500 Class 2 Slides

github.com/THOMASELOVE/2019-500

2019-01-31

Agenda for Class 2

- A Conceptual Example: Aspirin and Mortality in Heart Patients
  - How can we avoid being misled?
  - Causal Effects as comparing potential outcomes
- Discussing Assignment 1: The DIG Trial and Logistic Regression
- The Hormone Replacement Therapy Story
  - Can Selection Bias Explain the Story?
- Rosenbaum (2017) Chapters 1-4 (Part I. Randomized Experiments)
  1. A Randomized Trial
  2. Structure
  3. Causal Inference in Randomized Experiments
  4. Irrationality and Polio
- Tools for Assessing Causal Effects
  - Subclassification and Cochran's Example
  - Using Matched Sets to Adjust for Overt Bias
- Defining and Motivating the Propensity Score

A Motivating Example (Aspirin and Mortality)

Aspirin and Mortality in Heart Patients

Suppose you want to understand the effect of aspirin (acetylsalicylic acid: ASA) on mortality among patients undergoing stress echocardiography.

- What is the population?
- What is the outcome?
- What are the treatments?

Potential Outcomes and The Aspirin Study

Potential Outcomes and The Aspirin Study

Potential Outcomes and The Aspirin Study

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ASA and Mortality in Heart Patients

Suppose you want to understand aspirin's effect on all-cause five-year mortality among patients undergoing stress echocardiography.

- Comparing ASA to "No ASA"
- What are the potential outcomes here?

Potential Outcomes and The Aspirin Study

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Potential Outcomes and The Aspirin Study

Potential Outcomes and The Aspirin Study

Aspirin – "No Aspirin" Effect =

–

ASA and Mortality in Heart Subjects

- Suppose you want to study the effect of aspirin (acetylsalicylic acid: ASA) on all-cause mortality.
- You identify an interesting group of Subjects as those undergoing stress echocardiography.
  - Your goal is to compare ASA Subjects to "no ASA" Subjects

What would be the **ideal** study?

Step 1. Identify a large group of Subjects from the population at Time 0.

- We want to understand the causal effect of aspirin on all-cause five-year mortality among patients undergoing stress echocardiography.
- Having identified a set of patients, what is the ideal study?

Step 2?

ASA and Mortality: Ideal Study

Identify a large group of patients from population at Time 0

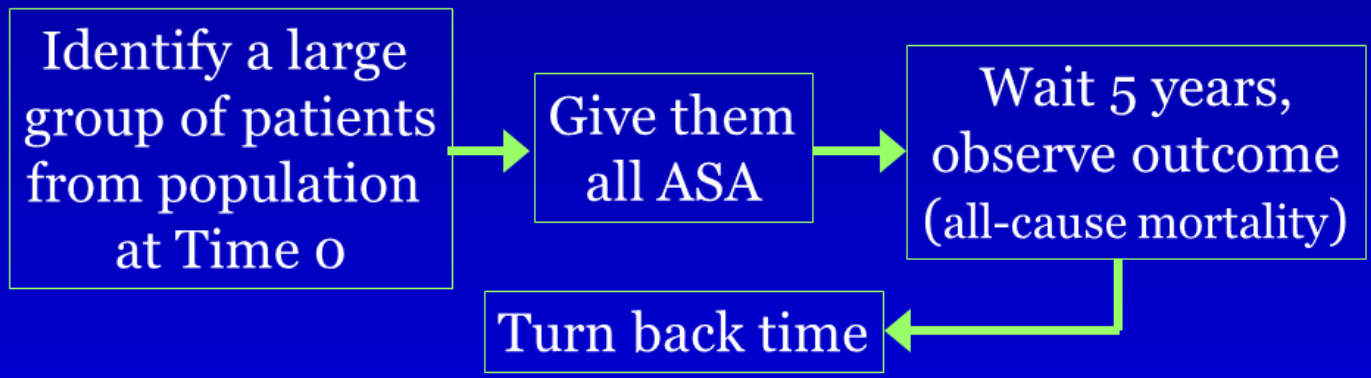
ASA and Mortality: Ideal Study

Identify a large group of patients from population at Time 0

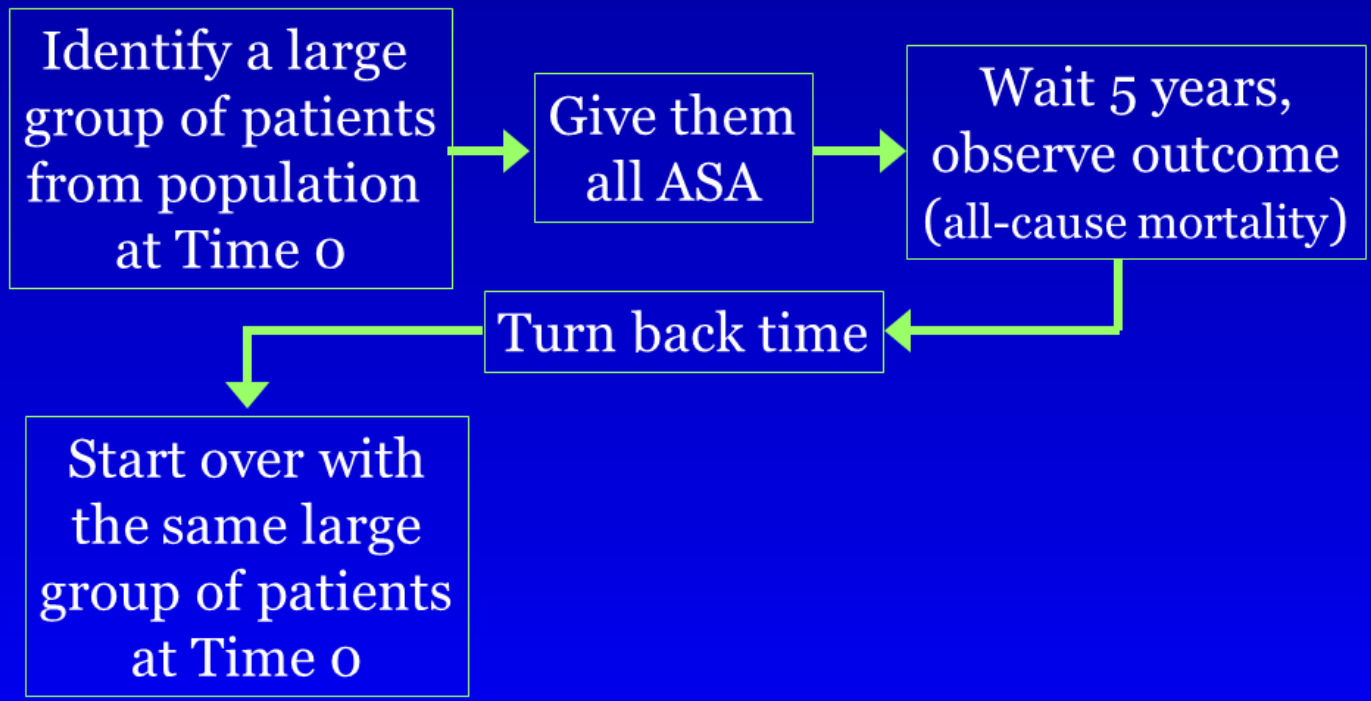
Give them all ASA

ASA and Mortality: Ideal Study

ASA and Mortality: Ideal Study



ASA and Mortality: Ideal Study



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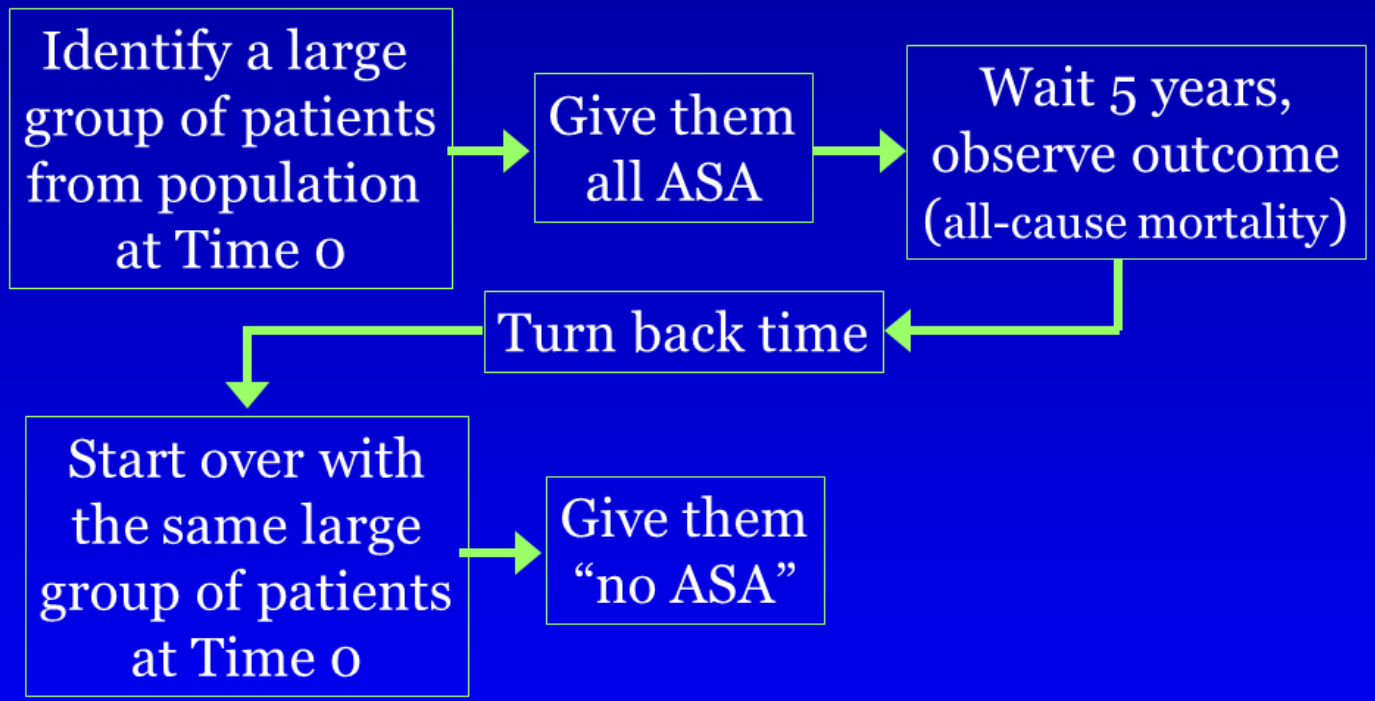

