Direct and indirect effects

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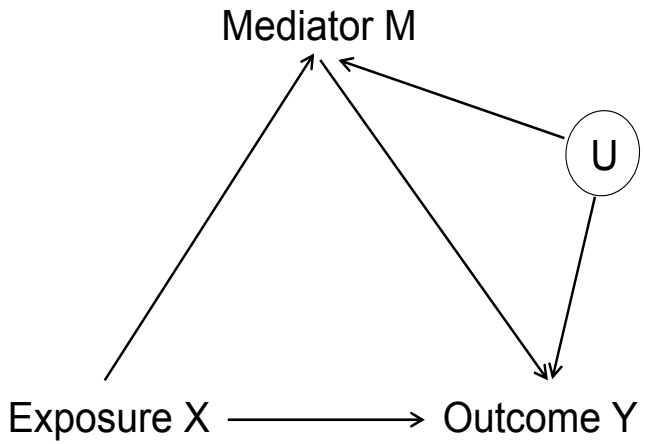
Mediation analysis

Mediation analysis is one approach towards inferring mechanism: by attempting to disentangle

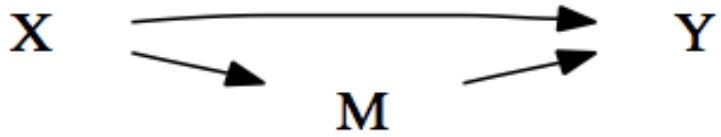
- direct effects: that part of the exposure effect which is not mediated by a given set of potential mediators.
- indirect / mediated effects: that part of the exposure effect which is mediated by a given set of potential mediators.



The Baron-Kenny approach

- The standard approach, due to Baron and Kenny (1986), focuses on linear models (with independent errors):

$$\begin{aligned} Y &= \theta_0 + \theta_1 X + \theta_2 M + \epsilon_Y \\ M &= \beta_0 + \beta_1 X + \epsilon_M \end{aligned}$$



- They interpret θ_1 as the direct effect and $\theta_2\beta_1$ as the indirect effect of a unit increase in the exposure w.r.t. mediator M.

Overview

There are broadly two lines of research:

1. effect decomposition: *how to decompose a total effect into direct and indirect components?*
   - What exactly do we mean by direct and indirect effect?
   - How to decompose effects in non-linear models?

