

# Causal Inference Methods and Case Studies

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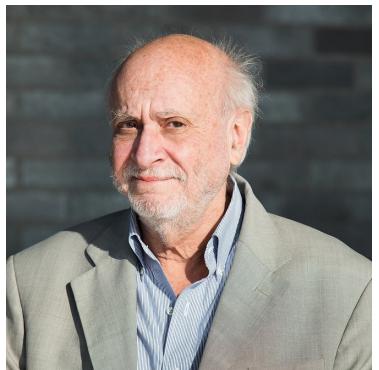
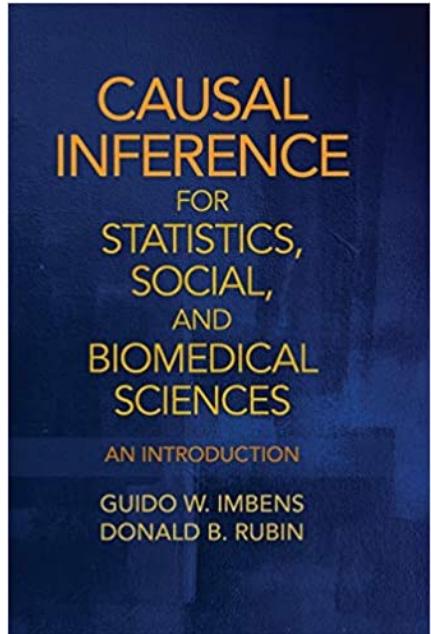
Jingshu Wang

# Lecture 1

Topic: Introduction with examples

- Course logistics
- Introduction with four examples
  - Would high HDL cholesterol level be protective against heart disease?
  - Does maternal smoking have a beneficial effect to reduce infant mortality?
  - Phase 3 randomized trial for the COVID-19 vaccine
  - Effect of compulsory school attendance on schooling and earnings

# Textbook and assignments



Donald B. Rubin



Guido W. Imbens

E-source freely accessible from the UChicago account:  
<https://doi-org.proxy.uchicago.edu/10.1017/CBO9781139025751>

Or buy a hard copy at Amazon.com

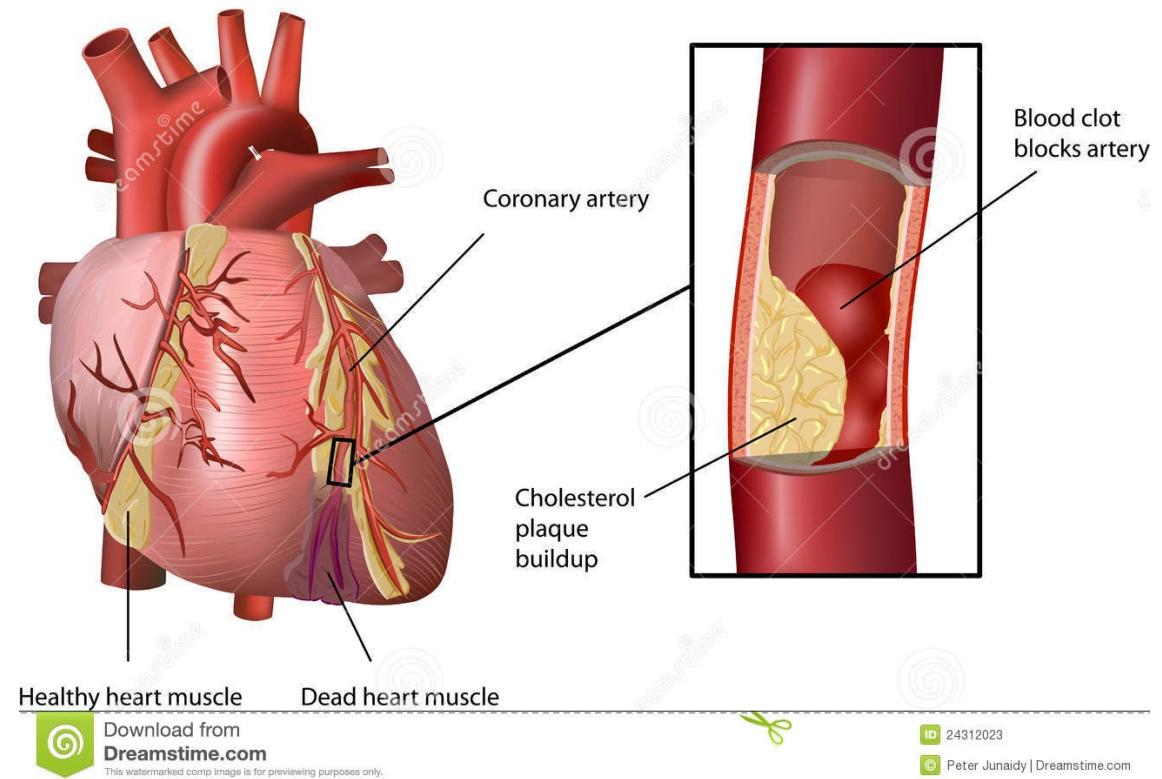
Most examples and lecture materials come from the textbook

## Assignments:

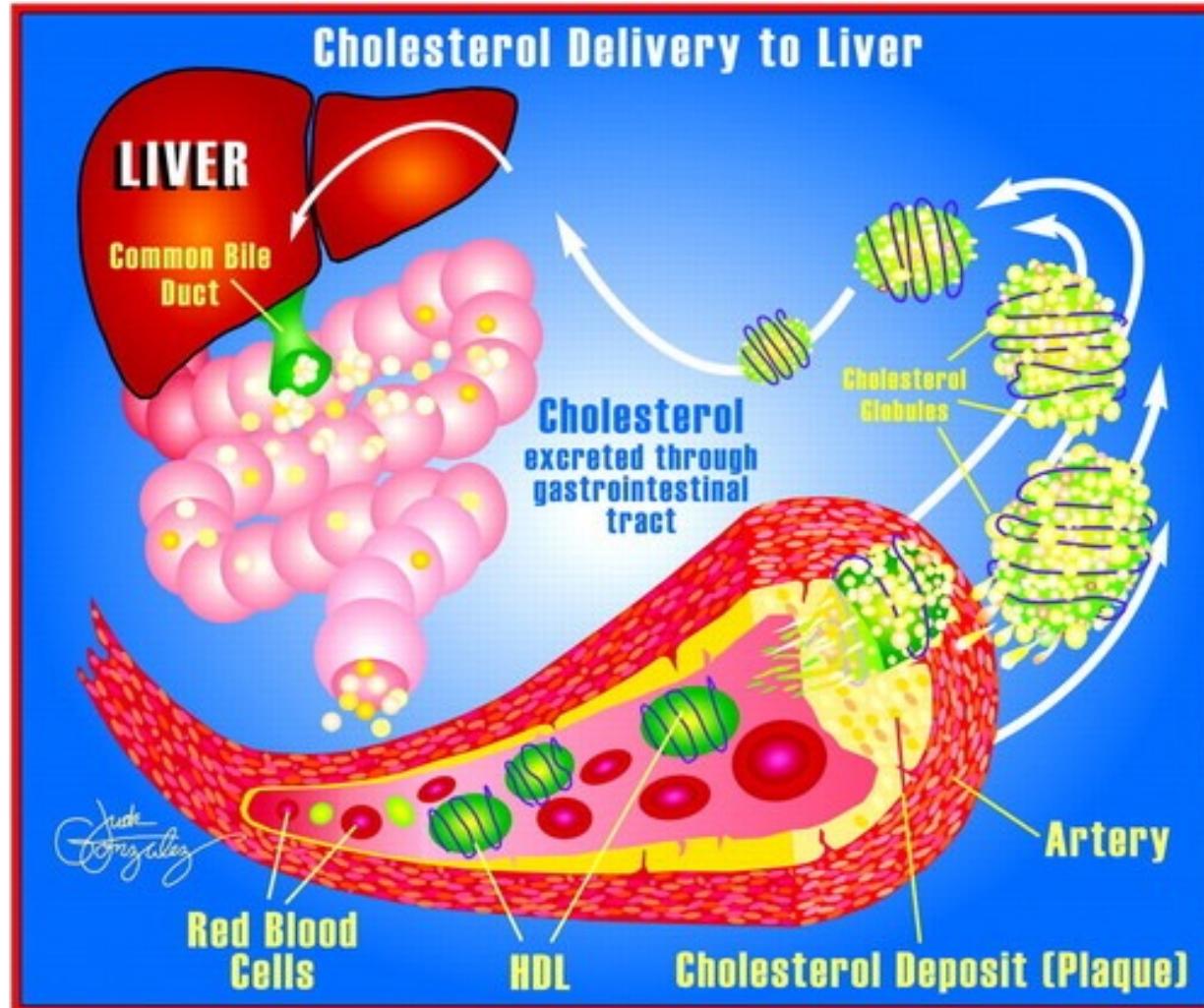
- Four homework assignments (40%)
- HW1 will be released before 3/29 and is due on 4/7 11:59pm
- Homework are submitted via Gradescope
- Two quizzes (20%) 4/15 and 5/13
- Final project (40%): more details later

## Example 1

Would high HDL cholesterol level be protective against heart disease?



