Mediation analyses with the ltmle and medoutcon packages

Estimation of controlled direct effects and randomized Natural Direct/Indirect Effects

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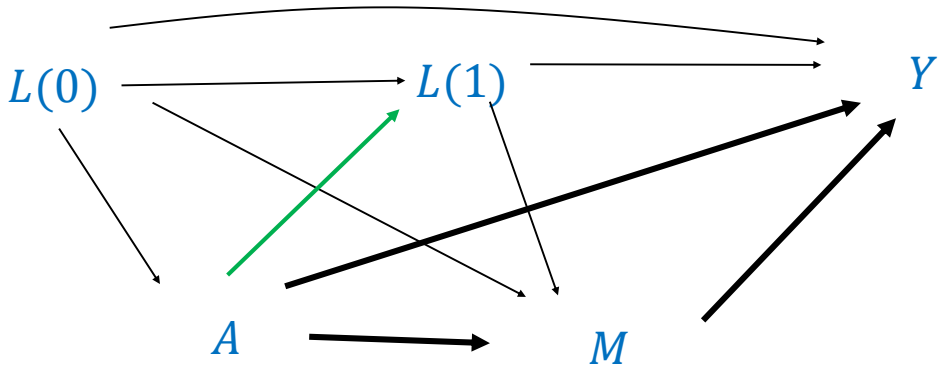
Main context for the afternoon session

In the presence of confounders $L(1)$ of the mediator-outcome relationship, affected by the exposures A



In the simulated example `df`, we also have an $(A * M) \rightarrow Y$ interaction

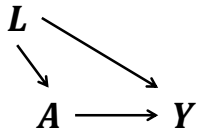
But before, if we need some reminders

- Reminders ⇒ Slide 4 to slide 49
  - Average Total Effect — slides 4-8
  - Mediation causal estimands — slides 9-10
  - CDE and NDE/NIE — slides 11-26
  - 3 way and 4 way decomposition — slide 27-33
  - Other estimators — slide 34
    - G-computation — slides 35-37
    - IPTW — slides 38-43
  - MSM — slides 44-48

- Afternoon session — from the slide 50

Average Total Effect (ATE)

1) and 2) Describe the structural causal model with a DAG and specify the observed data and their link with the causal model



For the ATE, we need:

- The exposure of interest A
- The outcome Y
- Baseline confounders, L *(are there any unmeasured confounders?)*

3) Translate the scientific question into a formal causal quantity, defined with counterfactuals

- Scientific question: *what would be the difference between the average outcome in a population where everyone had been exposed to $A = 1$ and the same population had everyone been unexposed ($A = 0$)?*
- Express the causal quantity of interest (causal estimand) using counterfactual notations

$$ATE = \mathbb{E}(Y_{A=1}) - \mathbb{E}(Y_{A=0})$$

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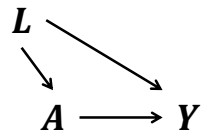
Example with the Average Total Effect (ATE)



4) Assess identifiability of the causal estimand

- **Exchangeability (randomisation) assumption** = no residual unmeasured confounding

$$(Y_a \perp\!\!\!\perp A|L)$$

- **Consistency assumption** = is the exposure to A well defined?

$$Y = Y_a \text{ if } A = a$$

- **Positivity assumption** = every individual could be theoretically exposed or unexposed to A

If $P(L = l) \neq 0$, then $P(A = 0|L = l) > 0$ and $P(A = 1|L = l) > 0$

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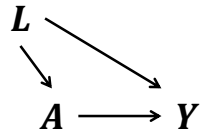
Statistical estimand of the ATE



4) Assess identifiability of the causal estimand

Based on those causal assumptions,
we can represent the target causal quantity (causal estimand)
as a parameter of the observed distribution (statistical estimand)

The causal estimand is: $ATE = \mathbb{E}(Y_{A=1}) - \mathbb{E}(Y_{A=0})$

We have:

$$\mathbb{E}(Y_a) = \sum_{l \in L} \mathbb{E}(Y_a|L = l)P(L = l)$$

Under the randomisation assumption $(Y_a \perp\!\!\!\perp A|L)$

$$\mathbb{E}(Y_a) = \sum_{l \in L} \mathbb{E}(Y_a|A = a, L = l)P(L = l)$$

Under the consistency assumption $Y_a = Y$ if $A = a$ and the positivity assumption $P(A = a|L = l) > 0$

$$\mathbb{E}(Y_a) = \sum_{l \in L} \mathbb{E}(Y|A = a, L = l)P(L = l)$$

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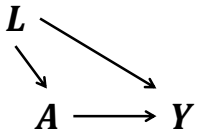
Hernan & Robins. 2006;60(7):578-586 and Nguyen TQ et al. J Causal inference 2022;10(1):246-279

Statistical estimand of the ATE



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Based on those causal assumptions,
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as a parameter of the observed distribution (statistical estimand)

The causal estimand is: $ATE = \mathbb{E}(Y_{A=1}) - \mathbb{E}(Y_{A=0})$

The statistical estimand is

$$ATE = \sum_{l \in L} \mathbb{E}(Y|A=1, L=l)P(L=l) - \sum_{l \in L} \mathbb{E}(Y|A=0, L=l)P(L=l)$$

This is called the **"g-formula"**

Hernan & Robins. 2006;60(7):578-586 and Nguyen TQ et al. J Causal inference 2022;10(1):246-279

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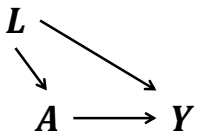
Average Total Effect (ATE)



5) And 6) State the statistical estimation problem, and estimate

The distribution of the observed (O) data can be written as the product

$$P(O) = P(Y, A, L) = \underbrace{P(Y|A, L)}_{\text{Model of the outcome, denoted } \bar{Q}(A,L) = \mathbb{E}(Y|A,L)} \times \underbrace{P(A|L)}_{\text{Propensity score or "treatment mechanism" } g = P(A|L)} \times P(L)$$

Estimators will be defined using:

- Models of the outcome $\bar{Q}(A, L)$ ⇒ trad. regression, g-computation, and other g-methods
- Propensity scores $g(L)$ ⇒ Inverse probability of treatment weighting
- Or both $\bar{Q}(A, L)$ and g(L) ⇒ doubly robust estimators

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Causal mediation analysis

Several quantities of interest have been defined using counterfactual notations

2-Way decomposition (1)		
Controlled Direct Effect	CDE_m	$\mathbb{E}(Y_{a,m}) - \mathbb{E}(Y_{a^*,m})$
Eliminated Effect	EE	$[\mathbb{E}(Y_a) - \mathbb{E}(Y_{a^*})] - [\mathbb{E}(Y_{a,m}) - \mathbb{E}(Y_{a^*,m})]$
2-Way decomposition (2)		
Pure Natural Direct Effect	PNDE	$\mathbb{E}\left(Y_{a,M_{a^*}}\right) - \mathbb{E}\left(Y_{a^*,M_{a^*}}\right)$
Total Natural Indirect Effect	TNIE	$\mathbb{E}\left(Y_{a,M_a}\right) - \mathbb{E}\left(Y_{a,M_{a^*}}\right)$
2-Way decomposition (3)		
Total Natural Direct Effect	TNDE	$\mathbb{E}\left(Y_{a,M_a}\right) - \mathbb{E}\left(Y_{a^*,M_a}\right)$
Pure Natural Indirect Effect	PNIE	$\mathbb{E}\left(Y_{a^*,M_a}\right) - \mathbb{E}\left(Y_{a^*,M_{a^*}}\right)$
2-Way decomposition (4)†		
Marginal Randomised Direct Effect	MRDE	$\mathbb{E}\left(Y_{a,G_{a^*\|L(0)}}\right) - \mathbb{E}\left(Y_{a^*,G_{a^*\|L(0)}}\right)$
Marginal Randomised Indirect Effect	MRIE	$\mathbb{E}\left(Y_{a,G_{a\|L(0)}}\right) - \mathbb{E}\left(Y_{a,G_{a^*\|L(0)}}\right)$
2-Way decomposition (5)		
Conditional Randomised Direct Effect	CRDE	$\mathbb{E}\left(Y_{a,\Gamma_{a^*\|L(0),L(1)}}\right) - \mathbb{E}\left(Y_{a^*,\Gamma_{a^*\|L(0),L(1)}}\right)$
Conditional Randomised Indirect Effect	CRIE	$\mathbb{E}\left(Y_{a,\Gamma_{a\|L(0),L(1)}}\right) - \mathbb{E}\left(Y_{a,\Gamma_{a^*\|L(0),L(1)}}\right)$

2-way decompositions

With 1 direct effect
+ 1 "indirect" effect

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Causal mediation analysis

Several quantities of interest have been defined using counterfactual notations

3-Way decomposition, with $a = 1$, $a^* = 0$ and binary M		
Pure Natural Direct Effect	PNDE	$\mathbb{E}\left(Y_{1,M_0}\right) - \mathbb{E}\left(Y_{0,M_0}\right)$
Mediated Interactive Effect	MIE	$\mathbb{E}\left((Y_{1,1} - Y_{1,0} - Y_{0,1} + Y_{0,0}) \times (M_1 - M_0)\right)$
Pure Natural Indirect Effect	PNIE	$\mathbb{E}\left(Y_{0,M_1}\right) - \mathbb{E}\left(Y_{0,M_0}\right)$
4-Way decomposition, with $a = 1$, $a^* = 0$ and binary M		
Controlled Direct Effect	CDE_0	$\mathbb{E}\left(Y_{1,0}\right) - \mathbb{E}\left(Y_{0,0}\right)$
Mediated Interaction Effect	MIE	$\mathbb{E}\left((Y_{1,1} - Y_{1,0} - Y_{0,1} + Y_{0,0}) \times (M_1 - M_0)\right)$
Reference Interaction Effect	RIE	$\mathbb{E}\left((Y_{1,1} - Y_{1,0} - Y_{0,1} + Y_{0,0}) \times M_0\right)$
Pure Natural Indirect Effect	PNIE	$\mathbb{E}\left(Y_{0,M_1}\right) - \mathbb{E}\left(Y_{0,M_0}\right) = \mathbb{E}\left((Y_{0,1} - Y_{0,0}) \times (M_1 - M_0)\right)$

3-way
and 4-way
decompositions

Direct + indirect
+ $(A * M)$ interaction effects

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Causal mediation analysis

We start with 2 causal quantities of interest in mediation analysis

1. Controlled direct effects (and the eliminated effect)

2. Natural direct effects and Natural indirect effects

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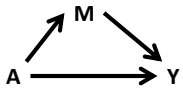
CDE, Natural Direct & Indirect Effects

1) Controlled Direct Effect (Pearl, 2001)

- Based on a joint counterfactual intervention on both A and M



« Change the level of exposure to A: $do(A = a)$ *versus* $do(A = a^*)$ and keep the value of *M* constant : $do(M = m)$ »

Notation : for simplification purpose, we denote $Y_{A=a,M=m}$ by Y_{am}

- For an individual i, A has a direct effect on Y, for a "controlled" value of M if :

$$Y_{am}(i) \neq Y_{a^*m}(i)$$

The controlled direct effect (CDE) is defined using the counterfactual notation

$$CDE_m = \mathbb{E}(Y_{am}) - \mathbb{E}(Y_{a^*m})$$

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CDE, Natural Direct & Indirect Effects

1) **Controlled Direct Effect** (Pearl, 2001)

Interpretation :

- What would be the remaining effect of A on Y if we kept constant the value of the mediator M (for example keeping $M = 0$)?
- It corresponds to an effect of A on Y which is not mediated by M

In case of $A * M$ interaction:
the controlled direct effect of A on Y depends on the chosen value for M ($M = m$)

Without any $A * M$ interaction:
the controlled direct effect of A on Y does not depend on the chosen value for M

- *Note* : Initially, *controlled direct effects* were defined alone without any complementary "indirect effect"

$\Rightarrow$ frustrating when we want to discuss about mediating mechanisms

En 2013, VanderWeele suggested to use the notion of « proportion eliminated » : $\mathrm{PE} = \frac{ATE - CDE_m}{ATE} = \frac{EE}{ATE}$

$ATE - CDE_m$ is not a valid mediated effect: it can be non-null only because of $(A * M) \rightarrow Y$ even if there is no mediation through M

CDE, Natural Direct & Indirect Effects

1) **Controlled Direct Effect** (Pearl, 2001)