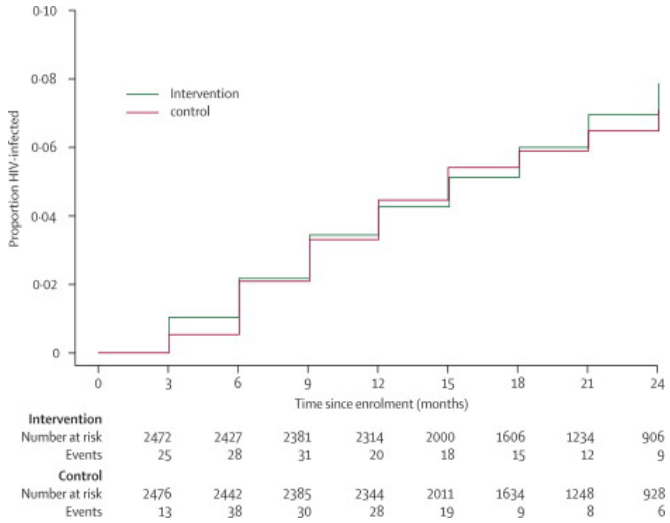
Overview

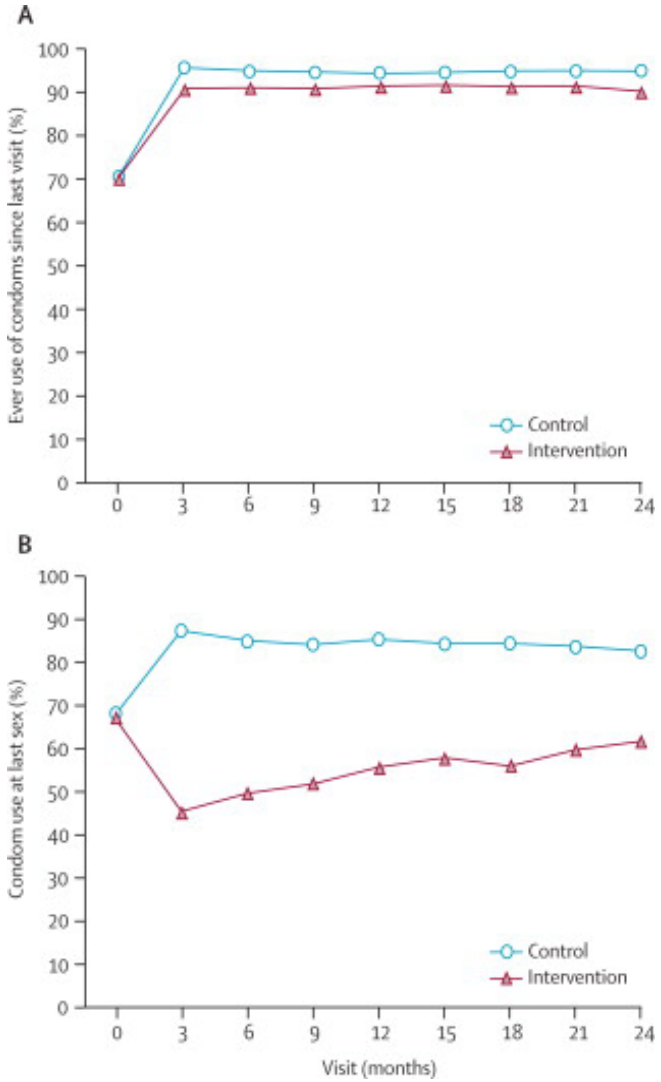
There are broadly two lines of research:

1. effect decomposition: *how to decompose a total effect into direct and indirect components?*
   - What exactly do we mean by direct and indirect effect?
   - How to decompose effects in non-linear models?
2. confounding: *how to deal with complex confounding patterns?*

The MIRA trial

Padian et al.,
Lancet 2007



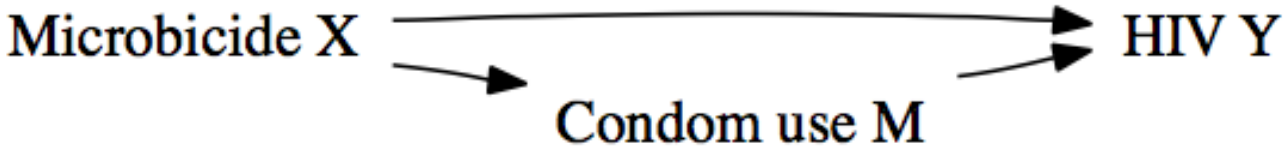


Controlled direct effects

controlled direct effect (Robins and Greenland, 1992; Pearl, 2001)

The effect of exposure on outcome that would be observed if the mediator were controlled uniformly at a fixed value.

The MIRA trial

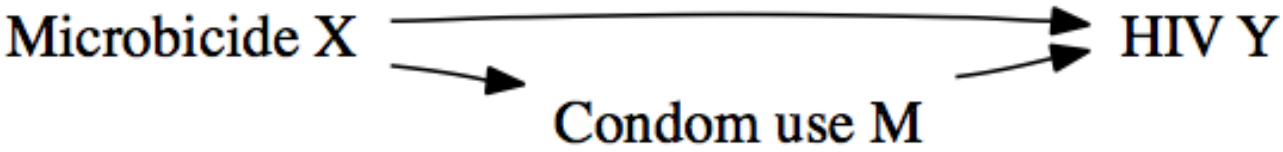


controlled direct effect in the absence of condom use

- Let $Y(x, m)$ denote the counterfactual HIV status under exposure $X = x$ (1: HIV prevention; 0: control) and frequency of condom use $M = m$.
- The difference in HIV risk that we would observe in a randomized microbicide trial if condoms were not available:

$$E\{Y(1,0) - Y(0,0)\}$$

The MIRA trial



controlled direct effect under a 100% condom use frequency

The difference in HIV risk that we would observe in a randomized microbicide trial if condoms were always used:

$$E\{Y(1,1) - Y(0,1)\}$$

This direct effect is likely 0.

Natural direct effects

- In this setting, it is not realistic to think of forcing the mediator to be the same for all subjects.
- Natural direct effects (Robins and Greenland, 1992; Pearl, 2001) allow for natural variation in the level of the mediator between subjects.

