac{\hat{P}(d^*|C,\mathbf{M})\hat{P}(d^*)}{\hat{P}(d|C,\mathbf{M})\hat{P}(d^*|C)}$
- The performance of these weights can usually be improved even further by censoring their extreme values—for example, at the 1st and 99th percentiles

Summary

- Multivariate natural direct and indirect effects can be estimated via weighting with two different GLMs for the probability of exposure
- These estimators are consistent provided that the assumptions required for identification are satisfied and provided that the models used for the exposure are correctly specified
- Limitations
  - Difficult to use and often unstable with continuous or many valued exposures
  - Highly sensitive to model misspecification

Regression imputation

- Multivariate natural direct and indirect effects can also be estimated using a regression imputation approach
- Unlike the other approaches we've considered, regression imputation does not require models for the mediators or for the exposure; rather, it only requires a series of models for the outcome

Regression imputation

- Regression imputation is implemented through a series of steps:

1. Fit a model for the outcome given the exposure and baseline confounders
   - Impute outcomes from this model under $D = d$ and $D = d^*$
2. Fit another model for the outcome given the exposure, confounders, and mediators
   - Impute outcomes from this model under $D = d$
3. Fit a third model for the imputed outcomes from the prior step
   - Impute outcomes from this model under $D = d^*$
4. Compute effect estimates using the different imputed outcomes

Regression imputation

- Step 1: Fit a model for the outcome and construct imputations
  - Fit a model for the outcome given the baseline confounders and the exposure, denoted by $q(Y|C,D)$
    - Let $\hat{q}(Y|C,D)$ denote this model with its parameters estimated by least squares or maximum likelihood
  - Impute potential outcomes under d^* by setting $D = d^*$ for all sample members and computing predicted values, given by $\hat{Y}(d^*) = \hat{q}(C, d^*)$
  - Impute potential outcomes under d by setting $D = d$ for all sample members and computing predicted values, given by $\hat{Y}(d) = \hat{q}(C, d)$

Regression imputation

- Step 2: Fit another model for the outcome and construct imputations
  - Fit a model for the outcome given the baseline confounders, the exposure, and the vector of mediators, denoted by $h(Y|C, D, \mathbf{M})$
    - Let $\hat{h}(Y|C, D, \mathbf{M})$ denote this model with its parameters estimated by least squares or maximum likelihood
  - Impute potential outcomes under d and $\mathbf{M}(D)$ by setting $D = d$ for all sample members and computing predicted values, given by $\hat{Y}\big(d, \mathbf{M}(D)\big) = \hat{h}(C, d, \mathbf{M})$

Regression imputation

- Step 3: fit a model for the imputed outcomes and construct imputations
  - Fit a model for the imputed outcomes constructed in the previous step given the baseline confounders and exposure, denoted by $\tau\left(\hat{Y}\left(d, \mathbf{M}(D)\right) \middle| C, D\right)$
    - Let $\hat{\tau}\left(\hat{Y}\left(d, \mathbf{M}(D)\right) \middle| C, D\right)$ denote this model with its parameters estimated by least squares or maximum likelihood
  - Impute potential outcomes under d and $\mathbf{M}(d^*)$ by setting $D = d^*$ for all sample members and computing predicted values, given by $\hat{Y}\left(d, \mathbf{M}(d^*)\right) = \hat{\tau}\left(\hat{Y}\left(d, \mathbf{M}(D)\right) \middle| C, d^*\right)$

Regression imputation

- Step 4: compute effect estimates
  - Compute differences between means of the imputed outcomes as follows…

$$\widehat{MNDE}(d,d^*) = \frac{1}{n}\sum\left[\hat{Y}\left(d,\mathbf{M}(d^*)\right) - \hat{Y}(d^*)\right]$$

$$\widehat{MNIE}(d,d^*) = \frac{1}{n}\sum\left[\hat{Y}(d) - \hat{Y}\left(d,\mathbf{M}(d^*)\right)\right]$$

$$\widehat{ATE}(d,d^*) = \frac{1}{n}\sum\left[\hat{Y}(d) - \hat{Y}(d^*)\right]$$

Summary

- Multivariate natural direct and indirect effects can be estimated via regression imputation with a series of linear models for the outcome

- These estimators are consistent provided that the assumptions required for identification are satisfied and provided that the models used for estimation are correctly specified