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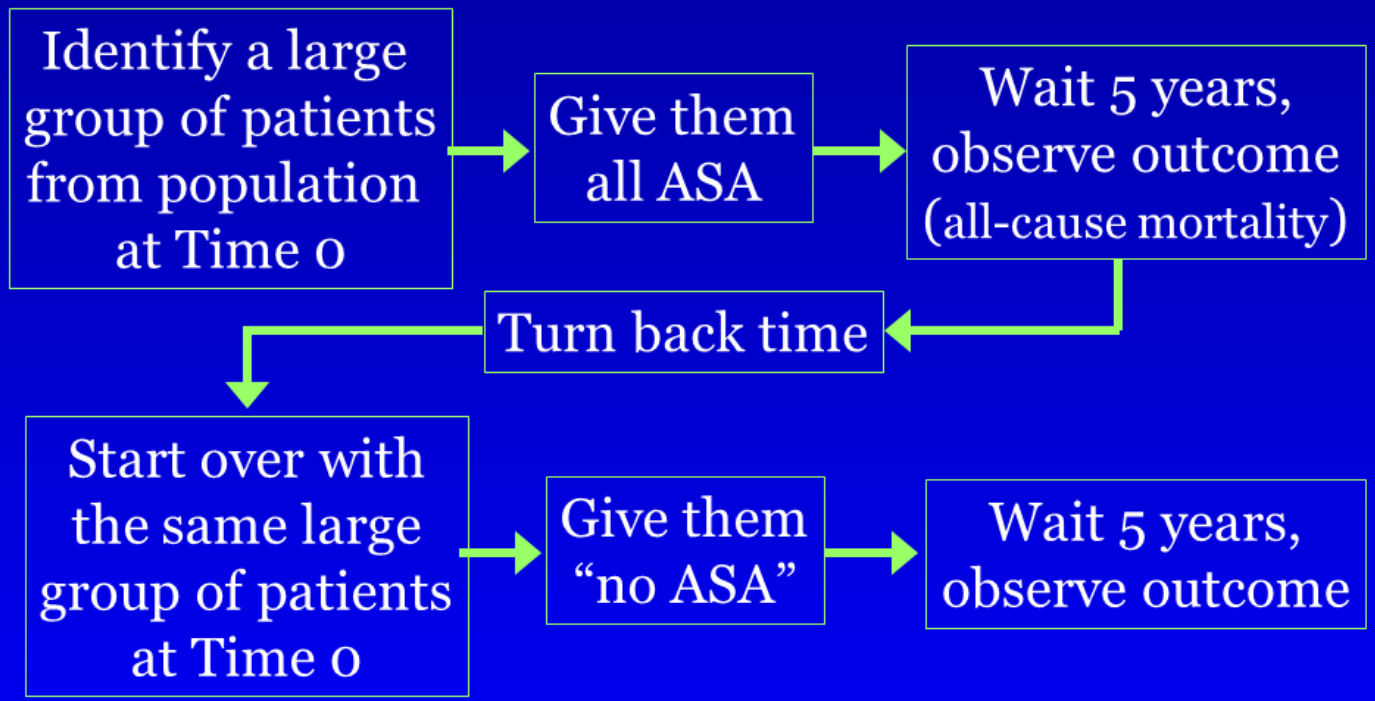

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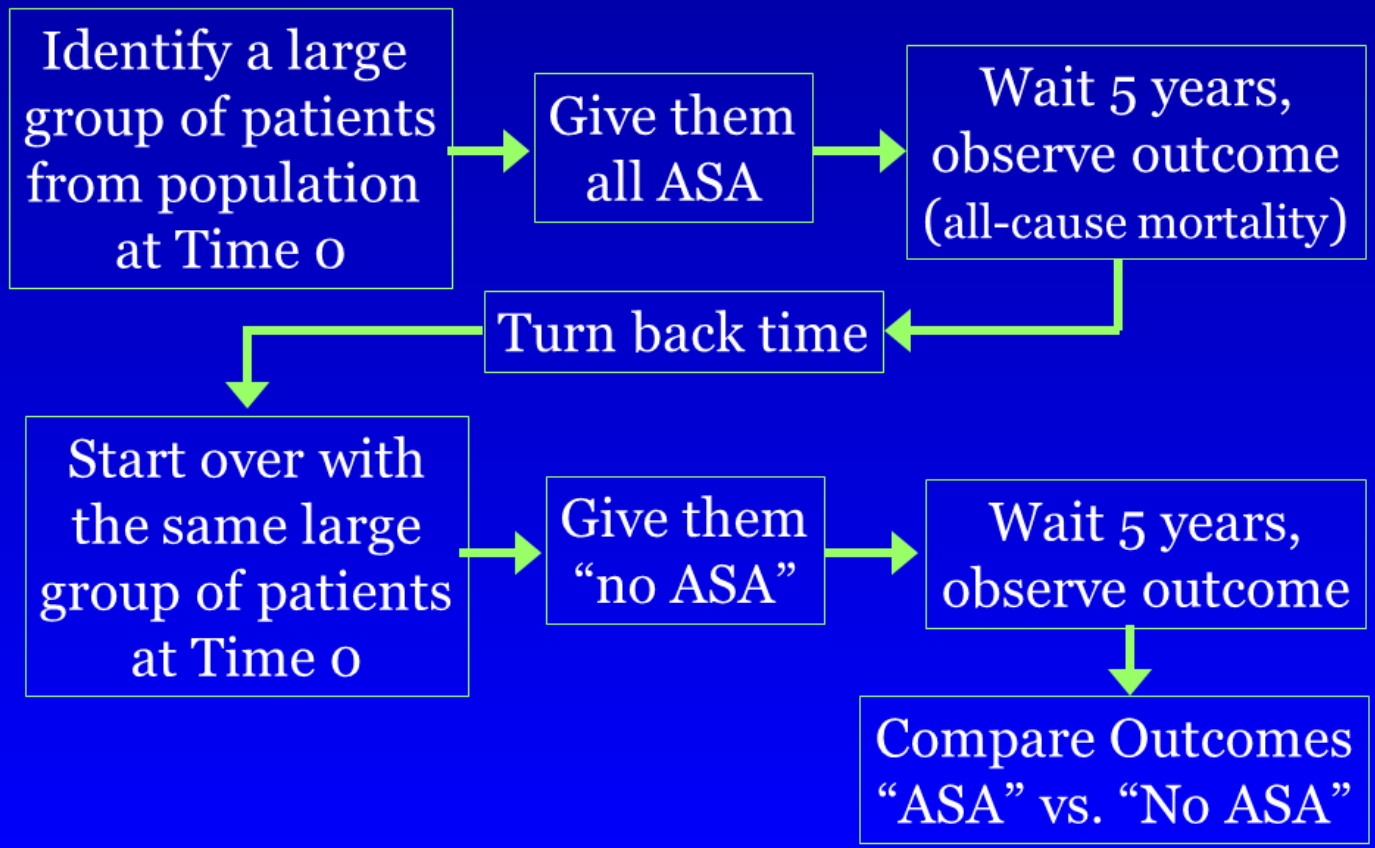

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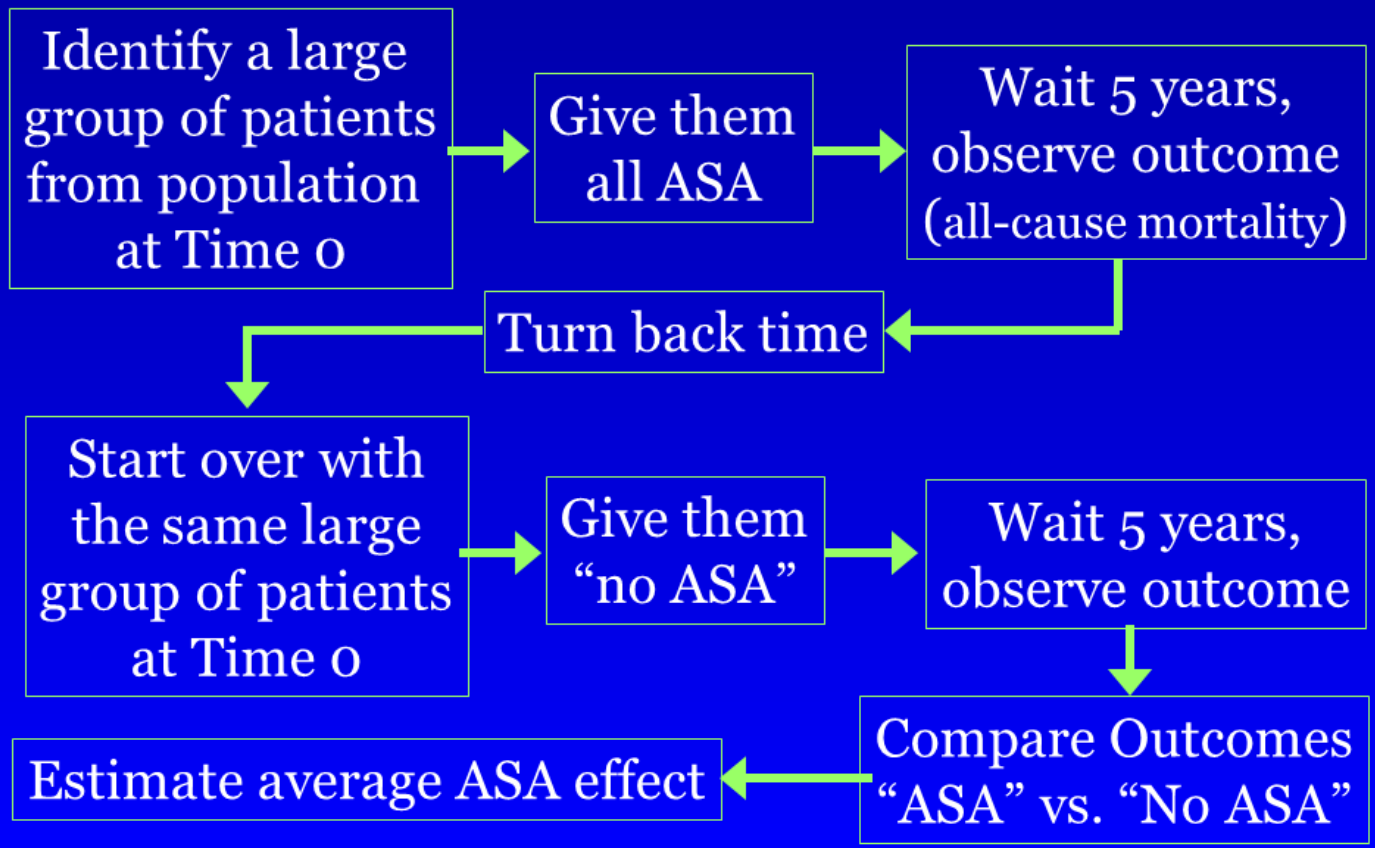


