A Modicum of Causal Inference Theory

Eric J Tchetgen Tchetgen

Departments of Biostatistics and Epidemiology,
Harvard University

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Introduction

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2. Effect of a cause: assess the effect of a well defined exposure or intervention. e.g. does smoking cause lung cancer? does AZT prevent the advent of AIDS among HIV infected patients?

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    - e.g. smoking and lung cancer.

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- Gives conditions under which "association is causation", therefore standard statistical methods may be used.
- Generally makes explicit assumptions needed for the identification of causal effects, and allows for the derivation of new statistical methods when standard and familiar methods fail.

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Our causal paradigm consists of :

- Defining causal quantities, this will be done in terms of counterfactuals.
- Stating assumptions necessary to identify causal quantities (nonparametrically).
- Defining a mathematical model to deal with the curse of dimensionality.
- performing statistical inference which includes testing and estimating the magnitude of a causal effect given the observed data.

Part I:Causal Effects of a Point Exposure

Counterfactuals

- Suppose you are contemplating taking an aspirin for your headache, and the outcome Y denotes whether or not you are headache free within say the next hour.

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- As a thought experiment, you may think of two potential outcome variables either of which may be observed depending on whether or not you decide to take the aspirin. That is:

$$\left\{ \begin{array}{c} Y_0 : \textit{headache outcome after not taking aspirin} \\ Y_1 : \textit{headache outcome after taking aspirin} \end{array} \right\}$$

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- The english sentence: 'aspirin has no causal effect on my headache outcome $Y \Leftrightarrow$ a mathematical statement about my potential outcomes $Y_1 = Y_0$.
- Similarly, we can think of an individual with a beneficial causal effect of aspirin if $Y_1 > Y_0$, or one with a harmeful causal effect of aspirin $Y_1 < Y_0$.

Counterfactuals

- The fundamental problem of causal inference is that you only observe one of the two potential outcomes.

$$Y = AY_1 + (1 - A)Y_0$$

The outcome corresponding to the treatment you did indeed take. That is Y_A is the factual outcome, and Y_{1-A} is the counterfactual.

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- So that if in the data sample, you happen to be a person with $A = 1$, we observe Y_1, and Y_0 is missing, and vice versa for a person with $A = 0$.
- Therefore, it is impossible to evaluate individual causal effects. This is fundamentally a missing data problem. The only difference is that the full data is never observed with probability one.

Counterfactuals

- However, all is not lost, as under some assumptions, we can still say something about population causal effects. For instance, consider the following finite population version of the previous headache example.

ID	Y_0	Y_1	$Y_1 - Y_0$
1	0	0	0
2	1	0	-1
3	0	1	1
4	1	0	-1
5	1	0	-1
6	0	1	1
7	1	0	-1
8	0	0	0

Counterfactuals

- A commonly used population causal effect is given by the average causal effect:

$$\psi = E(Y_1 - Y_0) = E(Y_1) - E(Y_0) = 1/4 - 1/2 = -1/4$$

Note that this estimand can be written as a functional of the two marginal distributions of Y_0, and Y_1, without requiring their joint distribution This is going to be key to identifying ψ.

Randomization

Identification through randomization: Suppose we randomize our population of patients with a headache to either aspirin or no aspirin with equal probability 1/2. So that the observed data corresponds to columns four and five of the following table and you don't see the first two columns.

ID	Y_0	Y_1	A	Y
1	0	0	0	0
2	1	0	1	0
3	0	1	0	0
4	1	0	1	0
5	1	0	0	1
6	0	1	1	1
7	1	0	0	1
8	0	0	1	0

Randomization

Now consider the following parameter based on the observed data

$$\tau = E\left(Y|A=1\right) - E\left(Y|A=0\right) = 1/4 - 2/4 = -1/4$$

so that in this population, the crude association τ between A and Y appears to coincide with the average causal effect of A on Y. We will formally prove this below.

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- (CA) Consistency Assumption: $Y = Y_A$ w.p.1
- (RA) Randomization Assumption: $\{Y_0, Y_1\} \amalg A$
- If CA and RA hold, then $\psi = E(Y_1) - E(Y_0) \overset{RA}{=}$
  $E(Y_1|A=1) - E(Y_0|A=0) \overset{CA}{=} E(Y|A=1) - E(Y|A=0) = \tau.$

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- Note that the randomization assumption is simply saying that since A is determine say by a coin flip, it should be completely independent of patients' pretreatment characteristics.
- It helps to think of the potential outcomes $\{Y_0, Y_1\}$ as being underlying pretreatment latent variables that exist prior to the random treatment assignment, and therefore, should be unrelated to the latter.

Randomization

- Note however that this RA does not imply $Y \amalg A$ since by the consistency assumption $Y = AY_1 + (1 - A)Y_0$ is determined by treatment and therefore is a posttreatment variable.

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- In fact, $Y \amalg A$ holds if and only if the null hypothesis $Y_1 \stackrel{D}{=} Y_0$ holds and is also implied by the so-called sharp null hypothesis $Y_1 = Y_0$ a.s.

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- So that the average causal effect of A and Y is identified by the crude association between A and Y.
- This gives a formal justification for using randomized studies to validly assess the effect of interventions. Note that we have assumed the absence of non-compliance, blinding and missing or censored data. We will return to these issues later.

Observational Study:The Case of Point exposure

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- Then we say that there are no unmeasured counfounders for the effect of A on Y.

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- Conceptually, this can be achieved only if we are able to measure all common causes of A and Y (that is all risk factors for Y that also determine A).

Observational Study:The Case of Point exposure

- Next we show that the no unmeasured confounding assumption is sufficient to again identify $\{E(Y_a) : a\}$ and thus $\psi = E(Y_1) - E(Y_0)$ Without loss of generality, suppose L is categorical; then
  $E(Y_a) = E(E(Y_a|L)) = \sum_l E(Y_a|L=l) f_L(l)$
  $\overset{NUCA}{=} \sum_l E(Y_a|A=a, L=l) f_L(l)$
  $\overset{CA}{=} \sum_l E(Y|A=a, L=l) f_L(l)$
  $\equiv g(a)$

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- Thus $\psi = g(1) - g(0) = \sum_l \{E(Y|A=1,L=l) - E(Y|A=0,L=l)\} f_L(l)$ is the *standardized risk difference*.

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  $\sum_l \{E(Y|A=1,L=l) - E(Y|A=0,L=l)\} f_L(l)$ is the *standardized risk difference*.
- Under NUCA, we see that crude association$\neq$causation, as
  $\sum_l E(Y_a|A=a,L=l) f_L(l) = E(Y_a)$
  $\neq E(Y|A=a) = \sum_l E(Y|A=a,L=l) f_L(l|A=a)$.

Observational Study:The Case of Point exposure

- So that the crude risk difference does not have a causal interpretation. However, if NUCA holds, and either of the following conditions holds:

$$Y \amalg L|A \text{ or } A \amalg L \tag{1}$$

then $E(Y_a) = E(Y|A = a)$ and L is a non-confounder, so that this implies that RA actually holds.

Observational Study:The Case of Point exposure

Proof:

- In the first case,
  $E(Y_a) = \sum_l E(Y|A=a, L=l) f_L(l)$
  $= \sum_l E(Y|A=a) f_L(l) = E(Y|A=a)$;

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- In the second case,
  $E(Y_a) = \sum_l E(Y|A=a, L=l) f_L(l)$
  $= \sum_l E(Y|A=a, L=l) f_L(l|A=a) = E(Y|A=a)$

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- In general,the point exposure G-formula is written

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$$E\left(Y_a\right) = \int E\left(Y|A = a, L = l\right) dF(l)$$

- The left-hand side is the mean of a counterfactual (latent variable), the right–hand side is a functional of the observed data, which is always well defined but only has a causal interpretation under the no unmeasured assumption.

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  - $E\left(Y_a|V=v\right)=\int E\left(Y|A=a,L=l\right)dF(l|V=v)$, where V is contained in L
  - $f\left(Y_a|V=v\right)=\int f\left(Y|A=a,L=l\right)dF(l|V=v)$.

G-computation

- Given the observed data $O_i = (Y_i, A_i, L_i)$, G-computation generally refers to nonparametric inference on the G-formula $g(a) = \sum_l E(Y|A = a, L = l) f_L(l)$.

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- A natural nonparametric estimator of $g(a)$ is given by the nonparametric pluggin estimator, which requires nonparametric estimates of $E(Y|A = a, L = l) = b(a, l)$ written $\widehat{b}(a, l)$ and of $F_L(l)$ written $\widehat{F}_L(l)$.

G-computation

- Until otherwise stated, assume both A and L are categorical variables with low to moderate number of levels, so that $\widehat{b}(a, l)$ is given by the stratified sample average:

$\widehat{b}(a, l) = \sum_{i=1}^{n} I\left(A_i = a, L_i = l\right) Y_i / \sum_{i=1}^{n} I\left(A_i = a, L_i = l\right)$
and $\widehat{f}_L\left(l\right) = n^{-1} \sum_{i=1}^{n} I\left(L_i = l\right)$

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and $\widehat{f}_L\left(l\right) = n^{-1} \sum_{i=1}^{n} I\left(L_i = l\right)$

- The nonparametric estimator of the G-formula is given by:

$$\begin{aligned}
\widehat{g}(a) &= \sum_{l} \widehat{b}(a,l) \widehat{f}_L\left(l\right) = \sum_{l} \widehat{b}(a,l) n^{-1} \sum_{i=1}^{n} I\left(L_i = l\right) \\
&= n^{-1} \sum_{i=1}^{n} \sum_{l} \widehat{b}(a,l) I\left(L_i = l\right) = n^{-1} \sum_{i=1}^{n} \widehat{b}(a, L_i)
\end{aligned}$$

G-computation Asymptotic Distribution

One can show that

$$
\begin{aligned}
& n^{1/2}\left(\widehat{g}(a)-g\left(a\right)\right) \\
= \quad & n^{-1/2}\sum_{i=1}^{n}\left\{\frac{I\left(A_i=a\right)}{f_{A|L}\left(A_i|L_i\right)}\left(Y_i-b(A_i,L_i)\right)+b(a,L_i)-g\left(a\right)\right\}+o_p(1) \\
= \quad & n^{-1/2}\sum_{i=1}^{n}IF_i\left(a\right)+o_p(1) \\
\sim \quad & N\left(0,E\left(IF_i\left(a\right)^2\right)\right)
\end{aligned}
$$

G-computation:Mathematical Interlude

A wald type 95%CI for $\psi = g(1) - g(0)$ is given by:

$$\widehat{g}(1) - \widehat{g}(0) \pm 1.96 \sqrt{n^{-1} \sum_i \left(\widehat{IF}_i(0) - \widehat{IF}_i(1) \right)^2}$$

where $\widehat{IF}_i(a) = \left\{ \frac{I(A_i=a)}{\widehat{f}_{A|L}(a|L_i)} \left(Y_i - \widehat{b}(A_i, L_i) \right) + \widehat{b}(a, L_i) - \widehat{g}(a) \right\}$,
and $\widehat{f}_{A|L}(a|L_i = l) = \frac{\sum_i I(A_i=a, L_i=l)}{\sum_i I(L_i=l)}$ is the nonparametric estimator of $f_{A|L}(a|L_i = l)$,the probability of receiving treatment $A = a$ given $L = l$.

