
Looking for a Few Good Mediators with “Causal” Modeling

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Overview

- **Motivate mediation problem in terms of dissection of black box interventions for two studies.**
- **Define mediation analyses in terms of causal mediation modeling framework based on potential outcomes.**
- **Current methods assume that the mediation variables are randomized even when the baseline treatment is randomized.**

Overview

- **Extend a causal modeling approach for non-adherence to estimating direct effects**
- **Compare with Standard Regression and Principal Stratification (PS; Frangakis and Rubin 2002; Jo and Muthen 2001).**
- **Present simulation and data analysis results for the two studies.**

Two tradeoffs:

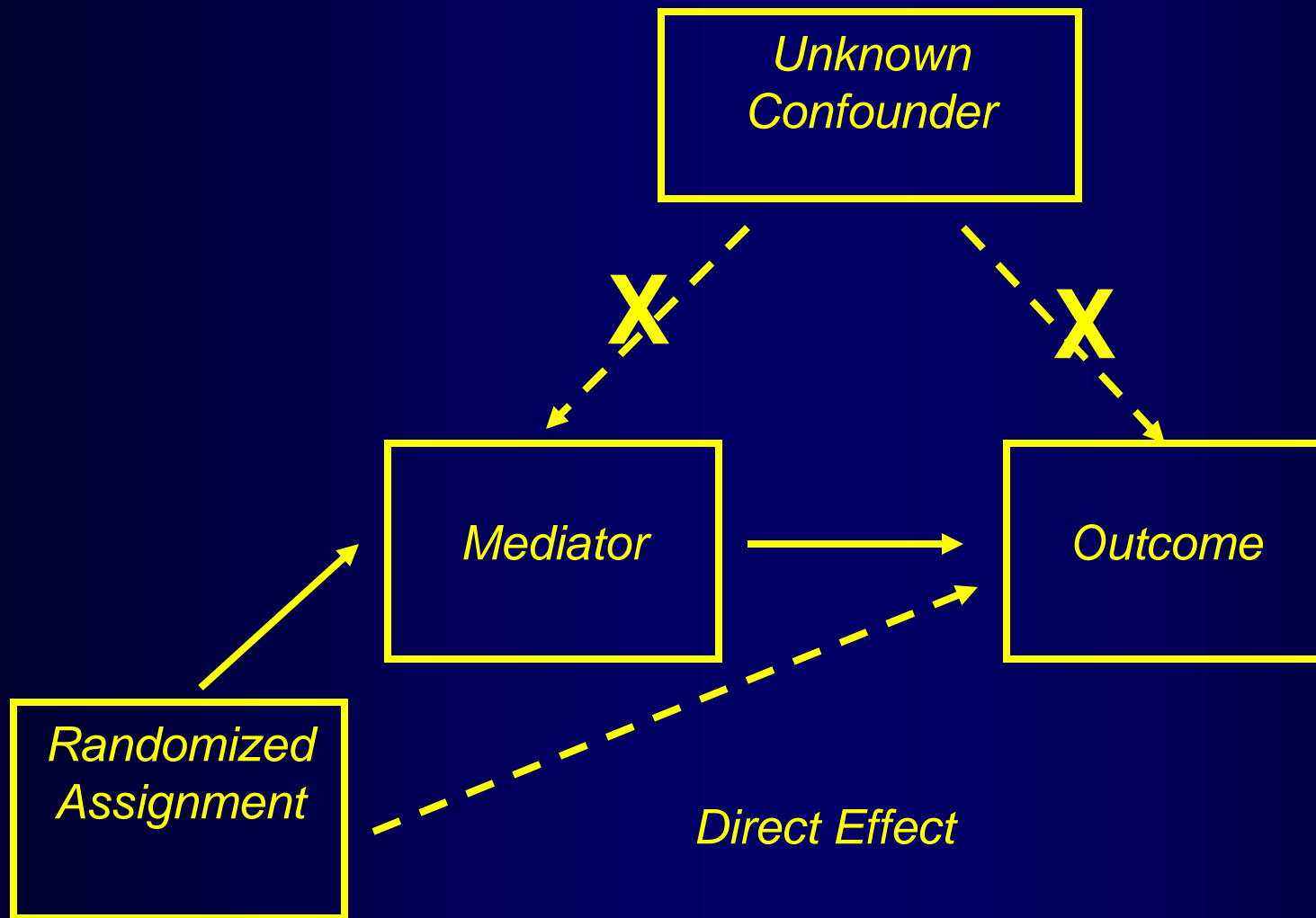
1) Trade the untestable assumption of a randomized mediation factor for untestable no-interaction assumptions?

