Assessing In/Direct Effects: from Structural Equation Models to Causal Mediation Analysis

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Overview of Course

Part 1a: Motivation & basics of causal modelling

Part 1b: Introduction to mediation: definitions, assumptions, LSEMs, mediational g-formula

Part 2a: Mediation analysis using natural effects models with medflex

Part 2b: Special topics: treatment-induced confounding, interactions, multiple mediators etc.
Course Aims

• Introduce main concepts and principles of causal mediation modelling and inference

• ... to help you get a start when reading more advanced research papers on the topic

• And: give you a first idea of practical implementation in R.

Many references at the end — but also: please ask us!
Statistics in Practice!

Not only “How to...?”

But also:

• What models and methods are suitable for the research question?
• ... and under what assumptions will they give useful and reliable results?
• ... are these assumptions plausible / testable / defendable in any given data setting?
Motivation
Example: Randomised placebo-controlled trial

Wanted: effect of a new drug over and above the placebo effect; i.e. want the direct effect of the drug, not its indirect effect via ‘patient’s expectation’.

**Note:** here, we investigate the target of inference, the direct effect, **by design**.

Can use similar ideas to investigate indirect placebo effect.

Often, such trials not possible

⇒ need suitable assumptions and methods.
Example: Randomised placebo-controlled trial

⇒ keep this design in mind as possible target trial for mediational research questions.

**Target trial**: to clarify your (causal) research question, describe your *ideal* trial — putting aside practical / ethical and financial issues, but not the laws of physics.  

(Hernán et al, 2008)
What Triggers Public Opposition to Immigration? Anxiety, Group Cues, and Immigration Threat

Ted Brader  University of Michigan
Nicholas A. Valentino  The University of Texas at Austin
Elizabeth Suhay  University of Michigan

We examine whether and how elite discourse shapes mass opinion and action on immigration policy. One popular but untested suspicion is that reactions to news about the costs of immigration depend upon who the immigrants are. We confirm this suspicion in a nationally representative experiment: news about the costs of immigration boosts white opposition far more when Latino immigrants, rather than European immigrants, are featured. We find these group cues influence opinion and political action by triggering emotions—in particular, anxiety—not simply by changing beliefs about the severity of the immigration problem. A second experiment replicates these findings but also confirms their sensitivity to the stereotypic consistency of group cues and their context. While these results echo recent insights about the power of anxiety, they also suggest the public is susceptible to error and manipulation when group cues trigger anxiety independently of the actual threat posed by the group.


©2008, Midwest Political Science Association
Example: Attitudes to immigration

\( A \) = binary: report on pos./neg. aspects of immigration \((randomised)\)
\( M \) = (quasi-contin.) mediator: level of anxiety
\( Y_1 \) = (quasi-contin.) measure of attitude
\( Y_2 \) = binary measure of attitude (pro/con)
\( C \) = observed covariates: gender, age, income, education etc.
Example: Attitudes to immigration

\[ A = \text{binary: report on pos./neg. aspects of immigration (randomised)} \]
\[ M = \text{(quasi-contin.) mediator: level of anxiety} \]
\[ Y_1 = \text{continuous measure of attitude (scale)} \]
\[ Y_2 = \text{binary measure of attitude (pro/con)} \]
\[ C = \text{observed covariates: gender, age, income, education etc.} \]

Question: role of anxiety in forming attitude towards immigration?
Example: SES and Health

How much do tumor stage and treatment explain socioeconomic inequalities in breast cancer survival? Applying causal mediation analysis to population-based data

Ruoran Li¹ · Rhian Daniel²,³ · Bernard Rachet¹,³

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Abstract Substantial socioeconomic inequalities in breast cancer survival persist in England, possibly due to more advanced cancer at diagnosis and differential access to treatment. We aim to disentangle the contributions of differential stage at diagnosis and differential treatment to the socioeconomic inequalities in cancer survival. Information on 36,793 women diagnosed with breast cancer during 2000–2007 was routinely collected by an English population-based cancer registry. Deprivation was determined for each patient according to her area of residence at the time of diagnosis. A parametric implementation of the mediator showed in particular that up to thirty per cent of the higher mortality in most deprived patients could be mediated by differential surgical treatment. This study illustrates the importance of using causal inference methods with routine medical data and the need for testing key assumptions through sensitivity analyses. Our results suggest that, although effort for earlier diagnosis is important, this would reduce the cancer survival inequalities only by a third. Because of data limitations, role of differential surgical treatment may have been under-estimated.
Example: SES and Health