G-computation:Mathematical Interlude

- The term $b(a, L_i) - g(a)$ reflects the variability due to the estimation of $F_L(l)$, whereas $\frac{I(A_i=a)}{f_{A|L}(a|L_i)}(Y_i - b(a, L_i))$ captures the variability due to the estimation of $b(a, L_i)$.

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- It is interesting to note that the influence function and thus the variance of $\widehat{\psi} = \widehat{g}(1) - \widehat{g}(0)$ depends on the treatment process $\left\{f_{A|L}(a|L_i) : a\right\}$,even though the pluggin estimator described above appears not to.

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- In fact, we give a different representation of the nonparametric estimator of the G-formula which makes explicit its dependence on the estimated treatment process.

G-computation:dual representation

- It can be shown that the nonparametric G-computation estimator $\widehat{g}(1) - \widehat{g}(0)$ has a dual representation as an inverse-probability of treatment weighted (iptw) estimator:

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- $\widehat{g}(a) = \sum_l \widehat{b}(a, l)\widehat{f}_L(l) = \frac{\sum_{s=1}^{n} I(A_s{=}a) Y_s \widehat{f}^{-1}_{A|L}(A_s|L_s)}{\sum_{s=1}^{n} I(A_s{=}a) \widehat{f}^{-1}_{A|L}(A_s|L_s)}$

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- $\widehat{f}_{A|L}\left(a|L=l\right)=\frac{\sum_i I(A_i=a,L_i=l)}{\sum_i I(L_i=l)}$ is the nonparametric estimator of the treatment conditional probability mass function $f_{A|L}\left(a|L=l\right)$.

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- So that the nonparametric G-formula estimator has a (exact) dual representation as an inverse-probability-of-treatment weighted (iptw) estimator, and this also shows that the latter is asymptotically efficient.

G-computation:dual representation

- One can easily show (try it) that the iptw estimator $\widehat{g}(a)$ is the solution to the estimating equation:$\sum_{i=1}^{n} \frac{I(A_i=a)}{\widehat{f}_{A|L}(a|L_i=l)} (Y_i - \widehat{g}(a)) = 0.$

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- In contrast to the estimating equation for the conditional mean $\mu(a) = E(Y|A=a)$ given by: $\sum_{i=1}^{n} I(A_i = a)(Y_i - \widehat{\mu}(a)) = 0$.

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- We again see that if $f_{A|L}(a|L_i = l) = f_A(a)$, then $E(Y|A=a) = E(Y_a)$ and association is causation.

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- One can easily show (try it) that the iptw estimator $\widehat{g}(a)$ is the solution to the estimating equation:$\sum_{i=1}^{n} \frac{I(A_i=a)}{\widehat{f}_{A|L}(a|L_i=l)} (Y_i - \widehat{g}(a)) = 0$.
- In contrast to the estimating equation for the conditional mean $\mu(a) = E(Y|A=a)$ given by: $\sum_{i=1}^{n} I(A_i = a)(Y_i - \widehat{\mu}(a)) = 0$.
- We again see that if $f_{A|L}(a|L_i = l) = f_A(a)$, then $E(Y|A=a) = E(Y_a)$ and association is causation.
- If $f_{A|L}(a|L_i = l) \neq f_A(a)$ and L is a risk factor of Y, then to obtain a counterfactual mean $E(Y_a)$, the recipe is to weight the estimating function for the conditional mean by $\widehat{f}^{-1}_{A|L}(a|L_i = l)$ to adjust for confounding by L.

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- Moreover $E(Y|A=1,L=l)=24+12l$ so that L predict Y given A.

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- Do a similar calculation for $E\left(Y_0\right)$

Parametric G-computation.

- As before, the goal is to estimate the average causal effect:

$$\begin{aligned}\psi &= g(1) - g(0) \\ &= \int \{E(Y|A=1, L=l) - E(Y|A=a, L=l)\} \, dF_L(l)\end{aligned}$$

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- The debilitating effect of high dimensional L on nonparametric inference of ψ is commonly referred to as the 'curse of dimensionality'.

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- For binary Y, one may use the logistic regression model $b(A, L; \eta) = (1 + \exp(-(A, L')\,\eta))^{-1}$ and obtain $\widehat{\eta}$ by maximizing the logistic likelihood function.

Parametric G-computation

- For a linear model $b(A, L; \eta)$,the standard approach to obtain estimates $\widehat{\eta}$ of η is with ordinary least-square which solve the normal equations

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- In contrast to its nonparametric counterpart, the parametric G-computation estimator described above does not generally have a nice dual representation as an iptw estimator.
- Moreover, it is susceptible to model misspecification as the regression model for $E(Y|A, L)$ will invariably be hard to correctly specify when L is high dimensional; for instance, if we have omitted higher order interactions or nonlinear regressors; therefore, a different approach is needed.

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- That is, specify a model $\pi(L;\alpha)$ for the conditional probability of taking treatment $f_{A|L}(1|L)$, say $\pi(L;\alpha) = (1+\exp(-(L')\alpha))^{-1}$ indexed by a finite dimensional vector α. $\pi(L;\alpha)$ is a standard logistic regression thus $\widehat{\alpha}$ may be obtained from maximum likelihood theory with data (A_i, L_i) $i = 1, ..., n$.

Parametric iptw estimation

- The parametric iptw estimator of ψ is defined as

$$\widehat{\psi}_{iptw} = \frac{\sum_{s=1}^{n} I(A_s = 1) Y_s \pi^{-1}(L_s; \widehat{\alpha})}{\sum_{s=1}^{n} I(A_s = 1) \pi^{-1}(L_s; \widehat{\alpha})} - \frac{\sum_{s=1}^{n} I(A_s = 0) Y_s (1 - \pi(L_s; \widehat{\alpha}))^{-1}}{\sum_{s=1}^{n} I(A_s = 0) (1 - \pi(L_s; \widehat{\alpha}))^{-1}}$$

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- Whenever L is high dimensional, it will generally be difficult to correctly specify a parsimonuous model for $f_{A|L}(1|L)$, therefore $\widehat{\psi}$ may end up being significantly biased due to model misspecification.

Doubly robust estimation

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- An estimator that satisfies this latter property is known as a *doubly robust* estimator.

Doubly robust estimation

- Given estimated parametric models $\pi\left(L;\widehat{\alpha}\right)$, $b(A,L;\widehat{\eta})$, a doubly robust estimator of the average causal effect is given by :

$$\begin{aligned}\widehat{\psi}_{dr} &= n^{-1}\sum_i\left(b(1,L_i;\widehat{\eta})+\frac{I\left(A_i=1\right)}{\pi\left(L_i;\widehat{\alpha}\right)}\left(Y_i-b(A_i,L_i;\widehat{\eta})\right)\right)\\ &\quad -n^{-1}\sum_i\left(b(0,L_i;\widehat{\eta})+\frac{I\left(A_i=0\right)}{\left(1-\pi\left(L_i;\widehat{\alpha}\right)\right)}\left(Y_i-b(A_i,L_i;\widehat{\eta})\right)\right)\end{aligned}$$

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- One can show that $\widehat{\psi}_{dr}$ is consistent if either $E(Y|A,L)=(A,L')\,\eta$, or $f_{A|L}\left(A|L_i\right)=\pi\left(L;\alpha\right)$ but not necessarily both are correctly specified.

Part II:Longitudinal Causal Effects

Causal Diagrams

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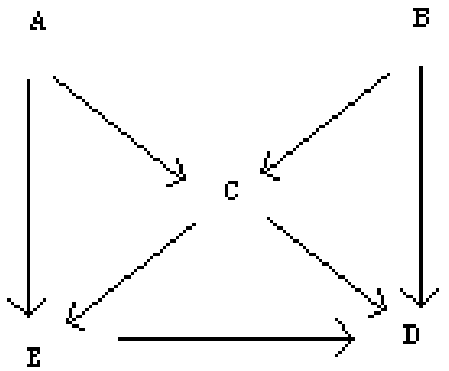
  4. And there are no other important confounders besides sex, bronchial reactivity and air pollution

Causal Diagrams

- These assertions can be incorporated in the following diagram



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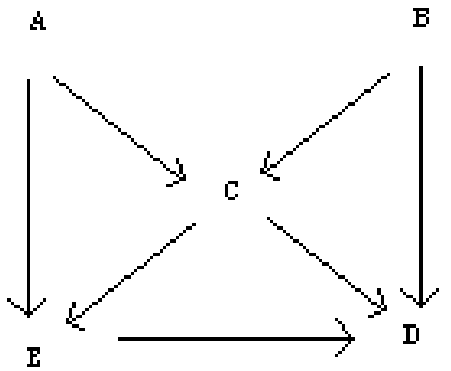

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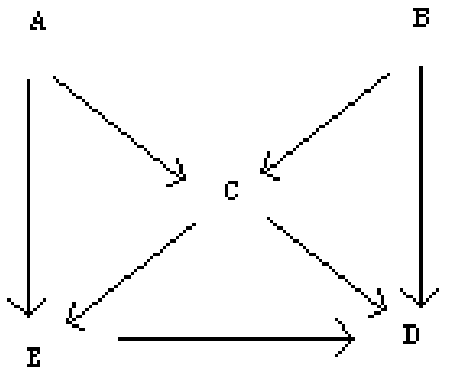

  - The points representing the variables are called the vertices/nodes of the graph; any line or arrow connecting two variables in the graph is an arc/edge.
  - Arrows represent direct links from causes to effects, that is not mediated by any other variable. Example: the arrow linking A and C represents a direct effect of A on C.

