Maternal characteristics, childhood growth and eating disorder: a study of mediation using `gformula`

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Early exposures and distal outcomes

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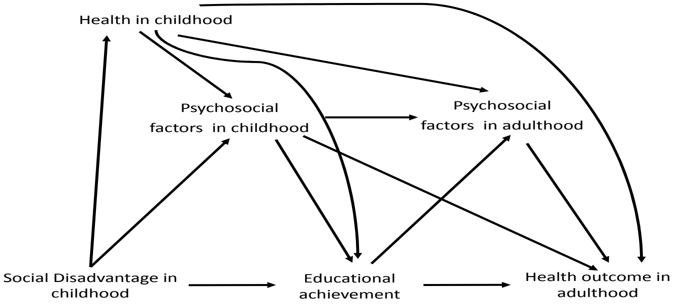

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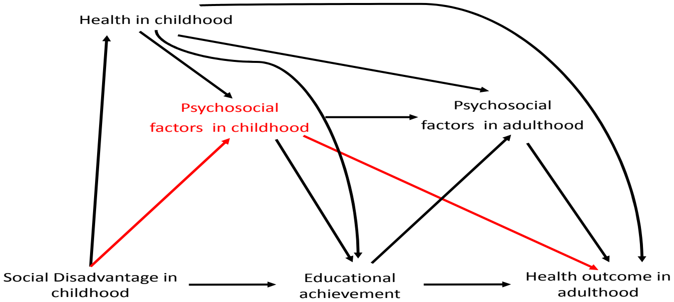

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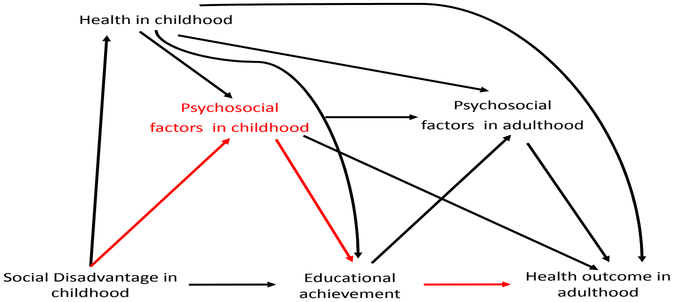

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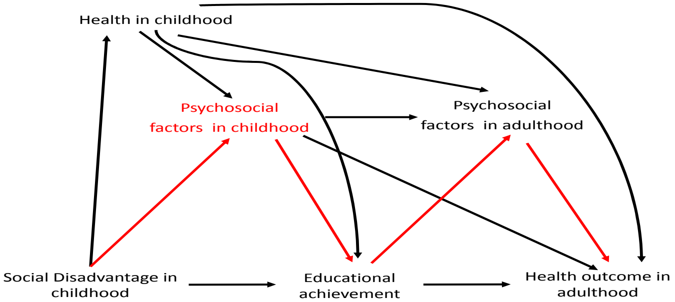

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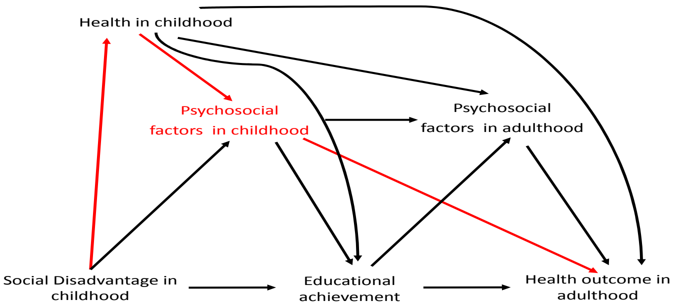

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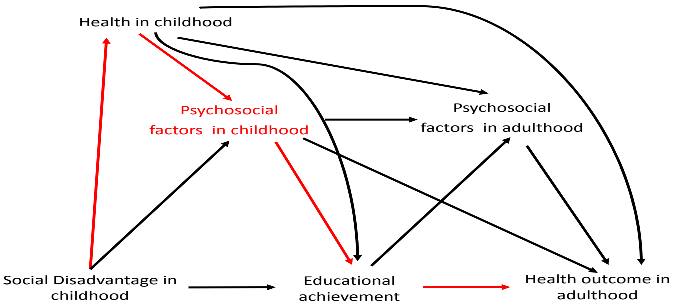

