EPIDEMIOLOGY REVIEW – PH 207X

WEEK 1 - EPIDEMIOLOGY

Definition of Epidemiology
A commonly cited definition for Epidemiology is "*the study of the distribution and determinants of disease frequency in man*" This definition implies two quantitative aspect of epidemiology:

1. Measuring **disease distribution** in regards to person, place, and time (**descriptive epidemiology**)
2. Measuring the association between a **disease and it determinants** (**analytic epidemiology**).

Prevalence – Measuring the "existence" of disease in a population
Incidence – Occurrence of disease in a population over time (the disease does not exist already)

Primary concern of epidemiology – find risk factors of a disease and quantifying the magnitude of their effects on the disease. Such a process begins with a **measure of association** between a risk factor and a disease, followed by an argument that this measure reflects the causal effect of that risk factor on the disease. In practice, there are often many explanations for an observed association between a risk factor and a disease. Arguing that an observed measure of association reflects a causal effect involves eliminating other possible explanations for the observed association. Hennekens and
Buring (Epidemiology in Medicine. Little, Brown and Co; Boston: 1987) state that these alternative explanations fall under the broad headings of

1. Confounding
2. Bias
3. Chance

Clinical Epidemiology

Clinical epidemiology applies the concepts and techniques of epidemiology, statistics, and decision analysis to clinical problems. Clinical epidemiology emphasizes the study of patients, physicians, and systems of health care. ***The focus is on diagnosis, prognosis, and treatment of disease but it also studies the etiology of disease****. Exposures and outcomes are informed by clinical and biologic knowledge as well as broader environmental and societal determinants. Distinctive areas of clinical epidemiology are the development of diagnostic and prognostic models.* ***The gold standard for the study of medical treatments is the randomized clinical trial****. Observational analyses of treatments are necessary to gain estimates of their impact in real world clinical practice and to screen for rare effects. These observational analyses of medical interventions face the distinctive hurdle of confounding by indication and/or contraindication*

Role of measurement in Epidemiology

Descriptive epidemiology - Measuring disease distribution in regards to person, place, and time. requires the specification of appropriate **outcome measures**. **Proportions, rates, percentiles** and means are examples of outcome measures.

Analytic epidemiology - Measuring the association between a disease and it determinants. requires the specification of a **measure of association** to compare the values for the outcome measures in different subgroups that are defined by the exposure. **Odds Ratios, Risk Ratios and Mean Differences** are examples of commonly used measures of association.

Types of measurement

1. Nominal (The simplest example of a nominal variable is the **binary indicator variable** (**dummy variable**) that uses integer values to indicate membership in one of two categories of a factor of interest (eg., Male = 1, Female = 0)

2. Ordinal - **Ordinal variables** have **categorical responses** with a well-defined order among categories. The numerical values assigned to the categories of an ordinal variable reflect the relative positions for these categories but may not necessarily reflect the distance between these categories on an underlying continuous scale. (eg., classification of different stages of disease)

3. **Interval** – Values for **interval variables** reflect not only the order among categories/levels of the variable, but also reflect the distances between these categories/levels (eg., temperature, height, etc)

4. **Ratio** – Values for ratio variables not only reflect order and distances between categories/levels, **but these variables also contain a natural zero value, representing the absence of the quantity that is being measured**. This provides a natural anchoring point for the interpretation of values on this scale. Examples of ratio scales include temperature measured on the Kelvin Scale (where 0 = lack of molecular movement and the absence of temperature) and the age of individuals. Not only is a 50 year-old half way between the age of a 40 year-old and a 60 year-old, but also he/she is also twice as old as a 25-year old.

A **continuous variable** may be interval or ratio in scale, depending on the existence of a natural zero value.