Fig. 1 Direct Acyclic Diagram (DAG) depicting the causal relationships between deprivation and survival status in breast cancer patients. Year of diagnosis and region are considered as baseline confounders, with potentially an arrow to each node in the diagram, and thus are not shown in this DAG.
Aside

Note:

The direct or the indirect effect do not exist...
– always relative to the (set of) mediator(s) considered.
– even with given mediators, may depend on other choices.
Quick Tour: Causal Modelling
Association vs. Causation

\textbf{do(\cdot)-Notation}

\textbf{Association:} observing $A$ helps to predict $Y$.

\textbf{Causation:} manipulating $A$ changes distribution of $Y$.

\textbf{Notation:} $\text{do(\cdot)}$ for intervention \hspace{1cm} (cf. Pearl, 2000, various)

\[ P(Y \mid \text{intervene to set } A = a) = P(Y \mid \text{do}(A = a)) \]

often used together with \textit{causal directed acyclic graphs (DAGs)}. 
Association vs. Causation

Potential Responses (PRs)

**Association:** observing $A$ helps to predict $Y$.

**Causation:** manipulating $A$ changes distribution of $Y$.

**Alternative notation:** potential response $Y(a)$ (cf. Rubin, 1974)

$Y(a) =$ value that $Y$ would take if an intervention sets $A = a$.

$$P(Y \mid \text{intervene to set } A = a) \approx P(Y(a))$$

also know as counterfactuals, because $\{Y(a), Y(a') ; a \neq a'\}$ can logically not be observed together.

⇒ need counterfactuals for certain mediation effect parameters.
Identification

\[ E(Y|\text{do}(A = a)) \text{ or } E(Y(a)) \] is identified

with \( C \) pre-exposure covariates

from observational data on \((Y, A, C)\) under

Assumption of no unobserved confounding given \( C \):

- graphically: all backdoor-paths from \( A \) to \( Y \) blocked by \( C \);
- with potential responses: \( Y(a) \perp \perp A \mid C \).

Consistency: if \( A = a \) then \( Y = Y(a) \).
G-Formula

Identified by the \textbf{g-formula} (standardisation)

\[ E(Y|\text{do}(A = a)) \text{ or } E(Y(a)) \]

\[ = \sum_c E(Y \mid A = a, C = c) P(C = c) \]

\[ \Rightarrow \text{can identify e.g. average causal effect (A binary)} \]

\[ ACE = E(Y(1)) - E(Y(0)). \]

\textit{(g-formula: Robins (1986))}
Direct and Indirect Effects
Background

- Traditionally (in many fields): mediation = path analysis, based on **linear structural equation models** (LSEMs).

- **Advantage**: LSEMs simple parameterisation with apparently intuitive meaning of parameters in terms of direct effects.

- **Disadvantage**: LSEMs overly simplistic, do not carry over to non-linear settings (e.g. binary variables, odds-ratios...).
Model-free definition of (in)direct effects:

Wanted: notions of (in)direct effects that do not pre-suppose a certain parametric model.

⇒ ideal trial for research question, e.g. placebo-type trick
⇒ & use do(·) or potential responses to define our target!
Notation

\[ Y = \text{response} \]
\[ M = \text{mediating variable(s)} \]
\[ A = \text{exposure / treatment} \]

\[ Y(a, m) \] potential response under intervention in \( A \) and \( M \)
or also \( p(y \mid \text{do}(A = a, M = m)) \)

\[ M(a) \] pot. response of mediator under intervention in \( A \)

**Consistency:** if \( A = a \) then \( Y = Y(a) = Y(a, M(a)) \).
**Controlled Direct Effect**

**First idea:** intervene in $A$ while fixing $M$ (e.g. at baseline)

\[
CDE = E(Y|\text{do}(A = a, M = 0)) - E(Y|\text{do}(A = a', M = 0))
\]

or with PRs

\[
CDE = E(\{Y(A = a, M = 0)\} - \{Y(A = a', M = 0)\})
\]

**Advantage:** CDE conceptually simple; identifying conditions straightforward; can be related to parameters of variety of regression models; *will suffice in many applications.*

**Disadvantage:** *no corresponding notion of indirect effect* — in fact: $M$ could be prior / post $A$ or both could be independent of each other with same $CDE$.

