500 Class 2 Slides

github.com/THOMASELOVE/2020-500

2020-01-23

Agenda for Class 02

- The Hormone Replacement Therapy Story
  - Can Selection Bias Explain the Story?
- Tools for Assessing Causal Effects
  - Subclassification and Cochran's Example
  - Using Matched Sets to Adjust for Overt Bias
- Defining and Motivating the Propensity Score
- Matching using the Propensity Score: The Key Ideas

Also . . .

- Homework 1: The DIG Trial (and Logistic Regression)
- Rosenbaum Chapters 1-2 (Part I. Randomized Experiments)
  1. A Randomized Trial
  2. Structure

The Hormone Replacement Therapy Story

Testing out Cause and Effect: Comparing Potential Outcomes

- The causal effect of a treatment is based on a comparison of two potential outcomes.
  - Outcome patient would have if treated.
  - Outcome patient would have if untreated.
- Causal effect = Treated - Untreated difference (or ratio, or whatever)

The key problem is that we only get to observe **one** of these outcomes.

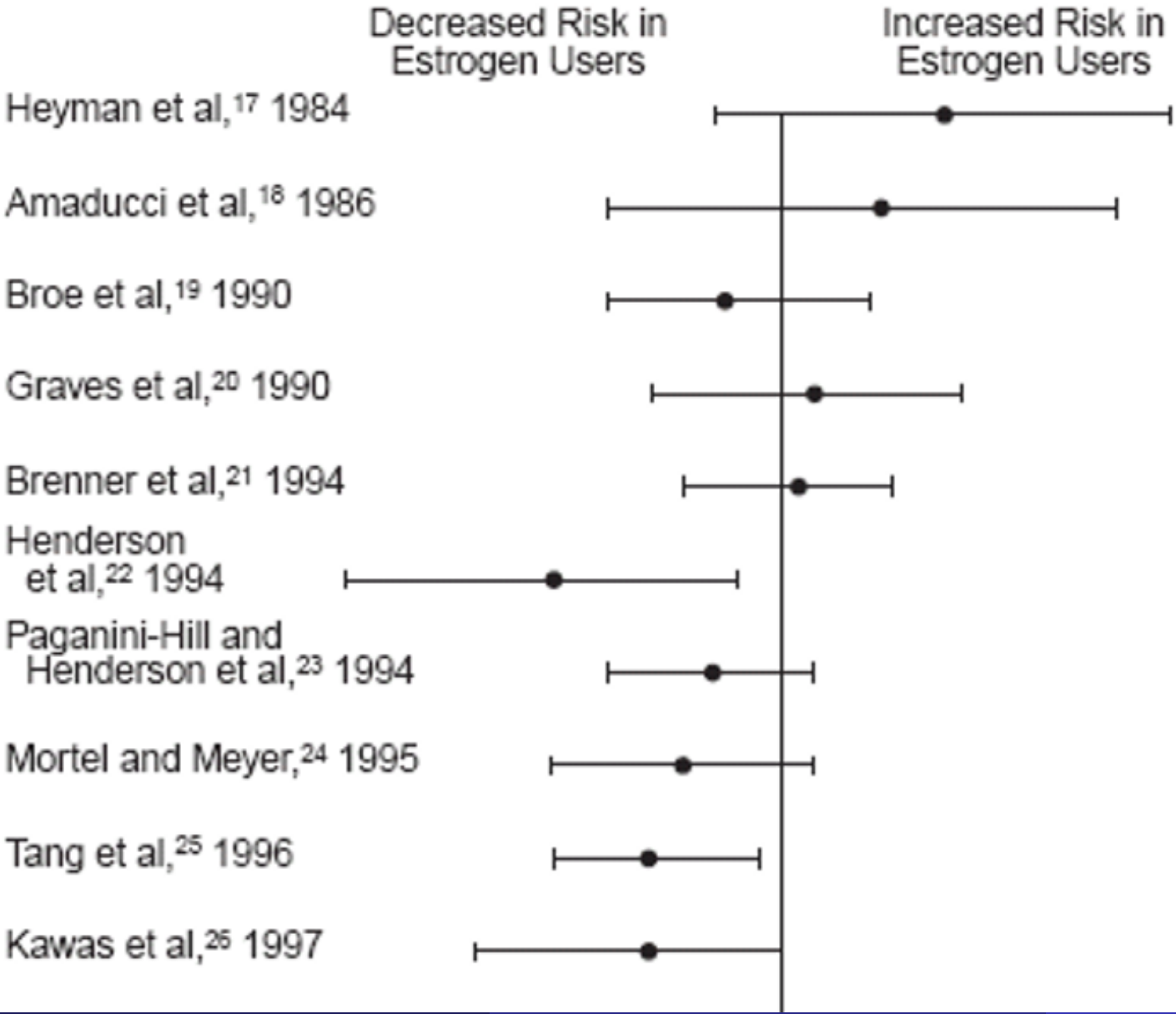
Hormone Replacement Therapy and Dementia

1998 Meta-Analysis[1]

- Estrogen associated with a 29% decreased risk of dementia
- Promising results for Alzheimer's disease (see next slide)

[1] Yaffe et al 1998

1998 Meta-Analysis of Estrogen & Alzheimer's Disease



Hormone Replacement Therapy and Dementia

- 2001: "Estrogen and HRT users have . . . a 20% to 60% reduction in the risk of Alzheimer's disease."

Hormone Replacement Therapy and Dementia

BUT

- These studies discussed in the 1990s are, for the most part,
  - small in size
  - short in duration
  - non-randomized,
  - and uncontrolled.
- The largest and most methodologically sound observational study (Barret-Connor et al. 1993 JAMA) of the effect of estrogen use on *cognition* in non-demented women showed no benefit.

Hormone Replacement Therapy and Dementia

- 2001: "Estrogen and HRT users have . . . a 20% to 60% reduction in the risk of Alzheimer's disease."[2]
- 2005: "Estrogen with or without progestin, given to women 65 years and older . . . substantially increases the risk of dementia of any cause and cognitive decline."[3]

[2] Burkman et al. August 2001 Am J Obstet Gynecol

[3] Craig et al. March 2005 Lancet Neurol

Cache County Memory Study

Prospective study of incident dementia[4]

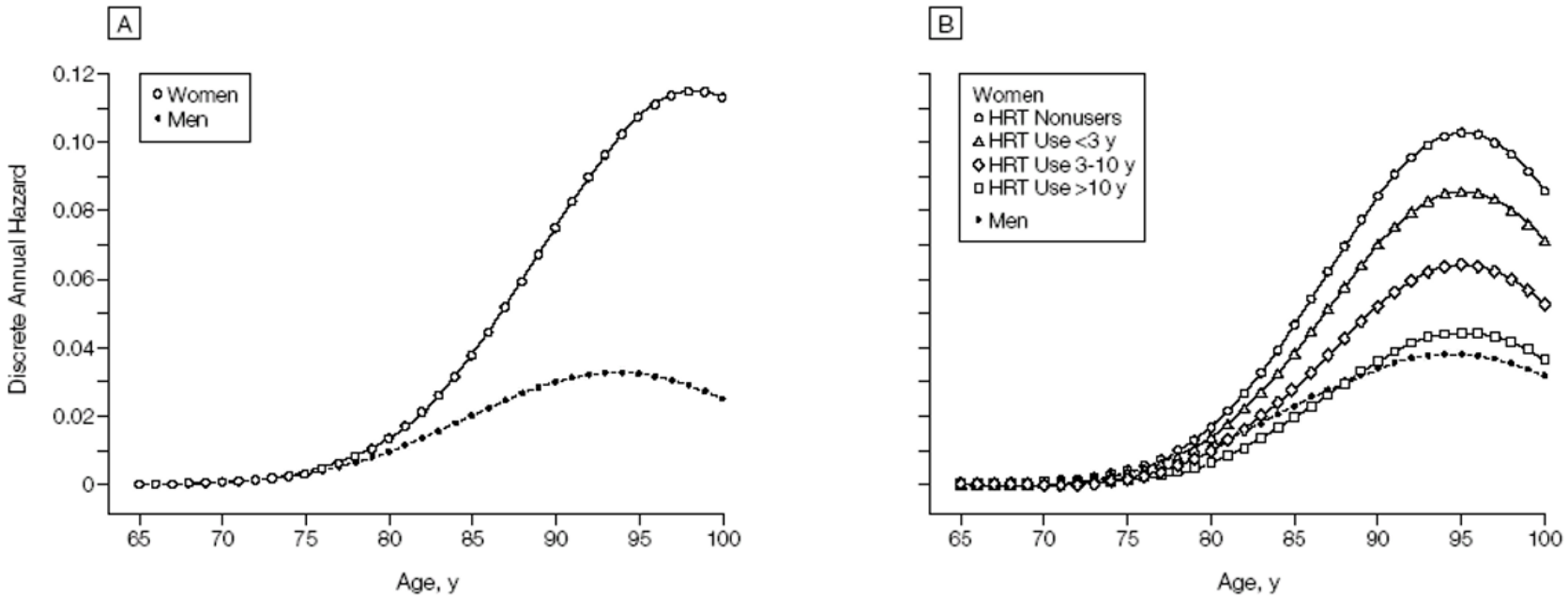
- This was a prospective study of incident dementia among 1357 men and 1889 women residing in a single county in Utah. Patients were first assessed in 1995-97, with follow-up 3 years later.
- Adjustments in models included terms for age and age squared, years of education, and presence of 1 or 2 APOE $\epsilon 4$ alleles, and interactions.

Figure on next slide...

[4] Zandi et al. 2002

Cache County Memory Study

Figure 2. Estimated Discrete Annual Hazard of Alzheimer Disease for Men and Women by Age, and by Duration of Hormone Replacement Therapy Use for Women



Both figures indicate risks estimated for an individual with the mean value of 13 years of education and no ϵ4 alleles at *APOE*. A, The curves depict the annual hazards predicted by fitting the base model including an age-by-sex interaction term. The annual hazard for Alzheimer disease (AD) appears similar for men and women before 80 years of age but diverges rapidly afterward with an excess risk found in women. B, The curves depict the annual hazards predicted by fitting model 7 of Table 3 to the women with available hormone replacement therapy (HRT) exposure information and, in filled circles, the corresponding annual hazards for men after omitting the terms for HRT. There were 35 instances of incident AD among 1357 men. Ordinate values for women differ slightly from those in panel A due to omission of women lacking HRT exposure information, several of whom experienced incident dementia.

Conclusions from Cache County

- Women using HRT had a reduced risk of AD compared with non-HRT users (adjusted HR is 0.59).
- Risk varied with duration of HRT use, so that a woman's sex-specific increase in risk disappeared entirely with more than 10 years of treatment.
- Conclusions: Prior HRT use is associated with reduced risk of AD, but there is no apparent benefit with current HRT use unless such use has exceeded 10 years.

WHIMS (Women's Health Initiative Memory Study)

Randomized, controlled trial, reported in 2003[5]

- 4,352 post-menopausal women age 65 or more
- Estrogen + Progestin HRT
  - increased risk (hazard ratio 2.05) for probable dementia
  - treating 434 women age 65+ with combination HRT would cause one new dementia case.
  - NS impact on mild cognitive impairment

[5] Shumaker et al 2003, Shumaker et al 2004, Espeland et al 2004

WHIMS Baseline Comparisons

No significant baseline differences between the two arms of the trial in

- Age, Education,
- Smoking, Diabetes, Prior HRT or Aspirin use,
- or 3MSE score.

Significant differences (comparing E & P to placebo) in

- History of Stroke (1.0% vs. 1.9),
- Statin use (12.0 vs. 9.8), and
- Adherence (E & P less than Placebo)

HRT and Cardiovascular Disease

- Stampfer et al 1985 [Nurses' Health Study] . . . "estrogen reduces the risk of severe CHD."

HRT and Cardiovascular Disease

- Stampfer et al 1985 [Nurses' Health Study] . . . "estrogen reduces the risk of severe CHD."
- Col et al 1997 (JAMA) . . . "HRT should increase life expectancy for nearly all postmenopausal women"

HRT and Cardiovascular Disease

- Stampfer et al 1985 [Nurses' Health Study] . . . "estrogen reduces the risk of severe CHD."
- Col et al 1997 (JAMA) . . . "HRT should increase life expectancy for nearly all postmenopausal women"
- WHI trial 2002 (JAMA) . . . "(HRT) should not be initiated or continued for primary prevention of coronary heart disease."