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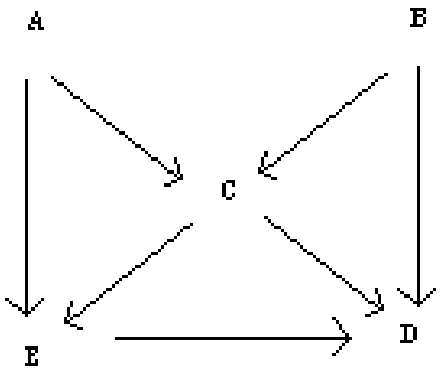

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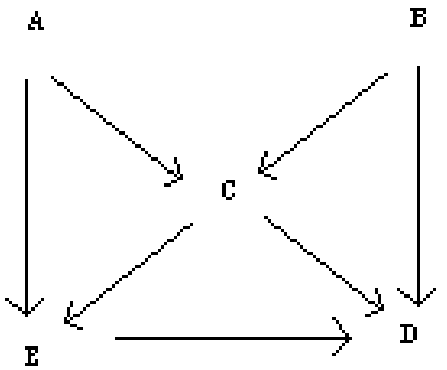

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- a node within a path is said to *intercept* the path: Example C intercepts the paths A-C-D and E-C-D.

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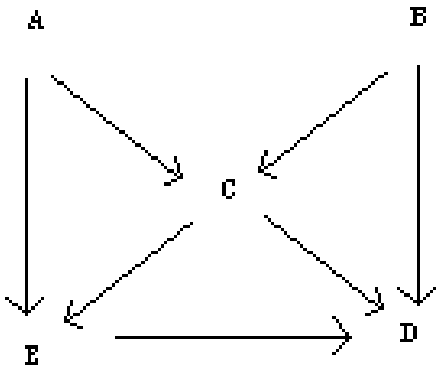

- X is an *ancestor or cause* of Y$\Leftrightarrow$there is a directed path leading out of X into Y. So that Y is a descendant of X. Example: A.B and C are ancestors of E and D, which in turn are descendants of A,B and C.

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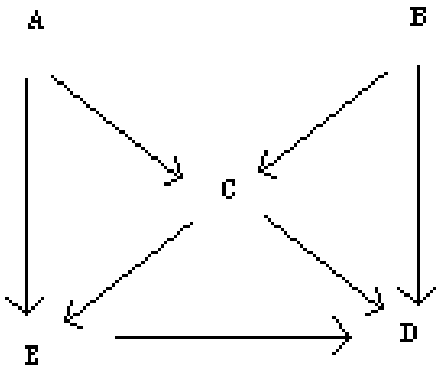

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- X is a parent of Y if there is a single headed arrow from X into Y: in such a case Y is called a child of X. Example: A and C are parents of E, whereas C and E are children of A.

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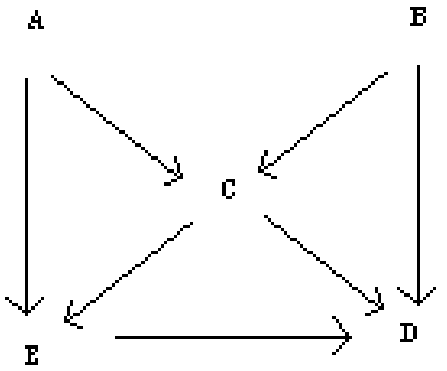

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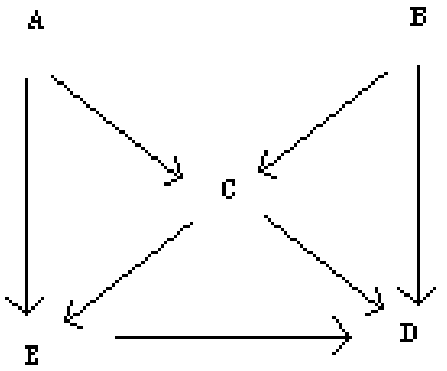

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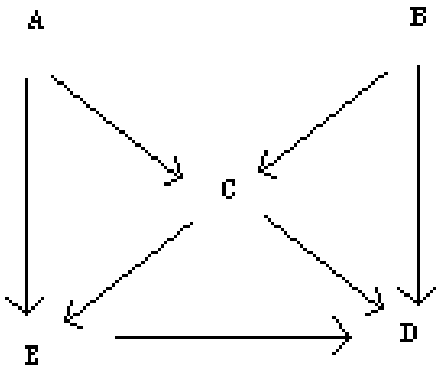

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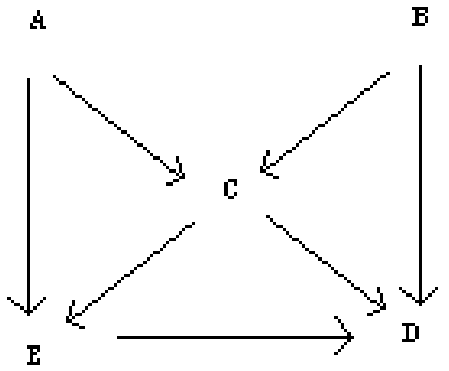

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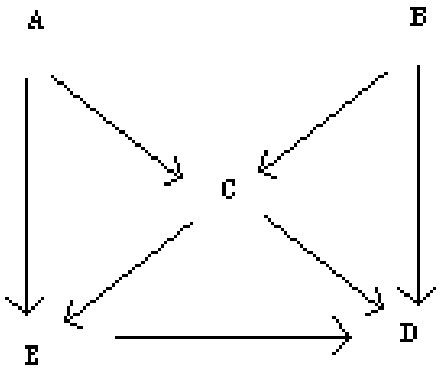

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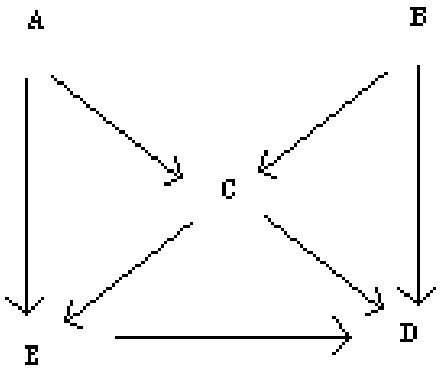

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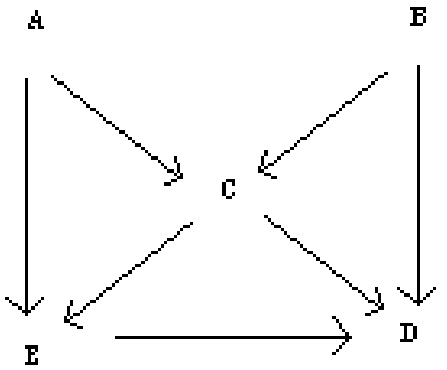

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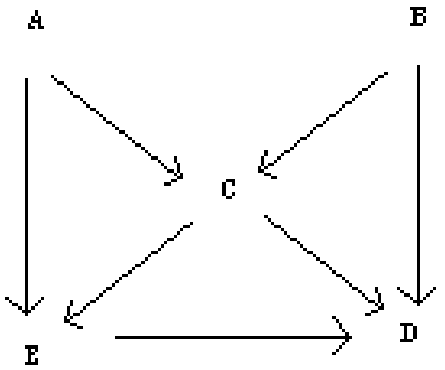

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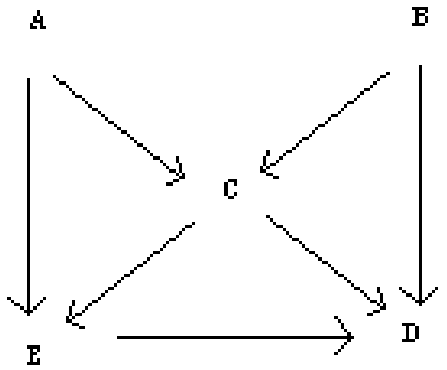

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- Graphs also encode 'associations' between variables: absence of an unblocked path between two variables $\Rightarrow$statistical independence variables. e.g: A and B are marginally independent. In other words,marginally associated covariates require the presence of an unblocked path on the graph.