# Beneficial effect of high HDL cholesterol levels?



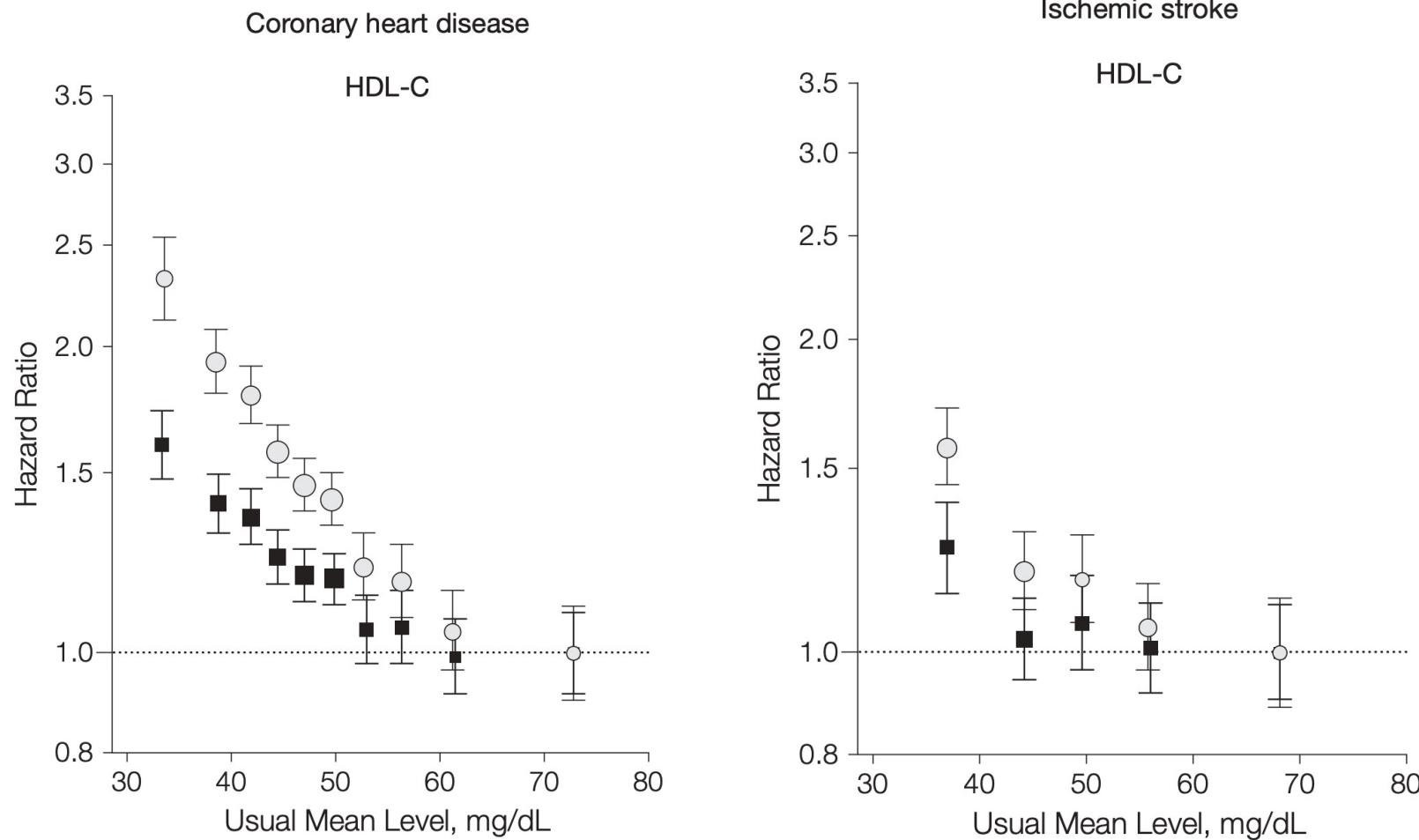
- Scientists believed that HDL cholesterols (HDL-C) are “good cholesterols” and have several beneficial effects
- Most important ability is to drive a process called **“reverse cholesterol transport”**
- HDL is a “mop” that helps to extract excess cholesterol deposited in blood vessel walls and deliver it back to the liver
- If this is true, we can design a drug to increase HDL-C to help reducing the risk of heart disease
- Can we find empirical evidence to support this hypothesis?

# Beneficial effect of high HDL cholesterol levels?

An empirical study to evaluate relationship between HDL-C and the risk of vascular disease  
[Major lipids, apolipoproteins, and risk of vascular disease. *JAMA*, 2009.]

- Individual records were supplied on 302,430 people without initial vascular disease from 68 long-term prospective studies, mostly in Europe and North America.
- Researchers in total observed 8857 nonfatal myocardial infarctions, 3928 coronary heart disease [CHD] deaths, 2534 ischemic strokes, 513 hemorrhagic strokes, and 2536 unclassified strokes
- Researchers compared the risk of vascular disease (measured by the hazard rate, a higher hazard rate corresponds to a higher risk of getting the disease) across individuals having different HDL-C levels.
- They used a regression analysis to adjust for confounding factors including age, sex, systolic blood pressure, smoking status, history of diabetes, body mass index, and lipid measures
- **Hazard ratio:** ratio of the hazard rate between two different groups of individuals

# Beneficial effect of high HDL cholesterol levels?



○ Adjusted for age and sex only  
■ Further adjusted for several risk factors

- The paper suggested a **strong negative association** between the HDL-C level and risk of vascular disease
- After adjusting for confounding factors, the negative association is weaker, though it's still significant
- Does this suggest the beneficial effect of HDL-C?

# Beneficial effect of high HDL cholesterol levels?

A randomized double-blind study for a drug increasing HDL-C levels

[Effects of torcetrapib in patients at high risk for coronary events. *New England journal of medicine*, 2007]

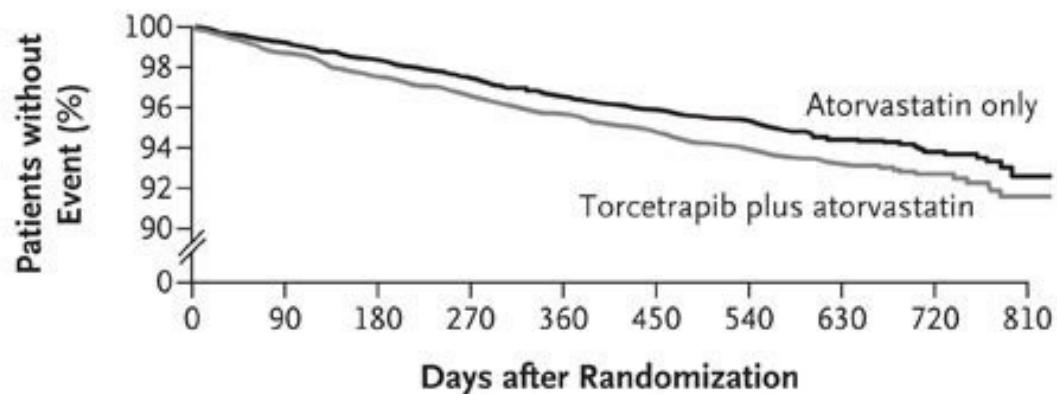
- The drug torcetrapib: a potent CETP inhibitor that can increase HDL-C levels
- Scientists conducted a randomized, double-blind study involving 15,067 patients at high cardiovascular risk. The patients received either torcetrapib plus atorvastatin or atorvastatin alone. (atorvastatin: an FDA approved drug to treat heart disease)
- The primary outcome was the time to the first major cardiovascular event, time to death from coronary heart disease, nonfatal myocardial infarction, stroke, or hospitalization for unstable angina

# Beneficial effect of high HDL cholesterol levels?

**Table 2.** Changes from Baseline at 3 Months and 12 Months in Selected Measures.\*

Variable	Change at 3 Months			Change at 12 Months		
	Atorvastatin Only	Torcetrapib plus Atorvastatin	P Value	Atorvastatin Only	Torcetrapib plus Atorvastatin	P Value
Lipids (absolute change) — mg/dl						
Cholesterol						
Total	+1.6±20.5	+5.1±23.9	<0.001	+2.1±22.4	+9.3±26.3	<0.001
High-density lipoprotein	+0.5±6.2	+29.0±14.4	<0.001	+0.5±6.8	+34.2±17.0	<0.001
Low-density lipoprotein	+0.6±15.8	-20.5±20.8	<0.001	+0.9±17.1	-21.5±22.7	<0.001