2) Trade bias for variability?

Motivating Context

- **Problem:** “Dissecting” black box interventions in two randomized suicide studies:
 1. A randomized suicide prevention study based on a depression care management intervention for treating depression in 298 elderly depressed primary care patients (Suicide Prevention Study)
 2. A randomized suicide therapy study based on cognitive behavioral therapy intervention for 120 adult patients who have previously made at least one suicide attempt (Suicide Therapy Study)

Conventional Mediation Methods



To assess the tradeoff of assumptions, we use the statistical language of “potential outcomes” or “counterfactuals”

Assumes a Platonian set of parallel universes for each person that are identical except for distinguishing factors:

(All other things being equal...)

The factor that helps distinguish the parallel universes can be determined in one of at least three ways:

1) Treatment Assignment (“R”) -- ITT effect

2) Whether the patient exhibits the mediator level (“M”)

3) 1) and 2)

There is a philosophical debate among advocates of using subject behavior (mediation factor) to define these parallel universes (at least among statisticians).

Can you obtain causal inference for something you cannot control (e.g., non-study therapy or medication intervention)?

We have as many parallel universes as there are options (treatment, mediation factor, or both).

Each parallel universe then corresponds to a prospective outcome (i.e., the outcome that would occur in a particular parallel universe)

The potential outcome for the universe that corresponds to reality is the **observed outcome.**

The potential outcomes for the universes that do not correspond to reality are **counterfactual outcomes.**

While the causal methods start out with parallel universe idea of potential outcomes, they eventually have to link to the real world (observed data).

How do we do this?

History has been debating this for 1000's of years.

**Development of potential outcome world
starts with deduction vs. induction battle**

Plato vs. Aristotle

Mill vs. Hume

Popper vs. Marx, Freud

Neyman vs. Fisher

RA Fisher advocated randomization as the only way to link potential outcomes to observed outcomes.

But do we need randomization assumption for mediators or can we rely on baseline randomization and other untestable assumptions?

**Mediation methods without assuming
mediators are randomized**

**Principal stratification (stratifying on
post-randomization factors)**

**Structural Mean Models (analogous to
standard mediation regression
approach)**

Principal stratification

Do not decompose treatment effects into direct and indirect effects!

Stratify on latent classes representing prospective mediation behavior.

Four latent classes

1) Compliant mediating

**Assignment to encouragement
treatment → Take medication**

**Assignment to usual care →
Do not take medication**

2) Defiant mediating

Reverse of compliant mediating.