Selection Bias?

Comparing NHS (OS) to WHI (RCT)

- Healthy User Effect
  - Women with healthy behaviors may select to use postmenopausal hormones. (prevention bias)
- In the NHS,
  - HRT users tended to have better CV risk profiles
  - HRT users were generally better educated
  - Perhaps women taking HRT / ERT were "compliant" and such people have lower CHD risk.
  - HRT users have more contact with physicians, and are perhaps more health conscious, generally.

So... How Can We Avoid Being Misled?

1. What differentiates an observational study from a randomized controlled trial?
   - One key element: potential for selection bias.
2. What is selection bias, and why should I care about it?
   - Baseline characteristics of comparison groups are different in ways that affect the outcome.
   - We often split this into **overt** bias we observe in our measures
   - As compared to **hidden** bias across measures we didn't think to observe.
3. What can be done to deal with selection bias in observational studies?
   - **Propensity score** methods for overt bias.
   - *Sensitivity analyses* to deal with hidden bias.

Homework 1

Task 2: The DIG trial

1. What comparison do you want to make? (And what comparison did the DIG trial want to make?)
2. Why is this of interest? What (direction of) effect is hypothesized?
3. What are the key measures to help address your question of interest?
    - The exposure/treatment (and how will you confirm receipt)
    - The primary outcome (and what type of variable)
    - The important covariates (related to exposure or to outcome, measured prior to exposure)

Task 3: Fitting a Logistic Regression Model

- See answer sketch after 3 PM, and the r-basics materials.
- There will be more opportunities to demonstrate this set of skills.

Tools for Assessing Causal Effects

Assessing the Causal Effect of an Exposure on an Outcome

Objective: Draw causal inferences between [use of exposure vs. non-use] and outcome

- Standard Approach: Risk Adjustment
- Problem: Selection Bias (exposed people are different from unexposed people at baseline, in ways that affect the outcome)
- Idea: Compare exposed to unexposed subjects that looked similar (had similar propensity for exposure) prior to the exposure decision

Overt, but no Hidden Bias Model

Two units with the same value of the covariates **x** have the same probability π of receiving the exposure.

- An observational study is **free of hidden bias** if the unknown π_js are known to depend only on the observed covariates x_j.
- Sometimes this is referred to as "randomization based on covariates"

How can we adjust for overt bias?

Simplest approach: stratify on the covariates **x**

- Exact stratification - two units are in the same stratum only if they have the same value of x.
- If there is no hidden bias and we stratify exactly, then all units in the same stratum have the same probability of treatment, so we can use methods appropriate for a randomized experiment.

A Simple Survival Comparison

Status at 30 days	Alive	Dead	Pr(Alive)
Without Exposure	80	120	0.40
With Exposure	130	70	0.65

- Without Exposure (perhaps as estimated by historical records) only 40% of subjects survived.
- With Exposure, we see a "clinically meaningful" improvement (65% of subjects survived.)
- p value from Fisher's exact test is < 0.001.

But was this a randomized trial, or an observational study?

Simple Survival Comparison

Suppose in addition to

- our **outcome** (Alive or Dead at 30 days)
- and **exposure** status,

we also had a **covariate**, say, sex, available for each subject. Suppose 200 of the subjects in the study are Male, and 200 are Female.

Suppose also that sex might be related to the outcome.

- Can we adjust for sex's effect in assessing the impact of our exposure on that same outcome? How?

Stratification in our Survival Comparison

ALL PATIENTS	Alive	Dead	Pr(Alive)
Without Exposure	80	120	0.40
With Exposure	130	70	0.65

Now, 200 of these subjects are Male, and 200 are Female.

Survival Comparison among Male Subjects

MALE	Alive	Dead	Pr(Alive)
Without Exposure	40	60	0.40
With Exposure	40	60	0.40

No difference between the exposed and unexposed group in terms of survival, among males. Is that also the story for our female subjects?

Survival Comparison among Female Subjects

MALE	Alive	Dead	Pr(Alive)
Without Exposure	40	60	0.40
With Exposure	40	60	0.40

FEMALE	Alive	Dead	Pr(Alive)
Without Exposure	40	60	0.40
With Exposure	90	10	0.90

Stratification allows comparison adjusting for sex.

Cochran's Smoking Example

Cochran's Smoking Example

Outcome: mortality rates of US male [1] cigarette smokers, [2] cigar/pipe smokers and [3] non-smokers

US Death Rates per 1,000 person-years

Smoking Group	Unadjusted Death Rate
Non-Smokers	20.2
Cigarettes only	20.5
Cigars, pipes	35.5

Cochran's Smoking Example

Outcome: mortality rates of US male [1] cigarette smokers, [2] cigar/pipe smokers and [3] non-smokers

Let's look at an important covariate - any suggestions?

Cochran: US Death Rates per 1000 person-years

Smoking Group	Mean Age in Years	Unadjusted Death Rate
Non-Smokers	54.9	20.2
Cigarettes only	50.5	20.5
Cigars, pipes	65.9	35.5

Now, how could we adjust for the impact of age on our estimates of the death rate?

Subclassification on Age (3 subclasses)

Divide the subjects into 3 subclasses on the basis of age (low, middle, high)

1. Calculate "low age" mortality rate in each smoking group
2. Then calculate "middle age" and finally "high age" mortality rate in each smoking group
3. Within the "non-smokers" combine the "low", "middle" and "high" mortality rate estimates by weighting according to the population proportions of "low", "middle" and "high" age.
4. Repeat to obtain estimates for "cigarettes only" and "cigars, pipes"

Cochran: US Death Rates per 1000 person-years

Smoking Group	Mean Age	Unadjusted Death Rate	Adjusted for Age
Non-Smokers	54.9	20.2	20.3
Cigarettes only	50.5	20.5	28.3
Cigars, pipes	65.9	35.5	21.2

Cochran's Smoking Example

Outcome: mortality rates of US male [1] cigarette smokers, [2] cigar/pipe smokers and [3] non-smokers

- Subclassification on the covariate **age**
- Key Finding: Five subclasses are often sufficient to remove over 90% of the bias due to the subclassifying variable or covariate[6].
  - Even as few as 2 or 3 subclasses can have a big impact.

[6] Cochran WG 1968 *Biometrics* 24, 205-213.

Why can't we always just do direct adjustment like this for covariates?

- Because we don't (typically) have only one covariate.
- As the number of covariates increases, the number of subclasses grows exponentially
  - 2 categories for each of p covariates yields 2^p subclasses.
- Also, if p is large, some subclasses will contain no units, or will contain only exposed or unexposed units but not both.

A solution? Propensity scores.

Aspirin Use and Mortality (Gum 2001)

6174 consecutive adults at CCF undergoing stress echocardiography for evaluation of known or suspected coronary disease[7].

- 2310 (37%) were taking aspirin (treatment).
- Main Outcome: all-cause mortality
  - Median follow-up: 3.1 years
- Univariate Analysis: 4.5% of aspirin patients died, and 4.5% of non-aspirin patients died.
  - Unadjusted Hazard Ratio: 1.08 (0.85, 1.39)

[7] Gum PA et al. 2001

Matching on the Covariates, X

- We can create a **matched sample**, where we match treated subjects to control subjects, on the basis of their covariates.
  - Simplest is exact matching - but this can pose problems unless we have few covariates to deal with, with very limited possible values.
  - Often exact stratification or matching is impossible, but when it is, things go smoothly.

What's the difference between Aspirin Users and the other patients?

Variable	Aspirin Users	No Aspirin
Patients	2,310	3,864
Age, Mean (SD)	62 (11)	56 (12)
Male, %	77.0	56.1

Might it be reasonable to match up patients who are the same gender and similar in age? Or to stratify into groups by age and gender?

What's the difference between Aspirin Users and the other patients?

Variable	Aspirin Users	No Aspirin
Patients	2,310	3,864
Age, Mean (SD)	62 (11)	56 (12)
Male, %	77.0	56.1
Prior CAD, %	69.7	20.1
Beta Blocker, %	35.1	14.2

But now what do we do?

- How can we match on Age **and** Gender **and** history of CAD **and** beta-blocker prescription?
- Or (if that's not hard enough) how about the complete set of 31 covariates?

Using Matched Sets or Strata to Adjust for Overt Selection Bias

- Observe a set of p covariates, collected in $\mathbf{X}$
- Even if each covariate is binary, there are 2^p possible values of $\mathbf{X}$
  - Many subjects are likely to have unique values of $\mathbf{X}$.
- Realistic Goal: compare treated and control groups with similar distributions of $\mathbf{X}$, even if matched individuals have differing values of $\mathbf{X}$

Key tool for doing this well: propensity score

What Do We Want to Know about a Clinical or Health System Intervention[8]?

- Response: Can we estimate the impact of the intervention? Can we estimate costs and benefits?
- Predictors: Can we "mine" for attributes that help predict response to the intervention?
- Evaluation: Can we fairly estimate the average health impact of our intervention?
- Target Evaluation: Can we identify likely responders? Subgroup analyses?

[8] from a marketing list at www.anabus.com

The Data You Wish You Had

Subject	Health if exposed	if unexposed
A	12	8
B	7	4
C	7	3
D	12	9

ALL potential outcomes available!

The Data You Wish You Had

Subject	Health if exposed	if unexposed	Exposure Effect
A	12	8	4
B	7	4	3
C	7	3	4
D	12	9	3

Wouldn't this be great!

Grim Reality

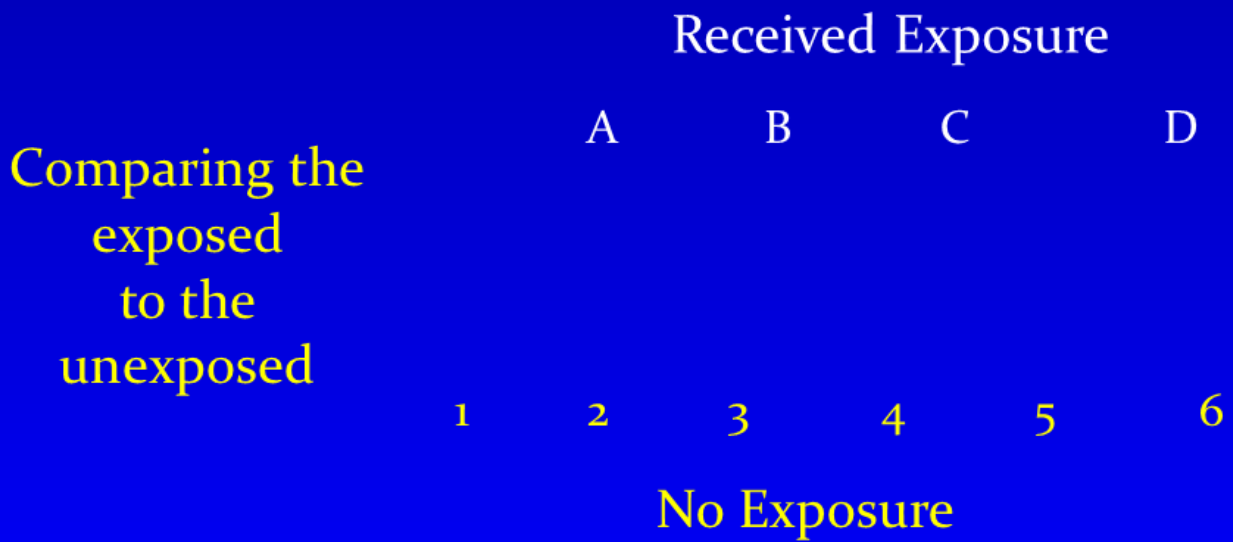
Subject	Health if exposed	if unexposed	Exposure Effect
A	12	?	?
B	7	?	?
C	?	3	?
D	?	9	?

Causal inference is a **missing data** problem.