## B Major Cardiovascular Events



### No. at Risk

Atorvastatin only	7534	7479	7406	7340	7255	5627	3872	1965	898	103
Torcetrapib plus atorvastatin	7533	7434	7345	7267	7177	5567	3838	1953	888	107

- Torcetrapib does greatly increase HDL-C levels
- The survival probability for the group with torcetrapib decreases even a bit faster
- The randomized trial suggests the failure of the drug
- Why is there a contradiction?  
We may have not adjusted for enough confounding factors

## Example 2

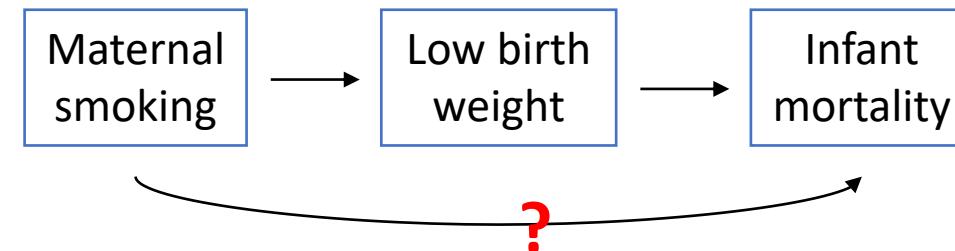
Does maternal smoking have a beneficial effect to reduce infant mortality?



# Maternal smoking, birth weight and perinatal mortality

How does a smoking mother affect her baby?

- Researchers have observed that women who smoke have smaller infants since long time ago (Simpson, 1957)
- Birth weight is a strong predictor of neonatal and infant mortality
- Low birthweight (babies who are born weighing less than 2,500 grams, average newborn weights about 8 pounds) account for 60–80% of all neonatal deaths [4 million neonatal deaths: When? Where? Why? *Lancet*, 2005]
- Question: besides reducing the babies' birthweight, are there other effects of maternal smoking on infant health?

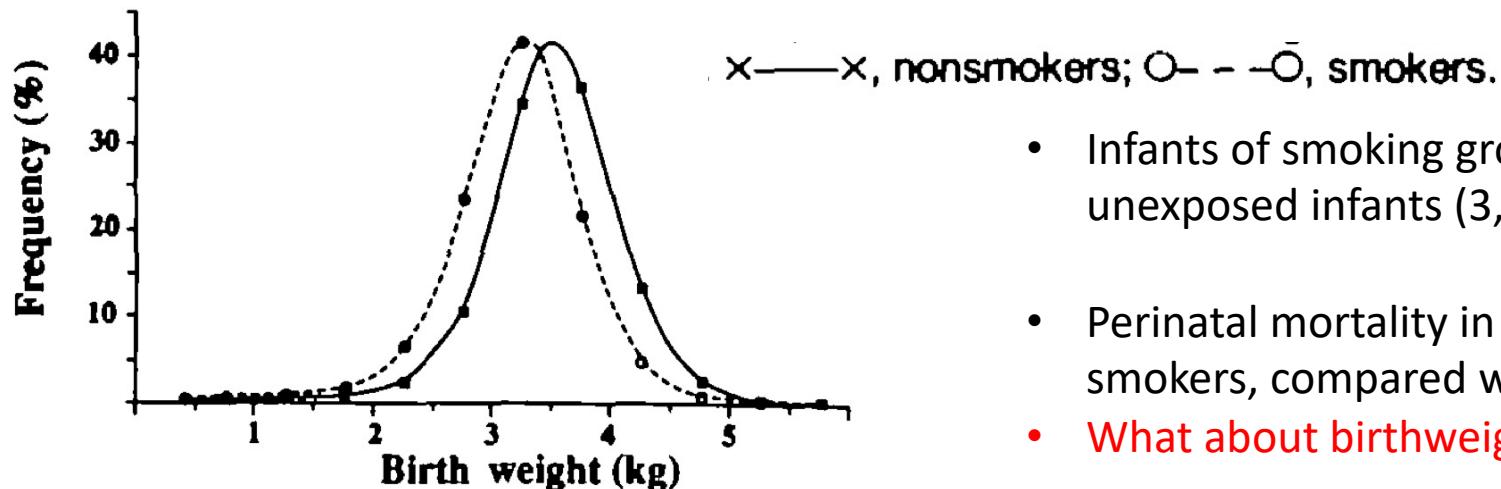


# Maternal smoking, birth weight and perinatal mortality

An analysis by Wilcox

[Birth weight and perinatal mortality: the effect of maternal smoking. *American journal of epidemiology*, 1993.]

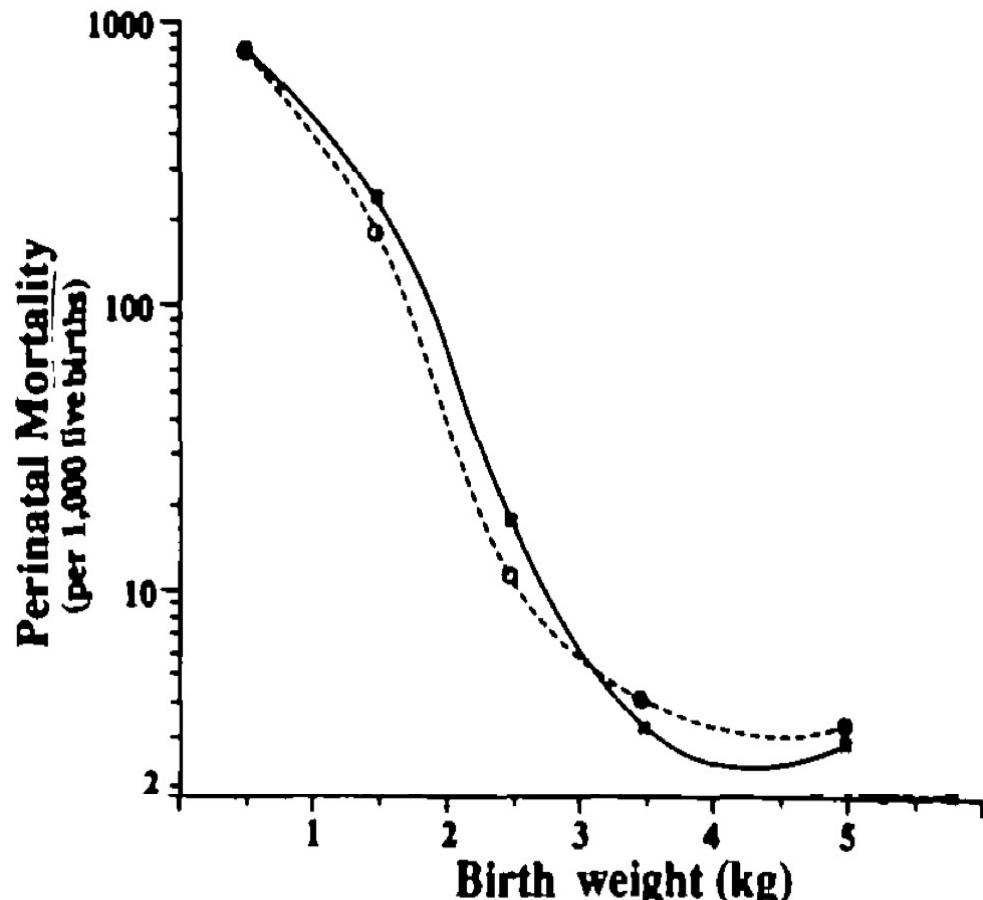
- Data source: a file of Missouri vital statistics records for 1980-1984, assembled as part of the National Institute of Child Health and Human Development Multinational Study of Birth Weight-specific Perinatal Mortality Rates
- perinatal mortality: stillbirths plus deaths in the first 28 days
- Two groups of samples: mothers who had reported no smoking during pregnancy and those who reported smoking at least one pack of cigarettes a day
- 215,428 babies in the first group (unexposed group) and 42,270 babies in the second group (exposed group)



- Infants of smoking group were, on average, 320 g lighter than unexposed infants (3,180 g compared with 3,500 g).
- Perinatal mortality in Missouri is 14.5/ 1,000 infants born to smokers, compared with 10.4 for unexposed infants.
- **What about birthweight-adjusted mortality rate?**

# Maternal smoking, birth weight and perinatal mortality

X—X, nonsmokers; O—O, smokers.



