# Mediation

Part 4 of Summary of the Harvard Workshop on Causal Modelling

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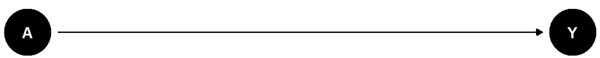
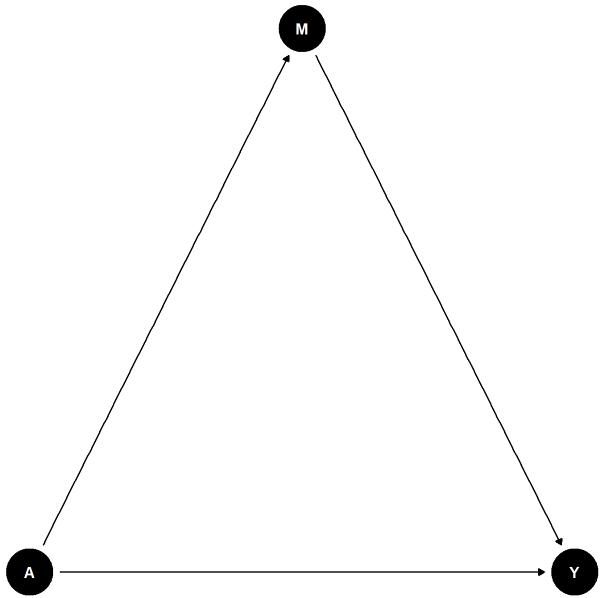
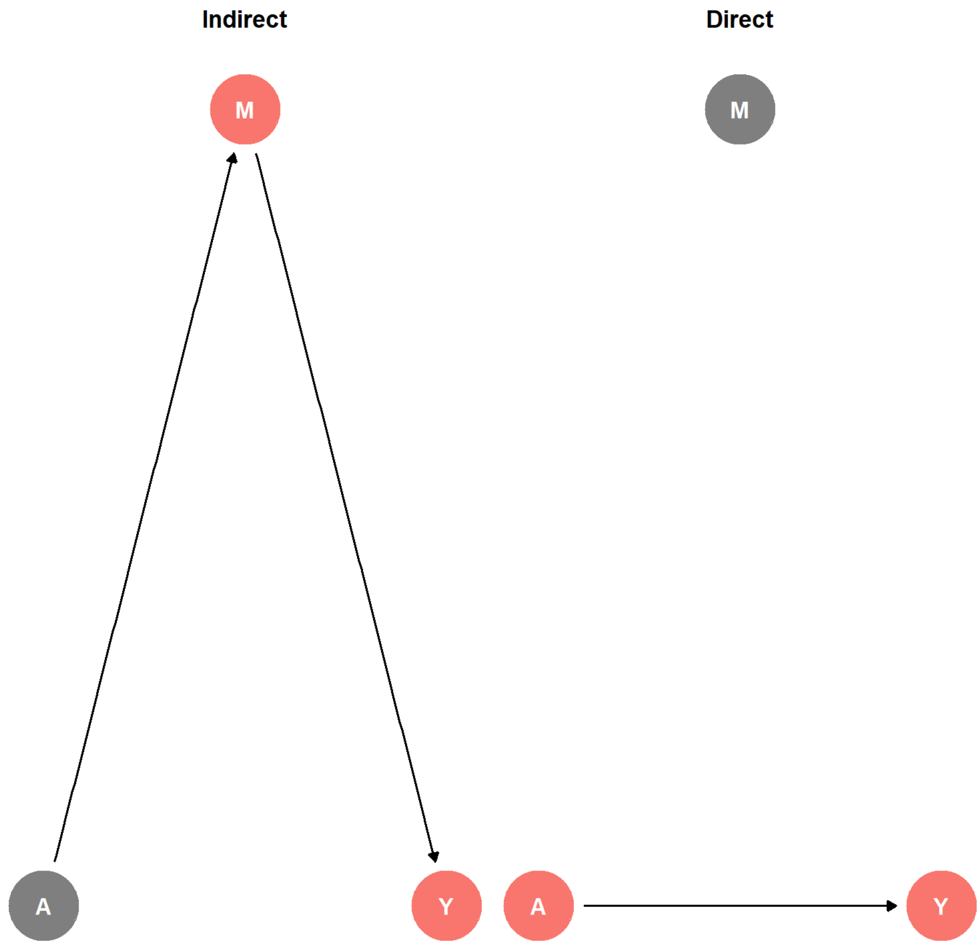
# Mediation






- (1) Indirect effect of A on Y through M
- (2) Direct effect of A on Y (effect that is not through M)

# Standard approach (The difference method)

- Total effect: $E[Y|A=a, C=c] = \alpha_0 + \alpha_1 A + \ldots$
- Indirect effect: $E[Y|A=a, C=c, M=m] = \beta_0 + \beta_1 A + \ldots$

Direct effect = Total effect - Indirect effect

# Problem 1: Mediator outcome confounding

# Adjusting for M creates collider stratification bias

# Problem 2: Exposure-mediator interactions

# Counterfactual framework for mediation

## Some definitions

- $Y_a$: counterfactual **outcome** when exposure $A$ is set to level $a$
- $M_a$: be the counterfactual value of the **mediator** when exposure $A$ is set to level $a$
- $Y_{am}$: counterfactual outcome when exposure $A$ is set to $a$ and $M$ to $m$