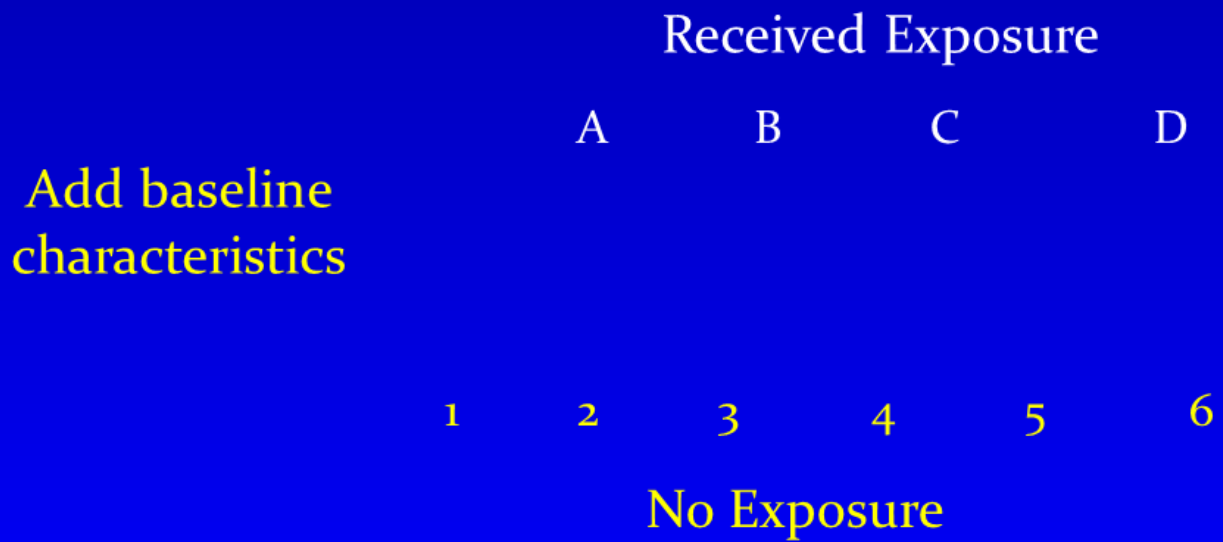
How should we fill in those question marks?

Matching and Causal Effects

Causal Analysis



Causal Analysis



Causal Analysis

Received Exposure

A B C D

Add baseline characteristics

1 2 3 4 5 6

No Exposure

Causal Analysis

Received Exposure

A B C D

Add baseline characteristics

1 2 3 4 5 6

No Exposure

Causal Analysis

Received Exposure

A

B

C

D

Add baseline characteristics

1 2 3 4 5 6

No Exposure

Causal Analysis

Received Exposure

A B C D

Add baseline characteristics

1 2 3 4 5 6

No Exposure

Causal Analysis

Received Exposure

A B C D

Which pairs should we compare?

1 2 3 4 5 6

No Exposure

Causal Analysis

Received Exposure

A B C D

Which pairs should we compare?

1 2 3 4 5 6

No Exposure

Causal Analysis

"Comparing Apples to Apples"

Received Exposure

A B C D

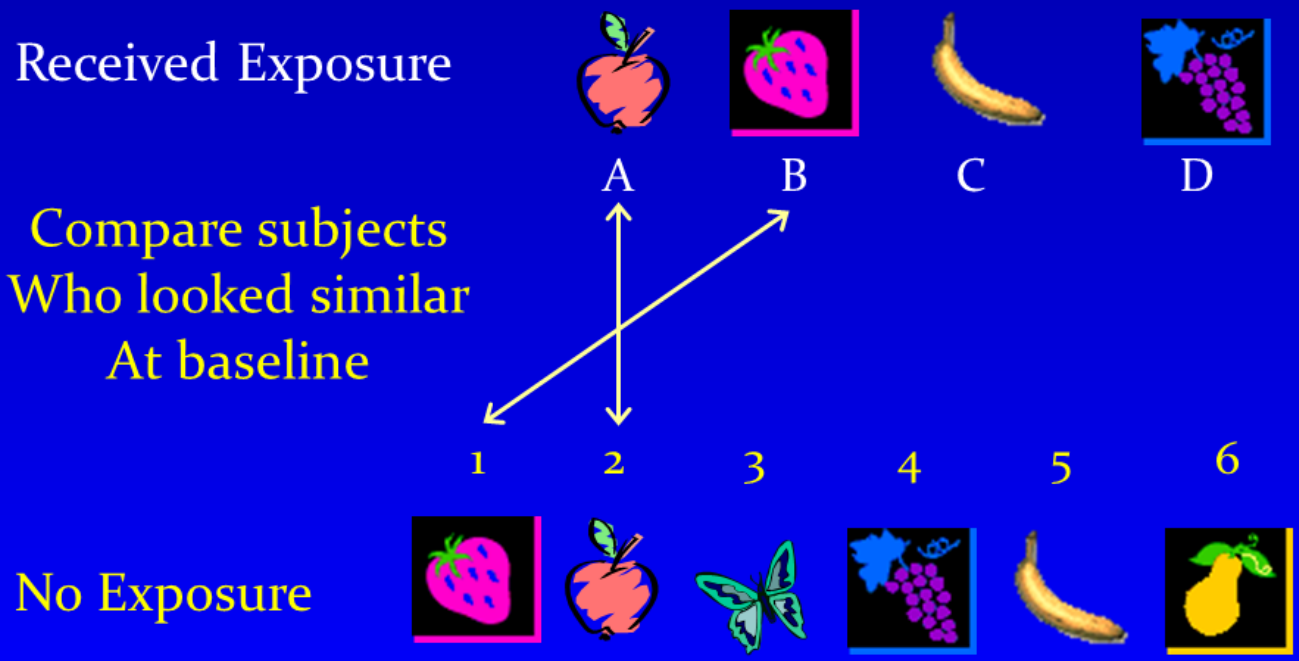
Which pairs should we compare?

1 2 3 4 5 6

No Exposure

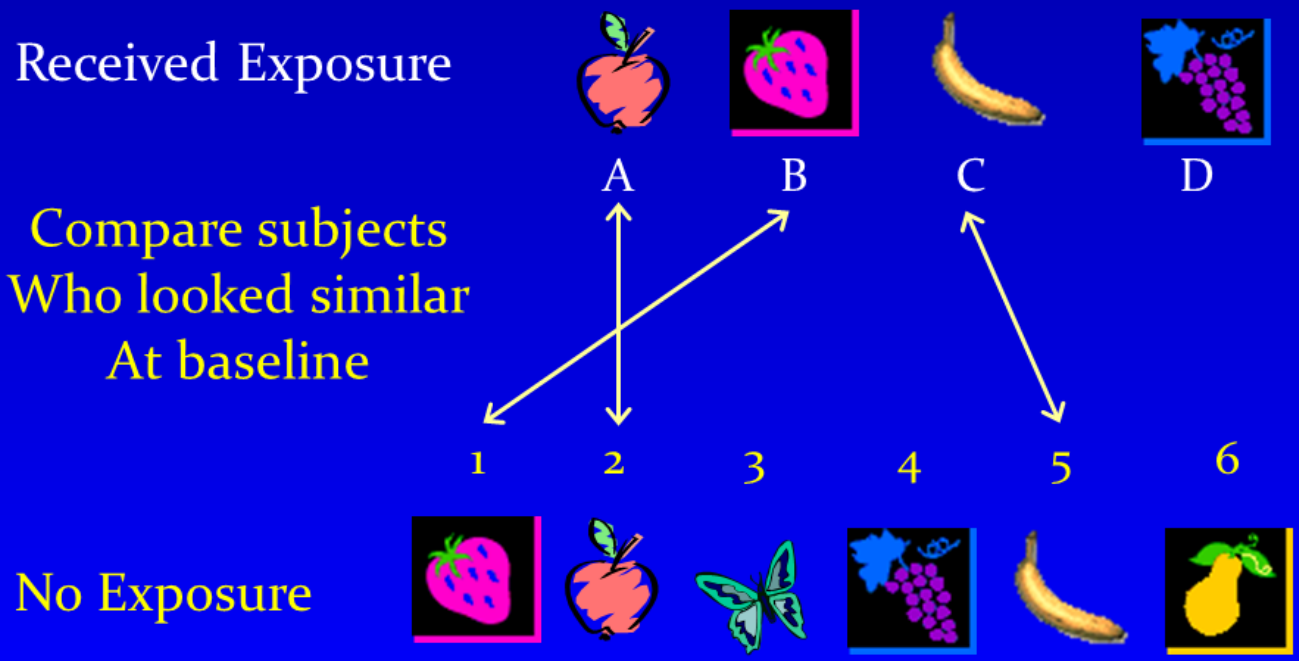
Causal Analysis

"Comparing Apples to Apples"



Causal Analysis

"Comparing Apples to Apples"



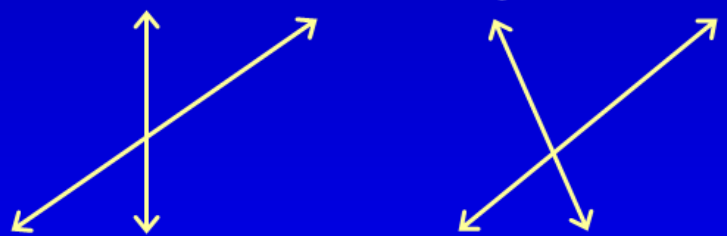
Causal Analysis

"Comparing Apples to Apples"

Received Exposure

A B C D

Compare subjects
Who looked similar
At baseline



1 2 3 4 5 6

No Exposure

The Propensity Score

The Propensity Score

Definition: The conditional probability that a subject receives an exposure given the values of their vector of covariates.

- PS = Pr(exposed | covariates)

Reduces the baseline information to a single, composite summary of the covariates, between 0 and 1.

- Of course, we know whether a subject in fact either receives or doesn't receive the exposure.
- But we will estimate this probability for each subject as a convenient way of expressing the impact of covariate information on the exposure assignment decision, as a scalar value between 0 and 1.

Estimating the Propensity Score (most common approach)

Estimate a Logistic Regression Model:

- Y = Exposure Group
  - 1 = exposed, 0 = unexposed
- Predictors are the observed covariates

Use anything related to exposure decisions that can be collected prior to exposure assignment.

Propensity Scores = Predicted Pr(exposure) for each subject, i.e. the **fitted values**

Why Estimate the Probability that a subject was "exposed"?

- Using Pr(subject would have been exposed), we create a quasi-randomized experiment.
- If we have two subjects, one treated and one control, with the same propensity score, we can imagine that these two subjects were randomly assigned to each group - just as if we were doing an experiment!
- Except that here we can't assume that we control for anything that we didn't measure.

