Randomized Experiments with Noncompliance

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Introduction

- "Noncompliance" is an important problem in randomized experiments involving humans

- Includes e.g. switching subjects to standard therapy when experimental therapy fails

- "Intent-to-treat" (ITT) is a standard approach and is endorsed by FDA, journals, etc.

- Analyzes the data "as-randomized"

ITT

"Analyses that include all randomized patients in the groups to which they were randomly assigned, regardless of their compliance with the entry criteria, regardless of the treatment they actually received, and regardless of subsequent withdrawal from treatment or deviation from the protocol."

Workgroup for the Biopharmaceutical Section of the American Statistical Association

ITT

- Simple
- Encourages complete follow-up
- Estimates “use-effectiveness”? (Many protocol deviations mirror events that would happen in normal medical practice? Protease inhibitors?)
- Conservative (but not for equivalence studies)

CPCRA Oral Ganciclovir Study

- ~40% of AIDS patients get CMV retinitis
- Ganciclovir is the standard treatment (1994)
- Oral ganciclovir as a prophylactic intervention for CMV retinitis in HIV/AIDS
- NIH-funded, double-blind, placebo-controlled randomized study, n=994
- September, 1995, *The Lancet*

Title: *ORAL GANCICLOVIR FAILS TO PREVENT CMV IN HIV TRIAL* , By: McCarthy, Michael, Lancet, 00995355, 9/30/95, Vol. 346, Issue 8979

Database: *Academic Search Premier*

Section: NEWS

ORAL *GANCICLOVIR* FAILS TO PREVENT CMV IN HIV TRIAL

Oral ***ganciclovir*** has failed to prevent symptomatic cytomegalovirus (CMV) infections in a double-blind, placebo-controlled trial involving 994 patients with advanced HIV infection. The results of this US National Institute of Allergy and Infectious Diseases' Community Programs for Clinical Research on AIDS (CPCRA) study seems to contradict those of a similar trial indicating that oral ***ganciclovir*** significantly reduces CMV disease in HIV-infected patients. That study, conducted by the drug's manufacturer Syntex Research (now Roche Bio-science), was halted in 1994, after an interim analysis found that only 16% had developed CMV disease, compared with 30% in the placebo group.

In the CPCRA (protocol 023) study 662 volunteers were assigned to a treatment group and 332 to a placebo. Participants had to have CD4 cell counts of 100 or fewer per uL of blood, evidence of CMV infection (by serology or culture) but no CMV disease. Patients in the treatment group took 3 g ***ganciclovir*** daily. The primary endpoint of the trial was symptomatic CMV disease, defined as CMV retinal disease, diagnosed by ophthalmological examination, or CMV gastrointestinal mucosal disease, diagnosed on biopsy or on necropsy. Average follow-up was 15 months.

"Oral ***ganciclovir*** did not prevent symptomatic CMV disease to a clinically or statistically significant degree", the NIAID concluded in its Sept 18 announcement. Also, oral ***ganciclovir*** caused significantly more adverse effects than did placebo.

CPCRA Oral Ganciclovir Study (cont.)

- "Syntex" study completed in early 1995 showed 49% reduction in CMV retinitis
- CPCRA study allowed placebo subjects to take oral ganciclovir
- Analysis was by ITT
- 2.1 months in placebo arm versus 9.3 months in the treatment arm

Naïve Alternatives to ITT

- "as-treated"
- "per-protocol"
- "censored method"
- "transition method"

Depending on the relationship between compliance and outcome, these can all be biased.

No simple solution to this complex problem!

Fictituous Study

- Randomized study comparing T and C
- Y_T or Y_C known for all subjects
- All C patients comply
- Some T patients revert to C early in the study due to toxicity
- T's toxicity is less tolerable to sicker patients

ITT

- Dilutes the T effect with patients who did not take T
- Downward bias in estimation of the T effect

"What are the expected outcomes for a typical patient instructed, in the course of a clinical trial, to take the treatment to which he/she was assigned?"

Per Protocol

- Estimates the T effect from a group stripped of poorer prognosis patients

- Upward bias in estimation of the T effect

"What are the differences between average T outcomes for patients who choose to adhere to recommended treatment T and outcomes for patients who choose to adhere to recommended treatment C?"