Identifiability assumptions:

1. Consistency
2. Positivity
   - If $P(l(0)) \neq 0$, then $\forall a \in \{0,1\}$, $P(A = a | l(0)) > 0$
   - $\forall a \in \{0,1\}$, if $P(a, l(1), l(0)) \neq 0$, then $P(M = m | l(0), a, l(1)) > 0$
3. Sequential randomization assumptions
   - A1 – No unmeasured confounding between A and Y, given $L(0)$

$$(A \perp\!\!\!\perp Y_{a,m} \mid L(0))$$

   - A2 – No unmeasured confounding between M and Y, given $L(0)$, A and $L(1)$

$$(M \perp\!\!\!\perp Y_{a,m} \mid A = a, L(0), L(1))$$

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CDE, Natural Direct & Indirect Effects

1) **Controlled Direct Effect** (Pearl, 2001)

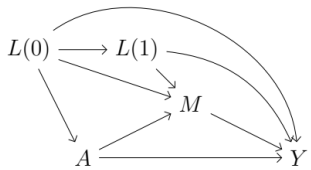
The causal estimand is: $CDE_m = \mathbb{E}(Y_{A=1,M=m}) - \mathbb{E}(Y_{A=0,M=m}) = \mathbb{E}(Y_{1,m}) - \mathbb{E}(Y_{0,m})$

Under the causal assumptions, and according to the causal model,

the causal quantity $\mathbb{E}(Y_{a,m})$ can be identified by

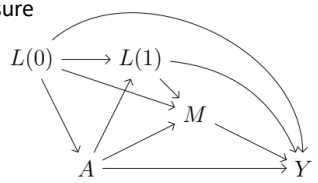
$$\mathbb{E}(Y_{am}) = \sum_{l(0),l(1)} \mathbb{E}(Y|l(0), A=a, l(1), M=m)P[l(0), l(1)]$$

Without intermediate confounder affected by the exposure



$$\mathbb{E}(Y_{am}) = \sum_{l(0),l(1)} \mathbb{E}(Y|l(0), A=a, l(1), M=m)P(L(1)=l(1)|a, l(0))P[l(0)]$$

With intermediate confounder affected by the exposure



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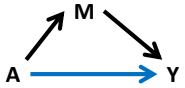
CDE, Natural Direct & Indirect Effects

2a) **Natural Direct Effect** (Pearl, 2001)

- Based on a joint counterfactual intervention on both A and M



Using counterfactual notations, the Pure Natural Direct Effect (PNDE) is defined as

$$PNDE = \mathbb{E}(Y_{a,M_{a^*}}) - \mathbb{E}(Y_{a^*,M_{a^*}}) = \mathbb{E}(Y_{1,M_0}) - \mathbb{E}(Y_{0,M_0})$$

The counterfactual intervention is:

- Changing the value of A from $A = 0$ to $A = 1$ … $do(A = 1)$ *versus* $do(A = 0)$
- … while keeping the value of M constant to $M = M_0$, (i.e. the individual value of M one would naturally observed under the hypothetical intervention setting $A = 0$) $do(M = M_0)$

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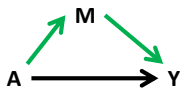
CDE, Natural Direct & Indirect Effects

2b) **Natural Indirect Effect** (Pearl, 2001)

- Based on a joint counterfactual intervention on both A and M



Using counterfactual notations, the Total Natural Indirect Effect (TNIE) is defined as:

$$TNIE = \mathbb{E}\left(Y_{a,M_a}\right) - \mathbb{E}\left(Y_{a,M_{a^*}}\right) = \mathbb{E}\left(Y_{1,M_1}\right) - \mathbb{E}\left(Y_{1,M_0}\right)$$

The counterfactual intervention is:

- Changing the value of M from
  - M_0 = the expected individual value expected under $\mathrm{do}(A = 0)$
  - to M_1 = the expected individual value expected under $\mathrm{do}(A = 1)$
- … while keeping the exposure *A* constant to the value $A = 1$

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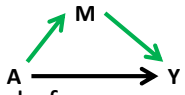
CDE, Natural Direct & Indirect Effects

2a) and 2b) bis **Alternatively**

- Based on a joint counterfactual intervention on both A and M



Instead of…

- the Pure Natural Direct Effect
  $PNDE = \mathbb{E}\left(Y_{1,M_0}\right) - \mathbb{E}\left(Y_{0,M_0}\right)$
- and the Total Natural Indirect Effect
  $TNIE = \mathbb{E}\left(Y_{1,M_1}\right) - \mathbb{E}\left(Y_{1,M_0}\right)$

Where $ATE = PNDE + TNIE$

keeping the value of M constant to $M = M_1$ instead of M_0

We can define …

- the Total Natural Direct Effect
  $TNDE = \mathbb{E}\left(Y_{1,M_1}\right) - \mathbb{E}\left(Y_{0,M_1}\right)$
- and the Pure Natural Indirect Effect
  $PNIE = \mathbb{E}\left(Y_{0,M_1}\right) - \mathbb{E}\left(Y_{0,M_0}\right)$

Where $ATE = TNDE + PNIE$

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CDE, Natural Direct & Indirect Effects

2) **Natural direct and indirect effects** (Pearl, 2001)

- Pros
  - Based on the composition assumption $\mathbb{E}(Y_a) = \mathbb{E}(Y_{a,M_a})$,

    the total effect $ATE = \mathbb{E}(Y_1) - \mathbb{E}(Y_0) = \mathbb{E}(Y_{1,M_1}) - \mathbb{E}(Y_{0,M_0})$

    is equal to the sum of the direct and indirect effects
    $ATE = PNDE + TNIE = [\mathbb{E}(Y_{1,M_0}) - \mathbb{E}(Y_{0,M_0})] + [\mathbb{E}(Y_{1,M_1}) - \mathbb{E}(Y_{1,M_0})]$
  - Useful to understand mechanisms = what are the mediated pathways?

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CDE, Natural Direct & Indirect Effects

2) **Natural direct and indirect effects** (Pearl, 2001)

- Cons

$$ATE = PNDE + TNIE = [\mathbb{E}(Y_{1,M_0}) - \mathbb{E}(Y_{0,M_0})] + [\mathbb{E}(Y_{1,M_1}) - \mathbb{E}(Y_{1,M_0})]$$

  - Interpretation is rather "abstract", because they refer to "cross-world" quantities that are not observable in the real world
  - **Moreover with this definition, natural direct and indirect effect are not identifiable in some causal structures implying intermediate confounding (which are probably frequent in "everyday" datasets)**

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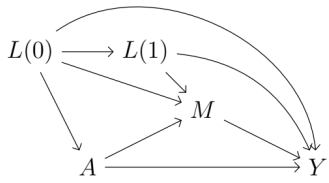
Identifiability of direct and indirect effects

According to the assumed causal model, some direct and indirect effects might be identifiable or not, using observational data

Situation 1

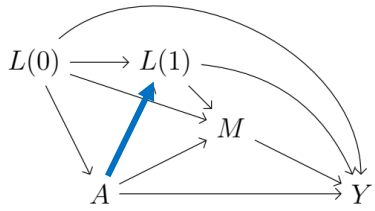


Controlled direct effect: identifiable

Natural direct and indirect effects: identifiable

We can use traditional regression approaches to estimate them (Baron & Kenny causal steps)

Situation 2



Controlled direct effects: identifiable
BUT traditional regression approaches are not adapted +++
Other estimators are necessary (g-computation, IPTW, double robust approaches…)

Natural direct and indirect effects: not identifiable with intermediate confounders $L(1)$ of the $M \rightarrow Y$ relationship affected by the exposure A

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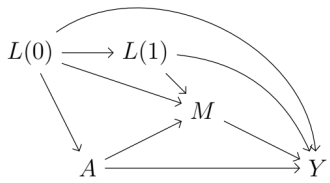
G-formula for the Natural Direct and Indirect effects

Situation 1



In the situation 1,
and under the following randomisation assumptions

i) No unmeasured confounding between A and Y, given $L(0)$
$(A \perp\!\!\!\perp Y_{a,m} \mid L(0))$
ii) No unmeasured confounding between M and Y, given $L(0)$ and $L(1)$
$(M \perp\!\!\!\perp Y_{a,m} \mid A = a, L(0), L(1))$
iii) No unmeasured confounding between A and M, given $L(0)$
$(A \perp\!\!\!\perp M_a \mid L(0))$
iv) No confounder $L(1)$ of the $M - Y$ relationship
is affected by A $(M_{a^*} \perp\!\!\!\perp Y_{am} \mid L(0), L(1))$

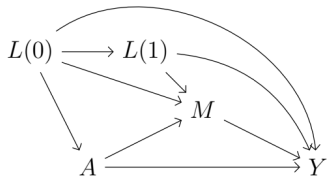
$\mathbb{E}\left(Y_{a,M_{a'}}\right)$ can be identified by

$$\mathbb{E}\left(Y_{a,M_{a'}}\right) = \sum_{l(0)}\sum_{l(1)}\sum_{m} \mathbb{E}\left(Y_{a,M_{a'}} \middle| l(0), l(1)\right) P(M_{a'} = m | L(0), l(1)) P(l(0), l(1))$$

$$\mathbb{E}\left(Y_{a,M_{a'}}\right) = \sum_{l(0)}\sum_{l(1)}\sum_{m} \mathbb{E}(Y | l(0), a, l(1), m) P(M = m | L(0), a', l(1)) P(l(0), l(1))$$

G-formula for the Natural Direct and Indirect effects

Situation 1



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i) No unmeasured confounding between A and Y, given $L(0)$
$(A \perp\!\!\!\perp Y_{a,m} \mid L(0))$
ii) No unmeasured confounding between M and Y, given $L(0)$ and $L(1)$
$(M \perp\!\!\!\perp Y_{a,m} \mid A = a, L(0), L(1))$
iii) No unmeasured confounding between A and M, given $L(0)$
$(A \perp\!\!\!\perp M_a \mid L(0))$
iv) No confounder $L(1)$ of the $M - Y$ relationship
is affected by A $(M_{a^*} \perp\!\!\!\perp Y_{am} \mid L(0), L(1))$

NDE and NIE can be identified using the following g-formula

$$\Psi^{\text{PNDE}} = \sum_{l(0),l(1),m} [\mathbb{E}[Y \mid m, l(1), A = 1, l(0)] - \mathbb{E}[Y \mid m, l(1), A = 0, l(0)]] \times \mathbb{P}(M = m \mid l(1), A = 0, l(0)) \times \mathbb{P}(L(0) = l(0), L(1) = l(1))$$

$$\Psi^{\text{TNIE}} = \sum_{l(0),l(1),m} \mathbb{E}[Y \mid m, l(1), A = 1, l(0)] \times [\mathbb{P}(M = m \mid l(1), A = 1, l(0)) - \mathbb{P}(M = m \mid l(1), A = 0, l(0))] \times \mathbb{P}(L(0) = l(0), L(1) = l(1))$$

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2-way decomposition using traditional regressions

Estimation of the Average Total Effect (ATE)

For quantitative outcomes (quality of life) or even binary outcomes (death),
the $ATE = \mathbb{E}(Y_{A=1}) - \mathbb{E}(Y_{A=0})$ can be estimated using a traditional linear regression to express the total effect on the RD scale

$$\mathbb{E}(Y|A, L) = \alpha_0 + \alpha_A A + \alpha_{L(0)} L(0)$$

$$\widehat{\Psi}_{trad}^{ATE} = \hat{\alpha}_A$$

Robust standard errors (sandwich or bootstrap) should be used when applying this approach

Alternatively for binary outcomes, we can use a logistic regression and express the total effect on the OR scale

$$\text{logit}\, P(Y = 1|A, L) = \alpha_0 + \alpha_A A + \alpha_{L(0)} L(0)$$

$$\widehat{\Psi}_{trad}^{ATE}|L(0) = \exp \hat{\alpha}_A$$

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2-way decomposition using traditional regressions

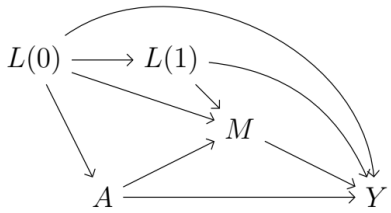
Estimation of the Controlled Direct Effect and Natural Direct and Indirect Effects