Causal Analysis

Causal Analysis

Received Exposure .62

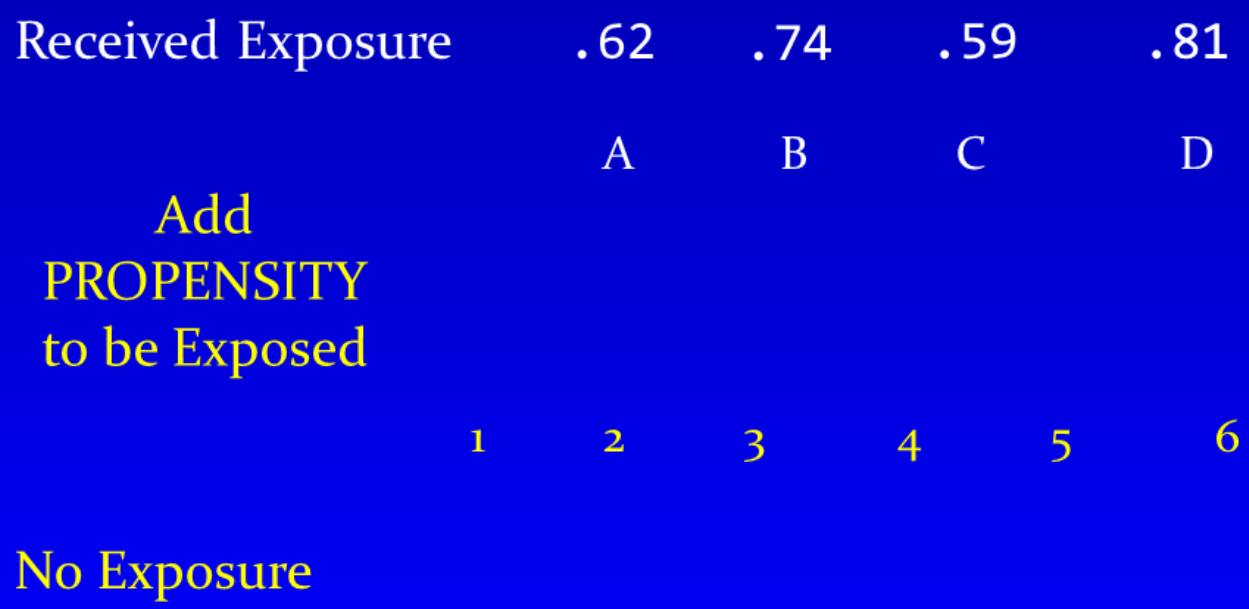
A B C D

Add
PROPENSITY
to be Exposed

1 2 3 4 5 6

No Exposure

Causal Analysis



Causal Analysis

Received Exposure

.62	.74	.59	.81
A	B	C	D

Add PROPENSITY to be Exposed

1	2	3	4	5	6
.74	.62	.36	.80	.58	.23

No Exposure

Causal Analysis

Received Exposure

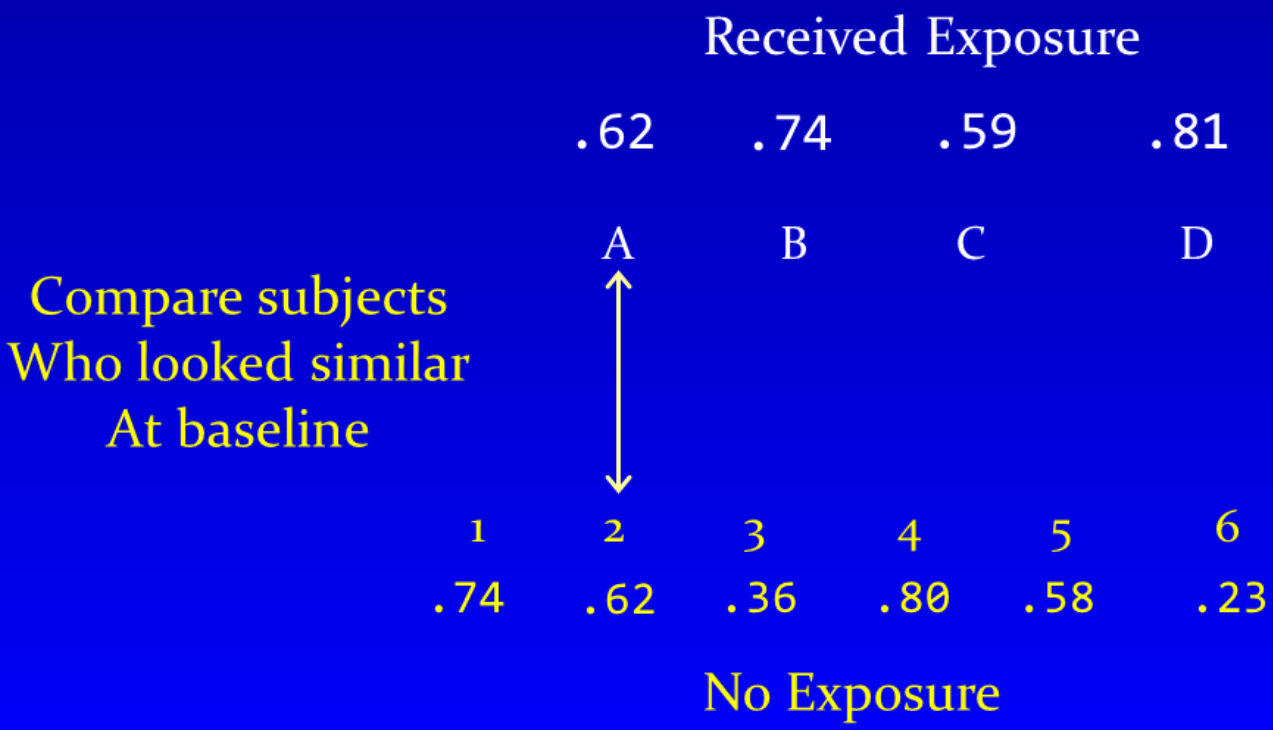
.62	.74	.59	.81
A	B	C	D

Which pairs should we compare?

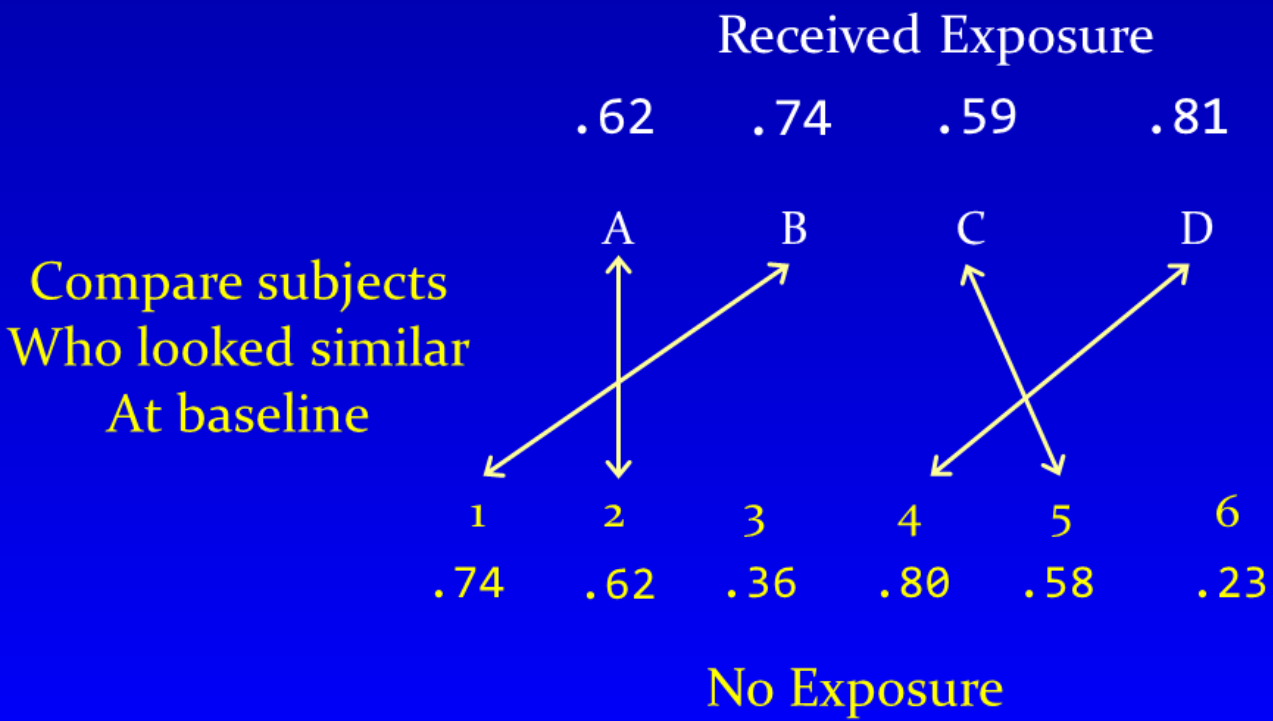
1	2	3	4	5	6
.74	.62	.36	.80	.58	.23

No Exposure

Causal Analysis



Causal Analysis



Grim Reality

Subject	Health if exposed	Health if unexposed	Exposure Effect
A	12	?	?
B	7	?	?
C	?	3	?
D	?	9	?

Improving Grim Reality

Subject	Propensity for Exposure	Health if exposed	if unexposed
A	0.80	12	?
B	0.50	7	?
C	0.51	?	3
D	0.79	?	9

- Can we use the propensity score to guide our matching approach?
- Can we plug in resulting estimates for our question marks?

Propensity Score Matching yields a new Database

Subject	PS	Health if exposed	if unexposed	Exposure Effect
A	0.80	12	[9]	[3]
B	0.50	7	[3]	[4]
C	0.51	[7]	3	[4]
D	0.79	[12]	9	[3]

Now, we can estimate the **impact of the exposure** on each matched patient.

How Do We Use the Propensity Score?

1. Start with a sample where the exposed subjects don't look very much like the unexposed subjects.
2. Adjust the sample (in some manner) to make the distributions of exposed and unexposed subjects look more similar prior to exposure.
3. This will let us attribute the differences we see in outcomes between these adjusted samples more easily to the exposure's causal effect, and not so much to the original differences between the groups.

- To do this, we estimate the propensity score: the probability of receiving the exposure for each subject given their covariate values.
- Then, we use the propensity score in one of the ways listed on the next slide to fuel our estimates of causal effects.

Methods for Using Propensity Scores

- Subclassification / Stratification on the Propensity Score
- Direct (Regression) Adjustment using the Propensity Score
- Matching using the Propensity Score
- Weighting using the Propensity Score
- Combining Approaches for More Robust Estimation

I'll demonstrate R code for all of these ideas soon, but first, we'll discuss them without the hassle of trying to get the machine to run them for us.

Rosenbaum, Chapters 1-2

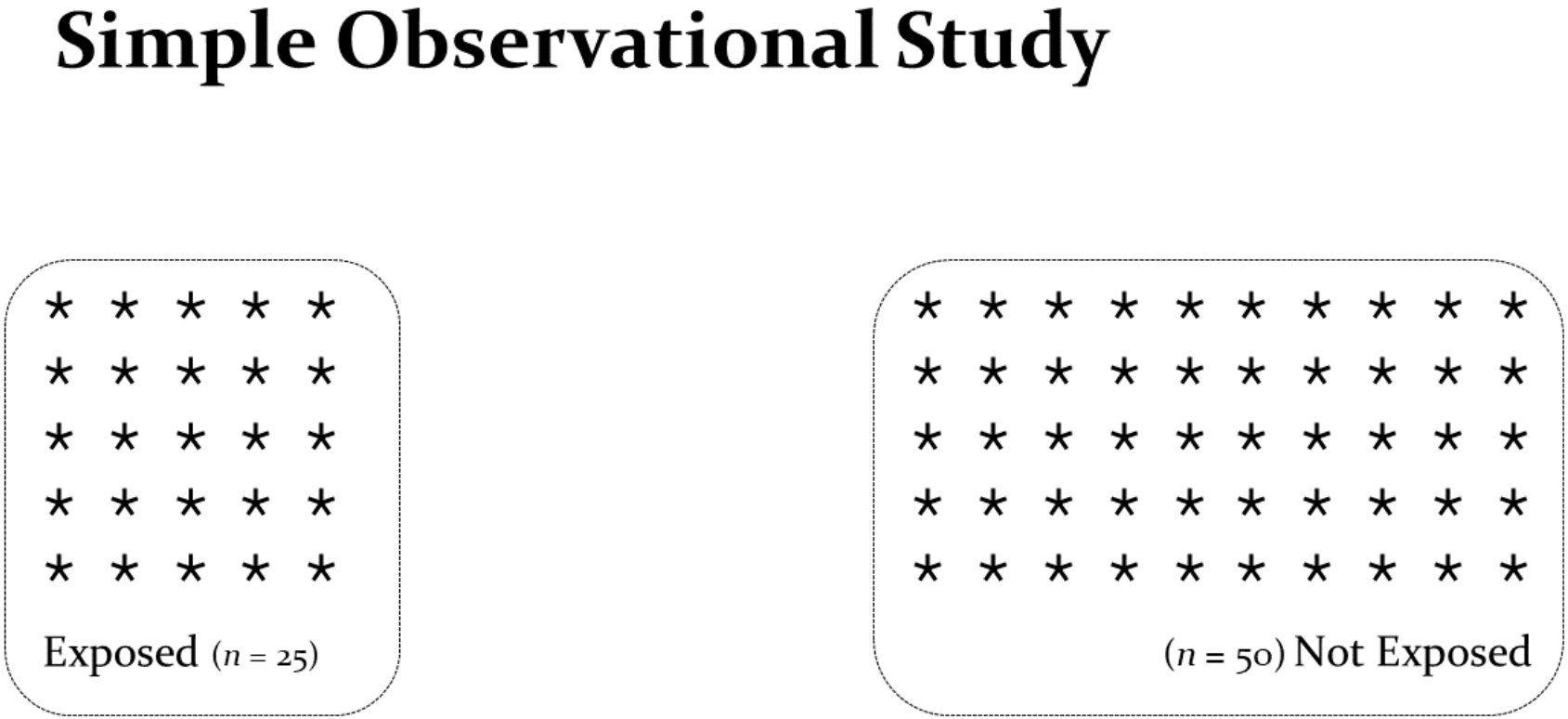
Rosenbaum, Part I

1. A Randomized Trial
2. Structure
3. *Causal Inference in Randomized Experiments*
4. *Irrationality and Polio*

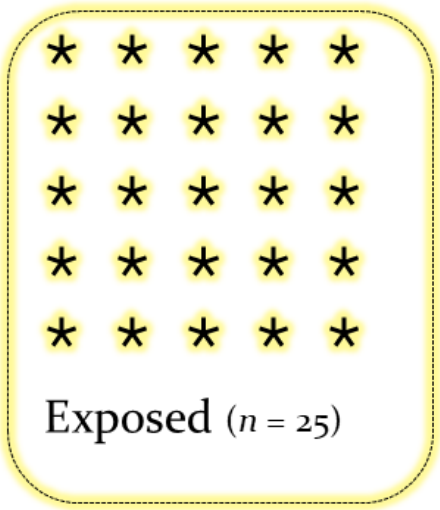
- What was the most **important** thing you learned from reading Chapters 1-2?
- What was the **muddiest**, least clear thing that arose in your reading?
- What questions are at the front of your mind now?

