N of 1 and Novel Within-Subject Trial Methods

Columbia University Medical Center

Karina W Davidson, PhD, MASc

Funded by the National Heart Lung and Blood Institute 1R01 HL115941 & K24 HL084034

National Cancer Institute Contract 15X142

ME-1403-12304 from PCORI

Questioned Assumptions

1. Treating complex, relapsing/recurring diseases/symptoms has presumed that that the ‘problem’ is binary (present or absent).

- There may be some diseases/symptoms, that while enduring, are not binary, and are time-varying (depression, stress, weight, smoking, exercise, blood pressure, epilepsy, migraine, glucose control, drug use, cancerous cell proliferation, estradiol levels)

Questioned Assumptions

2. Treatment target identification is best conducted by averaging across persons
   - There may be person-specific treatment targets (so the treatment is unique to a person)

Questioned Assumptions

3. Dose is best identified by averaging across persons

- There may be person-specific dose levels (so the dose of treatment required by one person differs from the dose required by another)

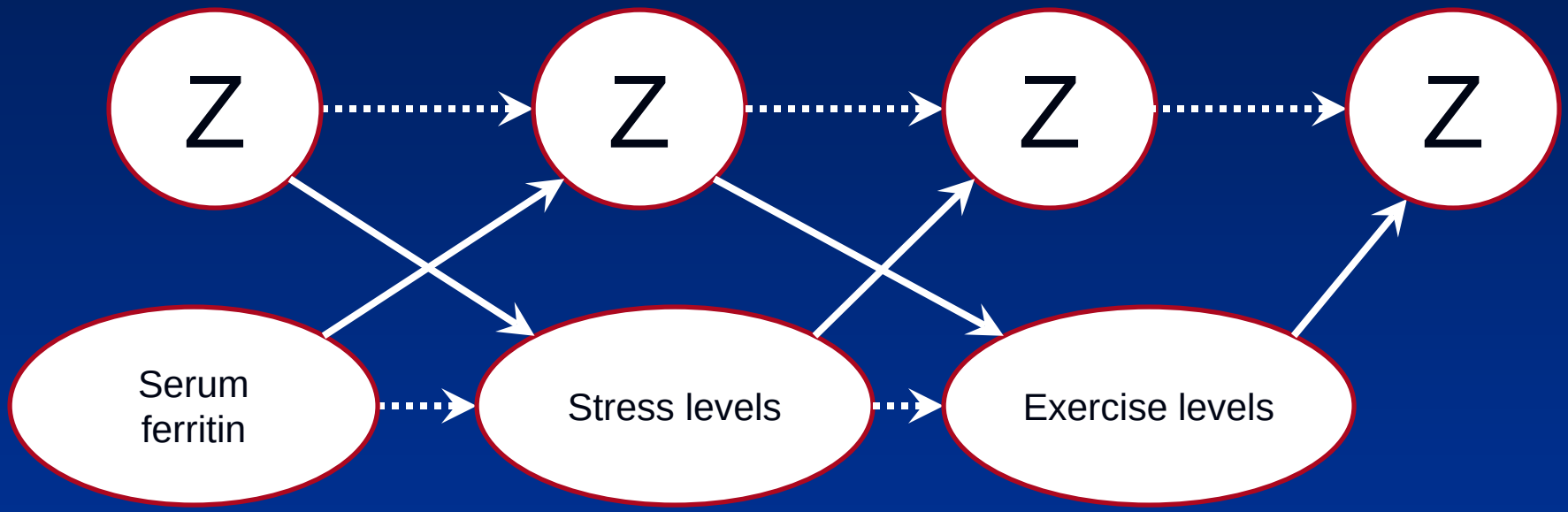
4. Dose-response is best identified by averaging across persons

- There may be person-specific dose-responses (so the time-lag between dose exposure and response found in one person differs from the time-lag found in another)

Which Treatment?

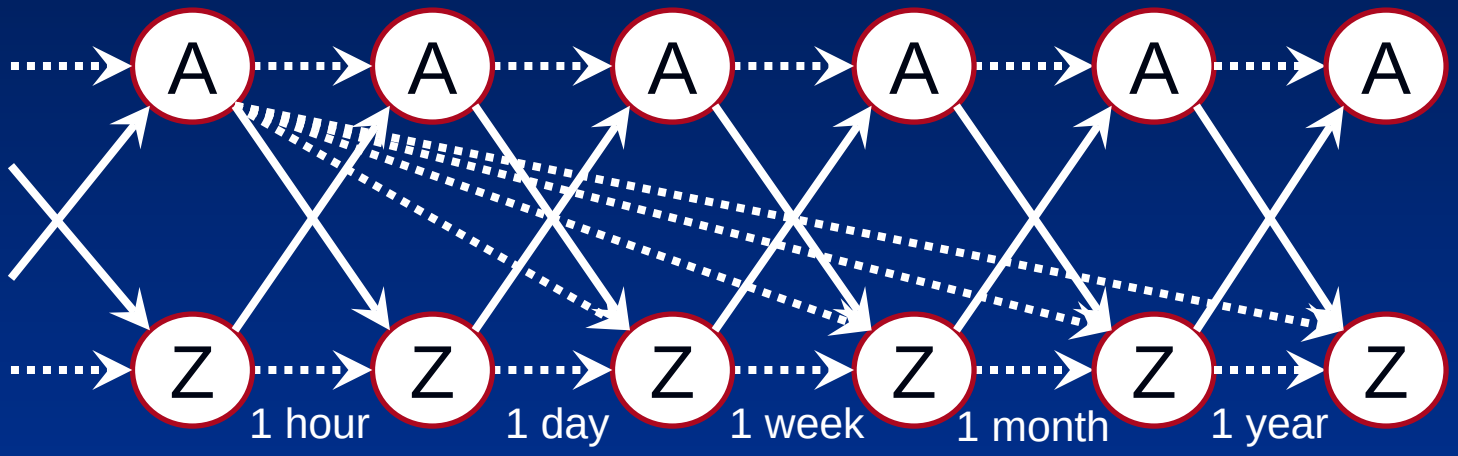
- One for everyone?
- 3-4 for everyone?
- One for different subgroups?
- 3-4 for different subgroups?
- One for one person?
- 3-4 for one person?

