

Measures of Association

Mabel Carabali

EBOH, McGill University

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Opioid Toxicity Deaths among Adolescents and Young Adults

Pre-Pandemic

March 17, 2019 - March 16, 2020

115 deaths

During Pandemic

March 17, 2020 - March 16, 2021

169 deaths

Adolescent and Young Adult Opioid Toxicity Deaths **During the Pandemic**

Demographics

2 in 3 

deaths occurred among **males**

>90%

of deaths occurred among
young adults (aged 18-24)

After adjusting for population size, the
rate of deaths among young adults was

5X higher

than among adolescents (aged 15-17)

Living Arrangement

7 in 10 

deaths occurred in **private residences**,
with 63% occurring at their home address

1 in 8

experienced
homelessness



Opioid Toxicities and Access to Treatment among Adolescents and Young Adults in Ontario
Ontario Drug Policy Research Network (2023)

What's an Association?

Our common objective of epidemiologic research:

- The effect of exposure X on the occurrence of outcome Y
 - But we can rarely observe or even estimate this effect directly.
- It involves the same people at the same time in contrasting exposures, which is **impossible**.
- We **observe an association** between the *Exposure* and *Outcome* among study subjects, which estimates a population association.

"The observed association will be a poor substitute for the desired effect, if it is a poor estimate of the population association, or if the population association is not itself close to the effect of interest." ME4 (2020)

What's an *Effect* ?

Effect here means the end point of a causal mechanism, i.e., identifying the type of outcome that a cause produces.

EXAMPLE: "*Liver cirrhosis is an effect of chronic excessive alcohol consumption*".

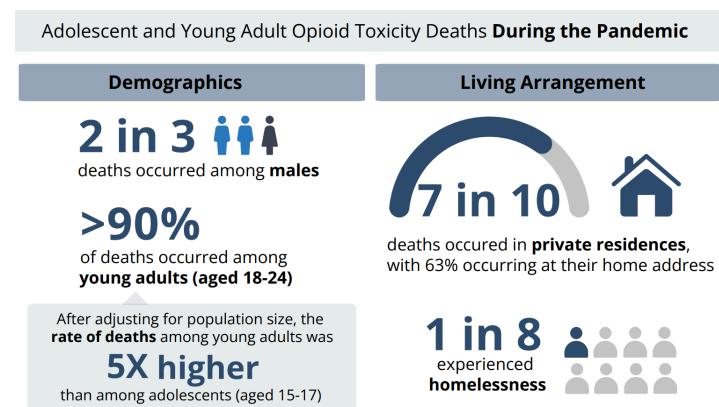
- This use of the term effect **merely** identifies liver cirrhosis as **one consequence of chronic excessive alcohol consumption**.
 - **Compared** to something else (e.g., Abstinence or another level of consumption).
 - Cirrhosis may **Not be the only** effect of chronic excessive alcohol consumption.
 - May **change** across populations and or over time.

"An effect of some factor is thus relative to the outcomes, to the population, and to the time frame."
[ME4 (2020)]

Exposure vs Cause

An exposure (usually denoted as X) is a *potential causal characteristic*, "a factor that produces an outcome"

- Could be the *sole* or *compounded cause*¹ of an Outcome. Can be a behavior, a treatment/intervention, a social condition, a health condition, a genetic trait...



¹ For more on Sufficient Component Causal Framework and Bradford Hill criteria, in this course we focus on potential outcomes and causal DAGs for approaches to causal inference.

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Exposures vs Causes

Etiology

Go to:

Causes of opioid overdose can include:

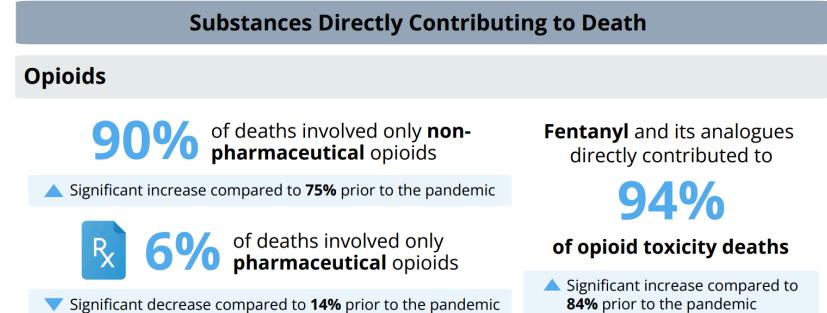
- Complications of substance abuse
- Unintentional overdose
- Intentional overdose
- Therapeutic drug error

Risk of opioid overdose increases in the following:

- Those that take escalating doses
- Return to use after cessation
- Those with severe medical and psychiatric conditions such as depression, HIV, and lung/liver disease
- Those that combine opioids and sedative medications
- Male gender
- Younger age (20 to 40 years)
- White non-Hispanic race

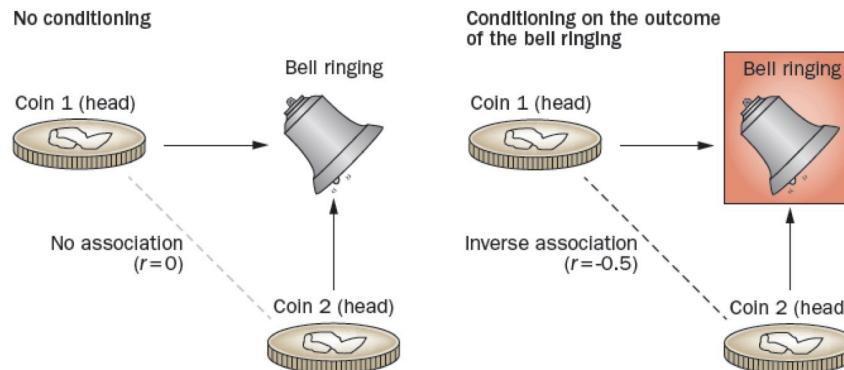
Opiod Overdose Schiller EY, Goyal A, Mechanic OJ. Opioid Overdose. In: StatPearls. Treasure Island (FL): StatPearls Publishing; July 21, 2023.

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Not every Association between Exposure an Outcome is "*Causal*"

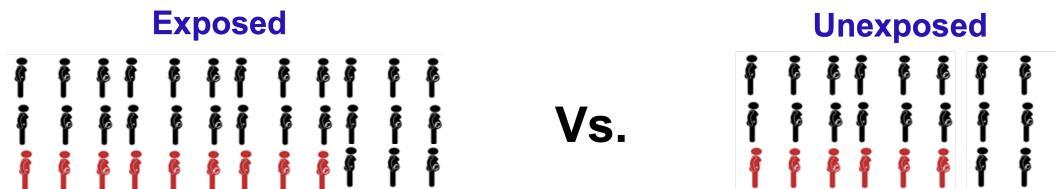
Recall:



At the population level, we assess the effects with measures of occurrence and we **estimate the associations by contrasting such measures of occurrence in the population.**

Absolute vs. Relative measures

- Absolute effect measures are **differences** in occurrence measures.
- Relative effect measures are **ratios** of occurrence measures.



Null Value

Absence of contrast on either the Absolute (Difference) and Relative (Ratio) Scales

$$R_{exp} - R_{Non-exp} = 0$$

and

$$\left(\frac{R_{exp}}{R_{Non-exp}} \right) = 1$$

Absolute vs. Relative measures

- Absolute effect measures are **differences** in occurrence measures.
- Relative effect measures are **ratios** of occurrence measures.



Sample	Outcome +	Outcome -	Risk Among Exposed	Risk Among Non-Exposed	Risk Difference	Risk Ratio
63	9/36	6/27	0.25	0.22	0.03	1.12

Key elements: Exposure, Outcome & Measures of Occurrence !

The 2x2 Table

- A summary table of observations.

		Outcome		
		Outcome	No.Outcome	Total
Exposed	A	B	A+B	
No Exposed	C	D	C+D	
Total	A+C	B+D	A+B+C+D	

The 2x2 Table

From the previous example:

		Outcome		Total
		Dead	Alive	
Exposed	9	27	36	27
	9	18	27	
Total	18	45	63	

The measures are:

Sample	Outcome +	Outcome -	Risk Among Exposed	Risk Among Non-Exposed	Risk Difference	Risk Ratio
63	9/36	6/27	0.25	0.22	0.03	1.12

Key elements: Exposure, Outcome & Measures of Occurrence !

Absolute measures: Risk Differences

The RD provides the absolute change in risk

- Indicates how much of the effect is attributable to exposure
- It does not provide information about the magnitude of the shift on the estimates 1 to 16% or 81 to 96%?
- Clinical vs statistical importance
- Public Health Relevance

Relative Measures: Risk Ratios

- Relative measures are popular and practical
- Easier to obtain
 - Dichotomous outcomes!
- Useful in both causal inference and prediction

Interpretability?

- RR's magnitude change according to the coding scheme

Example: $(0 \text{ to } 1) \neq (2 \text{ to } 1)$

Why not both?

- It's possible to see a reduction in absolute estimates, but an increase in relative measures (and vice versa)

These are complimentary estimators! Both tell you something different about the data

- In fact, STROBE and CONSORT guidelines now advise researchers to publish both measures

115 deaths vs 169 = 47% increase vs 54 more deaths?

In an epidemiological utopia, researchers would run the model of their choice, obtain relative and absolute estimates, and publish these along with the baseline/background risk

But we live in the real world, so we're more likely to encounter...