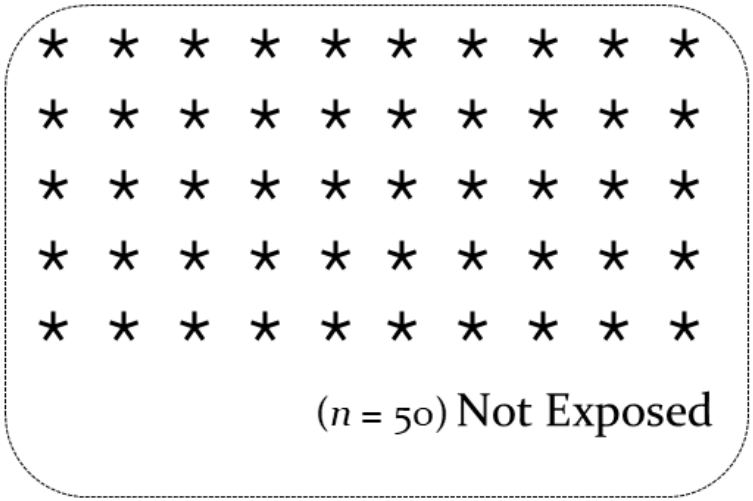
Using the Propensity Score: Some Schematics

A Simple Observational Study

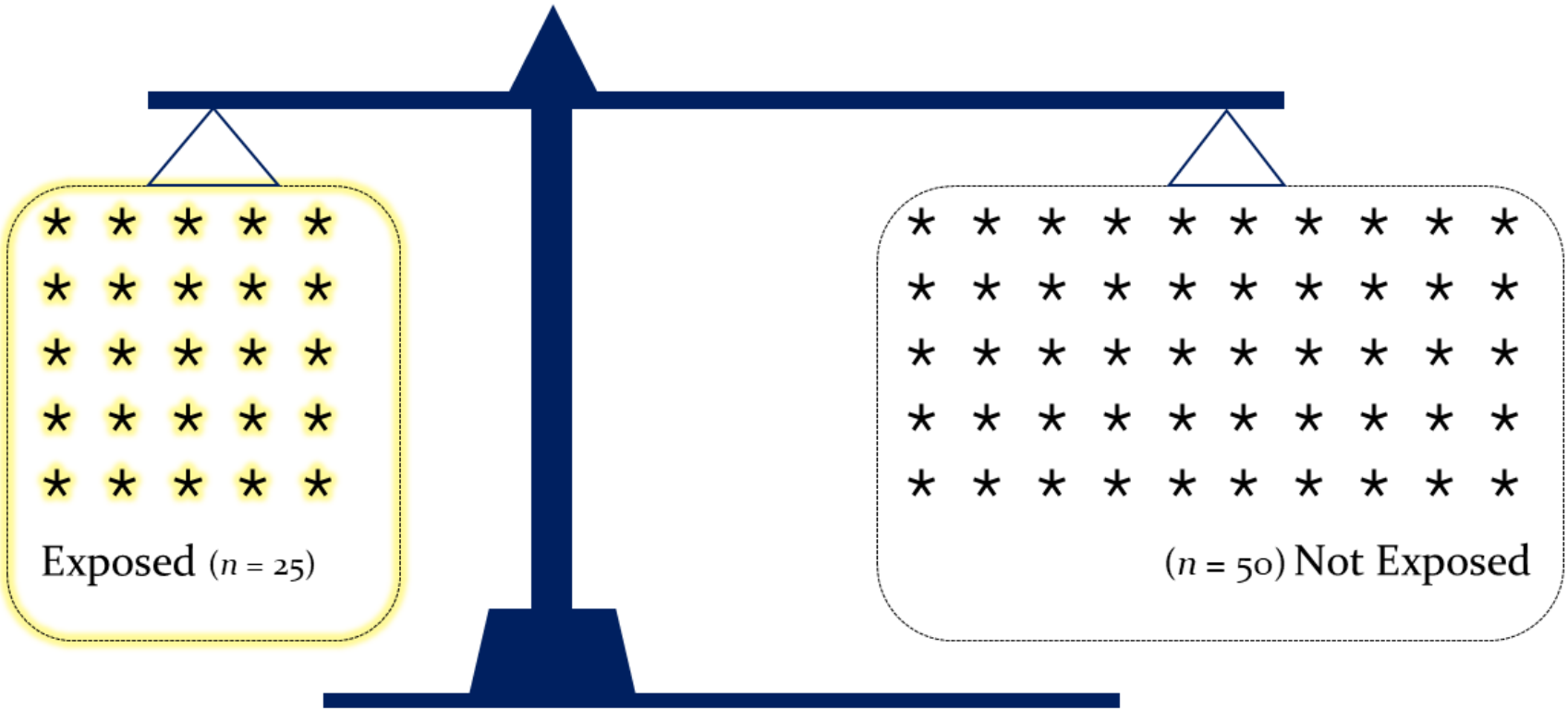


Apply the Exposure





To estimate causal effects, we need the baseline covariates to be in balance...



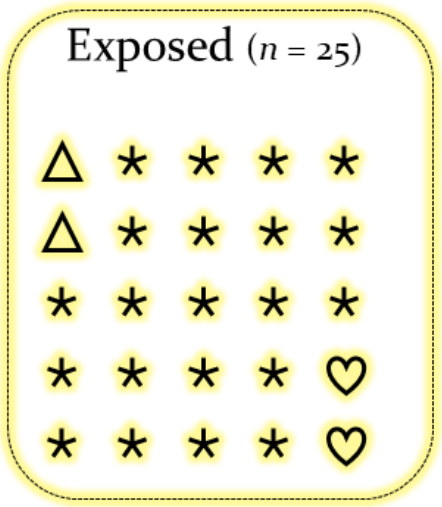
Model Without the Propensity Score

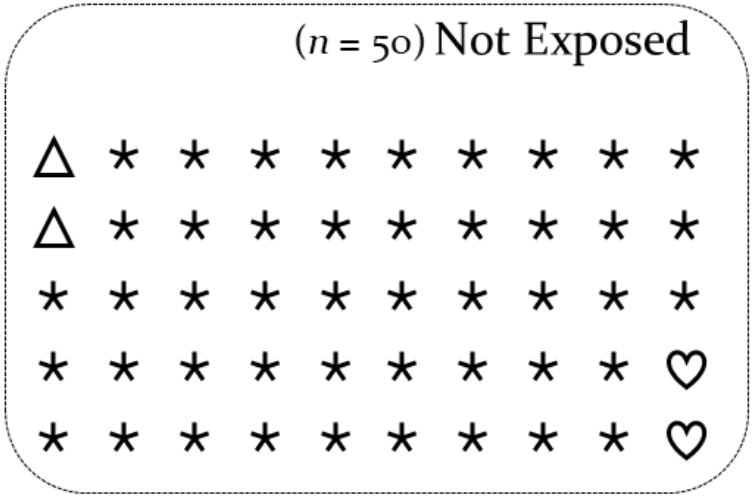
Outcome = $ß_0$ + $ß_1$*Exposure,

for pool of 75 subjects

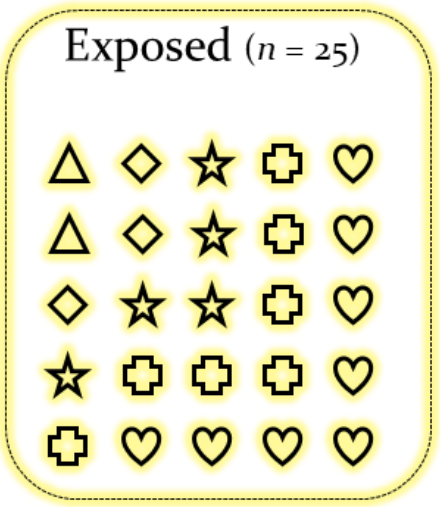
We interpret $ß_1$ as the exposure's effect.

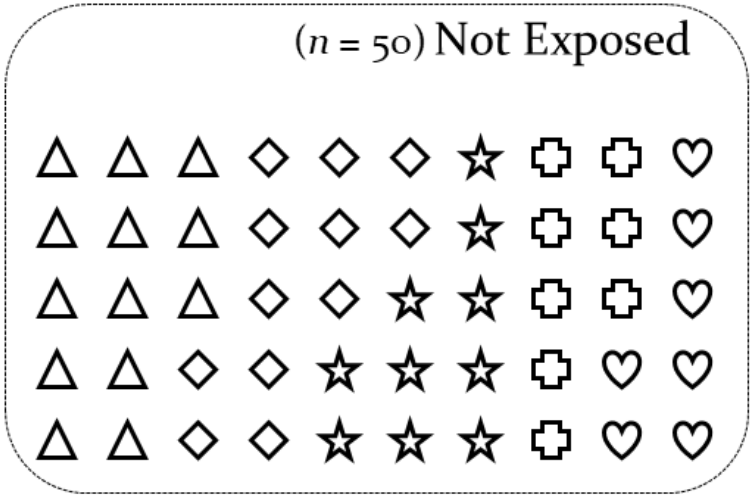
Subjects vary, within exposure groups...



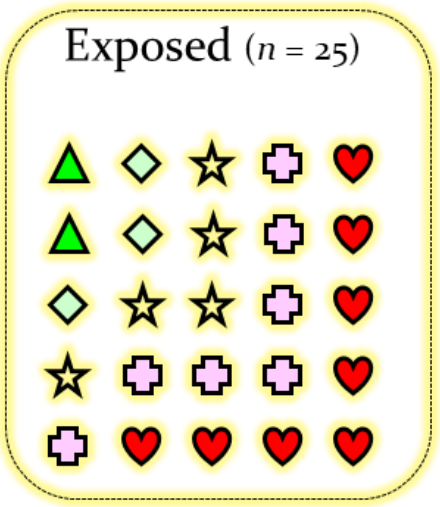


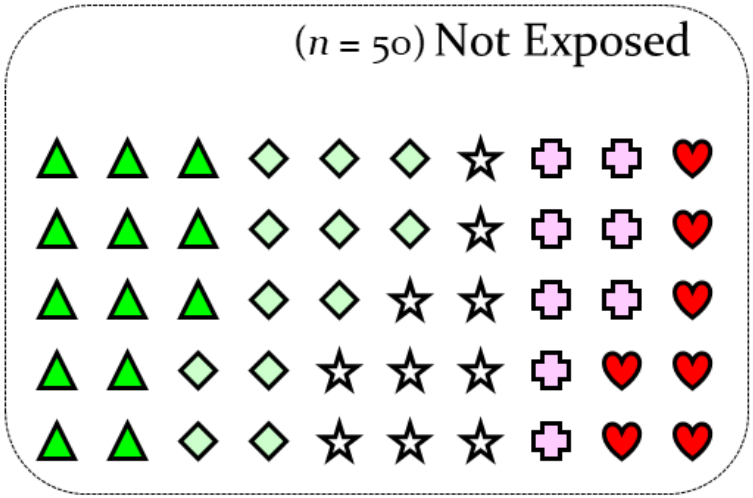
Actually, they vary quite a bit ...