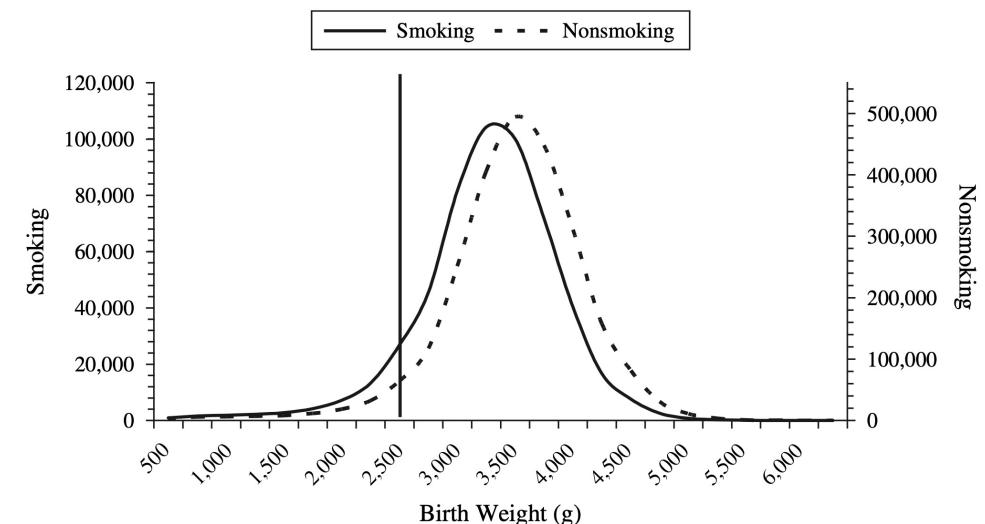
- Surprisingly, among infants less than 3 kg, weight-specific mortality rates are lower for exposed infants than unexposed.
- Would this suggest a beneficial direct effect of maternal smoking towards infant mortality?

# Maternal smoking, birth weight and perinatal mortality

Another data analysis

[The birth weight “paradox” uncovered?. *American journal of epidemiology*, 2006]

- Data source: all infants born alive in the United States in 1991 through the national linked birth/infant- death data sets assembled by the National Center for Health Statistics (about 3 million babies for analysis)
- birth-weight-specific infant mortality is calculated by stratify the babies into 250g categories, and calculate the birth mortality within each category
- Researchers also adjust of other potential confounders: maternal age, gravidity, education, marital status, race/ethnicity, and prenatal care via logistic regression
- We observe a similar weight reduction for the smoking group (3,145g v.s. 3,370g)

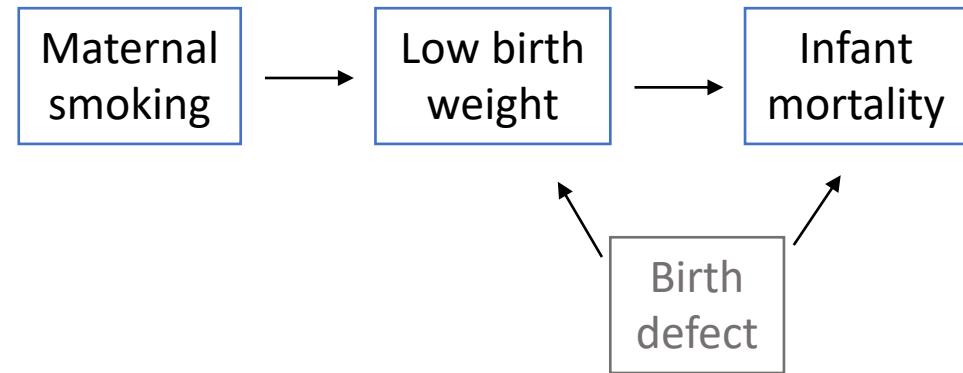


# Maternal smoking, birth weight and perinatal mortality



- Low birthweight infant: infant mortality rate ratio for exposed versus nonexposed infants was 0.79 (95% CI: 0.76, 0.82)
- infant mortality rate ratio is 1.80 (95 percent CI: 1.72, 1.88) among infants with higher birth weights.

- A possible explanation of the birthweight paradox



- Both maternal smoking and birth defects (or malnutrition) can cause low birth weight
- For the unexposed group baby with low birth weight, they are more likely to have birth defects than the exposed group, which can directly increase infant mortality

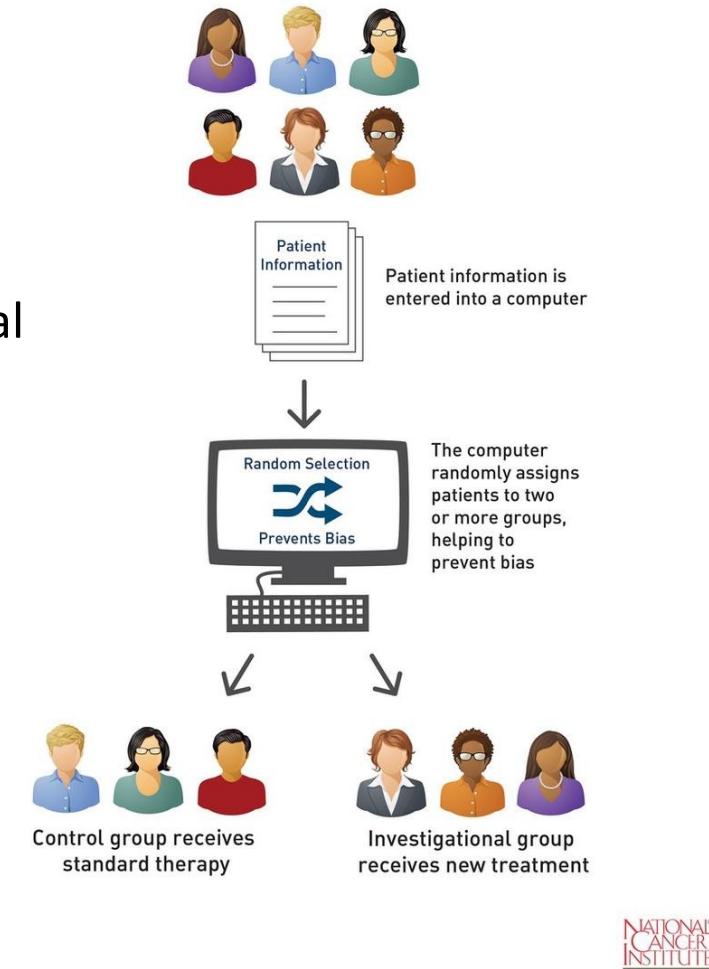
## Example 3

Phase 3 randomized trial  
for the COVID-19 vaccine



# Phase 3 randomized trial for the Moderna vaccine

- On December 18, 2020, FDA approved an emergency use authorization (EUA) for the Moderna vaccine against COVID-19
- The EUA is based a rigorous evaluation of the safety, effectiveness and manufacturing quality of the vaccine
- Randomized, placebo-controlled trials is the gold standard for FDA approval

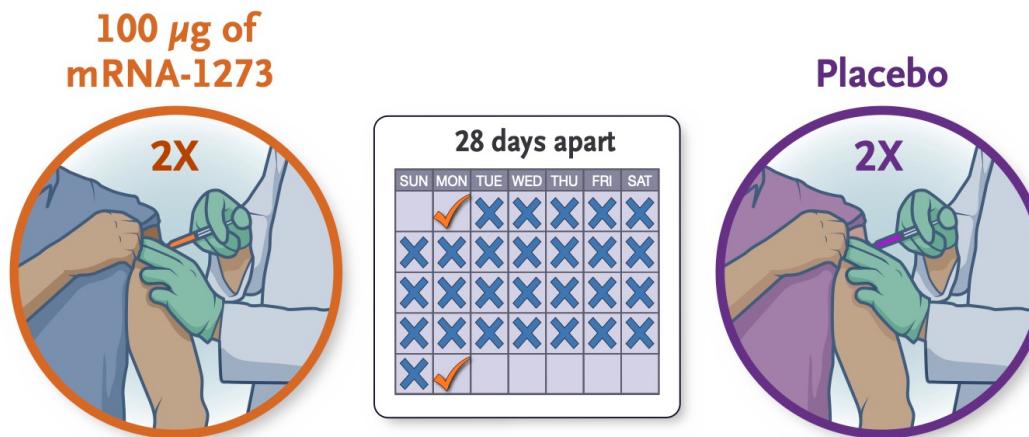


# Phase 3 randomized trial for the Moderna vaccine

Phase 3 randomized trial for the Moderna vaccine

[Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. *New England journal of medicine*, 2020.]

- The phase 3 randomized, observer-blinded, placebo-controlled trial was conducted at 99 centers across the United States
- The trial enrolled 30,420 volunteers who were randomly assigned in a 1:1 ratio to receive either vaccine or placebo (15,210 participants in each group).
- Patients receive two intramuscular injections of mRNA-1273 (100  $\mu\text{g}$ ) or placebo 28 days apart.