As-Treated

- Assigns the non-compliers to C
- Strips T of poor prognosis patients
- Upward bias in estimation of the T effect

"What are the differences between average outcomes for patients who take T as compared to those who take C, where the C group contains more patients with poor prognosis?"

Rubin Causal Model

$Y_i(j)$ = "health" outcome (e.g. survival) for subject *i* if assigned to treatment *j*, *j*=1,2

SUTVA

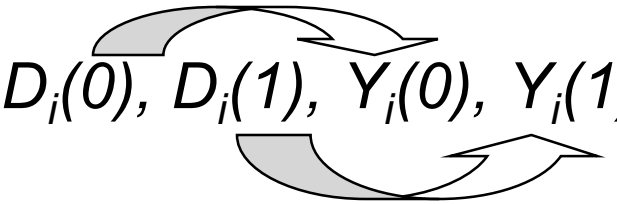
ITT causal effect of assignment for subject *i*
= $Y_i(1)$-$Y_i(0)$

Average ITT Causal Effect: $\Sigma(Y_i(1)-Y_i(0))/N$

"Fundamental Problem of Causal Inference"

Rubin Causal Model

$D_i(j)$ = "treatment" outcome for subject i if assigned to treatment j, j=1,2



Complier, if $D_i(0)=0$ and $D_i(1)=1$

Never-taker, if $D_i(0)=0$ and $D_i(1)=0$

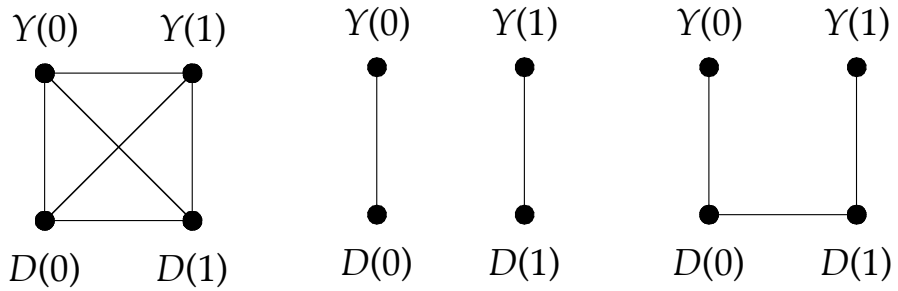
Always-taker, if $D_i(0)=1$ and $D_i(1)=1$

Defier, if $D_i(0)=1$ and $D_i(1)=0$

Rubin Causal Model

"Complier Average Causal Effect" (CACE)
= ave($Y_i(1)$-$Y_i(0)$ | $D_i(0)$=0 and $D_i(1)$=1)

For compliers, can attribute the effect on *Y* of assignment to treatment to the effect of receipt of treatment?



Common Assumptions

"(Weak) Exclusion Principle"

$Y_i(1) = Y_i(0)$ for all i such that $D_i(1) = D_i(0)$

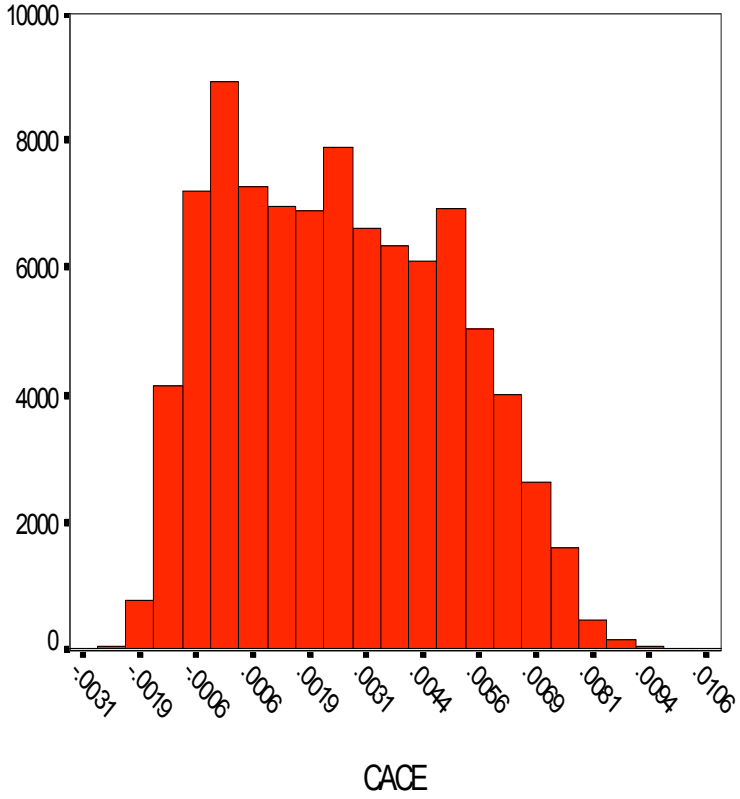
"Monotonicity"