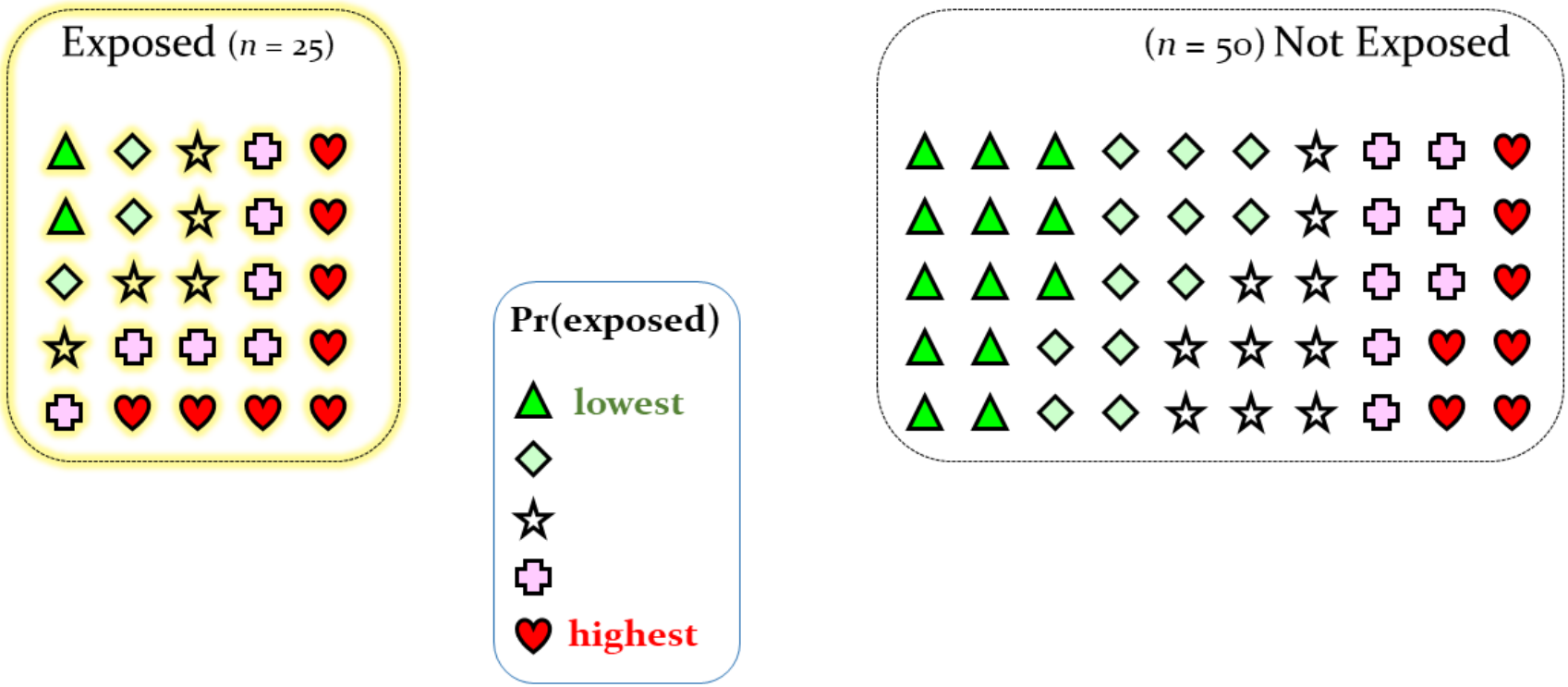


Actually, they vary even more than that

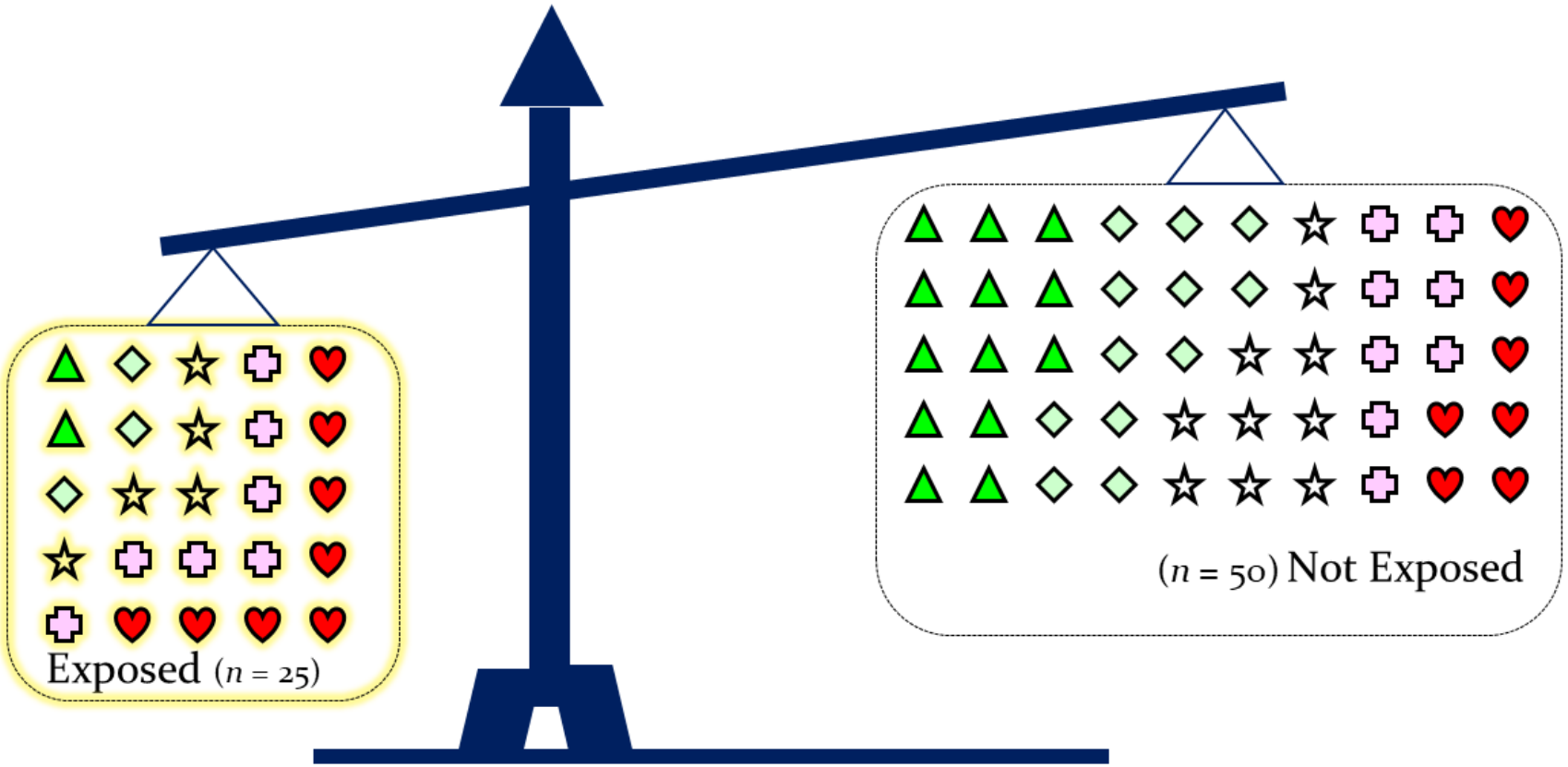




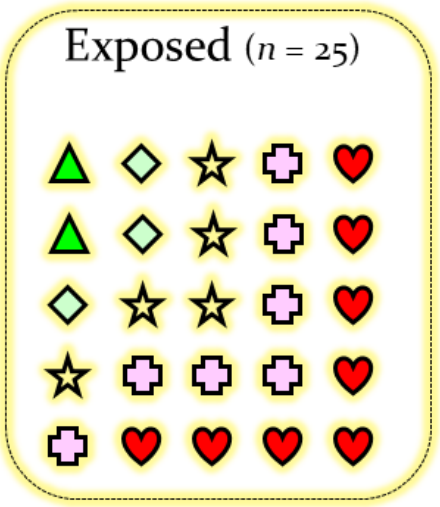
Characterize by propensity to receive the exposure...

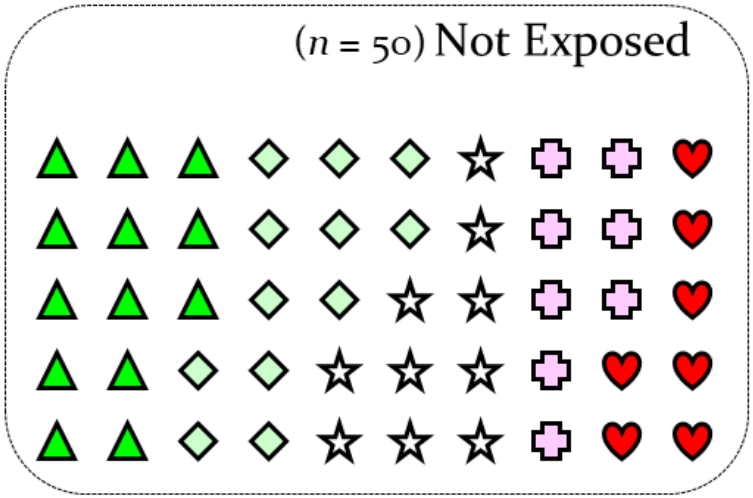


Are baseline characteristics in balance?



Comparing Exposure Groups Fairly?



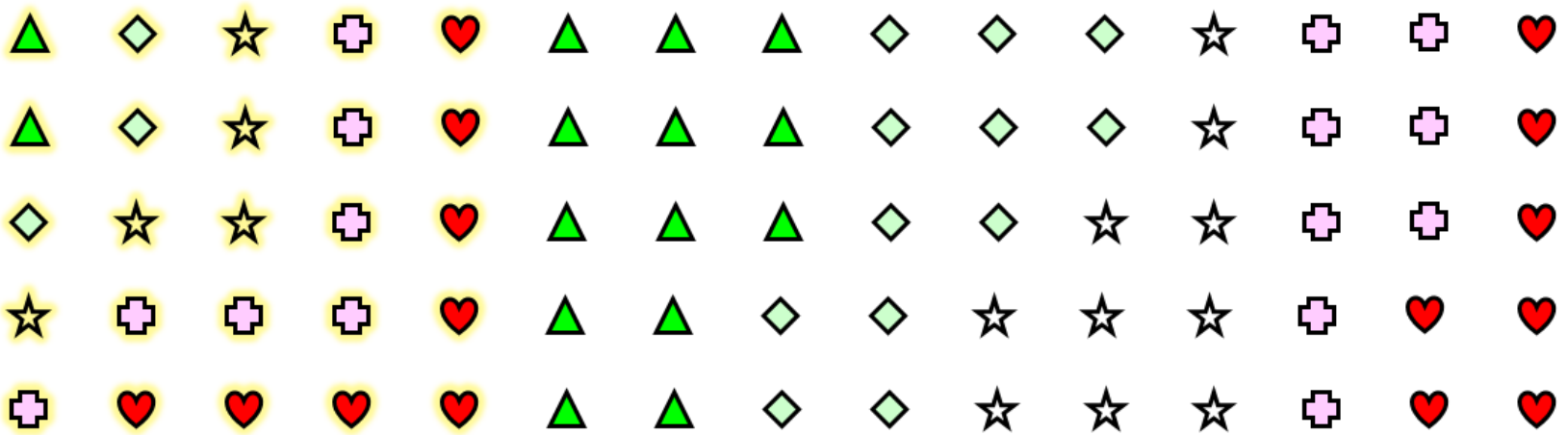


Model Without the Propensity Score

Outcome = $ß_0$ + $ß_1$*Exposure,

for pool of 75 subjects

We interpret $ß_1$ as the exposure's effect.

