

# ***How Should We Handle Non-Compliance in Randomized Trials?***

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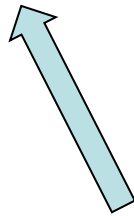
# ***How Should We Handle Non-Compliance in Randomized Trials?***

The traditional, 3-step answer:

1. Minimize it by using incentives or other methods to support and encourage compliance.
2. Minimize it by excluding participants who are not likely to comply with the intervention to be randomized.
3. Ignore remaining, minimal non-compliance, using an intention-to-treat (ITT) analysis approach.

# ***What words should we use?***

- Attrition
- Dropout
- Lost to follow-up
- Retention



Missing data, Independent  
of the Treatment

- Compliance
- Adherence
- Attendance
- Participation
- Utilization



Treatment Specific, not  
related to missing data

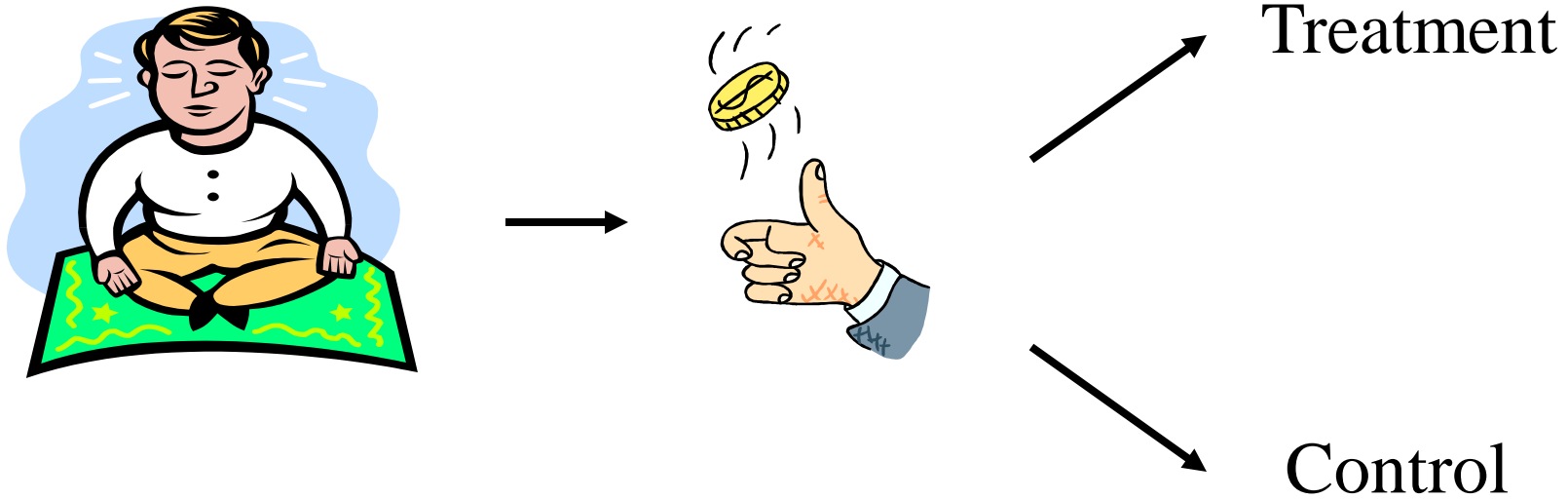
# Overview

- Non-compliance vs. attrition (lost to follow-up).
- The randomized controlled trial (RCT) is a powerful way to avoid confounding, but...
- Non-compliance is usually **minimized** by design in the typical RCT (e.g., by excluding participants who are at high risk for non-compliance), and then **ignored** analytically (e.g., by using an intention-to-treat approach).

## Discussion Questions:

- Do design procedures that minimize non-compliance in typical RCTs threaten the external validity (generalizability) of the findings?
- Does ignoring non-compliance with the standard ITT approach lead to any biases when examining intervention efficacy?
- What are some alternatives?