# Phase 3 randomized trial for the Moderna vaccine

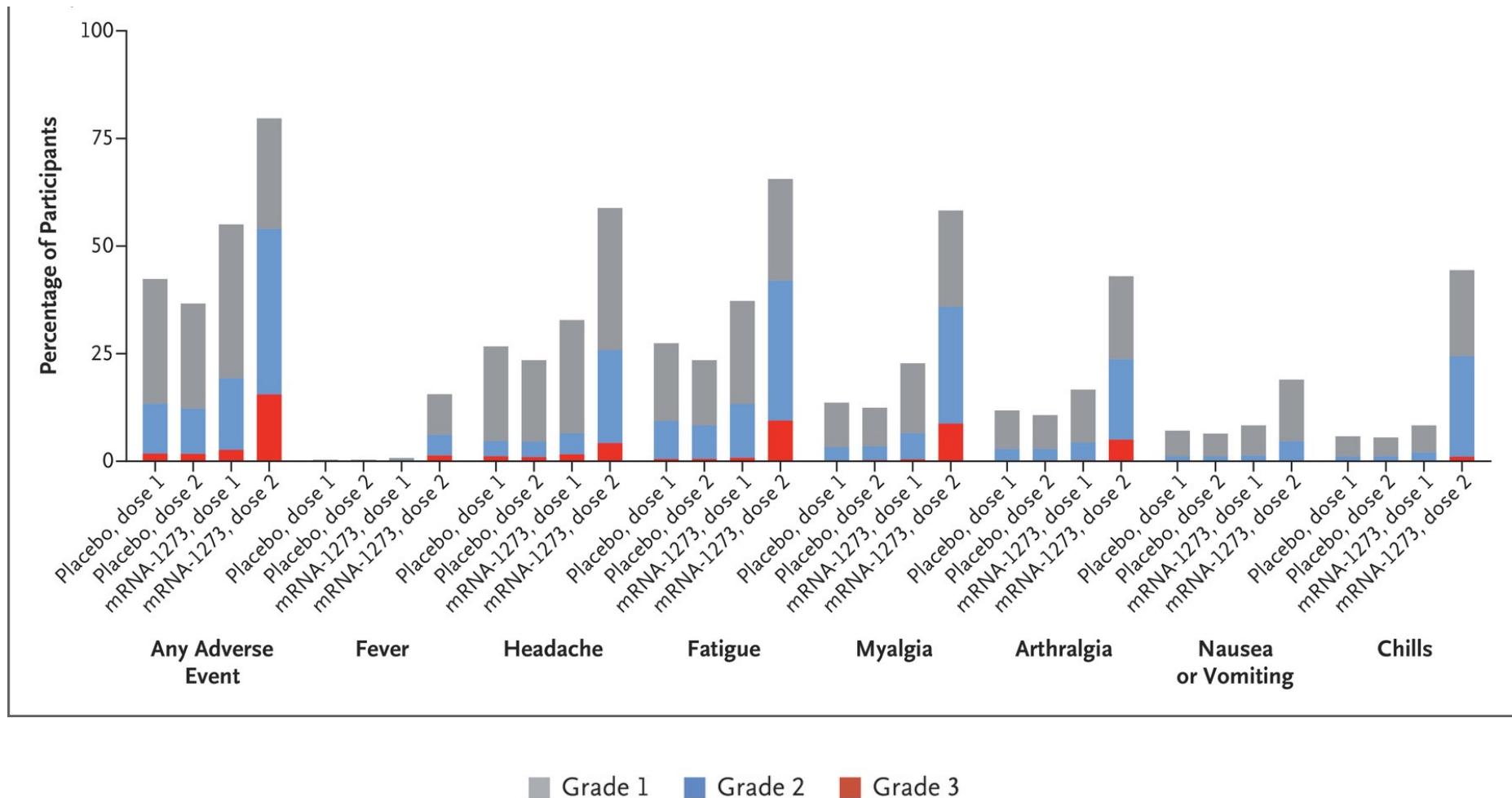
- Because of randomization, characteristics of individuals are well balanced between the two groups

**Table 1.** Demographic and Clinical Characteristics at Baseline.\*

Characteristics	Placebo (N=15,170)	mRNA-1273 (N=15,181)	Total (N=30,351)
Sex — no. of participants (%)			
Male	8,062 (53.1)	7,923 (52.2)	15,985 (52.7)
Female	7,108 (46.9)	7,258 (47.8)	14,366 (47.3)
Mean age (range) — yr	51.3 (18–95)	51.4 (18–95)	51.4 (18–95)
Age category and risk for severe Covid-19 — no. of participants (%)†			
18 to <65 yr, not at risk	8,886 (58.6)	8,888 (58.5)	17,774 (58.6)
18 to <65 yr, at risk	2,535 (16.7)	2,530 (16.7)	5,065 (16.7)
≥65 yr	3,749 (24.7)	3,763 (24.8)	7,512 (24.8)
Hispanic or Latino ethnicity — no. of participants (%)‡			
Hispanic or Latino	3,114 (20.5)	3,121 (20.6)	6,235 (20.5)
Not Hispanic or Latino	11,917 (78.6)	11,918 (78.5)	23,835 (78.5)
Not reported and unknown	139 (0.9)	142 (0.9)	281 (0.9)
Race or ethnic group — no. of participants (%)‡			
White	11,995 (79.1)	12,029 (79.2)	24,024 (79.2)
Black or African American	1,527 (10.1)	1,563 (10.3)	3,090 (10.2)
Asian	731 (4.8)	651 (4.3)	1,382 (4.6)
American Indian or Alaska Native	121 (0.8)	112 (0.7)	233 (0.8)
Native Hawaiian or Other Pacific Islander	32 (0.2)	35 (0.2)	67 (0.2)

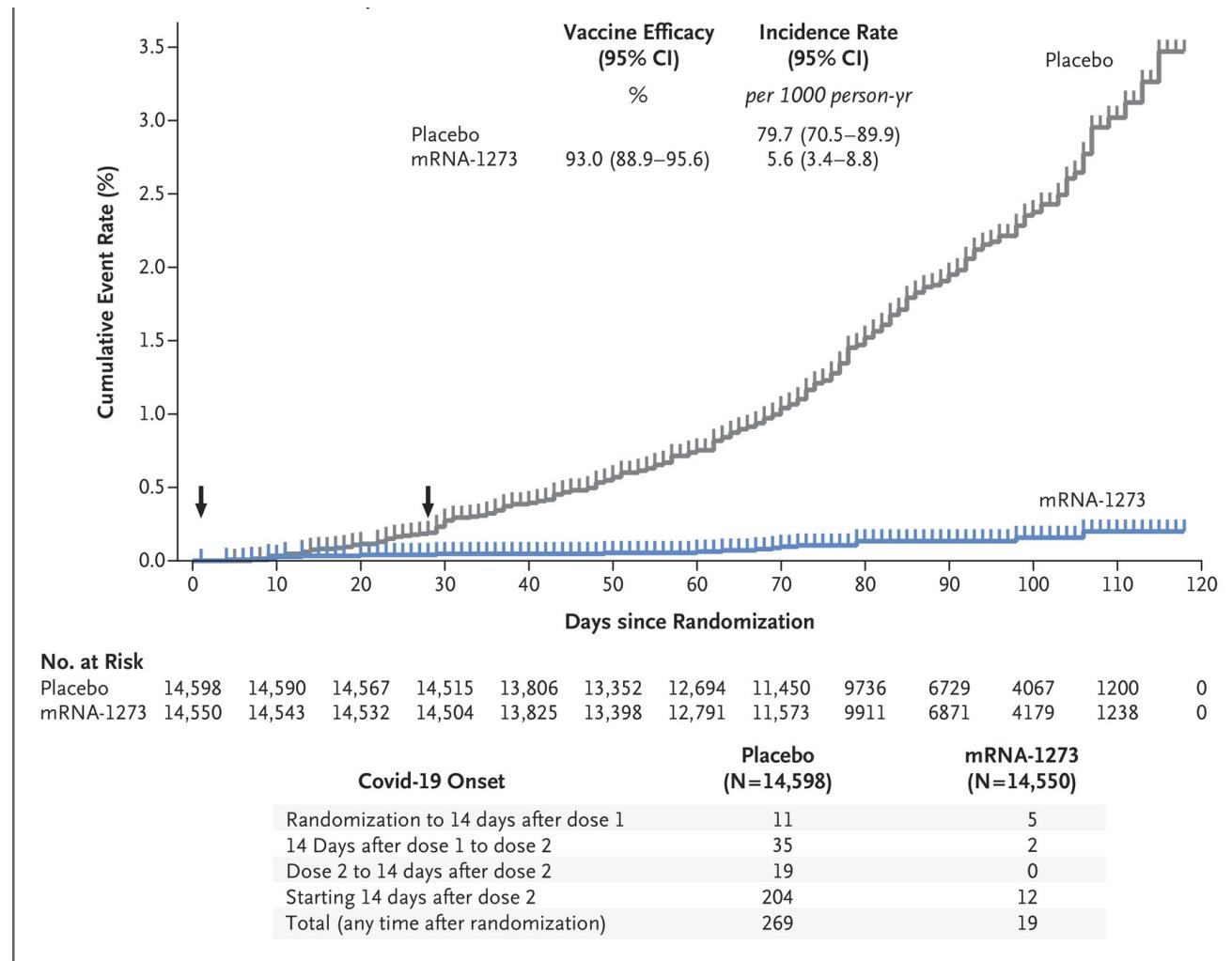
# Phase 3 randomized trial for the Moderna vaccine