Outcome measures for binary variables

Proportions - **Proportions** relate the size of the population that have (or develop) the disease to the total size of the population of interest (**part/total measure**). **Values for proportion range from 0.0 to 1.0**

Odds - Odds are an alternative measure of the likelihood of belonging to a particular category of a nominal variable. For example, the odds of disease measures the size of the population who have (or develop) the disease to the size of the population that does not have (or does not develop) the disease (a part/non-part measure). **The value for Odds range from 0.0 to +ve infinity**

The value for odds is easily calculated from the value for a proportion by the following transformation

odds = (proportion)/(1 - proportion)

Alternatively, the value for a proportion can be calculated from the value for an odds by the following formula:

proportion = (odds)/(1 + odds)

Relationship between Proportions and Odds.

Prevalence	Prevalence Odds
0.01	0.01
0.02	0.02
0.03	0.03
0.05	0.05
0.10	0.11
0.20	0.25
0.30	0.43
0.40	0.67
0.50	1.00
0.60	1.50
0.70	2.33
0.80	4.00
0.90	9.00
0.95	19.00
0.97	32.33
0.98	49.00
0.99	99.00

The previous table demonstrates that values for two proportions that are very close to one another (e.g. (0.01 and 0.02), or (0.98 and 0.99)) may have values for the corresponding odds that are also close to one another (0.01 and 0.02 for the first pair) or far apart (49.00 and 99.00 for the second pair). **This implies that a measure of association that suggests large differences between values for two odds may not necessarily imply large differences between values for the corresponding proportions.** Although a proportion may be a more intuitive outcome measure for a nominal variable, a particular analysis may require that the odds be the outcome measure of choice (e.g. logistic regression).

Prevalence = Proportion (# with / total subjects)

Prevalence measures how much outcome (disease) exists in the population **at a point in time**. Time can be a chronologic date (eg., 2011), a person's age (at age 60), in terms of life time events (at the time of retirement)

Prevalence usually is defined as the proportion of people who have the disease at that point in time.

Prevalence = Proportion = (# with disease)/(total #)

If there were 100 people watching me right now, and 30 were wearing eyeglasses, then the prevalence of wearing eyeglasses (prevalence of having eye conditions) would be

Prevalence = # / total = 30/100 = 30%

Alternatively, I could turn that prevalence into an odds and report the prevalence odds

Odds = # with / # without = 30/70 = 43%

Sex	Age Group	Number at Exam	Number with CHD	Prevalence
Female	30-40	415	0	0/415= .00
	41-50	908	6	6/908= .01
	51-60	795	38	38/795=.05
	> 60	372	26	26/372=.07
Male	30-40	339	6	6/339=.02
	41-50	731	24	24/731=.03
	51-60	584	37	37/584=.06
	> 60	290	57	57/290=.20

One possible explanation for the higher prevalence of CHD among men is that men might be at higher risk for developing coronary heart disease. Therefore a group of men would show a higher **incidence** for developing CHD than a comparable group of women.

Another reason for the higher prevalence of CHD among men might be that men live longer with their heart disease.

We hope those associations represent the true, causal effect of a risk factor on an outcome. However, before we can conclude that an association reflects a causal effect of a risk factor we have to exclude three possible alternative explanations: **bias, confounding, or chance.**

Bias -- For example, it may be that men and women really do have the same prevalence of disease, but maybe men see their physicians more often and are tested more often for CHD. If so, the reason for the higher prevalence of CHD among men might be due to a measurement bias: the underreporting of CHD among women.

Confounding -- A fourth possible explanation for the higher prevalence of CHD is that men and women have the same risk of developing disease based on their sex, but men have more additional risk factors (e.g. smoking hypertension, …) that increases their risk of CHD and leads to a higher incidence of CHD (and their higher prevalence).

Chance -- Finally, suppose that in general, men and women have the same prevalence of CHD. However, your data contain only a sample of men and a sample of women. Because of sampling variability (chance), the observed prevalence of CHD among men in our data may be higher than what exists in general among all men.

