

Effect of acyclovir on herpetic ocular recurrence using a structural nested model (and some context)

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CORRECTING FOR NON-COMPLIANCE IN RANDOMIZED TRIALS USING RANK PRESERVING STRUCTURAL FAILURE TIME MODELS

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Key Words and Phrases: causal inference; counterfactual models; survival analysis; censored data.

ABSTRACT

We propose correcting for non-compliance in randomized trials by estimating the parameters of a class of semi-parametric failure time models, the rank preserving structural failure time models, using a class of rank estimators. These models are the structural or strong version of the "accelerated failure time model with time-dependent covariates" of Cox and Oakes (1984). In this paper we develop a large sample theory for these estimators, derive the optimal estimator within this class, and briefly consider the construction of "partially adaptive" estimators whose efficiency may approach that of the optimal estimator. We show that in the absence of censoring the optimal estimator attains the semiparametric efficiency bound for the model.

ACYCLOVIR FOR THE PREVENTION OF RECURRENT HERPES SIMPLEX VIRUS EYE DISEASE

THE HERPETIC EYE DISEASE STUDY GROUP*

ABSTRACT

Background Long-term treatment with antiviral agents has been shown to prevent recurrences of genital and orofacial herpes simplex virus (HSV) disease, but it is uncertain whether prophylactic treatment can prevent recurrences of ocular HSV disease.

Methods We randomly assigned 703 immunocompetent patients who had had ocular HSV disease within the preceding year to receive 400 mg of acyclovir or placebo orally twice daily. The study outcomes were the rates of development of ocular or nonocular HSV disease during a 12-month treatment period and a 6-month observation period.

Results The cumulative probability of a recurrence

terior uvea (iritis) represents a more serious form of the disease that can cause permanent visual loss. No treatment has been demonstrated to prevent recurrences of ocular HSV disease, and neither antiviral drugs nor other treatments are routinely prescribed after the resolution of acute HSV eye infections.

Acyclovir is a potent and specific antiviral agent that is effective in the treatment of and prophylaxis against nonocular HSV infection. Controlled trials have established that oral acyclovir significantly reduces the rate of recurrent genital^{2,3} and orofacial^{4,5} HSV infections in otherwise healthy persons. Some studies in animals have shown that systemic acyclovir

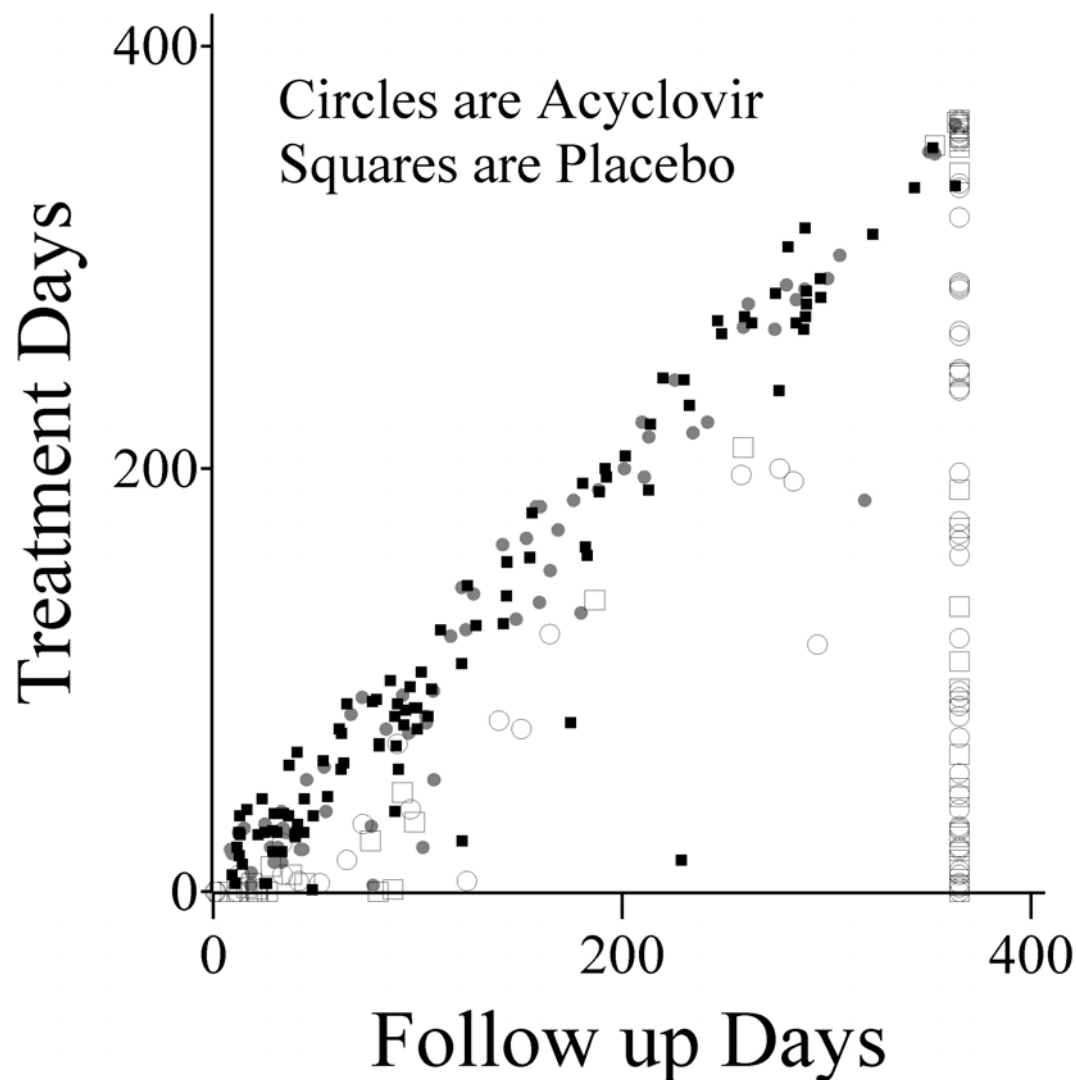
Herpetic Eye Disease Study (HEDS)