# *Randomization*



**T<sub>x</sub>**



**C<sub>o</sub>**



With a large enough sample size, random assignment eliminates imbalances between Treatment and Control groups on all known ***and unknown*** covariates or potential confounding factors.

# ***Key Characteristics of the Good RCT***

## ***(Altman et al., 2001 – the CONSORT Statement)***

- Specific inclusion or eligibility criteria.
- Random allocation sequence assigning participants to treatment or control conditions.
- Concealment of the random allocation sequence from those with direct or indirect contact with participants.
- Blinding or masking where feasible.
- Standardization of the interventions including training and manualization.
- Appropriate sample size as determined by power calculations (usually before the onset of the trial).
- Use of reliable and valid outcome measures.
- Procedures to minimize non-compliance and attrition.
- Intention-to-treat analysis of the outcome data.

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- ***Intention-to-treat analysis of the outcome data.***



**T<sub>x</sub>**



**C<sub>o</sub>**



## Compliers

## Non-compliers

**T<sub>x</sub>**



**C<sub>o</sub>**



ITT – Compares all participants assigned to Tx and Control conditions. Ignores compliance and non-compliance, but maintains control on confounding.

Treatment Received – Compares Tx compliers with all Controls. This is also common, but it re-introduces possible selection factor confounds.

Other approaches?

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## Discussion Questions:

- Do design procedures that minimize non-compliance in typical RCTs threaten the external validity (generalizability) of the findings?
- Does ignoring non-compliance with the standard ITT approach lead to any biases when examining intervention efficacy?
- One approach that 1) allows for non-compliance, 2) does not ignore non-compliance analytically, and 3) does not bias the test of intervention efficacy is known as the **Complier-Average Causal Effect (CACE) model**.