Week 3 – Incidence

Incidence -- **Incidence refers to the occurrence of new cases of a disease (outcome) in a population over a period of time.** It involves following a group of people who are at risk for developing the developing the disease and recording the outcomes that occur. **Unlike prevalence, which is measured at a point in time, incidence requires a period of follow-up.**

For eg., the from the FHS dataset, we find,

1. The size of the population at risk (1406 deaths occurred in 4420 subjects during 24 years of follow-up)

2. The amount of follow-up time observed (1406 deaths occurred during 88,389.45 person-years of follow-up)

These reflect 2 types of calculations

1 – Cumulative Incidence
2 – Incidence Rate

Cumulative Incidence / Estimated Risk / Average RIsk

Cumulative Incidence is defined as the proportion of people who develop a disease (outcome) during a fixed period of follow-up. As a **proportion**, the value for the Cumulative Incidence can range for as **low as 0.0 (when there are no deaths) and 1.0 (when everyone dies)**.

(# Deaths)/(# At Risk) =1406/4420 = 0.33

The direct calculation of the Cumulative Incidence as shown above requires knowledge of the mortality outcomes for all of the 4420 subjects who were followed. **For example, if a subject were lost-to-follow-up, then his/her mortality outcome would be unknown and you would not know whether or not to include that person in the numerator of the calculation for the Cumulative Incidence**. Fortunately, we have complete follow-up for mortality in these data.

Year	Population A			Population B			Population C		
	# At Risk	# Deaths	Person-years	# At Risk	# Deaths	Person-years	# At Risk	# Deaths	Person-years
1	100	10	95	100	2	99	100	10	95.0
2	90	10	85	98	2	97	91	9	85.5
3	80	10	75	96	2	95	83	8	77.0
4	70	10	65	94	34	77	74	7	69.5
Total		40	320		40	368		34	327

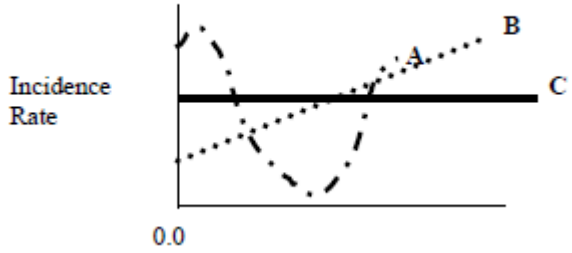
Each population has 100 subjects at risk at the beginning of the study. 40 deaths occur in Population A and in Population B, leading to identical values for the 4-year Cumulative Incidence of Death

40/100 = 0.40

Incidence Rate

An alternative measure of incidence is the Incidence Rate (also labeled as the Instantaneous Risk, Hazard Rate, or Incidence Density). It refers to the instantaneous risk of developing the outcome at a point in time during the follow-up period, among those at risk at that time. The value for the Incidence Rate may be constant over the period of follow-up or may vary over time, showing periods of high and low values. This is depicted by the three Incidence Rate functions, IR(t), that are shown in the following figure:

Examples of Incidence Rate functions (IR(t)).



A - The Incidence Rate function depicted by the "roller-coaster" graph (A) may pertain to a study that records deaths among patients undergoing a major surgical procedure (e.g. coronary bypass surgery or transplant

surgery). Patients may be at high risk of dying during and initially after the surgery, as depicted by the higher values for the Incidence Rate function. However, if patients survive this critical period, then they may go through a period of lower risk.

B - The Incidence Rate function depicted by the increasing line (B) might be expected from following subjects for a long period of time. As the follow-up time increase, the subjects at risk for developing an outcome at a point in time become older and are at higher risk for developing the outcome.

C - The Incidence Rate function depicted by the flat line (C) might be expected from a study with a short period of follow-up, where the risk of developing the outcome might not change over the period of follow-up.

