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Study Design

John McGready
The Johns Hopkins University

Randomized/controlled study design

Methods of randomization

Natural experiments

Observational studies

Case/control studies



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Section A

Making the Case for Randomized Controlled Studies

The Dangers of Self-Selection

A study was performed to look at the effect of a drug, Clofibrate, on mortality rates for individuals with heart disease

- ★ *Individuals were followed for five years after administration of the drug*

The Dangers of Self-Selection

Coronary heart disease

★ *Results from group randomized to take Clofibrate*

		Mortality
Clofibrate	Compliers	.15
	Non-compliers	.25

(p < .01)

The Dangers of Self-Selection

Coronary heart disease

★ *Results from group randomized to take placebo*

		Mortality
Placebo	Compliers	.15
	Non-compliers	.25
		($p < .01$)

The Dangers of Self-Selection

Randomized trial

Clofibrate

N = 1,103

Five Year Mortality

20%

Placebo

N = 2,789

21%

Continued

The Dangers of Self-Selection

Randomized trial

- ★ *No significant difference ($p > .20$) between the treatment and placebo groups!*

No difference between TX groups

- ★ *The compilers and non-compilers were similar with respect to other variables (age, etc.)*

A Randomized Control Group

Important for accounting for many kinds of biases

Hypertension study

- ★ *Enrolled individuals with **elevated** blood pressure*
- ★ *Treated patients*
- ★ *Then compared before-and-after blood pressure using paired t-tests*

The second measurement of blood pressure (the “after” measurement) may tend to decrease—not because of the efficacy of treatment but because the initial extremely high measurements (the “before” measurements) were statistical flukes

Naive paired t-test could lead one to conclude incorrectly that treatment is effective

- ★ *Regression toward the mean refers to the phenomenon that if a variable is extreme on the first measurement then later measurements may not be as extreme*

The problem is that there is selection bias:

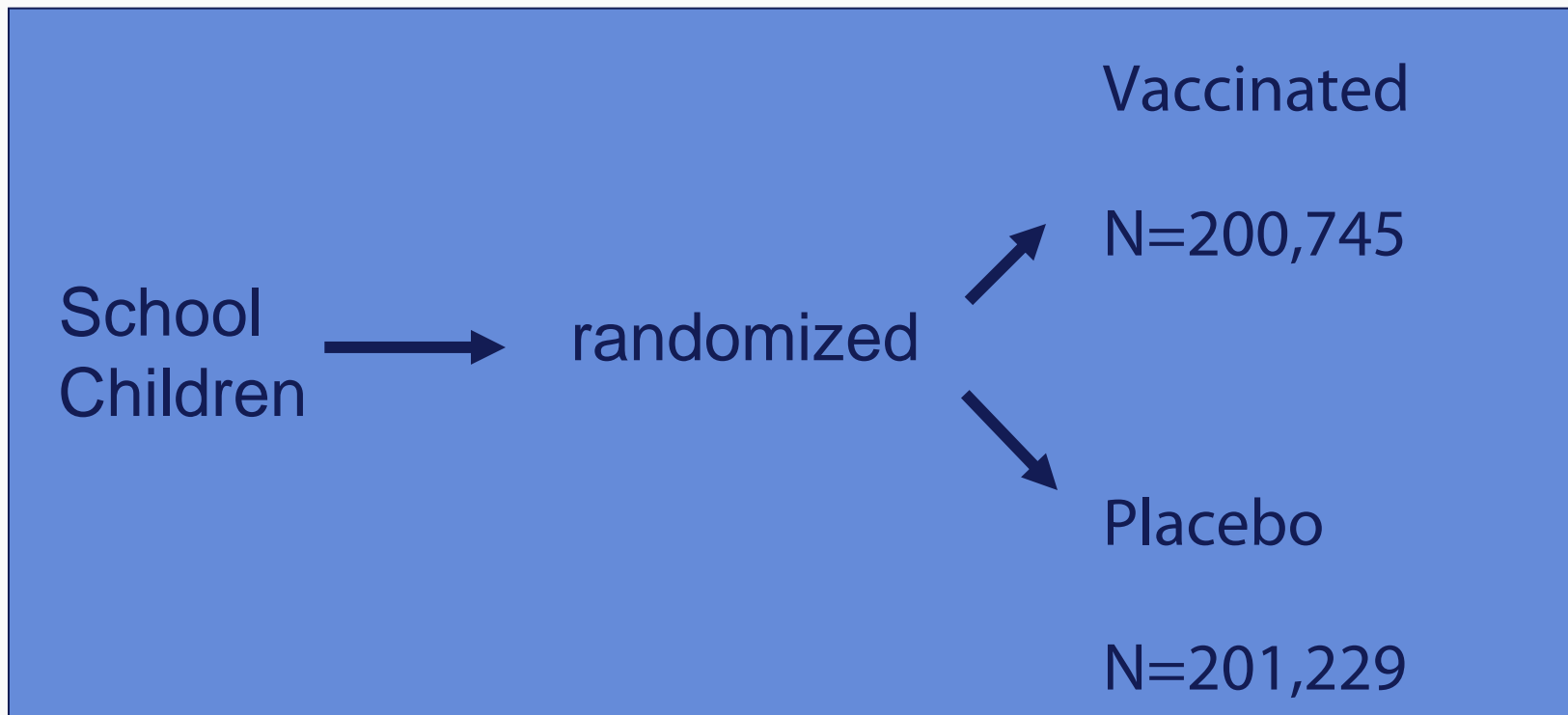
- ★ *We are selecting for inclusion in the study only those with elevated blood pressure*
- ★ *Many of those included may not “truly” have elevated blood pressure but appear elevated because of measurement errors*