Between Subject Treatment identification



Z = Depressive symptoms

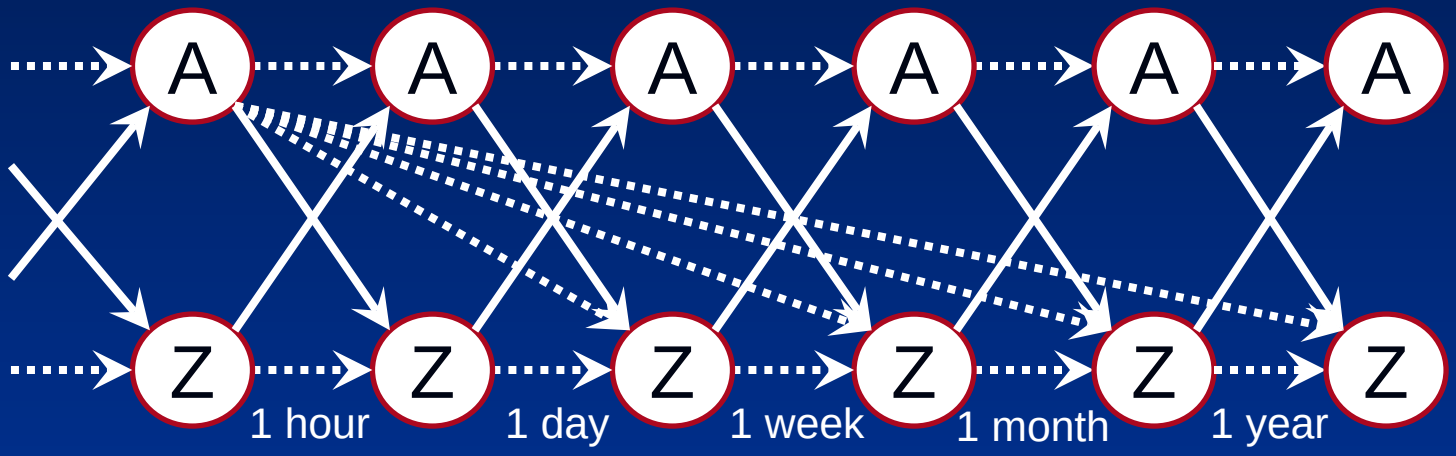
Between Subject Cross-lagged



A = Putative treatment

Z = Depressive symptoms

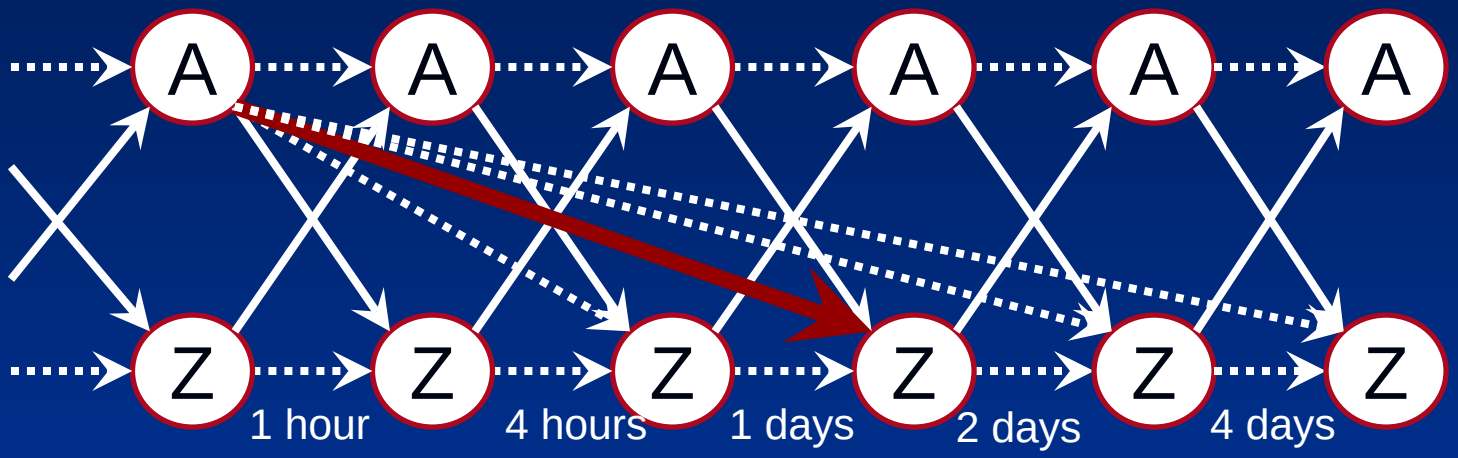
Would you get the same answer from a n=1 model?