ASA & Mortality: Next Best Study

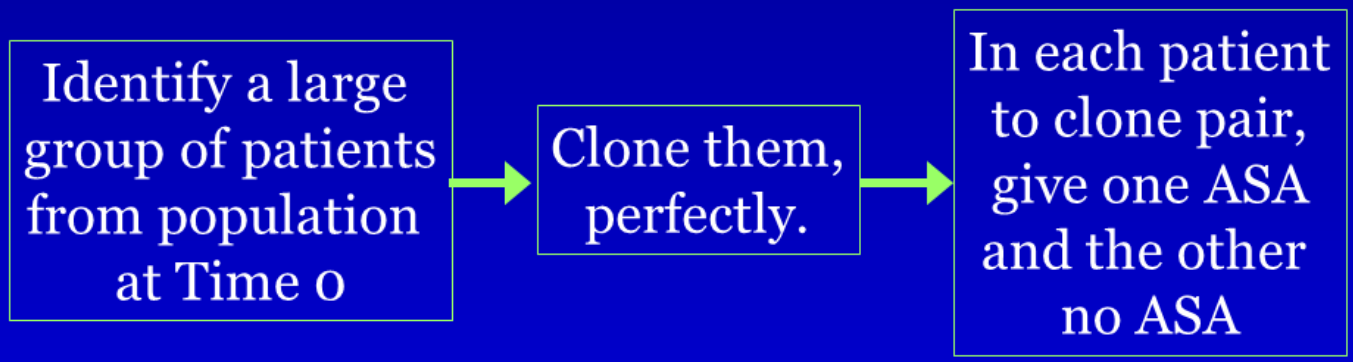
Identify a large group of patients from population at Time 0

ASA & Mortality: Next Best Study

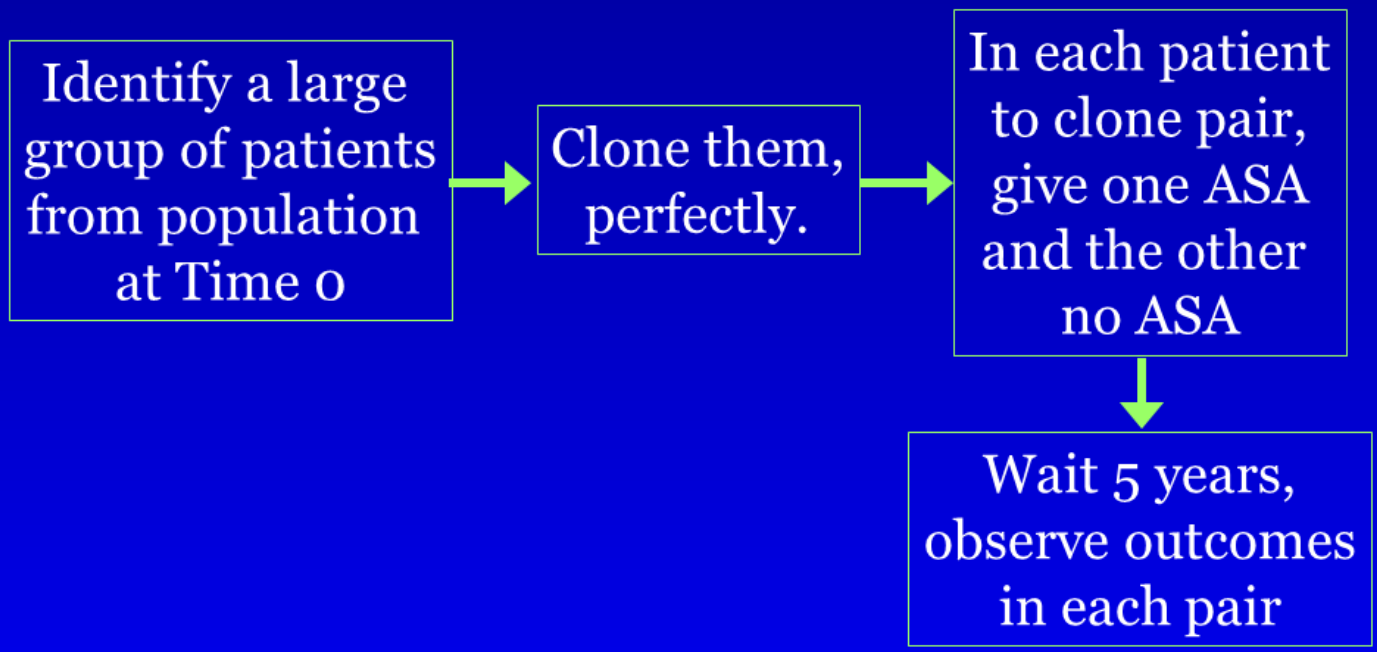
Identify a large group of patients from population at Time 0

Clone them, perfectly.

ASA & Mortality: Next Best Study



ASA & Mortality: Next Best Study



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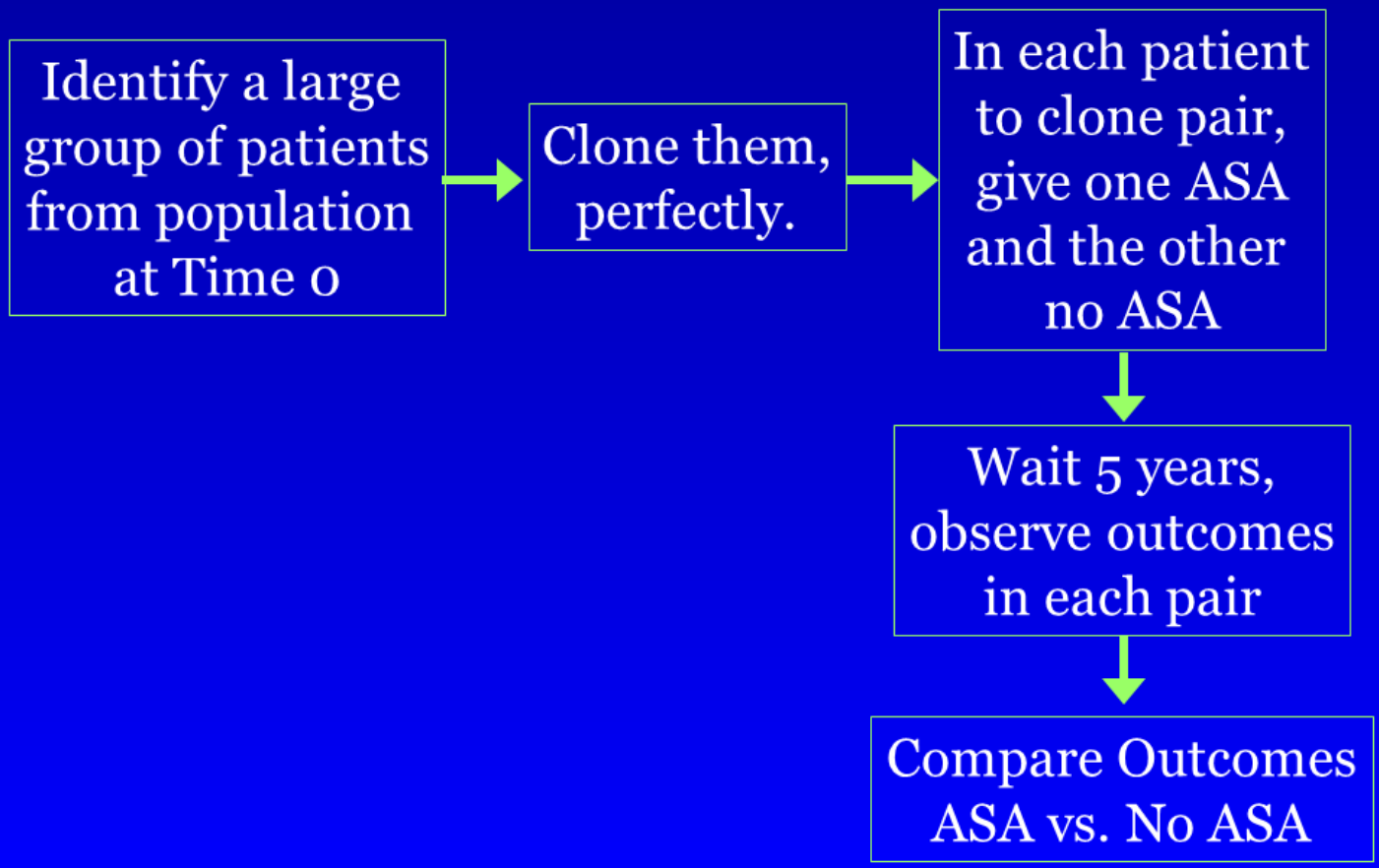