One solution

- ★ *Have a control group*
- ★ *Take before-after measurements on both groups*
- ★ *Any selection biases would be present in both groups*

1954 Salk Polio Vaccine Trial

Example of a famous randomized trial



Continued

1954 Salk Polio Vaccine Trial

At the end of the follow-up period there were 82 cases in the vaccine group and 162 in the placebo group

Subsequently analyses report slightly different numbers because some false positives were discovered in each of the two groups

Results in 2 x 2 Table Format

	Vaccine	Placebo
Polio	82	162
No Polio	200,663	201,067
	200,745	201,229

Continued

Results in 2 x 2 Table Format

How to test for an association between vaccine and polio? (Flashback to 611!)

$$H_o: p_1 = p_2$$

$$H_a: p_1 \neq p_2$$

Where p_1 is the percentage of children with polio in vaccine group, p_2 is the percentage in the placebo group

Results in 2 x 2 Table Format

How to test for an association between vaccine and polio? (Flashback to 611!)

- ★ *Can use either Fisher's Exact test or Chi-Squared test (Why?)*

With FET, $p < .001$

Many epidemiological studies are concerned with estimating an association between two dichotomous (binary) variables

★ *Example: Exposure-disease association*

Randomized study design with control group is a type of *prospective cohort study*

Prospective cohort studies

- ★ *Choose a fixed number with and without exposure*
- ★ *Follow subjects for set time period and determine who has disease/outcome of interest*

Measures of association

- ★ *Difference in proportions*
- ★ *Relative risk (ratio of proportions)*
- ★ *Odds ratio*



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Section A

Practice Problems

1. Define selection bias in a study. Can you suggest an example (hypothetical or otherwise) of possible selection bias?

2. Give a concise explanation of the utility of having a randomized control group in a scientific study.



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Section A

Practice Problem Solutions

1. Define **selection bias** in a study. Can you suggest an example (hypothetical or otherwise) of possible selection bias?

1. **Selection bias** occurs when subjects assigned to a treatment group differ from those subjects assigned to a comparison group, because the subjects effectively chose which group they would belong to.

2. Give a concise explanation of the utility of having a randomized control group in a scientific study

2. A randomized control group equalizes the treatment and control groups on all other factors, allowing for the “pure investigation” of treatment effect



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Section B

Methods of Randomization

We want to assign a group of subjects to one of two groups—Treatment A or Treatment B

★ *How can we do this in a random manner?*

Random assignment

- ★ *Flip a coin*
 - “Heads”—Tx A*
 - “Tails”—Tx B*

Roll a six-sided die (from a pair of dice)

- ★ *Even number—Tx A*
- ★ *Odd number—Tx B*

Table of random numbers

- ★ Practical Statistics for Medical Research, *Altman*,
Table B13

Computer generated random numbers

- ★ *STATA*

“Almost” Random Assignment

Alphabetical

- ★ *Tx A = patients with last name A–M*
- ★ *Tx B = patients with last name N–Z*