⇒ does not fully capture what we might mean by ‘mediation’.
G-Formula for $CDE$

Under

(1) no-unobserved-confounding of $A$ and $Y$ given $C_1$ and

(2) no-unobserved-confounding of $M$ and $Y$ given $(A, C_1, C_2)$:

$$E(Y(a,m)) = \sum_{c_1,c_2} E(Y \mid A = a, M = m, C_2 = c_2, C_1 = c_1) \times P(C_2 = c_2 \mid A = a, C_1 = c_1)P(C_1 = c_1).$$

(General identification of joint effects see Shpitser & Pearl (2006))
**Motivation**

In placebo trial, $M$ is not controlled at fixed value — instead ‘pretend’ $A$ has different value:

Control (placebo) group will think they receive treatment, but they do not receive active ingredient.

(Unethical, but logically feasible.)

$\Rightarrow$ mediator is $M(a')$, while actual treatment is different $A = a$. 
Natural (In)Direct Effects

Definition (Robins & Greenland, 1992; Pearl 2001)

\[
NDE = E(Y(a', M(a')) - Y(a, M(a')))
\]

\[
NIE = E(Y(a, M(a')) - Y(a, M(a)))
\]

Or: other contrasts, e.g. relative risks.
Effect decomposition

Assuming only consistency; no particular parametric model.

Total effect =

\[ E(Y(a') - Y(a)) = E(Y(a', M(a')) - Y(a, M(a))) \]
\[ = E(Y(a', M(a')) - Y(a, M(a')) + E(Y(a, M(a')) - Y(a, M(a))) \]
\[ = NDE + NIE \]

⇒ proportion mediated = \( \frac{NIE}{NDE + NIE} \)
Interactions

**Note**, if (outcome) model non-linear / with interactions, typically:

\[
E(Y(1, M(1)) - Y(0, M(1))) \neq E(Y(1, M(0)) - Y(0, M(0)))
\]

\[\text{total DE (NDE)} \neq \text{pure DE}\]

and similar for indirect effects...
**Interactions**

*Note,* if (outcome) model non-linear / with *interactions*, typically:

\[ E(Y(0, M(1)) - Y(0, M(0))) \neq E(Y(1, M(1)) - Y(1, M(0))) \]

- *pure IE* (NIE)
- *total IE*
Nested Counterfactual

Key quantity: nested counterfactual \( Y(a, M(a')) \)

— genuinely counterfactual (‘cross-world’).

Interpretation in terms of do(·) based on extended model:

assume \( A \) can be separated into an aspect \( A^M \) affecting only \( M \) and another aspect \( A^Y \) affecting only \( Y \):

\[ \Rightarrow \text{target of inference } E(Y \mid \text{do}(A^Y = a, A^M = a')). \]

(Robins & Richardson, 2011; Didelez, 2019)
Separable Effects

⇒ can make sense of $Y(a, M(a'))$ in terms of augmented system (DAG) and do-interventions — placebo-type trial!

Observational data: always $A \equiv A^M \equiv A^Y$; identification??