- Vaccine Safety (even the placebo group can observe some adverse events)



# Phase 3 randomized trial for the Moderna vaccine

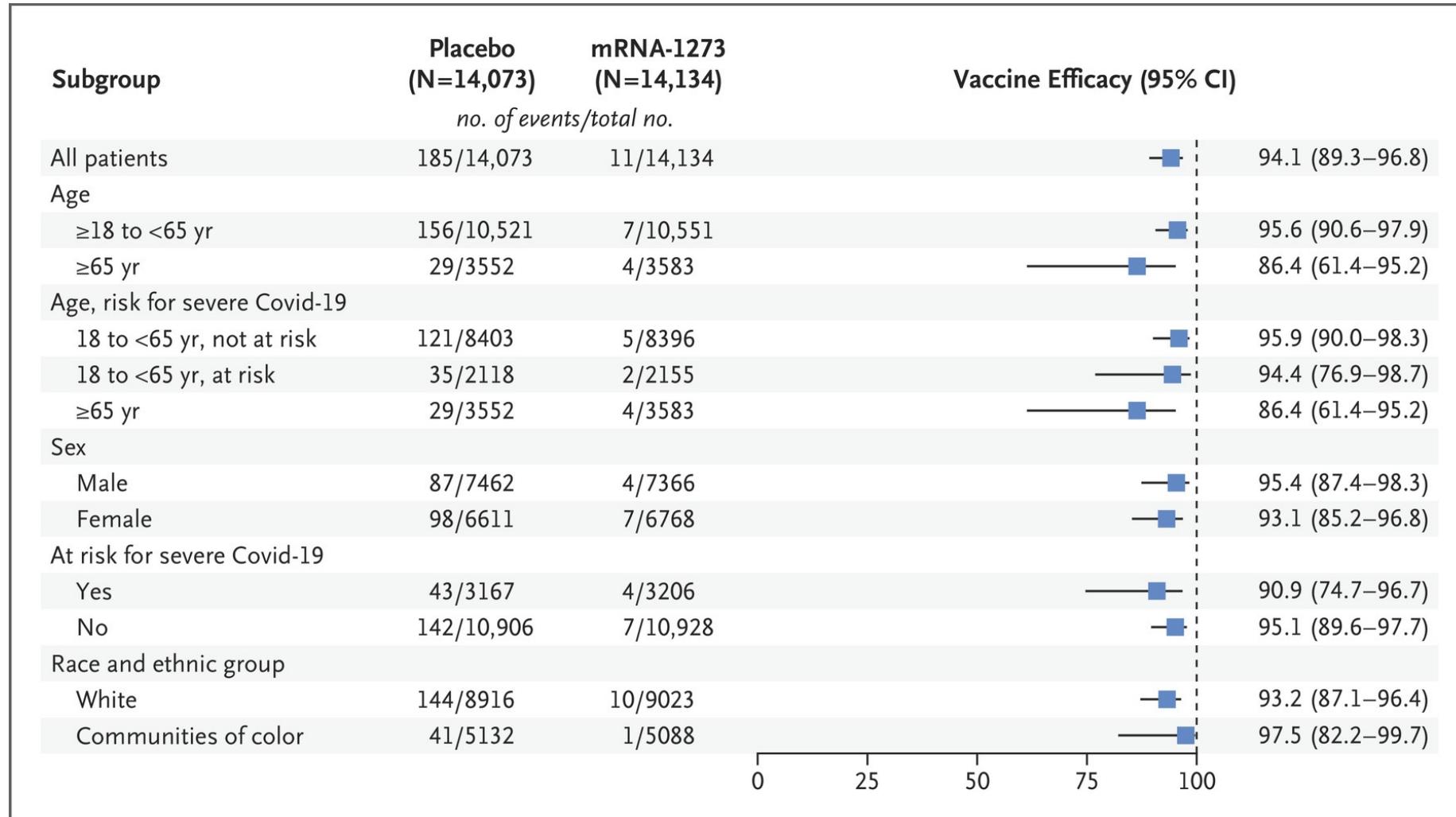
- Vaccine Effectiveness



# Phase 3 randomized trial for the Moderna vaccine

- Vaccine Efficacy in subgroups

Vaccine efficacy  $\approx 1 - \text{odds ratio}$

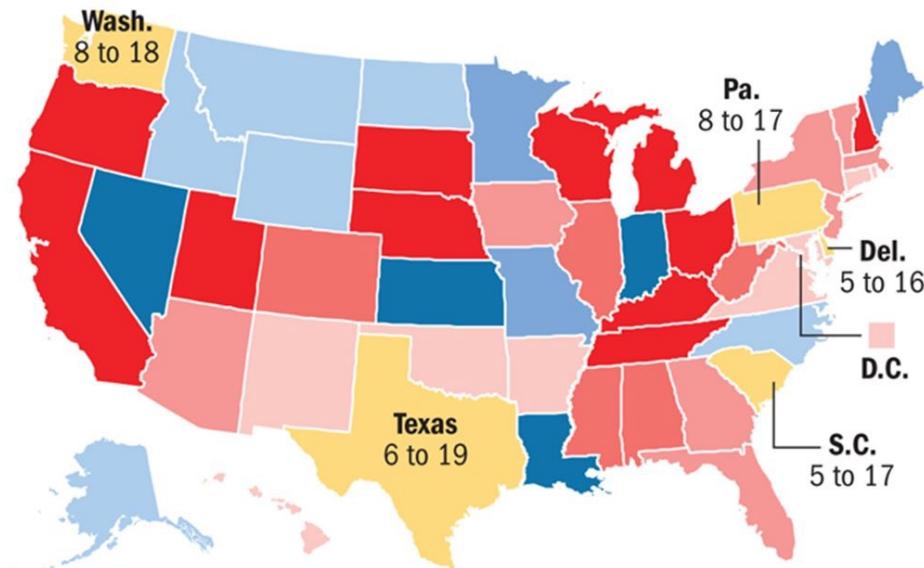


## Example 4

Effect of compulsory school attendance on schooling and earnings

### Compulsory school attendance laws, minimum and maximum age limits

AGE OF REQUIRED SCHOOL ATTENDANCE, 2017



Note: For specifics regarding each state's law, go to [nces.ed.gov](https://nces.ed.gov)

Source: National Center for Education Statistics

Post-Gazette

# The impact of compulsory schooling on earnings

- Scientists aim to assess whether students who attend school longer receive higher earnings as a result of their increased schooling
- Say, we think that the weekly wages can depend on both the education levels and a person's own ability, family background et. al...

$$\log(\text{Weekly wage}_i) = \beta_0 + \beta_1 \text{Schooling}_i + \beta_2 \text{Ability}_i + \text{noise}_i$$

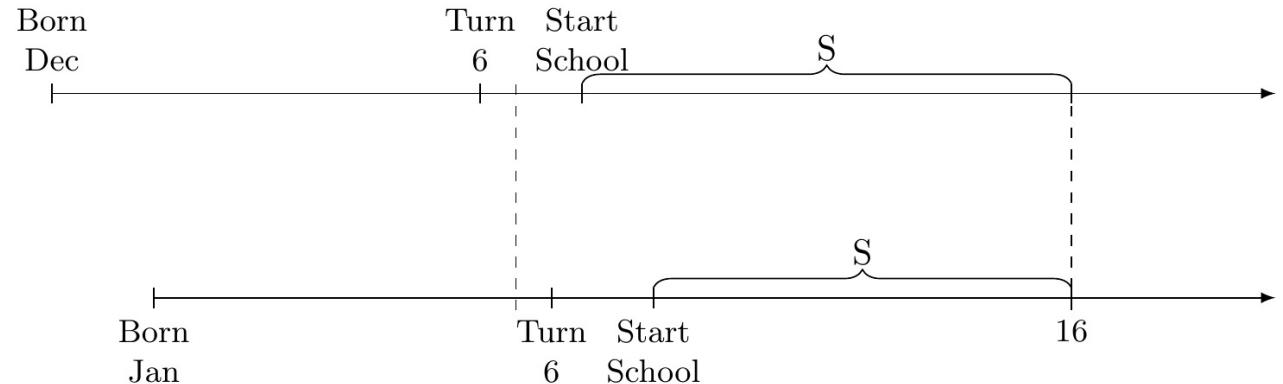
- If we can not measure one's ability, and one's ability is correlated with one's education level, then if we only regress weekly wages on schooling, then we will have a biased estimate of the effect of schooling
- How can we adjust for the bias? (ability here is called an unmeasured confounding factor)
- We want to find **an instrument** that is associated with schooling and is guaranteed to be independent from the unmeasured confounding of ability

# The impact of compulsory schooling on earnings

A study by two economists J.D. Angrist and A.B. Krueger

[Does compulsory school attendance affect schooling and earnings?. *The Quarterly Journal of Economics*, 1991.]