**Compliers**

**Non-compliers**

**T<sub>x</sub>**



**C<sub>o</sub>**



**Compliers**

**Non-compliers**

**T<sub>x</sub>**

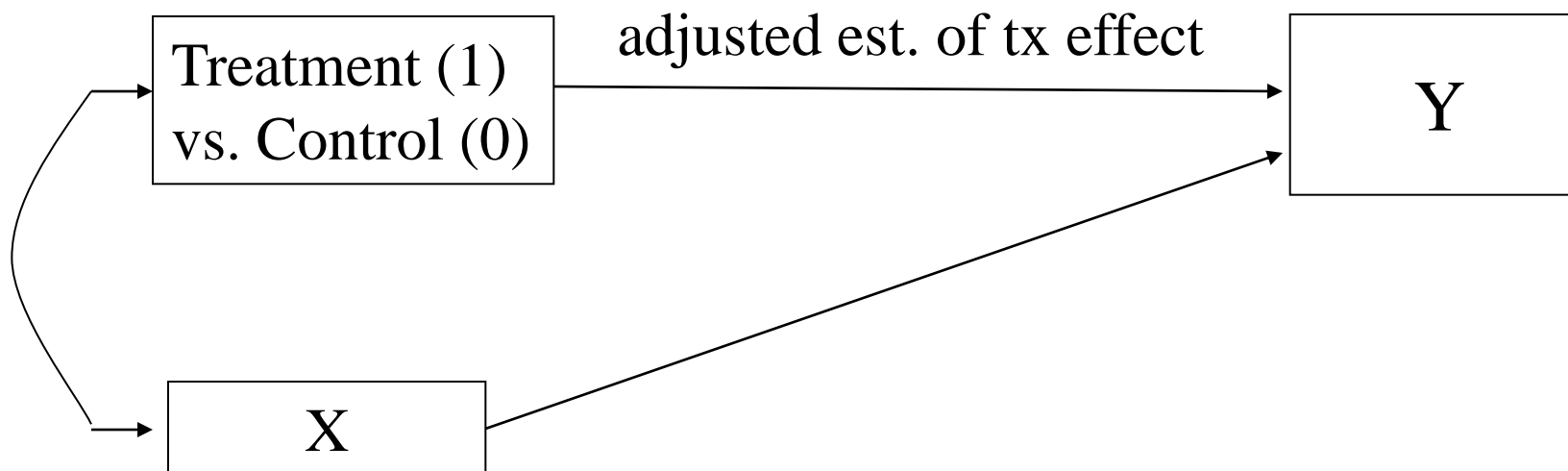


**C<sub>o</sub>**

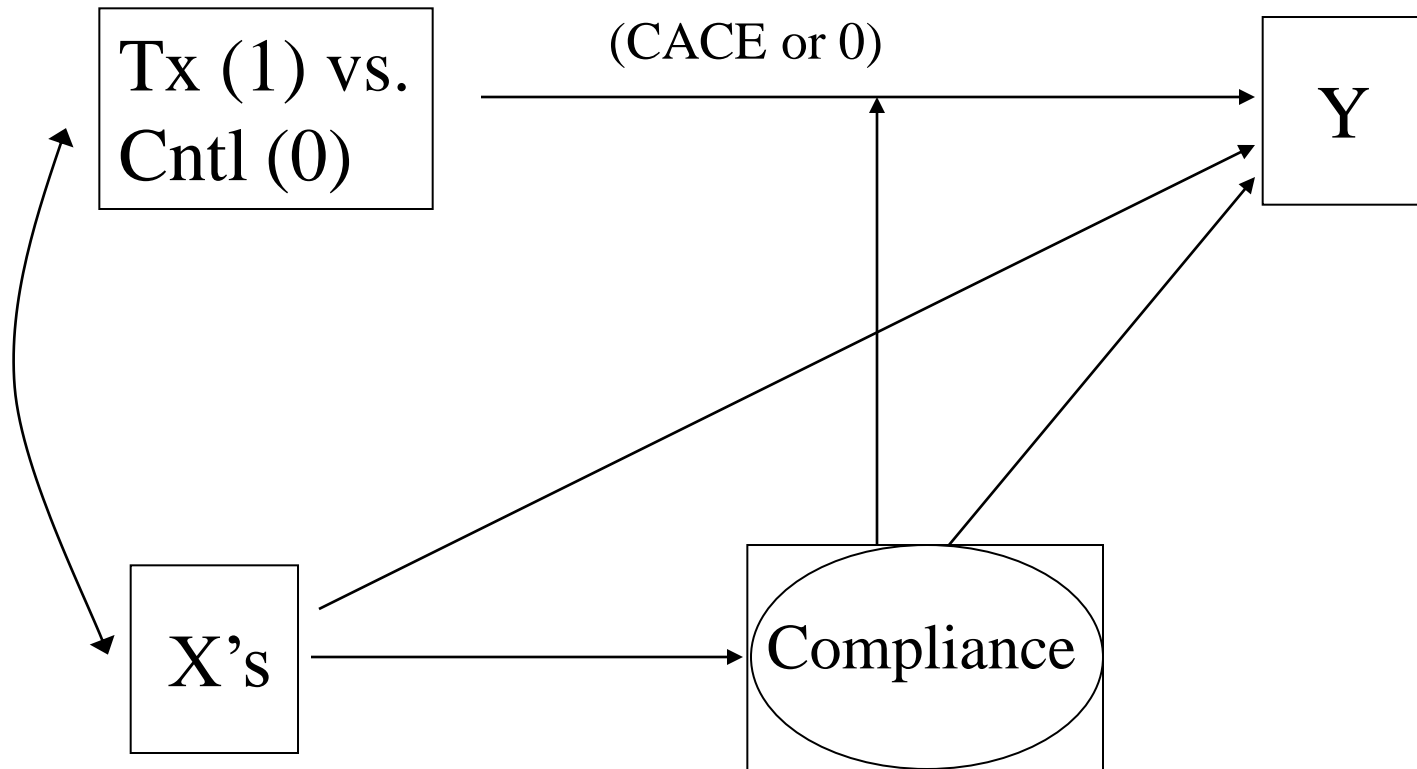


Problem: How do we estimate compliance status in a no-treatment control group? *Answer: Statistical magic!*