A = Putative cause/treatment

Z = Depressive symptoms

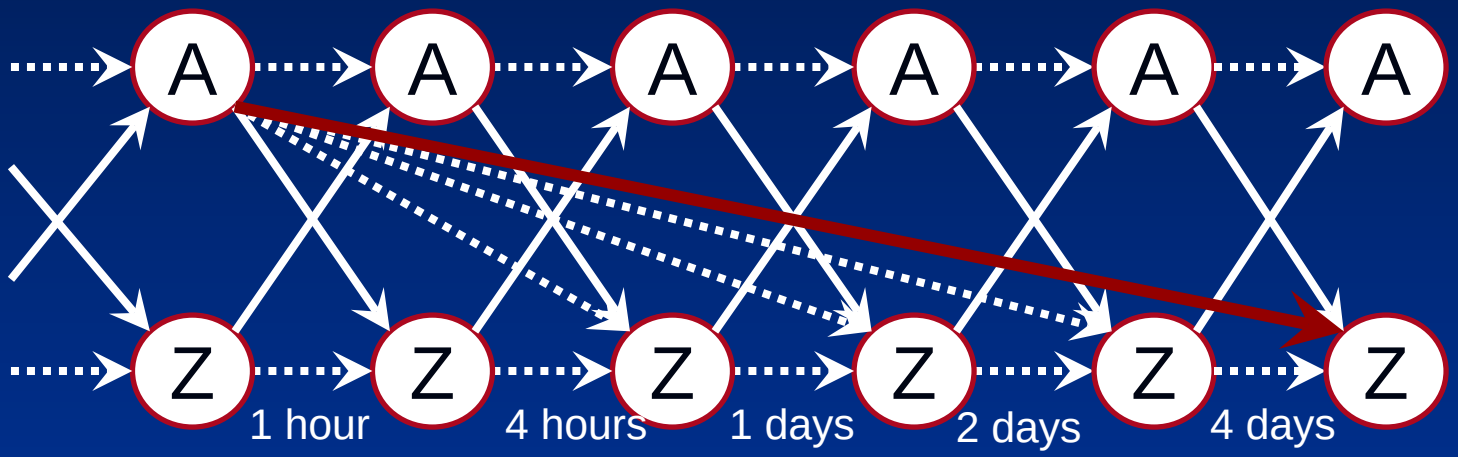
Person 1



A = Vitamin D3 levels

Z = Depression

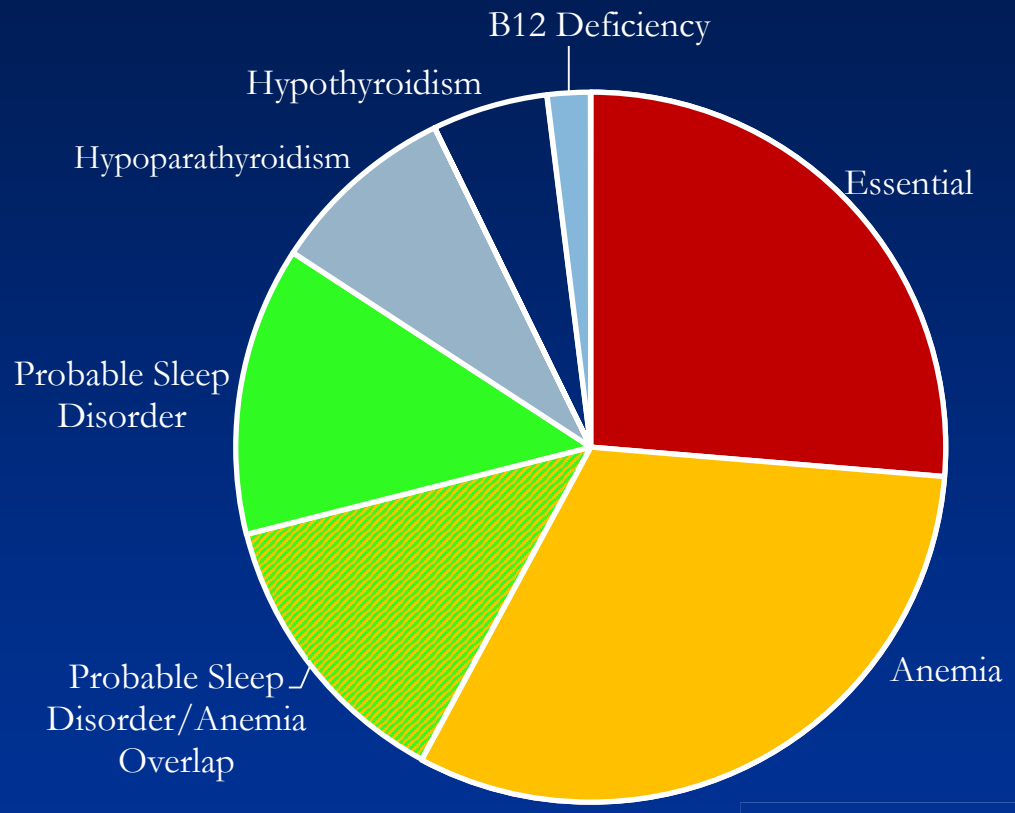
Person 2



A = Vitamin D3 levels

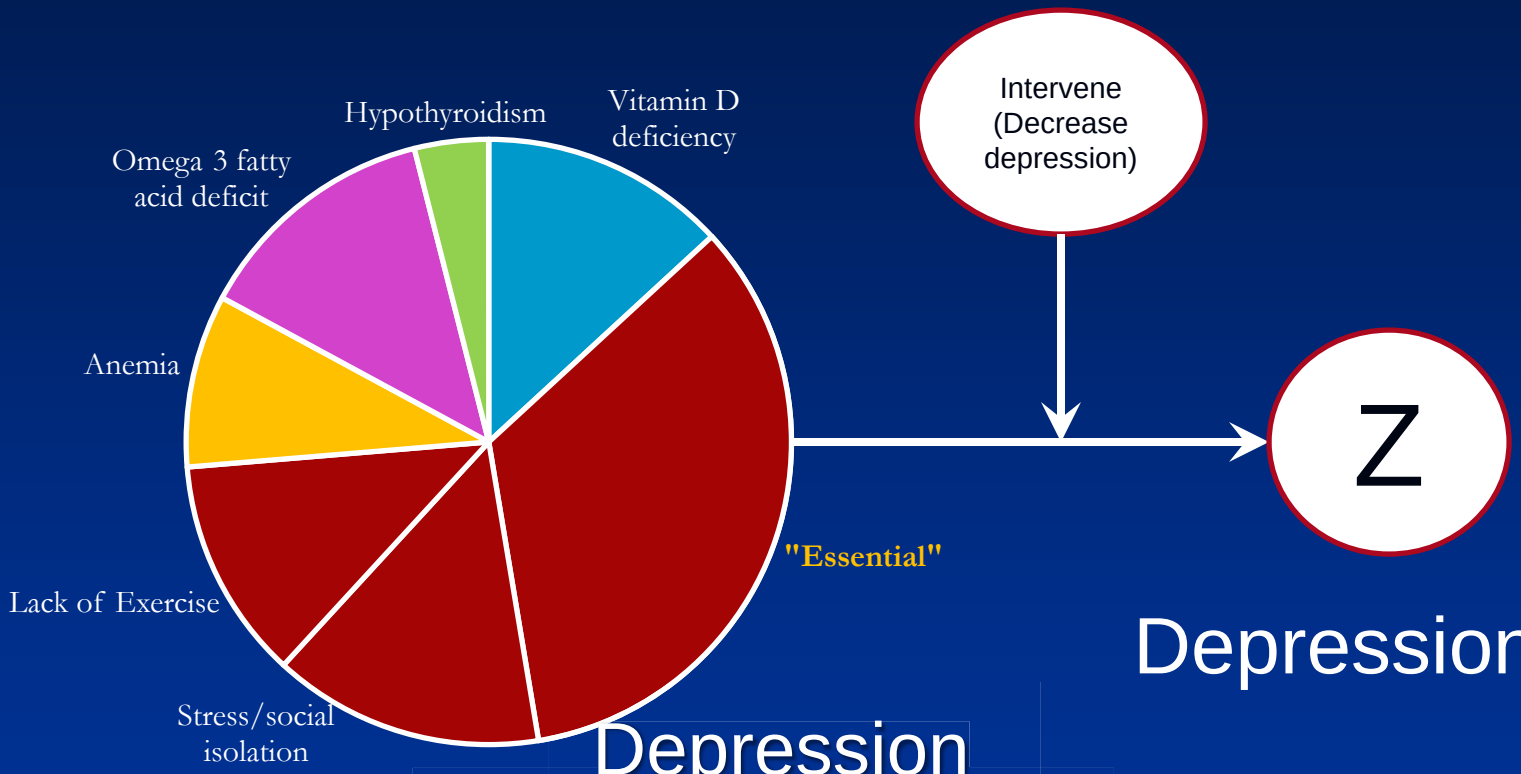
Z = Depression