$D_i(1) \geq D_i(0)$ for all i, with inequality for at least one subject.

Vitamin A Example

- Villages in Northern Sumatra
- Receive or not to receive vitamin supplements for a one-year period

Type	Assignment Z	Take Vitamin? D	Survival? Y	Number (Total=23,682)
Complier or Never-Taker	0	0	0	74
Complier or Never-Taker	0	0	1	11,514
Never-Taker	1	0	0	34
Never-Taker	1	0	1	2,385
Complier	1	1	0	12
Complier	1	1	1	9,663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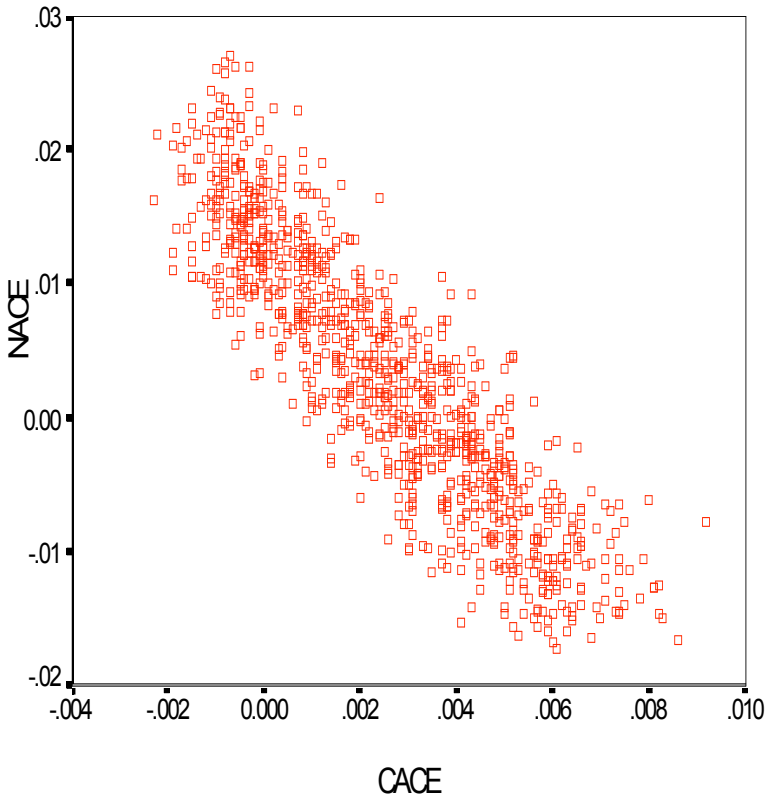
.0094
.0106
CACE