Traditional linear regression can be applied to estimate

- The CDE
- The PNDE and TNIE, or alternatively the TNDE and PNIE

But only if confounders of the $M - Y$ relationship are not affected by the exposure A

In the situation 1



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3-way decomposition and 4-way decomposition

Tyler VanderWeele defined 2 approaches to study the $A * M$ interaction more closely

- a 3-way decomposition (2013), using the following counterfactual notations

3-Way decomposition, with $a = 1$, $a^* = 0$ and binary M

Pure Natural Direct Effect	PNDE	$\mathbb{E}(Y_{1,M_0}) - \mathbb{E}(Y_{0,M_0})$
Mediated Interactive Effect	MIE	$\mathbb{E}((Y_{1,1} - Y_{1,0} - Y_{0,1} + Y_{0,0}) \times (M_1 - M_0))$
Pure Natural Indirect Effect	PNIE	$\mathbb{E}(Y_{0,M_1}) - \mathbb{E}(Y_{0,M_0})$

- Enables to isolate a "mediated interactive effect"
  $\mathbb{E}(Y_{1,1} - Y_{1,0} - Y_{0,1} + Y_{0,0})$ corresponds to the definition of a causal $A * M$ interaction effect on Y

Combined effect of $\{A = 1, M = 1\}$ vs $\{A = 0, A = 0\}$

Sum of $\{(A = 1)$ vs $(A = 0)$, while $M = 0\}$ + $\{(M = 1)$ vs $(M = 0)$ while $A = 0\}$

$$\mathbb{E}(Y_{1,1} - Y_{1,0} - Y_{0,1} + Y_{0,0}) = \mathbb{E}(Y_{1,1} - Y_{0,0}) - \{\mathbb{E}(Y_{1,0} - Y_{0,0}) + \mathbb{E}(Y_{0,1} - Y_{0,0})\}$$

Effect of $\{(M = 1)$ vs $(M = 0)$, while $A = 1\}$ *versus* effect of $\{(M = 1)$ vs $(M = 0)$, while $A = 0\}$

Effect of $\{(A = 1)$ vs $(A = 0)$, while $M = 1\}$ *versus* effect of $\{(A = 1)$ vs $(A = 0)$, while $M = 0\}$

$$\mathbb{E}(Y_{1,1} - Y_{1,0} - Y_{0,1} + Y_{0,0}) = \mathbb{E}(Y_{1,1} - Y_{1,0}) - \mathbb{E}(Y_{0,1} - Y_{0,0}) = \mathbb{E}(Y_{1,1} - Y_{0,1}) - \mathbb{E}(Y_{1,0} - Y_{0,0})$$

3-way decomposition and 4-way decomposition

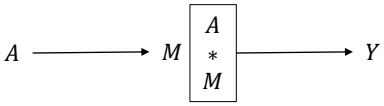
Tyler VanderWeele defined 2 approaches to study the $A * M$ interaction more closely

- a 3-way decomposition (2013)

3-Way decomposition, with $a = 1$, $a^* = 0$ and binary M

Pure Natural Direct Effect	PNDE	$\mathbb{E}(Y_{1,M_0}) - \mathbb{E}(Y_{0,M_0})$
Mediated Interactive Effect	MIE	$\mathbb{E}((Y_{1,1} - Y_{1,0} - Y_{0,1} + Y_{0,0}) \times (M_1 - M_0))$
Pure Natural Indirect Effect	PNIE	$\mathbb{E}(Y_{0,M_1}) - \mathbb{E}(Y_{0,M_0})$

- Enables to isolate a "mediated interactive effect"
  And $(M_1 - M_0)$ is the individual effect of $A \rightarrow M$
  $\Rightarrow$ Intuitively, the MIE is like a indirect effect, going from A to Y through the $A * M$ interaction and defined as a product of coefficient pathway



- In practice: the MIE is equal to the difference
  MIE = TNIE – PNIE
  and MIE = TNDE – PNDE

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3-way decomposition and 4-way decomposition

Tyler VanderWeele defined 2 approaches to study the $A * M$ interaction more closely

- and a 4-way decomposition (2014), using the following counterfactual notations

4-Way decomposition, with $a = 1$, $a^* = 0$ and binary M

Controlled Direct Effect	CDE_0	$\mathbb{E}(Y_{1,0}) - \mathbb{E}(Y_{0,0})$
Mediated Interaction Effect	MIE	$\mathbb{E}((Y_{1,1} - Y_{1,0} - Y_{0,1} + Y_{0,0}) \times (M_1 - M_0))$
Reference Interaction Effect	RIE	$\mathbb{E}((Y_{1,1} - Y_{1,0} - Y_{0,1} + Y_{0,0}) \times M_0)$
Pure Natural Indirect Effect	PNIE	$\mathbb{E}(Y_{0,M_1}) - \mathbb{E}(Y_{0,M_0}) = \mathbb{E}((Y_{0,1} - Y_{0,0}) \times (M_1 - M_0))$

"if the exposure A affects the outcome Y for a particular individual, then at least 1 of 4 things must be the case"

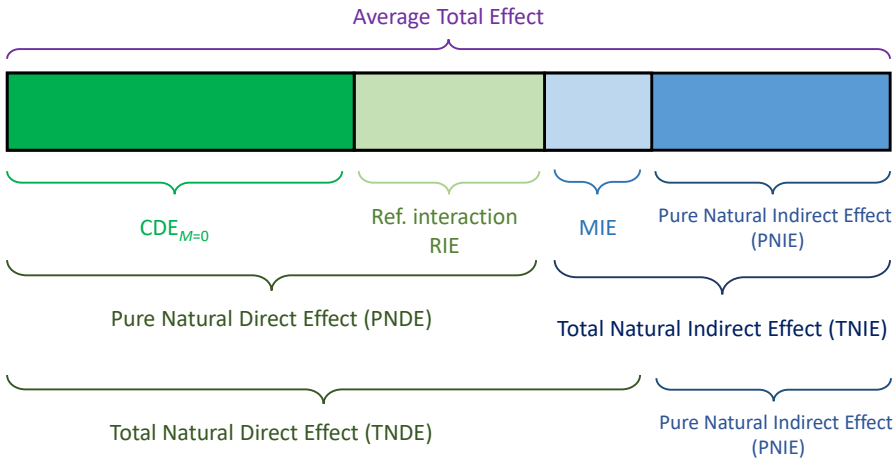
Gives further details on the $(A * M)$ interaction effect on Y

at the individual level, the reference interaction effects is present
only when the counterfactual $M_0 \neq 0$

3-way decomposition and 4-way decomposition

Tyler VanderWeele defined 2 approaches to study the $A * M$ interaction more closely

- and a 4-way decomposition (2014)



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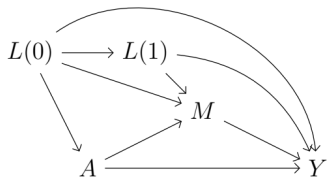
G-formula for the 3-way and 4-way decomposition

Situation 1



In the situation 1,
and under the following randomisation assumptions

i) No unmeasured confounding between A and Y, given $L(0)$
$(A \perp\!\!\!\perp Y_{a,m} \mid L(0))$
ii) No unmeasured confounding between M and Y, given $L(0)$ and $L(1)$
$(M \perp\!\!\!\perp Y_{a,m} \mid A = a, L(0), L(1))$
iii) No unmeasured confounding between A and M, given $L(0)$
$(A \perp\!\!\!\perp M_a \mid L(0))$
iv) No confounder $L(1)$ of the $M - Y$ relationship
is affected by A $(M_{a^*} \perp\!\!\!\perp Y_{am} \mid L(0), L(1))$

Same conditions than for Natural Direct and Indirect Effects

$$\Psi^{\text{PNDE}} = \sum_{l(0),l(1),m} [\mathbb{E}[Y \mid m, l(1), A = 1, l(0)] - \mathbb{E}[Y \mid m, l(1), A = 0, l(0)]] \times \mathbb{P}(M = m \mid l(1), A = 0, l(0)) \times \mathbb{P}(L(0) = l(0), L(1) = l(1))$$

$$\Psi^{\text{MIE}} = \sum_{l(0),l(1),m} [\mathbb{E}(Y \mid A = 1, M = 1, l(0), l(1)) - \mathbb{E}(Y \mid A = 1, M = 0, l(0), (l1)) - \mathbb{E}(Y \mid A = 0, M = 1, l(0), l(1)) + \mathbb{E}(Y \mid A = 0, M = 0, l(0), l(1))] \times [\mathbb{E}(M \mid A = 1, l(0), l(1)) - \mathbb{E}(M \mid A = 0, l(0), l(1)] \times \mathbb{P}(L(0) = l(0), L(1) = l(1))$$

$$\Psi^{\text{PNIE}} = \sum_{l(0),l(1)} [\mathbb{E}(Y \mid M = 1, l(1), A = 0, l(0)) - \mathbb{E}(Y \mid M = 0, l(1), A = 0, l(0))] \times [\mathbb{P}(M = 1 \mid l(1), A = 1, l(0)) - \mathbb{P}(M = 1 \mid l(1), A = 0, l(0))] \times \mathbb{P}(L(0) = l(0), L(1) = l(1))$$

Statistical estimands
for the
3-way decomposition

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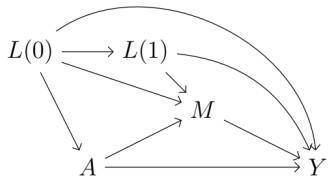
G-formula for the 3-way and 4-way decomposition

Situation 1



In the situation 1,
and under the following randomisation assumptions

i) No unmeasured confounding between A and Y, given $L(0)$
$(A \perp\!\!\!\perp Y_{a,m} \mid L(0))$
ii) No unmeasured confounding between M and Y, given $L(0)$ and $L(1)$
$(M \perp\!\!\!\perp Y_{a,m} \mid A = a, L(0), L(1))$
iii) No unmeasured confounding between A and M, given $L(0)$
$(A \perp\!\!\!\perp M_a \mid L(0))$
iv) No confounder $L(1)$ of the $M - Y$ relationship
is affected by A $(M_{a^*} \perp\!\!\!\perp Y_{am} \mid L(0), L(1))$

$$\Psi^{\text{CDE}_0} = \sum_{l(0),l(1)} [\mathbb{E}(Y \mid M = 0, l(1), A = 1, l(0)) - \mathbb{E}(Y \mid M = 0, l(1), A = 0, l(0))] \times \mathbb{P}(L(0) = l(0), L(1) = l(1))$$

$$\Psi^{\text{MIE}} = \sum_{l(0),l(1)} [\mathbb{E}(Y \mid A = 1, M = 1, l(0), l(1)) - \mathbb{E}(Y \mid A = 1, M = 0, l(0), (l1)) - \mathbb{E}(Y \mid A = 0, M = 1, l(0), l(1)) + \mathbb{E}(Y \mid A = 0, M = 0, l(0), l(1))] \times [\mathbb{E}(M \mid A = 1, l(0), l(1)) - \mathbb{E}(M \mid A = 0, l(0), l(1)] \times \mathbb{P}(L(0) = l(0), L(1) = l(1))$$

$$\Psi^{\text{RIE}} = \sum_{l(0),l(1)} [\mathbb{E}(Y \mid A = 1, M = 1, l(0), l(1)) - \mathbb{E}(Y \mid A = 1, M = 0, l(0), (l1)) - \mathbb{E}(Y \mid A = 0, M = 1, l(0), l(1)) + \mathbb{E}(Y \mid A = 0, M = 0, l(0), l(1))] \times \mathbb{P}(M = 1 \mid l(1), A = 0, l(0)) \times \mathbb{P}(L(0) = l(0), L(1) = l(1))$$

$$\Psi^{\text{PNIE}} = \sum_{l(0),l(1)} [\mathbb{E}(Y \mid M = 1, l(1), A = 0, l(0)) - \mathbb{E}(Y \mid M = 0, l(1), A = 0, l(0))] \times [\mathbb{P}(M = 1 \mid l(1), A = 1, l(0)) - \mathbb{P}(M = 1 \mid l(1), A = 0, l(0))] \times \mathbb{P}(L(0) = l(0), L(1) = l(1))$$

Statistical estimands for the 4-way decomposition

3-way decomposition and 4-way decomposition

We can use the same 2 traditional regression models than for the Natural (In)Direct effects