(Robins & Richardson, 2011; Didelez, 2019)
Mediational G-Formula

$C$ observed covariates, not affected by $A$ or $M$ (non-descendants)

Under identifying assumptions:

$$E(Y(a, M(a')))) = \sum_m E(Y \mid A = a, M = m, c) \times p(m \mid A = a', c)p(c)$$

(or conditionally on (subset of) $C$)
NDE/NIE: Identifying Assumptions

As before: consistency, positivity

No unobserved confounding

\[ Y(a, m) \perp A \mid C, \quad M(a) \perp A \mid C, \]
\[ Y(a, m) \perp M \mid (A = a, C) \]

Cross-world independence

\[ Y(a, m) \perp M(a') \mid C \]

Or: assume extended causal DAG with separable effects.
No unobserved $A-Y$ confounding given $C \perp Y(a, m) \perp A \mid C$:

**Note:** automatically true when $A$ randomised.
Key Assumptions – Graphically

No unobserved $A$-$M$ confounding given $C$ — $M(a) \perp A \mid C$:

Note: automatically true when $A$ randomised.
Key Assumptions – Graphically

No unobserved $M-Y$ confounding given $C$ —
$Y(a, m) \perp \perp M \ | \ (A = a, C)$:

Note: *NOT* automatically true even when $A$ randomised!
Cannot randomise $M$ in same experiment.
**Key Assumptions – Graphically**

**Cross-world independence:** \( Y(a, m) \perp \perp M(a') \mid C \)

e.g. no treatment-induced \( M - Y \) confounding by some \( L \), observed nor unobserved!

**Note:** cannot be verified in ANY experiment!
Why is treatment-induced confounding a problem?

\( Y(a, M(a')) = Y(a, L(a), M(a', L(a'))) \)

\( \Rightarrow \) no empirical joint information on \((L(a), L(a'))\)!

**Note:** under LSEM, problem resolved by assumption of constant individual-level effects. (DeStavola et al, 2015)

**Note also:** no problem for \(CDE\) — choose \(C_2 = L\).
Why is treatment-induced confounding a problem?

\[ Y(a, M(a')) = Y(a, L(a), M(a', L(a'))) \]

⇒ separation of paths due to \( L \) unclear

\( L \) also called ‘recanting witness’ (Avin et al, 2005)

Target of inference may not be meaningful / of any practical relevance. Instead: methods for multiple mediators.
(1) For certain parametric models for $p(y|a, m, c)$ and $p(m|a, c)$, analytic expressions for NDE and NDE can be derived, e.g. LSEM (R package `sem`), or see VanderWeele (2015)

(2) Fit ‘pieces’ of mediational g-formula and plug-in or use MC-methods

⇒ R package `mediation` by Imai et al (2010)

see also Stata command `gformula` Daniel et al. 2011
(3) Specify model for $E(Y(a, M(a'))) \) with explicit parameters for direct / indirect effect, possibly with interaction effect (use suitable / desired link function); fitting requires ‘imputing’ of missing information using auxiliary (working) models for either mediator or outcome;

⇒ R package medflex (Steen et al., 2017)

(4) Other more robust approaches exist but are complicated to implement (Tchetgen Tchetgen & Shpitser, 2012).
Structural equation models:
– responses as functions of inputs;
– functions invariant to how input comes about
  (by observation or intervention)!

**Example:** \( C := \epsilon_C, A := f_A(C, \epsilon_A), Y := f_Y(A, C, \epsilon_Y) \)
⇒ potential responses (binary \( A \)):

\[
Y(1) := f_Y(1, C, \epsilon_Y) \quad Y(0) := f_Y(0, C, \epsilon_Y)
\]

⇒ joint distribution of \((\epsilon_C, \epsilon_A, \epsilon_Y)\) induces 
  joint distribution of \((C, A, Y, Y(1), Y(0))\).
Example: $C := \epsilon_C$, $A := f_A(C, \epsilon_A)$, $Y := f_Y(A, C, \epsilon_Y)$

⇒ potential responses (binary $A$):

$$Y(1) := f_Y(1, C, \epsilon_Y) \quad Y(0) := f_Y(0, C, \epsilon_Y)$$

– without specification of $f(\cdot)$: non-parametric
– with independent $(\epsilon_C, \epsilon_A, \epsilon_Y)$: independent errors

⇒ “NPSEM-IE”
Linear SEMs (LSEMs)

Now: assume functional relations are all linear, e.g.

\[ Y := \alpha_1 A + \alpha_2 C + \epsilon_Y \]