# Total effect

$$Y_{1M_1} - Y_{0M_0}$$

# Nested counterfactuals

$$Y_{aM_{a*}}$$

For example:

$$Y_{0M_1}$$

The counterfactual outcome had you not received the treatment, but mediator at the counterfactual value it would have been had you received treatment.

| **A** | **M** | **Y** | $M_0$ | $M_1$ | $Y_{0M_0}$ | $Y_{1M_1}$ | $Y_{0M_1}$ | $Y_{1M_0}$ |
|---|---|---|---|---|---|---|---|---|
| 0 | 0 | 1 | 0 | | 1 | | | |
| 1 | 0 | 1 | | 0 | | 0 | | |
| 1 | 1 | 0 | | 1 | | 0 | | |

# Controlled Direct effect (CDE)

The difference in counterfactual outcomes when `(A=1)` compared to `(A=0)`, when `(M)` is fixed at `(m)`

$$E[CDE(m)|c] = E[Y|A=1,m,c] - E[Y|A=0,m,c]$$

# Natural Direct Effect (NDE)

Changing the treatment, but fixing the mediator at whatever level it would be had you not changed the treatment

$$E[NDE|C] = E[Y_{1,M_0} - Y_{0,M_0}|C]$$

$$= \Sigma_m \{E[Y|A=1,m,c] - E[Y|A=0,m,c]\} P(M=m|A=0,c)$$

# Natural Indirect Effect (NIE)

Fixing the treatment, the effect you see by changing the mediator, as if you had changed the treatment without actually changing the treatment itself

$$E[NIE|C] = E[Y_{1,M_1} - Y_{1,M_0}|C]$$

$$= \Sigma_m E[Y|A=1,m,c]\{P(M=m|A=1,c) - P(M=m|A=0,c)\}$$

# Proportion mediated

Total effect = NIE + NDE

PM = NIE/TE

- is imprecise (ie wide confidence intervals)
- Use the CI for the NIE to decide if there is any mediation occurring

# Identification: Parametric regression equations

- Fit a regression model $E[Y|A,M,C] = \theta_0 + \theta_1 a + \theta_2 m + \theta_3 am + \beta_3 c$
- Fit a regression model $E[M|A,C] = \beta_0 + \beta_1 a + \beta_2 c$
- compute analytically

# Analytic solutions

- $CDE = \theta_1 + \theta_3 m(a - a^\star)$
- $NDE = \theta_1 + \theta_3(\beta_0 + \beta_1 a^\star + \beta_3 c)(a - a^\star)$
- $NIE = \theta_2 \times \beta_1 + \theta_3 \times \beta_1 a(a - a^\star)$

# Monte Carlo Simulation (Very similar to chained regression equations for MI)

1. Fit model for M|A,C and Y|M,A,C using observed data
2. For each treatment level (eg A=0 and 1):
   - simulate the potential values for M|A
   - simulate the potential values for Y conditional on M and the value for A -average over these

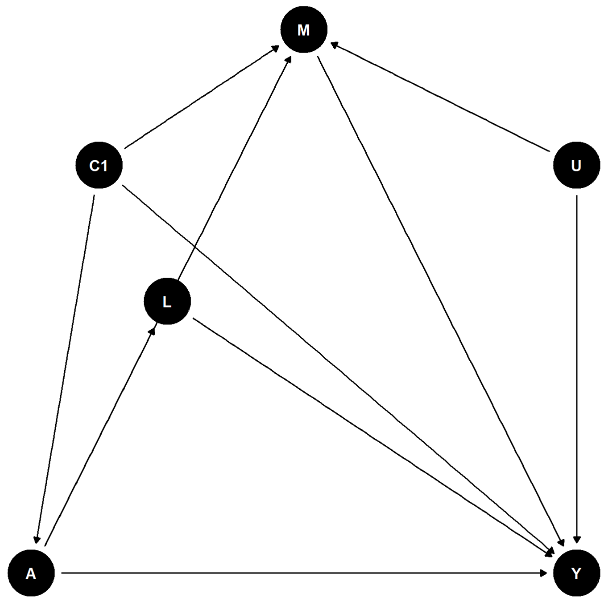
Confidence intervals taken from the percentiles form the bootstrapped samples

# Assumptions[1,2]

1. No unmeasured exposure-outcome confounders
2. No unmeasured mediator-outcome confounders
3. No unmeasured exposure-mediator confounders
4. **There is no mediator-outcome confounder that is affected by exposure**

[1] CDE only requires assumptions 1-2. [2] Randomisation ensures 1 and 3 hold.

# How do we deal with L when trying to estimate the CDE?




- Do we control for L 🤷‍♀️
- If we dont then confounding bias 😱
- if we do then we eliminate some of the effect of A through pathways other than M 😱
- Seem familiar??

# Marginal Structural Model for mediation

- Weight for p(A|C)
- weight for p(M|A,C,L)
- overall weight =

# Sensitivity analysis

- E-value = RR + sqrt(RR*(RR-1)).

The minimum confounding risk ratio (RR*{UY} and RR*{AU}) that would explain away any effect and its CI

# Thanks

**Slides** created via the R package **xaringan**. DAGs created via the R packages **Dagitty** and **ggdag**