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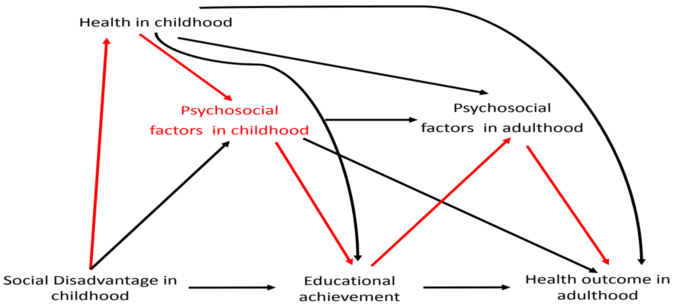

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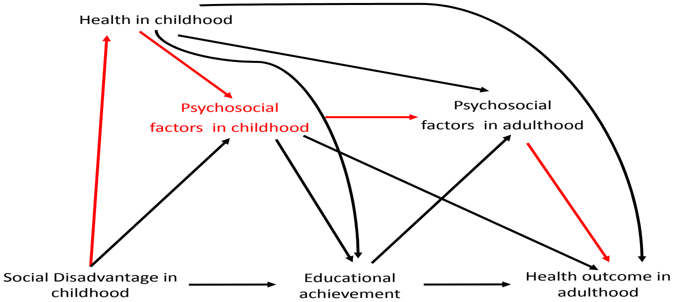

Mediation

- Focus on how the effect of an exposure is mediated via certain pathways
- Two main strands in the literature for the study of mediation:
  - Social sciences / psychometrics (Baron and Kenny, 1986)
  - Causal inference literature (Robins and Greenland, 1992; Pearl, 2001)
- They appear to be very different, but they are linked
- The second one may seem far too complex, but in fact is the one that poses fewer restrictions.

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Outline

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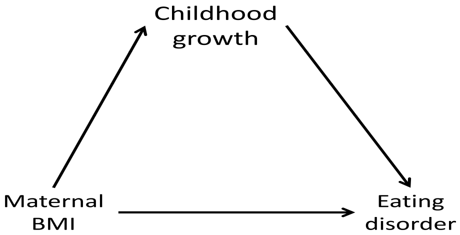
Motivating example
Eating disorders (ED) in adolescence

- ED comprise a variety of heterogeneous diseases
- Maternal factors possibly important (body size, education, *etc.*)
- Onset often around puberty
- Childhood growth a possible mediator



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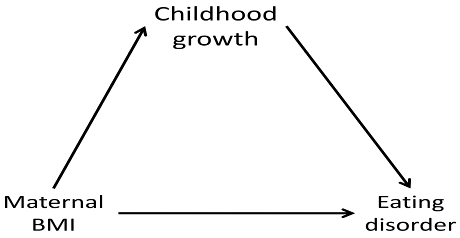
- mediated by childhood growth: the indirect effect,



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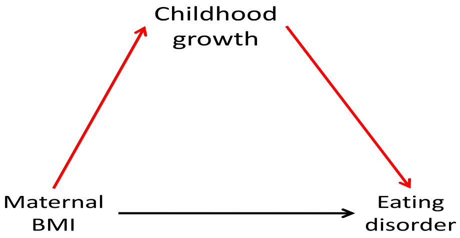

Mediation

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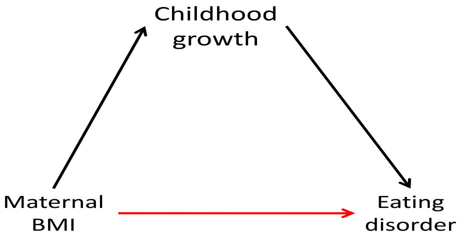
- mediated by childhood growth: the indirect effect,
- mediated via other factors: the direct effect.



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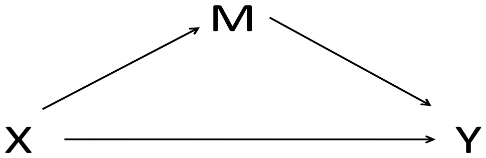
Exposure X, mediator M, outcome Y, (background) confounders C, and intermediate confounder L:



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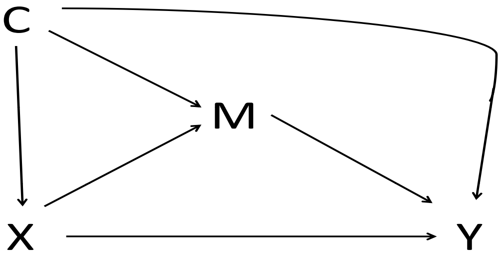

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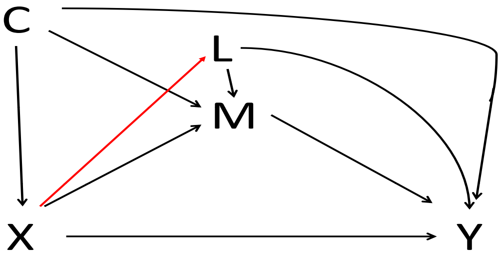