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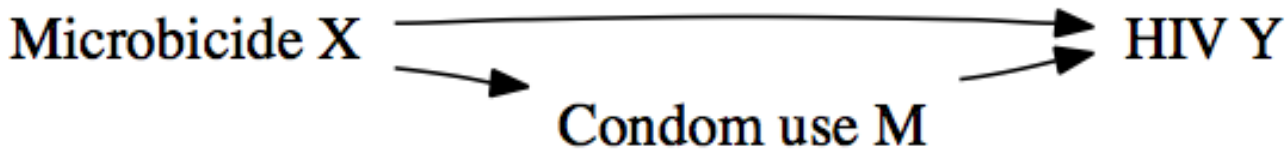
- Natural direct effects (Robins and Greenland, 1992; Pearl, 2001) allow for natural variation in the level of the mediator between subjects.
- A subject's natural level of the mediator is taken to be the (counterfactual) value $M(0)$ it would have taken if the exposure were 0.

The MIRA trial



natural direct effect

The difference in HIV risk that we would observe in a randomized microbicide trial if condom use remained as in the absence of microbicides:

$$E\{Y(1, M(0)) - Y(0, M(0))\}$$

It thus roughly expresses what the intention-to-treat effect would have been, had condom use not been affected.

Natural indirect effects

- This formalism also enables a meaningful definition of indirect effect.

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- Robins and Greenland (1992) define the total indirect effect as

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& & \text{total effect} & - & \text{natural direct effect} \\
= & & E\{Y(1, M(1)) - Y(0, M(0))\} & - & E\{Y(1, M(0)) - Y(0, M(0))\} \\
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- No similar result for controlled direct effects.

Summary: effect decomposition

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- Traditional Baron-Kenny approach decomposes total effects into direct and indirect components, but
  - interpretation is vague;
  - there is no natural extension to non-linear models
- Framework of natural direct effects enables effect decomposition regardless of the data distribution!

References on definitions and identification

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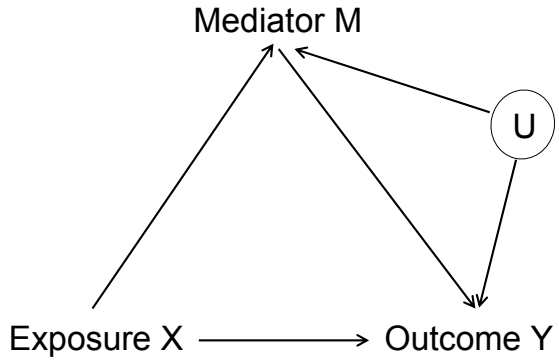
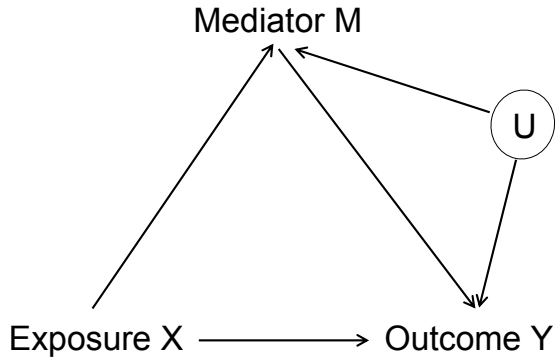
The standard approach



- From now on: controlled direct effects.
- These are commonly inferred by adjusting the association between exposure X and outcome Y for the mediator M (Baron and Kenny, 1986):

$$E(Y|X,M) = \gamma_0 + \gamma_1 X + \gamma_2 M$$

The standard approach



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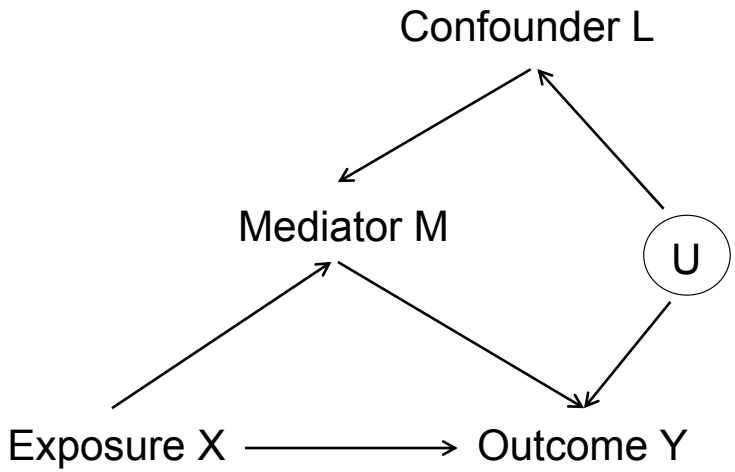
$$E(Y|X,M) = \gamma_0 + \gamma_1 X + \gamma_2 M$$

- Even when X is randomly assigned, this may introduce a collider-stratification bias.