Between Subject Prevalence



Depressed Patients
N=119

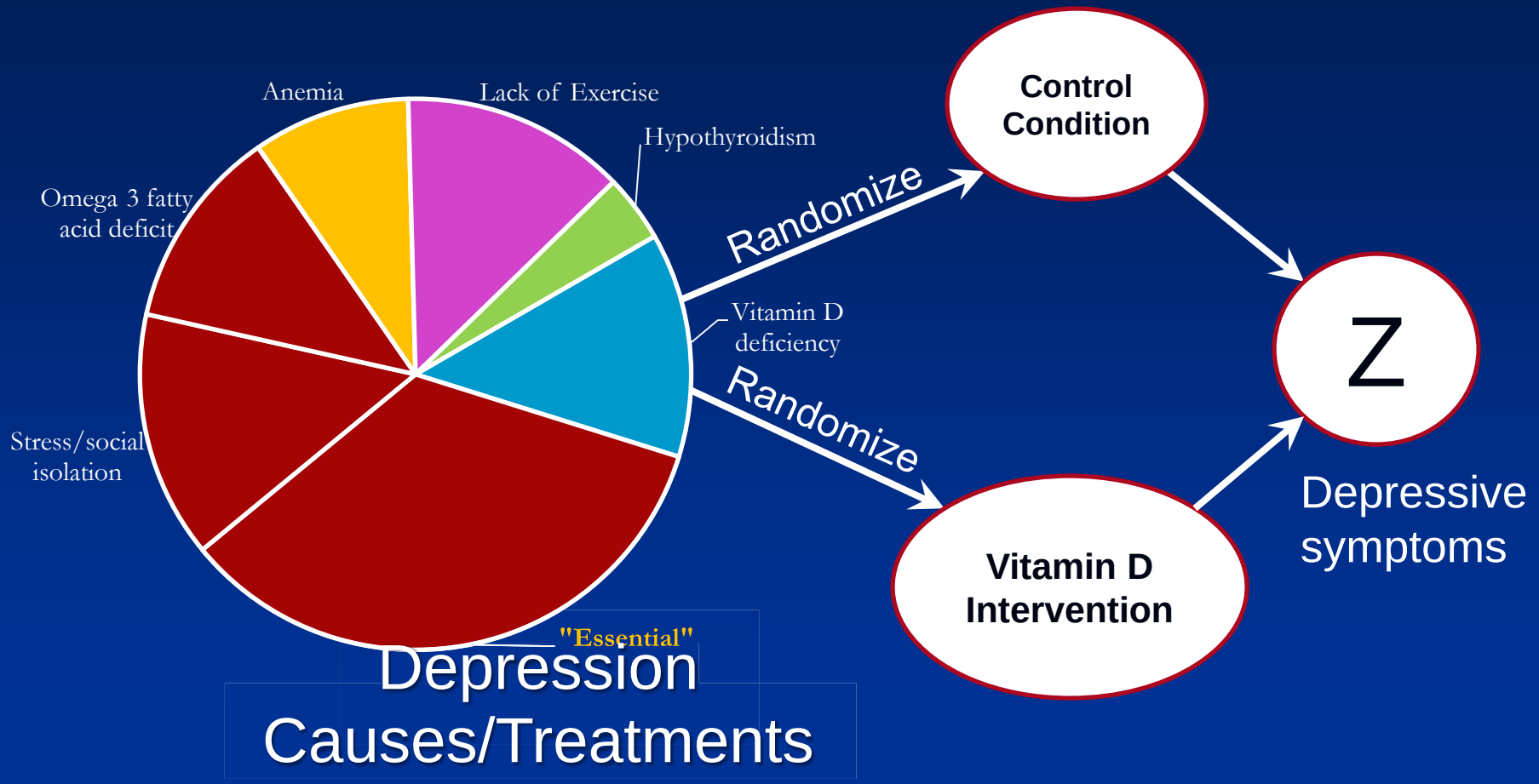
RCT Design 1 for Depression



RCT Design 1

- Normative design
- **Answers the question: Does A generic Depression intervention work for the hypothetical average person?**