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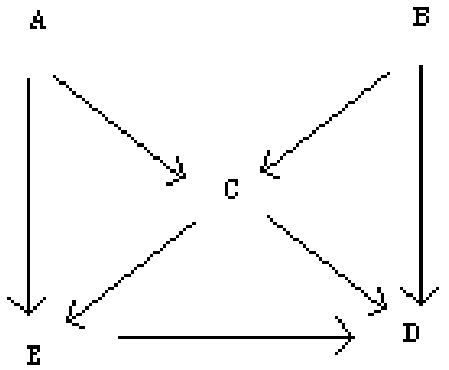

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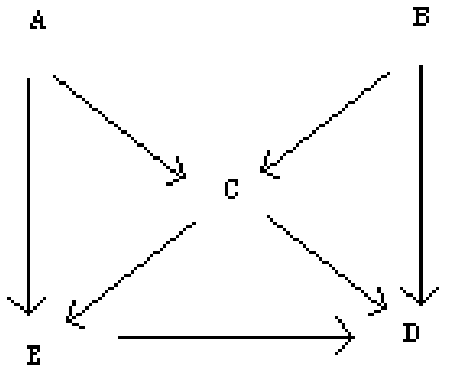

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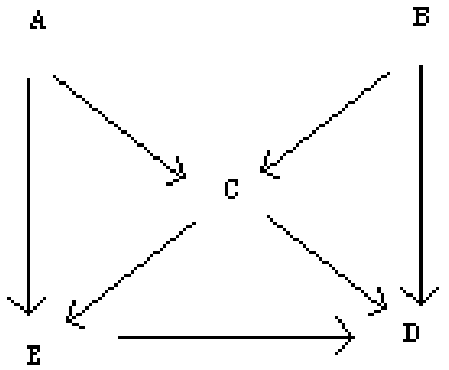

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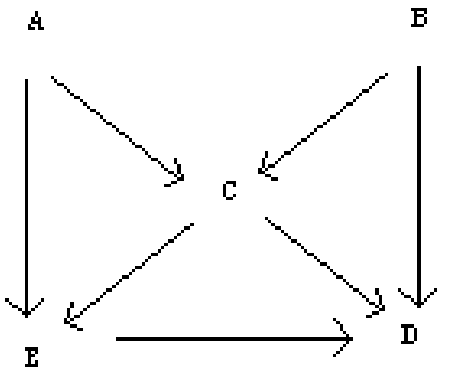

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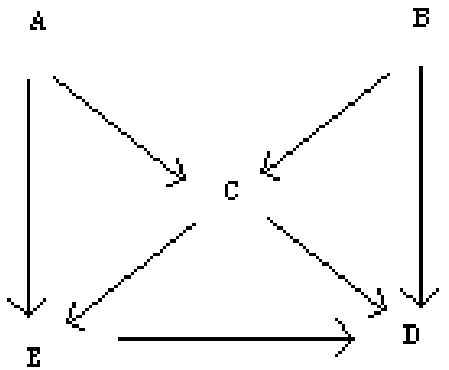

- Note that E-A-C-B-D is blocked at the collider C, but E-A-C-D and E-C-B-D are both unblocked backdoor paths.

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- For instance, the three backdoor paths between E and D could cancel out with the direct path to yield no marginal association between E and D.
- It should be clear that the presence or absence of blocked paths should not affect the association between variables. This is because the marginal association between two causes of an effect (ancestors of a collider) is fixed by the time both causes have occured; i.e. this association cannot be affected by consequences of these variables.

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- Counfounding is present if and only if exposure would remain associated with disease even if all exposure effects were removed, prevented or blocked.

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- Note that the effects of disease play no role in the above algorithm, since all paths from exposure to disease through descendants of disease must pass through a collider and are therefore blocked.

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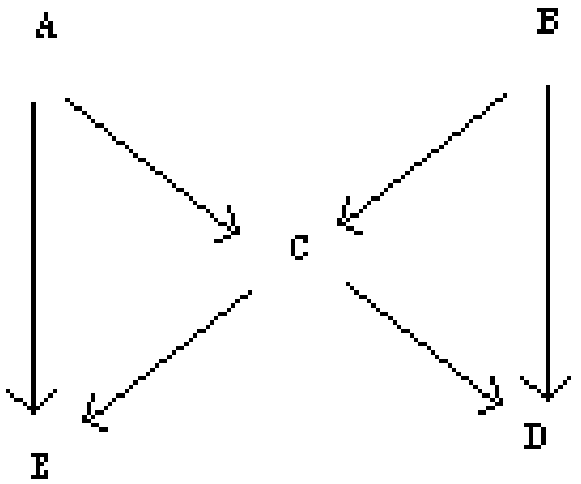
- Applying to our DAG, we see that A, C, and B are *potential confounders*



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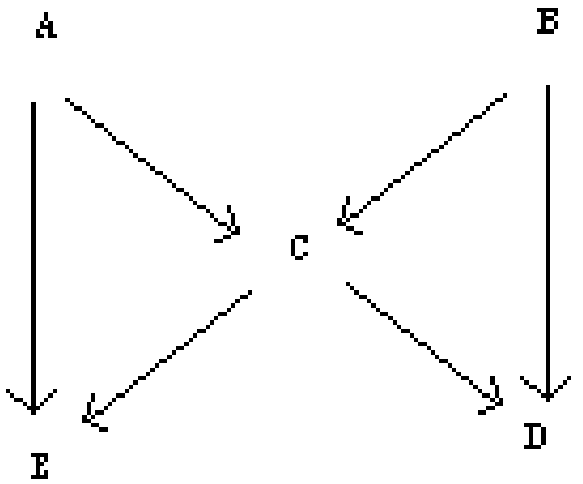

- The next natural question is whether and how one can control for confounding in assessing the effect of E on D.

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- With these criteria in mind, what is the smallest subset of variables from A,B and C that would be sufficient to control for confounding?

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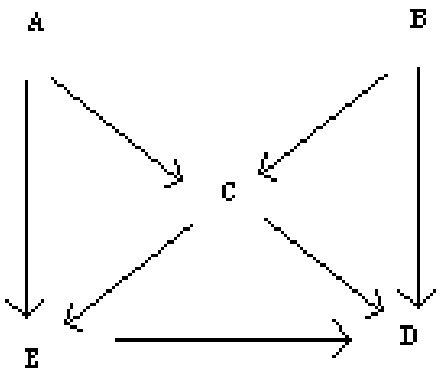

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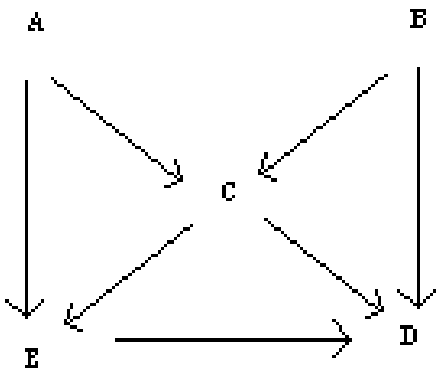

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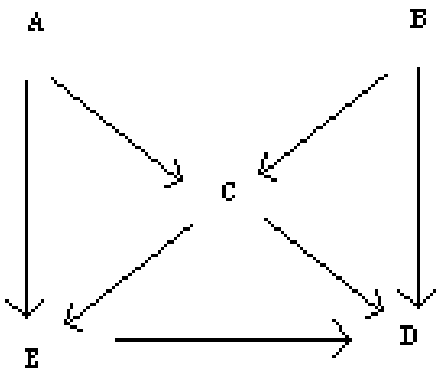

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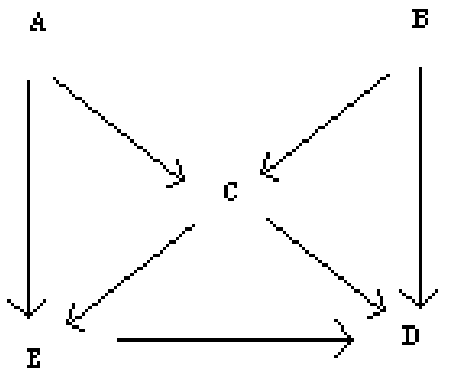

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  - Finally, conditioning on C alone seems promising as it blocks the path E-A-C-D, as well as the paths E-C-B-D and E-C-D. Thus standard logic would go as follows "... once we adjust for C, variables A and B would fail to satisfy one of the necessary conditions 2 and 3 required of confounders and therefore adjustment for C would control confounding by A and B as well as C".

DAGS and Confounding

- Is this right? Consider the following numerical example

	$A = 1$		$A = 0$	
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$C = 1$	800	600	400	200
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- We have
  $\Pr(A=1|B) = \Pr(A=1) = P(B=1|A) = P(B=1) = 0.5$. A, and B are marginally independent. Moreover, $P(C=1|A=1,B) - P(C=1|A=0,B) = .4$, and
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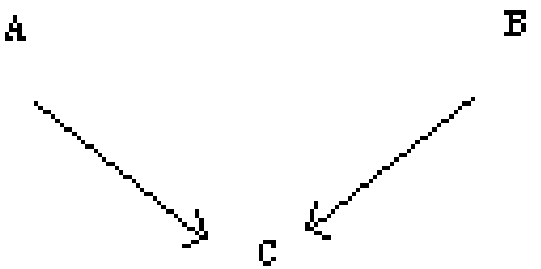

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  So that conditioning on C induces an association between A and B though they were marginally independent.
- This is an example of a general rule: If C is a common effect of A and B, then the association of A and B within levels of C will generally differ from the marginal association. This is a generalization of *Berkson's bias.*

DAGS and Confounding

- Returning to our original DAG, applying this rule tells us that conditioning on C can create an unblocked back door path from E to D: the association of A and B within levels of C can create an association of A and D indirectly, through B.

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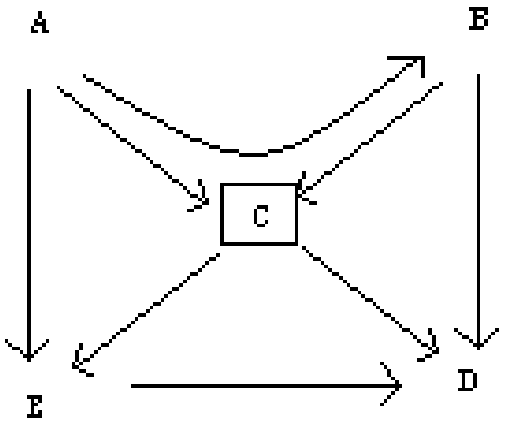

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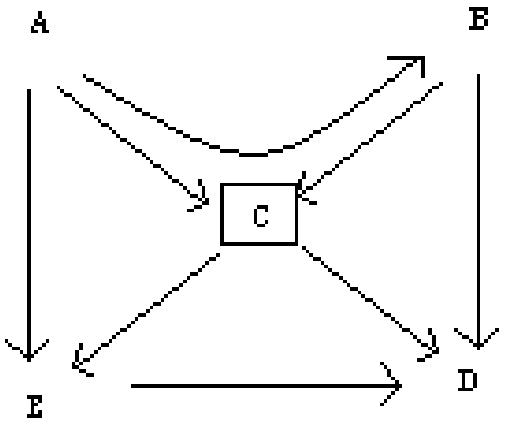

- However, conditioning on either A and C or B and C is sufficient. Why???