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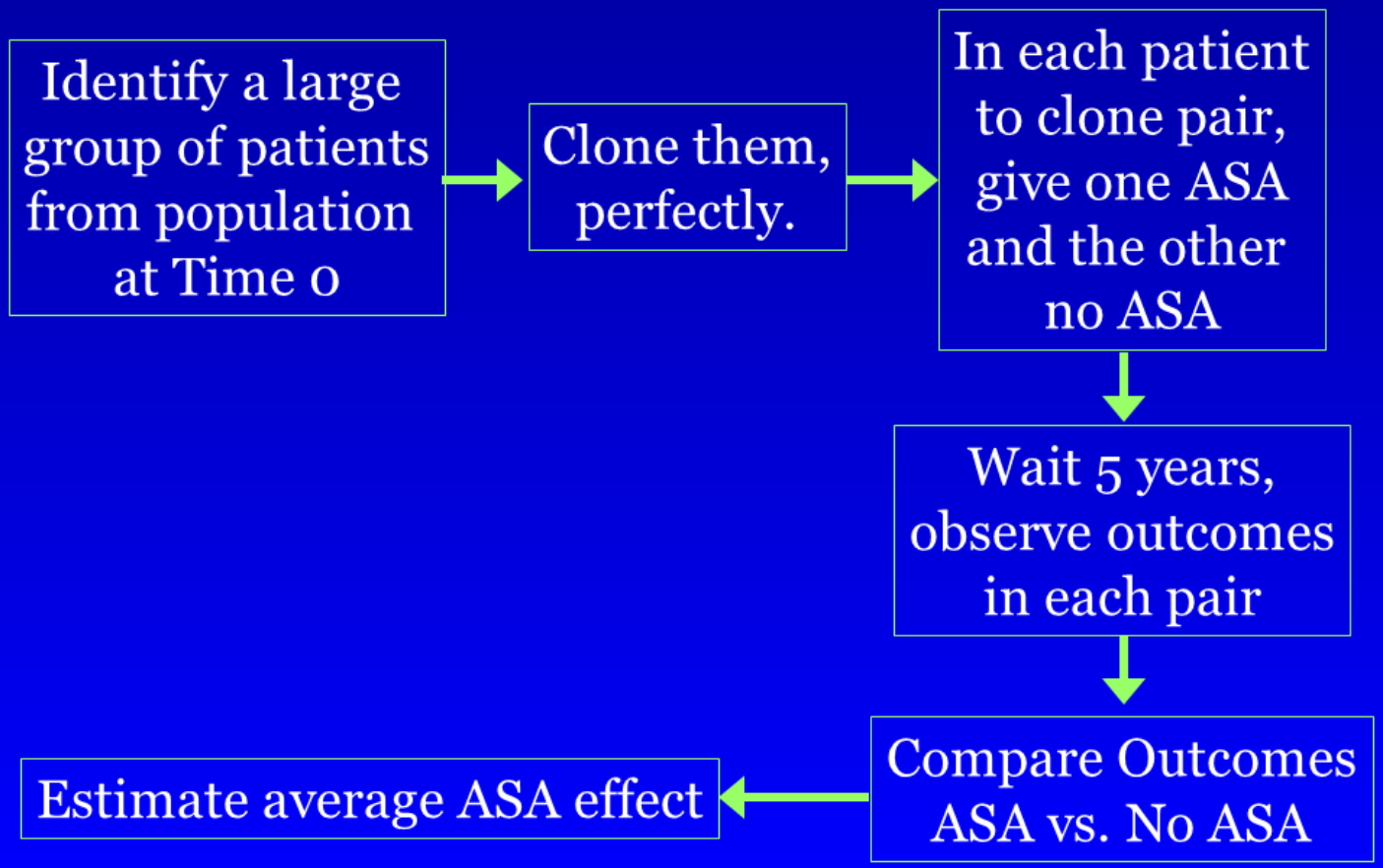
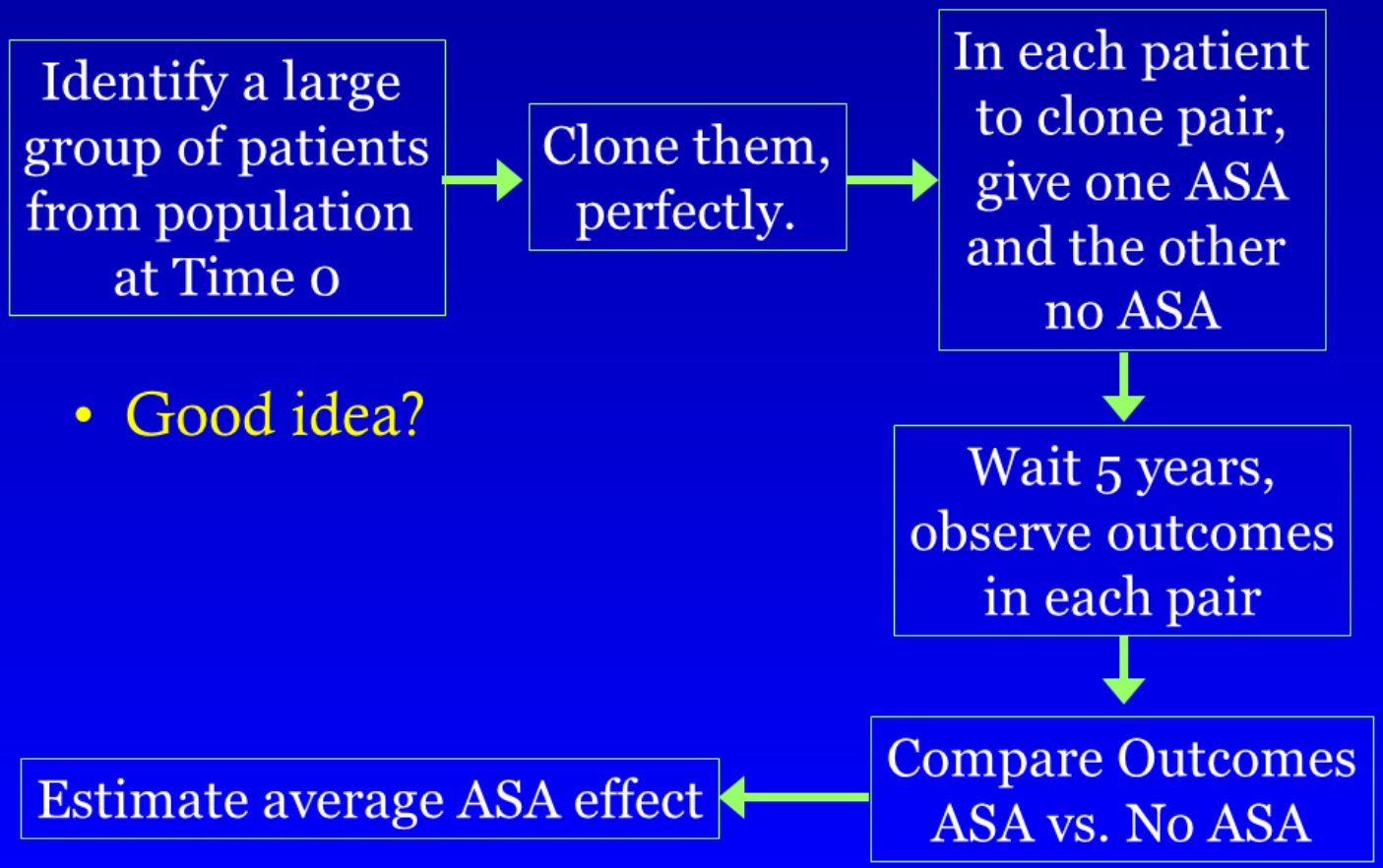
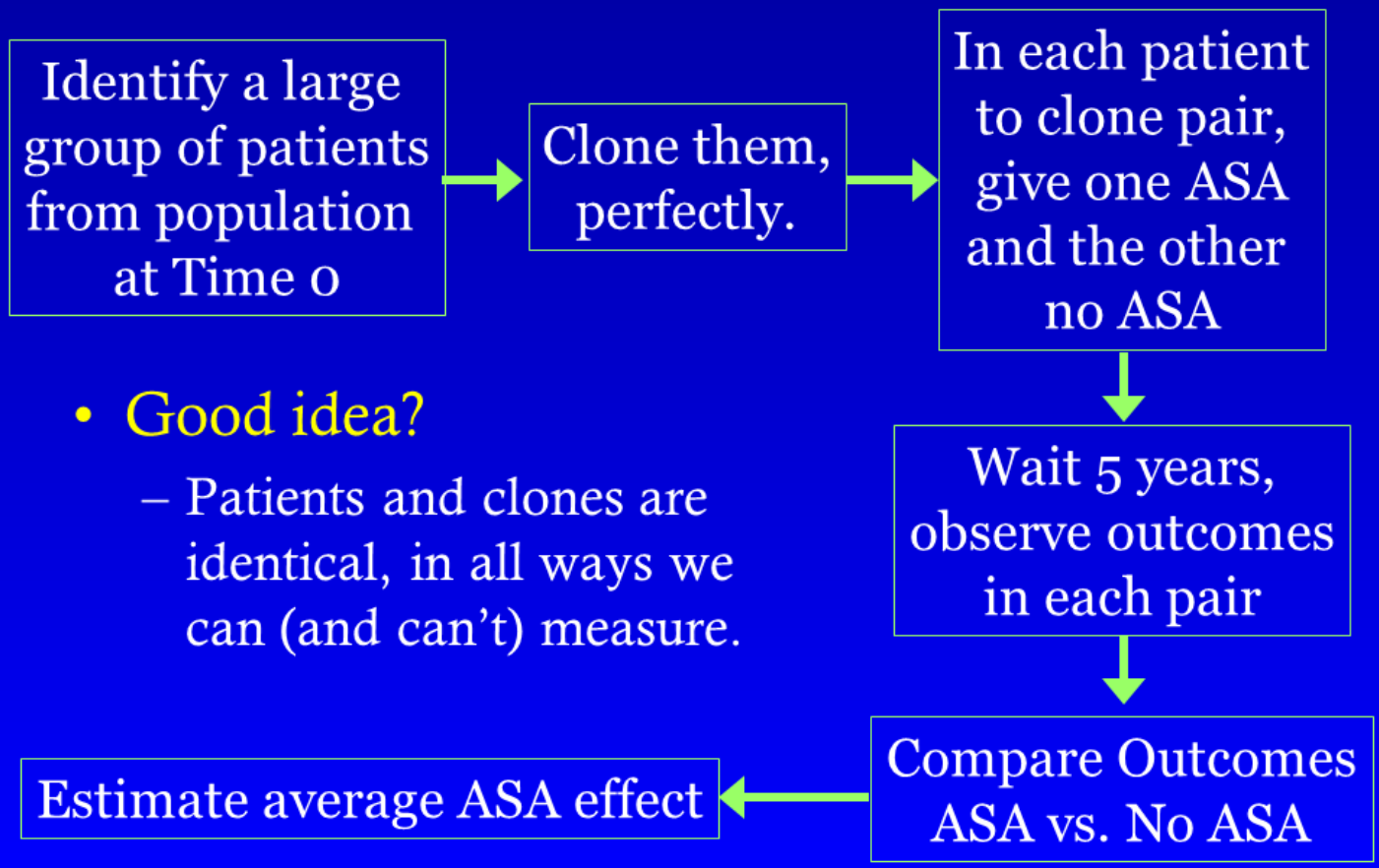


ASA & Mortality: Next Best Study



- Good idea?

ASA & Mortality: Next Best Study



- Good idea?
  - Patients and clones are identical, in all ways we can (and can't) measure.

ASA and Mortality in Heart Patients

- Designing the Study

We want to understand aspirin's effect on all-cause five-year mortality among patients undergoing stress echocardiography.

- OK.
- What's the best **practical** study?