- **HEDS Study Group *NEJM* 1998; 339: 300**
- **703 adults with ocular HSV inactive in prior month**
- **Randomized between 1992.67 and 1997.0**
- **365 days of 400 mg oral acyclovir or placebo**
- **Study visits at 1, 3, 6, 9, 12 months, and as needed**
- **Patients and physicians well masked**
- **Endpoint was first recurrence of ocular HSV**

Characteristics at randomization

	Acyclovir N = 357	Placebo N = 346
Male	55 %	52 %
Caucasian	80 %	78 %
Years of age	50 ± 18	48 ± 18
Severe	39 %	38 %

Number of days followed and treated



Methods

- **Nested structural AFT model**

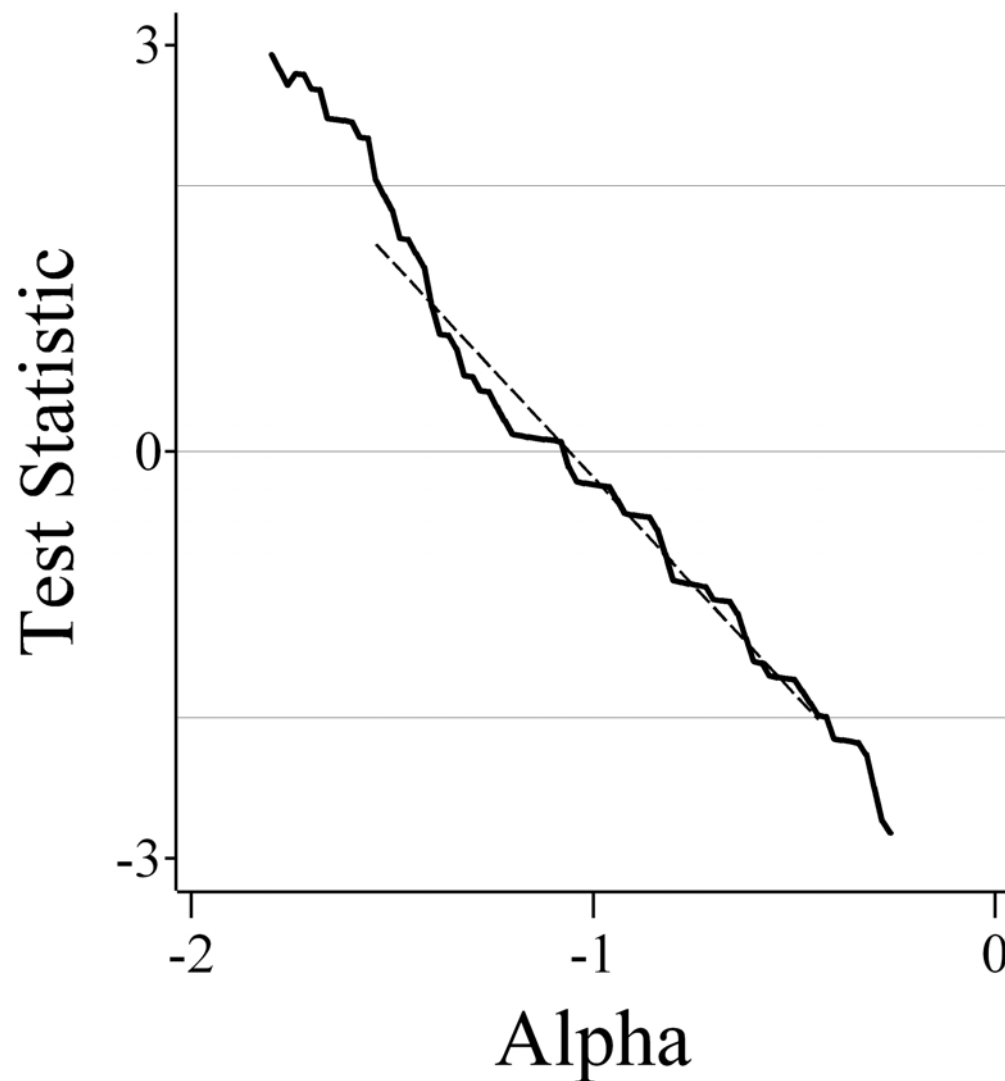
$$\mathbf{U}(i) = \int_0^{T(i)} \exp[-\alpha_0 X(i,t)] dt$$