Example applying 2 linear regressions:

$$\mathbb{E}(Y|a, m, l(0), l(1)) = \gamma_0 + \gamma_A a + \gamma_M m + \gamma_{AM}(a \times m) + \gamma_{L0} l(0) + \gamma_{L1} l(1)$$

$$\mathbb{E}(M|a, l(0), l(1)) = \beta_0 + \beta_A a + \beta_{L0} l(0) + \beta_{L1} l(1)$$

$PNDE|l(0), l(1) = \gamma_A + \gamma_{AM} \times (\beta_0 + \beta_{L0} l(0) + \beta_{L1} l(1))$

$MIE|l(0), l(1) = \gamma_{AM} \times \beta_A$

$PNIE|l(0), l(1) = \gamma_M \times \beta_A$

3-way decomposition

$CDE_{M=0}|l(0), l(1) = \gamma_A$

$RIE|l(0), l(1) = \gamma_{AM} \times (\beta_0 + \beta_{L0} l(0) + \beta_{L1} l(1))$

$MIE|l(0), l(1) = \gamma_{AM} \times \beta_A$

$PNIE|l(0), l(1) = \gamma_M \times \beta_A$

4-way decomposition

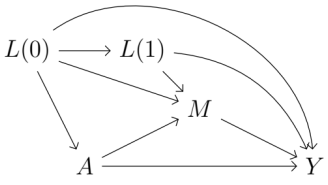
Practical examples – Traditional regressions

- The decomposition can be calculated using the `CMAverse` package
  - `Model = "rb"` and `estimation = "paramfunc"` for regression based estimation, using the closed-form parameters of the model
  - Specify variables
  - `EMint = TRUE` to specify the presence of an $A * M$ interaction effect on Y
  - Specify the families for the glm of the outcome and the glm of the mediator
  - Specify the values for $A = a$ and $A = a^*$
  - Specify the values of $M = m$ for the $CDE_{M=m}$
  - Specify the values of the baseline variables (effects are estimated conditional on those values)
  - Specify the method for the estimation of standard error and 95% CI (delta method or bootstrap)

Other estimators for causal quantities

- Other classical estimators can be used to estimate
  - The Average Total Effect (ATE)
  - The Natural Direct and Indirect Effects (PNDE/TNIE and TNDE/PNIE)

- For the ATE
- For the Natural Direct and Indirect Effects,



- Estimators
  - G-computation
  - Inverse Probability of Treatment Weighting and Inverse
- Marginal Structural Models

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G-computation

1) The Average Total Effect (ATE)

we already saw that

$$\Psi^{ATE}_{\text{gcomp}} = \mathbb{E}(Y_1) - \mathbb{E}(Y_0) = \sum_{l(0)} \{\mathbb{E}(Y|A=1, l(0)) - \mathbb{E}(Y|A=0, l(0))\} \times P\big(l(0)\big)$$

$$\Psi^{ATE}_{\text{gcomp}} = \sum_{l(0)} \{\bar{Q}(A=1, l(0)) - \bar{Q}(A=0, l(0))\} \times P\big(l(0)\big)$$

1. Fit a logistic or a linear regression to estimate $\overline{Q} = \mathbb{E}(Y \mid A, L(0))$
2. Use this estimate to predict an outcome for each subject $\hat{\overline{Q}}(A=0)_i$ and $\hat{\overline{Q}}(A=1)_i$, by evaluating the regression fit $\overline{Q}$ at $A=0$ and $A=1$ respectively
3. Plug the predicted outcomes in the g-formula and use the sample mean to estimate Ψ_{ATE}

$$\hat{\Psi}^{\text{ATE}}_{\text{gcomp}} = \frac{1}{n} \sum_{i=1}^{n} \left[\hat{\overline{Q}}(A=1)_i - \hat{\overline{Q}}(A=0)_i\right] \qquad (6.1)$$

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G-computation

2) Natural Direct and Indirect Effects

The statistical estimand of $\mathbb{E}\big(Y_{a,M_{a^*}}\big)$ is

$$\mathbb{E}\big(Y_{a,M_{a^*}}\big) = \sum_{l(0),l(1)} \sum_{m} \{\mathbb{E}(Y|l(0), A=a, l(1), M=m) \times P(M=m|l(0), l(1), A=a^*)\} \times P[l(1), l(0)]$$

We can directly use this formula using

- a model of the outcome
- And a model of the mediator
- And plug-in the formula individual prediction under $A=a$, or $A=a^*$
  to estimate $\sum_m \{\mathbb{E}(Y|l(0), l(1), A=a, M=m) \times P(M=m|l(0), l(1), A=a^*)\}$

- Then take the population-average

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Practical examples – g-computation

Situation without intermediate confounder of M-Y, affected by the exposure

- We need
  - a model of the outcome conditional on A, $L(0)$, $L(1)$, the mediator M and the $A * M$ interaction
  - and a model of the mediator conditional on $L(0)$ and $L(1)$
- Simple "plug-in" estimator
  - We simulate counterfactual values $\mathbb{E}(Y_{a,m})$ and $P(M_{a'} = 1)$ to estimate
    $\mathbb{E}\left(Y_{a,M_{a'}}\right) = \sum_{m\in\{0,1\}} \mathbb{E}(Y_{a,m}) \times P(M_{a'} = m)$
    $\mathbb{E}\left(Y_{a,M_{a'}}\right) = \mathbb{E}(Y_{a,0}) \times [1 - P(M_{a'} = 1)] + \mathbb{E}(Y_{a,1}) \times P(M_{a'} = 1)$
    and calculate the individual contrasts and take the population average
- Using the `CMAverse` package
  - `estimation = "imputation"` instead of `"paramfunc"`
  - To get estimation of the CDE, 2-way, 3-way and 4-way decomposition

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Inverse Probability of Treatment Weighting (IPTW)

1) The Average Total Effect (ATE)

It can be shown that the counterfactual $\mathbb{E}(Y_{A=a})$ can also be identified by

$$\mathbb{E}(Y_{A=a}) = \underbrace{\sum_{l(0)} \mathbb{E}(Y|A = a, L(0) = l(0))P(L(0) = l(0))}_{\text{G-computation}} = \underbrace{\mathbb{E}\left[\frac{I(A = a)}{g(A = a|L(0) = l(0))} \times Y\right]}_{\text{IPTW}}$$

IPTW: weighed values of the outcome, where the weights are defined using the propensity score $g(a|l(0))$

And also

$$\mathbb{E}(Y_{A=a}) = \frac{\mathbb{E}\left[\frac{I(A=a)\times g^*(A=a)}{g(A = a|L(0) = l(0))} \times Y\right]}{\mathbb{E}\left[\frac{I(A=a)\times g^*(A=a)}{g(A = a|L(0) = l(0))}\right]}$$

Stabilized IPTW

where $g^*(A = a)$ is any non-null function of A

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Inverse Probability of Treatment Weighting (IPTW)

1) The Average Total Effect (ATE)

So that the $\text{ATE} = \mathbb{E}(Y_a) - \mathbb{E}(Y_{a^*})$ can be estimated by

$$\widehat{\Psi}^{ATE}_{\text{IPTW}} = \frac{1}{n}\sum_{i=1}^{n} \frac{I(A_i = a)}{\widehat{g}(A_i = a \mid L(0)_i)} Y_i - \frac{1}{n}\sum_{i=1}^{n} \frac{I(A_i = a^*)}{\widehat{g}(A_i = a^* \mid L(0)_i)} Y_i$$

or by $$\widehat{\Psi}^{ATE}_{\text{sIPTW}} = \frac{\frac{1}{n}\sum_{i=1}^{n} \frac{I(A_i=a)g^*(A_i=a)}{\widehat{g}(A_i=a|L(0)_i)} Y_i}{\frac{1}{n}\sum_{i=1}^{n} \frac{I(A_i=a)g^*(A_i=a)}{\widehat{g}(A_i=a|L(0)_i)}} - \frac{\frac{1}{n}\sum_{i=1}^{n} \frac{I(A_i=a^*)g^*(A_i=a^*)}{\widehat{g}(A_i=a^*|L(0)_i)} Y_i}{\frac{1}{n}\sum_{i=1}^{n} \frac{I(A_i=a^*)g^*(A_i=a^*)}{\widehat{g}(A_i=a^*|L(0)_i)}}$$

using estimation of the propensity score $\hat{g}(A = a|L(0))$

+/- and $\hat{g}(A = a)$ for stabilised versions

Intuitively, applying weights creates a pseudo-population where confounders are balanced regarding the exposure variable

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Inverse Probability of Treatment Weighting (IPTW)

2) The Natural Direct and Indirect Effects

We saw that the counterfactual $\mathbb{E}\left(Y_{a,M_{a^*}}\right)$ can be identified by

$$\mathbb{E}\left(Y_{a,M_{a'}}\right) = \mathbb{E}\left\{\sum_m \mathbb{E}\left(Y_{a,M_{a'}} \middle| l(0), l(1)\right) \mathbb{P}(M_{a'} = m|L(0), l(1))\right\} \quad \text{G-comp}$$

It can be shown that it can also be identified by

$$\mathbb{E}\left(Y_{a,M_{a'}}\right) = \mathbb{E}\left\{Y \times \frac{1}{g_A(A = a|L(0))} \times \frac{g_M(M|A = a', L(0), L(1))}{g_M(M|A = a, L(0), L(1))}\right\} \quad \text{IPTW}$$

using estimation of the 2 propensity scores g_A and g_M

We will see a practical application later (with "conditional" direct/indirect effects) …

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Inverse Odds Ratio Weighting (IPTW)

2bis) The Natural Direct and Indirect Effects

Eric Tchetgen Tchetgen (2013) described another "weighted" procedure to estimate the PNDE and TNIE

1. Estimate the ATE of A on Y, using the appropriate model
2. Estimate the direct effect of A on Y, using a model weighted by the following odds ratio (in the group exposed to $A = 1$)

$$OR(M, A|L(0), L(1)) = \frac{\frac{g(M=1|A=1,L(0),L(1))}{1-g(M=1|A=1,L(0),L(1))}}{\frac{g(M=1|A=0,L(0),L(1))}{1-g(M=1|A=0,L(0),L(1))}} = \underbrace{\frac{\frac{g(A=1|M=1,L(0),L(1))}{1-g(A=1|M=1,L(0),L(1))}}{\frac{g(A=1|M=0,L(0),L(1))}{1-g(A=1|M=0,L(0),L(1))}}}$$

Using the version of the OR between A and M:
Model of A, conditional on M and baseline confounders

Inverse Odds Ratio Weighting (IPTW)

2bis) The Natural Direct and Indirect Effects

Eric Tchetgen Tchetgen (2013) described another "weighted" procedure to estimate the PNDE and TNIE

1. Estimate the ATE of A on Y, using the appropriate model
2. Estimate the direct effect of A on Y, using a model weighted by the following odds ratio
3. Estimate the TNIE of A on Y, as the difference between the ATE and the PNDE

Pros of this approach:

- With multiple mediators, we don't need to estimate a model for each mediator
- We don't need to make any assumptions regarding the $(A * M)$ interaction effect on the outcome

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Practical examples – IORW for the PNDE/TNIE

Estimation of the PNDE and TNIE by IORW

- We can do the calculation by hand:
  - Models of the outcome for the total effect and the direct effect
    - linear regression for risk difference,
    - logistic regression for OR
  - In practice for the model estimating the PNDE, we can apply:

  $w = 1$ for participants of the unexposed group ($A = 0$)

  and $W = \frac{1}{\frac{g(A=1|M,L(0),L(1))}{1-g(1=A|M,L(0),L(1))}}$ for participants of the exposed group ($A = 1$)
- Or we can use the `CMAverse` package
  - Arguments: `model = "iorw "`
    and `estimation = "imputation"`

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Marginal Structural Models (MSM)

Marginal Structural Models (MSMs) are models of the expected value of a counterfactual outcome.