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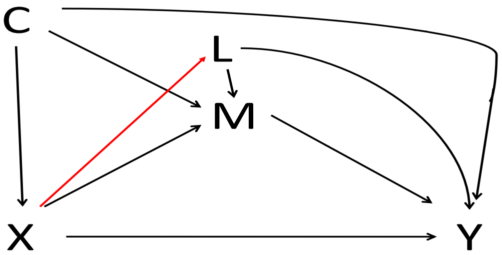

Causal inference literature:

- Many subtly different definitions of direct and indirect effect
- All involve counterfactuals (*i.e.* potential outcomes).

Potential outcomes

To make causal statements we need to compare the outcomes that would arise under different scenarios:

- $Y(x)$: the potential values of Y that would have occurred had X been set, possibly counter to fact, to the value x.
- $M(x)$: the potential values of M that would have occurred had X been set, possibly counter to fact, to the value x.
- $Y(x, m)$: the potential values of Y that would have occurred had X been set, possibly counter to fact, to the value x and M to m.

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- For simplicity consider the case where X is binary
- It also helps to start with the definition of *total causal effect*

Total Causal Effect (TCE): definition

The average total causal effect of X, comparing exposure level $X = 1$ to $X = 0$, can be defined as the linear contrast [1]:

$$TCE = E[Y(1)] - E[Y(0)]$$

This is a comparison of two hypothetical worlds: in the first, X is set to 1, and in the second X is set to 0.

Note that, in general: $TCE \neq E[Y|X = 1] - E[Y|X = 0]$.

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Total Causal Effect (TCE): identification

To identify $TCE = E[Y(1)] - E[Y(0)]$ we need to be able to infer $E[Y(1)]$ and $E[Y(0)]$ from the observed data.

This is possible if these assumptions are satisfied:

- consistency: $Y(x)$ can be inferred from observed Y when $X = x$
- conditional exchangeability: there is no unmeasured confounding between X and Y:

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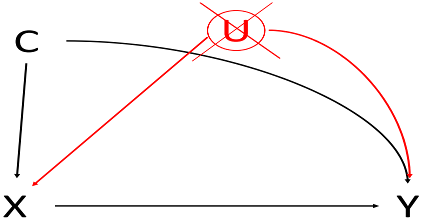

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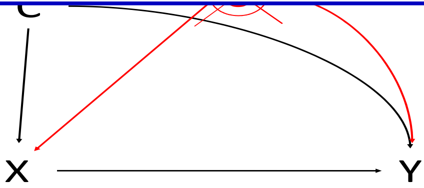
If these are satisfied, we can infer the TCE from the data



Controlled Direct Effect (CDE): definition

The average controlled direct effect of X on Y, when M is controlled at m, is:

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

This is a comparison of two hypothetical worlds:

- In the first, X is set to 1, and in the second X is set to 0.
- In both worlds, M is set to m.
- By keeping M fixed at m, we are getting at the direct effect of X, unmediated by M.
- In general $CDE(m)$ varies with m.

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Identification requires, as before, appropriate assumptions:

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$Y = Y(x, m)$ if $X = x$ and $M = m$

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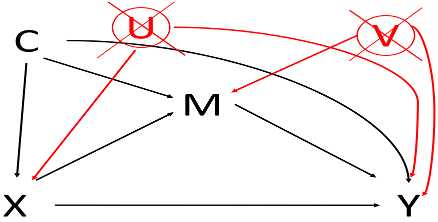

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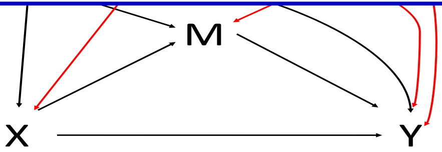

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Natural Direct Effect (NDE): definition

The average Natural Direct Effect of X on Y is:

$$NDE = E[Y(1, M(0))] - E[Y(0, M(0))]$$

This is a comparison of two hypothetical worlds:

- In the first, X is set to 1, and in the second X is set to 0.
- In both worlds, M is set to the natural value $M(0)$, *i.e.* the value it would take if X were set to 0.
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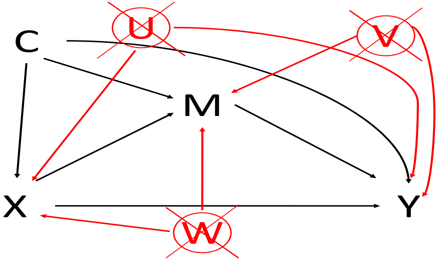