## *ITT Model with a Covariate (X)*

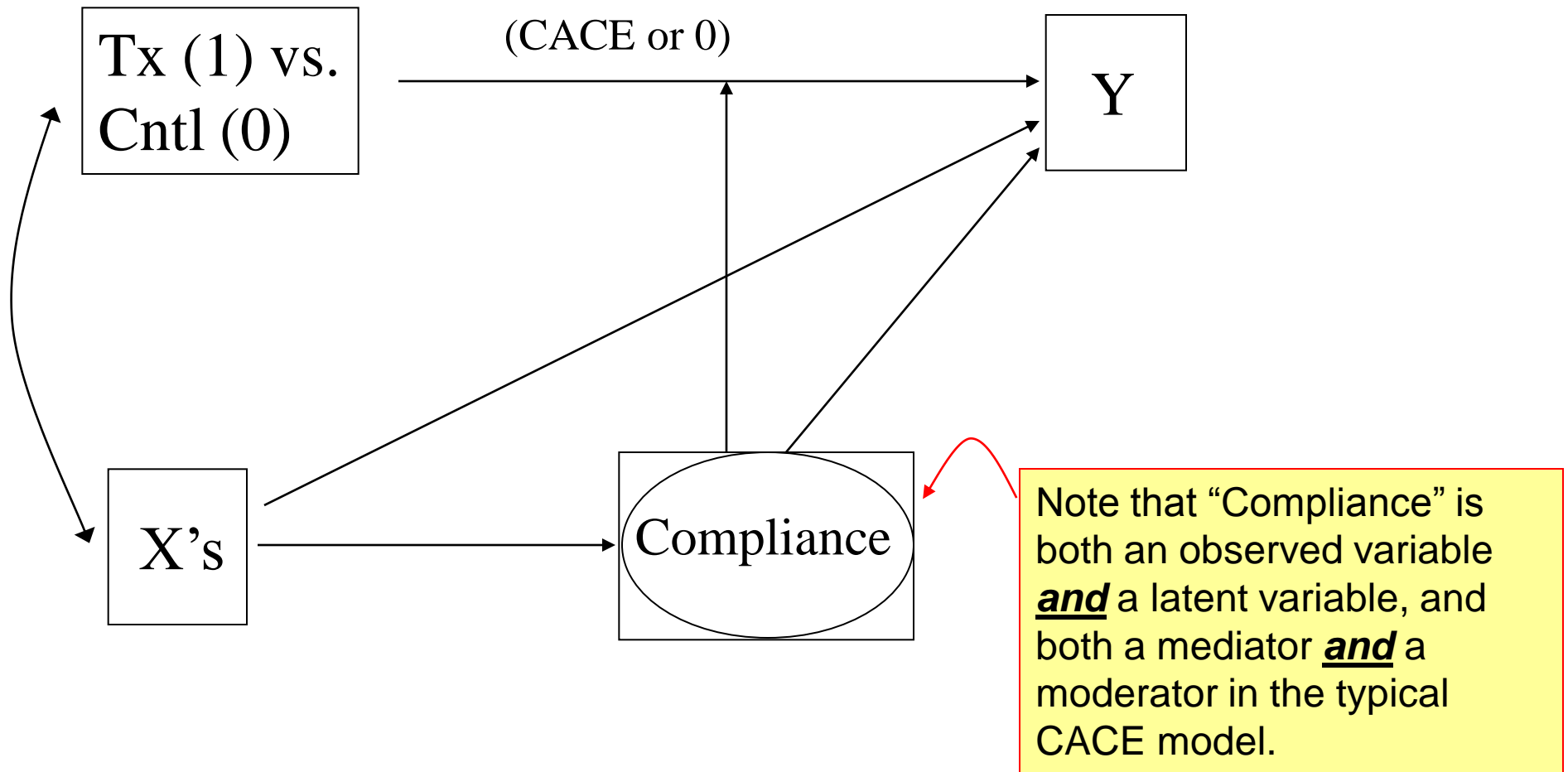