Telephone number/social security number

- ★ *Tx A = last digit odd*
- ★ *Tx B = last digit even*

Sequential

- ★ *Tx A = morning patients*
- ★ *Tx B = afternoon patients*

“Almost” Random Assignment

There are potential problems in the “Almost Random” assignment scheme

- ★ *I am going to ask you to list some potential problems at the end of this lecture!*

Simple Randomization (flip a coin)

Randomize individuals to one of two treatments

★ *If n is big, works great*

Randomize individuals to one of two treatments

★ *If n is small*

★ *May be imbalanced with respect to ...*

- Sample size
- Other variable

Potential Problems with Simple Randomization

Unequal sample sizes

- ★ *If study has very small sample size, there is no guarantee two groups will have equal sample size using simple randomization*

Potential Problems: Unbalanced Sample Sizes

Bad luck

- ★ *Unbalanced sample sizes*

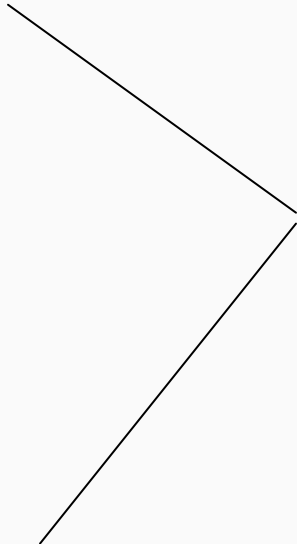
Bad luck (*worst case scenario*)

- ★ *All Tx A*
- ★ *None Tx B*

Example of Block Size of Four

Blocked randomization

- ★ *AABB*
- ★ *ABAB*
- ★ *ABBA*
- ★ *BABA*
- ★ *BAAB*
- ★ *BBAA*



These are the six different ways to arrange two As and two Bs

Example of Block Size of Four

Roll a die (#1–6) to determine pattern

- ★ *Each pattern has same probability of being chosen (one in six)*

Guarantees balance after every four patients

Example of Block Size of Four

Example—suppose 12 subjects total

- ★ *Roll Die Roll a “3”*
- ★ *“3” corresponds to ABBA*

Example of Block Size of Four

Assignments for first four subjects

Subject # 1 → Group A

Subject # 2 → Group B

Subject # 3 → Group B

Subject # 4 → Group A

Altman, p.87

★ *You can have blocks of any size*

Potential Problem with Simple Randomization

Imbalance on a key variable

- ★ *If study is very small, no guarantee groups are “comparable”*
- ★ *Solution—stratify*

Potential Problem: Imbalance on Key Variable

Stratify on age, then do block randomization

Young	ABBA	BABA
Old	BBAA	ABAB

Altman, p. 88–89



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Section B

Practice Problems

1. Referring to each of the “almost random” assignment methods detailed in this lecture (alphabetical, sequential, telephone/social security number), can you suggest how each method could yield a biased (non-random) assignment?

2. Compare block randomization to simple randomization.



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Section B

Practice Problem Solutions

1. Referring to each of the “almost random” assignment methods detailed in this lecture (alphabetical, sequential, telephone/social security number), can you suggest how each method could yield a biased (non-random) assignment?

Alphabetical

- ★ *It is possible that certain ethnicities are more likely to have names on the first or last half of the alphabet*
- ★ *This could skew the distribution in your assignment groups*

Sequential

- ★ *Morning visitors at a clinic could be different from afternoon visitors in terms of employment status, job type, and lifestyle*

Telephone number/social security number

- ★ *It is possible there existed underlying number assignment schemes related to subject characteristics—neighborhood, year of birth, income, etc.*

2. Compare block randomization to simple randomization

Block randomization is a method of randomization appropriate when the total number of available subjects is small.

Block Randomization

While simple randomization assigns subjects to a treatment group individually, block randomization assigns subjects to treatment groups in blocks of four

Each of the assignment blocks is balanced (equal number of treatment and control assignments) and blocks are selected by a random method