ASA & Mortality: RCT

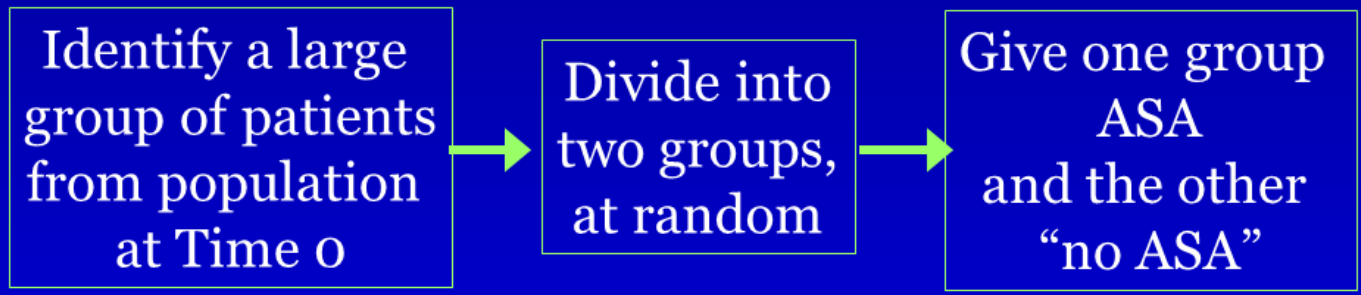
Identify a large group of patients from population at Time 0

ASA & Mortality: RCT

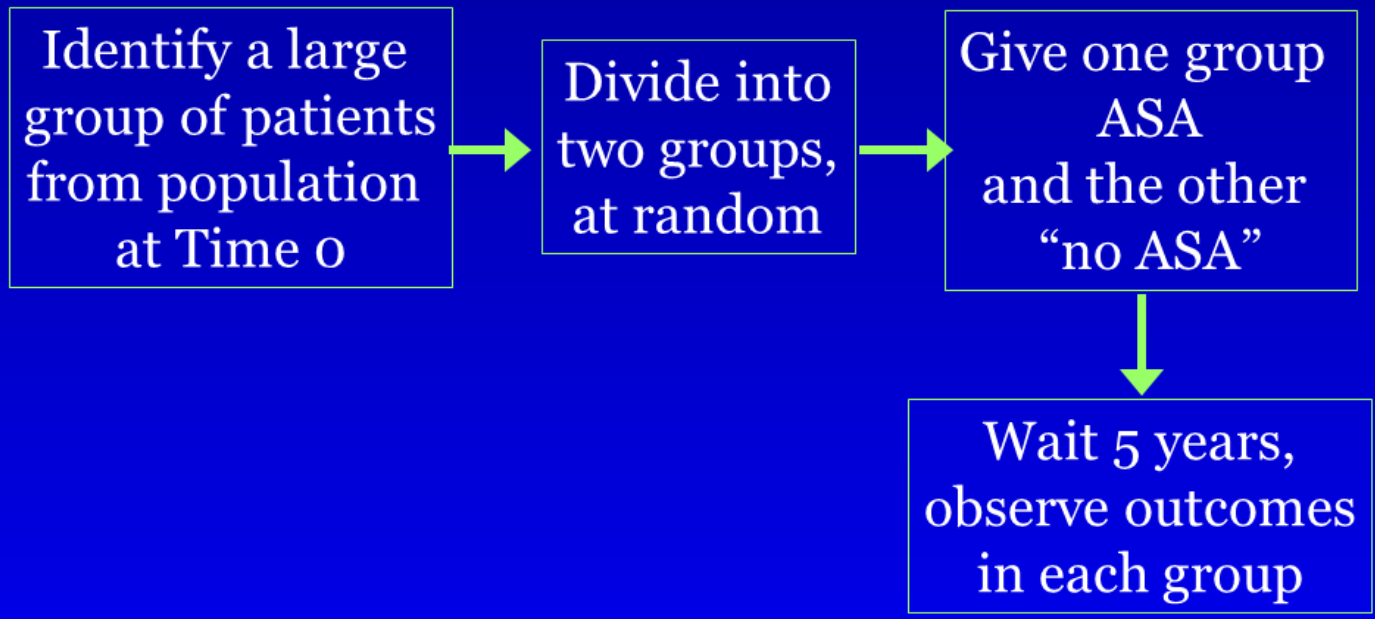
Identify a large group of patients from population at Time 0