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- Returning to our original DAG, applying this rule tells us that conditioning on C can create an unblocked back door path from E to D: the association of A and B within levels of C can create an association of A and D indirectly, through B.
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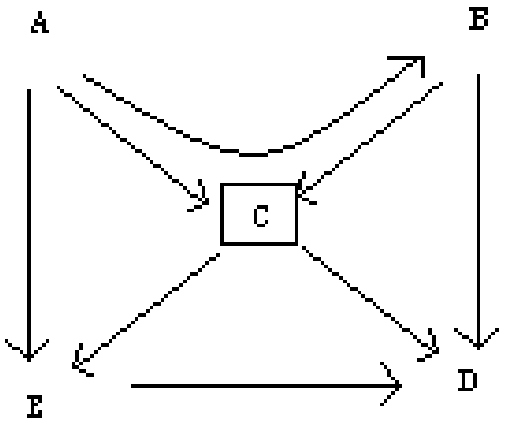
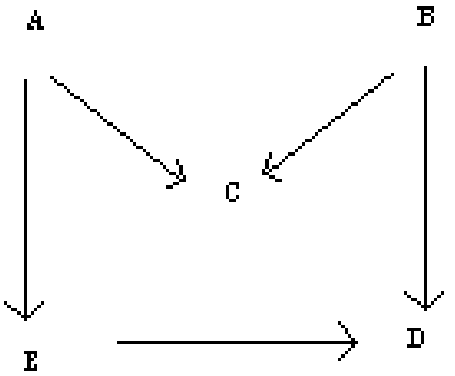


- However, conditioning on either A and C or B and C is sufficient. Why???
- Moreover, this illustrates that the popular criteria used to assess confounders is necessary but not sufficient.

DAGS and Confounding

- Another example where things can go terribly wrong:



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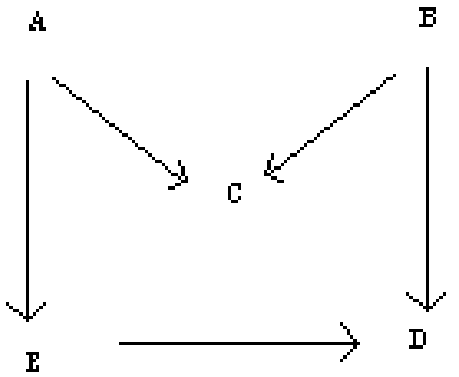

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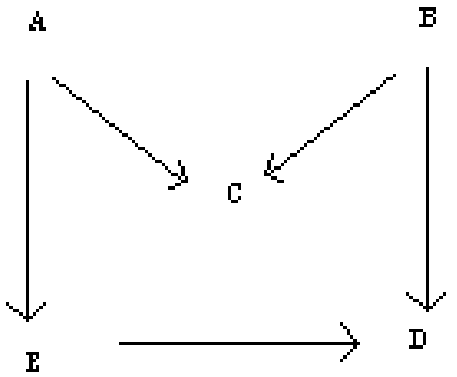

- Clearly there's no confounding according to the causal DAG given above;as the only backdoor path E-A-C-B-D is blocked by C. However, conventional wisdom will find that C is associated with E and associated with D given E, making it a potential confounder to adjust.
- In this DAG, conditioning on the collider C leads to confounding; worse if neither A nor B are observed as this would lead to untractable confounding.

DAGS and Confounding

- Take home message: statistical criteria are insufficient to characterize confounding, we need to first write down our causal DAG (explicit prior belief), from which we can decide which if any variables need to be conditioned on to control for confounding by using an "appropriate set of graphical rules".

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  - It is a rule to decide whether two variables are either *d-separated* (independent) , or *d-connected* (associated)
  - If two variables are d-separated without conditioning on other variables, then they are marginally independent; if they are d-separated only after conditioning on a set of third variables S, they are conditionally independent given S.

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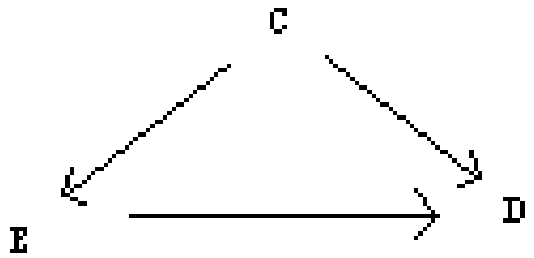
  - Does this work? Certainly in the asthma study, back door criterion gives S={A,C} or S={B,C}.

DAGS and Confounding

- Lets consider the following DAGs.

1)



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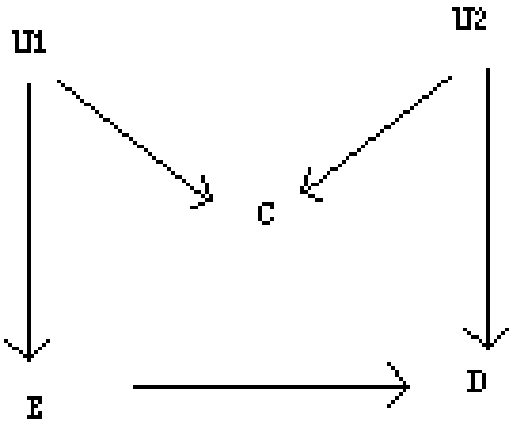

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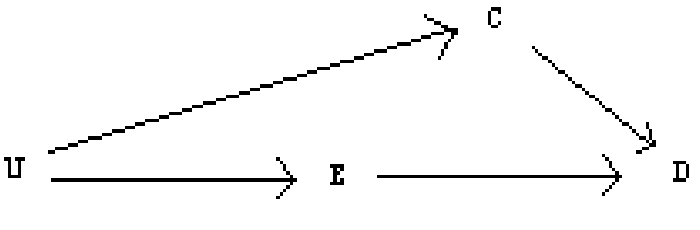

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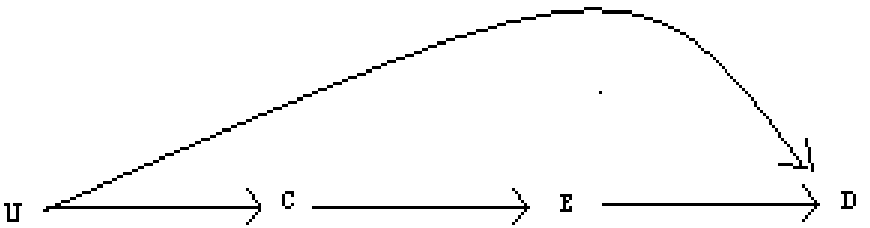

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- Suppose U variables were not collected by the investigator, using the backdoor criterion, is the effect of E on D identifiable in all DAGs?

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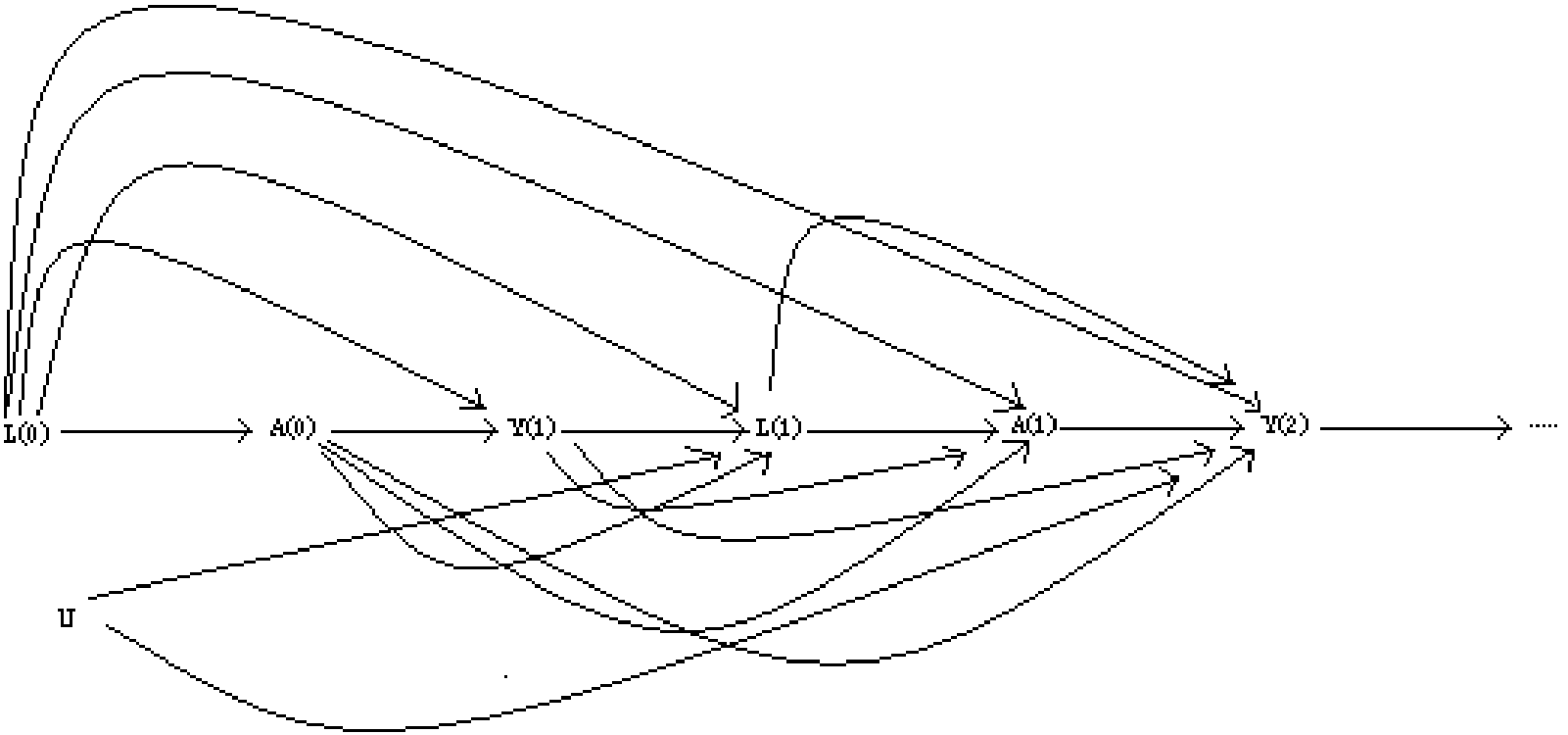