- Like the weighting approach, regression imputation is especially useful in analyses of multiple mediators because it obviates the need to correctly specify and fit a model for each mediator

Example: NLSY79

- 1979 National Longitudinal Study of Youth
  - Exposure (D)
    - sample member attended college before age 22
  - Outcome (Y):
    - standardized scores on the CES-D at age 40
  - Covariates (C):
    - race, gender, parental education, occupation, and income, household size, AFQT scores
  - Potential mediators ($\mathbf{M}$)
    - unemployment between age 35-40 (M_1)
    - household income between age 35-40 (M_2)

Example: NLSY79

- Many studies have documented that going to college seems to reduce the likelihood of becoming depressed later in life—but how does this effect come about?

- One possibility is that a more advanced education reduces depression by increasing the labor market prospects of adults, boosting both their employment and wages
  - Do unemployment and income jointly mediate the effect of college attendance on depression?

Example: NLSY79

- Using linear models, compute estimates for the $MNDE$ and $MNIE$ of education on depression operating through income and unemployment

```r
### wk 7 nlsy tutorial ###
rm(list=ls())

## load/install libraries ##
packages<-c("dplyr", "tidyr", "foreign", "foreach", "doParallel", "doRNG", "devtools")
install.packages(packages)

for (package.i in packages) {
  suppressPackageStartupMessages(library(package.i, character.only=TRUE))
  }

## load data ##
datadir <- "C:/Users/Geoffrey Wodtke/Dropbox/D/courses/2024-25_UOFCHICAGO/SOCI_40258_CAUSAL_MEDIATION/data/"
nlsy <- read.dta(paste(datadir, "nlsy79.dta", sep=""))

Y <- "std_cesd_age40"
D <- "att22"
M1 <- "ever_unemp_age3539"
M2 <- "log_faminc_adj_age3539"
C <- c("female", "black", "hispan", "paredu", "parprof", "parinc_prank", "famsize", "afqt3")

nlsy <- nlsy[complete.cases(nlsy[,c(C,D,M1,M2,"cesd_age40")]),] |>
  mutate(std_cesd_age40 = (cesd_age40 - mean(cesd_age40)) / sd(cesd_age40))
```

Example: NLSY79

- Using linear models, compute estimates for the $MNDE$ and $MNIE$ of education on depression operating through income and unemployment

```
## compute estimates w/ linear models ##

#load R functions
source("https://raw.githubusercontent.com/causalMedAnalysis/causalMedR/refs/heads/main/utils.R")
source("https://raw.githubusercontent.com/causalMedAnalysis/causalMedR/refs/heads/main/linmed.R")

#compute estimates
lin_est <- linmed(data = nlsy, D = D, M = c(M1, M2), Y = Y, C = C,
  interaction_DM = TRUE, interaction_DC = TRUE, interaction_MC = TRUE,
  boot = TRUE, boot_reps = 2000, boot_seed = 60637, boot_parallel = TRUE)
```

Example: NLSY79

- Using linear models, compute estimates for the $MNDE$ and $MNIE$ of education on depression operating through income and unemployment

```
lin_output <- data.frame(
  param = c("ATE(1,0)", "MNDE(1,0)", "MNIE(1,0)"),
  est = c(lin_est$ATE, lin_est$NDE, lin_est$NIE),
  ci_lo = c(lin_est$ci_ATE[1], lin_est$ci_NDE[1], lin_est$ci_NIE[1]),
  ci_hi = c(lin_est$ci_ATE[2], lin_est$ci_NDE[2], lin_est$ci_NIE[2]),
  pval = c(lin_est$pvalue_ATE, lin_est$pvalue_NDE, lin_est$pvalue_NIE)) |>
  mutate(across(.cols = !param, .fns = \(x) round(x, 3)))

print(lin_output)
```

```
> print(lin_output)
      param    est  ci_lo  ci_hi  pval
1  ATE(1,0) -0.113 -0.206 -0.014 0.020
2 MNDE(1,0) -0.035 -0.134  0.073 0.519
3 MNIE(1,0) -0.078 -0.121 -0.042 0.000
```