Calculation of Incidence Rate

IR = (total number of cases of disease)/(total amount of person-time)

Year	Population A			Population B			Population C		
	# Deaths	Person-years	Incidence Rate	# Deaths	Person-years	Incidence Rate	# Deaths	Person-years	Incidence Rate
1	10	95	0.11	2	99	0.02	10	95.0	0.11
2	10	85	0.12	2	97	0.02	9	85.5	0.11
3	10	75	0.13	2	95	0.02	8	77.0	0.10
4	10	65	0.15	34	77	0.02	7	69.5	0.10
Total	40	320	0.13	40	368	0.44	34	327	0.10

The Incidence Rate function for Population C is roughly constant of the four years of follow-up. The value for the constant Incidence Rate is

IR = 34/(327 person-years) = 0.10(cases/1 person year)

Similar calculations can be performed for Populations A and B but the resulting values ,(0.13cases/person-year) for Population A and (0.44cases/person-year) for Population B, are weighted averages for the different values for the Incidence Rate functions for these populations. The weights for these calculations are the amounts of person-time for each age-specific Incidence Rate. Mathematically, this is shown for Population B by the following equation:

$$\mathbf{40/368py} = [99\mathbf{(2/99py)} + 97\mathbf{(2/97py)} + 95\mathbf{(2/95py)} + 77\mathbf{(34/7py)}]/\ [(99+97+95+77)py]$$

The units can also be expressed in different time-units as follows –

1 case / 1 person year = 1 (cases/person year)
= 1 (cases/52 person-weeks) = 0.0192 (cases/person-week)
= 1 (cases/365 person-days) = 0.0027 (cases/person-day)
= 10 (cases/person-decade)
= 100 (cases/person-century)

In general, if the value for the Incidence Rate is small or the time period of follow-up is short, then the value for Cumulative Interval during this time period can be calculated from the following formula

CI = IR x (length of time period)

Although the One-year Cumulative Incidence listed above is similar to what would be calculated from the data in the above Table (10/100 = 0.10), the four-year cumulative incidence overstates what would be calculated from that data (34/100 =0.34). More importantly, the value for the 20-year Cumulative Incidence is mathematically not possible, since the value for a Cumulative Incidence cannot exceed 1.0. The overstated values listed in this calculation reflect a problem of not accounting for the diminishing size of the population at risk as subjects are followed over time. The following formula shows the general association between the Cumulative Incidence and the Incidence Rate when the latter is constant over time

$$CI = 1 - e^{(-IR \times (\text{time period}))}$$

Using this general formula for Population C yields the following values for the Cumulative Incidence for the different time periods list above

$$\text{One-year CI} = 1 - e^{(-.10 \times 1)} = 0.10$$
$$\text{Four-year CI} = 1 - e^{(-.10 \times 4)} = 0.33$$
$$\text{Ten-year CI} = 1 - e^{(-.10 \times 10)} = 0.63$$
$$\text{Twenty-year CI} = 1 - e\ e^{(-.10 \times 20)} = 0.86$$

The values for the one-year and four-year Cumulative Incidence (0.10 and 0.33, respectively) are very similar to those obtained from the data in the above Table (0.10 and 0.34, respectively).

There is also a mathematical relationship between the Prevalence of a disease and the Incidence Rate of that disease when we have a **steady state**. The steady state assumption implies that the Prevalence and the Incidence Rate of the disease are constant over a time period for a population of fixed size.

If there are N people in the Population and P = the Prevalence of disease then at any time

$$\#\text{ diseased subjects} = N(P)$$
$$\#\text{ non-disease subjects} = N(1-P)$$

If the D = average duration of disease, then the Cure Rate would equal 1/D. Thus for the steady state to remain, the following equation must hold

$$\text{Number cured} = \text{Number disease} = N(P)(1/D) = N(1-P)(IR)$$

This implies,

$$P/(1-P) = IR \times D$$

It follows that is the Prevalence of disease (P) is small that

$$\mathbf{P = P/(1-P) = IR \times D}$$

The important message from this calculation is not the mathematical relationship between Prevalence and Incidence in a steady state, but the general principal that Prevalence is function of Incidence and disease duration.