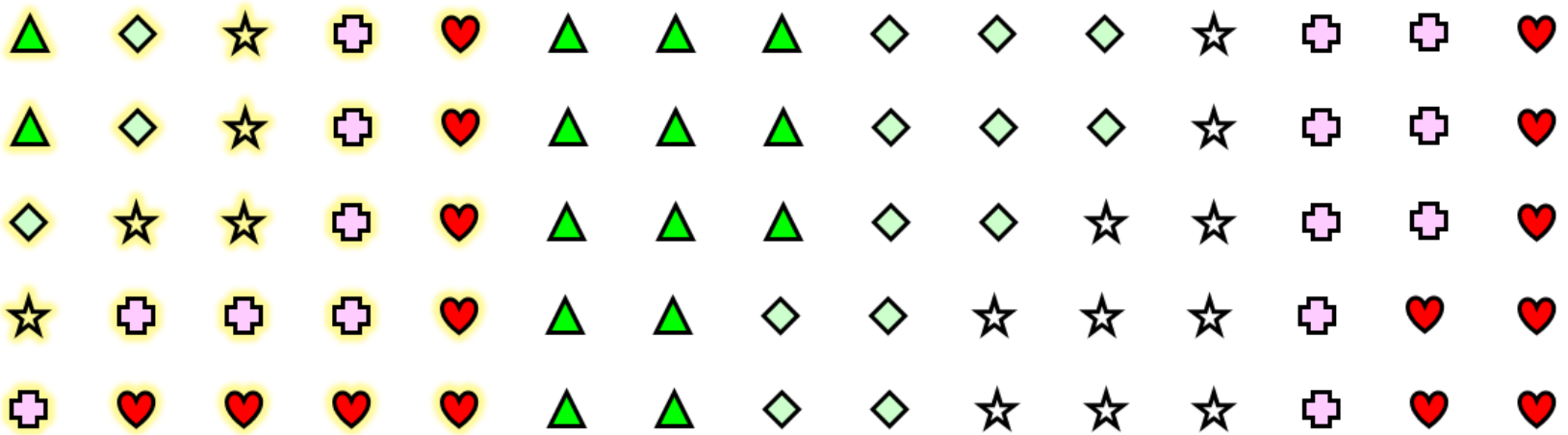


Could include covariates, as well...

$$\text{Outcome} = ß_0 + ß_1 * \text{Exposure} + ß_j * \text{Covariate}_j,$$

for pool of 75 subjects

Still interpret $ß_1$ as the exposure's effect, after covariate adjustment.

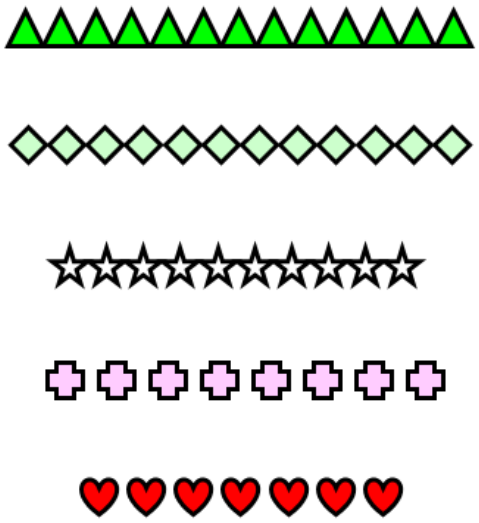


Propensity Score Matching

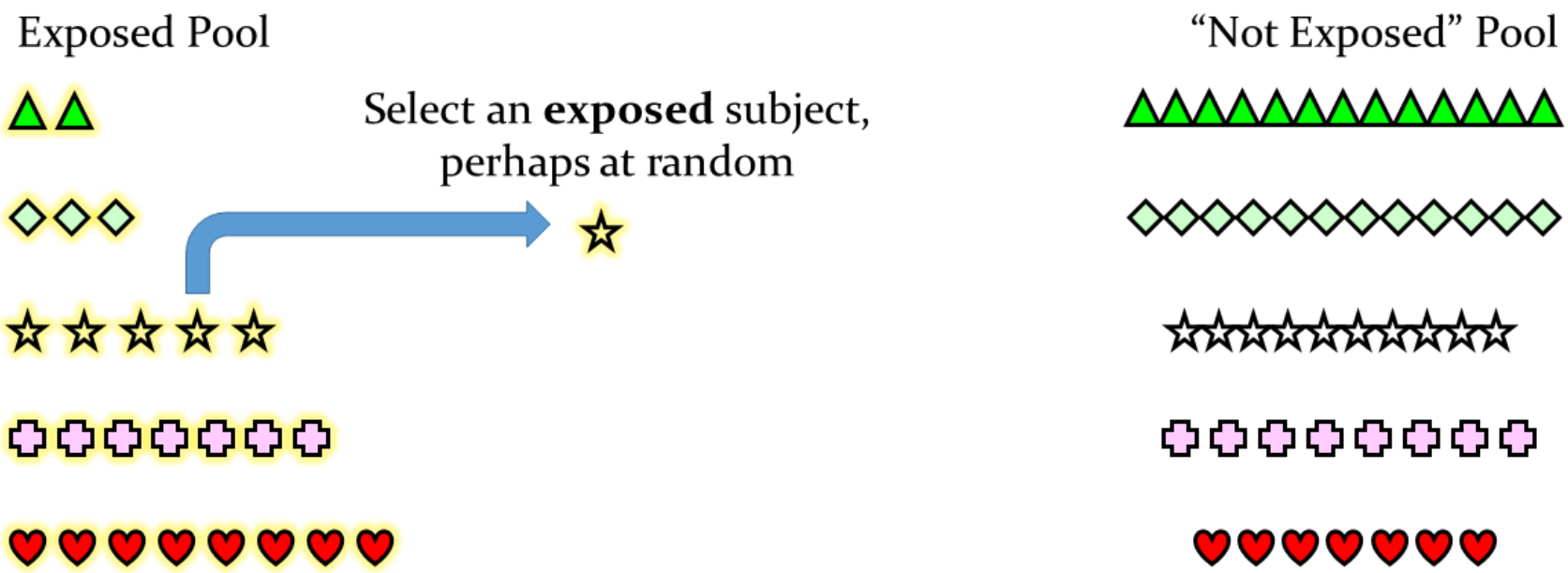
Propensity Score Matching (1:1)

Exposed Pool

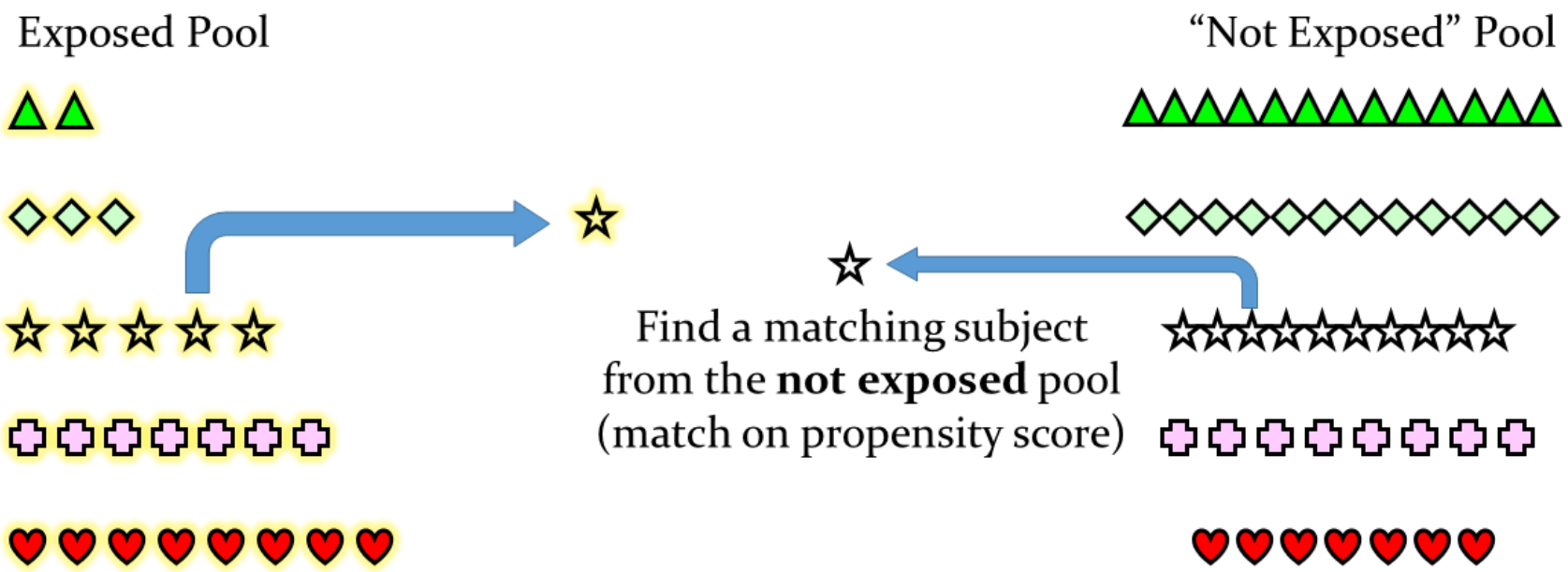
"Not Exposed" Pool



Propensity Score Matching (1:1)



Propensity Score Matching (1:1)



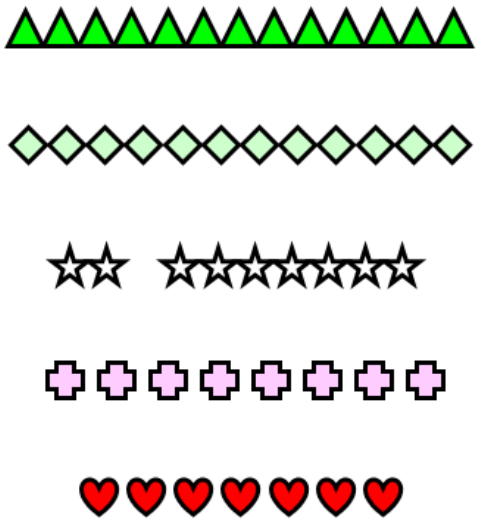
Propensity Score Matching (1:1)

Exposed Pool

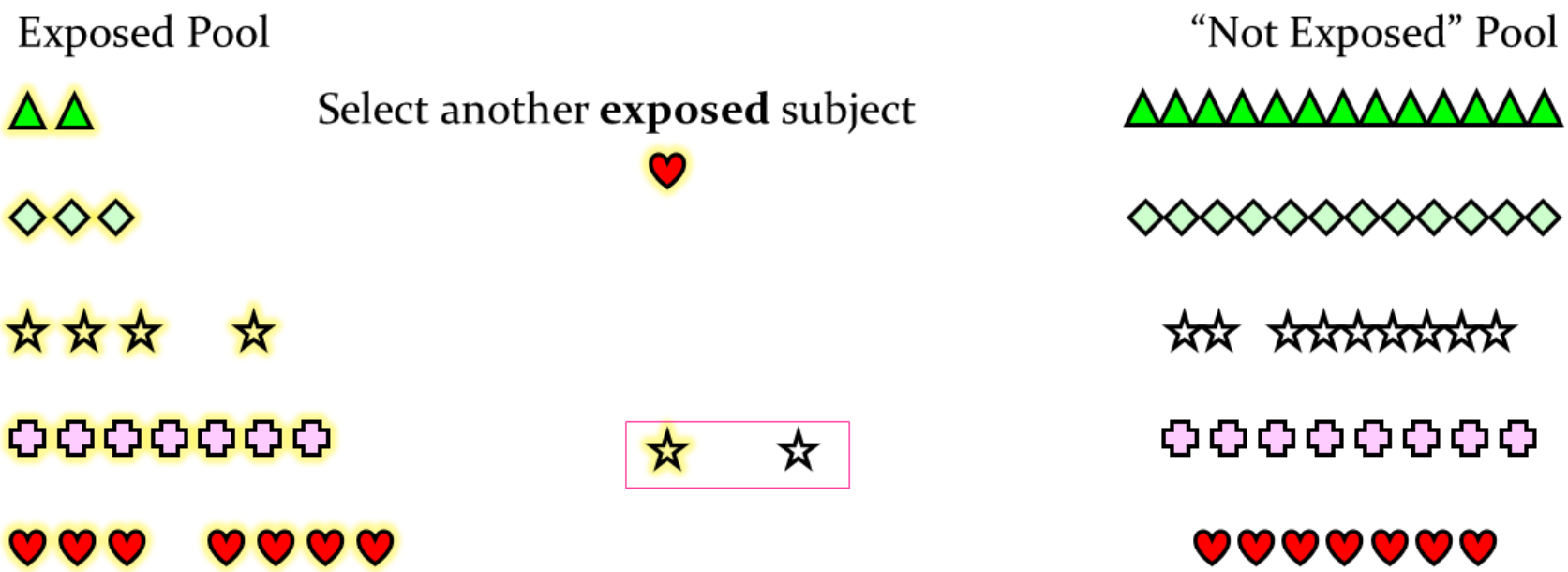
Form a matched pair

We're matching without replacement.