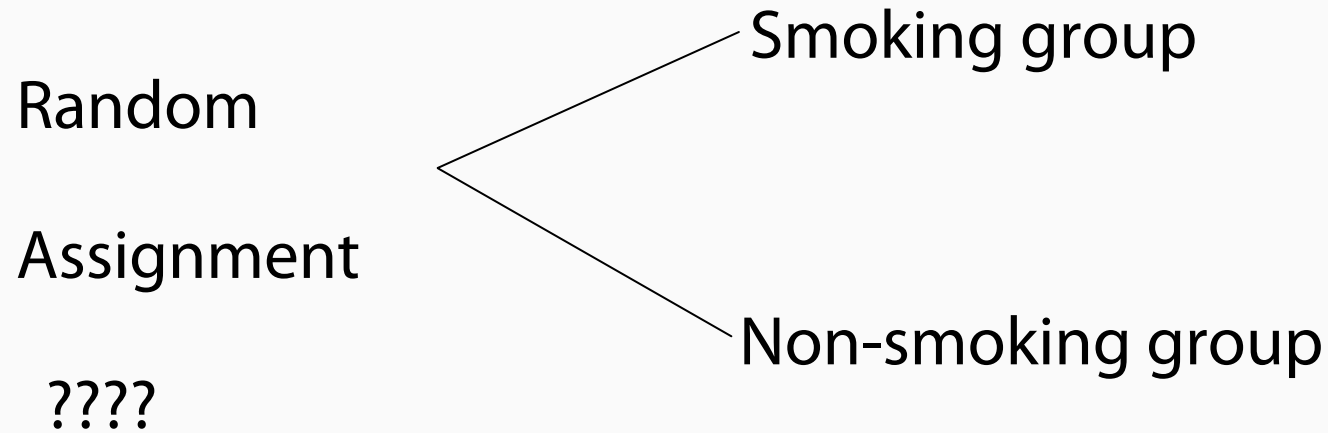
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Section C

But John, What If Randomization Is Not Possible?

Randomization Is Not Always Possible!

Unfortunately, you cannot always perform randomized trials!!



Almost as good as randomized study

- ★ *Individuals are assigned to groups because of completely “fortuitous reasons”*

Almost as good as randomized study

- ★ *Assignment may not have been based on a random number table or flip of a coin, but it is almost as good*
- ★ *Doesn't happen often, but when it does, it's good for researchers*

Cholera and water

Hemophiliacs and HIV

Cholera and Mortality in London—1800s

In 1852, a law was passed which required only unpolluted parts of the Thames river to be used for drinking water

There were multiple water companies in London at this time, including Lambert, Southwark, and Vauxhall

Cholera and Mortality in London—1800s

Only Lambert complied with the law

- ★ *Southwark and Vauxhall, as well as other companies, supplied customers with water from heavily polluted portions of the Thames*

Cholera and Mortality in London—1800s

Mortality rates per 100,000 persons by water company

	Water Company	
	<i>Lambert</i>	<i>Southwark and Vauxhall</i>
Before Water Law of 1852	12.5	11.8
After Water Law of 1852	3.7	13.0

Continued

Cholera and Mortality in London—1800s

Is treatment assignment “random?”

Are groups similar except for intervention (i.e., water companies)?

Both water companies competed for the same customers and served residents all throughout London

Natural Experiment of HIV Etiology of AIDS

Mortality rates per 1,000 person-years among HIV infected and uninfected hemophiliacs in the United Kingdom

	Severe Hemophilia	
	<i>Uninfected</i>	<i>Infected</i>
1985–1992	8.1	49.1
1977–1984	7.9	

Natural Experiment of HIV Etiology of AIDS

There were no other significant differences found between the infected and uninfected hemophiliacs

Non-Randomized Design: Observational Studies

Are children born to women who took Bendectin for nausea more likely to have birth defects?

Observational study

- ★ *Take a (random?) sample of mothers who gave birth in the past year*
- ★ *Compare Bendectin users vs. non-users*

A significant difference in the rates of birth defects could be explained by the following:

- ★ *Bendectin causes birth defects*
- ★ *Mothers who took Bendectin also took other drugs (maybe those other drugs are related to birth defects)*
- ★ *Mothers who took Bendectin are different in other ways (medical, socioeconomic)*

Sometimes this is the only type of study that can be done

Researchers need to anticipate control for other factors which may affect the outcome of interest

We will learn more about “controlling” for other factors in the rest of 612

Montreal: relative risk of HIV infection for intravenous drug users (IVDUS) by needle exchange program participation

	Relative Risk of HIV Infection	95% CI
Non-Participants	1.0	—
Consistent Users	10.2	3.3–31.5

Adjusted for ...