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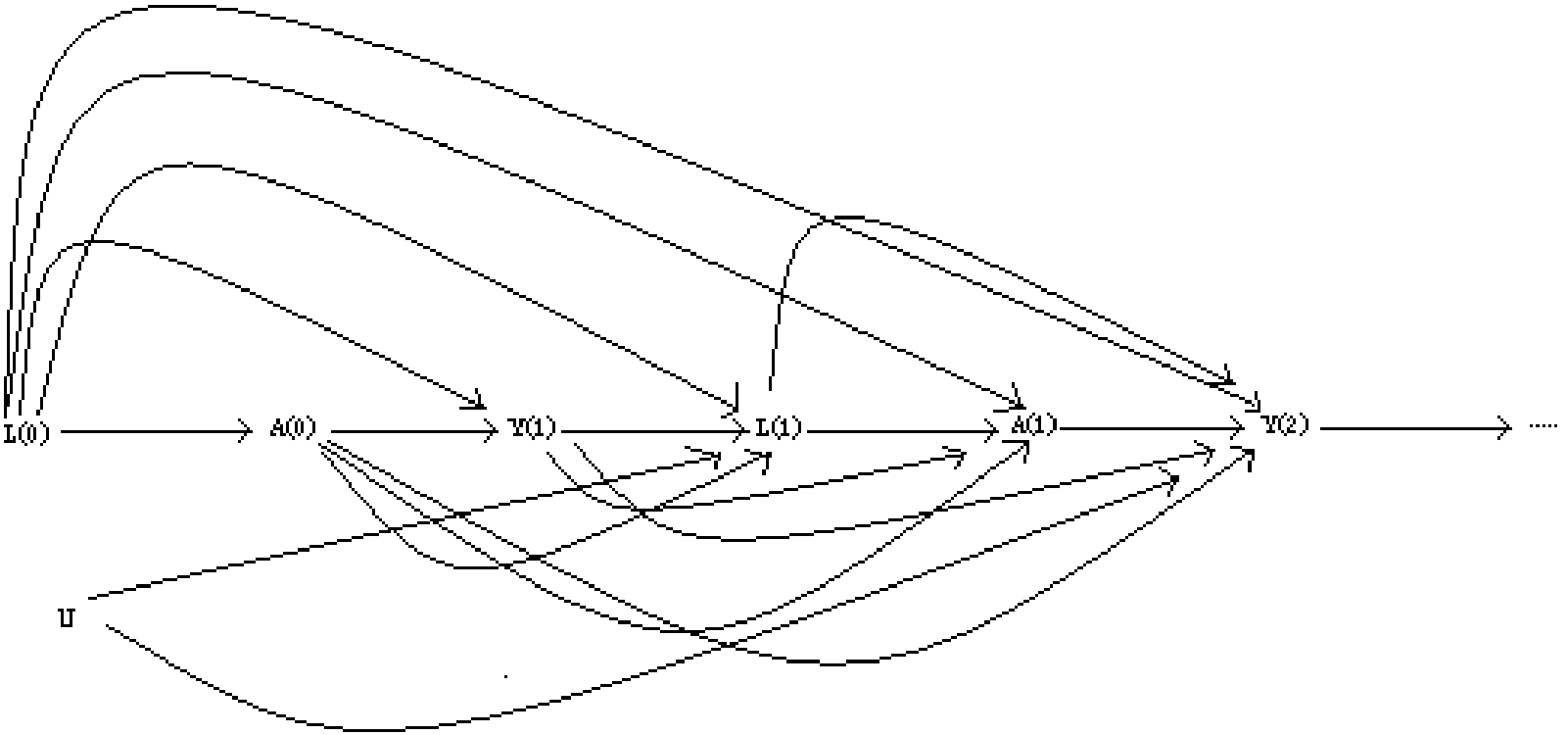

- U is an unmeasured common cause of some components of $L(1)$ and $Y(2)$.

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- A standard way to check whether say $A(0)$ and $A(1)$ has a direct effect on $Y(2)$ controlling for confounding is to use a regression model of the form:

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- Here we assume that model misspecification is absent.

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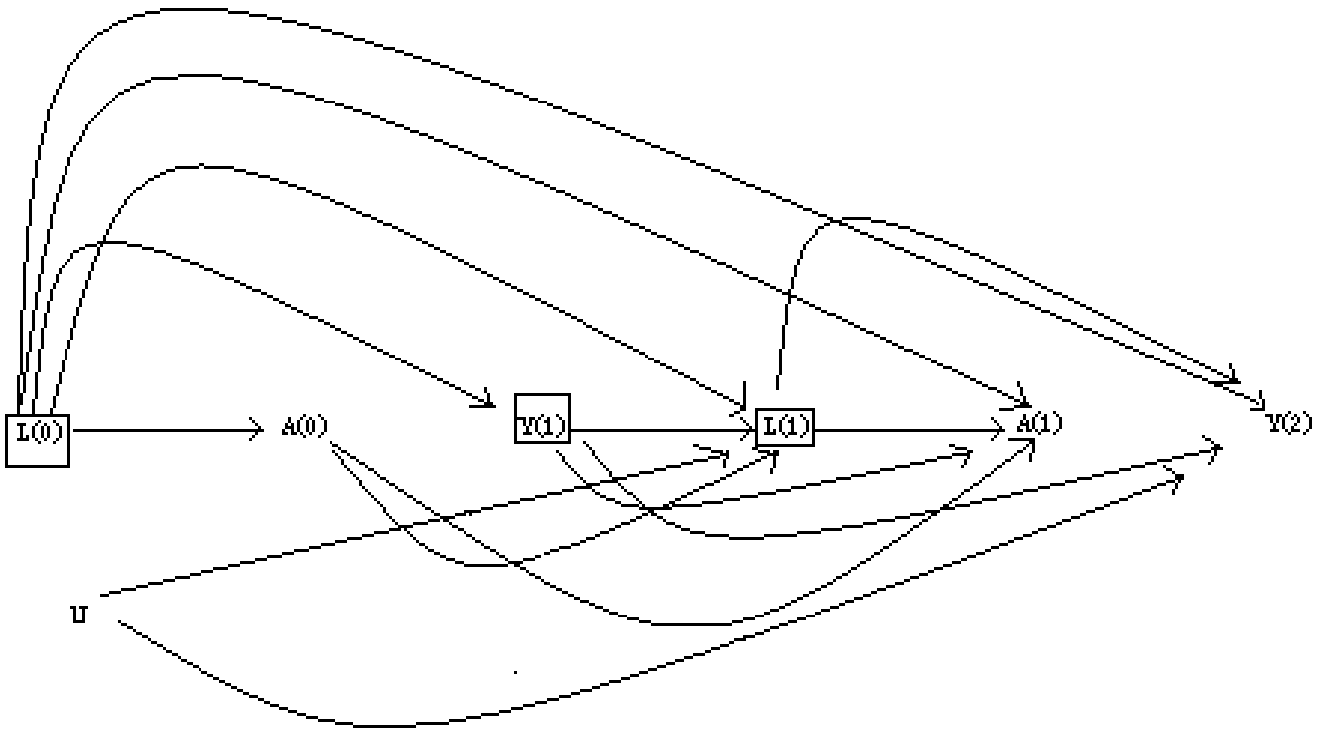

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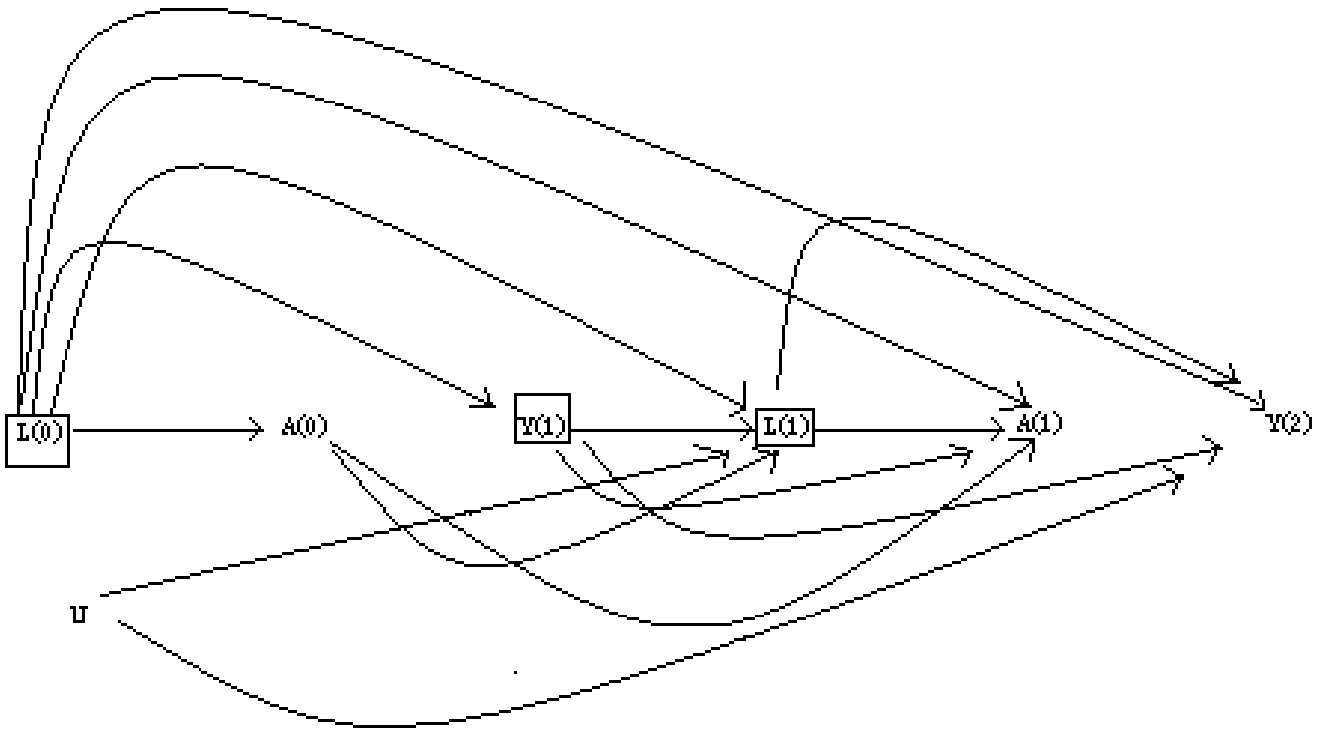

- Where as consistent with the causal null, we have dropped the directed arrows:$A(0) \rightarrow Y(1), A(0) \rightarrow Y(2), A(1) \rightarrow Y(2)$ and so on ...