# *SEM Model of CACE Effect with Covariates*

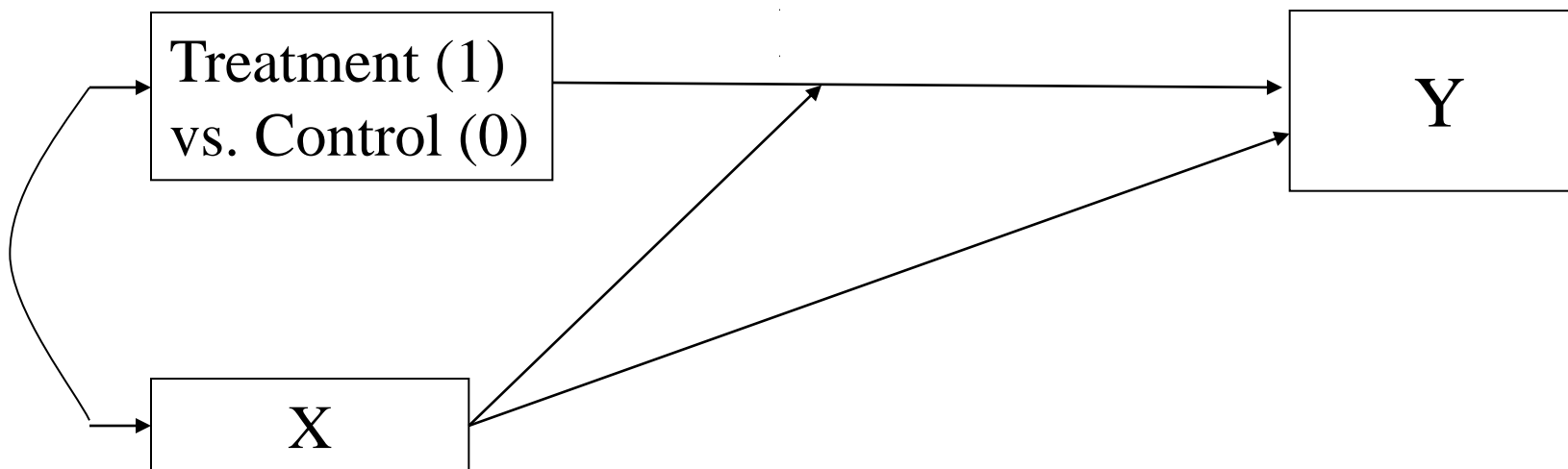