- ★ *I.V. drug use since last visit, number of times, borrowed I.V. equipment, number of times new equipment was used, practice of disinfection, matched on age, gender, language, year of birth*

New York City: relative risk of HIV infection for intravenous drug users (IVDUS) by needle exchange program participation

	Relative Risk of HIV Infection	95% CI
Non-Participants	1.0	—
Consistent Users	0.30	.1–.7

Adjusted for the following . . .

- ★ *Age, gender, race, frequency of injection*
- ★ *See also American Journal of Epidemiology, October, 1998, p. 713–716*

“It is possible that, despite the exhaustive data-driven process to identify confounders, some had been left unaccounted for . . . ”

“None of the studies reported was a randomized clinical trial, so a causal link cannot be inferred . . . we could not control for whatever factors led some subjects to use the syringe exchanges (potential self-selection bias)”



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Section C

Practice Problems

1. Compare the “natural experiment” to an observational study.
2. What are some potential issues that make the study of an outcome/exposure relationship more difficult with an observational study, than with a randomized study?



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Section C

Practice Problem Solutions

1. Compare the “natural experiment” to an observational study.

Both are used when the exposure or “treatment” of interest can not be randomly assigned (HIV, smoking, vegetarianism, etc.).

In the natural experiment, subjects are “assigned” to groups via a mechanism which acts randomly.

In observational studies, there may be other factors associated with group assignment.

2. What are some potential issues that make the study of an outcome/exposure relationship more difficult with an observational study, than with a randomized study?

The biggest issue stems from the fact that those “exposed” may be different than those “not-exposed” with respect to other characteristics that may also relate to the outcome of interest. This makes the task of getting a “clean estimate” of a outcome/exposure relationship more difficult.



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Section D

Another Non-Randomized Study Design:
The Case-Control Design

Researchers were interested in studying the association between alcohol consumption and esophageal cancer

Esophageal cancer is a rare condition—a prospective study would require a huge number of subjects

Another approach—choose subjects whose cancer status is known at the time of recruitment into the study

- ★ *In this scenario, researchers chose 200 cases and 775 controls and asked about alcohol consumption*

Resulting 2 x 2 Table

		Alcohol (gm/day)		
		> 80	< = 80	
CASE	96	104	200	
CONTROL	109	666	775	
		205	770	

Important questions

- ★ *Can we estimate the prevalence of esophageal cancer based on the results for this study?*
- ★ *Can we calculate the probability of cancer if you drink more than 80 grams of alcohol per day using this case-control study?*
- ★ *Can we compute the relative risk of cancer for those who drink > 80 grams of alcohol per day as compared to those who drink ≤ 80 grams per day?*

Important Caveat in Case-Control Studies

In case-control studies, the individuals with the disease (the cases) have been over-sampled

The percentage of subjects in your study who has disease is greater than in the population: hence the prevalence/risk in the sample is an overestimate of actual prevalence/risk, usually by a large factor

“Prevalence” in the sample is a function of the design of the study: in this example researchers set prevalence

(risk)

at ...

$$\frac{200}{200 + 775} = \frac{200}{975} \approx .21$$

Important Caveat in Case-Control Studies

The percentage of the population who has disease from a case-control study (i.e., the risk/prevalence of disease) cannot be correctly estimated from a case-control study

Hence, you can not estimate relative risk (RR) relating disease to exposure of interest

Relative Risk and Odds Ratios in Case-Control Studies

CANNOT compute relative risk from case-control study

CAN compute odds ratio from case-control study

Odds Ratios in Case-Control Studies

Recall, the estimated odds ratio of an outcome compares the observed odds of the outcome for two groups of individuals and is a function of the risk for each group

$$\hat{OR} = \frac{\hat{p}_1 / (1 - \hat{p}_1)}{\hat{p}_2 / (1 - \hat{p}_2)}$$

Odds Ratios in Case-Control Studies

Quick approach to computing odds ratio from a 2 x 2 table: Diagonal cross products!

		Alcohol (gm/day)		
		> 80	< = 80	
CASE	96	104	200	
CONTROL	109	666	775	
	205	770		

Continued

Odds Ratios in Case-Control Studies

Quick approach to computing odds ratio from a 2 x 2 table: Diagonal cross products!