- Because of the compulsory schooling laws, children born in different months of the year can start school at different ages and have different years of education
- So, they used season of birth as an instrument to understand the causal effect of schooling:
- School districts typically require a student to have turned age six by January 1 of the year in which he or she enters school
- students born earlier in the year enter school at an older age and attain the legal dropout age at an earlier point in their educational careers than students born later in the year
- Season of birth should be independent from other unmeasured confounding factors like ability, family of background ...



# The impact of compulsory schooling on earnings

- Empirical evidence showing that kids born in earlier seasons indeed have a shorter length of education

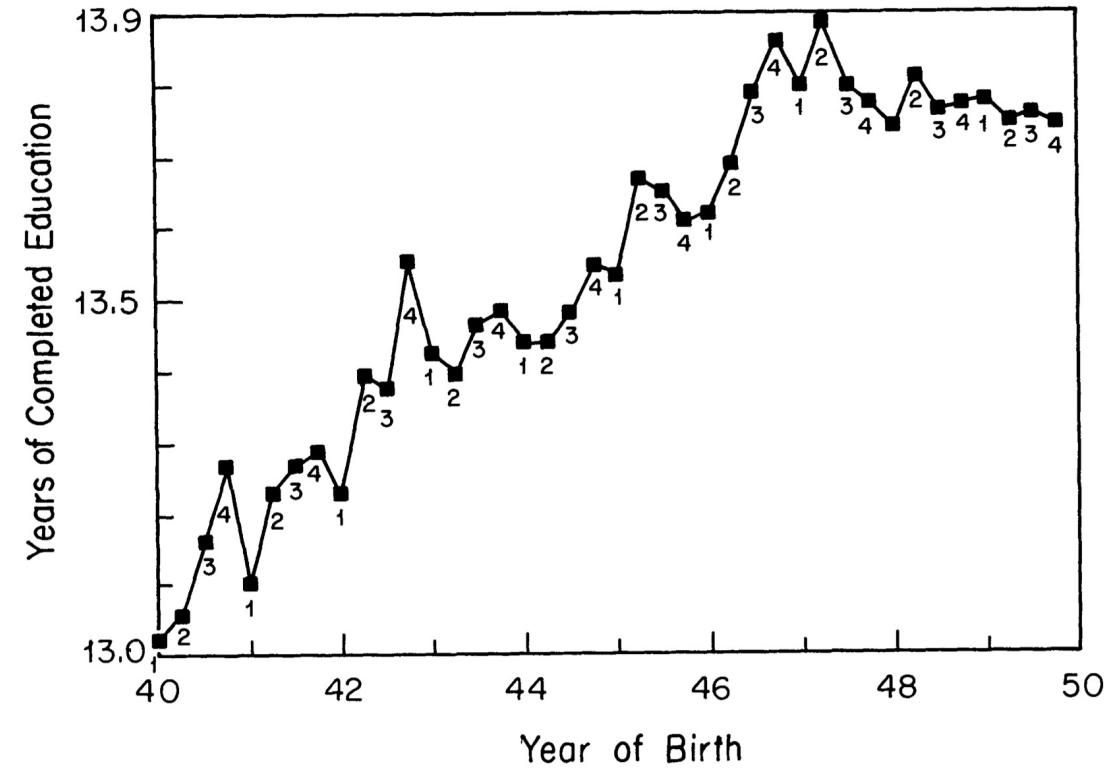
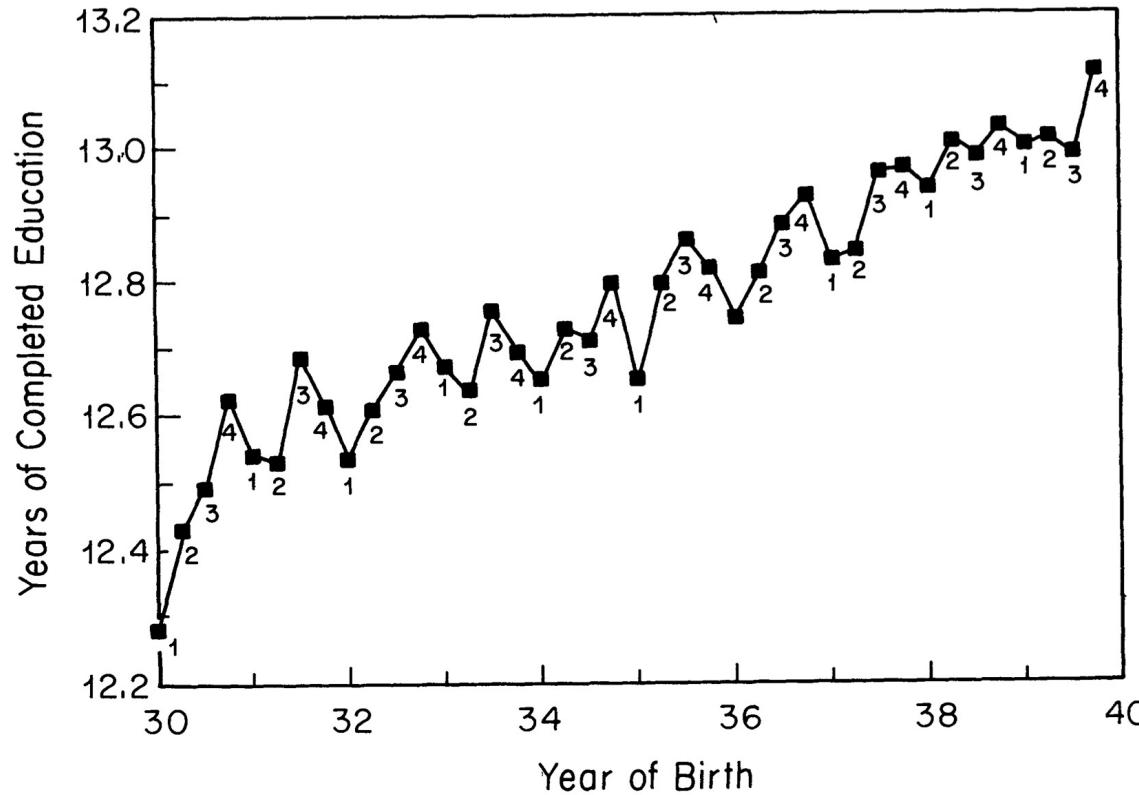