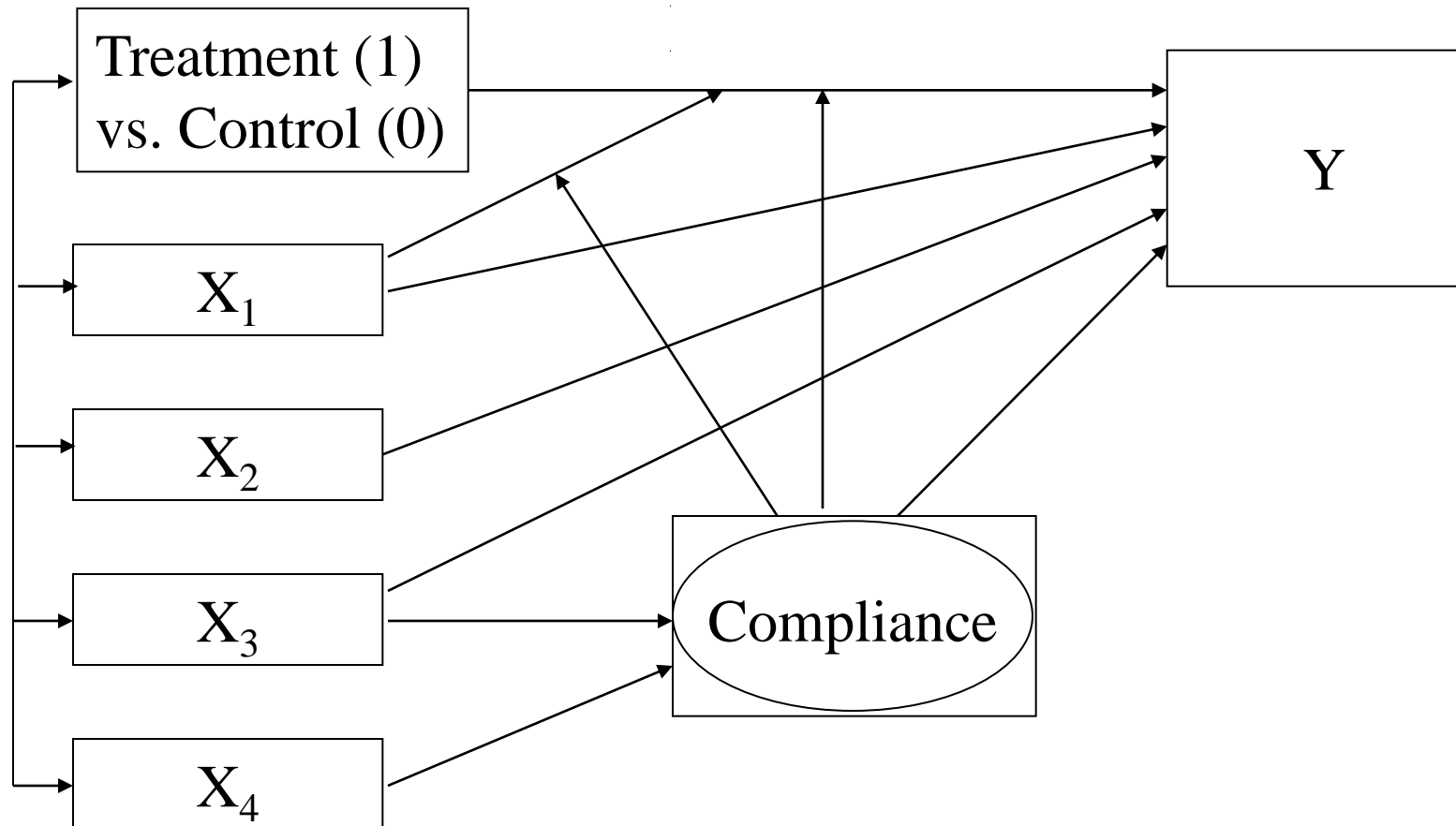
# *SEM Model of CACE Effect with Covariates*