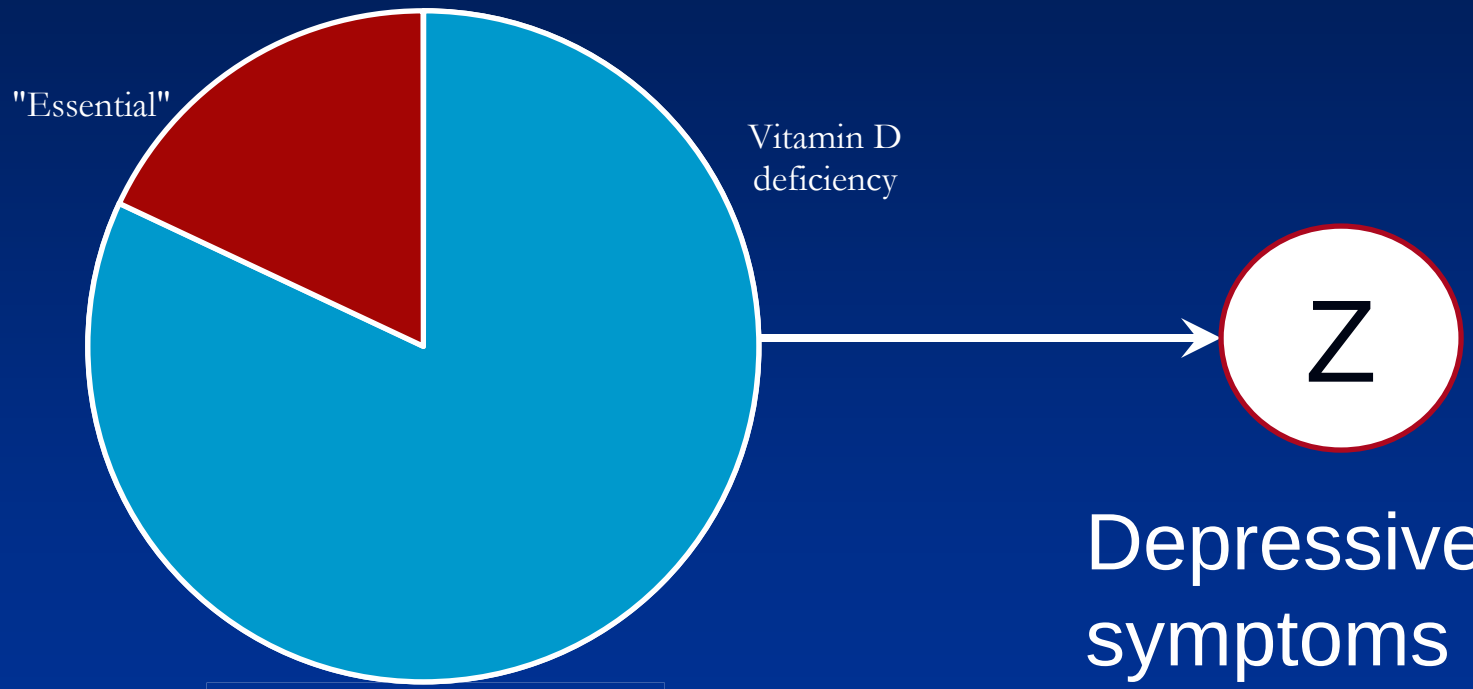
RCT Design 2 for Depression



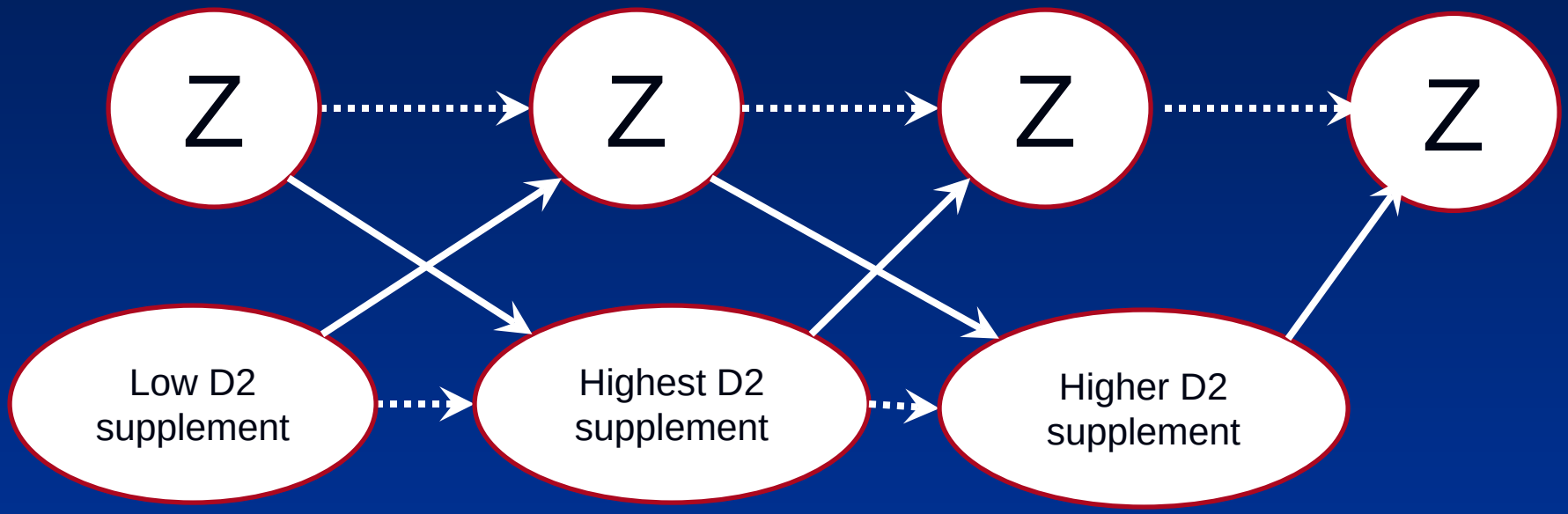
RCT Design 2

- Subgroup those at risk FIRST (by putative cause--D deficiency in this case)
- Randomize just within that smaller subgroup
- ‘Personalized’ comes in by grouping patients into smaller and smaller groups
- Still Normative design
- **Answers the question: In the subgroup with known cause/mechanism, does intervention improve depression for the hypothetical average person?**

RCT Design 3 (N of 1)

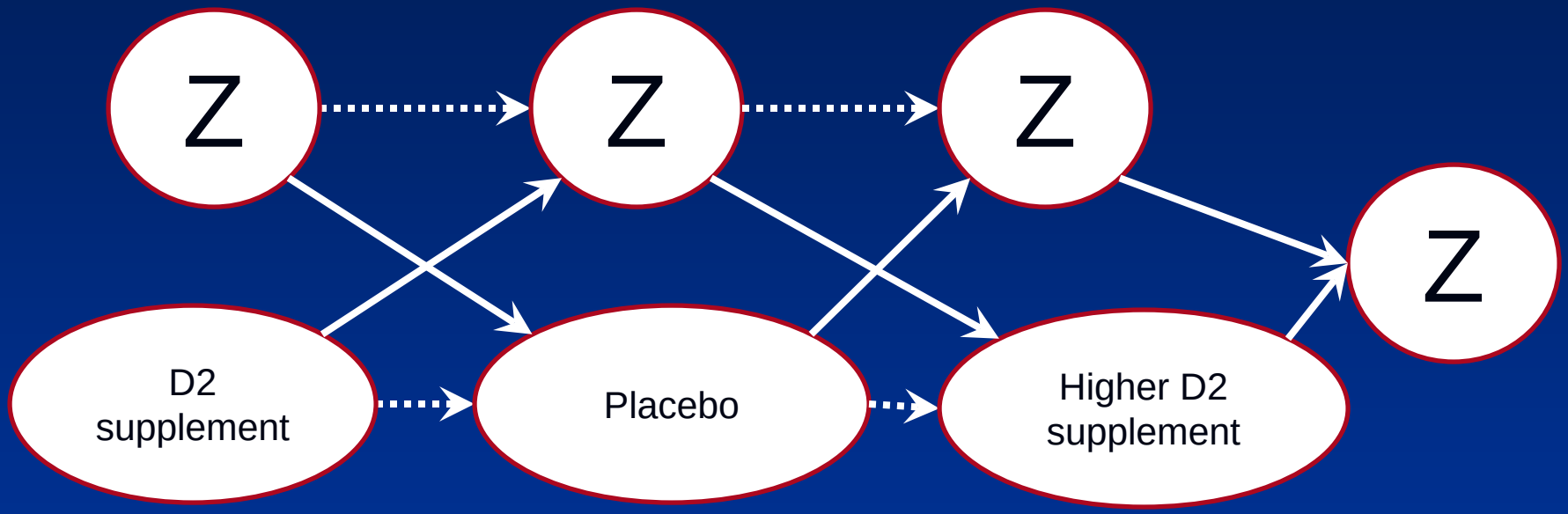


RCT Design 3a (open label)