Example: NLSY79

- Using the simulation approach, compute estimates for the $MNDE$ and $MNIE$ of education on depression through income and unemployment

```
#load R functions
source("https://raw.githubusercontent.com/causalMedAnalysis/causalMedR/refs/heads/main/medsim.R")

#specify models for M1 (logit), M2 (normal linear), and Y (normal linear)
formula_M1 <- paste(M1, "~",
  paste(paste(c(D, C), collapse = " + "), "+",
  paste(D, C, sep = ":", collapse = " + ")))

formula_M2 <- paste(M2, "~",
  paste(paste(paste(paste(c(D, M1, C), collapse = " + "), "+",
  paste(D, M1, sep = ":", collapse = " + ")), "+",
  paste(D, C, sep = ":", collapse = " + ")), "+",
  paste(M1, C, sep = ":", collapse = " + ")))

formula_Y <- paste(Y, "~",
  paste(paste(paste(paste(paste(paste(c(D, M1, M2, C), collapse = " + "), "+",
  paste(D, M1, sep = ":", collapse = " + ")), "+",
  paste(D, M2, sep = ":", collapse = " + ")), "+",
  paste(D, C, sep = ":", collapse = " + ")), "+",
  paste(M1, C, sep = ":", collapse = " + ")), "+",
  paste(M2, C, sep = ":", collapse = " + ")))

```

Example: NLSY79

- Using the simulation approach, compute estimates for the $MNDE$ and $MNIE$ of education on depression through income and unemployment

```
specs <- list(
  list(func = "glm", formula = as.formula(formula_M1), args = list(family = "binomial")),
  list(func = "lm", formula = as.formula(formula_M2)),
  list(func = "lm", formula = as.formula(formula_Y)))

#compute estimates
sim_est <- medsim(data = nlsy, num_sim = 1000, treatment = D, intv_med = NULL,
  model_spec = specs, seed = 60637, boot = TRUE, reps = 2000)

```

Example: NLSY79

- Using the simulation approach, compute estimates for the $MNDE$ and $MNIE$ of education on depression through income and unemployment

```
sim_output <- data.frame(
  param = c("ATE(1,0)", "MNDE(1,0)", "MNIE(1,0)"),
  est = c(sim_est$point.est[1], sim_est$point.est[2], sim_est$point.est[3]),
  ci_lo = c(sim_est$ll.95ci[1], sim_est$ll.95ci[2], sim_est$ll.95ci[3]),
  ci_hi = c(sim_est$ul.95ci[1], sim_est$ul.95ci[2], sim_est$ul.95ci[3]),
  pval = c(sim_est$pval[1], sim_est$pval[2], sim_est$pval[3])) |>
  mutate(across(.cols = !param, .fns = \(x) round(x, 3)))

print(sim_output)
```

```
> print(sim_output)
      param    est  ci_lo  ci_hi  pval
1  ATE(1,0) -0.119 -0.215 -0.020 0.012
2 MNDE(1,0) -0.036 -0.135  0.073 0.523
3 MNIE(1,0) -0.084 -0.133 -0.044 0.000
```

Example: NLSY79

- Using inverse probability weights, compute estimates for the $MNDE$ and $MNIE$ of education on depression through income and unemployment

```r
## compute estimates w/ inverse probability weighting ##

#load R functions
source("https://raw.githubusercontent.com/causalMedAnalysis/causalMedR/refs/heads/main/ipwmed.R")

#specify models for D
f_of_D_giv_C <- paste(D, "~", paste(C, collapse = " + "))
s_of_D_giv_CM1M2 <- paste(D, "~", paste(c(M1, M2, C), collapse = " + "))

#compute estimates
ipw_est <- ipwmed(data = nlsy, D = D, M = c(M1, M2), Y = Y,
  formula1_string = f_of_D_giv_C, formula2_string = s_of_D_giv_CM1M2,
  stabilize = TRUE, censor = TRUE,
  boot = TRUE, boot_reps = 2000, boot_seed = 60637, boot_parallel = TRUE)
```