- They are useful to summarise the causal relationship between the counterfactual outcome and
  - the exposure for the ATE
  - the exposure and the mediator for direct and indirect effects (CDE, NDE, NIE…)

  +/- subset of baseline confounder interesting to study effect modifiers
  - Very useful when the combine exposure to A +/- M +/- effect modifier is high-dimensional (for example with quantitative exposures, quantitative and/or multiple mediators, …)
- Parameters of the MSMs can be estimated by:
  - IPTW (the most known method)
  - G-computation
  - TMLE (double robust method)

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MSM for the ATE

We can express the expected counterfactual outcome $\mathbb{E}(Y_a)$ using the following MSM

$$\mathbb{E}(Y_a) = \alpha_0 + \alpha_A a$$

so that the $ATE = \mathbb{E}(Y_1) - \mathbb{E}(Y_0)$ can be expressed using the coefficients of the MSM:

$$\text{ATE} := (\alpha_0 + \alpha_A \times 1) - (\alpha_0 + \alpha_A \times 0) = \alpha_A$$

this one is not very useful because the exposure is not high-dimensional (binary) …

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MSM for the ATE

For example, if we want to study the effect modification of the exposure by sex,
a useful MSM = model of the expected counterfactual outcome conditional on sex

$$\mathbb{E}(Y_a \mid L_{\text{male}}(0)) = \alpha_0 + \alpha_A a + \alpha_{\text{male}} L_{\text{male}}(0) + \alpha_{A*L_{\text{male}}} (a \times L_{\text{male}}(0))$$

so that the $ATE|L_{\text{male}}(0) = \mathbb{E}(Y_1|L_{\text{male}}(0)) - \mathbb{E}(Y_0|L_{\text{male}}(0))$

can be expressed using the coefficients of the MSM:

$$\{\text{ATE} \mid L_{\text{male}}(0) = 0\} := \mathbb{E}(Y_1 \mid L_{\text{male}}(0) = 0) - \mathbb{E}(Y_0 \mid L_{\text{male}}(0) = 0) = \alpha_A$$
$$\{\text{ATE} \mid L_{\text{male}}(0) = 1\} := \mathbb{E}(Y_1 \mid L_{\text{male}}(0) = 1) - \mathbb{E}(Y_0 \mid L_{\text{male}}(0) = 1) = \alpha_A + \alpha_{A*L_{\text{male}}}$$

Coefficients α_A and $\alpha_{A*L_{\text{male}}}$ can be estimated by

- IPTW
- G-computation

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MSM for the Natural Direct and Indirect Effects

We can express the expected counterfactual outcome $\mathbb{E}\left(Y_{a,M_{a'}}\right)$ by the *mediation formula*

$$\mathbb{E}\left(Y_{a,M_{a'}} \mid L(0), L(1)\right) = \sum_m \mathbb{E}\left(Y_{a,m} \mid L(0), L(1)\right) \times \mathbb{P}\left(M_{a'} = m \mid L(0), L(1)\right)$$

or

$$\mathbb{E}\left(Y_{a,M_{a'}}\right) = \sum_m \mathbb{E}\left(Y_{a,m}\right) \times \mathbb{P}(M_{a'} = m)$$

In order to estimate the PNDE and TNIE (or TNDE and PNIE), we can estimate 2 MSMs

- a model of the counterfactual mediator (where g is a link function), for example:
$$g\left[\mathbb{P}(M_{a'} = 1)\right] = \beta_0 + \beta_A a'$$
- a model of the counterfactual outcome (where h is a link function), for example:
$$h\left[\mathbb{E}(Y_{a,m})\right] = \alpha_0 + \alpha_A a + \alpha_M m + \alpha_{A*M} a \times m)$$

where g and h are appropriate link functions

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Practical examples – MSM for the Natural Direct and Indirect Effects

- We can estimate the coefficients of the 2 MSMs required by
  - 8.4.1) By hand, using directly the coefficients of the MSMs estimated by IPTW of simulating counterfactual values using the MSMs
  - 8.4.2a) Using the `CMAverse` package, estimating the MSMs by IPTW
    - Example with the death outcome
    - `model = "msm"` and `estimation = "imputation"`
    - Families for the MSM of the outcome and the MSM of the mediator (`yreg, mreg`)
    - families for the model required for the weights `ereg` (for the exposure), `wmnomreg` and `wmdenomreg` for the nominator and denominator of the mediator's weight
  - 8.4.2b) Using the `CMAverse` package, estimating the MSMs by g-computation
    - Example with the quality of life outcome
    - `model = "gformula"` and `estimation = "imputation"`
    - We do not need the models for the weights `ereg, wmnomreg, wmdenomreg`

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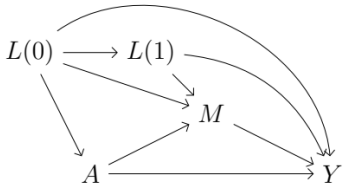
So far, … summary for causal mediation analyses

- In causal models without intermediate confounding affected by the exposure
- Estimation of
  - The Average Total Effect
    - traditional regression models
    - G-computation (simple plug-in estimator)
    - IPTW
    - MSM to study effect modification by sex
  - 2-way decomposition
    - traditional regression models — regmedint, CMAverse
    - G-computation (simple plug-in estimator) — mediation, CMAverse
    - IPTW, IORW — CMAverse
    - MSM estimated by IPTW or g-computation — CMAverse, medflex
  - 3-way and 4-way decomposition
    - traditional regression models — CMAverse
    - IPTW — CMAverse
    - G-computation — CMAverse



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Intermediate confounder affected by the exposure

- Natural Direct and Indirect Effects are not identifiable +++
- Controlled Direct Effects are identifiable
- Analogues of the Natural Direct and Indirect Effects are identifiable:
  - Randomised/interventional Natural Direct and Indirect Effects
    - Random draw of the counterfactual mediator distribution conditional on $L(0)$

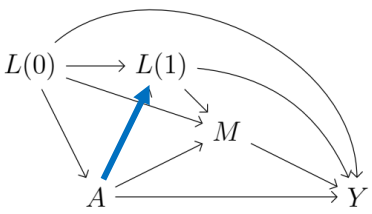
$$\begin{array}{lll} \text{Marginal Randomised Direct Effect} & \text{MRDE} & \mathbb{E}\left(Y_{a,G_{a^*|L(0)}}\right) - \mathbb{E}\left(Y_{a^*,G_{a^*|L(0)}}\right) \\ \text{Marginal Randomised Indirect Effect} & \text{MRIE} & \mathbb{E}\left(Y_{a,G_{a|L(0)}}\right) - \mathbb{E}\left(Y_{a,G_{a^*|L(0)}}\right) \end{array}$$

    - Random draw in the counterfactual mediator distribution conditional on $L(0)$ and $L(1)$

$$\begin{array}{lll} \text{Conditional Randomised Direct Effect} & \text{CRDE} & \mathbb{E}\left(Y_{a,\Gamma_{a^*|L(0),L(1)}}\right) - \mathbb{E}\left(Y_{a^*,\Gamma_{a^*|L(0),L(1)}}\right) \\ \text{Conditional Randomised Indirect Effect} & \text{CRIE} & \mathbb{E}\left(Y_{a,\Gamma_{a|L(0),L(1)}}\right) - \mathbb{E}\left(Y_{a,\Gamma_{a^*|L(0),L(1)}}\right) \end{array}$$

  - Analogues of the 3-way and 4-way decomposition

Situation 2



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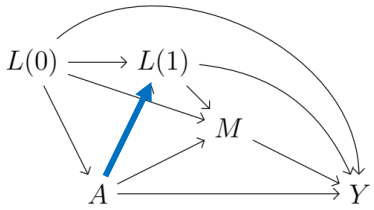
Controlled direct effects

Situation 2



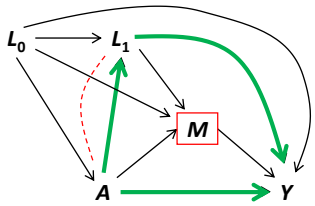
$\mathrm{CDE}_m \quad \mathbb{E}(Y_{a,m}) - \mathbb{E}(Y_{a^*,m})$

Identifiable under the usual condition

- Consistency, positivity
- Sequential randomisation assumptions
  - A1 – No unmeasured confounding between A and Y, given $L(0)$
  - A2 – No unmeasured confounding between M and Y, given $L(0)$, A and $L(1)$

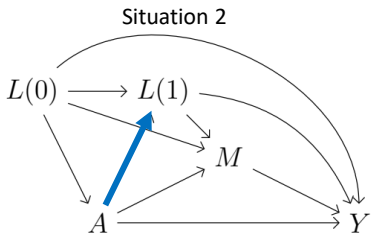
Estimators

- Methods based on traditional regressions cannot be used +++
  - CDE = direct effect of A on Y that does not go through M (in green)
  - Adjusting on M = adjusting on a collider adds spurious correlation between A and $L(1)$
  - Using a traditional regression of the outcome, we would need to adjust and not to adjust on $L(1)$!



Controlled direct effects

Situation 2



$\mathrm{CDE}_m \quad \mathbb{E}(Y_{a,m}) - \mathbb{E}(Y_{a^*,m})$

Identifiable under the usual condition

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- Sequential randomisation assumptions
  - A1 – No unmeasured confounding between A and Y, given $L(0)$
  - A2 – No unmeasured confounding between M and Y, given $L(0)$, A and $L(1)$

Estimators

- G-computation
  - Parametric g-computation
  - Iterative Conditional Expectation
  - Sequential g-estimator
- IPTW and MSM estimated by IPTW
- Double robust estimator (TMLE)

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Estimation of the Controlled Direct Effect by g-computation

1) Parametric g-computation

i. Fit a model to estimate the density of the intermediate confounder $L(1)$, given its past
$$\bar{Q}_{L(1)}(A) = P(L(1) = 1|L(0), A)$$

ii. Fit a model of the outcome Y, given its past
$$\bar{Q}_Y(A, L(1), M) = \mathbb{E}(Y|L(0), A, L(1), M)$$

iii. Simulate individual values of $L(1)_a$ using the estimated density at step (i), under the hypothetical scenarios setting $A = 0$ or $A = 1$

iv. Estimate mean values of the outcome under the hypothetical scenarios setting…
- $A = 0$ (or $A = 1$),
- $L(1) = l(1)_{A=0}$ (or $L(1) = l(1)_{A=1}$)
- and $M = m$

using the model estimated at step (ii).

v. Estimate the controlled direct effect by the sample mean
$$\Psi_{CDE_m} = \frac{1}{n}\sum_{i=1}^{n}[\bar{Q}_Y(A=1, L(1)=l(1)_{A=1}, M=m)_i - \bar{Q}_Y(A=1, L(1)=l(1)_{A=1}, M=m)_i]$$

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Estimation of the Controlled Direct Effect by g-computation

2) Iterative conditional expectation

i. Fit a model of the outcome Y, given its past
$$\bar{Q}_Y(A, L(1), M) = \mathbb{E}(Y|L(0), A, L(1), M)$$

ii. Use this estimate to predict an outcome for each subject $\bar{Q}_Y(A = a', M = m)$ in the hypothetical scenario setting $A = a'$ and $M = m$

iii. Fit a model of the predicted values obtained at step (ii), given A and $L(0)$
$$\bar{Q}_{L(1)} = \mathbb{E}(\bar{Q}_Y(A = a', M = m)|L(0), A)$$

iv. Use this estimate to predict the outcome $\bar{Q}_{L(1)}(A = a')$ for each subject, in the hypothetical scenario setting $A = a'$

v. Use the sample mean to estimate the controlled direct effet:

$$\Psi_{CDE_m} = \frac{1}{n}\sum_{i=1}^{n}[\bar{Q}_{L(1)}(A=1)_i - \bar{Q}_{L(1)}(A=0)_i]$$

Bang H, Robins JM. Doubly robust estimation in missing data and causal inference models. Biometrics. 2005 ;61(4) :962–973.

Petersen M, Schwab J, Gruber S, Blaser N, Schomaker M, van der Laan M. Targeted Maximum Likelihood Estimation for Dynamic and Static Longitudinal Marginal Structural Working Models. Journal of Causal Inference. 2014 ;2(2).