Z = Depressive symptoms

RCT Design 3b (randomized, controlled)

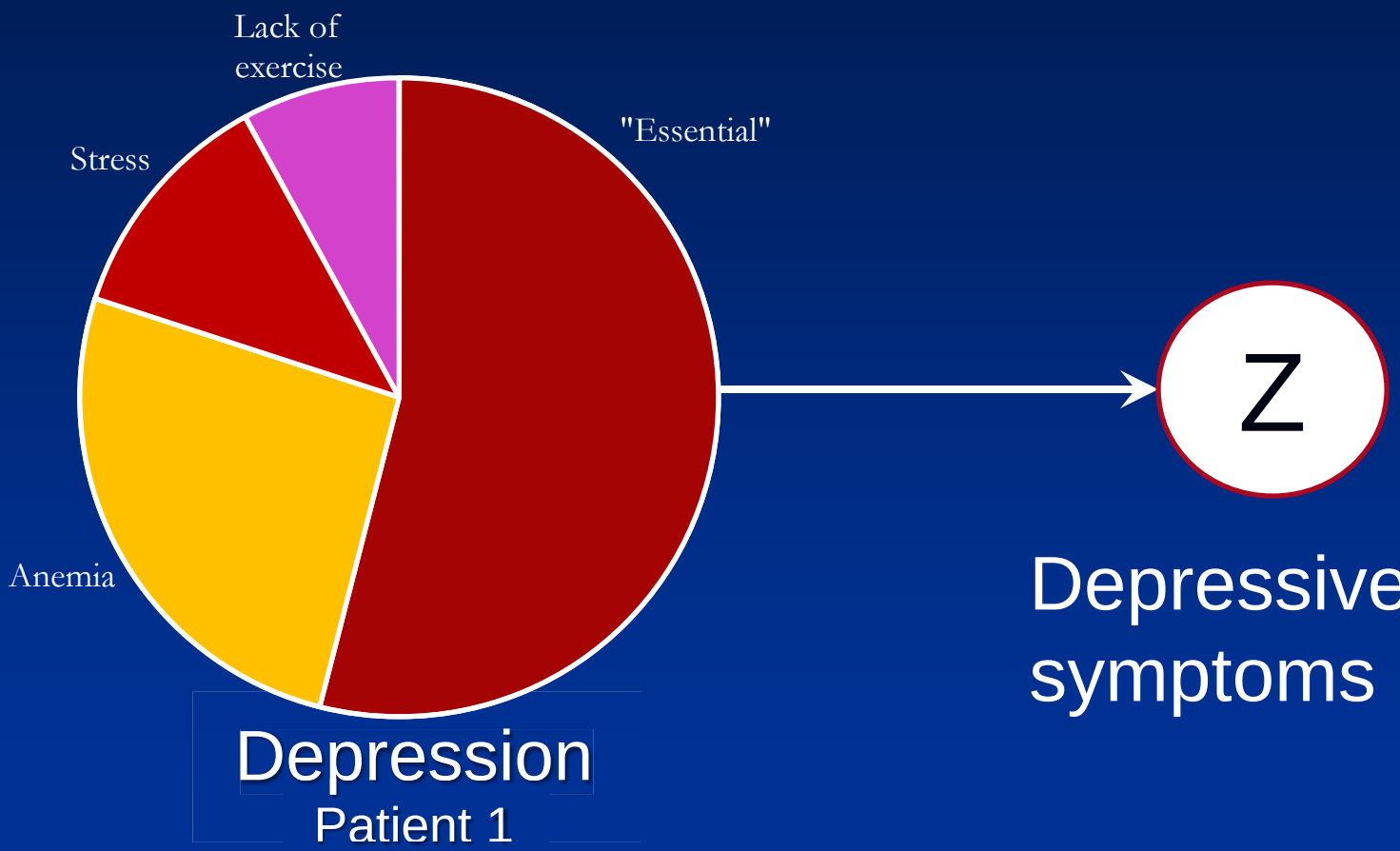


Z = Depressive symptoms

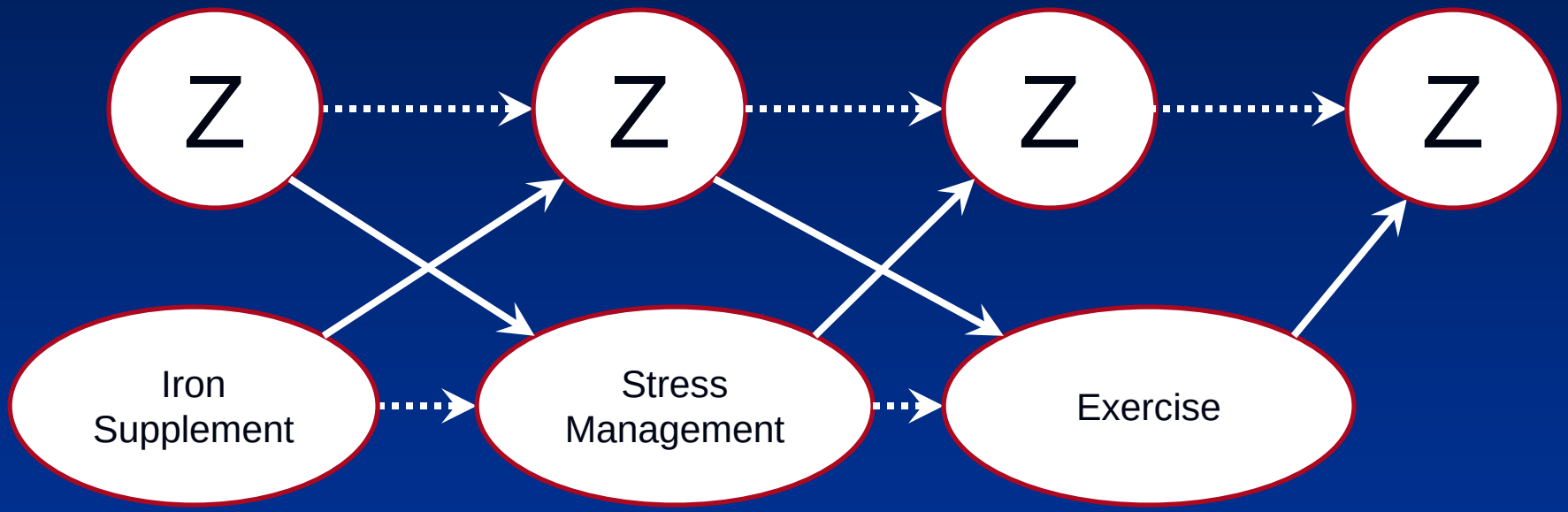
RCT design 3

- In Open label, randomize within patient to individualized dose of treatment
- In Controlled, randomize to placebo/sham or dose escalation within patient
- Individualized design, but tailored to patients specific cause for depression
- **Answers the question: If you treated the predominant underlying cause in depressed patients in intervention, did you improve depression IN THAT PERSON?**

RCT Design 4 (N of 1)

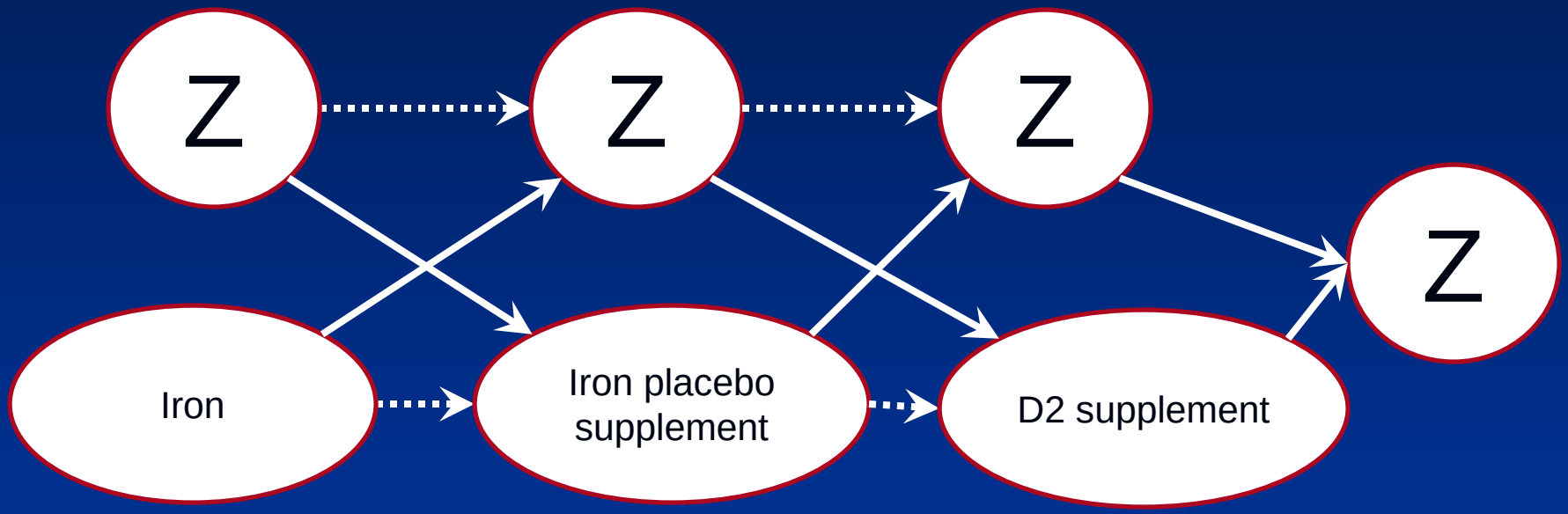


RCT Design 4a (open label)



Z = Depressive symptoms

RCT Design 4b (controlled)



Z = Depressive symptoms

RCT design 4

- In Open label version, randomize within patient to individualized treatment or usual care
- In Controlled version, randomize within patient to sham or treatments
- Individualized design, and tailored to patients specific causes/mechanisms for depression
- **Answers the question: If you intervene on idiographic underlying causes/mechanisms present in each patient, can you improve depression IN THAT PERSON?**

Example of RCT #4 (controlled)

- As is the case with most clinical decisions, predictions are necessary about a single concrete patient, rather than a hypothetical, normative one.
- For example, research has shown that Ritalin affects appetite across children, but this result may or may not apply to a single child, with many other co-existing difficulties.