Divide into two groups, at random

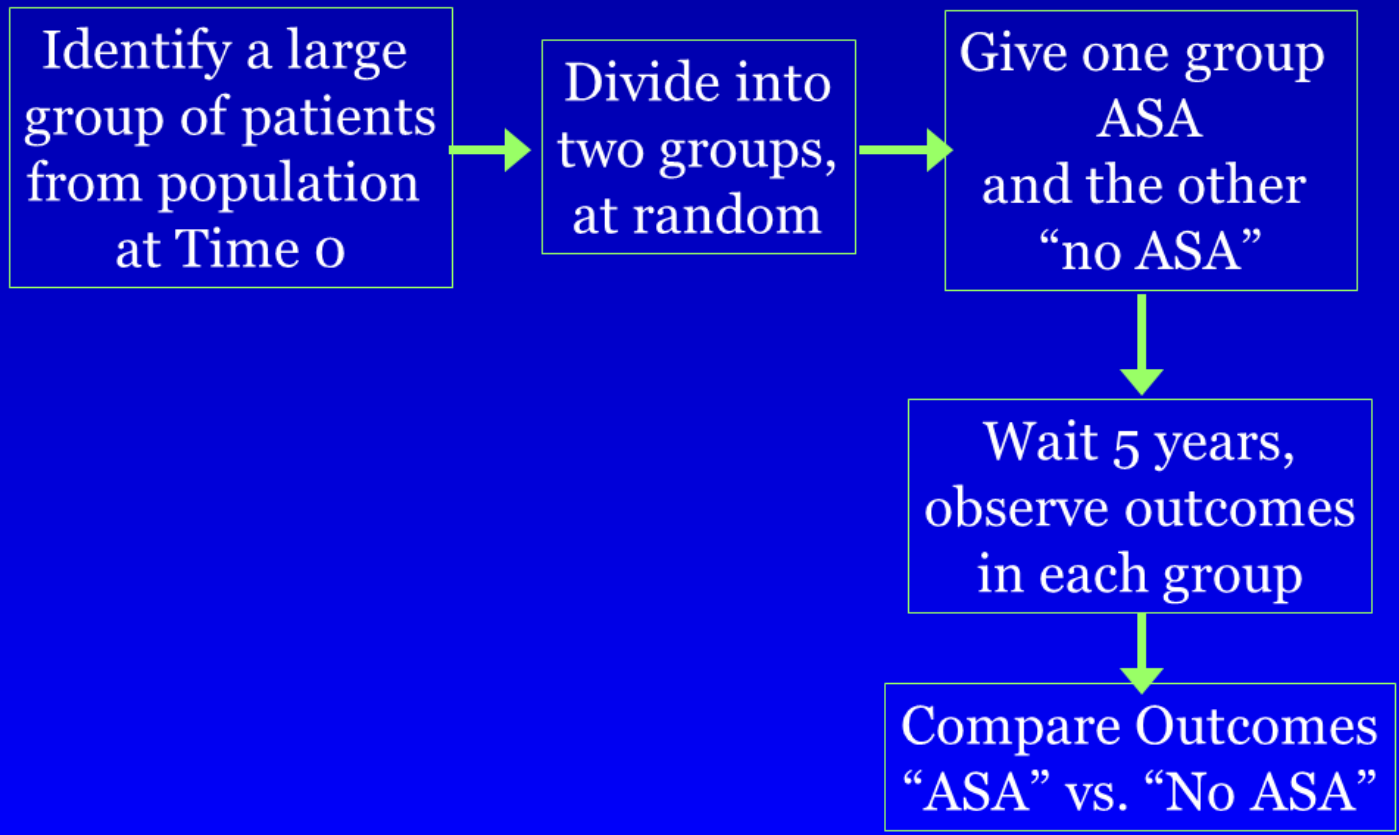
ASA & Mortality: RCT



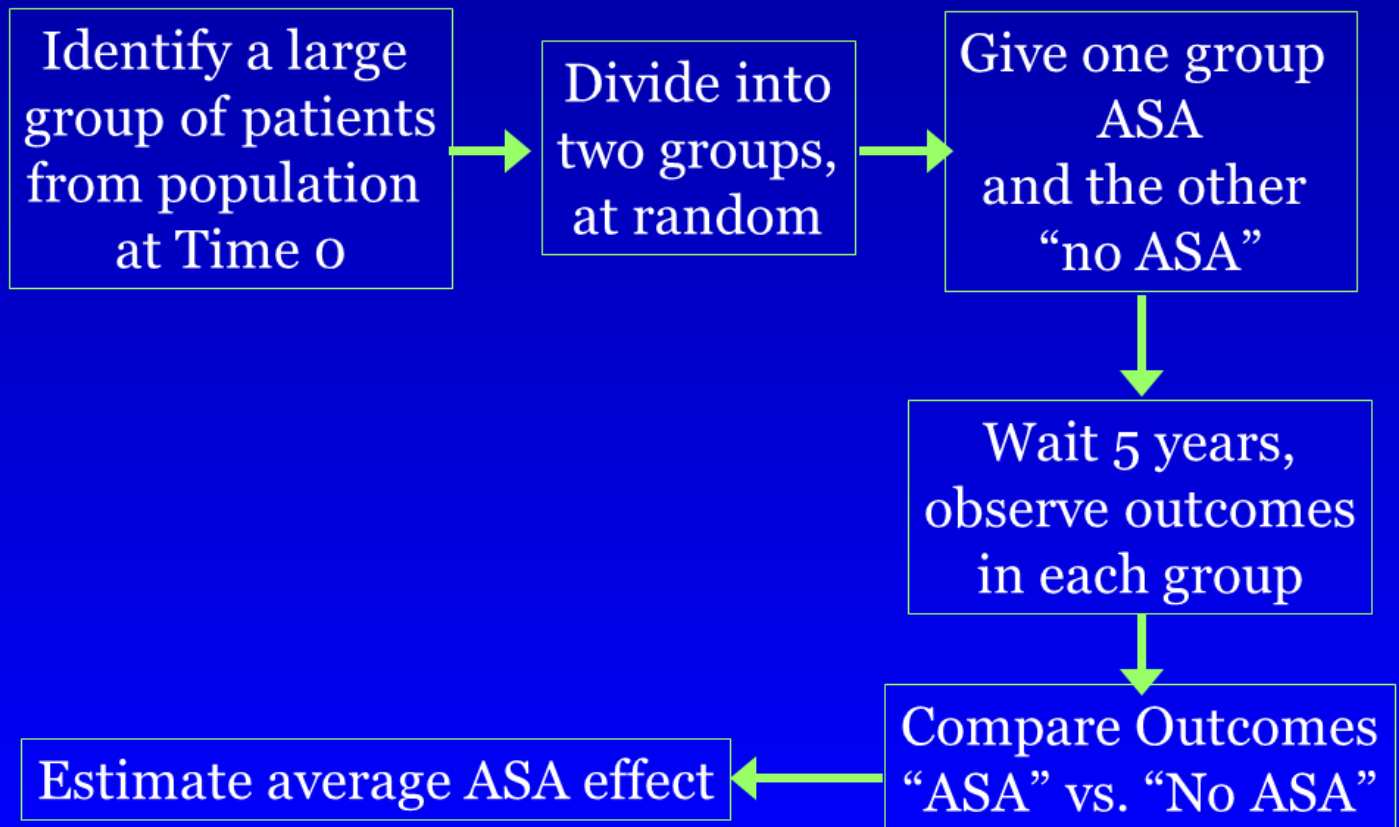
ASA & Mortality: RCT



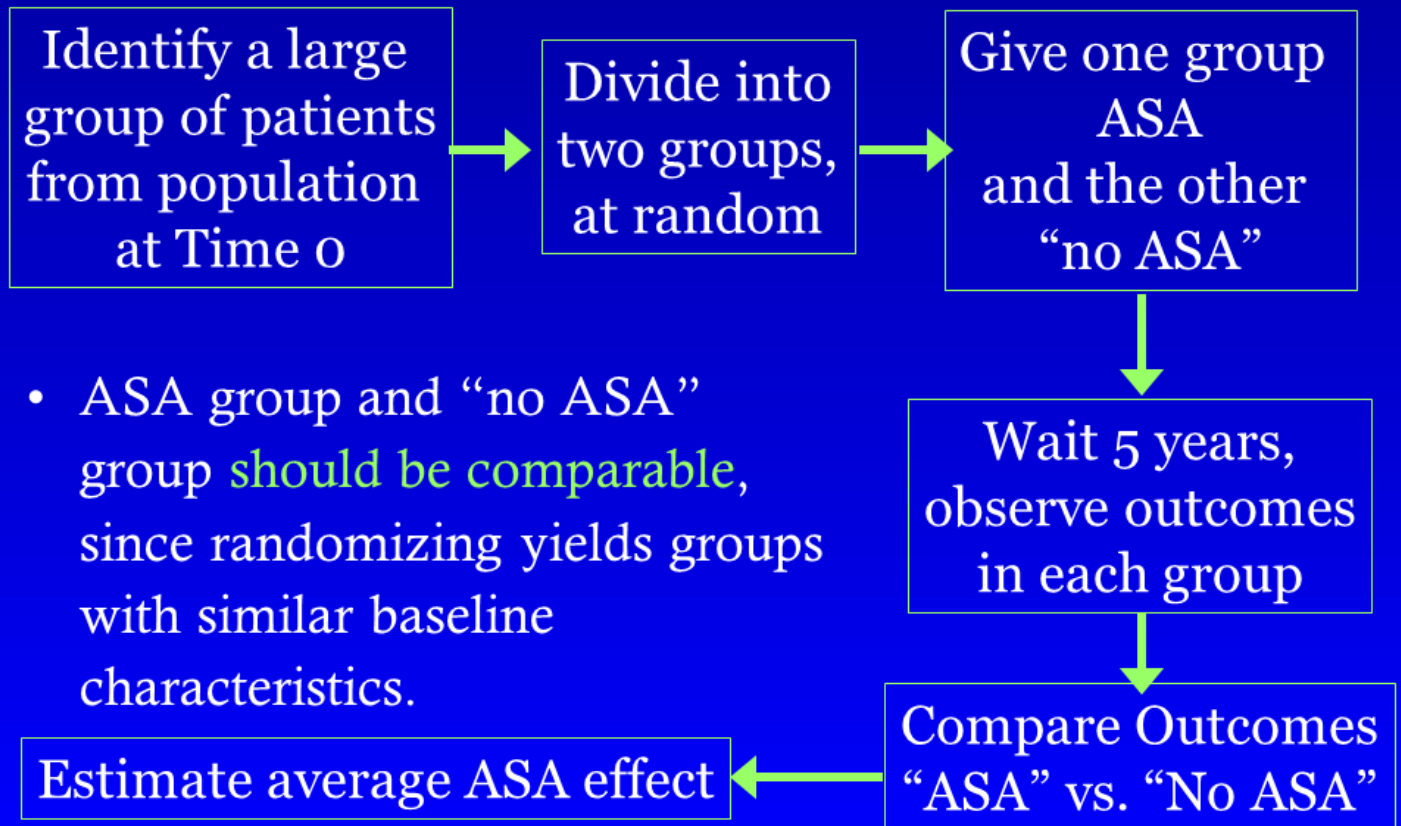
ASA & Mortality: RCT



ASA & Mortality: RCT



ASA & Mortality: RCT



- ASA group and "no ASA" group should be comparable, since randomizing yields groups with similar baseline characteristics.

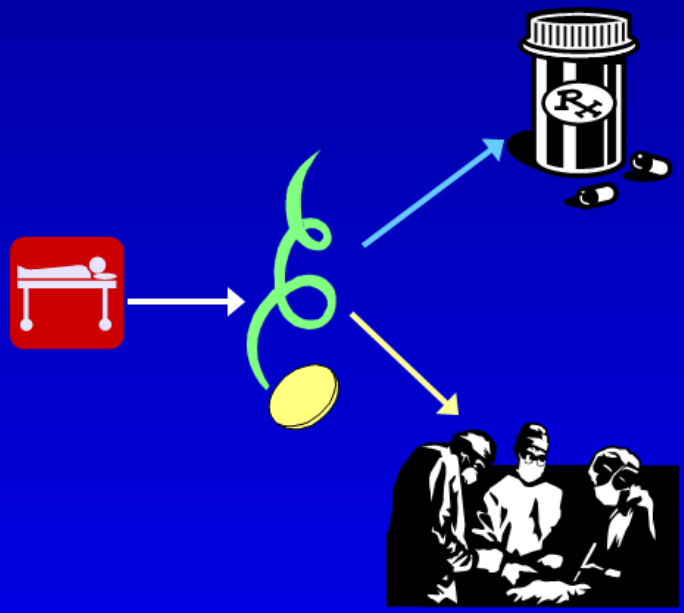
ASA and Mortality in Heart Patients

- Designing the Study

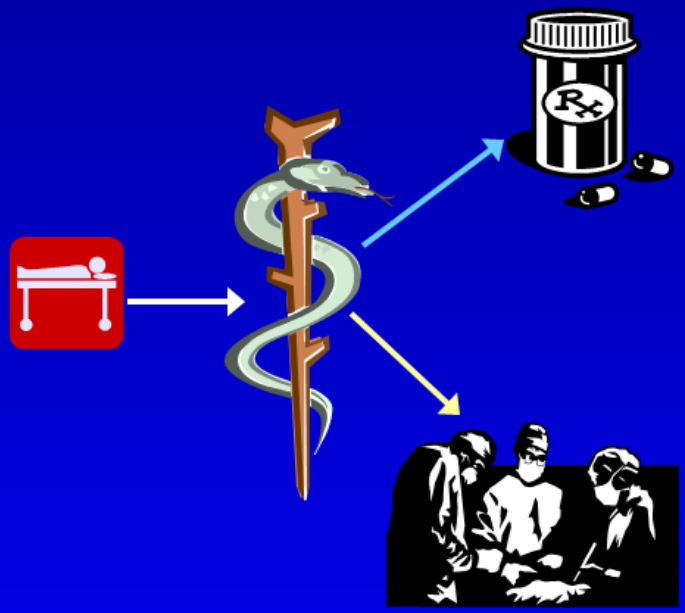
We want to understand aspirin's effect on all-cause five-year mortality among patients undergoing stress echocardiography.

- But what if we **cannot** do an RCT?

Randomized vs. Observational Studies



Randomization ensures that subjects receiving different treatments are comparable.



In observational studies, the researcher does not randomly allocate the treatments.

ASA & Mortality: **Observational Study**

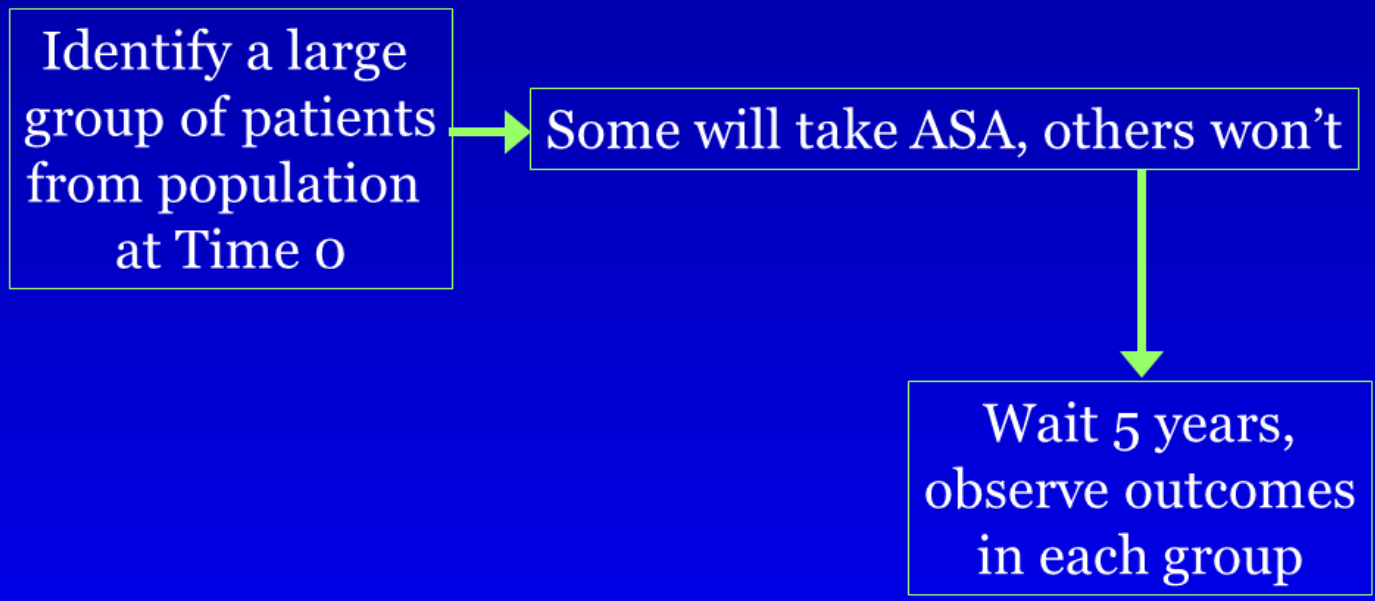
Identify a large group of patients from population at Time 0