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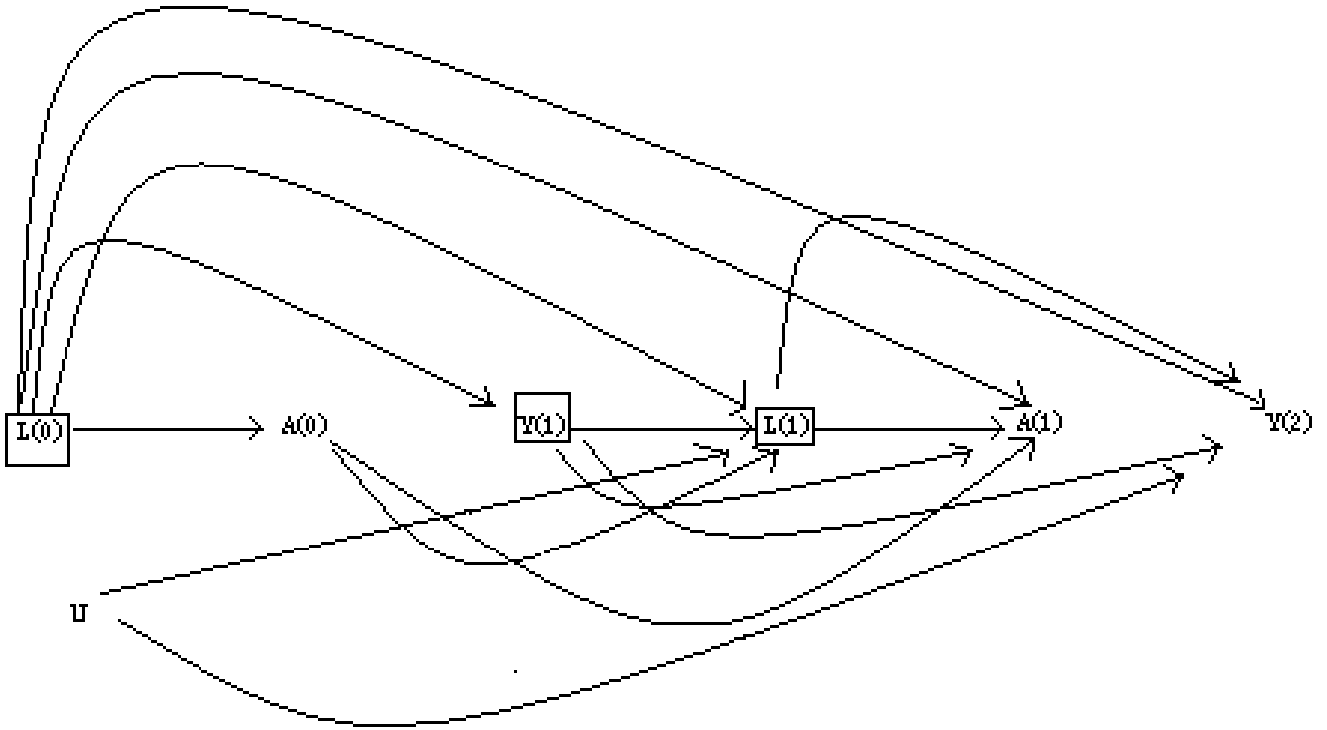

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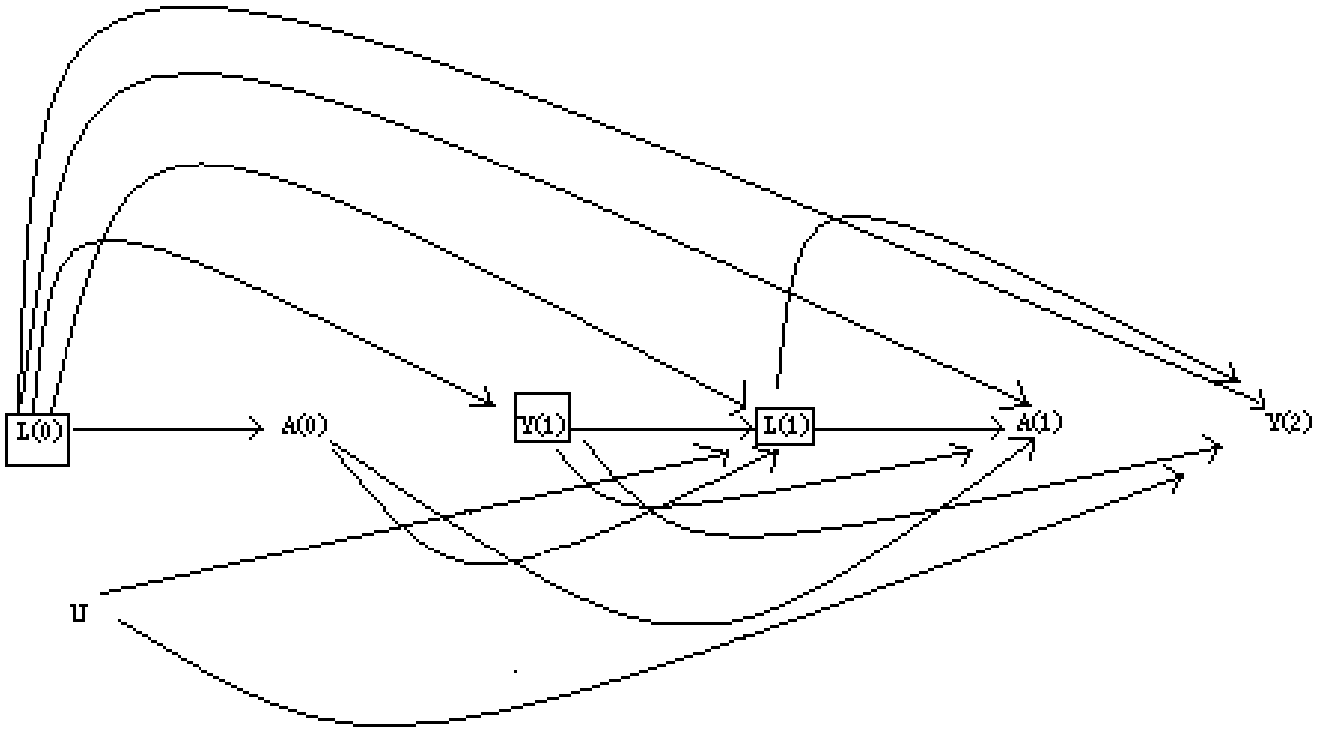

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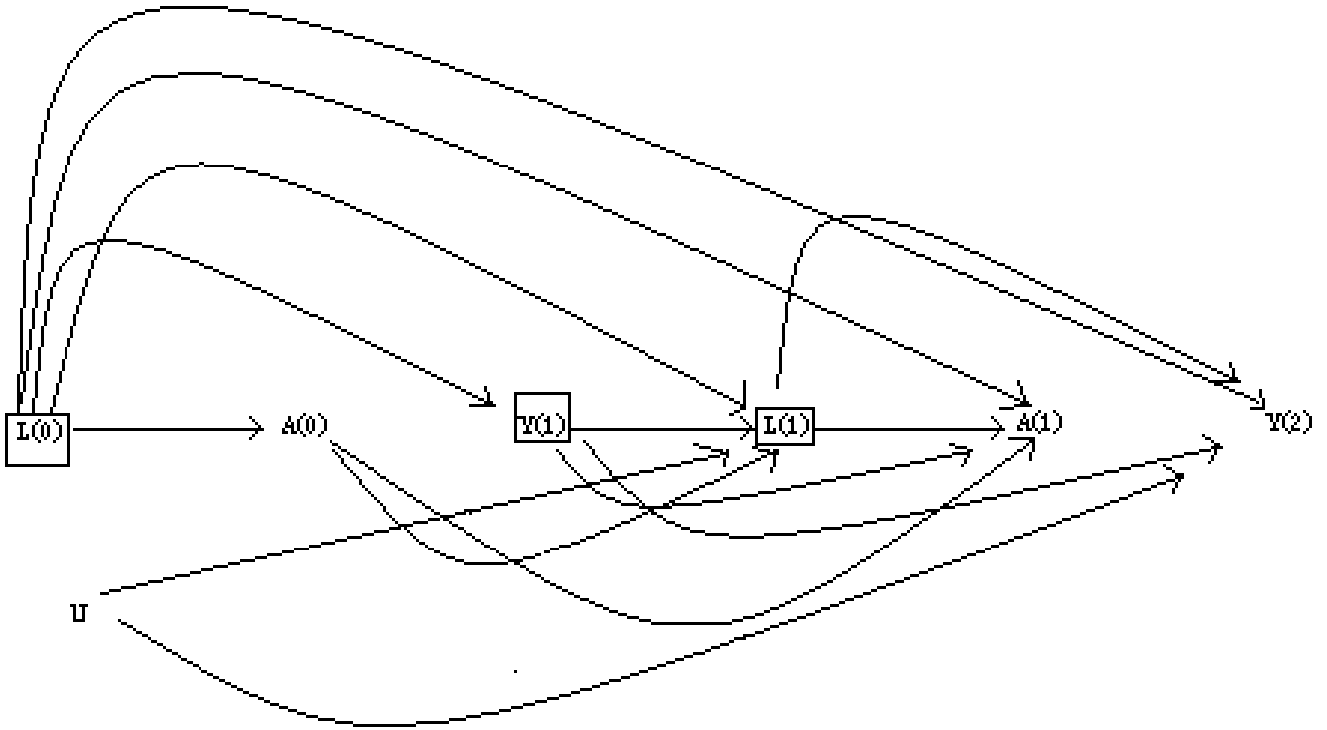