Example: NLSY79

- Using inverse probability weights, compute estimates for the $MNDE$ and $MNIE$ of education on depression through income and unemployment

```r
ipw_output <- data.frame(
  param = c("ATE(1,0)", "MNDE(1,0)", "MNIE(1,0)"),
  est = c(ipw_est$ATE, ipw_est$NDE, ipw_est$NIE),
  ci_lo = c(ipw_est$ci_ATE[1], ipw_est$ci_NDE[1], ipw_est$ci_NIE[1]),
  ci_hi = c(ipw_est$ci_ATE[2], ipw_est$ci_NDE[2], ipw_est$ci_NIE[2]),
  pval = c(ipw_est$pvalue_ATE, ipw_est$pvalue_NDE, ipw_est$pvalue_NIE)) |>
  mutate(across(.cols = !param, .fns = \(x) round(x, 3)))

print(ipw_output)
```

```
> print(ipw_output)
      param    est  ci_lo  ci_hi  pval
1  ATE(1,0) -0.167 -0.264 -0.053 0.003
2 MNDE(1,0) -0.100 -0.227  0.055 0.188
3 MNIE(1,0) -0.068 -0.141 -0.009 0.025
```

Example: NLSY79

- Using regression imputation, compute estimates for the $MNDE$ and $MNIE$ of education on depression operating through income and unemployment

```
## compute estimates w/ regression imputation ##

#define regression imputation function
impmed <- function(data) {

  df <- data

  Ymodel_CD <- lm(std_cesd_age40 ~ att22 * (female + black + hispan +
    paredu + parprof + parinc_prank + famsize + afqt3), data=df)

  idata <- df

  idata$att22 <- 0

  Y0hat <- predict(Ymodel_CD, newdata=idata, type="response")

  idata$att22 <- 1

  Y1hat <- predict(Ymodel_CD, newdata=idata, type="response")
```

Example: NLSY79

- Using regression imputation, compute estimates for the $MNDE$ and $MNIE$ of education on depression operating through income and unemployment

```
Ymodel_CDM <- lm(std_cesd_age40 ~
  att22 * (female + black + hispan + paredu + parprof + parinc_prank +
  famsize + afqt3 + log_faminc_adj_age3539 + ever_unemp_age3539), data=df)

idata <- df

idata$att22 <- 1

df$Y1MDhat <- predict(Ymodel_CDM, newdata=idata, type="response")

YhatModel_CD <- lm(Y1MDhat ~ att22 * (female + black + hispan +
  paredu + parprof + parinc_prank + famsize + afqt3), data=df)

idata <- df

idata$att22 <- 0

Y1M0hat <- predict(YhatModel_CD, newdata=idata, type="response")
```

```
  MNDE <- mean(Y1M0hat) - mean(Y0hat)
  MNIE <- mean(Y1hat) - mean(Y1M0hat)
  ATE <- MNDE + MNIE

  point.est <- list(ATE, MNDE, MNIE)

  return(point.est)
}
```

Example: NLSY79

- Using regression imputation, compute estimates for the $MNDE$ and $MNIE$ of education on depression operating through income and unemployment

```r
#compute point estimates
impmed.est <- impmed(nlsy)
impmed.est <- matrix(unlist(impmed.est), ncol=3, byrow=TRUE)

#compute bootstrap estimates
ncores <- detectCores()-2
my.cluster <- parallel::makeCluster(ncores, type="PSOCK")
doParallel::registerDoParallel(cl=my.cluster)
clusterExport(cl=my.cluster, list("impmed"), envir=environment())
registerDoRNG(60637)

impmed.boot <- foreach(i=1:2000, .combine=cbind) %dopar% {

  boot.data <- nlsy[sample(nrow(nlsy), nrow(nlsy), replace=TRUE),]

  boot.est <- impmed(data=boot.data)

  return(boot.est)
}

stopCluster(my.cluster)
rm(my.cluster)

impmed.boot <- matrix(unlist(impmed.boot), ncol=3, byrow=TRUE)
```

Example: NLSY79

- Using regression imputation, compute estimates for the $MNDE$ and $MNIE$ of education on depression operating through income and unemployment

```
#collate estimates
impmed.output <- data.frame(
  param = c("ATE(1,0)", "MNDE(1,0)", "MNIE(1,0)"),
  est = impmed.est[1:3],
  ci_lo = apply(impmed.boot, 2, function(x) quantile(x, prob=0.025)),
  ci_hi = apply(impmed.boot, 2, function(x) quantile(x, prob=0.975))) %>%
    mutate(across(c(est, ci_lo, ci_hi), ~round(.x, digits = 3)))

print(impmed.output)
```

```
> print(impmed.output)
      param    est  ci_lo  ci_hi
1  ATE(1,0) -0.119 -0.212 -0.023
2 MNDE(1,0) -0.062 -0.160  0.040
3 MNIE(1,0) -0.056 -0.093 -0.027
```