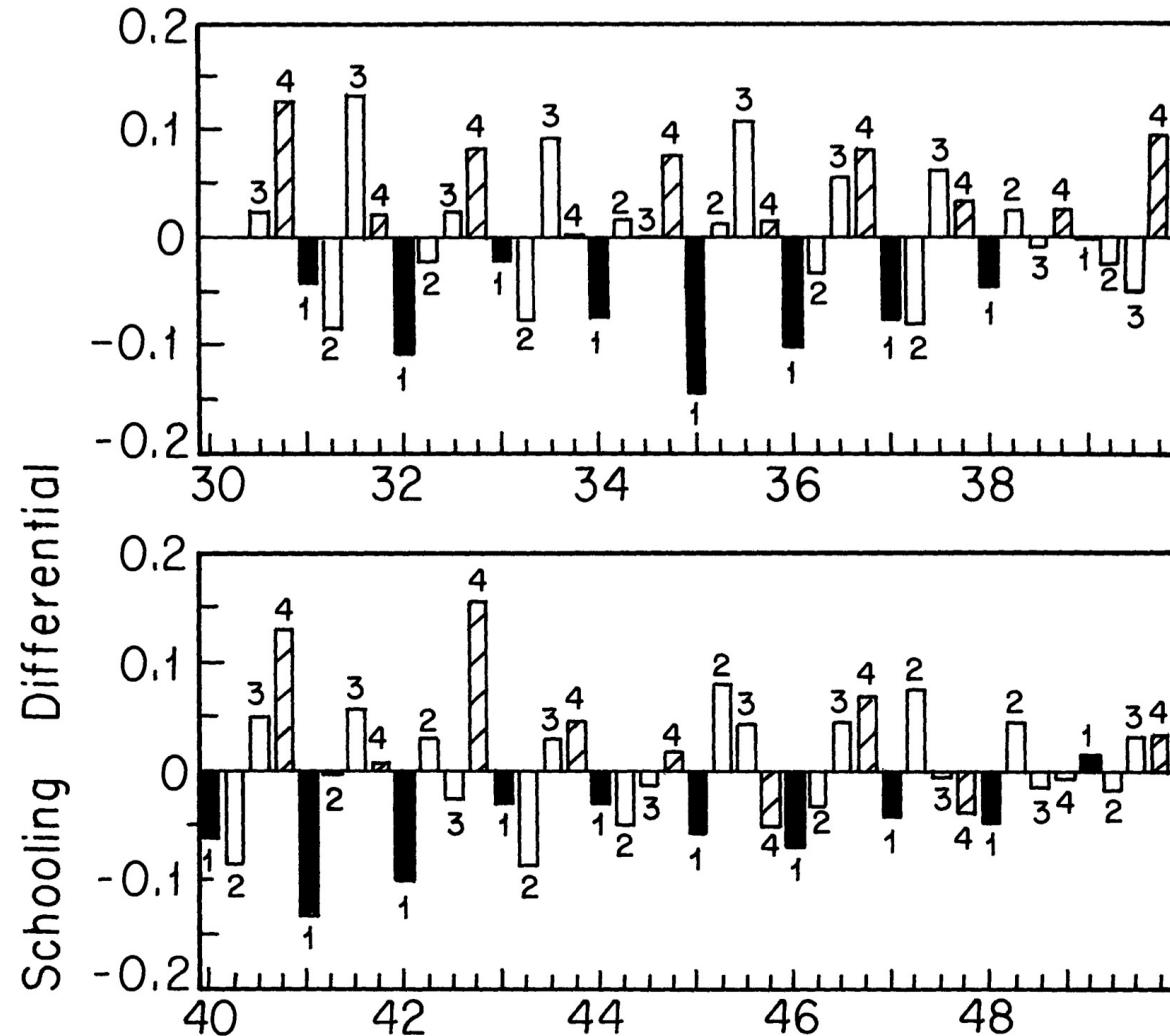
FIGURE I

Years of Education and Season of Birth  
1980 Census

Note. Quarter of birth is listed below each observation.

# The impact of compulsory schooling on earnings

- After removing the year trend



# The impact of compulsory schooling on earnings

- Kids born at earlier seasons are associated with a lower weekly earnings

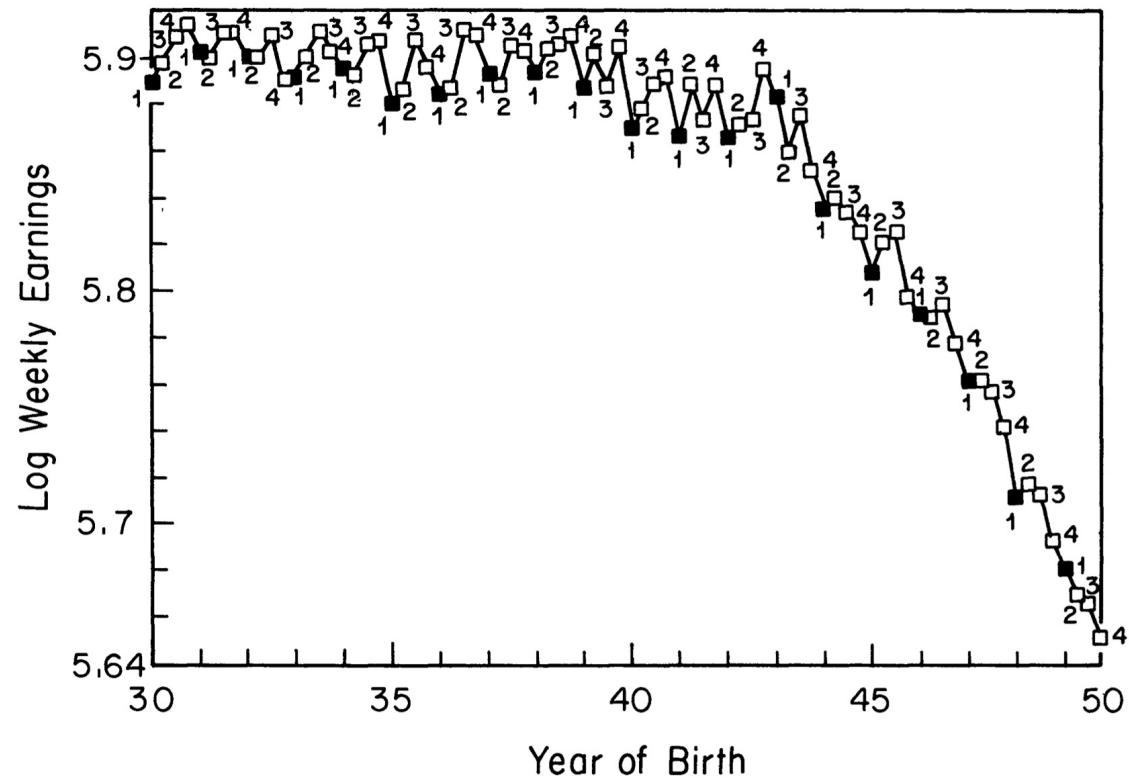


FIGURE V  
Mean Log Weekly Wage, by Quarter of Birth  
All Men Born 1930–1949; 1980 Census

## The logic of using the instrument:

- Kids born at later seasons tend to have a longer length of schooling due to the compulsory schooling laws
- Birth seasons are considered as completely randomized (natural experiment)
- Birth seasons can affect the weekly earnings only through its effect on the education years
- Then, the association between later birth seasons with higher weekly earnings suggests a causal effect of longer education years to increase weekly earnings

# Causal inference

- To summarize, most scientific questions are causal questions
- We know what causal effects mean as a human being

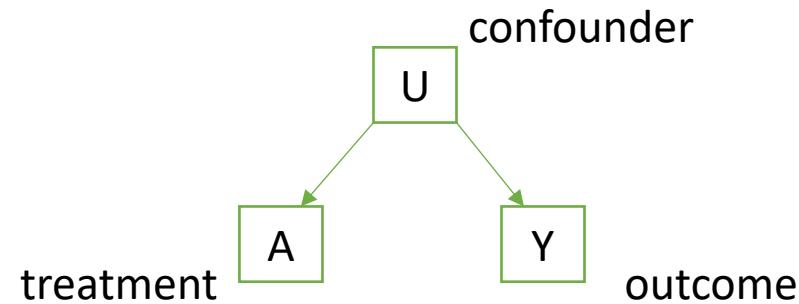
*I would rather discover one causal law than be King of Persia.*  
— Democritus

*We have knowledge of a thing only when we have grasped its cause.*  
— Aristotle, *Posterior Analytics*

- How to quantitatively define “causal effects” with mathematical notations?
  - When are regression adjustments correct? What variables should I include?
  - Are there other approaches that can help us identify and estimate a causal effect more reliably (require less assumptions and robust to violations of assumptions)

# Association $\neq$ Causation

- Confounding



- In randomized experiments, treatment is independent from confounders and is the gold standard for causal inference
  - How to perform statistical estimation for randomized experiments with minimum assumptions?
  - What if our randomized experiments are not perfect?
- In observational studies, we are always worried about Confounding
  - How do we adjust for known confounders?
  - How do we deal with unmeasured hidden confounders?

# Reference papers to read

Example 1:

- Assessment, R. E. L. I. A. B. L. E. (2009). Major lipids, apolipoproteins, and risk of vascular disease. *Jama*, 302(18), 1993-2000.  
<https://jamanetwork.com/journals/jama/article-abstract/184863>
- Barter, P. J., Caulfield, M., Eriksson, M., Grundy, S. M., Kastelein, J. J., Komajda, M., ... & Brewer, B. (2007). Effects of torcetrapib in patients at high risk for coronary events. *New England journal of medicine*, 357(21), 2109-2122.  
[https://www.nejm.org/doi/10.1056/NEJMoa0706628?url\\_ver=Z39.88-2003&rfr\\_id=ori:rid:crossref.org&rfr\\_dat=cr\\_pub%20%20www.ncbi.nlm.nih.gov](https://www.nejm.org/doi/10.1056/NEJMoa0706628?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%20%20www.ncbi.nlm.nih.gov)

Example 2:

- Wilcox, A. J. (1993). Birth weight and perinatal mortality: the effect of maternal smoking. *American journal of epidemiology*, 137(10), 1098-1104. <https://academic.oup.com/aje/article-abstract/137/10/1098/128195>
- Hernández-Díaz, S., Schisterman, E. F., & Hernán, M. A. (2006). The birth weight “paradox” uncovered?. *American journal of epidemiology*, 164(11), 1115-1120. <https://academic.oup.com/aje/article/164/11/1115/61454>

Example 3:

- Baden, L. R., El Sahly, H. M., Essink, B., Kotloff, K., Frey, S., Novak, R., ... & Zaks, T. (2020). Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. *New England journal of medicine*. <https://www.nejm.org/doi/full/10.1056/nejmoa2035389>

Example 4:

- Angrist, J. D., & Keueger, A. B. (1991). Does compulsory school attendance affect schooling and earnings?. *The Quarterly Journal of Economics*, 106(4), 979-1014. <https://www.jstor.org/stable/2937954>

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