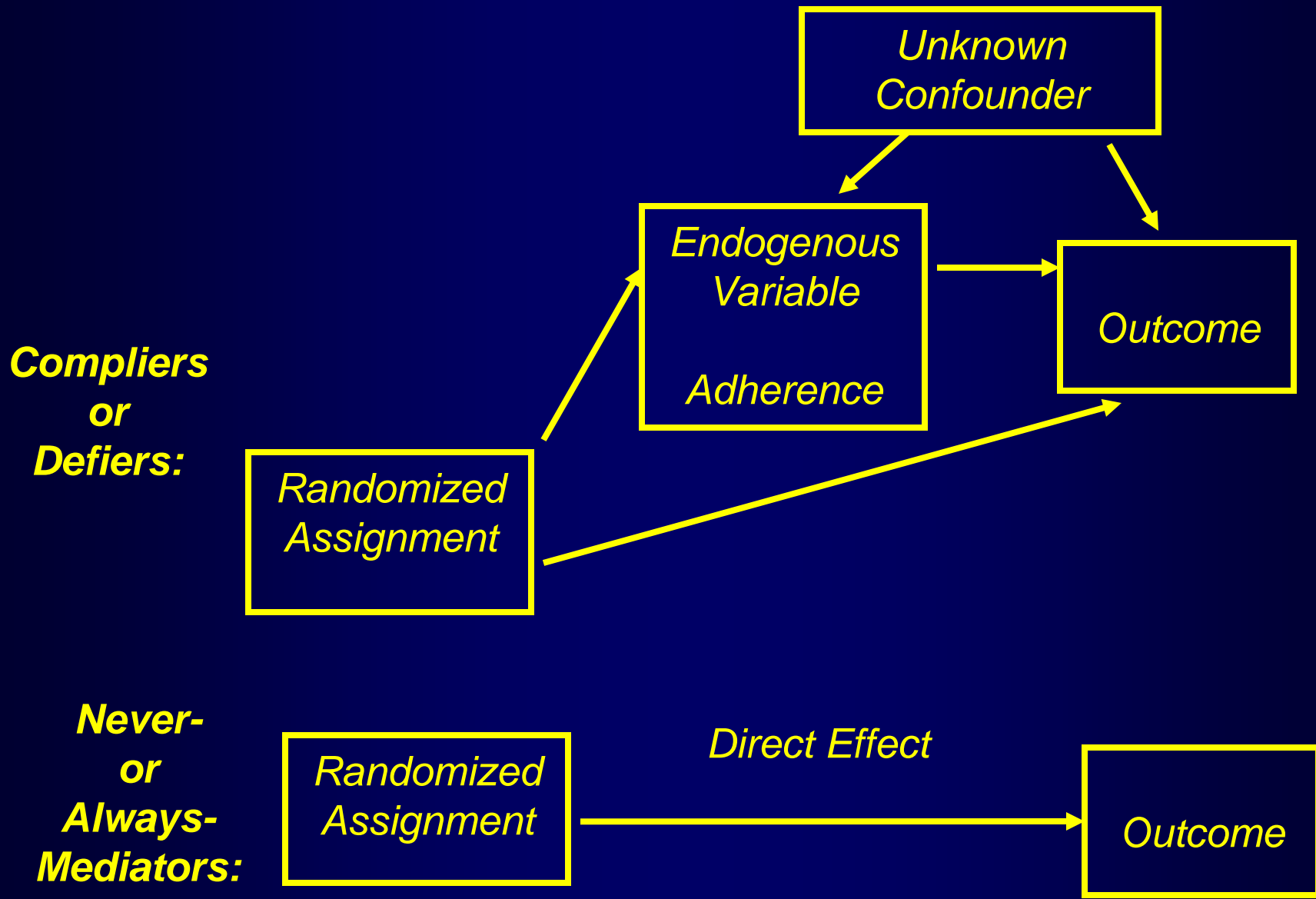
3) Never mediating

Regardless of treatment or control assignment → Never take medication

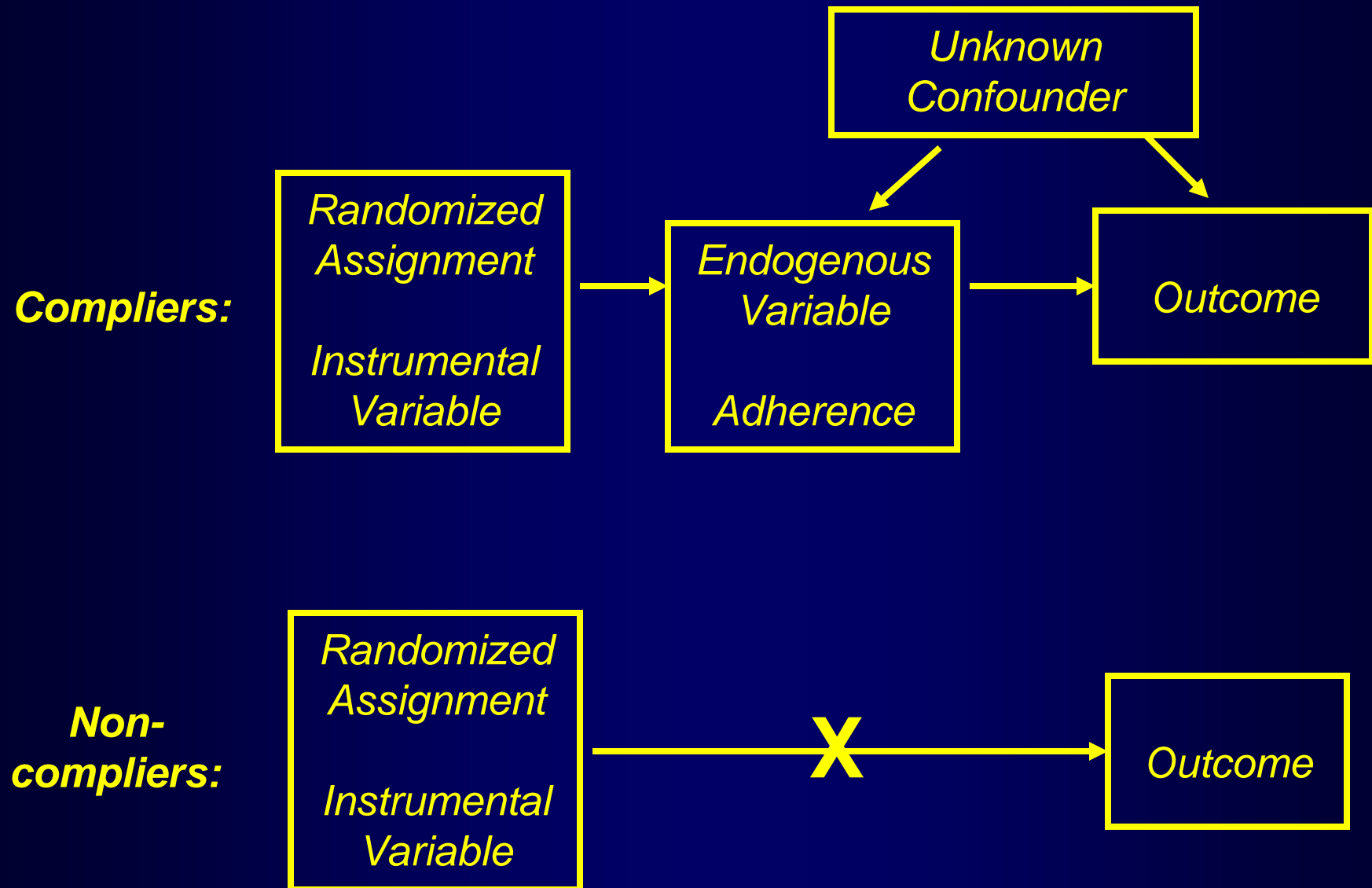
4) Always mediating

Regardless of treatment or control assignment → Always take medication

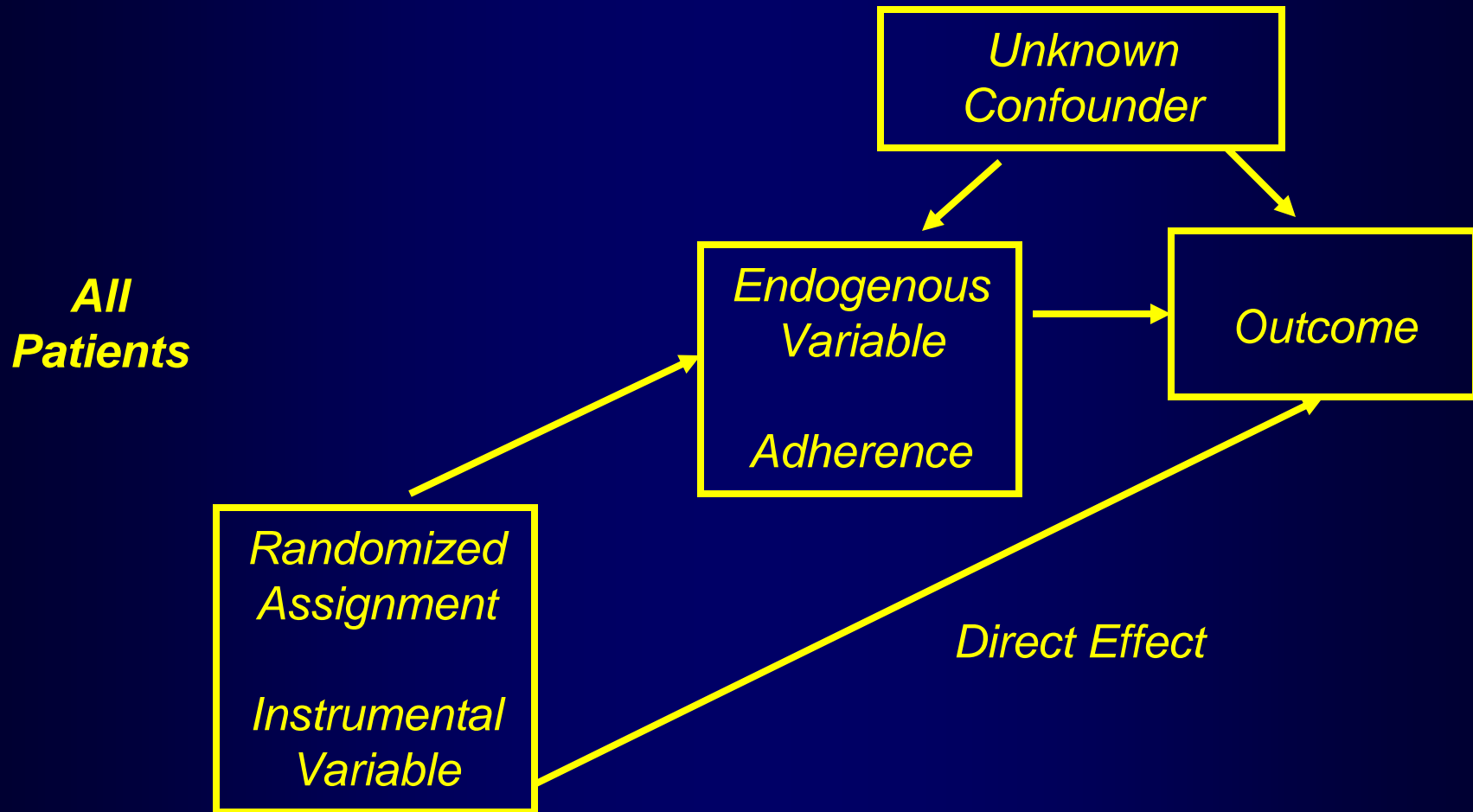
Principal Stratification Graph



IV Graph



SMM Graph



Notation for SMM

$Y_{r m}$ is the potential outcome in the universe corresponding to randomization level “r” and mediation level “m”.

$Y = Y_{r m}$ when the observed randomization and mediation levels are “r” and “m”, respectively.

All other $Y_{r' m'}$ potential outcomes are counterfactual outcomes.

Notation for PS Approach

Y_r is the potential outcome in the universe corresponding to randomization level “ r ”.

$Y = Y_r$ when the observed randomization levels is “ r ” .

All other Y_r potential outcomes are counterfactual outcomes.

Associations are based on the difference between groups of participants with respect to the observed outcome variable “Y”:

Direct effect of R:

$$E(Y | R=r, M=m) - E(Y | R=r', M=m)$$

Effect of M:

$$E(Y | R=r, M=m) - E(Y | R=r, M=m')$$