- $U(i)$ is event time for subject i under no exposure
- $T(i)$ is observed event time
- $X(i,t)$ is 1 if exposed to acyclovir on day t , else 0
- $\exp(-\alpha_0)$ is the time expansion factor

- **G-estimation**

- line-search across $\{\alpha\}$ for $\alpha^* = \alpha_0$
- α^* is the member of $\{\alpha\}$ yielding $f[U(i, \alpha^*)|R(i)] = f[U(i, \alpha^*)]$, where $R(i)$ indicates randomized group

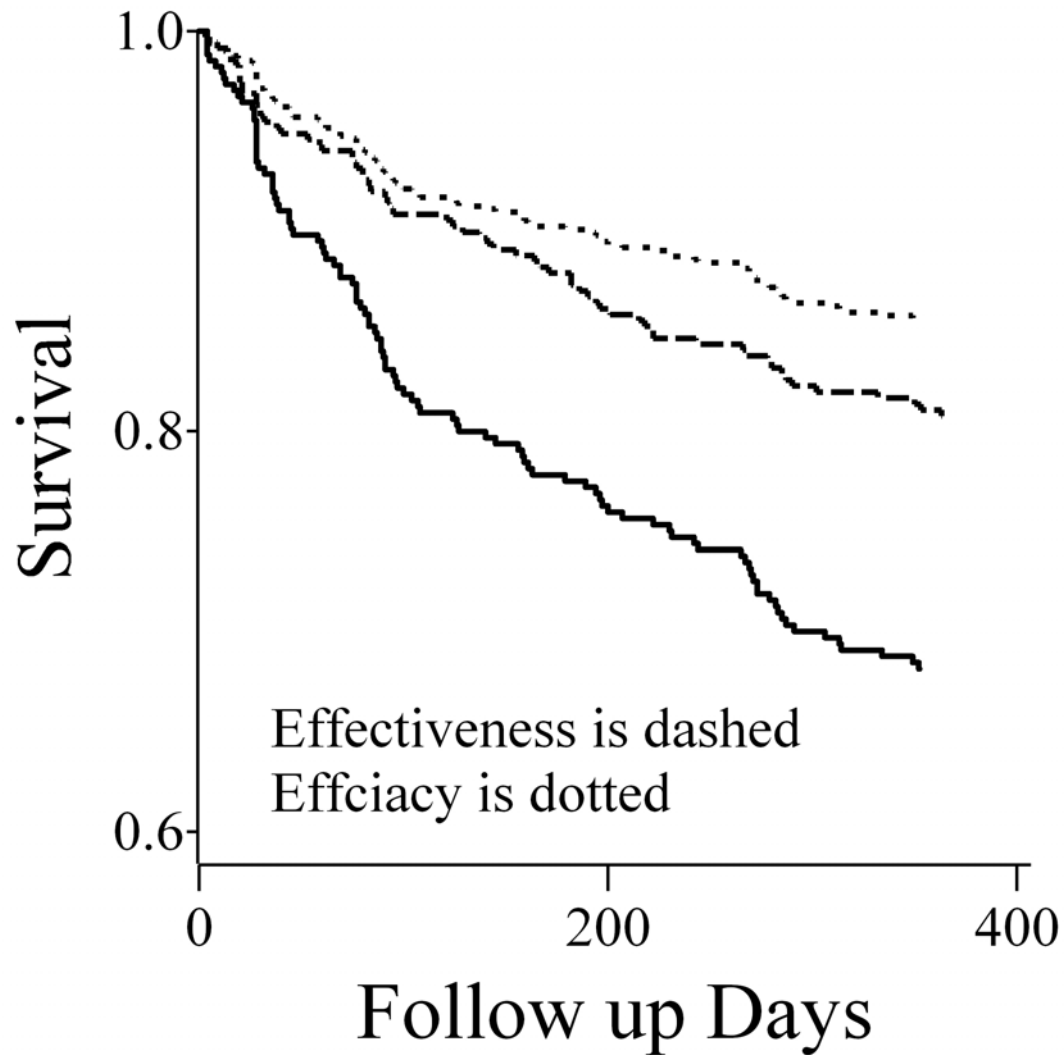
Alpha $\{\alpha\}$ versus test statistic