Practical examples – CDE_m by g-computation

- Parametric g-computation
  - See how the "true" value are calculated using the data generating function
- G-computation by Iterative Conditional Expectation (ICE)
  - Calculation by hand
  - Using the `ltmle` package
    - Define Q-formulas (g-formulas are not used with g-computation)
    - Specify the variables
    - Specify the contrast with `abar` argument
    - For the moment, keep `SL.library = "glm"`
    - `g-comp = TRUE`
    - Estimate 95% CI using bootstrap rather than the calculation based on the influence curve

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Estimation of the Controlled Direct Effect by IPTW

1) IPTW

The CDE_m can be estimated by IPTW or stabilised IPTW

- Weights are calculated using a propensity score of the exposure and of the mediator
  - Non-stabilised

$$\Psi^{\mathrm{CDE}_m} = \mathbb{E}\left[\frac{\mathbb{I}(A=1 \cap M=m)}{g(A=1 \mid L(0)) \times g(M=m \mid L(0), A, L(1))} Y\right] - \mathbb{E}\left[\frac{\mathbb{I}(A=0 \cap M=m)}{g(A=0 \mid L(0)) \times g(M=m \mid L(0), A, L(1))} Y\right]$$

  - Stabilised version

$$\hat{\mathbb{E}}(Y_{1,m}) - \hat{\mathbb{E}}(Y_{0,m}) = \frac{\sum_{i=1}^{n} \frac{\mathbb{I}(A_i=1 \cap M_i=m)}{\hat{g}(A_i=1|L(0)_i) \times \hat{g}(M_i=m|L(0)_i, A_i, L(1)_i)} Y_i}{\sum_{i=1}^{n} \frac{\mathbb{I}(A_i=1 \cap M_i=m)}{\hat{g}(A_i=1|L(0)_i) \hat{g}(M_i=m|L(0)_i, A_i, L(1)_i)}} - \frac{\sum_{i=1}^{n} \frac{\mathbb{I}(A_i=0 \cap M_i=m)}{\hat{g}(A_i=0|L(0)_i) \times \hat{g}(M_i=m|L(0)_i, A_i, L(1)_i)} Y_i}{\sum_{i=1}^{n} \frac{\mathbb{I}(A_i=0 \cap M_i=m)}{\hat{g}(A_i=0|L(0)_i) \times \hat{g}(M_i=m|L(0)_i, A_i, L(1)_i)}}$$

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Estimation of the Controlled Direct Effect by IPTW

2) Expressing the CDE_m using coefficients of an MSM

We can use the following MSM

$$\mathbb{E}(Y_{am}) = \alpha_0 + \alpha_A a + \alpha_M m + \alpha_{A*M} a \times m$$

So that the CDEm can be expressed using the coefficients of the MSM

$$\mathrm{CDE}_m = (\alpha_0 + \alpha_A a + \alpha_M m + \alpha_{A*M} a \times m) - (\alpha_0 + \alpha_A a^* + \alpha_M m + \alpha_{A*M} a^* \times m)$$
$$\mathrm{CDE}_m = \alpha_A (a - a^*) + \alpha_{A*M} \times (a - a^*) \times m$$

For a binary exposure :

$$\mathrm{CDE}_m = \alpha_A + \alpha_{A*M} \times m$$

The MSM can be estimated using a weighted regression of Y conditional on A and M, where the weights are the product of $sw_A \times sw_M$

$$sw_{A,i} = \frac{P(A=a_i)}{P(A=a_i|L(0)=l(0)_i)} \quad \text{and} \quad sw_{M,i} = \frac{P(M=m_i|A=a_i)}{P(M=m_i|A=a_i, L(0)=l(0)_i), L(1)=l(1)_i}$$

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Practical examples – CDE_m by g-computation

- IPTW for the CDE
- stabilised IPTW for the CDE

} Calculation by hand

- MSM estimated by stabilised IPTW
  - Using the `CMAverse` package
    - Add `postc = "L1"`
    - Same arguments than for Natural Direct/Indirect effects estimated using an MSM based on IPTW
  - Calculation by hand
  - Using the `ltmle` package
    - Specify the g-formulas +++
    - `iptw.only = TRUE`
    - 95% CI are based on the IPTW influence curve

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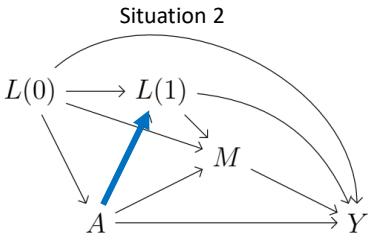
Marginal randomised/interventional Direct and Indirect Effects



$$\text{MRDE} \quad \mathbb{E}\left(Y_{a,G_{a^*|L(0)}}\right) - \mathbb{E}\left(Y_{a^*,G_{a^*|L(0)}}\right)$$
$$\text{MRIE} \quad \mathbb{E}\left(Y_{a,G_{a|L(0)}}\right) - \mathbb{E}\left(Y_{a,G_{a^*|L(0)}}\right)$$

defined by VanderWeele et al. (2014)

Interpretation:

- The mediator is a random draw in the counterfactual distribution of M, conditional on $L(0)$, under the scenarios $A = a$ or $A = a^*$
- The indirect effect is an analogue to all the directed paths going through M ($A \to L(1) \to M \to Y$ and $A \to M \to Y$)
- The sum of MRDE + MRIE = Overall effect = $\mathbb{E}\left(Y_{a,G_{a|L(0)}}\right) - \mathbb{E}\left(Y_{a^*,G_{a^*|L(0)}}\right)$ which can be different from the classic ATE
- MRIE does not capture a true mediational effect: it does not satisfy the "sharp null hypothesis"

(even if the effect of A is not mechanistically mediated by M for each individual, MRIE could still be non-null, cf. *Caleb Miles J R Stat Soc Series B Stat Methodol. 2023;85(4):1154-1172*)

- Not well defined in survival setting with possible events before the mediator

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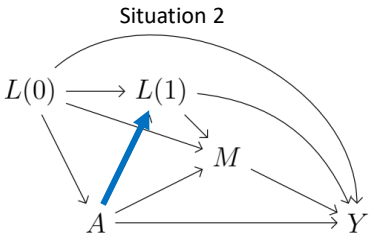
Marginal randomised/interventional Direct and Indirect Effects



$$\text{MRDE} \quad \mathbb{E}\left(Y_{a,G_{a^*|L(0)}}\right) - \mathbb{E}\left(Y_{a^*,G_{a^*|L(0)}}\right)$$
$$\text{MRIE} \quad \mathbb{E}\left(Y_{a,G_{a|L(0)}}\right) - \mathbb{E}\left(Y_{a,G_{a^*|L(0)}}\right)$$

Identifiable under the usual condition

- Consistency, positivity
- Randomisation assumptions
  - A1 – No unmeasured confounding between A and Y, given $L(0)$
  - A2 – No unmeasured confounding between M and Y, given $L(0)$, A and $L(1)$
  - A3 – No unmeasured confounding between A and M, given $L(0)$

Estimators

- G-computation
  - Parametric g-computation
  - Iterative Conditional Expectation
- 2 MSMs estimated by IPTW
- Double robust estimator (TMLE and one-step estimator)

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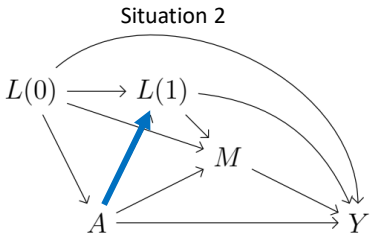
Marginal randomised/interventional Direct and Indirect Effects

$$\text{MRDE} \quad \mathbb{E}\left(Y_{a,G_{a^*|L(0)}}\right) - \mathbb{E}\left(Y_{a^*,G_{a^*|L(0)}}\right)$$
$$\text{MRIE} \quad \mathbb{E}\left(Y_{a,G_{a|L(0)}}\right) - \mathbb{E}\left(Y_{a,G_{a^*|L(0)}}\right)$$



We can get analogues of the 3-way and 4-way decomposition:

$$MIE = MR\ Total\ IE - MR\ Pure\ IE = \{\mathbb{E}(Y_{1,G_1|L(0)}) - \mathbb{E}(Y_{1,G_0|L(0)})\} - \{\mathbb{E}(Y_{0,G_1|L(0)}) - \mathbb{E}(Y_{0,G_0|L(0)})\}$$

$$RIE = MR\ Pure\ DE - CDE_{M=0} = \{\mathbb{E}(Y_{1,G_0|L(0)}) - \mathbb{E}(Y_{0,G_0|L(0)})\} - \{\mathbb{E}(Y_{1,0}) - \mathbb{E}(Y_{0,0})\}$$

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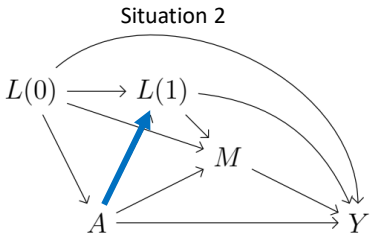
Conditional randomised/interventional Direct and Indirect Effects

$$\text{CRDE} \quad \mathbb{E}\left(Y_{a,\Gamma_{a^*|L(0),L(1)}}\right) - \mathbb{E}\left(Y_{a^*,\Gamma_{a^*|L(0),L(1)}}\right)$$
$$\text{CRIE} \quad \mathbb{E}\left(Y_{a,\Gamma_{a|L(0),L(1)}}\right) - \mathbb{E}\left(Y_{a,\Gamma_{a^*|L(0),L(1)}}\right)$$

defined by Zheng et van der Laan. (2017)



Interpretation:

- The mediator is a random draw in the counterfactual distribution of M, conditional on $L(0)$ and $L(1)$, under the scenarios $A = a$ or $A = a^*$
- The indirect effect corresponds to the path-specific effect, going only through M ($A \rightarrow M \rightarrow Y$)
- The sum of CRDE + CRIE = ATE
- CRIE does not capture all the mediational effect through the mediator :
  the path $A \rightarrow L(1) \rightarrow M \rightarrow Y$ is part of the direct effect
- Can be defined in survival setting with possible events before the mediator

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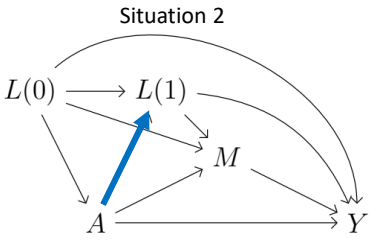
Conditional randomised/interventional Direct and Indirect Effects



$$\text{MRDE} \quad \mathbb{E}\left(Y_{a,G_{a^*|L(0)}}\right) - \mathbb{E}\left(Y_{a^*,G_{a^*|L(0)}}\right)$$
$$\text{MRIE} \quad \mathbb{E}\left(Y_{a,G_{a|L(0)}}\right) - \mathbb{E}\left(Y_{a,G_{a^*|L(0)}}\right)$$

Identifiable under the usual condition

- Consistency, positivity
- Randomisation assumptions
  - A1 – No unmeasured confounding between A and Y, given $L(0)$
  - A2 – No unmeasured confounding between M and Y, given $L(0)$, A and $L(1)$
  - A3 – No unmeasured confounding between A and M, given $L(0)$
  - A4 – No unmeasured confounding between A and $L(1)$, given $L(0)$

Estimators

- G-computation
  - Iterative Conditional Expectation
- IPTW
- Double robust estimator (TMLE)

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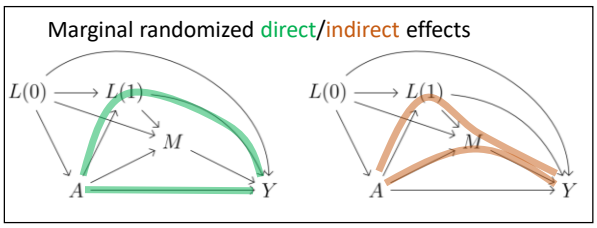
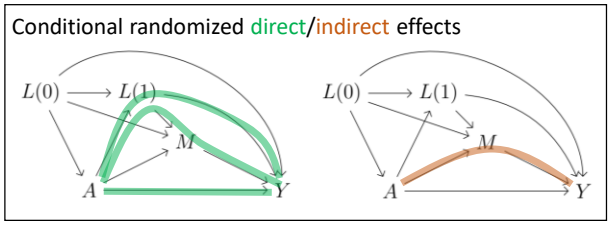
"Marginal" vs "conditional" randomised/interventional Direct and Indirect Effects

Difference between the « marginal » and the « conditional » versions





2-Way decomposition

Marginal Randomized Direct Effect	MRDE	$\mathbb{E}[Y_{aG_{a^*\|L(0)}} - Y_{a^*G_{a^*\|L(0)}}]$
Marginal Randomized Indirect Effect	MRIE	$\mathbb{E}[Y_{aG_{a\|L(0)}} - Y_{aG_{a^*\|L(0)}}]$

2-Way decomposition

Conditional Randomized Direct Effect	CRDE	$\mathbb{E}[Y_{a\Gamma_{a^*\|L(0),L(1)}} - Y_{a^*\Gamma_{a^*\|L(0),L(1)}}]$
Conditional Randomized Indirect Effect	CRIE	$\mathbb{E}[Y_{a\Gamma_{a\|L(0),L(1)}} - Y_{a\Gamma_{a^*\|L(0),L(1)}}]$