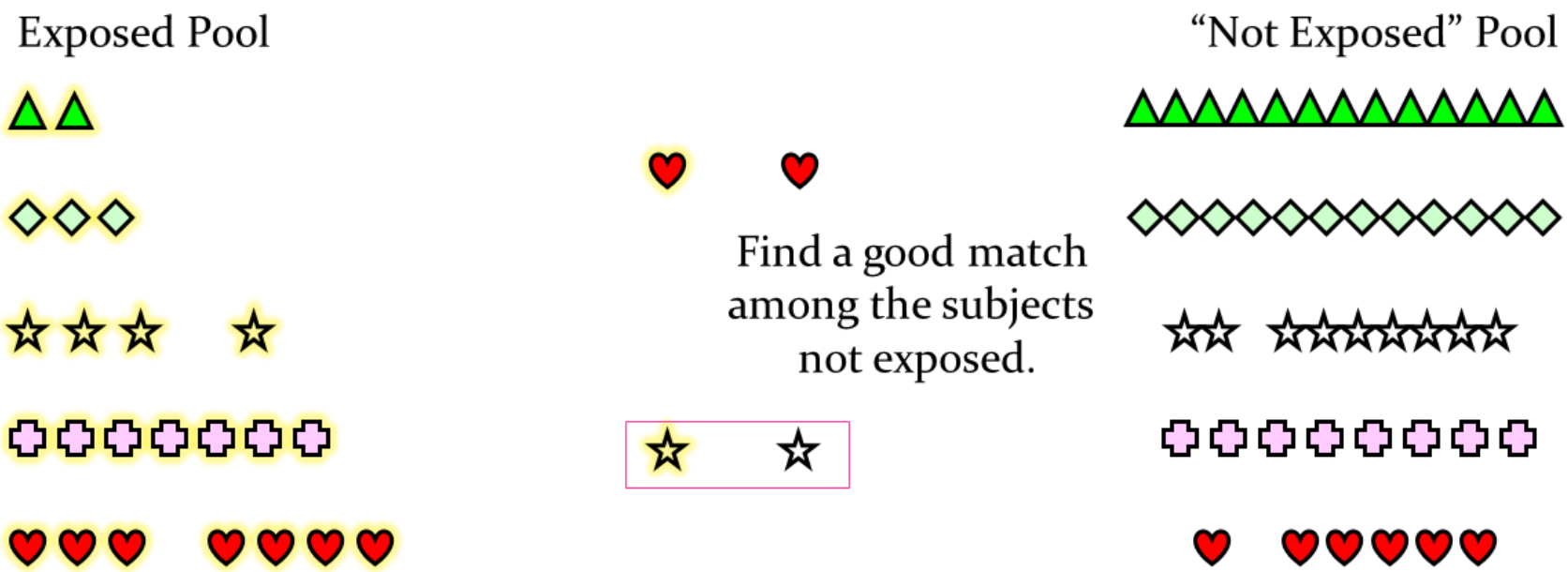
"Not Exposed" Pool



Propensity Score Matching (1:1)



Propensity Score Matching (1:1)

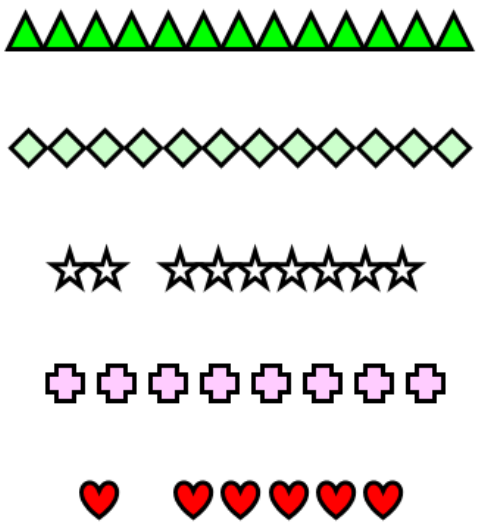


Propensity Score Matching (1:1)

Exposed Pool

A second matched pair!

"Not Exposed" Pool

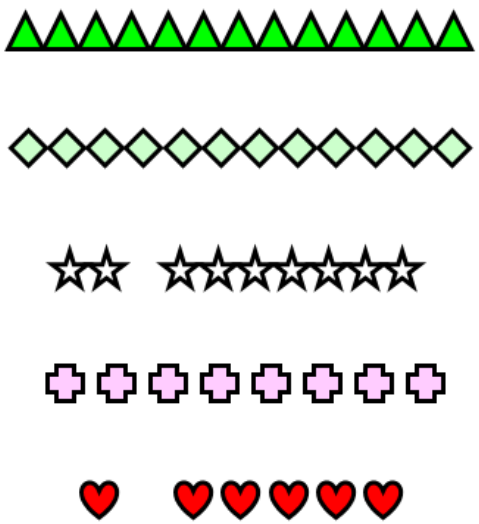


Propensity Score Matching (1:1)

Exposed Pool

Keep matching, until we can find no more acceptable matches

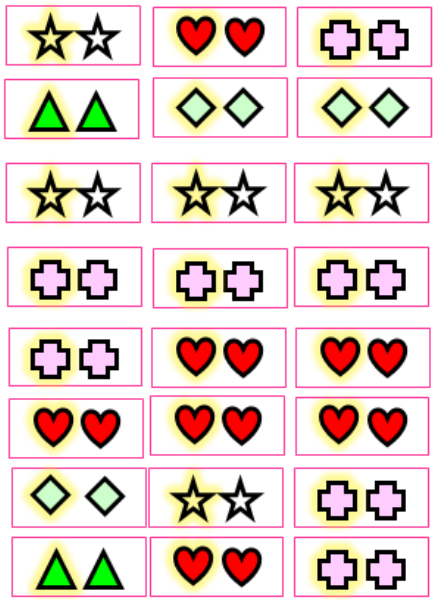
"Not Exposed" Pool



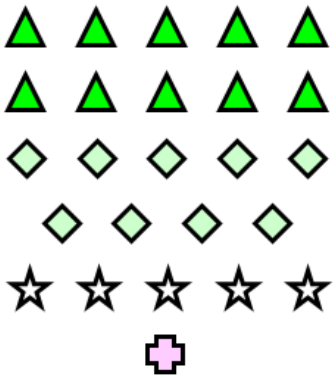
Propensity Score Matching (1:1)

Exposed Pool
(unmatched)

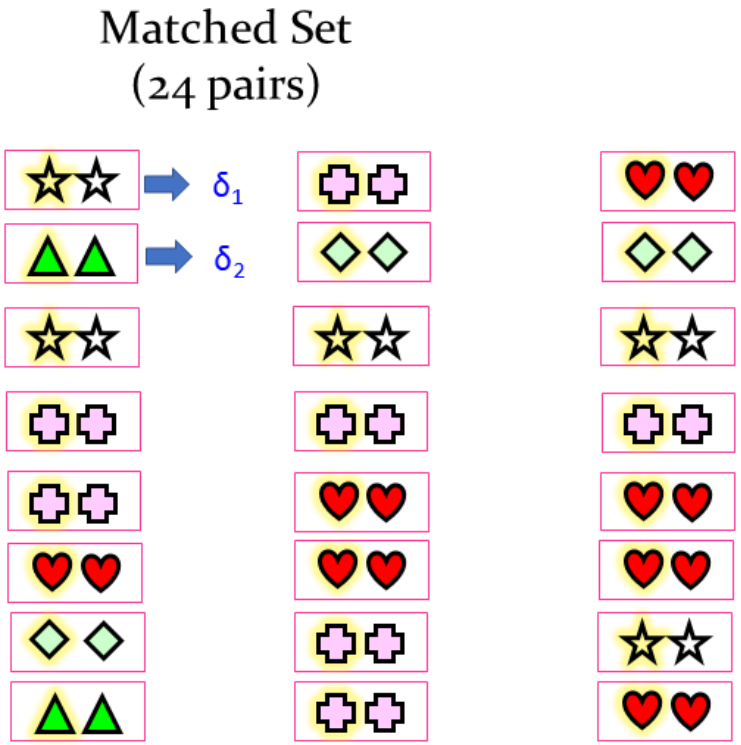
Matched Set
(24 pairs)



"Not Exposed" Pool
(unmatched)



Propensity Score Matching (1:1)

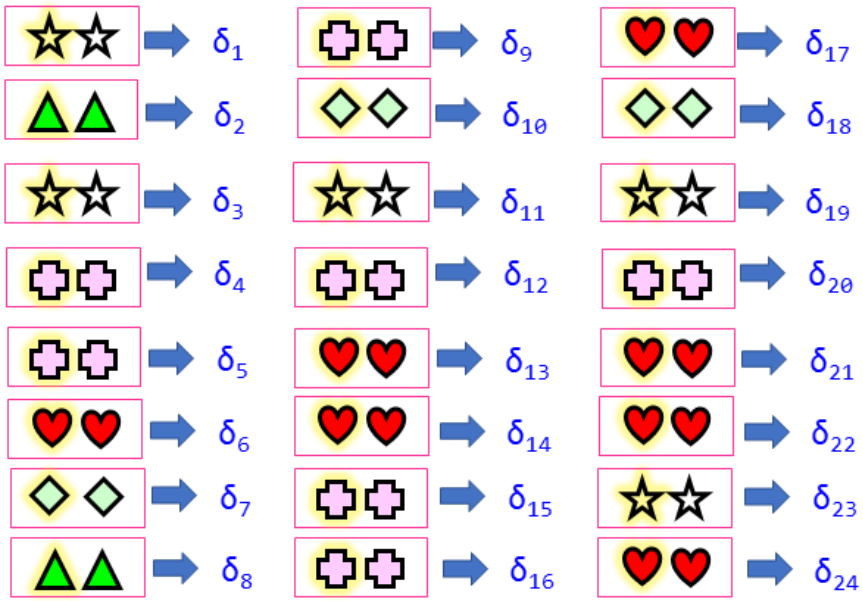


Within each matched pair, compare outcome in exposed subject to outcome in "not exposed" subject.

Estimated outcome effect Within a specific pair *j* is estimated by δ_j

Propensity Score Matching (1:1)

Matched Set
(24 pairs)



Within each matched pair, compare outcome in exposed subject to outcome in "not exposed" subject.

Use standard methods for matched samples (e.g., paired t tests) to estimate the causal effect of the exposure on the outcome based on the δ estimates from the pairs

What Propensity Scores Can and Cannot Do

- If we match exposed subjects to controls with similar propensity scores, we can (sort of) behave as if they had been randomly assigned to exposures.
- But if our propensity model misses an important reason why subjects are selected to an exposure, we'll be in trouble, and we'll **never know it**.

Next Time (Class 03) . . .

- Rosenbaum Chapter 3
  3. Causal Inference in Randomized Experiments
- Homework 2 due next Thursday.
- Time to get started on your project proposal? Now.

Lecture Topics

- Estimating the Propensity Score
- Using the Propensity Score to account for observed selection bias
  - through stratification/subclassification on the PS
  - through weighting on the PS
  - through direct adjustment for the PS
- Propensity Score Matching and Estimating Causal Effects