**Note:** implies constant individual level effect — for person \( i \):

\[ Y^i(1) - Y^i(0) = \alpha_1 \cdot 1 + \alpha_2 C^i + \epsilon_Y - \alpha_1 \cdot 0 - \alpha_2 C^i - \epsilon_Y = \alpha_1. \]

\( \Rightarrow \) makes maths very simple (also wrt. potential responses).
**Background on LSEM**

\[ Y = (Y_1, \ldots, Y_K) \text{ set of endogenous variables} \]

\[ X = (X_1, \ldots, X_L) \text{ set of exogenous variables} \]

General structure: 

\[ Y = BY + \Gamma X + \xi \]

\( B, \Gamma \) conformable matrices of parameters (coefficients)

\( \xi = \text{noise}, \xi \perp X \)

**Endogenous:** (interrelated) responses we are interested in

**Exogenous:** fixed by design, randomised or always conditioned
Background on LSEM

\[ Y = BY + \Gamma X + \xi \]

If \( B \) lower triangular \( \Rightarrow \) representable by DAG on \( (Y_1, \ldots, Y_K) \)

If \( \Psi = \text{Var}(\xi) \text{ diag.} \Rightarrow \text{no unobserved confounding} \)

If both \( \Rightarrow \) recursive model.

Further, let \( \Phi = \text{Var}(X) \).
Background on LSEM

\[ Y = B Y + \Gamma X + \xi \]

**Identification:**

place restrictions on \( B, \Gamma, \Psi, \Phi \) so that unique solutions in terms of \( \Sigma = Var(Y) \) exist.

\[ \Rightarrow \text{every recursive model is identified.} \]

Various sufficient rules for other models.

Generally no necessary & sufficient rules (Drton & Weihs, 2016).
LSEMs encompass

• path analyses
• measurement error models
• measurement models for latent constructs (e.g. IQ)
• growth curves
• factor analyses
• instrumental variables, etc.
Causal Mediation and LSEMs

Assume simple LSEM:

\[ M = \beta_0 + \beta_1 A + \beta_2 C + \epsilon_M \]
\[ Y = \theta_0 + \theta_1 A + \theta_2 M + \theta_3 C + \epsilon_Y \]

Hence:

\[ Y(a, M(a')) = \theta_0 + \theta_1 a + \theta_2 (\beta_0 + \beta_1 a' + \beta_2 C + \epsilon_M) + \theta_3 C + \epsilon_Y \]

re-arranging:

\[ Y(a, M(a')) = \theta_0 + \theta_2 \beta_0 + \theta_1 a + \theta_2 \beta_1 a' + (\theta_2 \beta_2 + \theta_3) C + \theta_2 \epsilon_M + \epsilon_Y \]

⇒ \textit{NDE} will be in terms of } \theta_1, \textit{NIE} in terms of } \theta_2 \beta_1
Causal Mediation and LSEMs

Path-Tracing

\[ Y(a, M(a')) = \theta_0 + \theta_2 \beta_0 + \theta_1 a + \theta_2 \beta_1 a' + (\theta_2 \beta_2 + \theta_3) C + \theta_2 \epsilon_M + \epsilon_Y \]

\[ \text{const.} \]
\[ \text{coeff. of } C \]
\[ \text{noise} \]

\[ \Rightarrow \text{path-tracing formula} \]

known from Baron & Kenny (1986)

total effect: \( \theta_1 + \beta_1 \theta_2 \).

Generalises to more complex LSEMs / graphs.
Limitations of LSEMs

Simplicity breaks down when using more complex models, e.g. when

\[ Y = \theta_0 + \theta_1 A + \theta_2 M + \theta^* AM + \theta_3 C + \epsilon_Y \]

Then \( Y(a, M(a')) = \text{const.} + \)

\[ + (\theta_1 + \theta^* \beta_0)a + \theta_2 \beta_1 a' + \theta^* \beta_1 aa' + (\theta_2 \beta_2 + \theta_3)C + (\theta^* \beta_2)aC \]

\[ \text{interact.} \]

\[ \text{interact.} \]

+ noise.
Limitations of LSEMs

Assume $M$ or $Y$ or both binary: LSEM not sensible (does not constrain $M, Y \in \{0, 1\}$).