Richard, 7.5 year old, 34 lbs, Nonorganic failure to thrive, ADHD; Oppositional defiant disorder. Already at 60 mg/day Ritalin. Hospitalized at request of pediatrician to increase Ritalin beyond maximum dose.

Interventions of Interest:

Lack of Medication	Lack of Structure
Lack of sleep	Exposure to Mother
Lack of food	Exposure to failure

For every two hour period during the day (for four weeks) masked school and the hospital staff completed a behavior analysis sheet, upon which the presence or absence of problematic behaviors were recorded, along with the presence or absence of the possible causal variables:

1. How much predictability/structure was there in his life? 1=none, 5= lots
2. How was his mood? 1=very negative, 5=very positive
3. Was there any oppositional behavior? (yes or no)
4. Did he appear fidgety or distractible? (yes or no)
5. Did he mention his mother? (yes or no)
6. Did his mother call or visit? (yes or no)
7. Did you see any obsessive/compulsive behavior? (yes or no)
8. Did he eat something (yes or no; calorie count if yes)
9. Did he have a failure experience? (yes or no)
10. Did he threaten you with running away? (yes or no)
11. Did he mention hurting or killing himself? (yes or no)
12. Did he mention hurting or wishing someone else was dead? (yes or no)

Also completed (Acters) scale as well as the Conners Teachers Rating form daily.

Results

1) Both the Teacher's Conners scale completed by teachers, as well as the Acters scale completed by the hospital staff, showed no significant Ritalin-related change in Richard's behavior.

2) 1050 calories daily on Ritalin, 1250 calories daily when not on Ritalin.