...Odds ratios

$$Odds = \left(\frac{P}{1-P} \right)$$

The Odds ratio is the relative contrasts of the Odds among Exposed and the Odds among Non-Exposed

$$OddsRatio = \left(\frac{\left(\frac{P_{exp}}{1-P_{exp}} \right)}{\left(\frac{P_{No-exp}}{1-P_{No-exp}} \right)} \right)$$

...Odds ratios

We are already aware of some key problems with odds and therefore odds ratios

- They overestimate risks
 - While probabilities are bounded [0, 1], **odds** can range from 0 to ∞
- They're not intuitive (except as an approximation of the risk ratio ¹)
- And most of the time we care about probabilities, not odds

¹ When probability is small (<0.10) or given the study design (e.g., case-cohorts) with rare outcomes

Risk Differences and Risk Ratios

Sample	Risk Among Exposed	Risk Among Non-Exposed	Risk Difference	Risk Ratio	Odds Ratio
63	0.25	0.22	0.03	1.12	1.17
63	0.17	0.15	0.02	1.12	1.15
630	0.017	0.015	0.002	1.12	1.15
630	0.25	0.22	0.03	1.12	1.17

Null Value

Absence of contrast on either the Absolute (Difference) and Relative (Ratio) Scales

$$R_{exp} - R_{Non-exp} = 0 ; \text{ or } \left(\frac{R_{exp}}{R_{Non-exp}} \right) = 1$$

Example:

Sample	Outcome +	Outcome -	Risk Exposed	Risk Non-Exposed	Risk Difference	Risk Ratio	Odds Ratio*
63	4/36	3/27	0.11	0.11	0	1	1

- Null Value (Absolute) = $(4/36) - (3/27) = 0$
- Null Value (Relative) = $(4/36) / (3/27) = 1$

Note

1. When the RR is above or below the null (>1 or <1) the ORs is FURTHER away from the Null.
2. When the absolute risk in each exposure groups are high, the OR will considerably overestimate the RR.

Some simulated Examples

- Generating 10 data-sets with the *same* structure.

```
set.seed(704)
z <- rnorm(500)
e <- matrix(NA,nrow=500,ncol=10) # create an empty matrix to put stuff in
for (i in 1:10) {                  # loop 10 times
  e[,i] <- ifelse((rnorm(500))>0.8,1,0) # create a new vector from a binomial
}
e <- as.data.frame(e) # change it into a data frame
names(e) <- c("A","B","C","D","E","F","G","H","I","J") # change the column names

# create a Y matrix with the specification from the questions
y <- ifelse(e==1,rbinom(5000,1,0.65),rbinom(5000,1,0.2))
y <- as.data.frame(y) # change the matrix to a dataframe
# change the names, paste0 says paste these two things together without a space between them
names(y) <- paste0("Y",letters[1:10])
```

Some simulated Examples

Verification of "mean" values across datasets.

```
##          A            B            C            D
## Min.   :0.000   Min.   :0.000   Min.   :0.000   Min.   :0.000
## 1st Qu.:0.000  1st Qu.:0.000  1st Qu.:0.000  1st Qu.:0.000
## Median :0.000  Median :0.000  Median :0.000  Median :0.000
## Mean    :0.234  Mean    :0.218  Mean    :0.198  Mean    :0.226
## 3rd Qu.:0.000  3rd Qu.:0.000  3rd Qu.:0.000  3rd Qu.:0.000
## Max.    :1.000  Max.    :1.000  Max.    :1.000  Max.    :1.000
##          E            F            G            H            I
## Min.   :0.000   Min.   :0.000   Min.   :0.000   Min.   :0.000   Min.   :0.00
## 1st Qu.:0.000  1st Qu.:0.000  1st Qu.:0.000  1st Qu.:0.000  1st Qu.:0.00
## Median :0.000  Median :0.000  Median :0.000  Median :0.000  Median :0.00
## Mean    :0.182  Mean    :0.222  Mean    :0.214  Mean    :0.212  Mean    :0.22
## 3rd Qu.:0.000  3rd Qu.:0.000  3rd Qu.:0.000  3rd Qu.:0.000  3rd Qu.:0.00
## Max.    :1.000  Max.    :1.000  Max.    :1.000  Max.    :1.000  Max.    :1.00
##          J
## Min.   :0.000
## 1st Qu.:0.000
## Median :0.000
## Mean    :0.192
## 3rd Qu.:0.000
## Max.    :1.000
```

Some simulated Examples

Using "hand calculations" formulas.

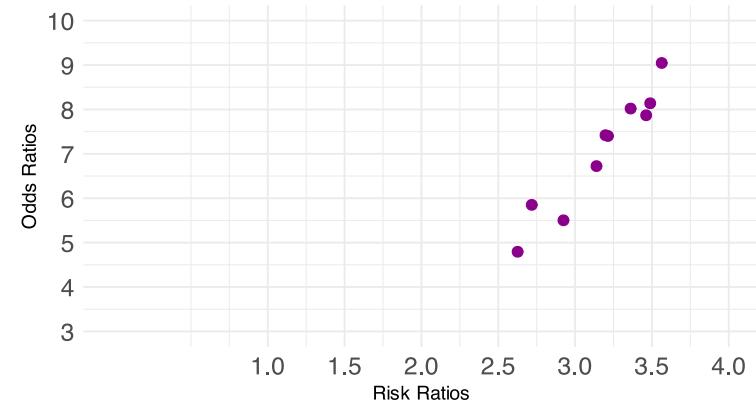
```
# Using lapply
tabs <- lapply(1:10,FUN=function(x) table(e[,x],y[,x]))
# With a loop create an empty data frame with the right dimensions
ests <- as.data.frame(matrix(NA,nrow=10,ncol=3))
# Name columns
names(ests) <- c("RD","RR","OR")

# Loop it up
for (i in 1:10) {
  x <- tabs[[i]]
  ests[i,1] <- x[2,2]/sum(x[2,])- x[1,2]/sum(x[1,]) #RD
  ests[i,2] <- (x[2,2]/sum(x[2,]))/ (x[1,2]/sum(x[1,])) #RR
  ests[i,3] <- (x[2,2]/sum(x[2,1]))/ (x[1,2]/sum(x[1,1])) #OR
}
```

Some simulated Examples

RD	RR	OR
0.38	2.92	5.50
0.46	3.49	8.14
0.43	3.14	6.72
0.49	3.56	9.05
0.35	2.63	4.79
0.45	3.20	7.42
0.45	3.21	7.40
0.46	3.46	7.87
0.47	3.36	8.02
0.41	2.72	5.85

Risk Ratios vs. Odds Ratios



Some simulated Examples

Using regressions¹ to obtain the estimates

```
set.seed(704)
yea.dat <- function(n) {
    E <- rbinom(n,1,0.55) #parameters for E
    Y <- rbinom(n,1,0.12) #parameters for Y

    return(data.frame(E=E,Y=Y)) #ask to return a data set with those parameters
}
sim100 <- lapply(1:100,FUN=function(x) yea.dat(400))
summary((sim100[[13]])) #; summary((sim100[[93]]))

##          E             Y
##  Min.   :0.00   Min.   :0.0
##  1st Qu.:0.00   1st Qu.:0.0
##  Median :1.00   Median :0.0
##  Mean   :0.56   Mean   :0.1
##  3rd Qu.:1.00   3rd Qu.:0.0
##  Max.   :1.00   Max.   :1.0
```

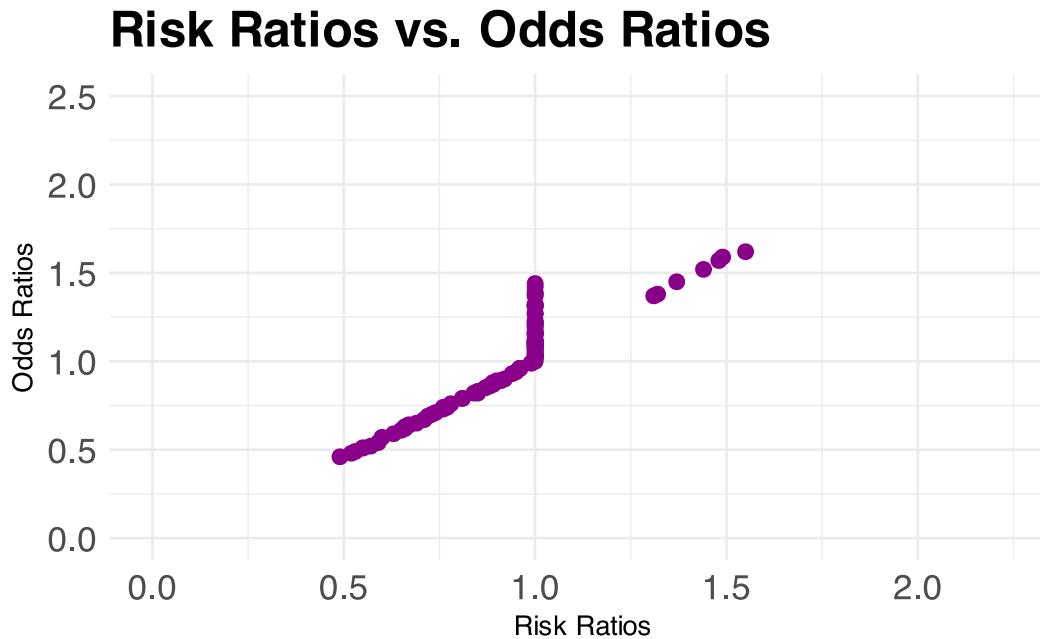
¹ Some of you may have advanced knowledge on regression analysis but since we have not explained it during the course this resource is only for illustration purposes.