Instead: e.g. logistic model for each of $p(m|a, c)$ and $p(y|m, a, c)$

$\Rightarrow NO$ simple (logistic) model for $E(Y(a, M(a')))!$
Example: Attitudes to immigration

(Brader et al, 2008)

\[ A = \text{treat} = \text{news report on pos/neg aspects of immigration}; \]
\[ M = \text{anxiety} = \text{anxiety (on scale 1-4)}; \]
\[ Y = \text{immigr} = \text{attitude towards immigration (quasi-contin.)}; \]

**Assumptions?**

- \text{treat randomised} \Rightarrow \text{no } A\text{- confounding}
- \( C = \{\text{gender, age, education, income}\} \) for \( M-Y \) confounding?
- consequences of news-report-style \( M-Y \) confounder?
  - other psychological pathways?
- (\text{constant individual level effects?})
Example: Attitudes to immigration
with `sem` package

\[ A = \text{treat} = \text{news report on pos/neg aspects of immigration}; \]
\[ M = \text{anxiety} = \text{anxiety (on scale 1-4)}; \]
\[ Y = \text{immigr} = \text{attitude towards immigration (quasi-contin.)}; \]

Specify structural equations:

```r
model.sem <- specifyEquations(text="
anxiety = beta1*treat + beta2*gendernum + beta3*age + beta4*education + beta5*income
immigr = theta1*treat + theta2*anxiety + theta3*gendernum + theta4*age + theta5*education + theta6*income")
```

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Example: Attitudes to immigration with \texttt{sem} package

\textbf{Fit SEM:} specify exogenous variables

\begin{verbatim}
model.sem.fit = sem(model.sem, data=framing,
                   fixed.x = c("treat", "gendernum", "age", "education", "income"))
\end{verbatim}
### Example: Attitudes to immigration with `sem` package

#### Fit SEM: output

| Parameter | Estimate | Std Error | z value | Pr(>|z|) |
|-----------|----------|-----------|---------|----------|
| beta1     | 0.466000769 | 0.132525094 | 3.5163210 | 4.375716e-04 |
| beta2     | 0.039374620 | 0.116201179 | 0.3388487 | 7.347237e-01 |
| beta3     | 0.002041275 | 0.003681156 | 0.5545201 | 5.792230e-01 |
| beta4     | -0.310775625 | 0.063003486 | -4.9326735 | 8.111169e-07 |
| beta5     | -0.013752784 | 0.015391525 | -0.8935296 | 3.715736e-01 |
| theta1    | 0.230781871 | 0.119012597 | 1.9391382 | 5.248451e-02 |
| theta2    | 0.366422677 | 0.054019887 | 6.7831070 | 1.176184e-11 |
| theta3    | -0.176641030 | 0.102014191 | -1.7315339 | 8.335658e-02 |
| theta4    | 0.001894623 | 0.003232903 | 0.5860438 | 5.578461e-01 |
| theta5    | -0.215787438 | 0.057791521 | -3.7338944 | 1.885416e-04 |
| theta6    | 0.024826881 | 0.013529851 | 1.8349708 | 6.651001e-02 |
| V[anxiety] | 0.879513365 | 0.076551812 | 11.4891253 | 1.496192e-30 |
| V[immigr] | 0.677569292 | 0.058974837 | 11.4891253 | 1.496192e-30 |
Example: Attitudes to immigration

Summary: assuming simple LSEM,
⇒ direct effect $\hat{\theta}_1 = 0.23$;
indirect effect $\hat{\beta}_1 \hat{\theta}_2 = 0.466 \times 0.366 = 0.17$
⇒ total effect $= \hat{\theta}_1 + \hat{\beta}_1 \hat{\theta}_2 = 0.4$

Proportion mediated: $0.17/0.4 = 0.425$

Note: LSEM not a good fit for these data, st.errors way too optimistic (assume normality).
LSEMs — Implementation

- Can do individual regressions ‘by hand’.
- Better: use R package `sem`
  ⇒ all regressions within one model (incl. standard errors)
- Also: R package `lavaan`
  ⇒ designed for mediation analysis;
  outputs desired (in)direct effects with st.errors.
- Many other SEM packages!
  Also many generalisations available.
Using Mediation G-Formula

Reminder:

\[ E(Y(a, M(a')))) = \sum_m E(Y | A = a, M = m, c) \times p(m | A = a', c)p(c) \]

Idea: assume parametric models for \( E(Y | A = a, M = m, C') \) and \( p(m | A = a', C') \) and combine.