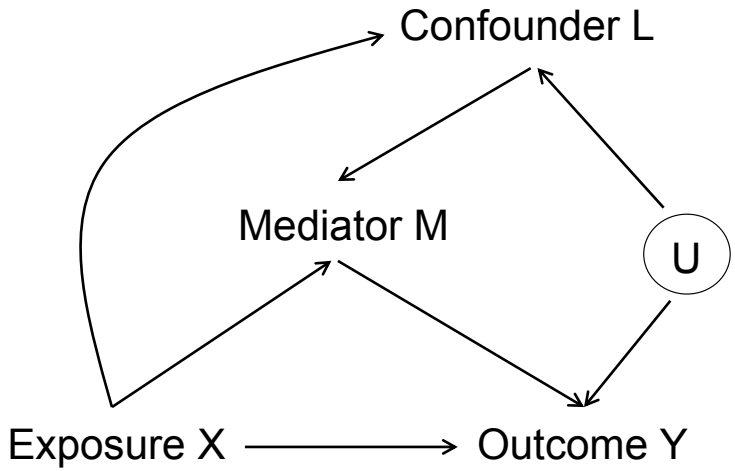
No unmeasured confounders



- We assume that all confounders L for the association between mediator and outcome have been measured.
- Additional adjustment for L removes this bias:

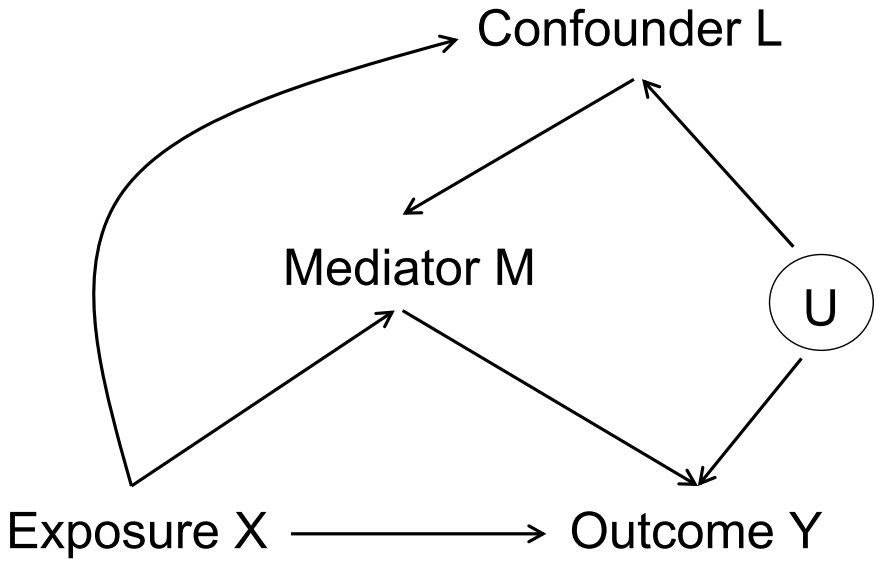
$$E(Y|X, M, L) = \gamma_0 + \gamma_1 X + \gamma_2 M + \gamma_3 L$$

The problem of intermediate confounding



- It is often realistic to believe that some of those confounders *L* are themselves affected by the exposure.
- Additional adjustment for *L* then continues to introduce bias.