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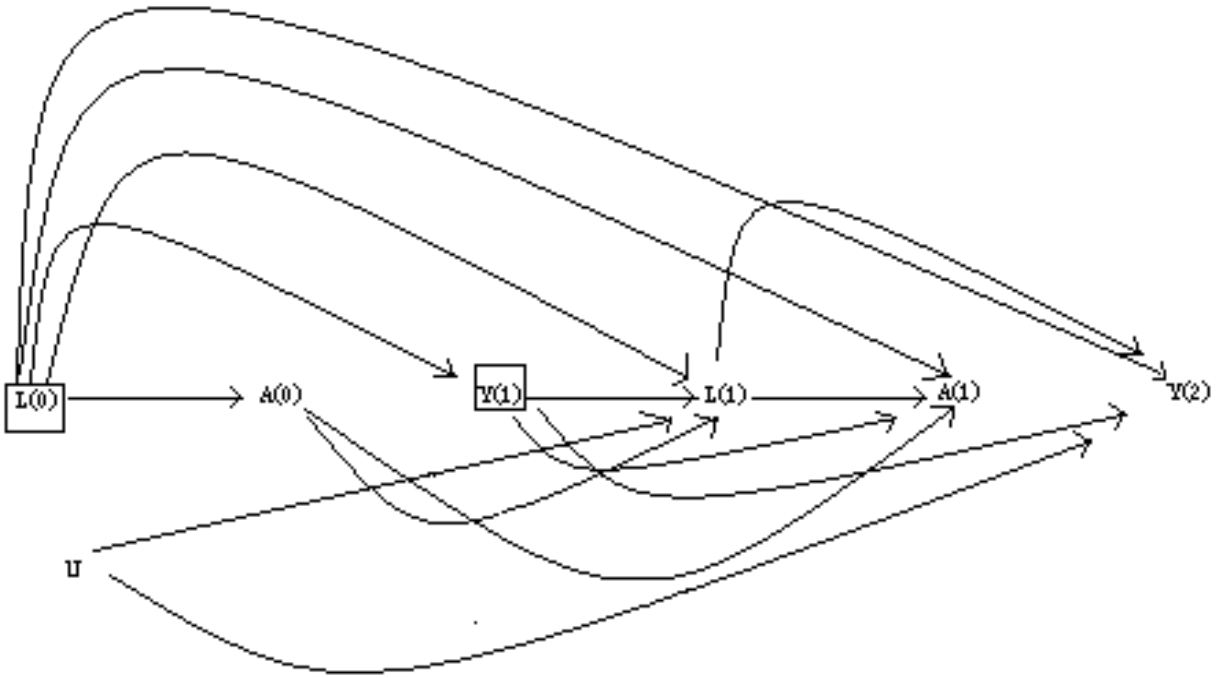

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- A new approach is needed.

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- e.g. $E\left(Y_{1,1}(2)\right) - E\left(Y_{0,0}(2)\right)$ is the causal difference in the mean CD4 count when on HAART at occasions 1 & 2 versus never receiving HAART.

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- This assumption essentially says that at $A(0)$ is randomized within levels of $L(0)$ and $A(1)$ is randomized within the joint levels of $A(0), L(0), Y(1), L(1)$.

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- The g-formula of Robins states that under these assumptions:

$$\begin{aligned} & E\left(Y_{a_0,a_1}(2)\right) \\ = \; & g\left(a_0, a_1\right) \\ = \; & \iiint E\left(Y|A(0)=a_0, A(1)=a_1, Y(1)=y_1, L_1=l_1, L_0=l_0\right) \\ & \times f_{L_1,Y(1)|A(0),L_0}\left(l_1, Y(1)=y_1|A(0)=a_0, L_0=l_0\right) \\ & \times f_{L_0}\left(l_0\right) dl_0 dY(1) dl_1 \end{aligned}$$

- Proof:

$$
\begin{aligned}
& E\left(Y_{a_0,a_1}(2)\right) \\
= & \int E\left(Y_{a_0,a_1}(2)|L_0=l_0\right) f_{L_0}\left(l_0\right) dl_0 \\
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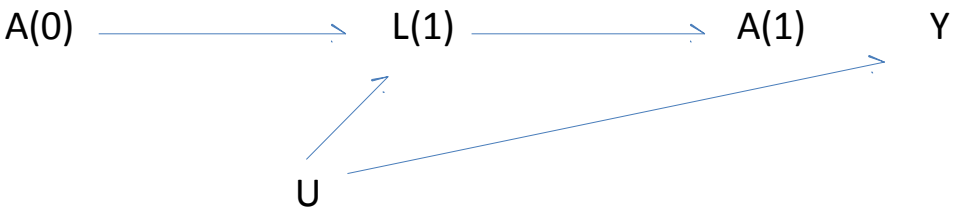
- It will generally be difficult to specify models for these quantities,such that the g-formula is not mis-specified.
- The main issue is that under standard parametrization, there is no parameter to encode the null hypothesis of no joint effect of (a_0, a_1).

Null Paradox

- For instance, consider the causal graph



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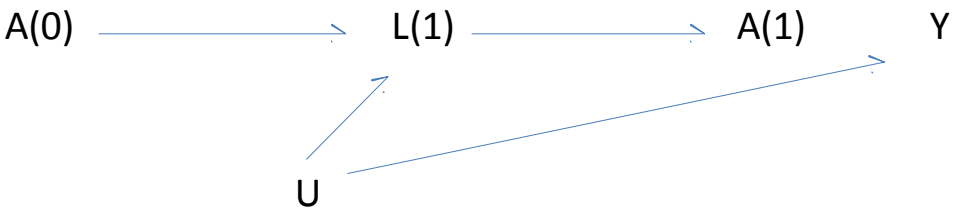

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- Suppose that $L(1)$ is binary and Y is continuous, so that the g-formula in this graph gives $E\left(Y_{a_0,a_1}\right) = \sum_{l_1=0}^{1} E\left(Y|A(0) = a_0, L(1) = l_1\right) \times f_{L(1)|A(0)}\ \left(l_1|A\left(0\right) = a_0\right) dl_1$

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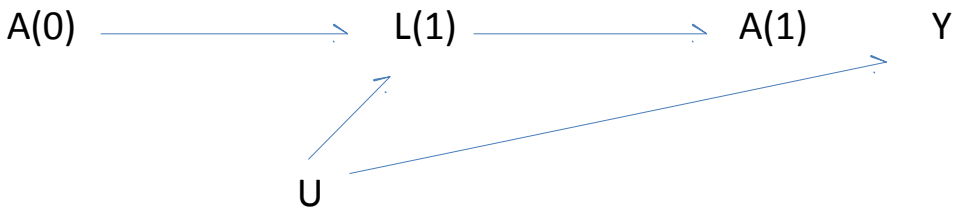

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- A standard modeling approach would fit a linear regression

$$E\left(Y|A_0 = a_0, A(1) = a_1, L(1) = l_1; \gamma\right) = \left(1, a_0, a_1, l_1\right)\gamma$$

  and a logistic regression

$$\text{logit}\,\Pr(L(1) = 1|A(0) = 0; \alpha) = (1, a_0)\alpha$$

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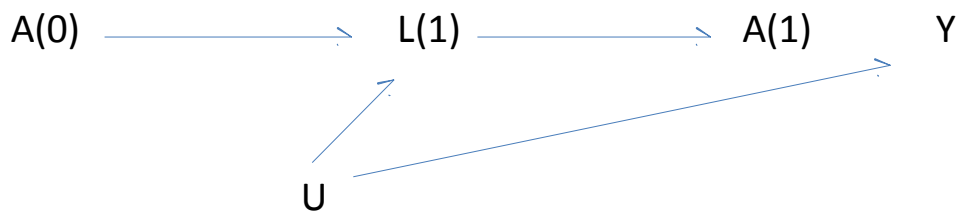

The estimated causal effect

$$\begin{aligned}
& \widehat{E}\left(Y_{a_0,a_1}\right) \\
= & \sum_{l_1=0}^{1}\left[E\left(Y|A(0)=a_0, A(1)=a_1, L(1)=l_1;\widehat{\gamma}\right)\right. \\
& \left.\times f_{L(1)|A(0)}\ \left(l_1|A\left(0\right)=a_0;\widehat{\alpha}\right)\right] \\
= & \left(1, a_0,\ \ a_1, \frac{\exp\left((1,a_0)\widehat{\alpha}\right)}{1+\exp\left((1,a_0)\widehat{\alpha}\right)}\right)\widehat{\gamma}
\end{aligned}$$

therefore $\widehat{E}\left(Y_{a_0,a_1}\right) \xrightarrow{P} E\left(Y_{a_0,a_1}\right)$ does not depend on $\left(a_0, a_1\right)$ if either $\gamma_1 = \gamma_2 = \gamma_3 = 0$ or $\gamma_1 = \gamma_2 = \alpha_2 = 0$

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- We need other kinds of models

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$$E\left(Y_{a_0,a_1}(2);\psi\right)$$

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- So that $E\left(Y_{a_0,a_1}(2);\psi\right) = E\left(Y_{0,0}(2);\psi\right) \Leftrightarrow \psi_1 = \psi_2 = 0$

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  - For each person in the study, compute the weight $W = f\left(A_0|L_0;\widehat{\alpha}_0\right) f\left(A_1|L_1, A_0, L_0, Y\left(1\right);\widehat{\alpha}_1\right)$ which corresponds to the estimated probability of receiving the treatment you did indeed receive.

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  - Regress $Y(2)$ on A_0 and A_1 using weighted least-squares (WLS) with weights W^{-1}, $\widehat{\psi}$ is the iptw estimate of ψ.

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- It is advisable to stabilize the weights by using $SW = \frac{f(A_0|L_0;\widehat{\alpha}_0)f(A_1|L_1,A_0,L_0,Y(1);\widehat{\alpha}_1)}{f(A_0|\widehat{\rho}_0)f(A_1|A_0;\widehat{\rho}_1)}$ instead of W, where $f\left(A_0|\widehat{\rho}_0\right)$ and $f\left(A_1|A_0;\widehat{\rho}_1\right)$ are estimated using finite dimensional logistic regression models.

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- dr estimation methods also available to partially protect against misspecified weights