Inference: bootstrap, or MC based on sampling distributions of parameters of both models.

⇒ reliance on correct specification of both models.

(Imai et al, 2010; Daniel et al, 2011)
Example: Attitudes to immigration with mediation package

Linear case: with continuous outcome — replicate `sem` results

```r
immigr.gFormula <- mediate(model.m = lm.model1, model.y = lm.model2, treat="treat", mediator="anxiety", boot = TRUE)  #use non-param bootstrap
```

Causal Mediation Analysis

Nonparametric Bootstrap Confidence Intervals with the Percentile Method

<table>
<thead>
<tr>
<th></th>
<th>Estimate</th>
<th>95% CI Lower</th>
<th>95% CI Upper</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACME</td>
<td>0.1708</td>
<td>0.0739</td>
<td>0.28</td>
<td>0.002 **</td>
</tr>
<tr>
<td>ADE</td>
<td>0.2308</td>
<td>-0.0228</td>
<td>0.46</td>
<td>0.074 .</td>
</tr>
<tr>
<td>Total Effect</td>
<td>0.4015</td>
<td>0.1436</td>
<td>0.62</td>
<td>0.002 **</td>
</tr>
<tr>
<td>Prop. Mediated</td>
<td>0.4253</td>
<td>0.1863</td>
<td>1.13</td>
<td>0.004 **</td>
</tr>
</tbody>
</table>
Example: Attitudes to immigration

with mediation package

Now: binary outcome, non-linear model

\[ \rightarrow \text{immigrbin} = \text{attitude towards immigration (binary: pro/con)}; \]

\[ \Rightarrow \text{linear model } p(m|a,c), \text{ logistic model } p(y|m,a,c) \]

```r
imai_m <- lm(anxiety ~ treat + gender + age + educ + income,
             data=framing)
imai_y <- glm(immigr_bin ~ treat + anxiety + gender + age + educ + income,
              family = binomial(link="logit"),
              data=framing)
```
Example: Attitudes to immigration with mediation package

Output: mean differences of probabilities!

<table>
<thead>
<tr>
<th></th>
<th>Estimate</th>
<th>95% CI Lower</th>
<th>95% CI Upper</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACME (control)</td>
<td>0.069929</td>
<td>0.031781</td>
<td>0.12</td>
<td>0.002 **</td>
</tr>
<tr>
<td>ACME (treated)</td>
<td>0.053625</td>
<td>0.020445</td>
<td>0.10</td>
<td>0.002 **</td>
</tr>
<tr>
<td>ADE (control)</td>
<td>0.125458</td>
<td>0.000975</td>
<td>0.24</td>
<td>0.050 *</td>
</tr>
<tr>
<td>ADE (treated)</td>
<td>0.109155</td>
<td>0.000878</td>
<td>0.21</td>
<td>0.050 *</td>
</tr>
<tr>
<td>Total Effect</td>
<td>0.179083</td>
<td>0.066660</td>
<td>0.28</td>
<td>0.008 **</td>
</tr>
<tr>
<td>Prop. Mediated (control)</td>
<td>0.390481</td>
<td>0.162717</td>
<td>0.96</td>
<td>0.006 **</td>
</tr>
<tr>
<td>Prop. Mediated (treated)</td>
<td>0.299444</td>
<td>0.101226</td>
<td>0.95</td>
<td>0.006 **</td>
</tr>
<tr>
<td>ACME (average)</td>
<td>0.061777</td>
<td>0.026817</td>
<td>0.10</td>
<td>0.002 **</td>
</tr>
<tr>
<td>ADE (average)</td>
<td>0.117306</td>
<td>0.000927</td>
<td>0.22</td>
<td>0.050 *</td>
</tr>
<tr>
<td>Prop. Mediated (average)</td>
<td>0.344962</td>
<td>0.134809</td>
<td>0.95</td>
<td>0.006 **</td>
</tr>
</tbody>
</table>

Suggests: a considerable proportion of the effect of reporting style on attitude is mediated by anxiety.