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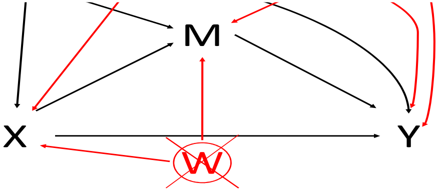

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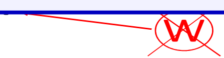
If these assumptions are satisfied: we can infer the *NDE* from the observed data
Note: the Natural Indirect Effect (*NIE*) is defined as $TCE - NDE$



Estimation

Wide range of options, for most combinations of M and Y:

- G-computation:
  - suitable for estimating $CDE(m)$ and NDE
  - can deal with intermediate confounding
  - flexible and efficient but heavy on parametric modelling assumptions
  - implemented in `gformula` (Daniel et al 2011)
- Semi-parametric methods (*e.g.*g-estimation) make fewer parametric assumptions

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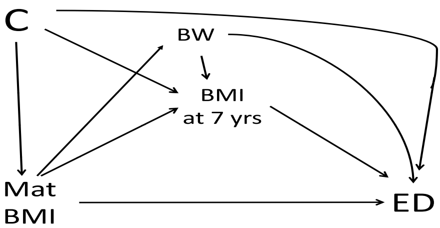

- Birth cohort with 3,500 girls, born in 1991-2
- Outcome (Y): Binge eating at age 13yrs (ED)
- Exposure (X): maternal pre-pregnancy BMI
- Mediator (M): child BMI at age 7 yrs (bmi7)
- Intermediate confounder (L): birth weight (BW)
- Confounders (C): Maternal education and mental disorders

Using gformula (Daniel *et al.* 2011)

Binary exposure: maternal BMI> 25 kg/m^2 (overbmi)

```
gformula <varlist>, mediation outcome(ED) exposure(overbmi)
obe mediator(bmi7) post_confs(BW) base_confs(lowed anyMH)
control(bmi7:0) ...
```

	G-computation estimate	Bootstrap Std. Err.	z	P>|z|
TCE	.1473497	.0252176	5.84	0.000
NDE	.0574193	.0242394	2.37	0.018
NIE	.0899304	.0101036	8.9	0.000
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TCE: Average ED score in the world where all mothers are set to BMI$>$25 minus that where they are set to BMI$\leq$25
($TCE = NDE + NIE$)

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NDE:Average ED score in the world where all mothers are set to BMI$>$25 minus that where they are set to BMI$\leq$25, with child BMI set at its natural value when the mother's BMI is set at $\leq$25

Using gformula (Daniel *et al.* 2011)

Binary exposure: maternal BMI$>25\ kg/m^2$ (overbmi)

```
gformula <varlist>, mediation outcome(ED) exposure(overbmi)
obe mediator(bmi7) post_confs(BW) base_confs(lowed anyMH)
control(bmi7:0) ...
```

	G-computation estimate	Bootstrap Std. Err.	z	P>|z|
TCE	.1473497	.0252176	5.84	0.000
NDE	.0574193	.0242394	2.37	0.018
NIE	.0899304	.0101036	8.9	0.000
CDE	.0575705	.0242823	2.37	0.018

$CDE = CDE(0)$: Average ED score in the world where all mothers are set to BMI$>$25 minus that where they are set to BMI$\leq$25, with child BMI set at 0 (bmi7 is standardized)

Using gformula (2)

Binary exposure and interactions

G-computations allows flexible specification of all association models.
⇒ Adding interactions between exposure overbmi, confounder BW and mediator bmi7:

gformula <*original varlist*> over_BW over_bmi7 , ...
derived(over_BW over_bmi7) derrules(over_BW:overbmi*BW, over_bmi7:overbmi*bmi7)

	G-computation estimate	Bootstrap Std. Err.	z	P>|z|
TCE	.1649645	.0263194	6.27	0.000
NDE	.0539651	.0251499	2.15	0.032
NIE	.1109994	.0174183	6.37	0.000
CDE	.0489107	.0235276	2.08	0.038

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G-computations allows flexible specification of all association models.
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Using gformula (3)

Continuous exposure

Replacing binary overbmi with continuous BMIpre (standardized):

gformula <*newvarlist*> , ...linexp

	G-computation estimate	Bootstrap Std. Err.	z	P>|z|
TCE	.0199475	.0033078	6.03	0.000
NDE	.0090645	.0029689	3.05	0.002
NIE	.010883	.001978	5.5	0.000
CDE	.0077757	.0027279	2.85	0.004