Note that if A does not affect $L(1)$, both effects are equal to the PNDE and PNIE

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Practical examples – Randomised/interventional Direct and Indirect Effects

MRDE and MRIE

- g-computation
  - Calculation by hand, by Iterative Conditional Expectation
- parametric g-computation
  - Using the CMAverse
- MRDE and MRIE, and 3-way and 4-way estimation
  using 1 MSM of the outcome + 1 MSM of the mediator,
  where the MSMs are estimated by IPTW or g-computation
  - Using the `CMAverse` package
    - Add `postc = "L1"`

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Doubly robust estimators

The objectives of doubly robust (targeted, semi-parametric, …) methods are to obtain:

- an unbiased estimator of the targeted parameter, if at least 1 model among
  - the model of the outcome $\bar{Q}(A,L)$
  - or the propensity score $g(A|L)$ is correctly specified
- an efficient estimator of the targeted parameter = with an optimal standard error
  (if both $\bar{Q}(A,L)$ and $g(A|L)$ are correctly specified)

- More generally, we aim to obtain an asymptotically linear estimator =
  - An estimator Ψ_n of the targeted parameter Ψ_0, such that it can be expressed as

$$\Psi_n = \Psi_0 + \frac{1}{n}\sum_{i=1}^{n} IC(O_i) + o_P\left(\frac{1}{\sqrt{n}}\right)$$

A negligible component

Where $IC(O_i)$ is the efficient influence curve (a function of the observed data), of mean 0

- It behaves like a sampling average

  $\Rightarrow$ consistent and asymptotically normal, with variance $var(\Psi_n) = \frac{1}{n} var[IC(O)]$

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Estimator of the ATE

1) Augmented-IPTW (one-step) estimator of the ATE

It can be shown that the efficient IC of the parameter $\Psi_0 := \mathbb{E}[\mathbb{E}(Y|A=1,L(0)]$ is

$$D^* := \frac{1}{g(A=1|L(0))}[y - \bar{Q}(A=A_i,L(0)] + \bar{Q}\big(A=1,L(0)\big) - \Psi_0$$

where D^* as a mean = 0

Using estimators of g and $\bar{Q}$, we can consider solving the equation

$$0 = \frac{1}{n}\sum_{i=1}^{n} D^*(\psi,\hat{g},\hat{\bar{Q}}) = \frac{1}{n}\sum_{i=1}^{n}\left\{\frac{A_i}{g(A=A_i|L(0))}[Y_i - \hat{\bar{Q}}\big(A=A_i,L(0)\big) + \hat{\bar{Q}}\big(A=1,L(0)\big) - \psi\right\}$$

This estimating equation has a unique solution

$$\hat{\psi}_{A-IPTW} = \underbrace{\frac{1}{n}\sum_{i=1}^{n}\left\{\hat{\bar{Q}}\big(A=1,L(0)\big)\right\}}_{\text{g-computation estimator}} + \overbrace{\underbrace{\frac{1}{n}\sum_{i=1}^{n}\left\{\frac{A_i}{\hat{g}(A=1|L(0))}\Big[Y_i - \hat{\bar{Q}}\big(A=A_i,L(0)\big)\Big]\right\}}_{\text{IPTW estimator}}}^{\text{Correction term for the g-comp estimator}}$$

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Estimator of the ATE

2) Targeted Maximum Likelihood estimator of the ATE

Another approach described by Marc van der Laan to obtain an asymptotically linear estimator of the ATE relies on the following procedure:

1. Estimate an initial estimate of the relevant part of the likelihood $\hat{\bar{Q}}\big(A=1,L(0)\big)$
2. Update the initial fit to "target toward making an optimal bias-variance trade-off for the target parameter Ψ_0"

In practice, using a parametric fluctuation model of $\hat{\bar{Q}}$, chosen so that the derivative of its log-likelihood loss function (score function) is equal to the appropriate component of the efficient influence curve

Estimating the functions $\bar{Q}$ and g with data-adaptive algorithms (machine learning) is useful for both approaches (one-step and TMLE),

The package we will use relies on the SuperLearner algorithm (ensemble learning)

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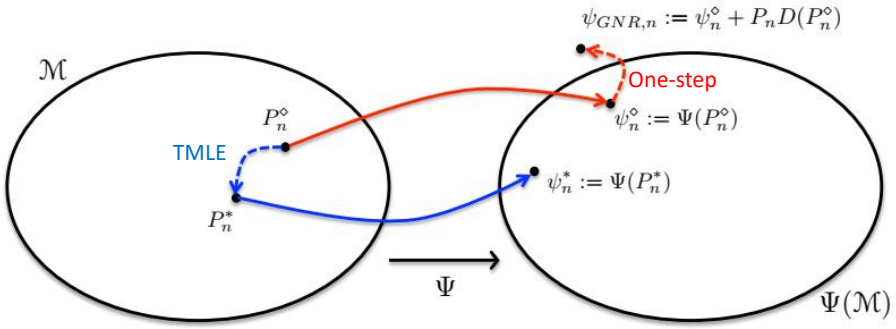
Estimator of the ATE

Difference between the one-step estimator and the TMLE estimator:

- The one-step performs an additive correction in the parameter space,
  so the estimation could fall out of the parameter space (could fail to be robust)
- The TMLE applies the correction in the model space,
  so that the final estimation is expected to be in the parameter space



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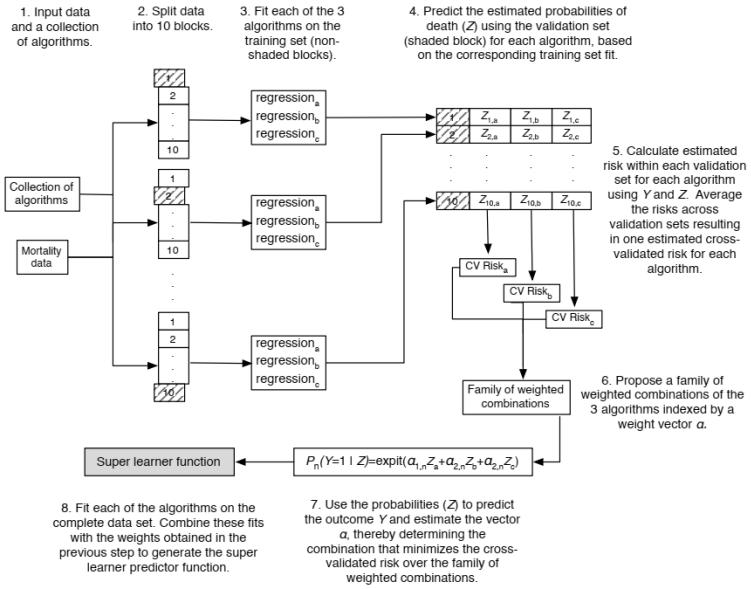
SuperLearner

https://cran.r-project.org/web/packages/SuperLearner/vignettes/Guide-to-SuperLearner.html



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SuperLearner

Article by R Phillips gives a useful guideline:

- Specify performance metric:
  - Binary outcome ⇒ mean negative log-likelihood loss
  - Continuous outcome ⇒ mean squared error loss
- Derive the effective sample size n_{eff}
  - Binary outcome ⇒ is the probability of 0 or 1 rare?
    $\Rightarrow n_{eff} = \min(n, 5 \times n_{rare})$ where $n_{rare} = n \times \min(p, 1-p)$
  - Continous outcome ⇒ $n_{eff} = n$
- Define V-fold cross-validation scheme
  - Number of fold depends on n_{eff}
- Form a library of candidate learners
  - Diversity of learning strategy (parametric, non-parametric …)
  - Use learners (to predict) + screeners (to select variables)
- Choose between SuperLearner or discrete SuperLearner

A difficulty for the CDE is that the outcome can be binary at first, then continous !

With the ltmle,
- We can specify the cross-validation process,
- Choose candidate learners
- But not choose between discrete or ensemble learning

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Practical examples – ATE estimated by TMLE

- TMLE of the ATE
  - Calculation by hand
  - Check that we get the same result with the `ltmle` package
  - Using the `SuperLearner` package
    https://cran.r-project.org/web/packages/SuperLearner/vignettes/Guide-to-SuperLearner.html
  - Among the data-adaptive algorithm, they recently developed the Highly Adative Lasso (HAL), with a fast rate of convergence, useful to estimate hyperparameters of TMLE and one-step estimators

    Available with the `hal9001` package
    https://tlverse.org/hal9001/articles/intro_hal9001.html

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TMLE of the CDE

Targeted Maximum Likelihood estimator of the CDE

A TMLE of the CDE can be obtained

- Following the steps of the g-computation by iterative expectation
- Update of the $\bar{Q}$ functions estimated at each step

- We can use the `ltmle` package
  - Initially to assess scenarios implying repeated exposure
  - In our case with mediation analysis, the mediator is a 2nd exposure following the first exposure A.

Practical examples – ATE estimated by TMLE

- TMLE of the CDE
  - Using the `ltmle` package
  - For binary outcome
  - For the continuous outcome
    - The continuous outcome is 1st transforms the outcome on a 0 to 1 scale, $Y^{transf} = \frac{Y - \min(Y)}{\max(Y) - \min(Y)}$ so that quasi-binomial parametric models can be used in the computation procedure.
    - The mean predictions are then back-transformed on the original scale.

One step estimator and TMLE of the marginal randomised Direct/Indirect Effects

Estimators described by Ivan Diaz *et al.*
(non parametric efficient causal mediation with intermediate confounders)

Where either the set of mediators or the set of $L(1)$ variable could be high-dimensional, but not both

See https://github.com/nhejazi/ser2024_mediation_workshop for a workshop presented by Nima Hejazi who maintains the `medoutcon` package

- One step estimator
- TMLE estimator

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Practical examples – rNDE and rNIE estimated by TMLE

- Using g-computation using Iterative Conditional Expectation (ICE)
  - See algorithm described in the handbook

- One-step estimator or TMLE of the MRDE and MRIE
  - Using the `medoutcon` package
  - Relies on the `tlverse` (https://tlverse.org/) and the `sl3` package for SuperLearning
  - The one-step estimator use cross-fitting instead of cross-validation
  - The TMLE estimation seems biased in some simple examples (not tested for this workshop)
    - It might be useful to check on simulations before using this package

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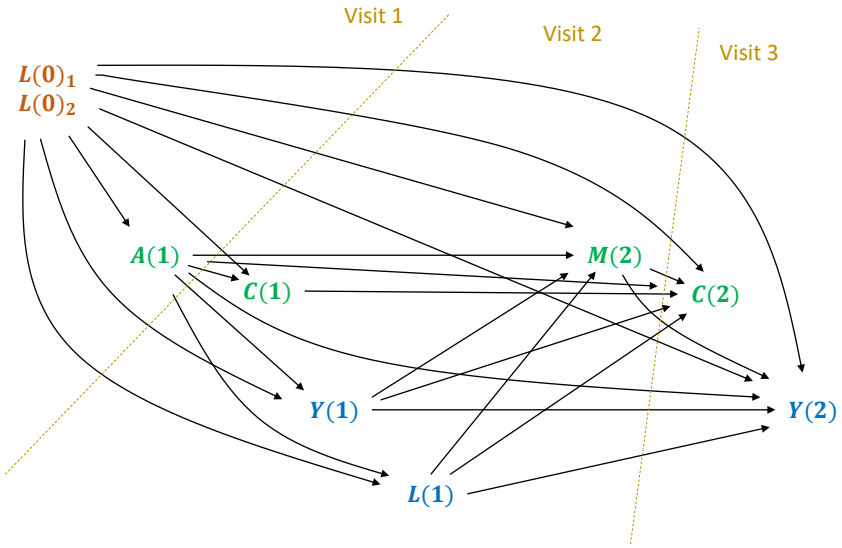
Survival setting

- Assuming non-informative censoring and no event before the occurrence of the mediator
  - Classic Cox models or additive survival can be applied
  - For example in the `CMAverse` package, the `mediation` package

- With informative censoring and events that can occur before the mediator
  - Possible for CDE estimated using the `ltmle` package
    - Censoring is declared as an exposure (treatment) variable, we will then emulate scenarios with uncensored participants
    - Events can be part of the $L(1)$ set of variables
  - Also possible for Randomised "Conditional" Direct/Indirect Effects, but this causal estimand is usually not the estimand we are looking for