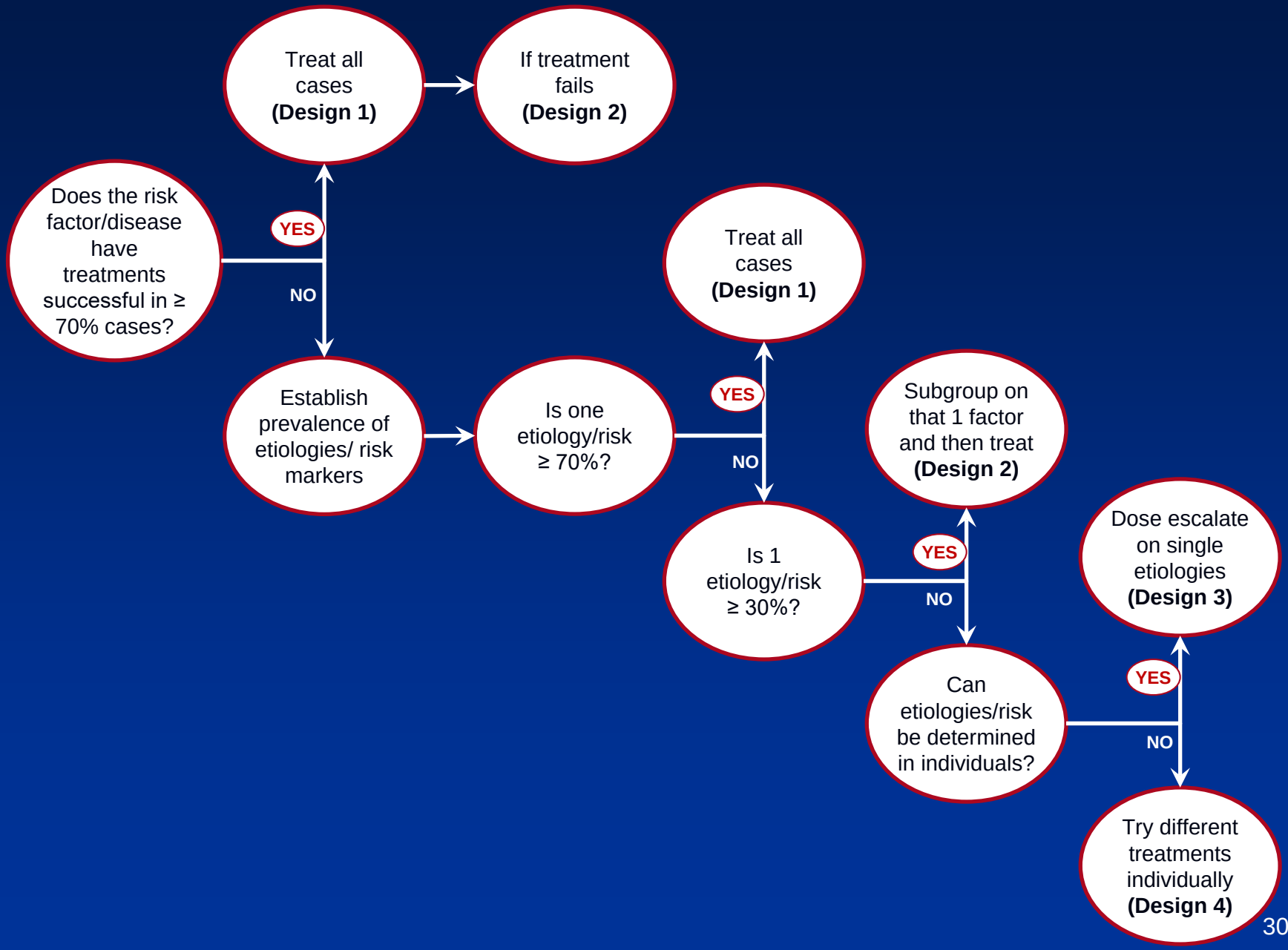
3) On Ritalin increase in tics and nervous movements was noted.

Results

	Distractible Behavior	Suicidal intent/ behavior	Threatening to hurt others	Caloric intake
Ritalin	8% (-r Ritalin)	11% (+r for Ritalin)		11%
Lack of Structure			18%	
Presence of Mother	24%	20%		16%
Failure experience			9%	
Caloric Intake			5%	

Disposition of Case

- Went to court with data, rather than abuse
- Little Richard went into individual foster care, and back to 30 mg/ritalin
- 6 months later, he had gained 22 lb, and there had been no suicidal or homicidal threats at school for almost 3 months.
- His mother had borne another infant
- (66 children had been placed in foster care out of one family of 7 siblings)


Treat all cases (Design 1)
If treatment fails (Design 2)
Does the risk factor/disease have treatments successful in ≥ 70% cases?
YES
NO
Establish prevalence of etiologies/ risk markers
Is one etiology/risk ≥ 70%?
YES
NO
Treat all cases (Design 1)
Is 1 etiology/risk ≥ 30%?
YES
NO
Subgroup on that 1 factor and then treat (Design 2)
Can etiologies/risk be determined in individuals?
YES
NO
Dose escalate on single etiologies (Design 3)
Try different treatments individually (Design 4)

"*One should obtain repeated measures on particular individuals and have an adequate basis for generalizing from idiographic analyses of individuals to regularities that characterize all individuals*"

John Nesselroade, too long ago (1991)

THANK YOU

COLUMBIA UNIVERSITY
MEDICAL CENTER

Funded by the National Heart Lung and Blood Institute

N01-HC-25197, P01HL088117-02

Do we need to determine Prevalence of “Essential” and Secondary Difficult Behavior causes?

YES. We need a normative, or common core of causes that we assess in ALL observational studies, with identical measures, so we can better understand prevalence normatively and within-subject

Do we need to determine Prevalence of “Essential” and Secondary Difficult Behavior causes Within-subject?

YES. We need a core of causes that we assess in many single patients, with identical measures, so we can better understand prevalence within-subject

Should we try RCT design 1?

YES. We should start treating to target, while keeping in mind that we also can be collecting prevalence information

Should we try RCT design 2?

YES. If we have some clear subgroups based on cause or mechanism which are reasonably prevalent, and if treatments are available.

Should we try RCT design 3 & 4?

YES. If we could set up a registry of reasonably prevalent Preventive Behavior causes/mechanisms, we could ask individual clinicians to run N of 1 trials (open and closed), and upload the results to a common registry.