ASA & Mortality: **Observational Study**

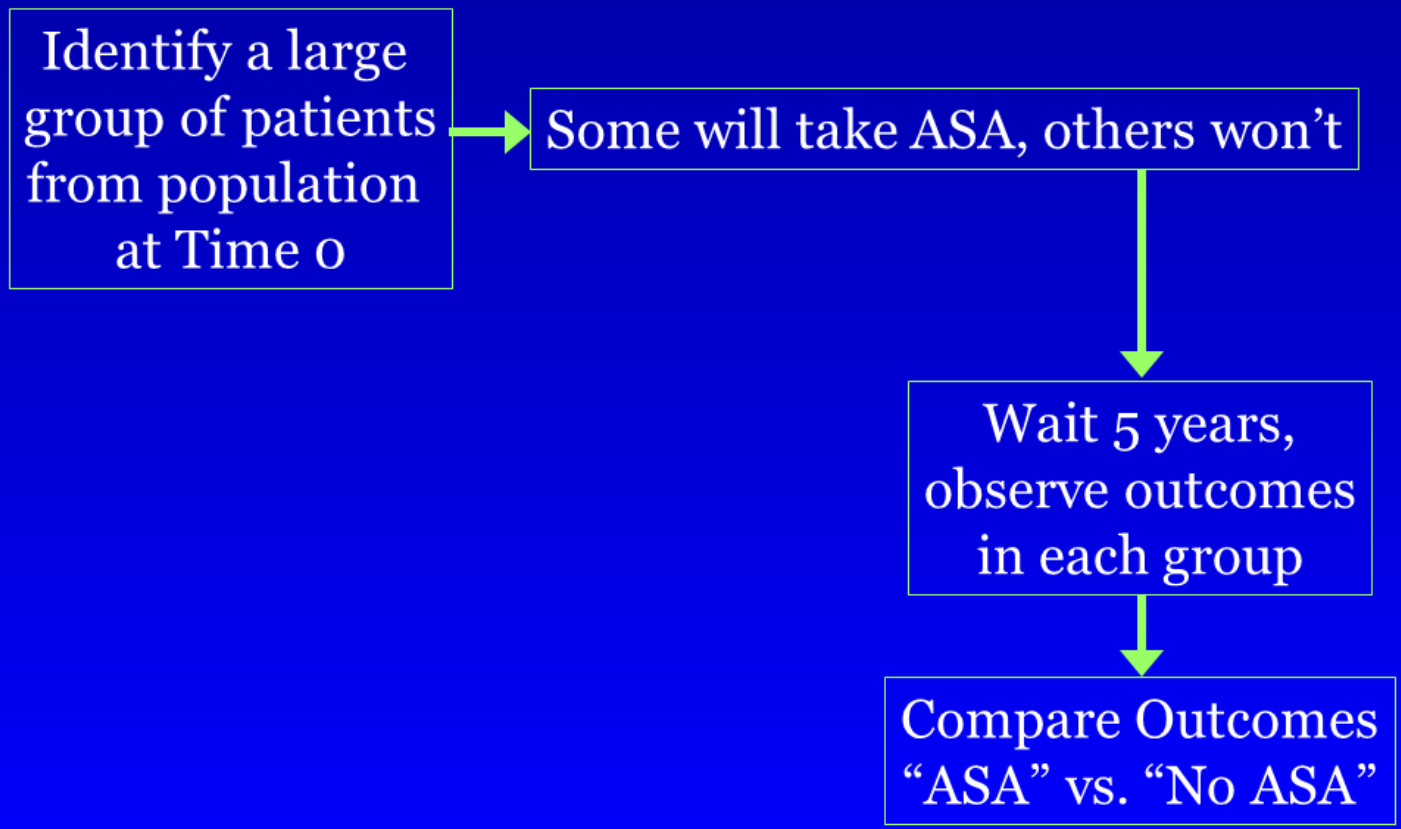
Identify a large group of patients from population at Time 0

→ Some will take ASA, others won't

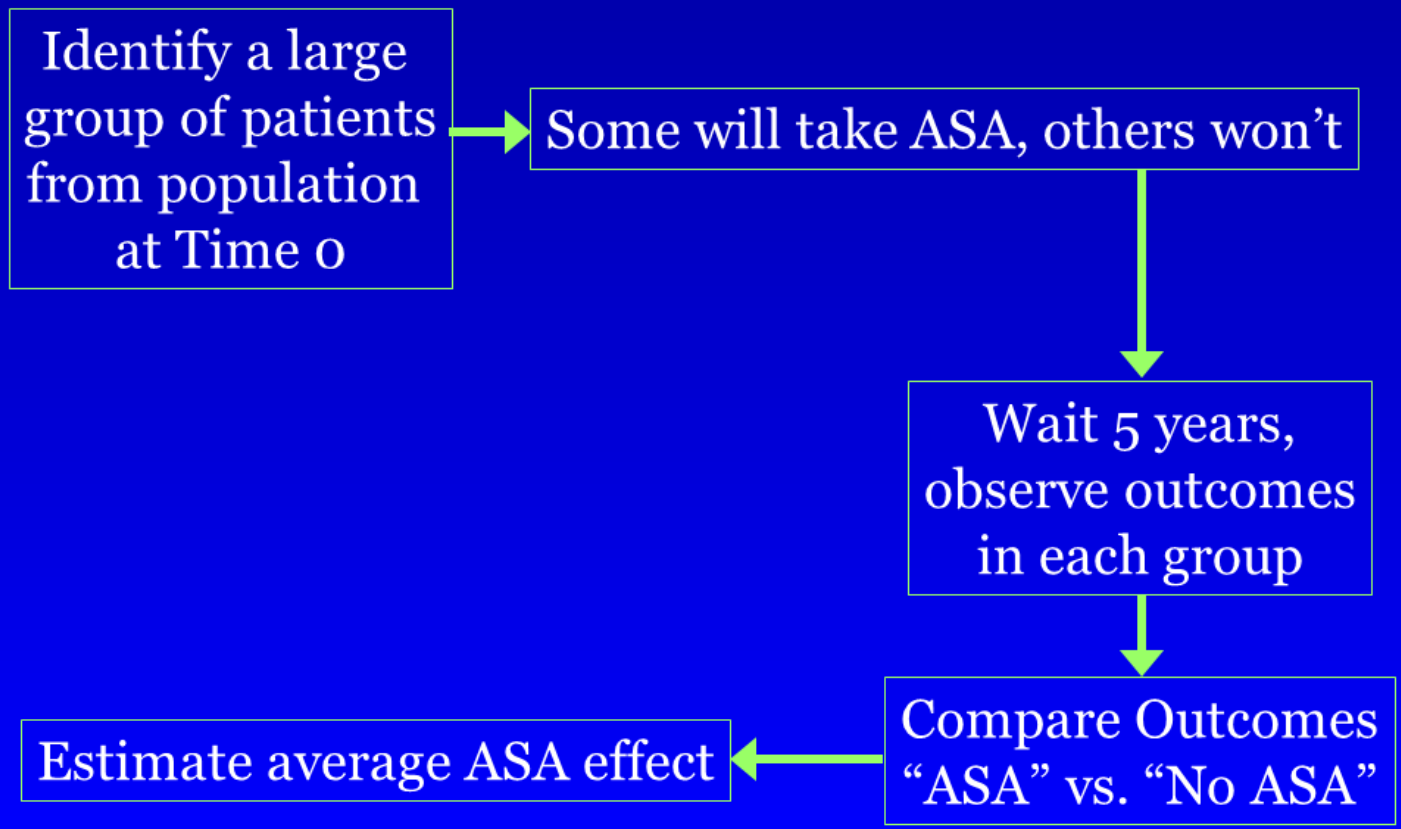
ASA & Mortality: **Observational Study**



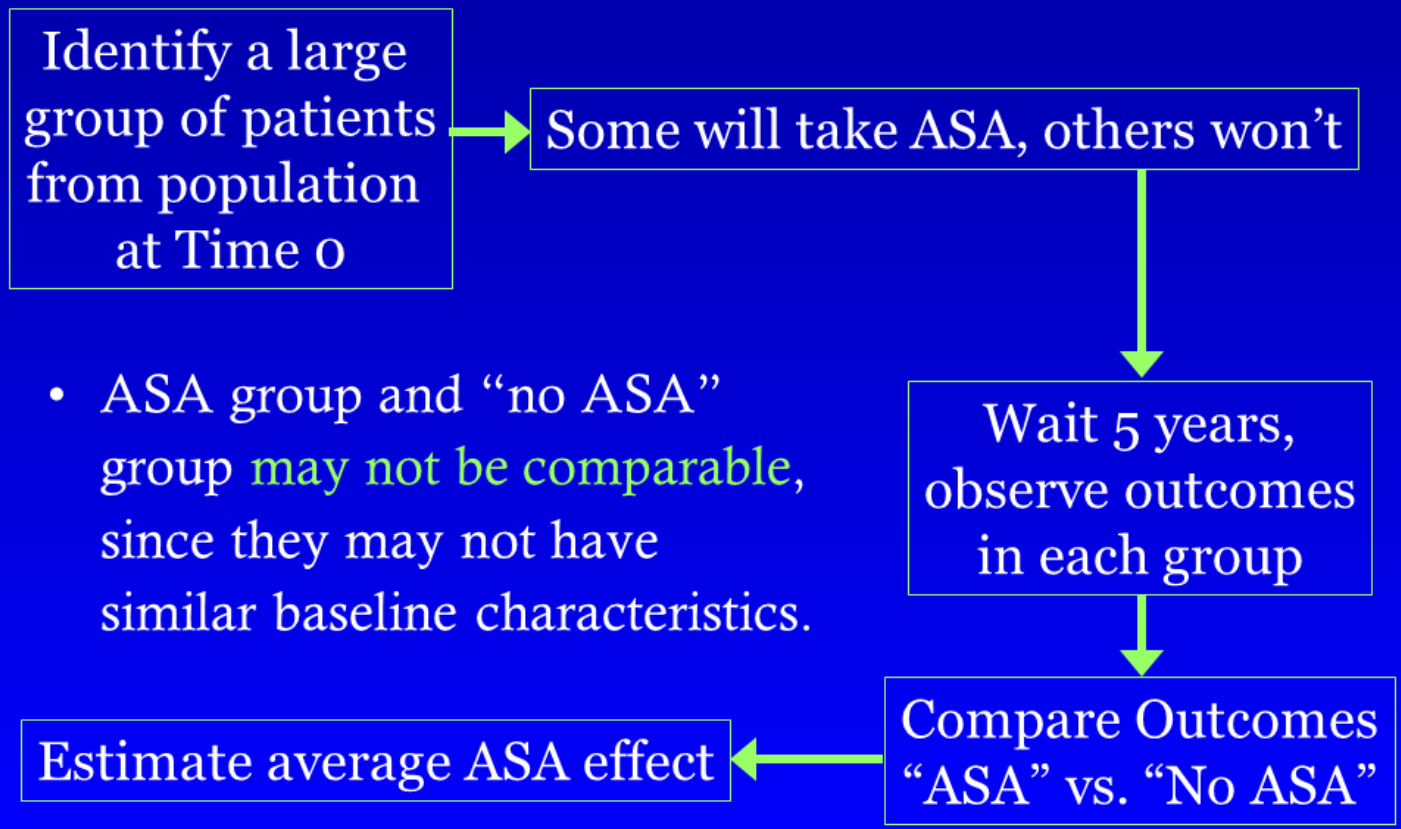
ASA & Mortality: **Observational Study**