Week 4 – Measures of Association

The **Causal Effect** of an exposure for an individual is the difference in the outcomes (Y) for that individual if given the exposure (Y_1) versus not given the exposure Y_0).

The **average causal effect of a risk factor for a population** is the difference in average counterfactual outcomes, $E(Y_1)$, when all members of the population receive the exposure and the average counterfactual outcomes ,$E(Y_0)$, when none of the members of the population receive it.

Average Causal Measures of Effect can be defined as

Casual Risk Difference = $E(Y_1) - (E(Y_0)$.
Causal Risk Ratio = $E(Y_1) / E(Y_0)$.
Causal Odds Ratio = $[E(Y_1) /(1-E(Y_1))] /[E(Y_0) /(1-E(Y_0))]$

(N.B. E(Y) refers to the statistical term of "expected value" of Y and represents the average (mean) of y)

Measures of Association

In epidemiology a **measures of association** compares the outcome measurement (Prevalence, Incidence Rate, …) in groups of subjects that are defined by categories of a risk factor of interest (exposure**).** Mathematically, **measures of association are either ratios or differences of an outcome measure in these groups**. In the absence of bias and confounding, these measures of association provide estimates for the causal effect of the risk factor on the outcome (measure of effect).

Outcome	Outcome Measure	Measure of Association
Nominal	Proportions (Cumulative Incidence, Estimated Risk) Incidence Rates Odds	Risk Ratio/Risk Difference Rate Ratio/Rate Difference Odds Ratio
Ordinal	Above Measures Medians (Percentiles)	Above Measures Ratio/Difference of Medians (Percentiles)
Continuous	Above Measures Averages	Above Measures Ratio/Difference of Averages

Binary Outcome

You only look at the D+ and the Total Columns in all these calculations (We will also need D- but only for Odds Ratio calculations)

A binary outcome may reflect a natural dichotomy (e.g. dead versus alive) or can be created from nominal, ordinal, or continuous outcome by collapsing categories (e.g. New York Heart Association Classes III and IV versus Classes I and II (Goldman et al.,1981)) or specifying a threshold value for a continuous variable to separate high from low outcomes (e.g. hypertension (SBP > 140) versus no hypertension). If the exposure of interest is also binary (e.g. current smoker vs. non-smoker), then data relating the exposure to the outcome can be displayed in a 2x2 table as follows"

Table displaying the relationship between a Binary Exposure (E, eg., smoking or non-smoking) and Disease (D) (eg., Death)

D

	+	-	Total
E+	a	b	N_1
E-	c	d	N_0
Total	M_1	M_0	T

If there are no losses-to-follow-up or losses due to competing risks, then the **Cumulative Incidence** of disease for the exposure groups provides estimates for the risk of disease for each group.

Cumulative Incidence (Risk) for a Binary Exposure

	Risk of Disease (Cumulative Incidence)	
Exposed Subjects (E+)	(# Death D+) / (# Exposed E+)	**$R_1 = a/N_1$**
Non-exposed Subjects (E-)	(# Death D+) / (# Not Exposed E-)	**$R_0 = c/N_0$**

Common Measures of Association based on Ratio or Differences of Estimated Risks

Risk Ratio (Relative Ratio)	Risk of Death for E+ / Risk of Death for E-	**$RR=R_1/R_0$**
Risk Difference (Attributive Risk)	Risk of Death for E+ - Risk of Death for E-	**$RR=R_1 - R_0$**
Disease Odds Ratio	Odds of Risk of Death for E+ / Odds of Risk of Death for E-	**$OR = [R_1 / (1 - R_1)] / [R_0 / (1 - R_0)]$**

Incidence Rate (Rate) for a Binary Exposure

	D+	Person-time	Incidence Rate
E+	a	K_1	**$R_1 = a/K_1$**
E-	c	K_0	**$R_0 = a/K_0$**
Total	M_1	T	