For both SMM and PS approaches, causal contrasts are based on difference between two potential outcome variables for the same individual:

SMM:

Direct effect of R:

$$E(Y_{r m} - Y_{r' m})$$

Effect of M:

$$E(Y_{r m} - Y_{r m'})$$

PS:

ITT effect of R within latent class:

$$E(Y_r - Y_{r'} | C=c)$$

**where “C” is latent class
corresponding to prospective
mediation level**

Estimation

For SMM approach, we use a weighted G-estimation estimating Equation approach

$$\text{G-estimation: } W (R-E(R)) f(Y) = 0$$

$$\text{IV estimation: } M'R(R'R)^{-1} (Y-E(Y)) = 0$$

G-estimation: $W(R-p) f(Y) = 0$

The W in G-estimation has two components:

1) fixed element for direct effect

2) ITT effect on mediator

As ITT effect on mediator goes up for subject, the subject's influence on the indirect effect goes up.

Estimation

For PS approach, estimation is based on a Bayesian, MCMC Approach.

Prior distributions

Sensitivity analysis to prior and model distributions

Need assumptions to go from potential outcome world to the observed outcome world.

1) SUTVA

2) Randomization of baseline intervention

3) Model assumptions

Stable Unit Treatment Value Assumption (SUTVA)

No effect of each subject's treatment assignment on the outcome of every other subject

The consistency of outcome if treatment were repeated with slight variations

Stable Unit Treatment Value Assumption (SUTVA)

Allows us to relate the potential variable world to observed outcomes and thus perform estimation

SUTVA may be vulnerable when interventions require each clinician treating multiple patients

Randomization Assumption for Baseline Intervention

Assignment of baseline intervention is balanced with respect to all known and unknown baseline confounders.

Randomization assumption for mediator factors conditional on covariates

Observed subject level of mediator is balanced with respect to all known and unknown baseline confounders.

Standard mediation make this assumption.

Model assumptions for PS approach

**Normality, with constant variance
across observed and unobserved
sub-groups**

Model assumptions for SMM approach

Large sample size for asymptotic requirements of the SMM approach

No interaction assumptions of the SMM approach

Model Assumptions PS, Standard Reg vs. SMM approaches

SMM approach requires fewer model assumptions, but this leads to greater variability than for other approaches.