Some simulated Examples

```
RRs <- sapply(sim100,FUN=function(x) {  
  results <- logbin(Y ~ E , data=x)$coef  
  return(round(exp(results[names(results)]=="E")),2))  
})  
  
ORs <- sapply(sim100,FUN=function(x) {  
  results <- glm(Y ~ E , family="binomial", data=x)$coef  
  return(round(exp(results[names(results)]=="E")),2))  
})  
  
sim_RRs<-round(quantile(RRs,probs = c(0.05,0.5,0.95)),2)  
sim_ORs<-round(quantile(ORs,probs = c(0.05,0.5,0.95)),2)
```

Some simulated Examples

```
##           5%   50%   95%
## sim_RRs  0.57  1.00  1.37
## sim_ORs  0.52  1.04  1.45
```



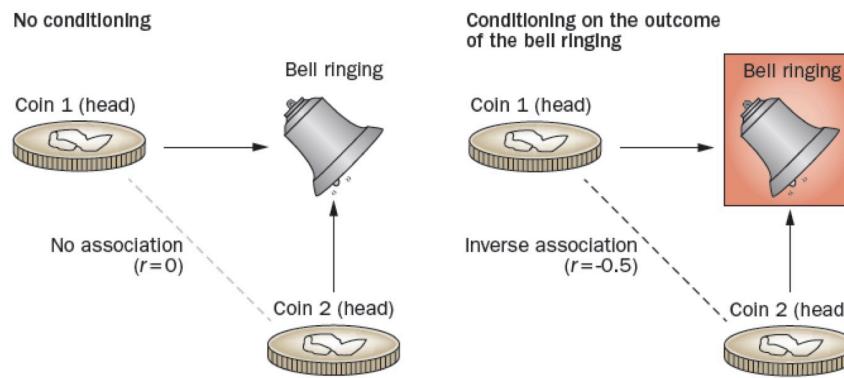
Associations Vs Causes

Pearl (2000) uses $Pr(Y = y | SET[X = x])$ to define the probability of an event if the condition $X = x$ were **enforced uniformly** over a population.

- The key to this definition: **it involves intervention, not observation.**
- Measures of effect can be built based on **SET** notation by creating contrasts of probabilities (or risks) across different X values.
- The **What If? Book**, express the same notion with $Y^{X=x}$.

Associations Vs Causes

Recall:



Be aware of the difference!

Measures of causal effect

Measures of **causal effect** require a contrast of two **counterfactual** quantities:

- $Pr(Y_i = y_i | SET[X_i = 1]) - Pr(Y_i = y_i | SET[X_i = 0])$

Measures of **association** involve a contrast of two **observed** quantities:

- $Pr(Y_i = y_i | X_i = 1) - Pr(Y_i = y_i | X_i = 0)$

Who are we interested in?

Target Population: The group of people about which the scientific or public health question is asked, in the **relevant etiologic time period**.

"Target Population" in Encyclopedia of Biostatistics, 2005 [Sander Greenland]

"The concept of a target population is an informal one, sometimes defined as "the population about which information is wanted" [1] or the "totality of elements which are under discussion and about which information is desired" [4] ...The word "target" emphasizes, however, that this population is not necessarily the same as the one that we end up sampling. The latter population is sometimes called the sampled population [1, 4] or (in epidemiology) the source population [6]". [1] Cochran, W.G. (1977). *Sampling Techniques*, 3rd Ed. Wiley, New York. [4] Mood, A.M., et al. (1974). *Introduction to the Theory of Statistics*. McGraw-Hill, New York. [6] Rothman, K.J. & Greenland, S. (1997). *Modern Epidemiology*, 2nd Ed. Lippincott, Philadelphia.

Potential Outcomes Framework

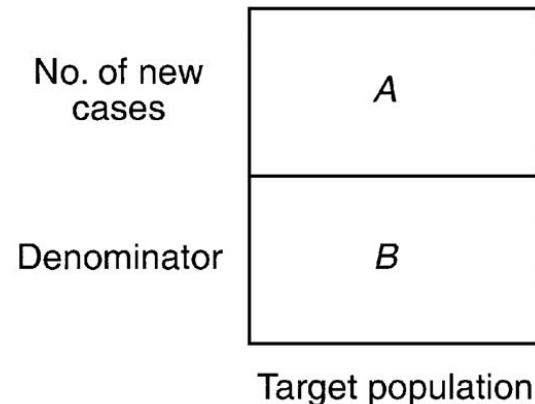
We are interested in the effect of exposure ($A = 1$) on the occurrence of disease ($Y = 1$)

- Suppose everyone in the **target population** of inference is unexposed ($A = 0$) and we can observe the distribution of Y in the population.
- We would like to also observe the distribution of Y had these same people been all exposed ($A = 1$)
 - This is “counter-to-fact”, and we call this condition the counterfactual
 - Each individual has their own **counterfactual** exposure
 - (what would have happened to me if ...)

Potential Outcomes Framework

- We can never observe both conditions in the same population (or individual).
 - That is, we cannot observe the distribution of disease under $A = 1$ and $A = 0$ within the same time period in the same cohort.
 - Thus we need to make an estimate under the condition we do not observe.
- To do so, we use a **substitute population**.
- Our goal is to choose a substitute population that will best mimic **what would have happened to the target population had they experienced the other exposure condition**.

Estimating Causal Effects¹



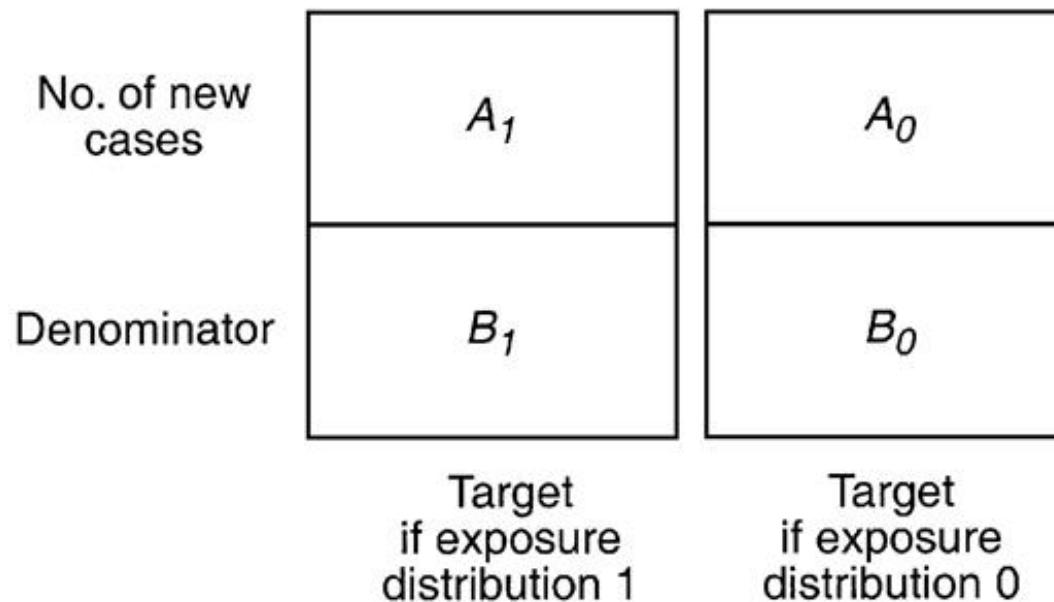
- If B = people at risk at the *beginning of the period*² = **incidence proportion, average risk**.
- If B = person-time at risk during the period, R = **person-time incidence rate**.
- If B = people who do *NOT* get disease by the end of the period, R = **incidence odds**.

¹ International Journal of Epidemiology, Volume 31, Issue 2, April 2002, Pages 422–429,
<https://doi.org/10.1093/intjepid/31.2.422>

² And all individuals are followed throughout the etiologic time period.

Define the causal effect

Define the counter-to-fact condition and outcome in the target:



Only possible to, at best, observe one of these conditions.

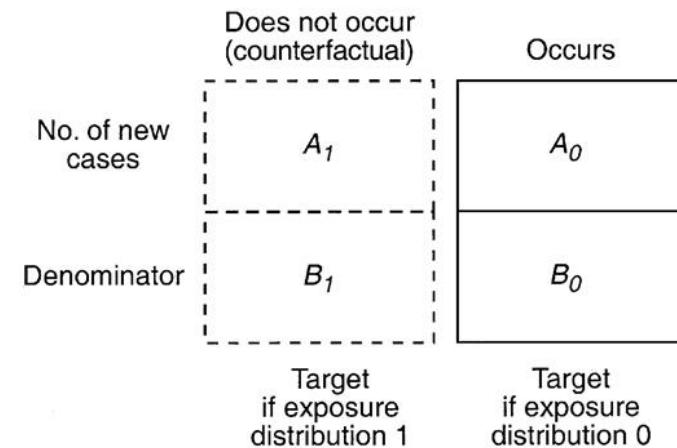
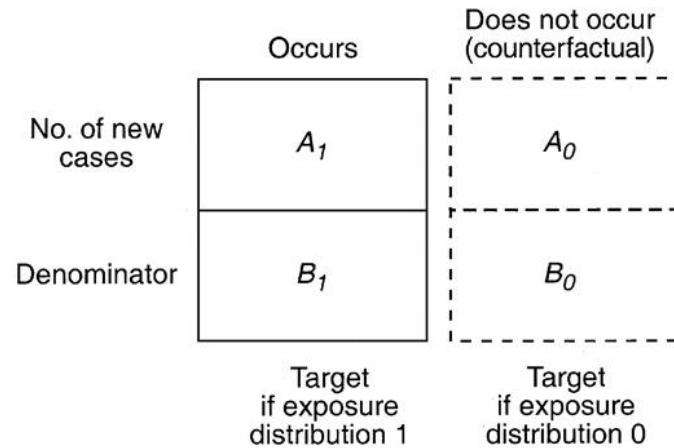
Define the causal effect

Let $R_1 = A_1/B_1$ and $R_0 = A_0/B_0$

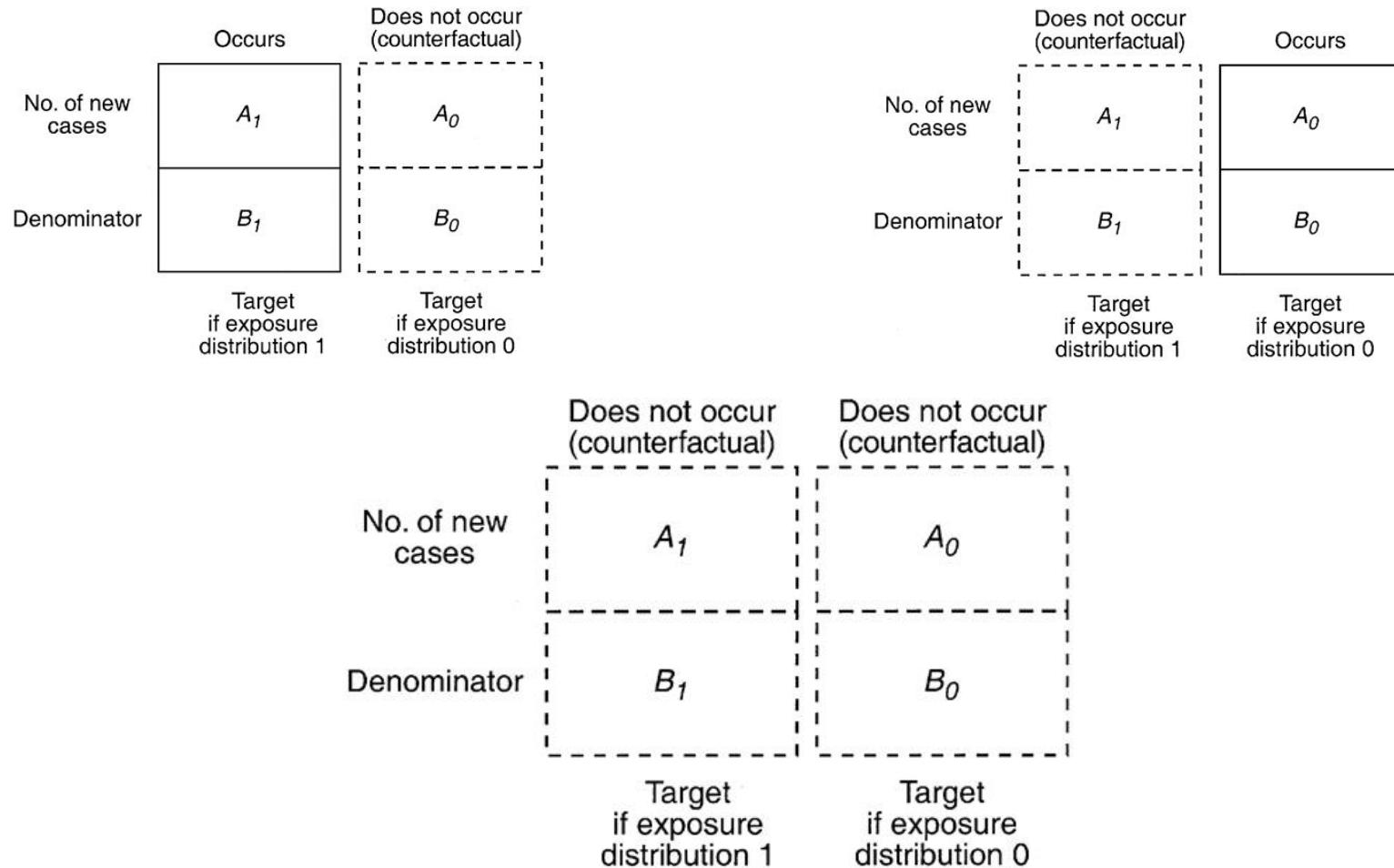
- $R_1 - R_0$ is the causal **difference measure** and
- R_1/R_0 is the **causal ratio measure**
- Both of these are causal contrasts (measures of effect).
- Here, the only possible reason for a difference between R_1 and R_0 is due to **exposure** because we are contrasting the **exact same people over the exact same time period**.
- But, we **cannot observe the causal contrast** because we cannot observe both conditions.

We require a substitute with observable information!

Can't observe the counterfactual



Can't observe the counterfactual

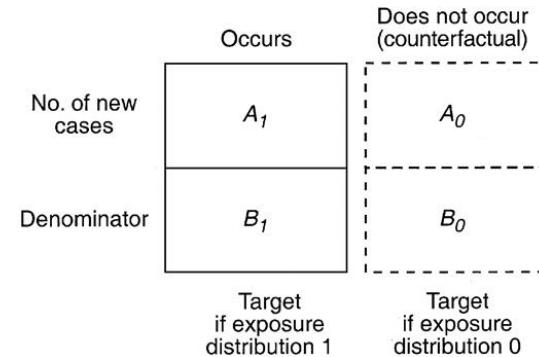


Can't observe the counterfactual

	Does not occur (counterfactual)	Does not occur (counterfactual)
No. of new cases	A_1	A_0
Denominator	B_1	B_0
	Target if exposure distribution 1	Target if exposure distribution 0

"Both R_1 and R_0 are counterfactual disease frequencies, both are hypothetical alternatives to the actual disease frequency that occurs under the actual exposure distribution (which is neither exposure distribution 1 nor 0), and therefore neither R_1 nor R_0 can occur and be observed." Maldonado & Greenland 2002

Can't observe the counterfactual



The impossibility of observing both halves of the causal contrast leads to the idea of substitute populations.

These are often:

- Different people observed during the same etiologic time period.
- The same people observed over two different time periods (case-crossover design).

Maldonado & Greenland 2002

Defining the substitute population

In a substitute population under **exposure distribution 1**, let

- C_1 be the name for the numerator of the disease-frequency measure,
- D_1 be the denominator (number of people or amount of person-time at risk).

In a substitute under **exposure distribution 0**, let

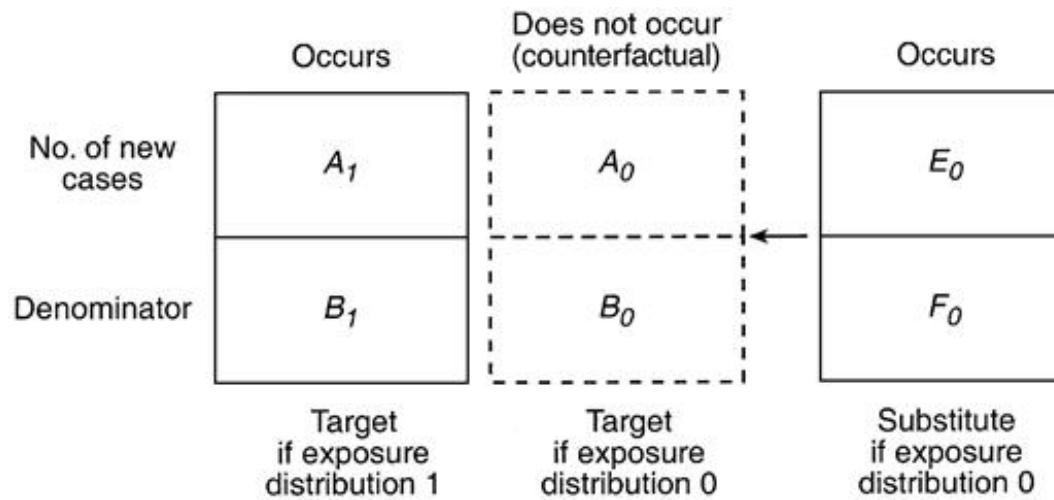
- E_0 be the numerator,
- F_0 be the denominator.

Exposure = 1, C_1/D_1

Exposure = 0, E_0/F_0

Defining the substitute population

Target experiences **exposure distribution 1**

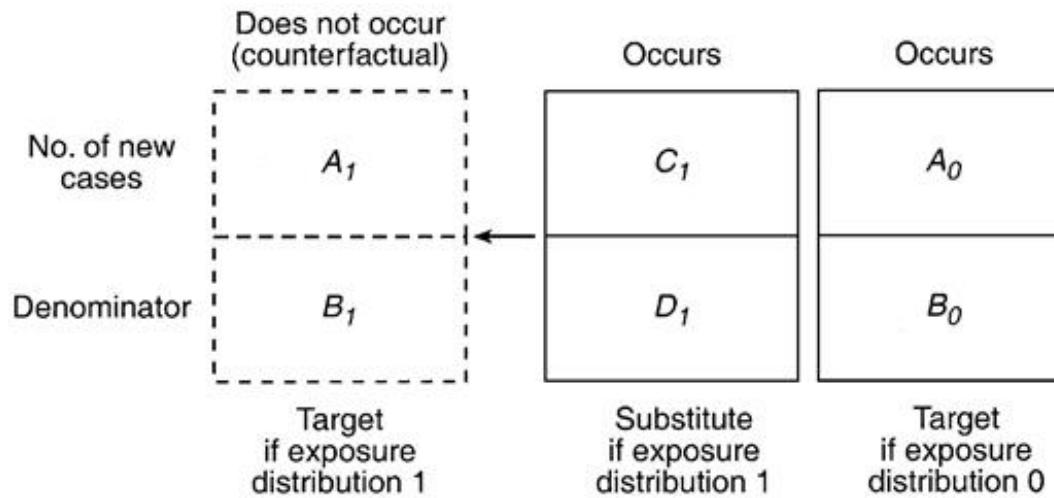


$$RR_{association} = \frac{R_1}{\text{Substitute for } R_0} = \frac{R_1}{E_0/F_0} = \frac{A_1/B_1}{E_0/F_0}$$

Maldonado & Greenland 2002

Defining the substitute population

Target experiences **exposure distribution 0**

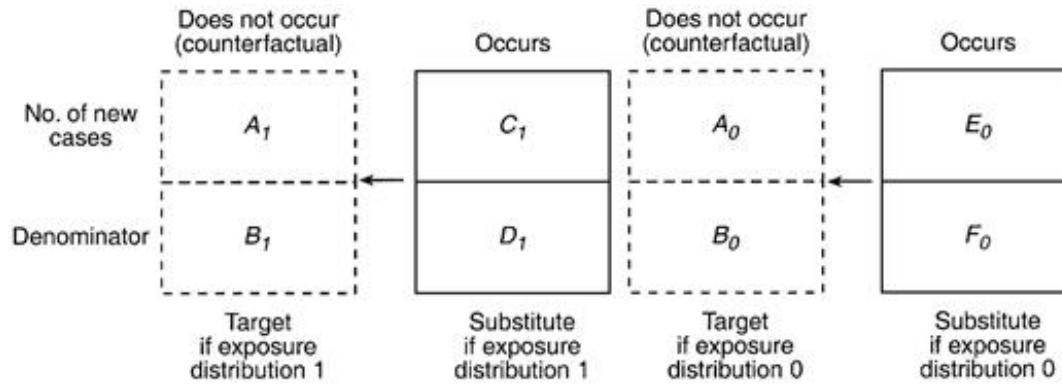


$$RR_{association} = \frac{\text{Substitute for } R_1}{R_0} = \frac{C_1/D_1}{R_0} = \frac{C_1/D_1}{A_0/B_0}$$

Maldonado & Greenland 2002

Defining the substitute population

Target experiences neither **exposure distribution 1 or 0**



$$RR_{association\bar{R}} \frac{\text{Substitute for } R_1}{\text{Substitute for } R_0} = \frac{C_1/D_1}{E_0/F_0}$$

Maldonado & Greenland 2002

Other Notation Used

- Greenland employs a probabilistic model of disease such that each individual i has a risk r_{1_i} of disease when $E = 1$ and a risk of r_{0_i} when $E = 0$.
- Survival probabilities: $S_{1_i} = 1 - r_{1_i}$ and $S_{0_i} = 1 - r_{0_i}$
- Odds: $w_{1_i} = r_{1_i}/s_{1_i}$ and $w_{0_i} = r_{0_i}/s_{0_i}$.
 - Only defined when survival probabilities are not equal to zero.

Notation Used

- The effect of exposure on the risk of an individual can be measured in terms of the risk difference $r_{1_i} - r_{0_i}$, risk ratio r_{1_i}/r_{0_i} , or the risk-odds ratio w_{1_i}/w_{0_i}
- The ratios will be undefined if the risk in the exposed group is 0 and
- The risk-odds ratio will be undefined if either survival probability is 0

Other Notation Used

In a cohort with N_1 $E+$ individuals and N_0 $E-$ individuals:

	$E+$	$E-$
$D+$	$A = \sum_1 r_{1i}$	$B = \sum_0 r_{0i}$
$D-$	$C = \sum_1 s_{1i}$	$D = \sum_0 s_{0i}$
Total	N_1	N_0

- Incidence proportions: A/N_1 and B/N_0 , interpretable as average risks in their respected groups
- Incidence odds: A/C and B/D , interpretable as ratios of the average risk to the average survival probabilities.

Defining the counterfactual

- Assuming **no confounding**¹
- Had the **exposure** been absent from the $E+$ group,
- The average risk would have been **the same** among the sub-cohorts that were in fact exposed and unexposed.

$$\left(\frac{\sum_1 r_{0i}}{N_1} \right) = \left(\frac{\sum_0 r_{0i}}{N_0} \right)$$

¹ More on confounding next lecture.

Risk Difference

Thus: The risk difference is interpretable as both:

- 1) the **absolute change in the average risk** of the exposed sub-cohort produced by exposure,

$$\left(\frac{\sum_1 r_{1i}}{N_1} \right) - \left(\frac{\sum_1 r_{0i}}{N_1} \right)$$

- 2) the **average absolute change in risk** produced by exposure among exposure individuals

$$\left(\frac{\sum_1 (r_{1i} - r_{0i})}{N_1} \right)$$

Expressions 1 and 2, on: Interpretation and choice of effect measures in epidemiologic analyses. S. Greenland (1987)

Risk Ratio

The incidence proportion ratio is given by

$$\left(\frac{A}{N_1} \right) / \left(\frac{B}{N_0} \right)$$

The risk ratio is interpretable as :

- 1) the **proportionate change in the average risk** of the exposed subcohort produced by exposure,

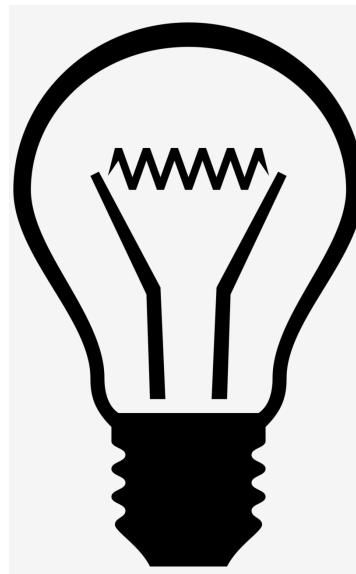
$$\left(\frac{\sum_1 r_{1i}}{N_1} \right) / \left(\frac{\sum_0 r_{0i}}{N_0} \right) = \left(\frac{\sum_1 r_{1i}}{N_1} \right) / \left(\frac{\sum_1 r_{0i}}{N_1} \right)$$

It **is not interpretable** as the average proportionate change in risk produced by exposure among exposed individuals:

$$\left(\frac{\sum_1 (r_{1i}/r_{0i})}{N_1} \right)$$

Expressions 3 and 4, on: Interpretation and choice of effect measures in epidemiologic analyses. S. Greenland (1987)

Incidence Proportion Ratio



However, **if the individual risk ratios are all equal** then the ratio of the average risks across exposure will be equal to the average of the individual risk ratios

A note on Risk Ratios

Risk Differences have a symmetric range [-1, 1]

But the risk Ratios have an *asymmetric* range:

- From 0 to 1, below the null
- From 1 to infinity above the null

This presents a challenge in the interpretation...

What's more "impressive" (RR = 2) or (RR= 0.2) ? ...

What's more "impressive" a (RR = 2) or a (RR= 0.2) ?

Two ways to find out:

Simple: the reciprocal of the value below the null = $1/0.2 = 5$, since $5 > 2$, then

- a RR of 0.2 is of larger magnitude (further away from the null) than a RR = 2

Elaborated: Take the absolute values of the natural logarithm (log or ln) of each value:

- $\log(3) = 0.693$
- $\log(0.3) = -1.609$

In absolute terms, $|\log(0.2)| > |\log(2)| = |-1.609| > |0.693|$

- Regression models for ratio measures generally operate on the log-scale (that's why we exponentiate to provide estimates and graph on the log scale).
- Note: Recall that on the log10 or ln scale, the null for a ratio measure is 0, not 1 – because $\log(1) = \ln(1) = 0$.
- Try it with 3 and 0.3, and with 5 and 0.5 and see what happens! :)

Incidence Odds Ratio

The incidence odds ratio is given by:

$$\left(\frac{A}{C} \right) / \left(\frac{B}{D} \right)$$

Thus, the odds ratio is interpretable as :

- 1) the proportionate change in the incidence odds in the exposed subcohort produced by exposure,

$$\left(\frac{\sum_1 r_{1i}}{\sum_1 s_{1i}} \right) / \left(\frac{\sum_0 r_{0i}}{\sum_0 s_{0i}} \right)$$

$$\left(\frac{\sum_1 r_{1i}}{\sum_1 s_{1i}} \right) / \left(\frac{\sum_1 r_{0i}}{\sum_1 s_{0i}} \right)$$

It **is not interpretable** as the proportionate change in the average odds in the exposed produced by exposure:

Incidence Odds Ratio

- Furthermore, neither of the last two expressions is equivalent to the average of the individual odds ratios among the exposed

$$\left(\frac{\sum_1 (w_{1i}/w_{0i})}{N_1} \right)$$

- The incidence odds ratio (**that we calculate**) lacks any simple interpretation in terms of exposure effect on the average risk or odds, or average exposure effect on individual risk or odds.

Incidence Odds Ratio

The incidence odds do not equal the simple averages of the risk odds:

This severely handicaps the interpretability of measures based on the incidence odds.

- It is not a measure of average causal effect (the RR and RD are) (Greenland 1987)
- Cannot be relied upon to reveal confounding (Greenland et al., 1999)

Incidence Odds Ratio

- If the individual ORs are all equal (which is the assumption made by a logistic model), then the ratio of the average odds will equal the average of the individual odds ratios.

But, the incidence odds ratio will need not equal that value!

Incidence Odds Ratio

- For example: Define a population where 10% of people have $r_{1i} = 0.60$ and $r_{0i} = 0.20$ and 90% of the people have $r_{1i} = 0.035$ and $r_{0i} = 0.006$
- Here, the individual ORs = 6.0 for every individual
 - the average of the individual ORs = 6.0
- Also, the ratio of the average odds equals 6.0 as well

But, the incidence odds ratio is equal to 3.9

Want to give it a try and calculate it?

Incidence Odds Ratio

- Because of this fact, the crude odds ratio can be smaller than any of the stratum-specific odds ratios, even if confounding is entirely absent
- This paradoxical behaviour will not occur with the risk difference or the risk ratio
- Unless, equal to the null (when $OR = RR = 1$) the OR will ***almost always*** be further away from the null than RRs.
 - 2nd exception is when **$OR = RR = 0$** , as would occur when risk in the exposed is 0 (zero), and risk in the unexposed is for example 0.6. In this case, the risk ratio is 0 and the OR is $\text{odds}(0)/\text{odds}(0.6)$, which is also 0.

More on [Epidemiology by design by Daniel Westreich](#)

Odds difference?

⚠ !! Nope, nope, nope!!!!!! ⚠ !!

✗ !! We never do this. !! ✗

Some simulated Examples - Common Outcome

```
set.seed(704)
yea.dat1 <- function(n) {
  E <- rbinom(n,1,0.55) #parameters for E
  Y <- ifelse(E==1, rbinom(n,1,0.85), rbinom(n, 1, 0.45)) #parameters for Y

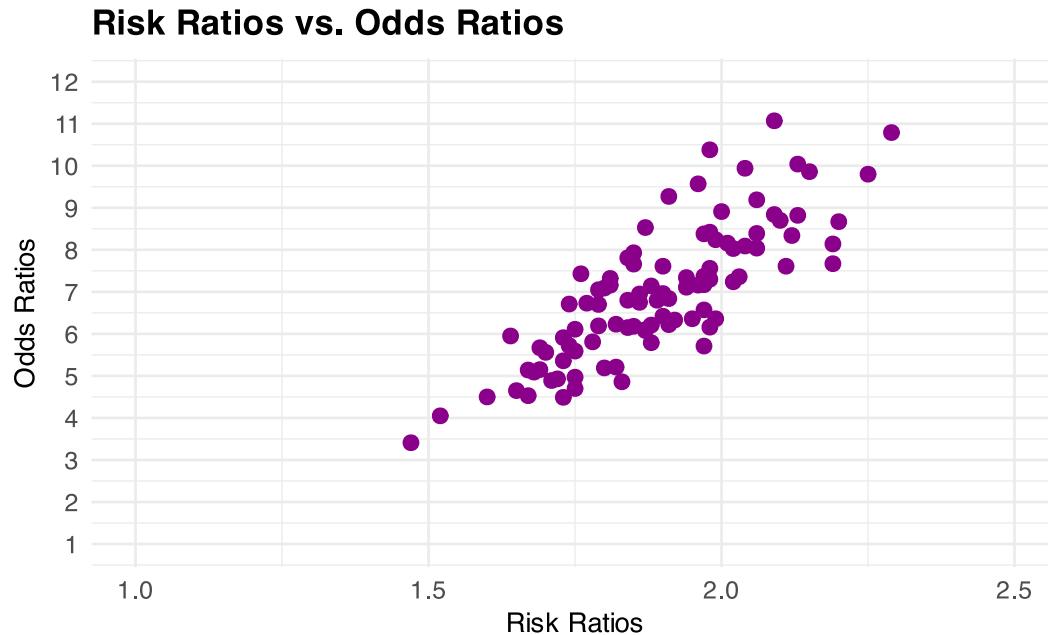
  return(data.frame(E=E,Y=Y)) #ask to return a data set with those parameters
}
sim100 <- lapply(1:100,FUN=function(x) yea.dat1(400))
RRs <- sapply(sim100,FUN=function(x) {
  results <- logbin(Y ~ E , data=x)$coef
  return(round(exp(results[names(results)]=="E")),2))
})

ORs <- sapply(sim100,FUN=function(x) {
  results <- glm(Y ~ E , family="binomial", data=x)$coef
  return(round(exp(results[names(results)]=="E")),2))
})

sim_RRs1<-round(quantile(RRs,probs = c(0.05,0.5,0.95)),2)
sim_ORs1<-round(quantile(ORs,probs = c(0.05,0.5,0.95)),2)
```

Some simulated Examples - Common Outcome

```
##           5% 50% 95%
## sim_RRs1 1.67 1.9  2.19
## sim_ORs1 4.64 7.0  10.40
```



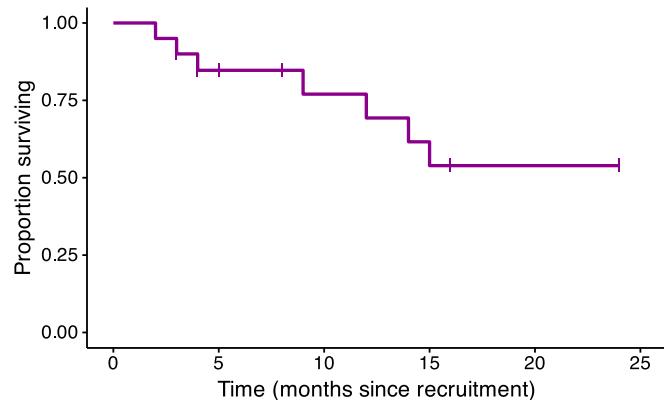
Key Takeaways

Only incidence difference and incidence ratios possess direct interpretations as measures of impact on average risk/hazard

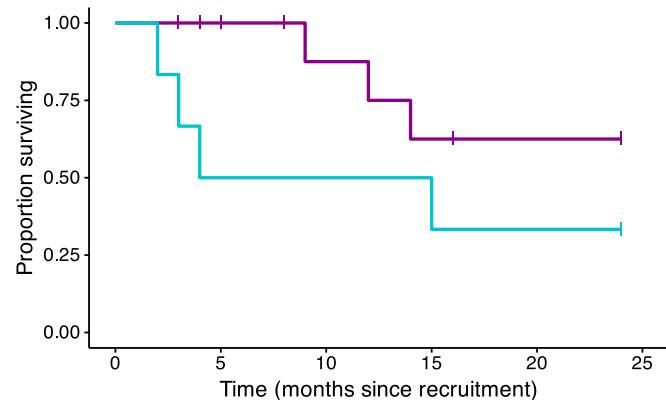
Consequently, odds ratios are useful only when they serve as incidence ratio estimates

Incidence Rate Differences and Ratio

From everyone's time...



... To contrast outcomes and time



Incidence Rate Differences and Ratio

- Incidence rate of outcome Y when X=1 is $IR(Y = 1|X = 1) = IR(Y|X = 1)$
- Incidence rate of outcome Y when X=0 is $IR(Y = 1|X = 0) = IR(Y|X = 0)$
- **Incidence rate difference:**
 - Range: $-\infty$ to ∞
 - Null value: 0
- **Incidence rate ratio:**
 - Range: 0 to ∞
 - Null value: 1

Relationship among Risk, Odds, and Incidence Rates

Question: If we calculated the risk ratio, odds ratio and rate ratio, which will be closest to the null? Furthest from the null?

Notation:

- R = Incidence Proportion("Risk"),
- $S = 1 - R$ ("Survival Proportion"),
- I = Incidence Rate
- T = interval length
- $i = 1$ if exposed; $i= 0$ if unexposed

Relationship among Risk, Odds, and Incidence Rates

Relations among relative risks

- In a closed population where the population at risk declines only slightly over the interval (implying that R must be small and S is close to 1): $R \cong I\Delta T \cong R/S$

This implies:

$$\left(\frac{R_1}{R_0} \right) \cong \left(\frac{I_1 \Delta T_1}{I_0 \Delta T_0} \right) \cong \left(\frac{I_1}{I_0} \right) \cong \left(\frac{R_1 S_1}{R_0 S_0} \right)$$

[Numerators] Holds if R_1 and R_0 are small enough so that S_1 and S_0 are close to 1

[Two Denominators on the right] Holds if exposure only has negligible effects on the person-time at risk

Relationship among relative risks

- If exposure causes the outcome, then $R_1 > R_0$ and $S_1 < S_0$.

$$1 < \left(\frac{R_1}{R_0} \right) < \left(\left(\frac{R_1}{R_0} \right) \times \left(\frac{S_0}{S_1} \right) \right) = \left(\frac{R_1/S_1}{R_0/S_0} \right)$$

- If exposure prevents the outcome, $R_1 < R_0$ and $S_1 > S_0$, such that:

$$1 > \left(\frac{R_1}{R_0} \right) > \left(\left(\frac{R_1}{R_0} \right) \times \left(\frac{S_0}{S_1} \right) \right) = \left(\frac{R_1/S_1}{R_0/S_0} \right)$$

In words: **The odds ratio is further from the null than the risk ratio**

Relationship among relative risks

- Now, if exposure is harmful ($R_1 > R_0$) then we would ordinarily expect exposure to reduce the person-time at risk ($T_1 < T_0$),
- and if exposure is preventive ($R_1 < R_0$) then we expect exposure to increase the person-time at risk ($T_1 > T_0$).
- Thus, when exposure is **harmful**:

$$1 < \left(\frac{R_1}{R_0} \right) \cong \left(\frac{I_1 \Delta T_1}{I_0 \Delta T_0} \right) < \left(\frac{I_1}{I_0} \right)$$

Relationship among relative risks

And when exposure is **preventive**:

$$1 > \left(\frac{R_1}{R_0} \right) \cong \left(\frac{I_1 \Delta T_1}{I_0 \Delta T_0} \right) > \left(\frac{I_1}{I_0} \right)$$

- In words: We would **ordinarily** expect the risk ratio to be closer to the null than the rate ratio. Under further conditions, the rate ratio will be closer to the null than the odds ratio (Greenland and Thomas, 1982)

Relationship among relative risks

Thus, we usually expect:

- Risk ratio nearest to the null
 - *implicitly* suggesting all events occur at the end of follow up
- Odds ratio furthest from the null
 - *implicitly* suggesting all events occur at the beginning of follow up
- Rate ratio somewhere in between
 - allows event to occur at any point in time

$$1 < \text{Risk Ratio} < \text{Rate Ratio} < \text{Odds Ratio}$$

¹ More on Epidemiology by design by Daniel Westreich

Prevalence Ratios

Recall that the prevalence odds is equal to the incidence rate multiplied by the average duration in a stationary, closed population. This implies:

$$POR = \left(\frac{PO_1}{PO_0} \right) = \left(\frac{I_1 \overline{D}_1}{I_0 \overline{D}_0} \right) = \left(\frac{I_1}{I_0} \right)$$

if the average duration of disease is unaffected by exposure.

Prevalence Ratios

- If prevalence is low, then the prevalence ratio is approximately equal to the incidence rate multiplied by average duration. This implies:

$$PR = \left(\frac{P_1}{P_0} \right) \cong \left(\frac{I_1 \overline{D}_1}{I_0 \overline{D}_0} \right) = \left(\frac{I_1}{I_0} \right)$$

if the average duration of disease is unaffected by exposure



N SERIES

PAINKILLER

51 of 53m

 Resume



2023 Limited Series   

 TV-MA language, nudity, sex, sexual violence, smoking, substances, violence

Cast: Matthew Broderick, Uzo Aduba, Taylor Kitsch, *more*

Genres: TV Dramas, TV Shows
Based on Books, Social Issue TV Dramas

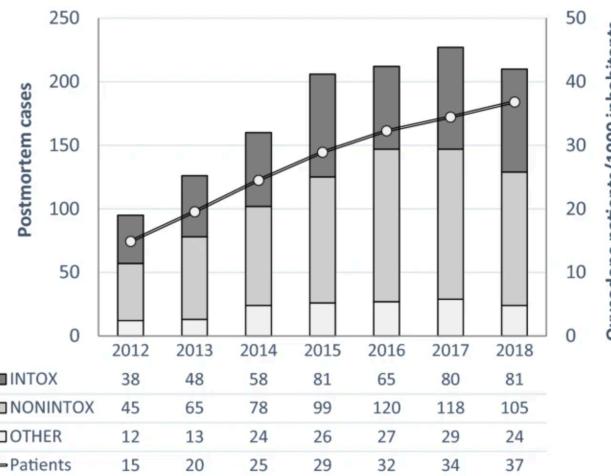
This show is: Provocative

S1:E1 "The One to Start With, The One to Stay With"

Oxycodone-Related Deaths: The Significance of Pharmacokinetic and Pharmacodynamic Drug Interactions¹

Key Points

- In oxycodone-related deaths, **41% did not have a prescription for oxycodone**, suggesting misuse as a risk factor.
- Drugs impairing the metabolism of oxycodone were very rarely prescribed.
- Compared to other deaths, persons dying from oxycodone intoxication were **5.6 times** more likely to have other CNS depressant drugs on board and **1.7 times** more likely to have them prescribed.



Trends (2012–2018) in the No. postmortem cases positive for oxycodone in femoral blood, and No. patients per 1000 inhabitants prescribed oxycodone, by (INTOX) or (NONINTOX)

¹ Jakobsson, G., et al. **Oxycodone-Related Deaths: The Significance of Pharmacokinetic and Pharmacodynamic Drug Interactions** Eur J Drug Metab Pharmacokinet 47, 259–270 (2022)

Illustrated Example

Table 2. Number of oxycodone prescriptions within 1 year before death.

Variable	INTOX (<i>n</i> = 451)	NONINTOX (<i>n</i> = 630)	Total (<i>n</i> = 1081)
Oxycodone prescribed	268 (59%)	443 (70%)	711 (66%)
Oxycodone dose (mg/day)	227 (50%)	371 (59%)	598 ^a (55%)
Median (range)	33 (0.20–1197)	26 (0.30–723)	30 (0.20–1197)
5–95 percentile	4.0–203	3.0–155	3.1–186
Oxycodone concentration (µg/g)			
Median (range)	0.30 (0.005–83)	0.050 (0.005–7.1)	0.10 (0.005–83)
5–95 percentile	0.020–2.1	0.007–0.39	0.008–1.0
Any PKI prescribed	7 (2%)	8 (1%)	15 (1%)
Any PDI prescribed ^b	379 (84%)	476 (76%)	855 (79%)
Only N05 ^c prescribed	184 (41%)	250 (40%)	434 (40%)
Only N02A ^d prescribed	17 (4%)	43 (7%)	60 (6%)
Both N05+N02A prescribed	178 (40%)	183 (29%)	361 (33%)

"The INTOX group was less likely to have oxycodone prescribed within 1 year before death (**41% vs. 30%, OR 0.62, CI 0.48–0.80**)"

¹ Jakobsson, G., et al. Oxycodone-Related Deaths: The Significance of Pharmacokinetic and Pharmacodynamic Drug Interactions Eur J Drug Metab Pharmacokinet 47, 259–270 (2022)

Illustrated Example... Let's reproduce the analysis

	Outcome		TOTAL
	INTOX	NONINTOX	
Oxycodone Prescribed	268	443	711
Oxycodone Non-Prescribed	183	187	370
Total	451	630	1081

Illustrated Example... Let's reproduce the analysis

```
oxydat1<-c(268, 443, 183, 187)

oxyOR1<- epi.2by2(oxydat1, method = "cross.sectional")
oxyOR1$tab

##          Outcome +      Outcome -      Total      Prev risk *
## Exposed +        268          443       711      37.69 (34.12 to 41.37)
## Exposed -        183          187       370      49.46 (44.25 to 54.68)
## Total            451          630      1081      41.72 (38.76 to 44.73)

round(oxyOR1$massoc.detail$OR.strata.wald, 2)

##      est lower upper
## 1 0.62  0.48   0.8
```

*"The INTOX group was less likely to have oxycodone prescribed within 1 year before death (**41% vs. 30%**, OR 0.62, CI 0.48–0.80)"*

What's clear and what's not here?

"The INTOX group was less likely to have oxycodone prescribed within 1 year before death (**41% vs. 30%**, OR= 0.62, CI 0.48–0.80)"

What's the reference group? Does the % make sense *vis a vis* the OR?

- Prescribed & INTOX = 268/451 = 0.59 ; Prescribed & NONINTOX = 443/630 = 0.7
- Non-Prescribed & INTOX = 183/451 = 0.41 ; Non-Prescribed & NONINTOX = 187/630 = 0.3

If "absence of prescription" was the exposure, then:

```
oxydat2<-c( 183, 187, 268, 443); oxyOR2<- epi.2by2(oxydat2, method = "cross.sectional")
oxyOR2$tab
```

	Outcome +	Outcome -	Total	Prev risk *
## Exposed +	183	187	370	49.46 (44.25 to 54.68)
## Exposed -	268	443	711	37.69 (34.12 to 41.37)
## Total	451	630	1081	41.72 (38.76 to 44.73)

```
round(oxyOR2$massoc.detail$OR.strata.wald, 2)
```

```
##      est lower upper
## 1 1.62  1.25  2.09
```

What's clear and what's not here?

```
oxydat2<-c( 268, 443, 183, 187 ); oxyOR2<- epi.2by2(oxydat2, method = "cross.sectional")
oxyOR2$tab
```

	Outcome +	Outcome -	Total	Prev risk *
## Exposed +	268	443	711	37.69 (34.12 to 41.37)
## Exposed -	183	187	370	49.46 (44.25 to 54.68)
## Total	451	630	1081	41.72 (38.76 to 44.73)

```
round(oxyOR2$massoc.detail$OR.strata.wald, 2)
```

```
##      est lower upper
## 1 0.62  0.48   0.8
```

What would be the actual interpretation of this OR?

More likely that: "*Prescription of oxycodone within 1 year before decreased the odds of dying from intoxication OR= 0.62, CI 0.48–0.80*" **What do you think?**

Illustrated Example

"The INTOX group was more likely to have a PDI drug dispensed than the NONINTOX group (84% vs. 76%, OR 1.7, CI 1.2–2.3) (see Table 2; Fig. 2)."

```
oxydat3<-c( 379, 476, 72, 154)  
oxyOR3<- epi.2by2(oxydat3, method = "cross.sectional")  
tbl(oxyOR3$massoc.summary[1:2,])
```

var	est	lower	upper
Prev risk ratio	1.391390	1.133565	1.707858
Prev odds ratio	1.703023	1.248264	2.323457

Illustrated Example

"Subjects in the INTOX group were more likely to have a PDI drug in their system (OR 5.6, CI 3.7–8.5)."

Table 3. Co-findings of pharmacodynamically (PDI) interacting substances

	Total	INTOX (<i>n</i> = 451)	NONINTOX (<i>n</i> = 630)	<i>p</i> value	Odds ratio (95% CI)
PDI drug	877 (81%)	422 (94%)	455 (72%)	< 0.001	5.6 (3.7–8.5)
N05 drug	718 (66%)	373 (83%)	345 (55%)	< 0.001	4.0 (3.0–5.3)
N02A drug	314 (29%)	147 (33%)	167 (27%)	0.03	1.3 (1.0–1.7)
Alcohol	260 (24%)	145 (32%)	115 (18%)	< 0.001	2.1 (1.6–2.8)

```
oxydat4<-c(422, 455, 29, 175)

oxyOR4<- epi.2by2(oxydat4, method = "cross.sectional")
kbl(oxyOR4$massoc.summary[1:2,], digits = 2)%>%kable_paper()
```

var	est	lower	upper
Prev risk ratio	3.38	2.4	4.77
Prev odds ratio	5.60	3.7	8.47

Illustrated Example

"INTOX group were more likely to have a previous substance use diagnosis (**29% vs. 14%, OR 2.6, CI 1.9–3.5**).... We found no significant difference with 14% of the suicides and 10% of the accidents presenting a mood affective diagnosis"

var	est	lower	upper
Prev risk ratio	1.39	1.13	1.71
Prev odds ratio	1.70	1.25	2.32

What did the authors do with the covariates?

Table 1 Demographic data of the 1081 cases included in the study

Variable	INTOX	NONINTOX	Total
Cases	451 (42%)	630 (58%)	1081 (100%)
Age group			
< 18	1 (0.2%)	2 (0.3%)	3 (0.3%)
18–35	115 (26%)	72 (11%)	187 (17%)
36–50	156 (35%)	75 (12%)	231 (21%)
51–64	105 (23%)	198 (31%)	303 (28%)
≥ 65	74 (16%)	283 (45%)	357 (33%)
Sex			
Female	173 (38%)	197 (31%)	370 (34%)
Male	275 (61%)	433 (69%)	708 (66%)
Missing	3 (0.7%)	0	3 (0.3%)
Body mass index			
Underweight (< 18.5)	16 (3.5%)	56 (8.9%)	72 (6.7%)
Normal weight (18.5–24.9)	116 (26%)	236 (38%)	352 (33%)
Pre-obesity (25.0–29.9)	151 (34%)	171 (27%)	322 (30%)
Obesity (≥ 30.0)	160 (36%)	149 (24%)	309 (29%)
Missing	8 (1.8%)	18 (2.9%)	26 (2.4%)
Place of death			
Hospital/intensive care	26 (5.8%)	136 (22%)	162 (15%)
Other care unit	12 (2.7%)	27 (4.3%)	39 (3.6%)
Private home	373 (83%)	377 (60%)	750 (69%)
Other/unknown	35 (7.8%)	71 (11%)	106 (9.8%)
Missing	5 (1.1%)	19 (3%)	24 (2.2%)
Manner of death			
Natural (disease)	1 ^a (0.2%)	346 (55%)	347 (32%)
Accident	182 (40%)	116 (18%)	298 (28%)
Suicide	138 (31%)	136 (22%)	274 (25%)
Homicide/police intervention	0	5 (0.8%)	5 (0.5%)
Unclear	130 (29%)	27 (4.3%)	157 (15%)

All CRUDE ORs?? No "adjusting"? ¹

5 Conclusions

We set out to investigate the significance of pharmacokinetic and pharmacodynamic interactions in oxycodone-related deaths. We can conclude that drugs impairing oxycodone metabolism were very rarely prescribed and dispensed both in intoxications as well as in nonintoxications. In contrast, pharmacodynamically interacting drugs were frequently prescribed and dispensed, and even more frequent was a co-finding in fatal oxycodone-related intoxications, suggesting that the associated risk needs to be addressed in clinical practice. Compared to other deaths, persons dying from oxycodone-related intoxication were 5.6 times more likely to have other CNS depressant drugs on board and 1.7 times more likely to have them prescribed and dispensed. We also found that, in oxycodone-related deaths, a significantly higher number of cases did not have a prescription for oxycodone, suggesting misuse or abuse as a risk factor. In addition, both doses and concentrations of oxycodone were

¹ More on confounding [here](#) and adjustment next lectures!

When to use which measure of Association

- Research Question
- Public Health Relevance
- Intervention (Design of/ Intervenable exposure?)
- Study design
- Contrasts requires assignment to group, which requires measurement of group membership For example, measurement of exposure
 - What will happen if the exposure is measured poorly?
- Since risks are only well-defined within a specific time-period, state that time-period.

Things to consider when measuring associations

- Be aware that in real life, we encounter:
 - Random Error
 - Systematic error
 - Competing Risks, Confounding, Selection Bias, Measurement Error
 - Methods related limitations
 - Clinical vs Statistical hurdles

Contrast (Association vs Impact)

Most contrasts can be used to assess either:

- Association (which is agnostic on the question of causality)
- Impact (which is causal). The risk difference, for example.

Certain measures, however, are implicitly causal and (probably) shouldn't be used to merely describe an association.

- Among these latter measures are **number needed to treat, and attributable contrasts**.

Population Attributable Fraction (PAF)

A population attributable fraction (PAF) can be thought of as

- "*The proportion of disease burden among the total population which is caused by the exposure*".
- That definition is explicitly causal.
- PAF is implicitly causal.
- "Attribution" implies cause, though we can argue over usage.

Calculated as $(P(Y) - P(Y^{x=0}))/P(Y)$ where,

- $P(Y)$ is the risk of the outcome in the whole population,
- $P(Y|X = 0)$ is the risk of the outcome in the unexposed.

Note that because most outcomes are caused by more than one thing, the sum of PAFs can be (and often are) greater than 100%. [Epidemiology by design by Daniel Westreich](#)

Example:

- Exposure to TB is a necessary cause of active TB: by definition.
 - So from the above, $P(Y_{TB\text{exposure}} = 0) = 0$, and so PAF = 100%.
- But not everyone exposed to TB develops active TB. There are other causes. E.g., being immunocompromised.
 - RD for immunocompromised status > 0; PAF>0.
- $PAF_{TB-\text{exposure}} + PAF_{\text{immunocompromised}} > 100$

This concept can be tied to Rothman's causal pies model of causality [Epidemiology by design by Daniel Westreich](#)

A measure related to PAFs

The **population attributable risk difference** is the difference between the risk of the outcome in the observed population and the risk of the outcome **if all exposure were removed**, that is:

$$P(Y) - P(Y^{x=0})$$

-The potential outcomes notation is *deliberate* here.

Epidemiology by design by Daniel Westreich

Remember our opioid example?

Assuming a cohort design:

```
oxydat4<-c( 422, 455, 29, 175)  
oxyOR4<- epi.2by2(oxydat4, method = "cohort.count")  
kbl(oxyOR4$massoc.summary, digits = 2)
```

var	est	lower	upper
Inc risk ratio	3.38	2.40	4.77
Inc odds ratio	5.60	3.70	8.47
Attrib inc risk *	33.90	28.08	39.73
Attrib fraction in exposed (%)	70.46	58.33	79.06
Attrib inc risk in population *	27.50	21.88	33.13
Attrib fraction in population (%)	65.93	52.96	75.32

Attributable Risk \cong Risk Difference

Number Needed to Treat

The number needed to treat (NNT) is the number of individuals who we would need to treat in order to **prevent** one bad outcome.

The NNT is calculated as $|RD|^{-1}$

- The inverse of the absolute value of the risk difference.
 - For a harmful exposure, we **keep the absolute value**, but describe the measure as a **number needed to harm**.

Epidemiology by design by Daniel Westreich

NNT

If the 5-year risk of death among treated is 10%, and among untreated is 20%,

- then how many people do you need to treat to prevent one death over five years?
- $|10\% - 20\%|^{-1} = |-10\%|^{-1} = 0.10^{-1} = 10.$
 - We must treat 10 people to prevent one death over five years.

Notation: $NNT = 1/|(P(Y|X=1) - P(Y|X=0))|$

What's the null value?

Epidemiology by design by Daniel Westreich

NNT

Often by convention, round NNT up to nearest integer - Can't treat half a person

- Conservative approach; doesn't always make sense.
- NNT implies causality more strongly than risk difference.
- Risk differences can be viewed as descriptive (although you should be specific and cautious about that)
- Just the difference in observed risks between two groups: not necessarily due to group identification.
- In contrast, NNTs explicitly discuss a treatment having a result: thus are expressing a causal effect.
- Explaining an NNT can become tricky outside of a trial setting because exposure (smoking) isn't always the same as treatment (cognitive behavioral therapy for smoking cessation).

Epidemiology by design by Daniel Westreich

QUESTIONS?

COMMENTS?

RECOMMENDATIONS?

Know the Signs of an Opioid Overdose



Blue or grey lips or nails



Dizziness and confusion



Can't be woken up



Choking, gurgling or snoring sounds



Slow, weak or no breathing



Drowsiness or difficulty staying awake

Suspect an Overdose?

CALL **911** or your local emergency number

Administer **naloxone** if you have it

Stay with the person until help arrives

You have the power to save a life.

Learn more at Canada.ca/Opioids
Together we can #StopOverdoses



Canada

The *Good Samaritan Drug Overdose Act* protects people from: Simple drug possession charges and Violation of conditions regarding simple possession.

- This law applies to the person who has overdosed, the person who seeks help and anyone at the scene when help arrives.

Incidence Odds Ratio

- For example: Define a population where 10% of people have $r_{1i} = 0.60$ and $r_{0i} = 0.20$ and 90% of the people have $r_{1i} = 0.035$ and $r_{0i} = 0.006$
- Here, the individual ORs = 6.0 for every individual
- the average of the individual ORs = 6.0
- Also, the ratio of the average odds equals 6.0 as well

But, the incidence odds ratio is equal to 3.9

Incidence Odds Ratio - Calculations

Rudimentary calculations

```
#10% pop  
0.6/(1-.6) #= 1.5 #r1  
0.2/(1-.2) #= 0.25 #r0  
  
#OR in 10%  
1.5/0.25 #= 6  
  
#OR 90%  
0.035 / (1-0.035) # = 0.03626943 #r1  
0.006/(1- 0.006) # = 0.006036217 #r0  
  
#OR in 90%  
0.03626943/0.006036217 #= 6.008636  
  
# OR average  
1.5+0.03626943 #= 1.536269  
1.536269/2 #= 0.7681345  
0.25+0.006036217 #= 0.2560362  
0.2560362/2 #= 0.1280181  
  
0.7681345/0.1280181 #= 6.000202
```

```
## IOR  
(0.6*0.1) + (0.035 *0.9) #= 0.0915  
(0.2*0.1) + (0.006*0.9) #= 0.0254  
#OR1  
0.0915/(1- 0.0915) #=0.1007155  
#OR0  
0.0254/(1-0.0254) #=0.02606197  
#IOR  
0.1007155/0.02606197 #3.864462
```