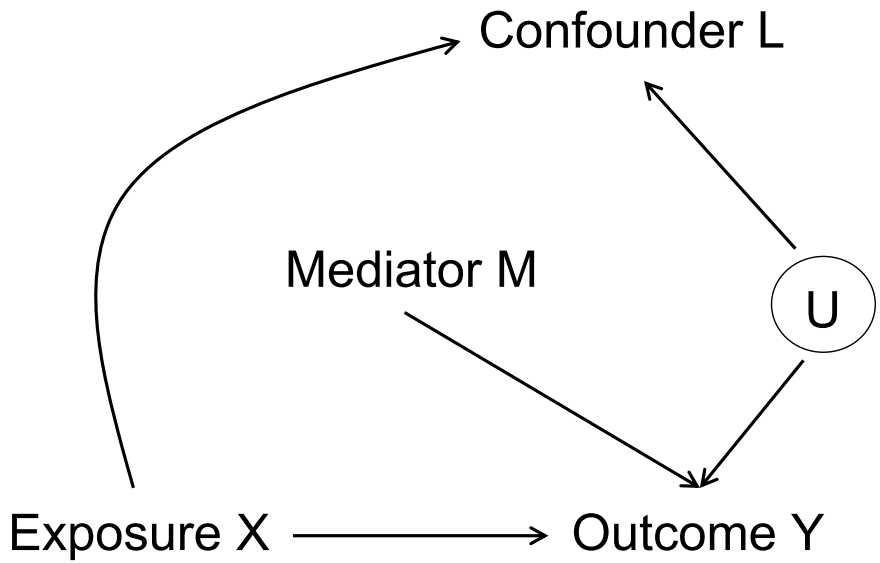
Inverse probability weighted estimation (1)



Robins (1999) proposes inverse weighting the data by

$$\frac{1}{f(M|X,L)}$$

Inverse probability weighted estimation (2)



This removes the association between the mediator and its causes, so that only a direct effect remains.

Inverse probability weighted estimation (3)

An estimate of the direct exposure effect β may thus be obtained by regressing outcome on exposure and mediator, after weighting each subject by

$$\frac{1}{f(M|X,L)}$$

interpretation

Fitting model

$$E(Y|X,M) = \alpha + \beta X + \gamma M$$

after inverse weighting by $1/f(M|X,L)$ yields estimates of the parameters in the marginal structural model (Robins et al., 2000)

$$E\{Y(x,m)\} = \alpha + \beta x + \gamma m$$

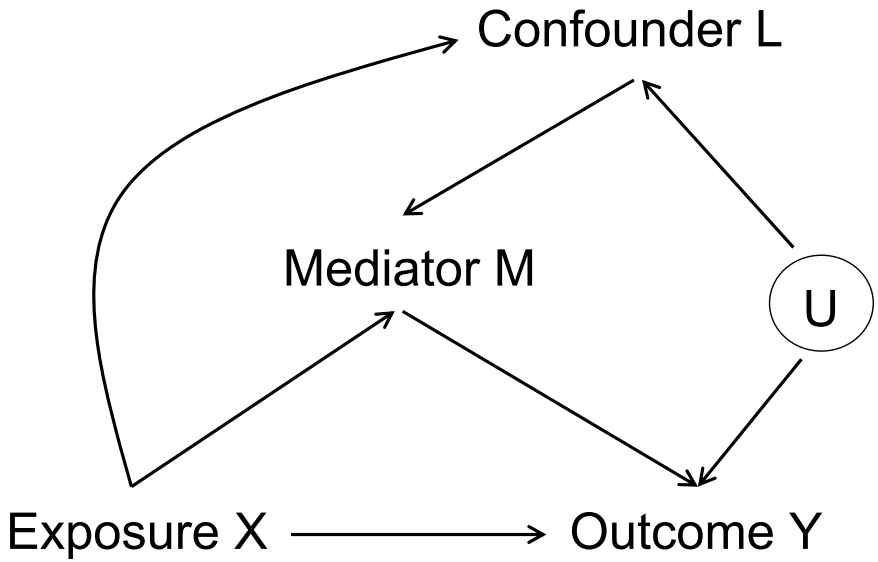
Limitations of inverse probability weighting

- IPW estimators may behave erratically in finite samples
  - when the mediator M is quantitative;
  - or has strong predictors X and L.
- This is because small densities $f(M|X,L)$ can make subjects with weight

$$\frac{1}{f(M|X,L)}$$

  highly influential.
- In view of this, G-estimators have been proposed (Robins, 1994; Goetgeluk, Vansteelandt and Goetghebeur, 2008; Vansteelandt, 2009).

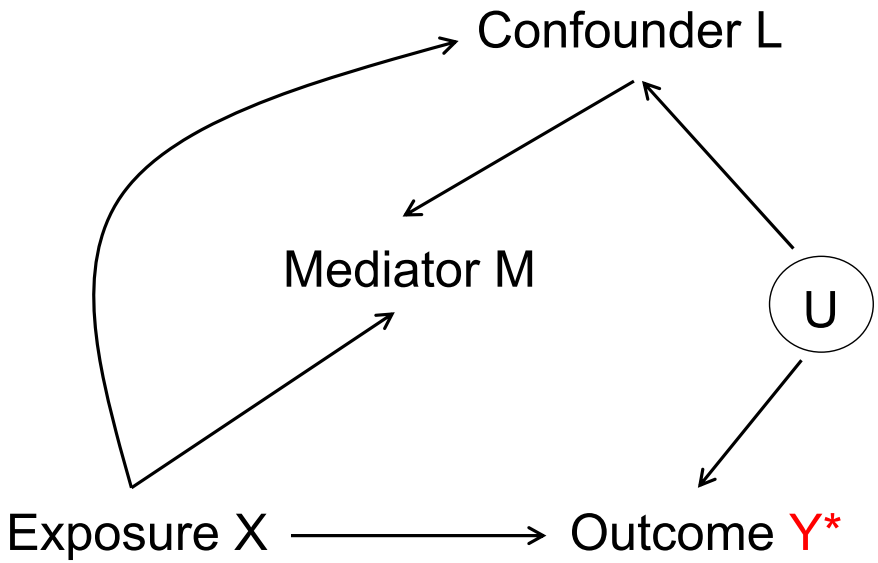
G-estimator (1)



First, remove the indirect effect from the outcome,
$Y^* \equiv Y - \hat{\gamma}M$, where $\hat{\gamma}$ is estimate from a regression model

$$E(Y|X, M, L) = \delta_1 + \delta_2 X + \delta_3 L + \gamma M$$

G-estimator (2)



Now only a direct effect remains.

G-estimator (3)

- We thus estimate the direct effect parameter β by fitting

$$E(Y - \hat{\gamma}M|X) = \alpha + \beta X$$

- The resulting parameter β can be interpreted as a controlled direct effect:

$$E\{Y(1, m) - Y(0, m)\} = \beta$$

Exposure-mediator interactions

When the model

$$E\{Y(x,m) - Y(0,m)|C\} = \beta_1 x + \beta_2 xm$$

is of interest, then we first fit the standard regression model

$$E(Y|X,M,L,C) = \delta_1 + \delta_2 X + \delta_3 L + \gamma M + \beta_2 XM + \lambda C$$

and next

$$E(Y - \gamma M - \beta_2 XM|X,C) = \alpha + \beta_1 X$$

Direct effects on the additive hazard scale

- Martinussen et al. (2011) extend G-estimation to additive hazard models.
- Their initial focus is on the difference in hazard functions

$$\begin{aligned}\gamma_{X,m}(t)dt =& E\left\{dN_{(1,m)}(t)|\mathcal{F}_{(1,m),t}\right\} \\ & - E\left\{dN_{(0,m)}(t)|\mathcal{F}_{(0,m),t}\right\}.\end{aligned}$$

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- This cannot be interpreted as a direct (causal) effect because the two subgroups may not be exchangeable.
- We will therefore define the controlled (cumulative) direct effect (Robins and Greenland, 1992; Pearl, 2001) of X on survival time T other than through M as

$$\Gamma_{X,m}(t) = \int_0^t \gamma_{X,m}(s)\, ds$$

Cumulative direct effect

This encodes a controlled direct effect because

$$\exp\left\{-\Gamma_{X,m}(t)\right\} = \frac{P\{T(1,m) > t\}}{P\{T(0,m) > t\}}$$

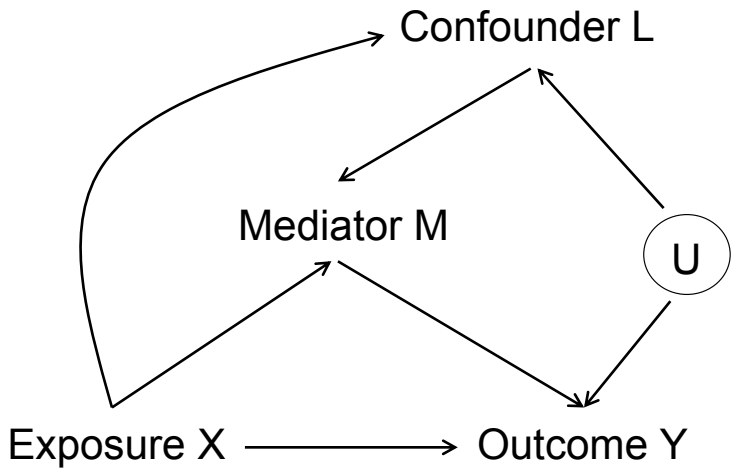
example: MIRA trial

This is the relative risk of avoiding HIV by time t on intervention versus control in the hypothetical situation where male condom use was uniformly kept at level m.

First stage: assess mediator effect

The mediator's effect on the survival time can be obtained from a standard Aalen additive hazards analysis (Aalen, 1989)

$$E\{dN(t)|\mathcal{F}_t, X, M, L\} = \{\psi_0(t) + \psi_X(t)X + \psi_M(t)M + \psi_L(t)L\}\, R(t)dt$$



Second stage: remove mediator effect

- We will now correct the event time by removing the mediator effect.
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$$dN(t) - \psi_M(t) M dt$$

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- The correction in the risk set is achieved by substituting $R(t)$ with

$$R(t) \exp\left\{ M \int_0^t \psi_M(s) ds \right\}$$

Third stage: estimate total effect on corrected counting process

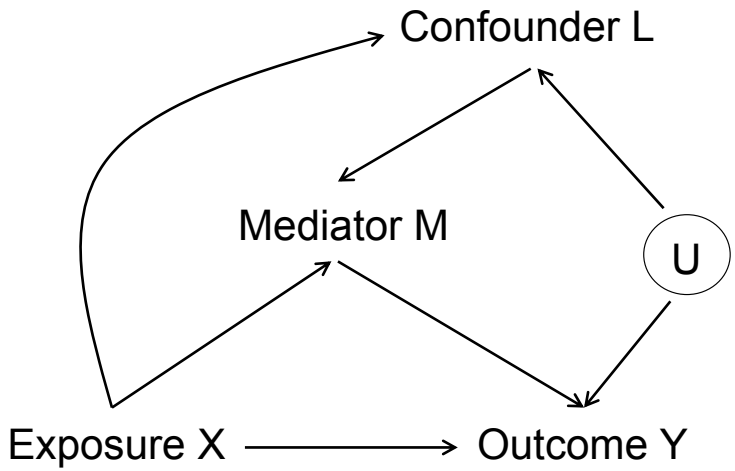
- From this, it can be shown that

$$\begin{pmatrix} 1 \\ X \end{pmatrix} \underbrace{R(t) \exp\left\{ M \int_0^t \psi_M(s) ds \right\}}_{\text{modification of risk set}} \times \underbrace{\{dN(t) - M\psi_M(t)dt - \gamma_0(t)dt - X\gamma_X(t)dt\}}_{\text{residual}}$$