Using gformula (3)

Continuous exposure

Replacing binary `overbmi` with continuous `BMIpre` (standardized):

`gformula` <*newvarlist*> `, ...linexp`

	G-computation estimate	Bootstrap Std. Err.	z	P>|z|
TCE	.0199475	.0033078	6.03	0.000
NDE	.0090645	.0029689	3.05	0.002
NIE	.010883	.001978	5.5	0.000
CDE	.0077757	.0027279	2.85	0.004

Using gformula (3)
Continuous exposure

Replacing binary `overbmi` with continuous `BMIpre` (standardized):

`gformula` <*newvarlist*> `, ...` `linexp`

```
-----------------------------------------------------------
        |  G-computation    Bootstrap
        |    estimate       Std. Err.        z      P>|z|
--------+--------------------------------------------------
TCE     |     .0199475       .0033078      6.03     0.000
NDE     |     .0090645       .0029689      3.05     0.002
NIE     |      .010883        .001978      5.5      0.000
CDE     |     .0077757       .0027279      2.85     0.004
```

This gives effects for 1 unit increase in (stand) Maternal BMI

Using gformula (4)

Categorical exposure

Replacing binary `overbmi` with categorical `bmicat` (coded: 0,1,2):

`gformula` <*varlist*> `, ...oce baseline(1)`

	G-computation estimate	Bootstrap Std. Err.	z	P>|z|
TCE(0)	-.1041429	.0152158	-6.84	0.000
TCE(2)	.1055137	.015159	6.96	0.000
NDE(0)	.0160151	.0163919	.98	0.329
NDE(2)	.0429508	.0143828	2.99	0.003
NIE(0)	-.1201579	.0125716	-9.56	0.000
NIE(2)	.0625629	.0067193	9.31	0.000
CDE(0)	-.0431978	.0143389	-3.01	0.003
CDE(2)	.0437326	.0143348	3.05	0.002

Using gformula (4)

Categorical exposure

Replacing binary `overbmi` with categorical `bmicat` (coded: 0,1,2):

`gformula` <*varlist*> `, ...oce baseline(1)`

	G-computation estimate	Bootstrap Std. Err.	z	P>|z|
TCE(0)	-.1041429	.0152158	-6.84	0.000
TCE(2)	.1055137	.015159	6.96	0.000
NDE(0)	.0160151	.0163919	.98	0.329
NDE(2)	.0429508	.0143828	2.99	0.003
NIE(0)	-.1201579	.0125716	-9.56	0.000
NIE(2)	.0625629	.0067193	9.31	0.000
CDE(0)	-.0431978	.0143389	-3.01	0.003
CDE(2)	.0437326	.0143348	3.05	0.002

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Results with "(0)" refer to BMI<18 (low) relatively to 18≤BMI<25 (normal);
those with "(2)" to BMI>25 relatively to normal BMI.

Outline

Summary

- The study of mediation implies causal questions
- Causal inference literature offers general definitions
- There is a choice of estimation methods, each asking a different causal question
- `gformula` offers a very flexible tool to estimate these estimands
- Their identification requires stringent, unverifiable, assumptions:
  "To claim that effects are causal, it is not sufficient to use causally defined effects." (Muthèn, 2011)
- Need for sensitivity analyses (Imai et al, 2010)

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Outline

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Additional slide

Alternative $CDE(m)$

- The inclusion of interaction terms implies that exposure effect is allowed to vary with the mediator
- Hence the CDE(m) will vary with the value assigned to M

Estimand	G-computation estimate	Bootstrap Std. Err.
CDE(0)	0.049	0.024
CDE (-1)	0.021	0.034
CDE (1)	0.077	0.032

G-computation formula for the CDE

Robins, 1986

- Lets look at how the CDE is estimated, when there is also an intermediate confounder L:

$$
\begin{aligned}
CDE(m,c) &= E\{Y(1,m)\,|\,C=c\} - E\{Y(0,m)\,|\,C=c\} \\
&= \int E\left(Y|C=c, X=1, L=l, M=m\right) f_{L|C,X}\left(l|c,1\right) dl \\
&\quad - \int E\left(Y|C=c, X=0, L=l, M=m\right) f_{L|C,X}\left(l|c,0\right) dl
\end{aligned}
$$

- This is the g-computation formula.
- It requires correct specification of these parametric associational models for $Y|C,X,L,M$ and $L|C,X$.
- Both models can be completely flexible: they can include non-linearities and interactions.
- By marginalising over $L|C,X$, intermediate confounding is appropriately dealt with.