

Direct and Indirect Effects

Give 4 examples:

Example 1: hormone replacement therapy and breast cancer

HRT may lead to increased BC screening

BC screening may lead to increased BC diagnosis

BC diagnosis associated with increased BC mortality

concern is that screening may distort “true” or biological effect of HRT

characterize relations among variables (sketch DAG)

what are causal parameters of interest?

Example 2:

Randomized trial of AZT/ZDV; drug to slow progression of HIV disease

subjects receiving high-dose AZT less likely to receive prophylaxis for
Pneumocystis Carinii pneumonia (PCP)

while trial being run, guidelines changed; PCP prophylaxis more uniformly
recommended

characterize relations

what causal questions are of interest?

Example 3:

Look at effect of oral hypoglycemic drugs on BP on outcomes (e.g., MI, mortality) in people with type II diabetes mellitus (DM)

oral hypoglycemics lead to lower blood sugar levels, lower hemoglobin A1C, etc.

lower blood sugar levels associated with lower mortality, etc.

ran randomized trial; placebo group had lower mortality

characterize relations among variables

what are causal parameters of interest?

Example 4:

Effect of speed limits on roads on traffic mortality

Higher speeds associated with increased mortality

Interstate highways nonetheless relatively safe; associated with lower mortality

To many people's surprise, raising speed limit did not result in increase in traffic mortality

Why?

Give possible explanation

characterize relations among variables

what are causal parameters of interest?

Contrast first 2 and last 2 settings

First 2 settings: interest is in direct effect of treatment, controlling (in physical sense) for second variable

Last 2 settings: practical interest is in overall effect of treatment

secondary variable used for explanation of overall effect

expand potential outcomes notation to represent joint effect of 2 variables (A and S)

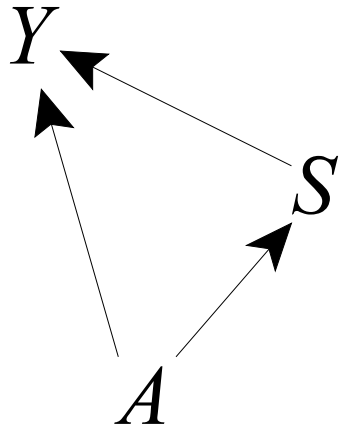
$Y^{a,s}$ outcome one would see if received level a of A and level s of S

Define direct effect of A controlling for S (for an individual)

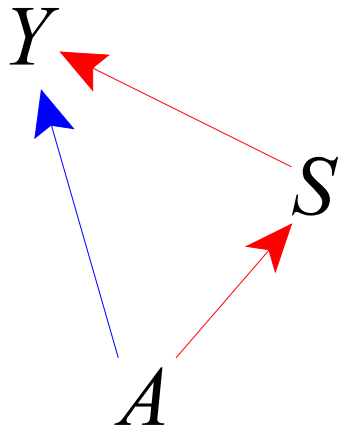
First loosely, using graph

Then more formally, using potential outcomes

intuition in nomenclature derives from graph



what is direct, indirect, overall effect?



blue: direct

red: indirect

define effects using potential outcomes

comparison of $Y^{a1,s}$, $Y^{a0,s}$

can have different direct effect of treatment at any level s of S (for same person)

interaction at individual level (may translate into interaction at population level)

here, both a and s potentially manipulable

interested in what would happen if manipulated in different ways

how do you choose reference level of S ?

2 types of direct effects (based on answers to this question):

manipulated direct effect: set S to common level s

- effect of HRT if always (never) screened
- effect of AZT if always (never) give PCP prophylaxis

natural direct effect: comparison of $Y^{a1,S^{a1}}$, $Y^{a0,S^{a1}}$

- effect of HRT if screening held to level it would assume if subject received (did not receive) HRT
- effect of AZT if PCP prophylaxis assumed level it would if subject received (did not receive) AZT

must choose reference level of main exposure to define natural effect

manipulated effect: effect of clear policy

natural effect: more explanatory in flavor

consider alternative worlds closer to observed one

define indirect effects using potential outcomes

need to use idea of natural effects

contrast of $Y^{a0,S^{a1}}$, $Y^{a0,s^{a0}} = Y^{a0,S}$ (alternative: $Y^{a1,S^{a1}}$, $Y^{a1,s^{a0}}$)

2 possible reference levels of treatment:

here, $a0$ is reference level

interpret for case of HRT:

effect of withholding HRT, allowing screening to assume level it would have assumed had subject been given HRT (compared to withholding HRT)

again, useful in considering mechanism

total effects = natural direct effects + natural indirect effects (when defined with same reference level of main treatment a)

can use this idea to characterize/define controlled indirect effect even though not defined “directly” in terms of contrast of two potential outcomes

can define effects for population or subset thereof:

e.g., $E(Y^{a1,s}|\cdot) - E(Y^{a0,s}|\cdot)$

estimation of manipulated effects:

For nonparametric identification of controlled effects, need variables which make both A and S ignorable (not necessarily same variable)

$$A \perp Y^{a,s} | X$$

$$S \perp Y^{a,s} | X, A, L$$

Need additional assumptions to identify natural effects

If L affected by A , will need methods covered in later unit

If $\{A, S\} \perp Y^{a,s} | X$, can identify $E(Y^{a,s} | X) = E(Y | X, A = a, S = s)$, etc.

Can direct effects be defined without reference to specific third variable S ?

No

Always many sorts of pathways, intermediate stages from exposure/treatment to outcome

Language implicitly assumes that direct, indirect effects defined with respect to third variable

Alternative definition of direct effects:

comparison of $Y^{a1,s}, Y^{a0,s}$ for subjects for whom $S=s$ no matter what treatment they receive (i.e., subjects for whom $S^{a1}=S^{a0}=s$)

e.g., $E(Y^{a1,s}|S^{a1}=S^{a0}=s) - E(Y^{a0,s}|S^{a1}=S^{a0}=s)$

descriptive, possibly explanatory definition

not prescriptive

effect of HRT for subjects whose screening not affected by HRT

looking at effect for subset of subjects

what is possible problem with approach in terms of definition?

Continuous variables, multivariate S

subset with $S^{a1}=S^{a0}=s$ vanishingly small

essentially defining direct effect away

approach interferes with thinking about mechanism of action of a treatment A

approach known as principal stratification