.03
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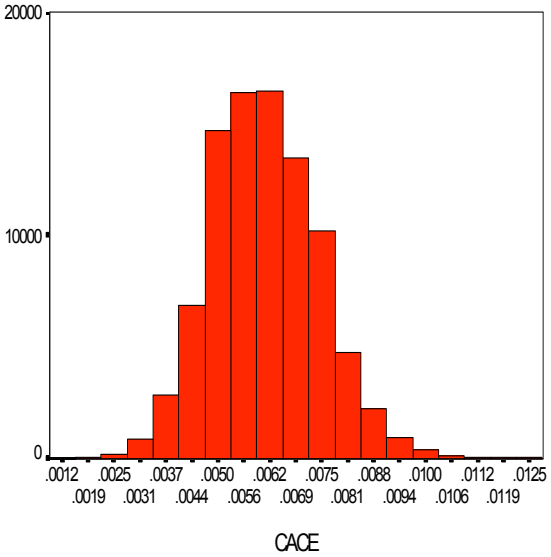
CACE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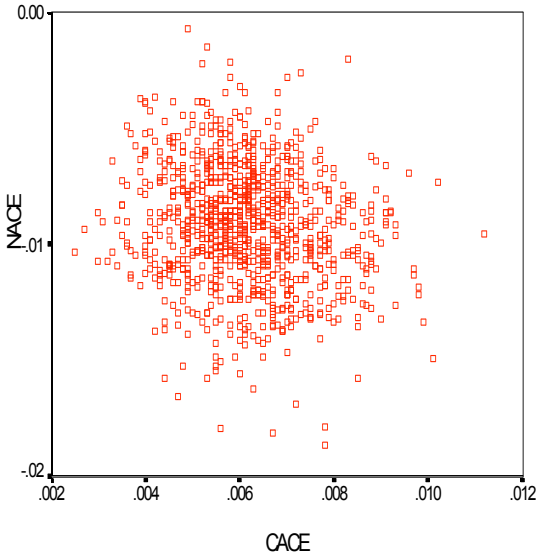
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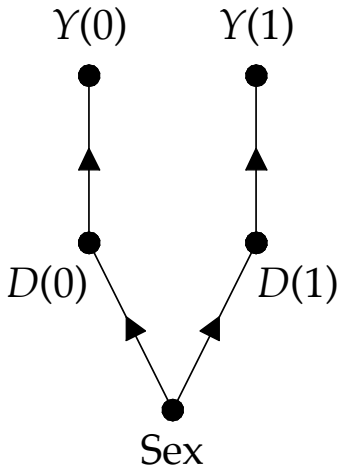
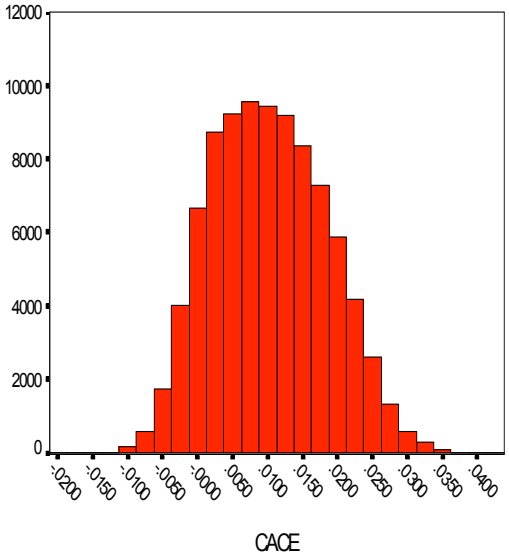
CACE


Y(0)
Y(1)
D(0)
D(1)
Sex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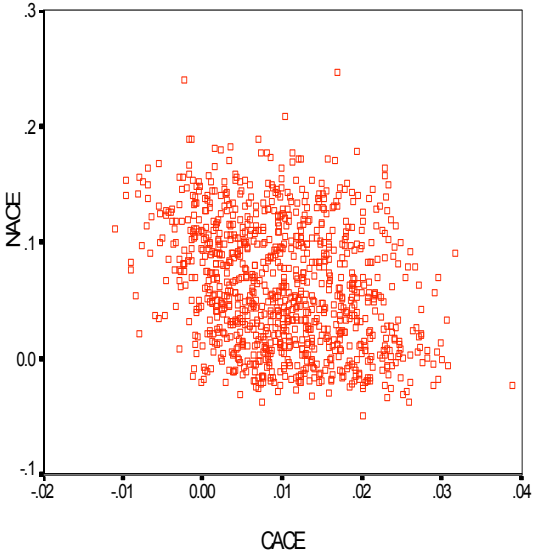
CACE