Simulation Results for the Suicide Prevention Study

Method	Simulation Statistic	Mediation Effect	Direct Effect
Standard SMM	Bias (%)	258%	31%
	Bias (%)	1%	0%
Standard SMM	% Coverage	2%	84%
	% Coverage	99%	95%
Standard SMM	MSE	14.37	1.46
	MSE	23.43	1.92

Simulation Results for the Suicide Therapy Study

Method	Simulation Statistic	Mediation Effect	Direct Effect
Standard SMM	Bias (%)	-28%	-10%
	Bias (%)	3%	5%
Standard SMM	% Coverage	73%	95%
	% Coverage	90%	97%
Standard SMM	MSE	25.11	7.10
	MSE	326.95	11.60

Descriptive Statistics for Suicide Prevention Study

Group	Mean Hamilton (STD)	Medication Proportion
Usual Care	13.55 (8.35)	0.45
Intervention	11.50 (7.38)	0.85
No Medication	13.14 (8.09)	
Medication	12.23 (12.23)	

ITT, Standard Regression, and SMM Results for Suicide Prevention Study

Method	Direct Effect	Mediation Effect
ITT	-3.12 (0.82) (-4.72,-1.51)	
Standard Regression	-2.67 (0.89) (-4.41,0.93)	-1.19 (0.94) (-3.03, 0.65)
SMM	-2.58 (1.27) (-5.07,0.10)	-1.43 (2.34) (-6.01,3.15)

Descriptive Statistics for Suicide Therapy Study

Group	Mean BDI (STD)	Non-study Therapy Proportion
Usual care	33.04 (12.39)	0.08
Intervention	30.79 (15.22)	0.25
No Therapy	32.24 (13.96)	
Therapy	30.12 (13.47)	

ITT, Standard Regression, and SMM Results for Suicide Therapy Study

Method	Direct Effect	Mediation Effect
ITT	-6.35 (2.53) (-11.37, -1.33)	
Standard Regression	-6.86 (2.60) (-12.01, -1.70)	-3.05 (3.46) (-9.92, 3.82)
SMM	-3.93 (3.09) (-9.98, 2.12)	14.59 (15.87) (-16.52, 45.69)

Principal Stratification Results for Suicide Prevention Study

Principal Stratum	ITT (STD)
Never (7%) Medication	-8.93 (6.01) (-17.06,1.37)
Always (36%) Medication	-1.94 (2.18) (-5.23,1.50)

Principal Stratification Results for Suicide Therapy Study

Principal Stratum	ITT (STD)
Never (66%) Non-CBT Therapy	-7.07 (4.44) (-24.51, 15.67)
Always (6%) Non-CBT Therapy	-8.14 (17.79) (-99.57, 91.38)

Possible reasons for SMM and standard approach discrepancies:

- 1) Confounding of the non-study therapy vs. depression outcome relationship**
- 2) Effect modification of the non-study therapy mediator on outcome by baseline study cognitive therapy**
- 3) Effect modification of baseline cognitive therapy on outcome by baseline depression or suicide ideation.**

1) Confounding: Stress may have reduced use of non-study therapy but increased depression

Evidence: Sign of non-study therapy effect reverses from standard regression to SMM approach

2) Effect modification: Effectiveness of the non-study therapy on depression may be enhanced by study cognitive therapy.

Patients may have learned to utilize information and problem-solving skills obtained from the study cognitive therapy and applied them to the non-study therapy that they had received.

3) Effect modification: The cognitive therapists may have provided more intensive therapy for patients with more suicide ideation or depression at baseline.

Nonetheless, the investigators believed that the cognitive therapy approach is standardized enough that such an interaction was not very likely.

Summary

- **A new method for assessing mediation without assuming mediator is randomized**
- **However the approach leads to more variability than standard mediator approaches.**
- **Is relaxing the randomization assumption worth this added variability and untestable no-interaction assumptions?**

Summary

- **SMM and standard approaches considered assume no interactions**
- **Trade-off between untestable assumptions**
- **Latent class analysis suggests that there may be interaction but much variability.**

Future

- **Reducing variability of SMM approach.**
- **Assessing currently untestable interaction assumptions**
- **Allowing for heterogeneity of treatment effects**
- **Extending to multiple mediators, longitudinal outcomes, binary outcomes**