ASA & Mortality: **Observational Study**



ASA & Mortality: **Observational Study**



- ASA group and "no ASA" group may not be comparable, since they may not have similar baseline characteristics.

How Do We Avoid Being Misled by Observational Studies?

- What differentiates an observational study from a randomized controlled trial?
  - One key element: potential for selection bias.
- What is selection bias and what can we do about it?
  - Baseline characteristics of comparison groups are different in ways that affect the outcome.

We will often distinguish between overt and hidden bias.

- Overt Bias (seen in data - propensity scores can help)
- Hidden Bias (required data not collected - requires sensitivity analyses)

Aspirin Use and Mortality - The Real Study

6174 consecutive adults at CCF undergoing stress echocardiography for evaluation of known or suspected coronary disease[1].

- 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)

More on this study to come.

[1] Gum PA et al. 2001

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 posted answer sketch.

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.

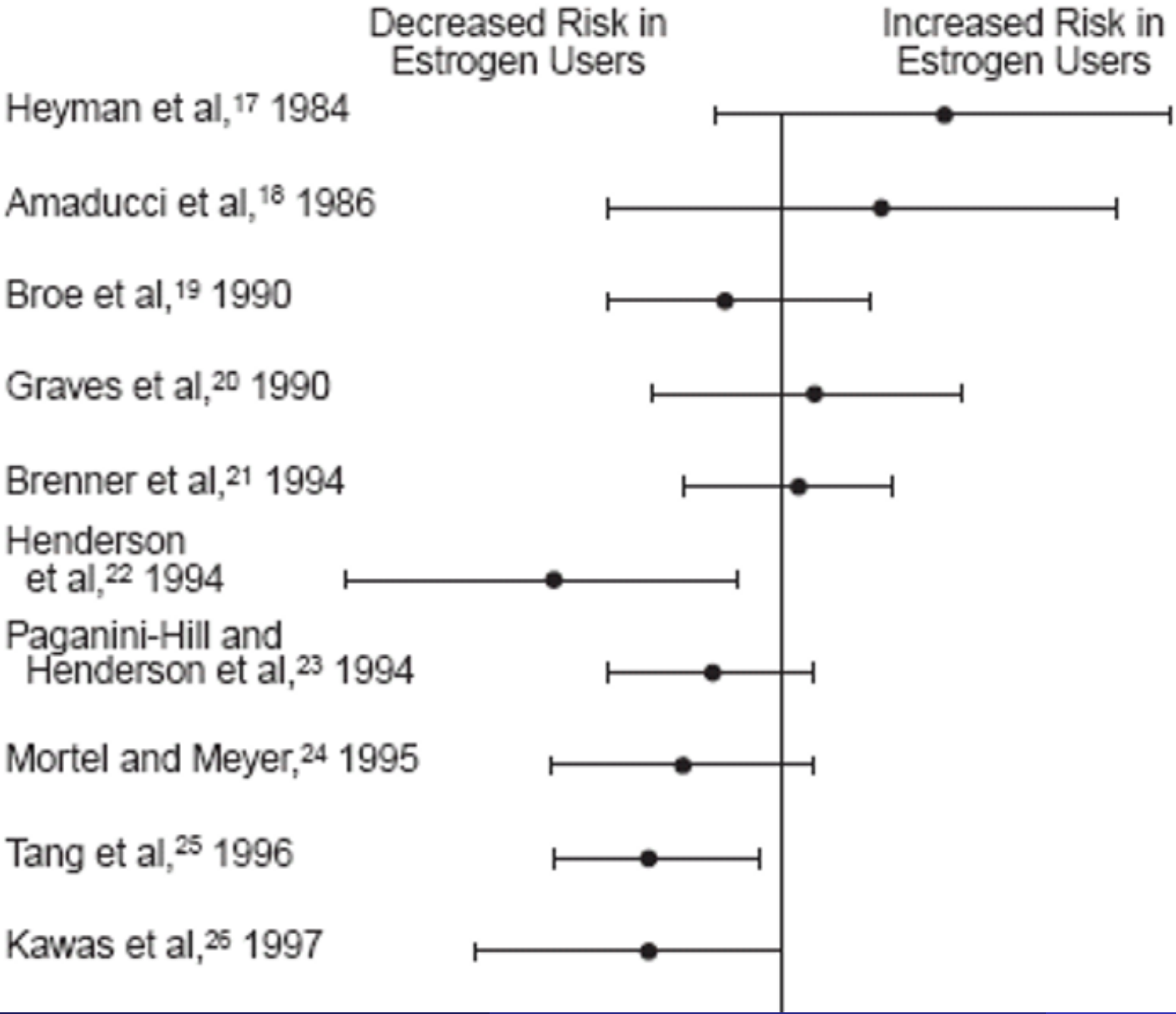
Hormone Replacement Therapy and Dementia

1998 Meta-Analysis[2]

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

[2] 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."[3]
- 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."[4]

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

[4] Craig et al. March 2005 Lancet Neurol

Cache County Memory Study

Prospective study of incident dementia[5]

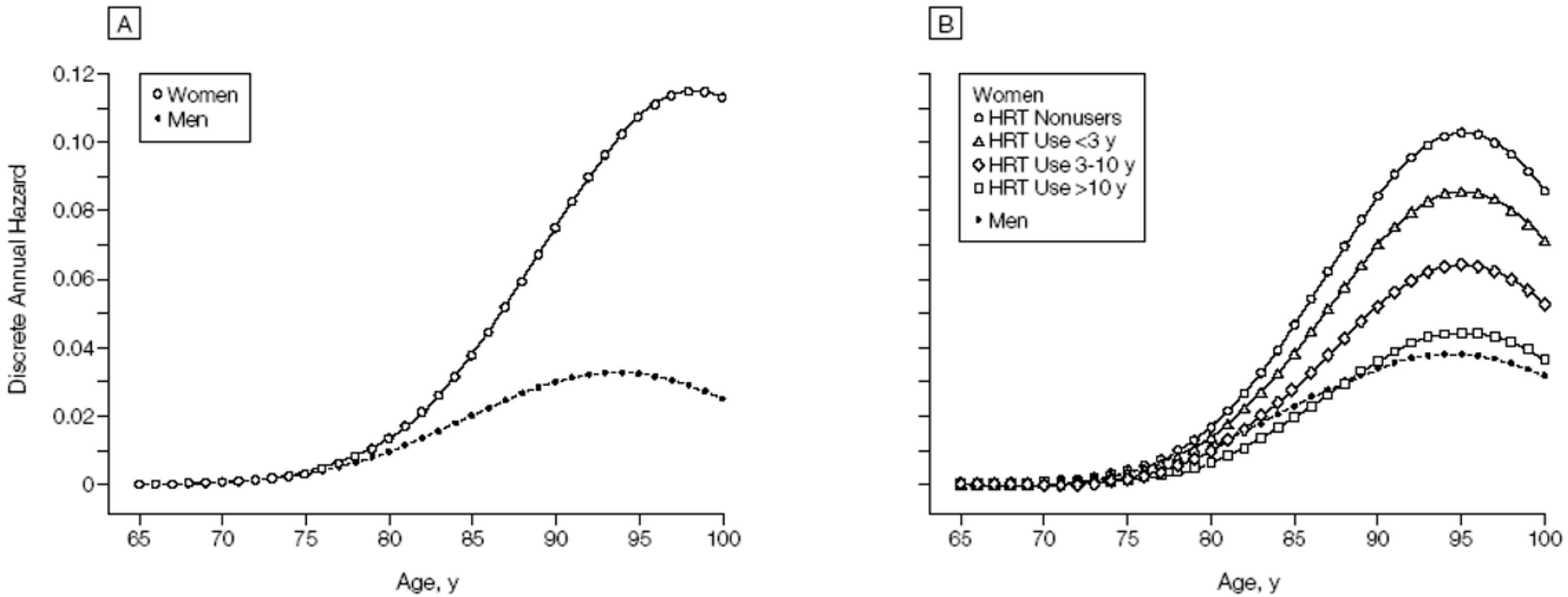
- This was a prospective study of incident dementia among 1357 men and 1889 women residing in a single county in Utah. Patients were first assessed in 1995-97, with follow-up 3 years later.
- Adjustments in models included terms for age and age squared, years of education, and presence of 1 or 2 APOE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

Figure on next slide...

[5] 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[6]

- 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

[6] 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.

Rosenbaum, Chapters 1-4

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 the book?
- What was the **muddiest**, least clear thing that arose in your reading?
- What questions are at the front of your mind now?

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[7].
  - Even as few as 2 or 3 subclasses can have a big impact.

[7] 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.

Next Time . . .

- Rosenbaum Chapters 5 and 6
  5. Between Observational Studies and Experiments
  6. Natural Experiments
- Homework 2: Fitting a "Propensity" model to the DIG data
- Returning to the Aspirin Example
- Matching and Causal Effects
- Estimating the Propensity Score
- Using the Propensity Score to account for observed selection bias