.3
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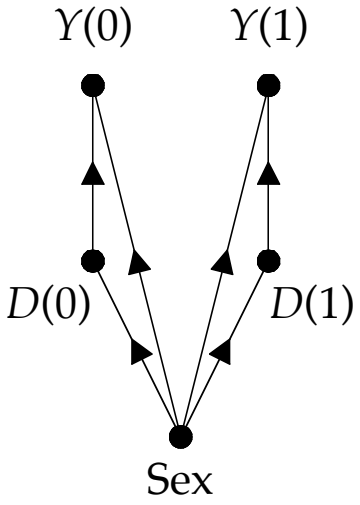
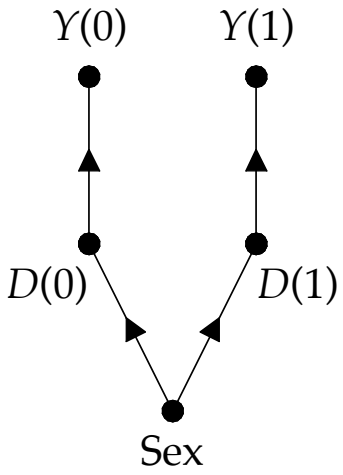

Y(0)
Y(1)
D(0)
D(1)
Sex



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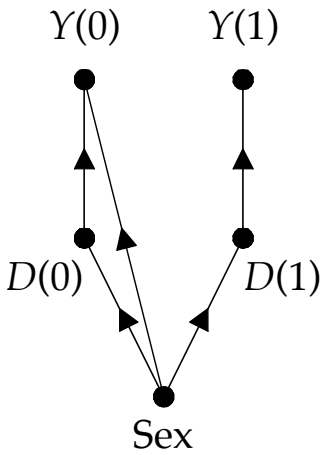

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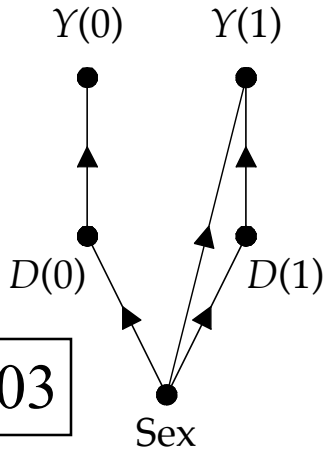

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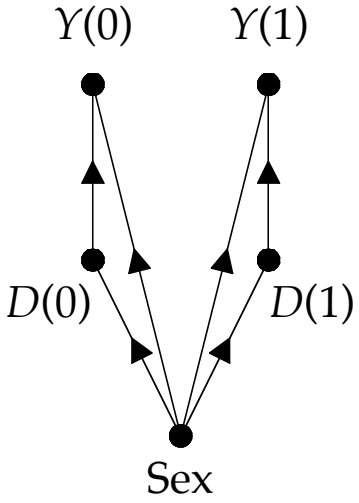

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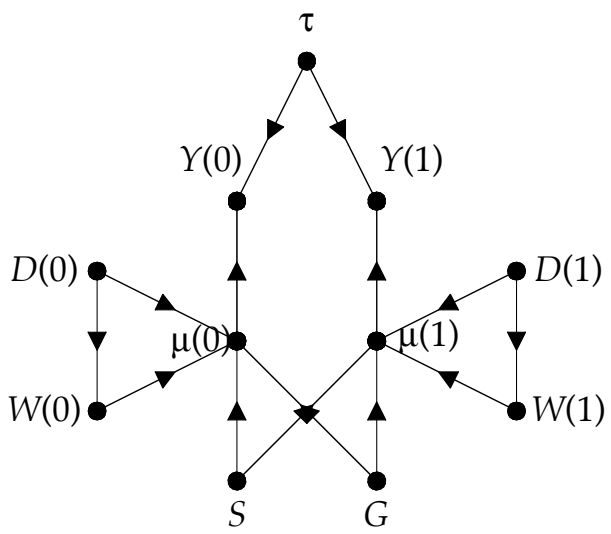
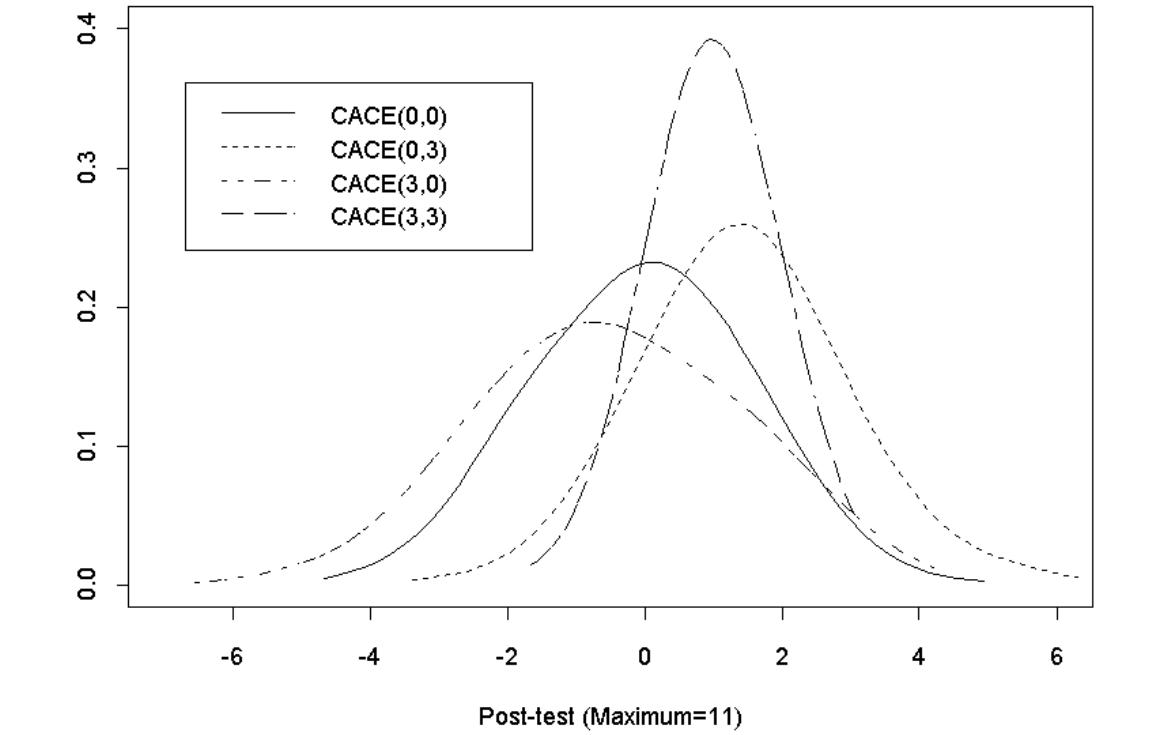
$$\frac{\Pr(M_1 \mid X^{obs})}{\Pr(M_0 \mid X^{obs})} = \int \frac{\Pr(M_1 \mid X^{obs}, X^{miss})}{\Pr(M_0 \mid X^{obs}, X^{miss})} \Pr(X^{miss} \mid X^{obs}, M_0) dX^{miss}$$

Educational Experiment

Variable Name	Possible Values	
Z_i	0,1	Random assignment
$D_i(j)$	0,1,2,3	Number of completed DIANA assignments, all students assigned to treatment j
$W_i(j)$	0,1,2,3	Number of completed Web assignments, all students assigned to treatment j
$Y_i(j)$	0-11	Score on the post-test, all students assigned to treatment j
G_i	Male, Female	Gender
S_i	8:30 or 12:30	Section


τ
Y(0)
Y(1)
D(0)
D(1)
μ(0)
μ(1)
W(0)
W(1)
S
G


CACE(0,0)
CACE(0,3)
CACE(3,0)
CACE(3,3)
0.0
0.1
0.2
0.3
0.4
-6
-4
-2
0
2
4
6
Post-test (Maximum=11)

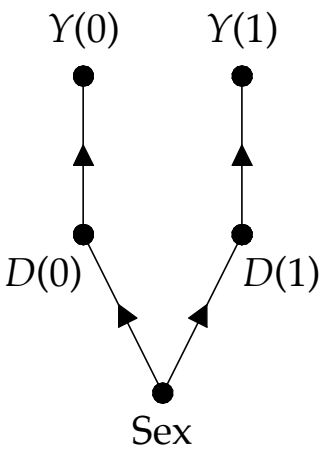
Causal Effect	No. of DIANA Assignments	No. of Web Assignments	Mean	SD
CACE(0,0)	0	0	-0.06	1.5
CACE(0,3)	0	3	+1.41	1.4
CACE(3,0)	3	0	-0.44	1.9
CACE(3,3)	3	3	+1.03	0.7

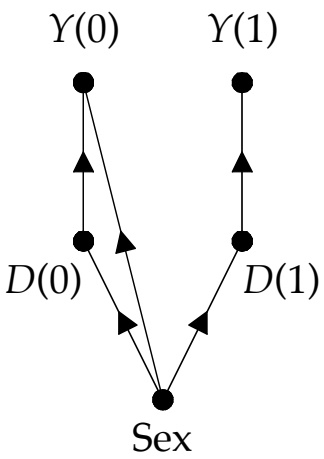
Conclusion

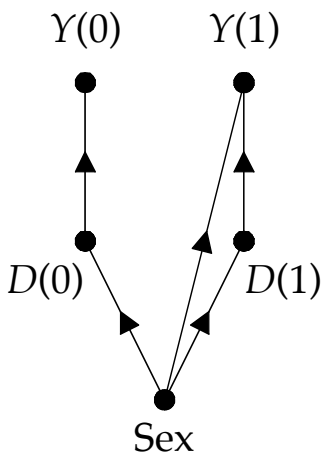
- The intent-to-treat proposal is too simple for the diverse ways in which treatment can be used and in which plans for treatment can be violated

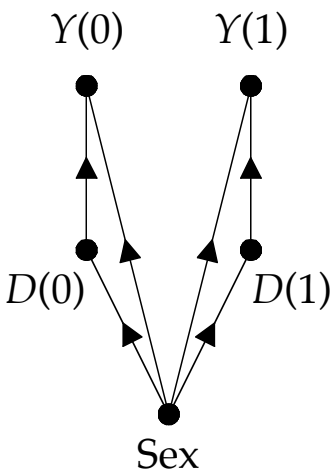
- The Rubin Causal Model provides an alternative/supplemental mode of analysis

- Dawid (1997) has challenged the philosophical basis









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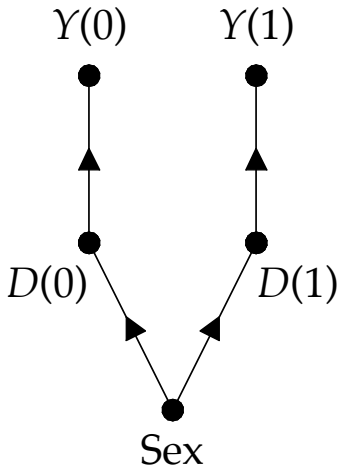

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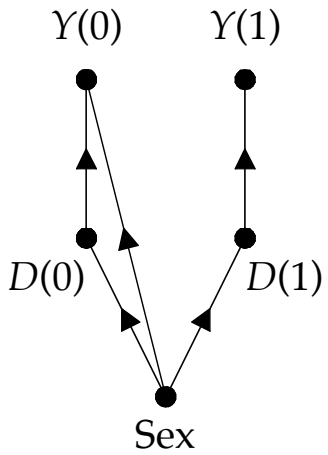

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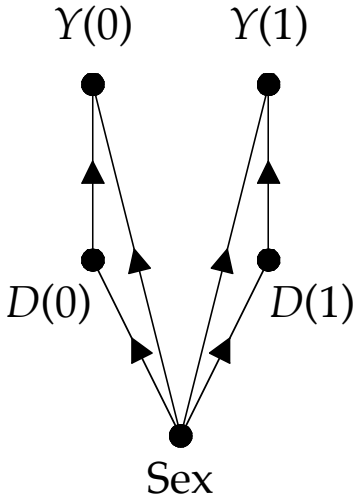

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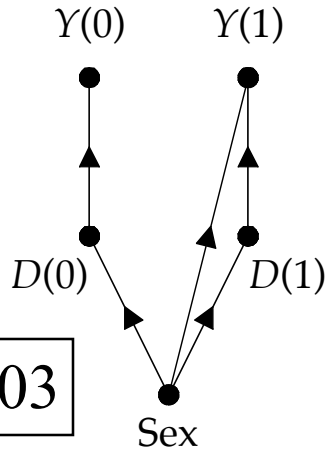

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