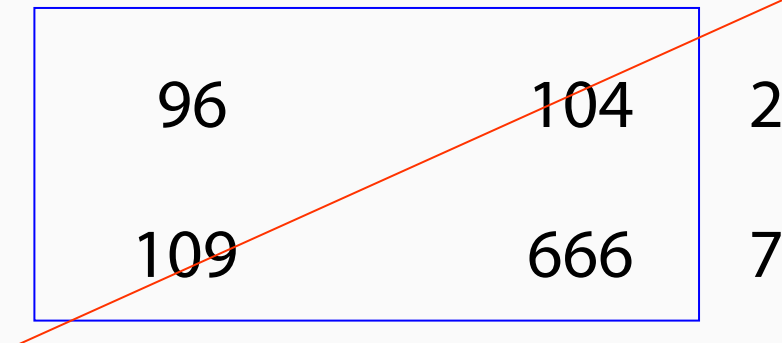
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Continued

Odds Ratios in Case-Control Studies

Quick approach to computing odds ratio from a 2 x 2 table: Diagonal cross products!

		Alcohol (gm/day)		
		> 80	< = 80	
CASE	96	104	200	
CONTROL	109	666	775	
	205	770		



Continued

Odds Ratios in Case-Control Studies

In the alcohol/esophageal cancer example:

$$\text{Odds Ratio Estimate } (\hat{OR}) = \frac{96 \times 666}{109 \times 104} = 5.64$$

Interpretation

- ★ *Individuals with high alcohol consumption (> 80 grams/day) are at over five times the odds of esophageal cancer compared to individuals with low alcohol consumption*

Important Caveat in Case-Control Studies

The odds ratio is very close to what the relative risk would be if you had performed a cohort study (provided the disease were rare, say $< 1/100$)

If disease is not rare, OR still follows same direction as RR, but may not be a very accurate estimate of RR

In the alcohol-esophageal cancer example, 5.64 is an estimate of the odds ratio based on a limited sample of data

It is not the population parameter odds ratio

Confidence intervals can be calculated that give the range of plausible values for the population odds ratio

If the 95% confidence interval for the odds ratio does not include one, it suggests that there is a significant association ($p < .05$)

How can you test if the population odds ratio is one or not?

- ★ *Fisher's exact test*
- ★ *χ^2 square test (approximation)*

“cci” command syntax—same setup as “csi” command that we saw in SR1

```
cci a b c d
```

Where a, b, c, d from appropriate 2 x 2 table:

		Exposure	
		Y	N
Disease	Y	a	b
	N	c	d

Alcohol/esophageal cancer example

```
cci 96 104 109 666
```

Recall the 2 x 2 table:

		Exposure	
		Y	N
Disease	Y	96	105
	N	109	666

```
. cci 96 104 109 666
```

	Exposed	Unexposed	Total	Proportion Exposed
Cases	96	104	200	0.4800
Controls	109	666	775	0.1406
Total	205	770	975	0.2103
	Point estimate		[95% Conf. Interval]	
Odds ratio	5.640085		3.937435	8.061794 (exact)
Attr. frac. ex.	.8226977		.7460276	.8759581 (exact)
Attr. frac. pop	.3948949			

chi2(1) = 110.26 Pr>chi2 = 0.0000

```
. cci 96 104 109 666
```

	Exposed	Unexposed	Total	Proportion Exposed
Cases	96	104	200	0.4800
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Attr. frac. pop	.3948949			

chi2(1) = 110.26 Pr>chi2 = 0.0000				

The 95% CI for the OR of esophageal cancer for those consuming > 80 grams of alcohol per day compared to those consuming 80 grams or less is 4.0 to 8.0

Odds Ratio and Case-Control Studies

Why would we even bother calculating the odds ratio when we can calculate relative risk?

- ★ *The odds ratio turns out to be important because you can calculate it either in cohort studies or case-control studies*
- ★ *The relative risk can only be calculated from cohort studies*

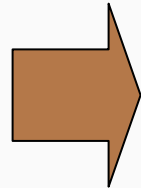
Luckily, as we saw in SR1, the odds ratio informs us about risk, and if the outcome of interest is rare overall, then the odds ratio is a good estimate for the relative risk

Odds Ratio and Case-Control Studies

Recall:

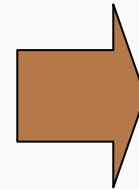
$$H_o: p_1 = p_2$$

$$H_a: p_1 \neq p_2$$



$$H_o: RR = 1$$

$$H_a: RR \neq 1$$



$$H_o: OR = 1$$

$$H_a: OR \neq 1$$

All three hypotheses testing for disease exposure relationship