Results

	Hazard Ratio	95% CI
Intent-to-treat	0.55	0.41, 0.75
Structural model	0.41	0.22, 0.76
As-treated	0.62	0.45, 0.84

Survival curves



Assumptions, Limitations

- **Assume potential outcomes of one participant are independent of potential outcomes of others**
- **Assume compliance information is correct**
- **Assume no heterogeneity in effect**
- **Weibull distribution assumed to obtain hazard ratio**
- **Dropout model assumed correct**

Context: We do not account for noncompliance in biomedical RCTs

***NEJM* volumes 352 and 353 in 2005**

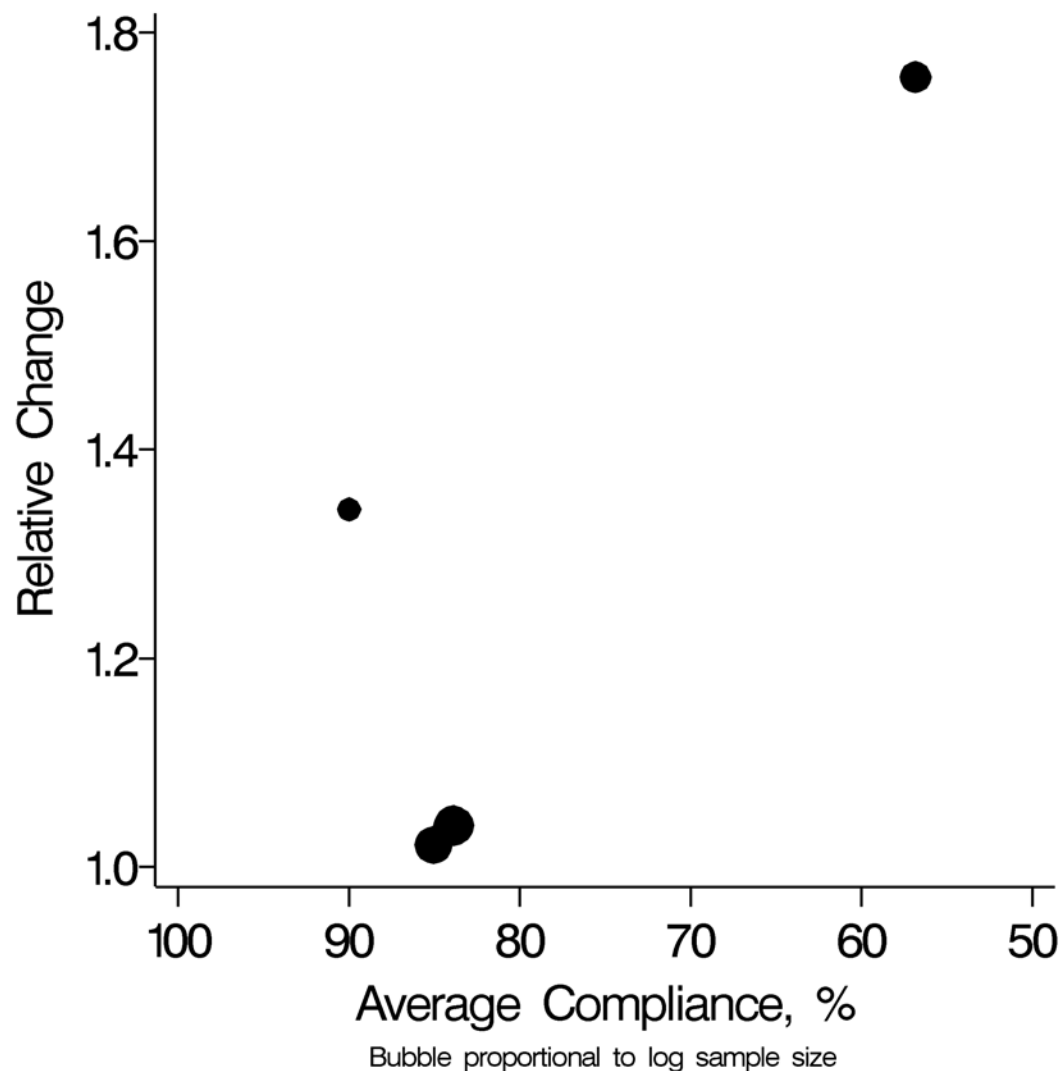
203 research articles

92 randomized clinical trials