Some indication for treatment-mediator interaction.
Notes on mediation

- Only outputs mean-differences
- Allows for survival outcomes
- Includes tools for sensitivity analysis
- Nothing to prevent *g-null paradox*...
G-Null Paradox
(Robins & Wasserman, 1997)

Note:
choice of models for \( p(y|a, m, c) \) and \( p(m|a, c) \) will implicitly restrict \( E(Y(a, M(a'))) \).

Example: combine linear (for \( Y \)) and logistic regression (for \( M \))
⇒ total effect can only be zero if both NDE and NIE are zero
— there is no canceling out of NDE and NIE possible.
⇒ might inadvertently impose undesirable restrictions!
Model for $E(Y(a, M(a')))$ (or suitable link-function), e.g.

$$E(Y(a, M(a'))) = \eta_0 + \eta_1 a + \eta_2 a'$$

or conditional on baseline covariates $C$

$$E(Y(a, M(a'))|C = c) = \eta_0 + \eta_1 a + \eta_2 a' + \eta_3 c$$

$\Rightarrow \eta_1, \eta_2$ explicit parameters for direct/indirect effects.

We never observe different values $a, a'$, so how on Earth should we ever be able to fit such a model???

$\Rightarrow$ Johan will tell you!
(L)SEMs versus G-Formula

- LSEMs mathematically simple, for practice too simple (?)
- LSEMs strong structural & parametric assumptions.
- G-formula: weaker structural assumptions, and flexible with parametric assumptions.
  But: typically no exact inference possible.
- mediation package only outputs mean differences.
- Careful: justify absence of treatment-induced confounding and avoid g-null paradox.
- Alternatives: natural effect models $\rightarrow$ Part 2
  or randomised intervention approach
  (Didelez et al, 2006; Vansteelandt & Daniel, 2016)
G-Formula versus NE Models

- In principle: the same (e.g. with saturated models)
- NE models avoid g-null paradox, and less parametric modelling altogether
- NE models use immediately interpretable parameters / less computationally intensive than MC methods
- NE models fit elegantly with separable effects interpretation in terms of \( E(Y|\text{do}(A^Y = a, A^M = a')) \)!
Separable effects approach of Robins & Richardson (2011) has been extended to

- survival settings with time-varying mediator (Didelez, 2019)
- ... using additive hazards model (Aalen et al, 2019)
- competing risks (Stensrud et al, 2019)
Time-To-Event Example

(Aalen et al, 2019)

- Data: RCT (SPRINT), $N = 9000$ — target: relative survival; method: adaptation of g-formula to survival outcome
- High-bp patients randomised to $A =$ intensive or standard trtm.
- $T =$ time to kidney failure (as side effect)
- $M_t =$ diastolic bp (rep. measured while alive)
Causal Mediation Analysis

Summary

For realistic and plausible data analyses:

must move away from linear SEMs.

Over many technical issues, must not forget most important points:

• What is the research question / target of inference and is it adequately addressed by causal mediation approaches?
  Do we believe at least hypothetically in separable effects?

• Are the identifying assumptions plausibly met?
  – no unobserved confounding especially of $Y$ and $M$?
  – no treatment-induced confounding of $Y$ and $M$?
Thank You!

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References II


References III


Didelez V (2019). Defining causal mediation with a longitudinal mediator and a survival outcome. Lifetime Data Analysis.


Robins JM (2003). Semantics of causal DAG models and the identification of direct and indirect effects. In Highly Structured
References VII


Robins JM, Richardson TS (2011). Alternative graphical causal models and the identification of direct effects. In: Causality and
References VIII

psychopathology: finding the determinants of disorders and their cures. Oxford University Press


**Shpitser I, Pearl J (2006).** Identification of joint interventional distributions in recursive semi-Markovian causal models. In:


