PATHWAYS

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biosocial influences on health

Current and new approaches to estimating causal pathways from observational data

Rhian Daniel and Bianca De Stavola

ESRC Research Methods Festival, 4th July 2012, 9.15am

Website http://pathways.lshtm.ac.uk
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UNIVERSITY OF CAMBRIDGE
Department of Geography

NCRM National Centre for Research Methods

LONDON SCHOOL of HYGIENE &TROPICAL MEDICINE

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Outline

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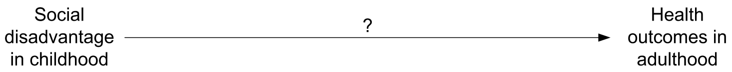
Why are we interested in pathways?

An example

- Being socially disadvantaged in childhood is associated with having poorer health outcomes in adulthood.

Why are we interested in pathways?

An example



- Natural first question: is this causal?

Why are we interested in pathways?

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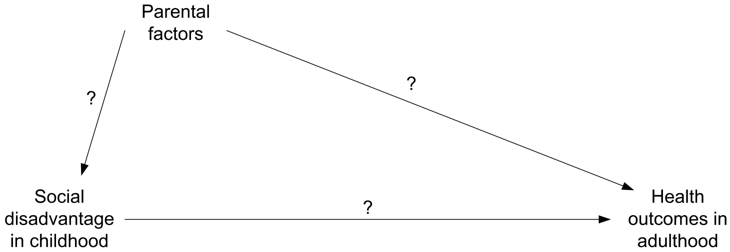

- Or explained by other things? (Confounding).

Why are we interested in pathways?

An example

- Suppose a causal effect can be established.

Why are we interested in pathways?

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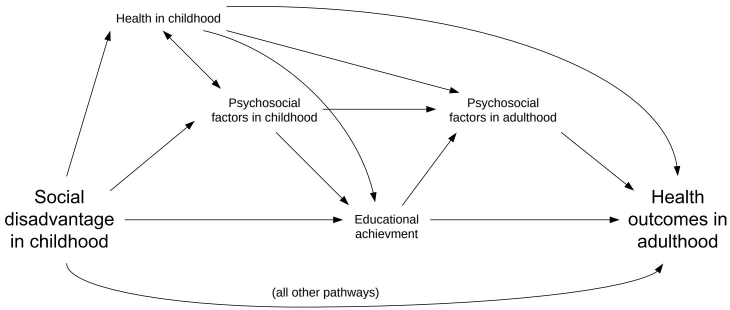

- Natural next step: how does this causal effect act?
- How important are the different pathways?
- Where should interventions be targeted?

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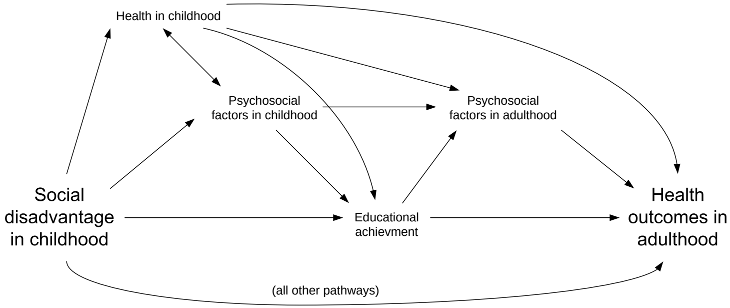

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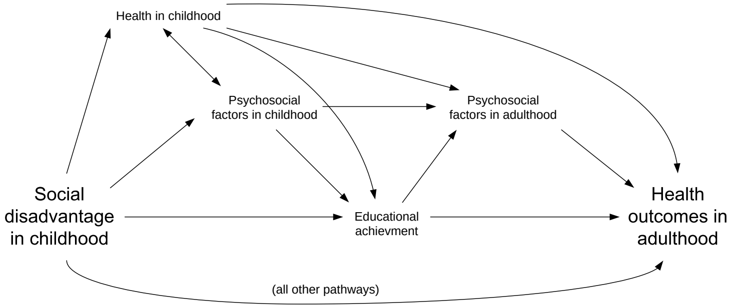

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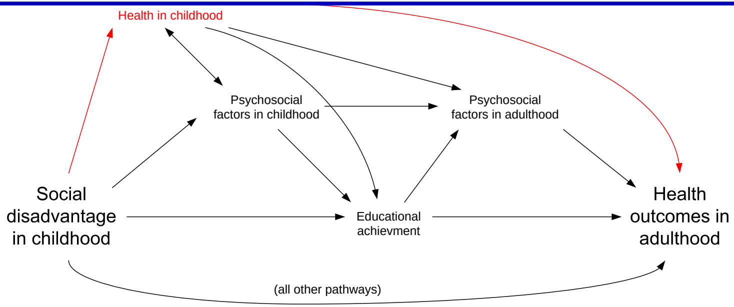

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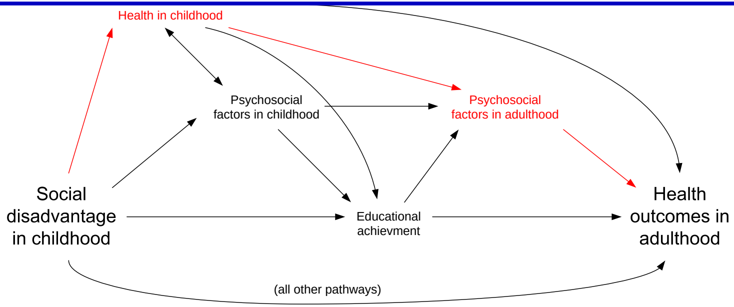

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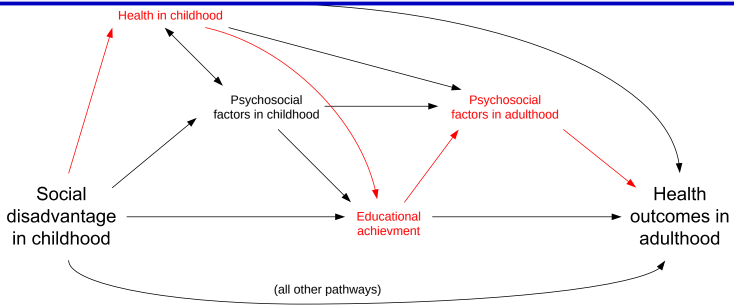

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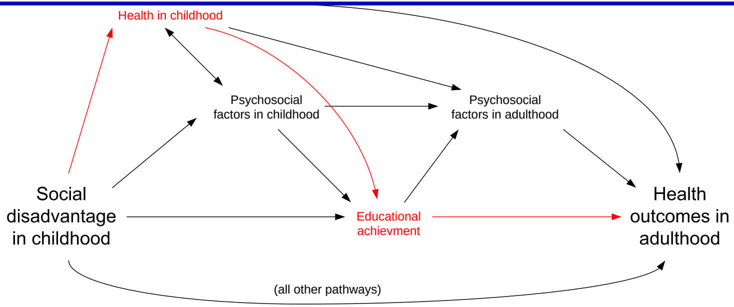

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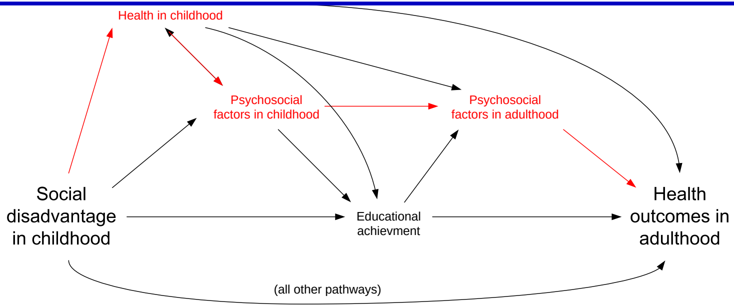

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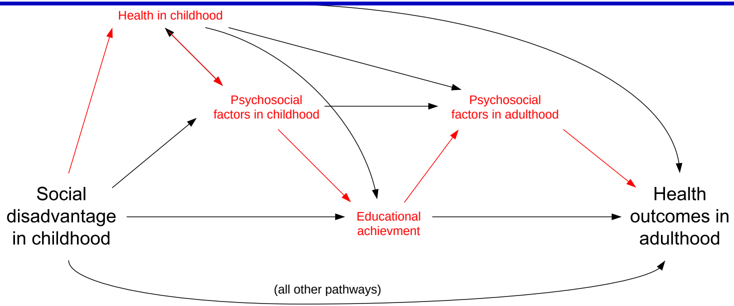

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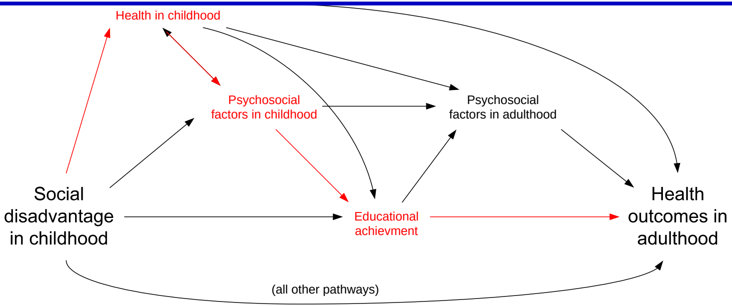

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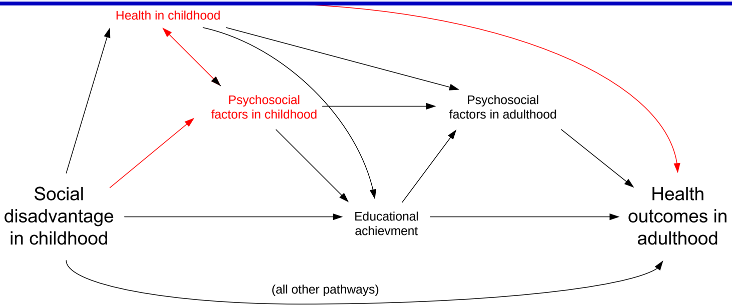

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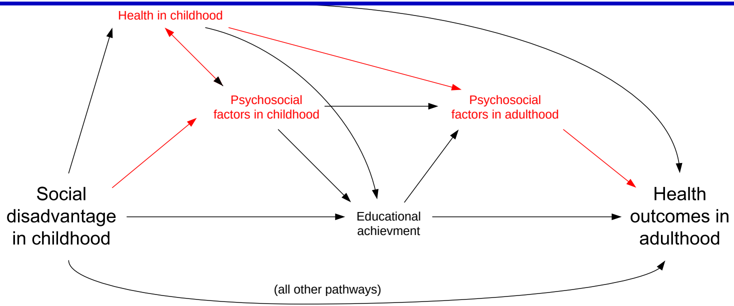

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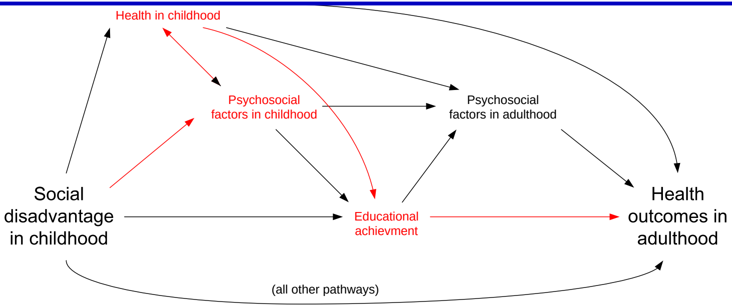

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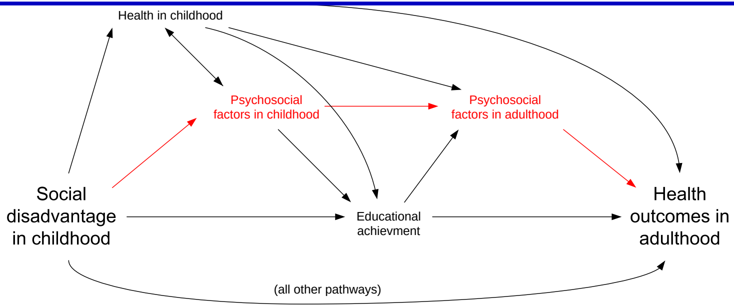

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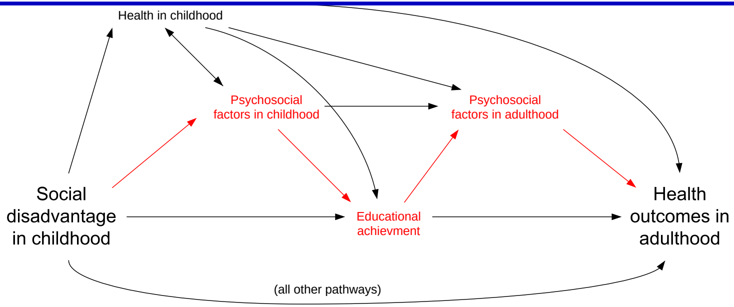

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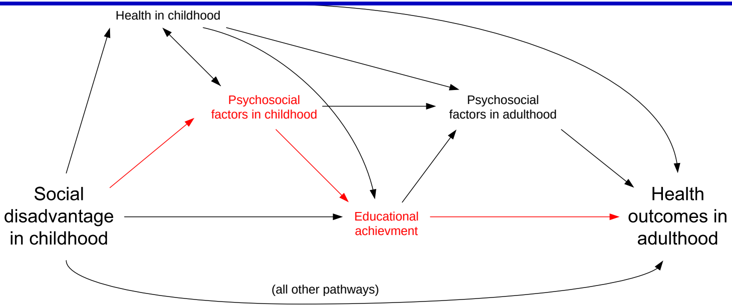

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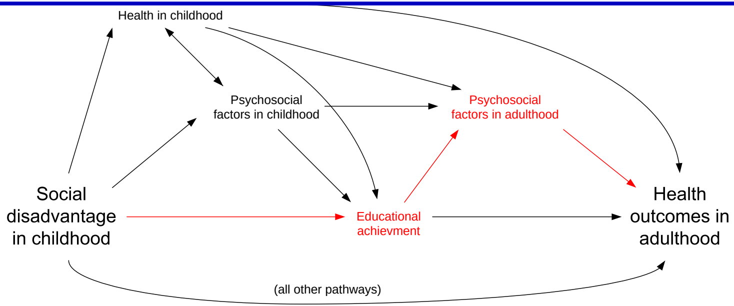

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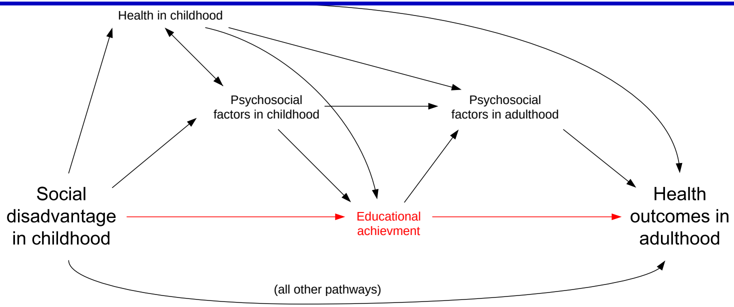

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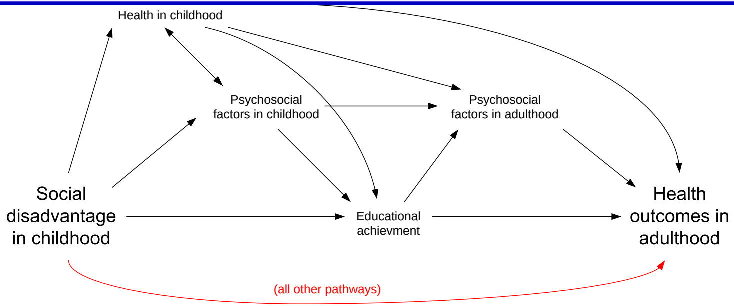

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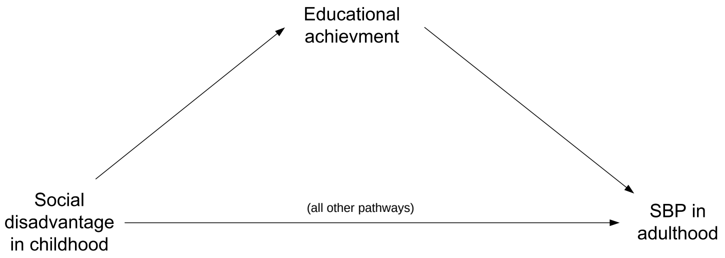
Outline

A simpler question

Two pathways



- Consider a much simpler (but still very challenging!) question.
- How much of the effect of social disadvantage in childhood on, say, systolic blood pressure in adulthood, is mediated by educational achievement?
- Only two pathways ('direct' and 'indirect').

A simpler question

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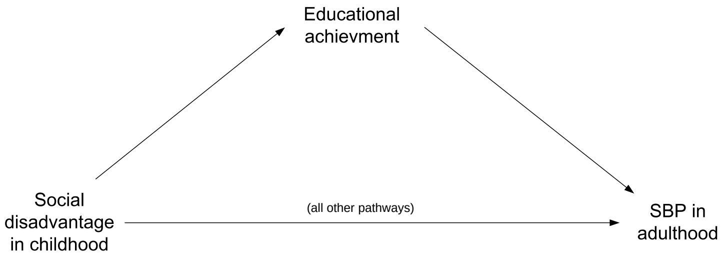

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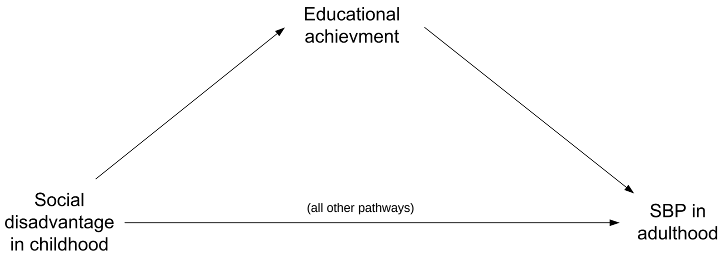

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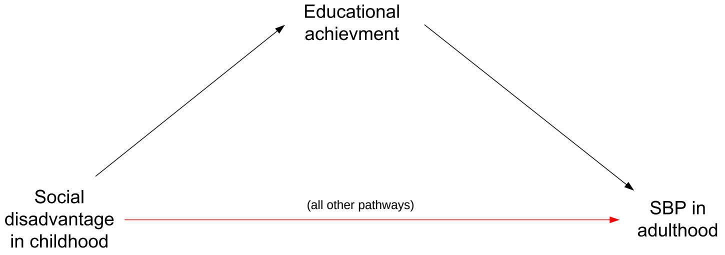

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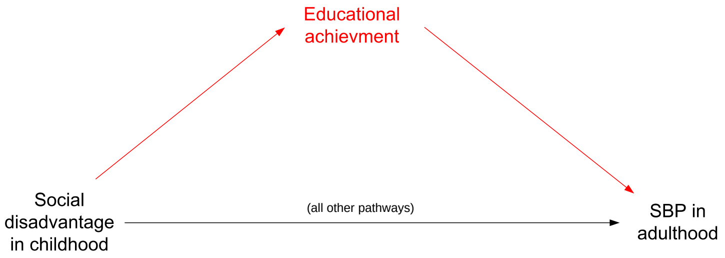

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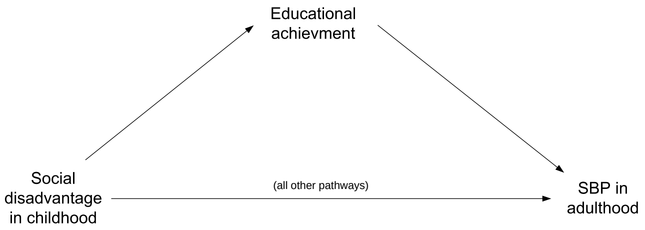
The curruent/old approach to estimating pathways

Combination of simple least squares regressions



- Suppose social disadvantage and educational achievement are each measured using a univariate continuous score.
- Write X for the exposure, M for the mediator and Y for the outcome.
- Let's explicitly include confounders C.

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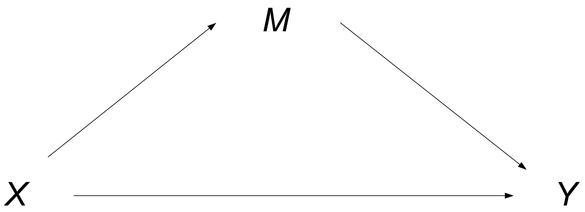

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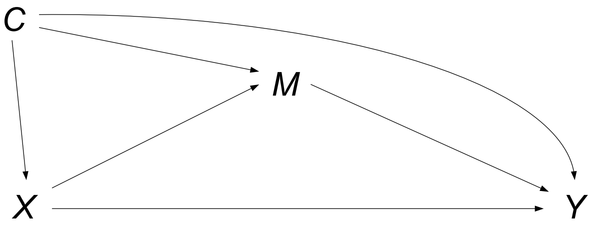

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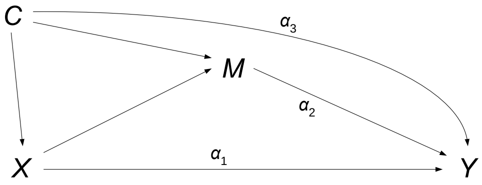
'Difference' method

Baron and Kenny, 1986



Consider two regression models:

$$E(Y|C,X,M) = \alpha_0 + \alpha_1 X + \alpha_2 M + \alpha_3^T C$$
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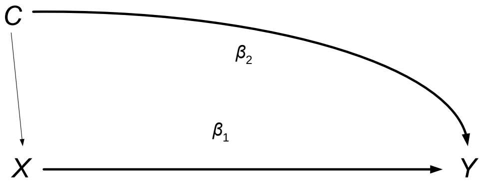

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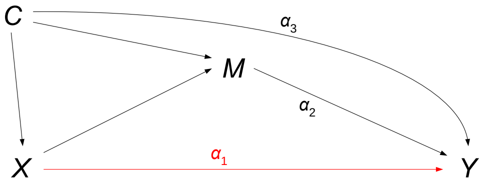

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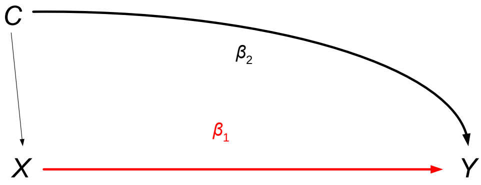

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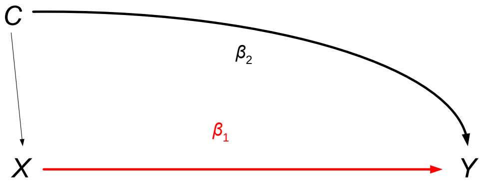

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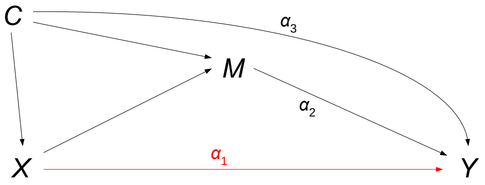

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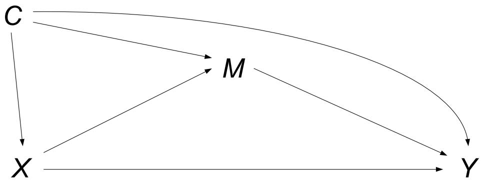

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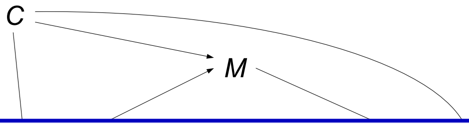

- Estimation via ordinary least squares.
- Various options (delta method, bootstrapping) to obtain SE for the indirect effect.

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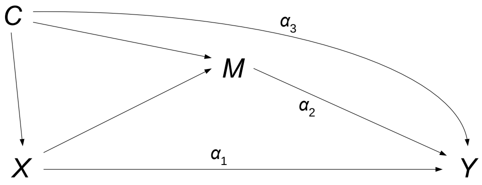
'Product' method

Wright, 1921



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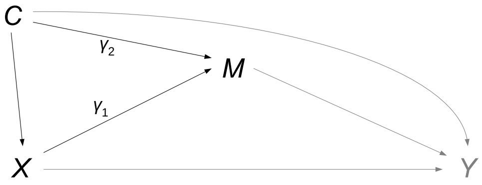

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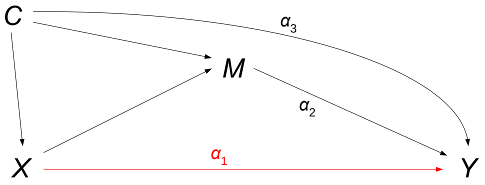

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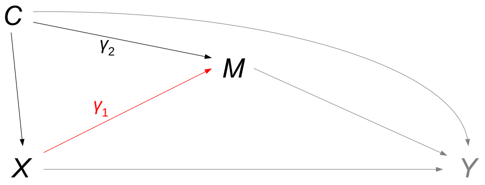

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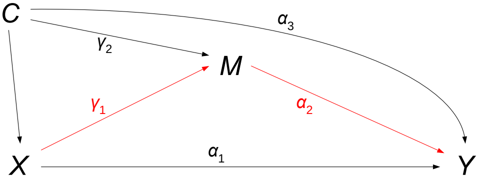

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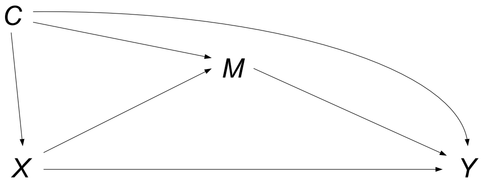
'Product' method

Wright, 1921



Alternatively, consider the two regression models:

$$E(Y \mid C, X, M) = \alpha_0 + \alpha_1 X + \alpha_2 M + \alpha_3^T C$$
$$E(M \mid C, X) = \gamma_0 + \gamma_1 X + \gamma_2^T C$$

- α_1 is (as before) the direct effect,
- and now $\gamma_1 \alpha_2$ is the indirect effect.
- These ('difference', 'product') are equivalent: $\beta_1 - \alpha_1 = \gamma_1 \alpha_2$.

Outline

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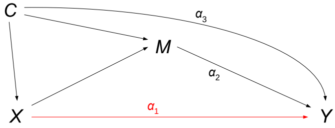
Problem 1: estimands and assumptions

Specific to this (associational) model; correspondence to direct/indirect vague



Consider the regression model that includes α_1:

$$E(Y \mid C, X, M) = \alpha_0 + \alpha_1 X + \alpha_2 M + \alpha_3^T C$$

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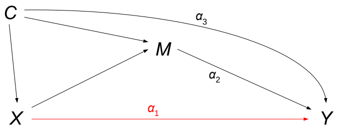

Consider the regression model that includes α_1:

$$E(Y \mid C, X, M) = \alpha_0 + \alpha_1 X + \alpha_2 M + \alpha_3^T C$$

- α_1 is just a parameter in an associational model.
- For two subjects with the same values of C and M, but values of X that differ by 1 unit, it is the expected difference in their values of Y.
- Under what conditions does this correspond to a direct effect?
- Does this question even make sense without a definition (other than α_1) of 'direct effect'?

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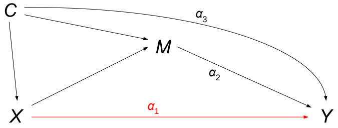

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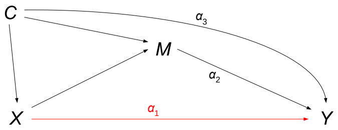

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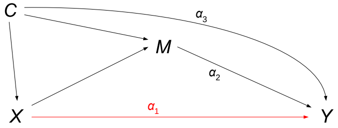

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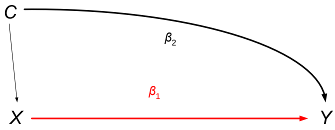

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$$E(Y|C,X) = \beta_0 + \beta_1 X + \beta_2^T C$$

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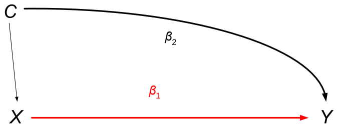

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$$E(Y \mid C, X) = \beta_0 + \beta_1 X + \beta_2^T C$$

- β_1 is the total causal effect of X on Y only if C is sufficient to control for all confounding between X and Y.
- There must surely be similar conditions for α_1 to be interpreted as a direct effect.
- No unmeasured confounding of M and Y? Of X and M? In addition to no unmeasured confounding of X on Y?
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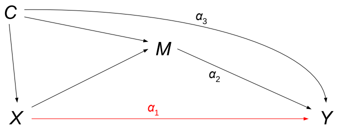

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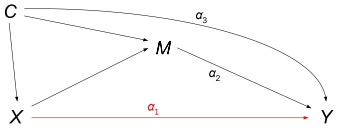

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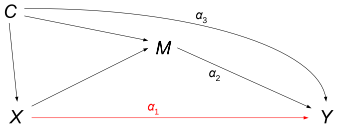

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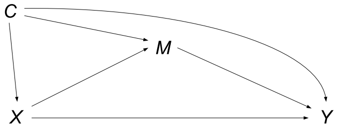

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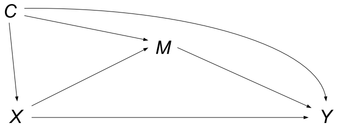

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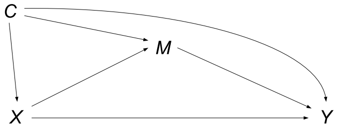

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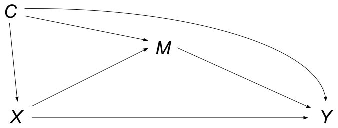

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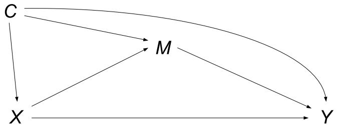

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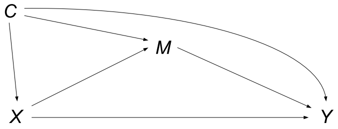

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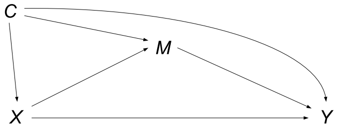

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- Non-linear link functions (eg for binary Y)?
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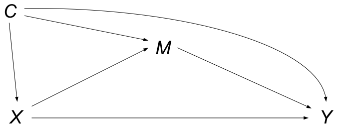

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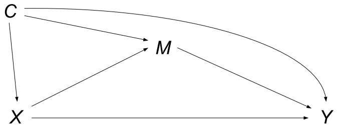

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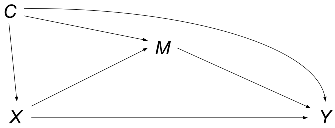

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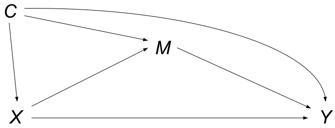

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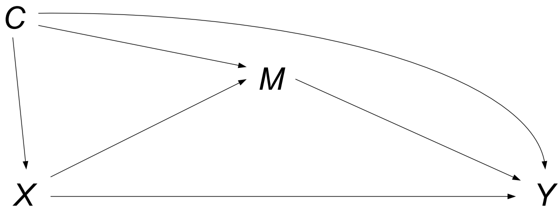

- Thus far, we have considered confounders C that are (potentially) common causes of X, M and Y.
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- eg childhood health in our example.

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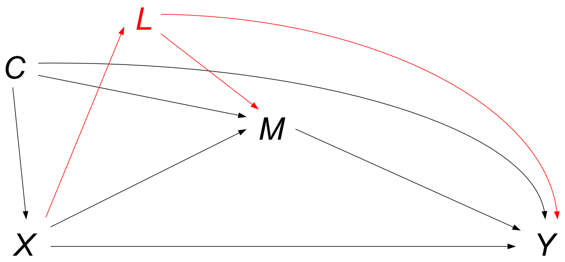

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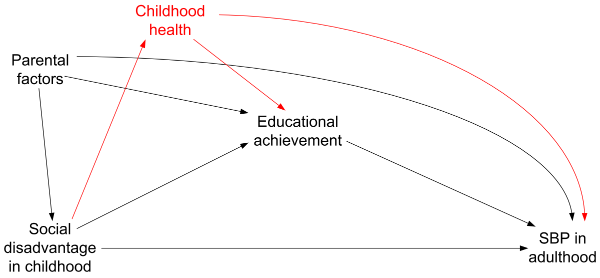

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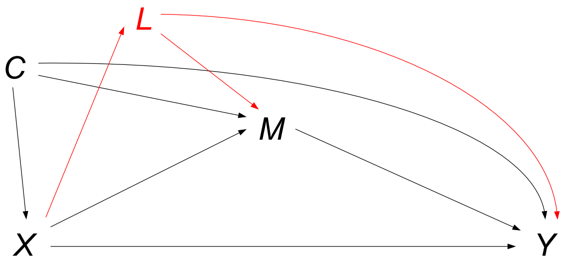

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- Let us ignore C for simplicity, and, let us even ignore the arrow from X to L at first, ie L is NOT an intermediate confounder in this diagram for now...

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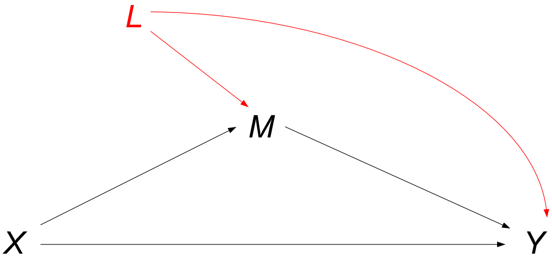

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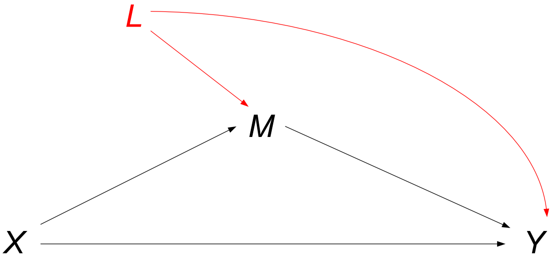

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- This model conditions on M.

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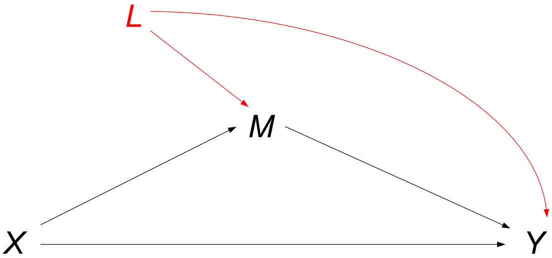

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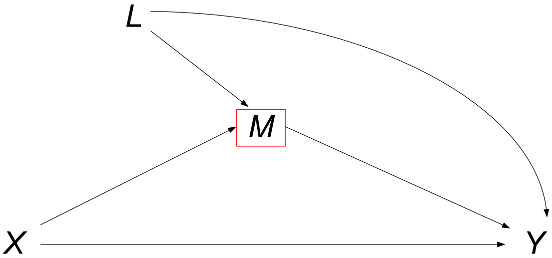

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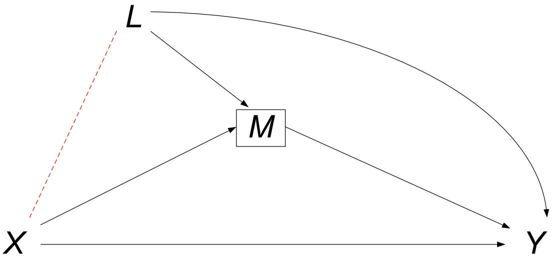
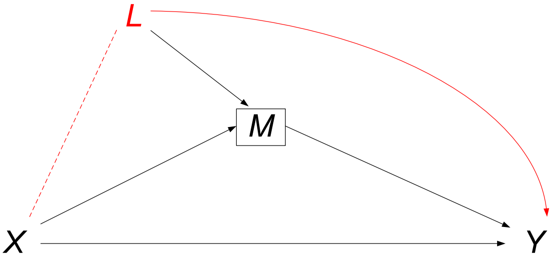


- Conditioning on M induces an association between X and L even if there was none there before (and would alter an existing association)—why?

Problem 3: intermediate confounding



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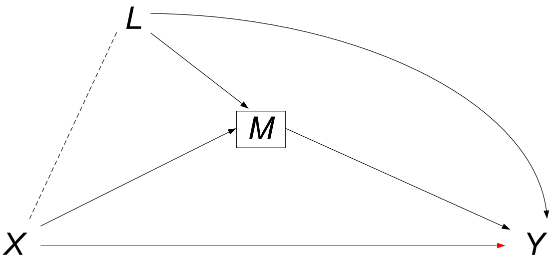

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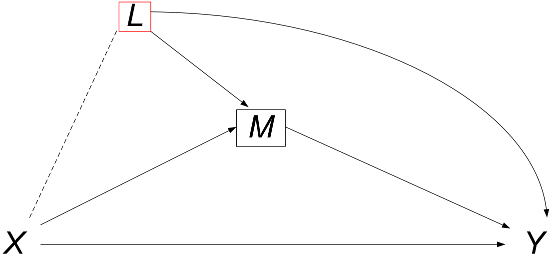

- A solution would be to include L in the model:

$$E(Y|X, M, L) = \alpha_0 + \alpha_1 X + \alpha_2 M + \alpha_3 L$$

—blocking the spurious association.

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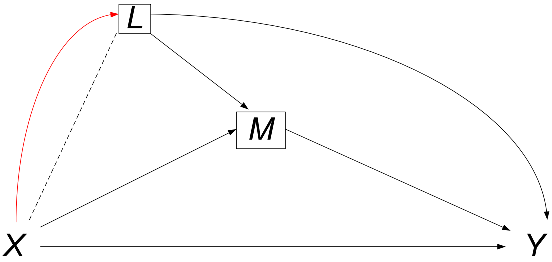

- But this is NOT a solution when L is affected by X.
- Since we block part of the direct effect (unmediated by M).
- Thus it is unclear how the 'old' approaches can be used when there is intermediate confounding.

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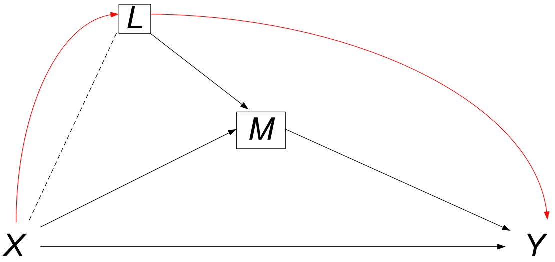

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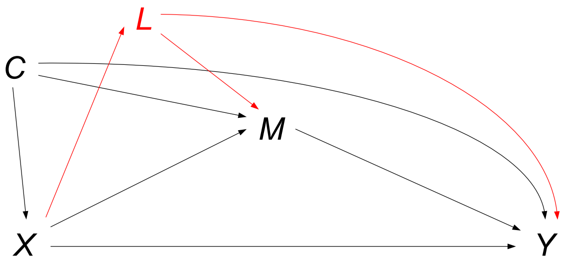

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  1. They give no model-free definitions of direct/indirect effect.
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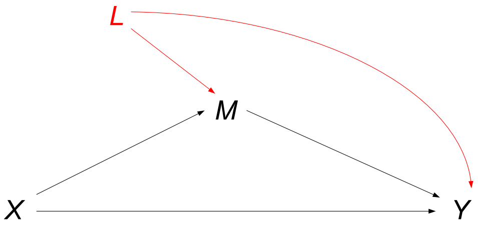
Direct and indirect effects are about causality



- Recall that if there are ignored common causes L of M and Y, the 'direct effect' we would naïvely estimate includes an association via this pathway...
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- Thus the whole enterprise makes sense only if we are talking about path-specific causal effects.
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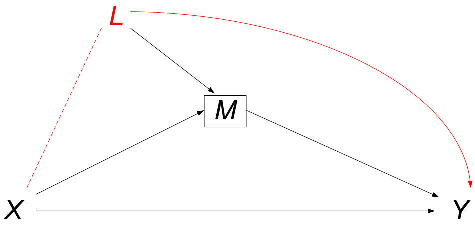

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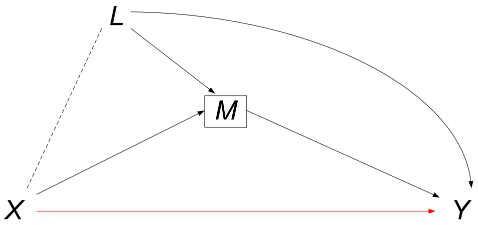

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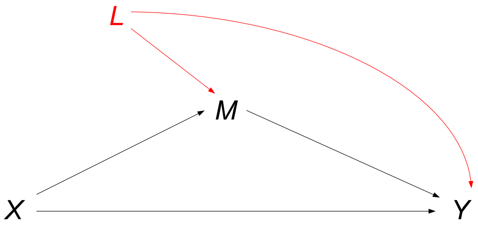

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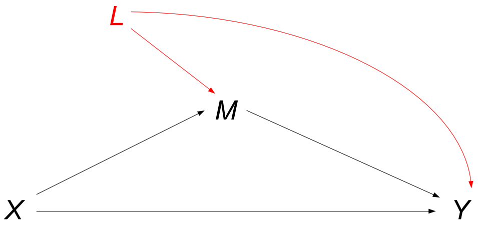

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Counterfactuals

- Causal, unlike associational, quantities are not just about describing this world, but involve a notion of how the world would have been had something been different.
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Counterfactuals

- Let $Y(x)$ be the value that Y would take if we intervened on X and set it (possibly counter to fact) to the value x.
- Let $Y(x, m)$ be the value that Y would take if we intervened simultaneously on both X and M and set them to the values x and m.
- Let $M(x)$ be the value that M would take if we intervened on X and set it to x.
- Let $Y\{x, M(x^*)\}$ be the value that Y would take if we intervened on X and set it to x whilst simultaneously intervening on M and setting it to $M(x^*)$, the value that M would take under an intervention setting X to x^*, where x and x^* are not necessarily equal.

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These counterfactuals are central to the (model-free) definitions of direct/indirect effects in causal inference.

Estimands

- Many (subtly different) counterfactual definitions of direct/indirect effects have been proposed.
- Direct effects:
  - Controlled direct effect (Pearl, 2001),
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Total causal effect

- The total causal effect of X on Y, conditional on $C = c$, expressed as a mean difference comparing x^* vs x is

$$\text{TCE}(c, x, x^*) = E\{Y(x^*)|C = c\} - E\{Y(x)|C = c\}.$$

- Note that this can also be written as

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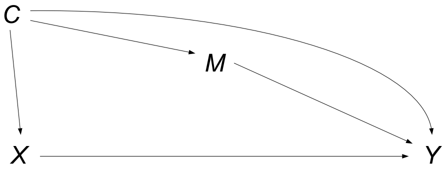

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- But in this case, the indirect effect would intuitively be zero.
- And so we cannot hope to find a definition of a controlled indirect effect (CIE) such that

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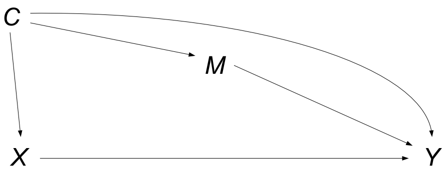

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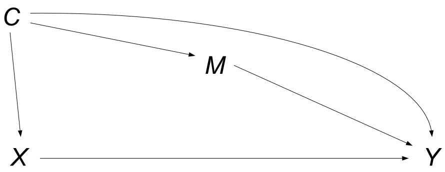

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- For this reason, it is useful to have a different definition of a direct effect.
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Pearl, 2001; Robins and Greenland, 1992

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Effect decomposition

Now we see that the sum of the natural direct and indirect effects is

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&\text{NDE}(c, x, x^*) + \text{NIE}(c, x, x^*) \\
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&\quad + E[Y\{x^*, M(x^*)\}|C = c] - E[Y\{x^*, M(x)\}|C = c] \\
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the total causal effect, as desired.

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- And how would we choose a particular set level? 7 GCSEs or 10?
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Effects on alternative scales

Risk ratio scale (NB these decompose multiplicatively)

$$\mathrm{TCE}^{\mathrm{RR}}(c,x,x^*) = \frac{E\{Y(x^*)|C=c\}}{E\{Y(x)|C=c\}},$$

$$\mathrm{CDE}^{\mathrm{RR}}(c,x,x^*,m) = \frac{E\{Y(x^*,m)|C=c\}}{E\{Y(x,m)|C=c\}},$$

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Effects on alternative scales

Odds ratio scale (NB these decompose multiplicatively)

$$\text{TCE}^{\text{OR}}(c,x,x^*) = \frac{E\{Y(x^*)|C=c\}/[1-E\{Y(x^*)|C=c\}]}{E\{Y(x)|C=c\}/[1-E\{Y(x)|C=c\}]},$$

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What next?

- Given clear definitions of the estimands we would like to estimate, we can give assumptions under which they can be identified from data and methods for doing so.
- Whenever counterfactual quantities are to be estimated from actual data, assumptions are needed to link the two.
- The assumptions come in three flavours:
  1. Consistency assumptions: allow linking of counterfactual outcomes such as $Y(x, m)$ with the actual outcome Y, for certain subjects.
  2. Exchangeability assumptions: allow linking certain subjects with certain other subjects so that counterfactuals not identified by consistency, can be estimated by borrowing information across subjects.
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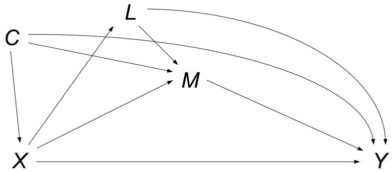
Assumptions for identification: TCE



- Consistency for $Y(x)$:

$$Y = Y(x) \text{ if } X = x$$

- Conditional exchangeability given C for X wrt Y:

$$Y(x) \perp\!\!\!\perp X \mid C \quad \forall x$$

- Essentially, this means no unmeasured confounding of the X–Y relationship.

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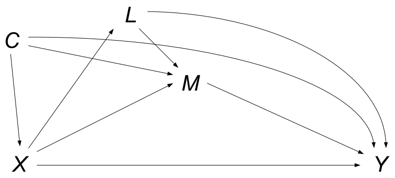

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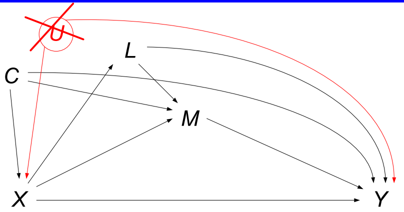

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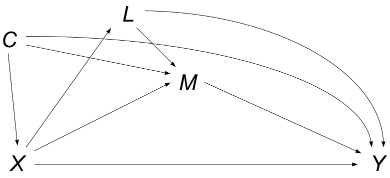

- Consistency for $Y(x, m)$:

$$Y = Y(x, m) \text{ if } X = x \text{ and } M = m$$

- Sequential conditional exchangeability given C for X wrt Y and given C, X, L for M wrt Y:

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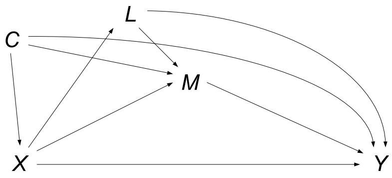

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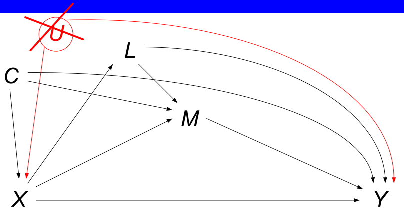

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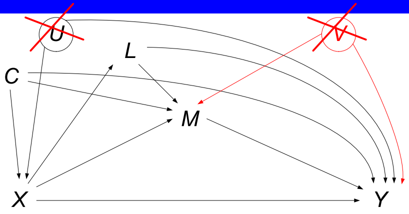

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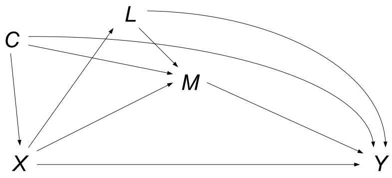
Assumptions for identification: NDE, NIE



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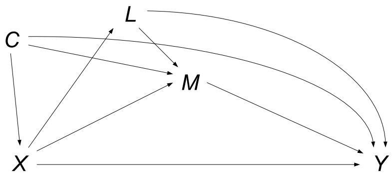

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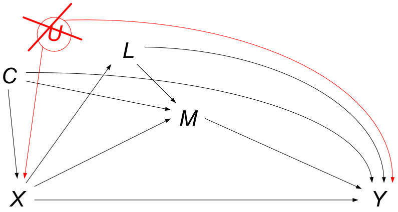

- Essentially, this means no unmeasured confounding of the X–Y, M–Y, or X–M relationships.
- Finally, in addition, either:
  - No intermediate confounding, or
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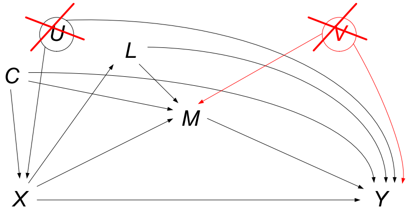

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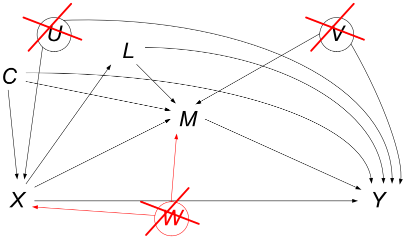

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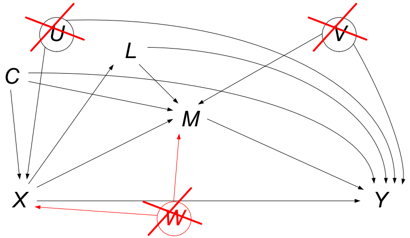

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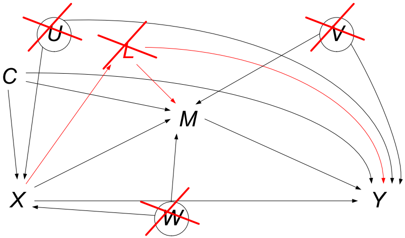

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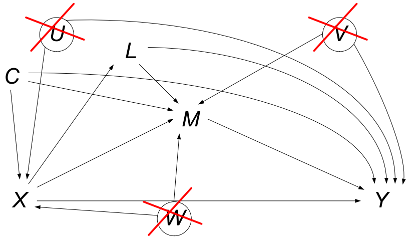

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Outline

G-computation formula for the CDE

Robins 1986

- Let's look at how the CDE is estimated:

$$\begin{aligned}
&\text{CDE}\,(c, x, x^*, m) = \\
&\qquad E\{Y(x^*, m)\,|\,C = c\} - E\{Y(x, m)\,|\,C = c\} \\
&= \int E(Y\,|\,C = c, X = x^*, L = l, M = m)\, f_{L|C,X}(l\,|\,c, x^*)\, dl \\
&- \int E(Y\,|\,C = c, X = x, L = l, M = m)\, f_{L|C,X}(l\,|\,c, x)\, dl
\end{aligned}$$

- 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.

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$$= \int E\left(Y\,|C = c, X = x^*, L = l, M = m\right) f_{L|C,X}\left(l\,|c, x^*\right) dl$$

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G-computation formula for the CDE

Robins 1986

- Let's look at how the CDE is estimated:

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Alternative semiparametric approches

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- In particular, the necessity to model $L|C,X$ can be problematic if L is high-dimensional.
- Alternative semiparametric methods from the causal inference literature do not require a model for $L|C,X$:
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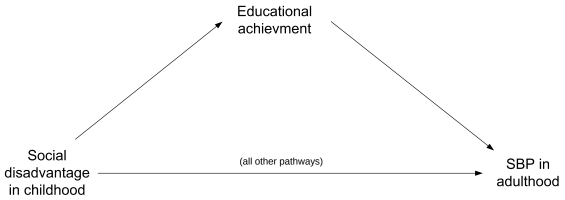
Outline

Multiple mediators



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- The definitions of direct and indirect effects extend easily to path-specific effects.
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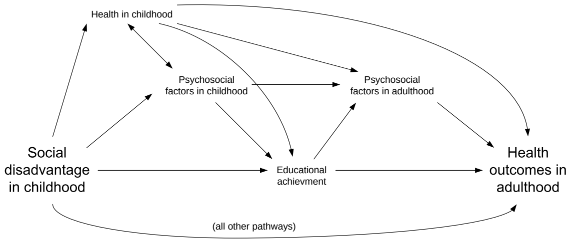

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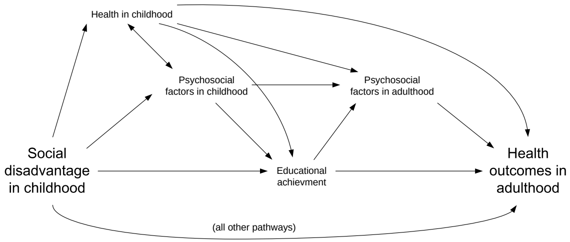

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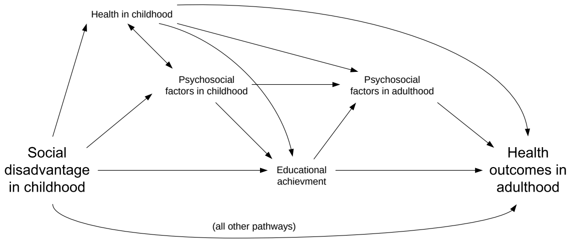

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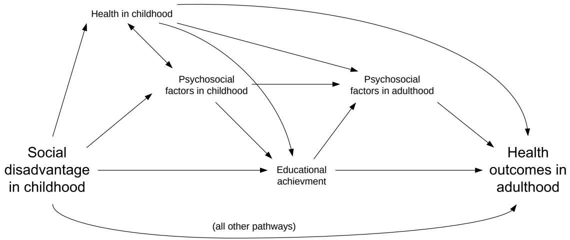

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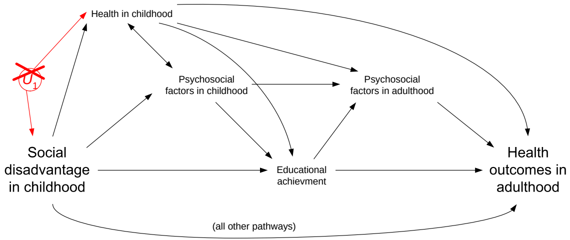

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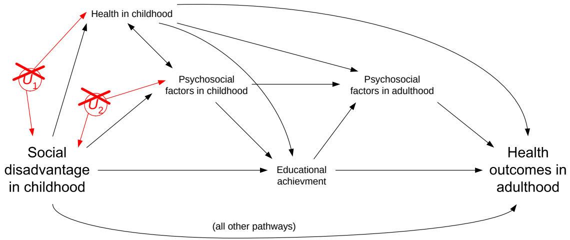

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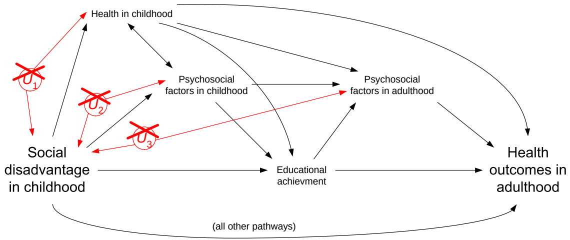

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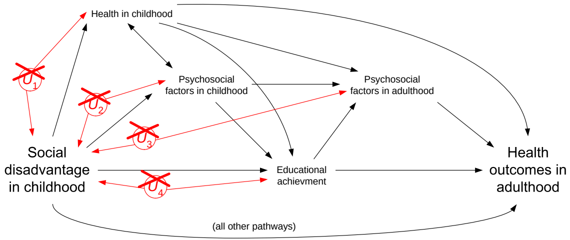

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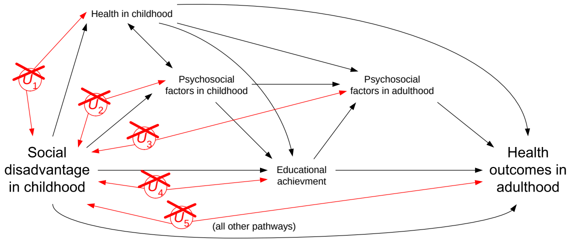

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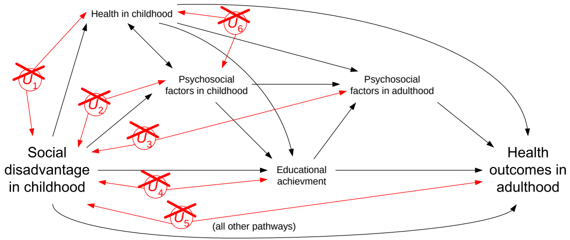

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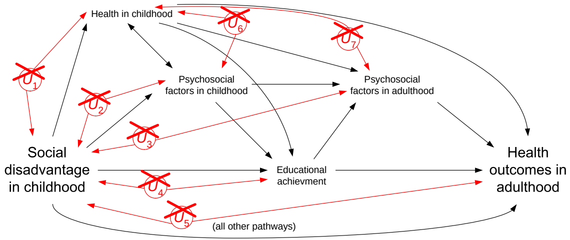

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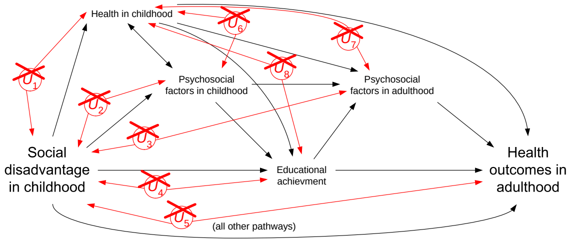

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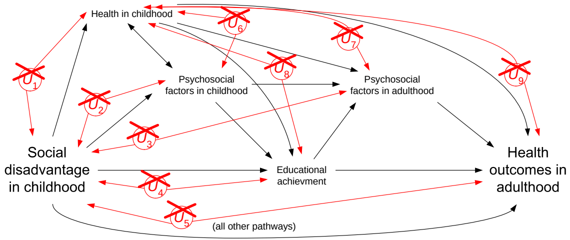

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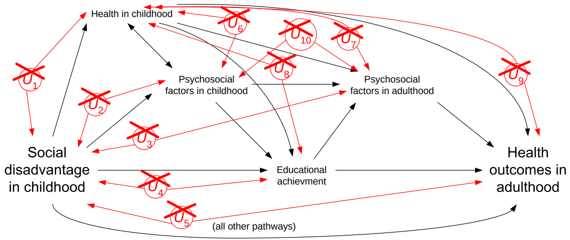

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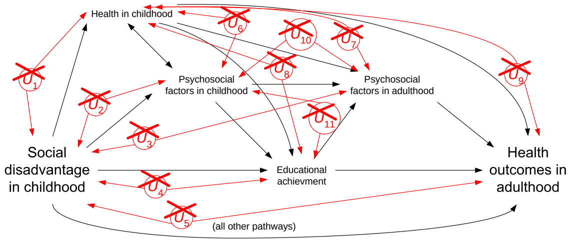

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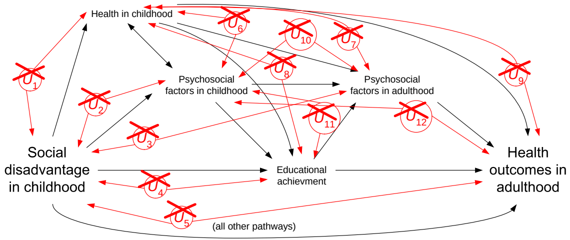

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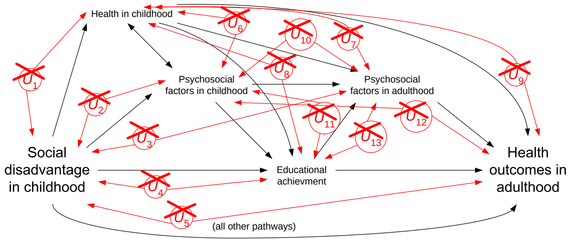

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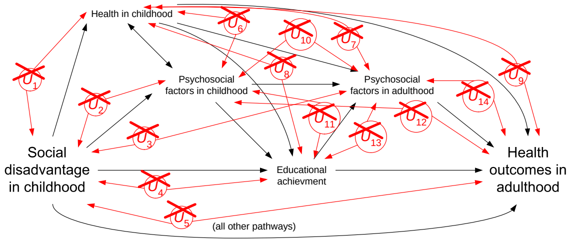

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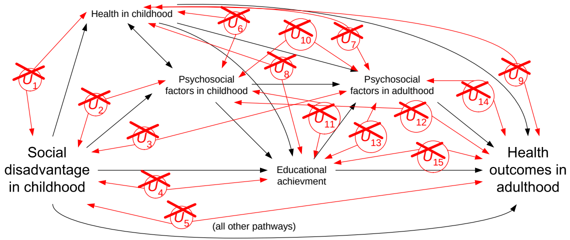

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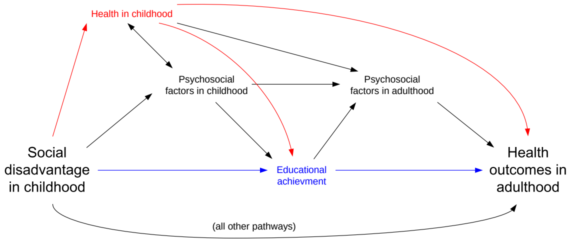

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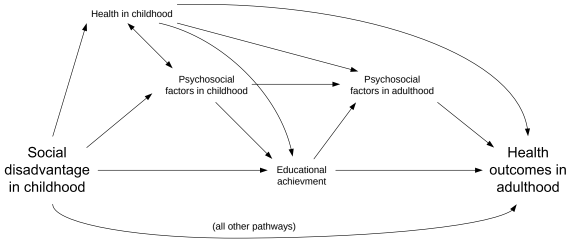

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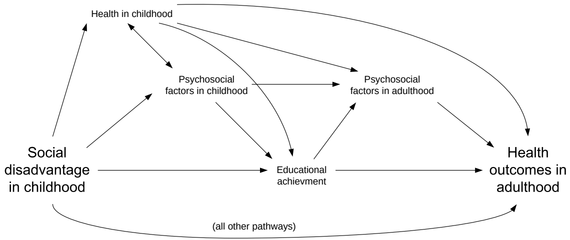

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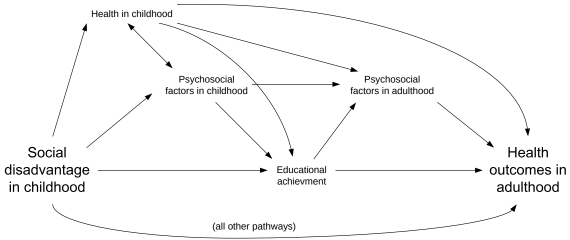

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