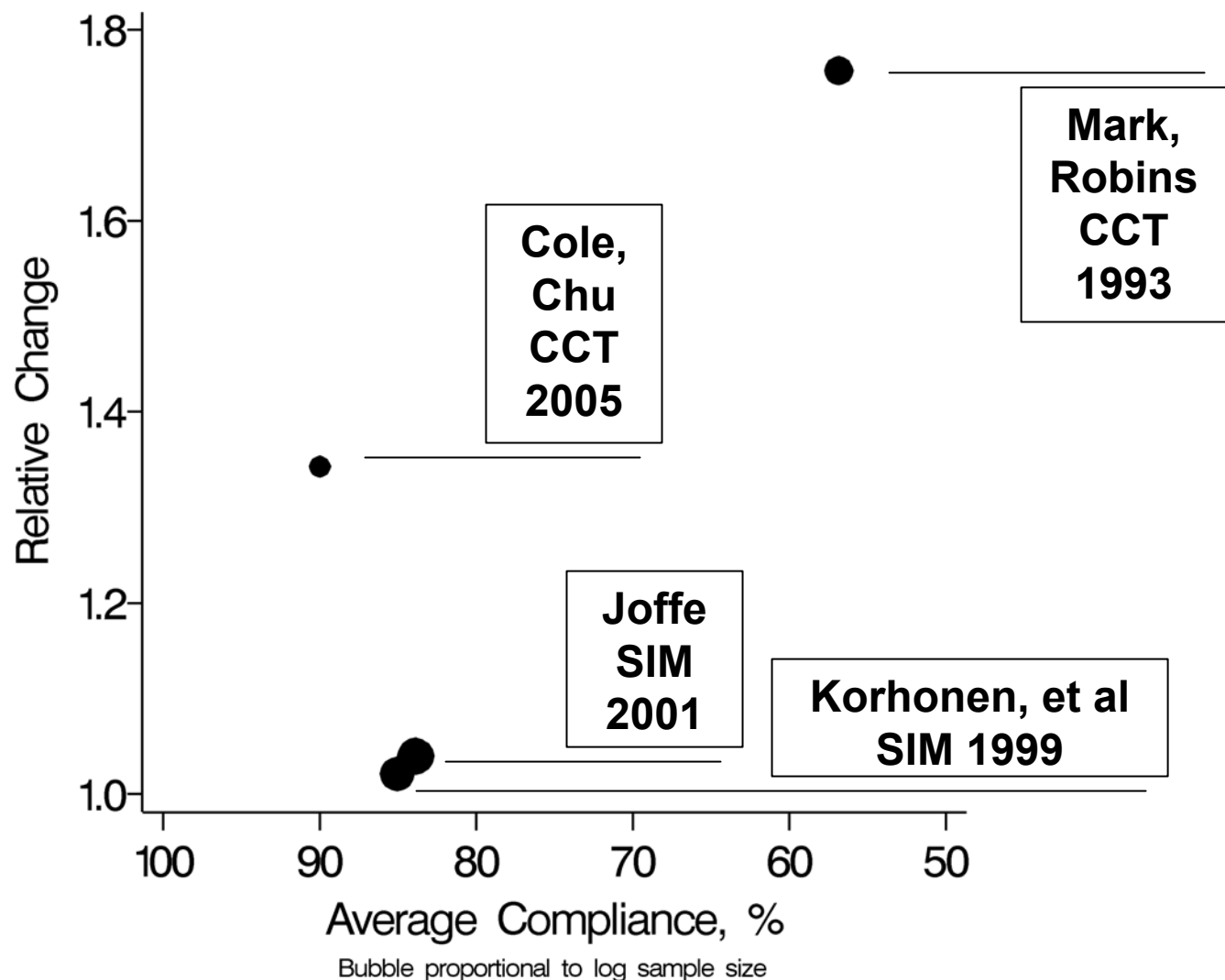
≥74 intention-to-treat analyses

0 analyses accounting for noncompliance

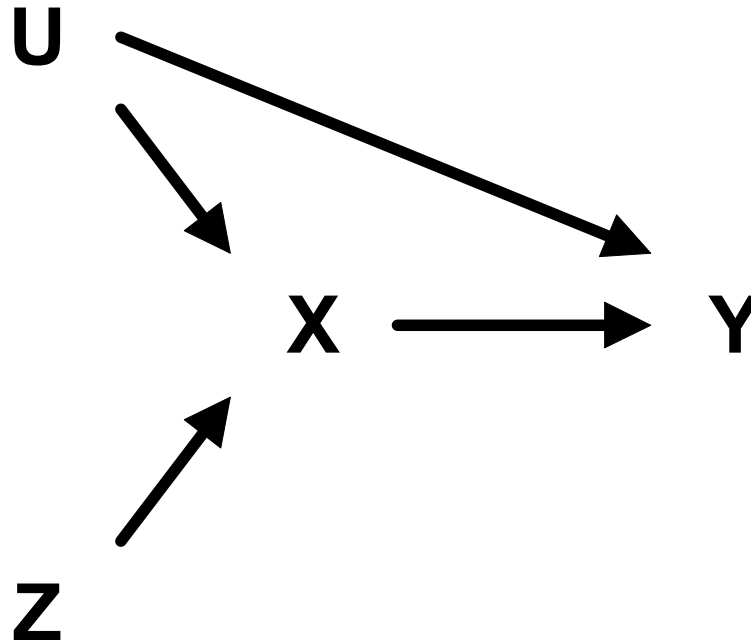
Context: When we do, it will only make a difference roughly half the time



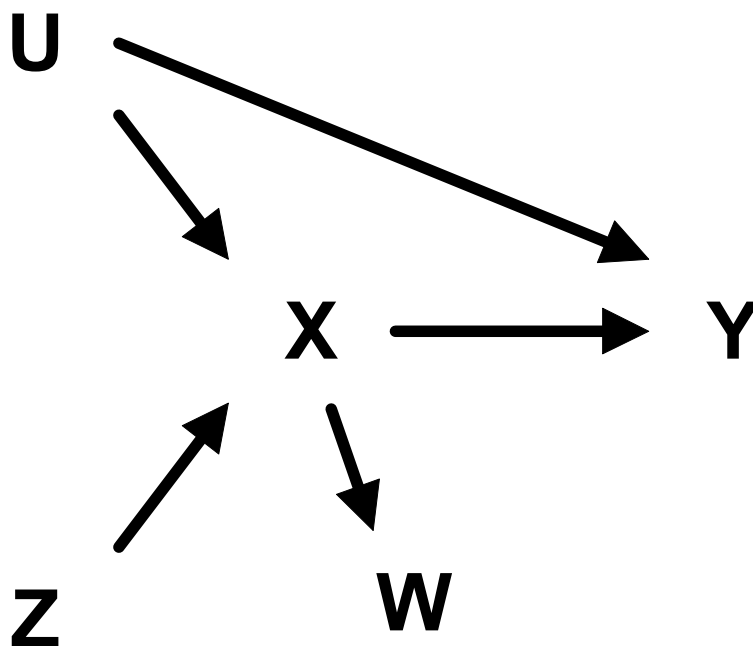
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Thank you for your time