Survival setting



Summary of statistical properties of the estimators

G-computation (and "model of the outcome" approaches)

- Unbiased if the $\bar{Q}$ functions are consistently estimated
- Immune to positivity violation
- But not an asymptotically linear estimator

IPTW

- Unbiased if the propensity scores (g functions) are consistently estimated
- Highly variable and unstable in case of positivity violation

  => can be improved by stabilized weights and weight truncation

TMLE- Double robust estimator

- Unbiased if at least the $\bar{Q}$ functions, or the propensity scores g is consistently estimated
- Statistically efficient if both are consistently estimated (interest of applying data-adaptive estimators)
- Semi-parametric or non-parametric estimator, coherent integration with a causal model depicted using DAGs
- Positivity violation can impact these good statistical properties

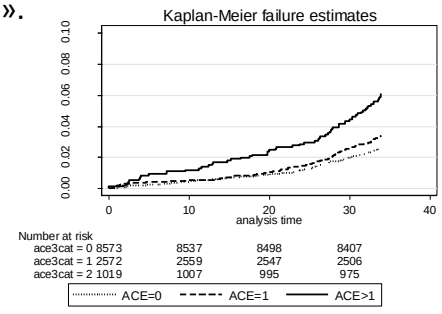
Longitudinal exposure/mediation ⇒ positivity violation

Adverse childhood experience and mortality before 55 years old

Kelly et al. Adverse childhood experience and premature all-cause mortality.
Eur J Epidemiol 2013;28:721-34

- Using data from the **British birth cohort NCDS 58**
- **Mortality was increased in case of Adverse Childhood Experience (ACE)**
- ACE : score from 0 to 6 (6 dimensions)

  « *intra-familial events or conditions causing chronic stress responses in the child's immediate environment (7 to 16 years old)* ».
  - Child in care (care service or foster care);
  - Household member:
    - in prison / probation
    - Parental separation
    - Mental illness
    - Alcohol abuse
  - Physical neglect



Longitudinal exposure/mediation ⇒ positivity violation

- Can the effect of the ACEs on mortality be explained by "health behavior" mediators between 16 and 55 years of age?
- Mediators of interest= **smoking, alcohol, obesity**

- In other words: had we been able to control for smoking, alcohol and obesity so that members never smoked, never drank too much, and were never obese, what would be the remaining effect of ACEs on mortality at 55?

⇒ Estimate the controlled direct effect of ACE on mortality, setting the values of the mediators to *smoking < 1 cig/day ; alcohol < 2-3 drinks/day ; obesity = "no"*

Average Total Effect $ATE = \mathbb{E}(Y_{ACE=2}) - \mathbb{E}(Y_{ACE=0})$

Controlled direct Effect $CDE_{\bar{M}=0} = \mathbb{E}(Y_{ACE=2,\bar{M}=0}) - \mathbb{E}(Y_{ACE=0,\bar{M}=0})$

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Longitudinal exposure/mediation ⇒ positivity violation

British NCDS 58 birth cohort

- N = 17,785 participants
- Outcome : mortality at 55 years old (4.4%)
- Exposures of interest: ACE and mediators (combination of 3 « behaviors »)
  - ACE

ACE = 0	68,9%
ACE = 1	22,1%
ACE = 2+	9,0%

  - Mediators of interest (binary variable) repeated over 6 follow-up visits

    smoking or alcohol or obesity : between 33% and 50% at each wave
- Baseline confounders (10 variables)
  - Parents' social position, overcrowding, sex, birthweight, breastfeeding, mother's age at birth, handicap or severe condition during childhood, bmi at 7 and 11 y.o.
- Time-varying confounders (4 or 5 variables at each wave)
  - Educational level/social class, Living in a couple, Perceived health, Disability/severe health problems, Psychological difficulties

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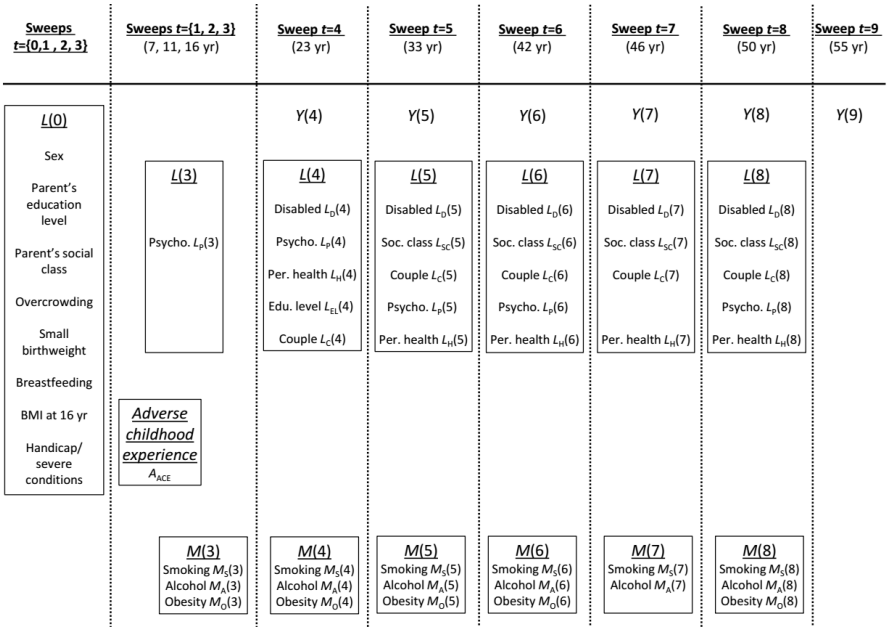
Longitudinal exposure/mediation ⇒ positivity violation



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Longitudinal exposure/mediation ⇒ positivity violation

High-dimensional setting results from:

- Exposures of interest defined by multiple variables: ACE and 6 mediators
- There are also several time-varying (intermediate) confounders

  Risk of practical positivity violation increases with large set of (continuous) baseline and intermediate confounders

Estimating causal effects rely on identifiability assumptions:

1. Consistency.

   If $(ACE = a, \bar{M} = \bar{m})$ for a given subjet i, then $Y_{ACE=a,\bar{M}=\bar{m}}(i) = Y(i)$

2. Sequential randomisation assumption.

   $Y_{a,\bar{m}} \perp\!\!\!\perp ACE \mid L(0)$ and $Y_{a,\bar{m}} \perp\!\!\!\perp M(t) \mid Pa(M(t))$

3. **Positivity**

   $P(ACE = a|L(0)) > 0$ and $P(M(t) = 0|Pa(M(t)) > 0$ *almost everywhere.*

   This assumption is more and more difficult to hold at the last measurements t

   $P(ACE = 2, \bar{M}(8) = 0) \approx 0.7\%$ ⇒ « practical » positivity violation is expected

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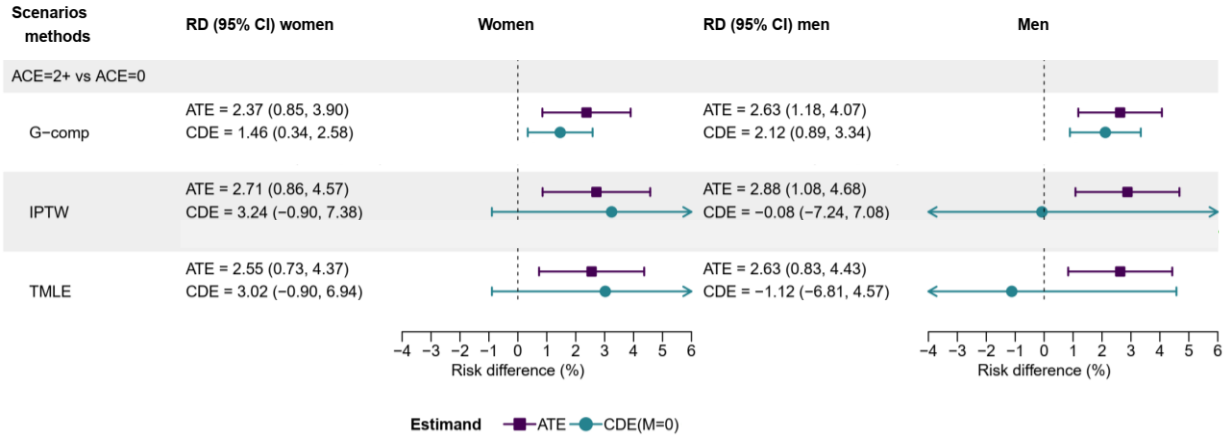
Longitudinal exposure/mediation ⇒ positivity violation

Results (using the ltmle R package, machine learning for IPTW and TMLE)



- Very precise confidence intervals for g-comp, known to be anti-conservative (immune to positivity violation)
- Very large confidence intervals for IPTW and TMLE (risk of bias and lack of efficiency due to practical positivity violation)

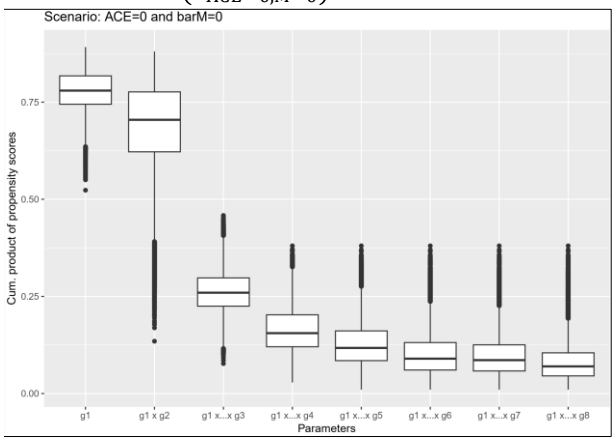
⇒ Can we trust the results? (doubtful)

Longitudinal exposure/mediation ⇒ positivity violation

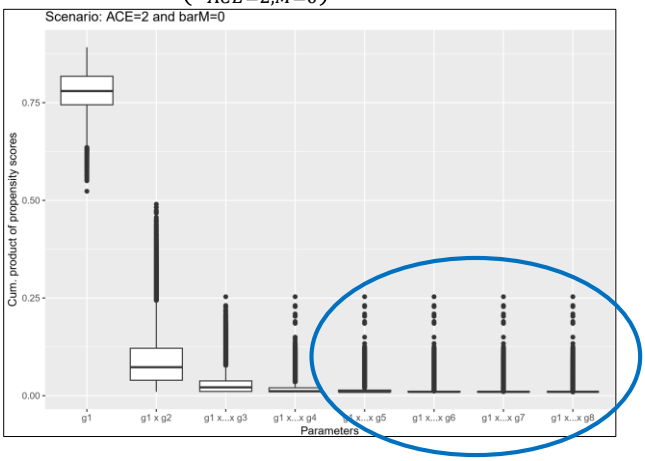
Diagnosis of practical positivity violation:

- inspecting the distribution of the cumulative products of propensity scores (g-functions)

Estimation of $\mathbb{E}(Y_{ACE=0,\bar{M}=0})$



Estimation of $\mathbb{E}(Y_{ACE=2,\bar{M}=0})$



Estimations are very weakly supported by the data (g-functions are used for IPTW and TMLE)

Additional topic

Multicategorical or multiple exposure and mediator

- Several methods/packages can deal with mediation through a set of multiple mediators
  - IORW
  - CMAverse
  - ltmle, medoutcon
- Several methods/packages can deal with multiple intermediate confounders affected by the exposure
  - G-computation by Iterative Conditional Expectation, ltmle
  - CMAverse (but requires to estimate a model for each variable in the $L(1)$ set

Additional topic

Continuous exposure or mediator

1) Using MSMs

- Estimate counterfactual outcomes under several scenarios associated with a grid of values for the exposure, for the mediator
- And summarise all the results using an MSM

2) Using stochastic interventions

- Shift or truncation of the continuous distribution
  - Diaz I. Assessing the Causal Effect of Policies: An Example Using Stochastic Interventions. Int J biostat 2013;9(2):161-174
  - Kennedy E. Nonparametric causal effects based on incremental propensity score interventions. JASA 2018
- Modified treatment policies
  - Package `lmtp` (Nicholas Williams)

Additional topic

Survival setting

- Marginal Randomised Direct and Indirect effects are not well defined in case of possible event before the occurrence of the mediator

- Recently, concept of separable effects has been used in survival settings with competing events (see M. Stensrud, J Young, J Robins, …)