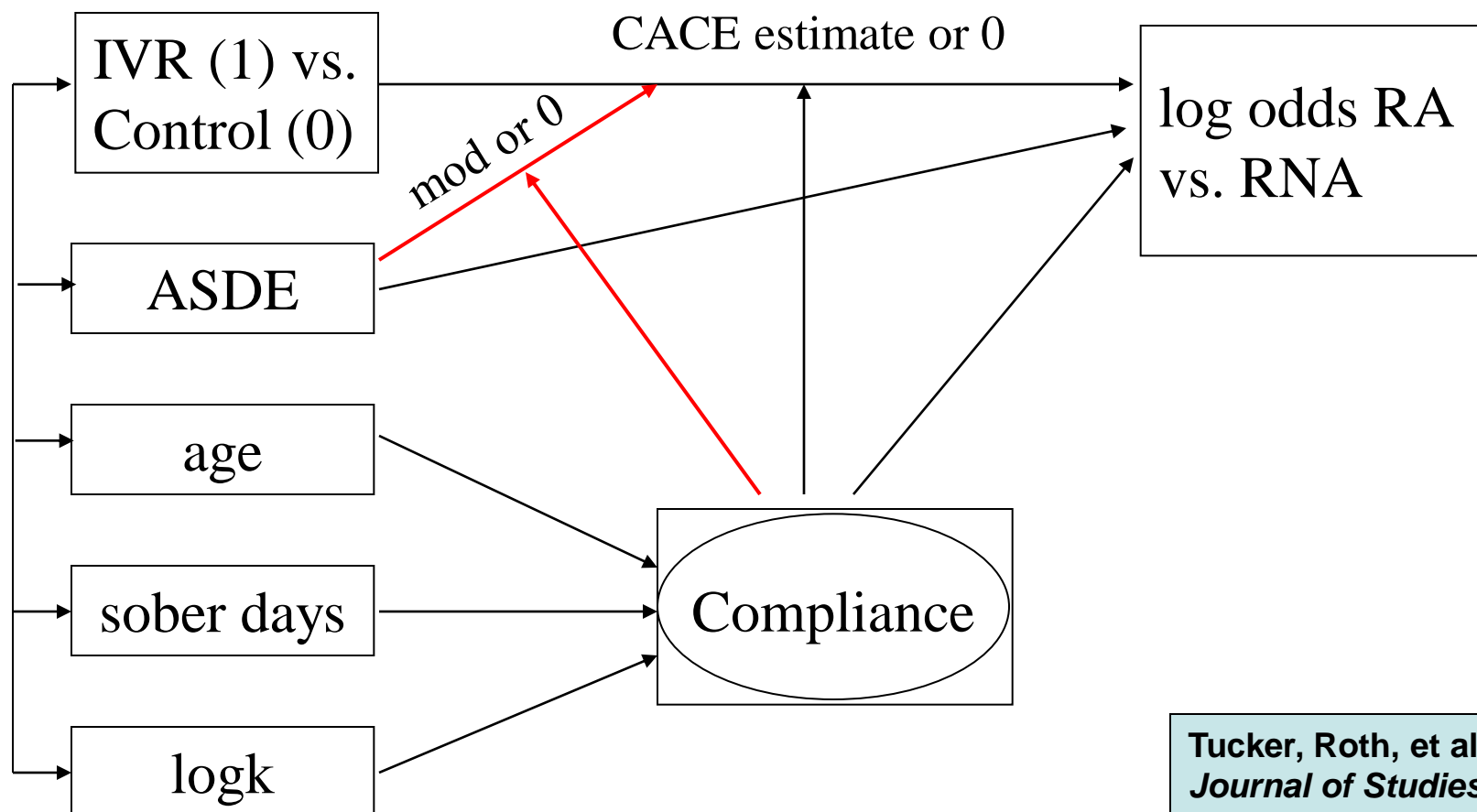
## *ITT Model with a Moderating Variable (X)*



## *SEM Model of a Modified CACE Effect*



# *SEM Model of a Modified CACE Effect*



Tucker, Roth, et al. (in press).  
*Journal of Studies on Alcohol  
and Drugs.*

## *A few important assumptions of the CACE model*

1. Compliance is dichotomous. A participant is either a complier or a non-complier. Typically, an attendance or utilization **threshold** is used to operationalize this.
2. Observed compliance is intervention-specific. Studies of multiple active treatments (e.g., comparative efficacy studies) have multiple compliance dimensions, complicating what would be meant by “compliers” and “non-compliers.”
3. The non-compliers randomized to the active treatment condition do not differ from the non-compliers randomized to the control condition. This is assumed for both the covariates/predictors **and for the outcome(s)**.
- 3a. Stated differently with respect to outcomes, observed non-compliers randomized to the active treatment group experience no treatment benefits or harmful effects from the treatment.

# ***Discussion and Parting Thoughts***

“You need not interpret every model you fit, especially those designed to guide interim decision making. When writing up findings for presentation and publication, we suggest that you identify a manageable subset of models that, taken together, tells a ***persuasive story parsimoniously***.”

(Singer & Willett, 2003; emphasis added by DLR)

“All models are wrong, but some are useful.”

(Box & Draper, 1987)