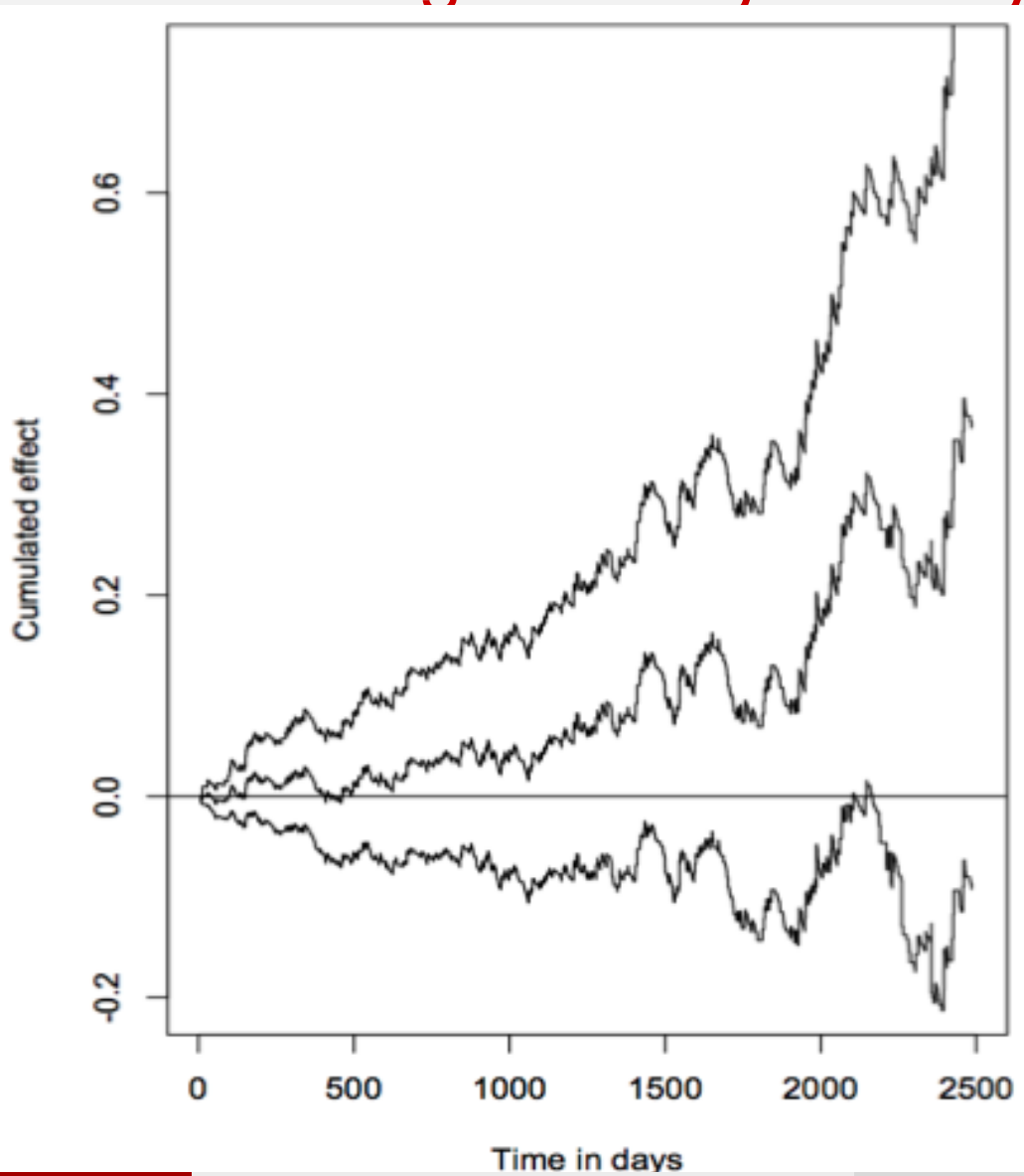
  is an unbiased estimating function.
- From this, a closed form estimator is obtained.

Application to Danish 1905 cohort

- Goal: direct effect of carrying apoe4 mutation on survival other than through activity of daily living.
- Intermediate confounding by cognitive functioning.



Direct cumulative effect of carrying apoe4 mutation on survival other than through activity of daily living



Confounding

- Traditional Baron-Kenny approach ignores confounding of the association between mediator and outcome.
- When, as often, such confounders are themselves affected by the exposure, standard regression methods are no longer applicable.
- Other ‘manipulations’ of causal diagrams needed.
- We have discussed 2 ‘generic’ approaches for controlled direct effects.

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- Traditional Baron-Kenny approach ignores confounding of the association between mediator and outcome.
- When, as often, such confounders are themselves affected by the exposure, standard regression methods are no longer applicable.
- Other ‘manipulations’ of causal diagrams needed.
- We have discussed 2 ‘generic’ approaches for controlled direct effects.
- Inverse probability weighting works by removing the association between mediator and exposure, and thus removing the indirect effect from the data.
- This approach works for any outcome type, but is essentially limited to discrete mediators.

G-estimation

- G-estimation works by removing the effect of mediator on outcome, and thus also removing the indirect effect from the data.
- This approach works for any mediator type and is much more powerful than inverse probability weighting, but cannot handle any type of outcome:
  - linear models for continuous outcomes (Vansteelandt, 2009);
  - log-linear models for positive-constrained outcomes (Vansteelandt, 2009);
  - logistic models for dichotomous outcomes (Vansteelandt, 2010);
  - additive hazard models for survival times (Martinussen et al., 2011).

References on intermediate confounding

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