Risk Ratio (Relative Ratio)	Risk of Death for E+ / Risk of Death for E-	**$RR=R_1/R_0$**
Risk Difference (Attributive Risk)	Risk of Death for E+ - Risk of Death for E-	**$RR=R_1 - R_0$**
Disease Odds Ratio	Odds of Risk of Death for E+ / Odds of Risk of Death for E-	**$OR = [R_1 / (1 - R_1)] / [R_0 / (1 - R_0)]$**

Example of Cumulative Incidence and Incidence Rate

Exposure **E+ = Smoking**
E- = Non-Smoking

Outcome **D+ = Death**
D- = No death

Cumulative Incidence

	Outcome			
Exposure	**D+ (Death)**	**D- (No death)**	**Total**	**Risk**
Smoker (E+)	**788**	1393	**2181**	(# exposed dead / # exposed) = **788/2181 = 0.36**
Non-Smoker (E-)	**762**	1491	**2253**	(# not exposed dead / # not exposed) = **762/2253 = 0.34**

Risk Ratio = **RR** = Risk of death being exposed / Risk of death being not exposed = 0.36/0.33 = 1.06
Risk Difference = **RD** = 0.36 – 0.33 = 0.03

Incidence Rate

Exposure	**D+ (Death)**	**Person-Years**	**Incidence Rate (Deaths / 10,000 Person Years)**
Smoker (E+)	**788**	44,440	(# exposed dead / # exposed) = **788/4.44 = 177.31**
Non-Smoker (E-)	**762**	46,675	(# not exposed dead / # not exposed) = **762/4.67 =163.26**

Risk Ratio = **RR** = Risk of death being exposed / Risk of death being not exposed = 177/163 = 1.06
Risk Difference = **RD** = 177-163 = 14 (cases per 10,000 person-years)

It should be noted that **the label RR may refer to either a Risk Ratio calculation** or a Rate Ratio calculation. Often the term Relative Risk (also labeled RR) is used to describe either calculation. However, as shown in the previous example, the value for the Risk Ratio and Rate Ratio will tend to differ, and the use of a single tem (Relative Risk) to describe two different results may be confusing.

Among Exposed : Attributable Proportions / Attributable Fraction / Attributable Risk Percent

If R_1 is the risk of developing an outcome among an exposed subject, then a question of interest might be how much of the magnitude of R_1 is actually caused by the exposure. If R_0 is the risk that an exposed subject would have had in the absence of the exposure then $(R_1 – R_0)$ is the extra risk that is caused by the exposure and the proportion of R_1 that is attributed to the exposure is

$$\textbf{Attributable Fraction (Exposed)} = (R_1 – R_0)/R_1 = (R_1/R_0 – R_0/R_0) / R_1/R_0 = \textbf{(RR -1)/RR}$$

A similar question for consideration is what proportion of the **average risk** in a population is attributed to some members of that population having the exposure of interest. This is a more of a public health consideration as the answer is linked to a specified population with a specific prevalence of exposure (p). The average risk is a population is

$$R_T = pR_1 + (1\text{-}p)R_0$$

The portion of the average risk that is attributable to the exposure (Attributable Fraction – Population) is

$$\begin{aligned}(R_T – R_0)/R_T &= [pR_1 + (1\text{-}p)R_0 – R_0]/ [pR_1 + (1\text{-}p)R_0] \\ &= [pR_1 \text{-}pR_0]/ [pR_1 \text{-}pR_0 + R_0] \\ &= [p(R_1 – R_0)] / [p(R_1 – R_0) + R_0] \\ &= [p(R_1/R_0 – R_0/R_0] / [p(R_1/R_0 – R_0/R_0) + R_0/R_0] \\ &= \textbf{[p(RR -1)] / [p(RR – 1) + 1]}\end{aligned}$$

So, in summary,

Attributable Fraction – Exposed = (RR – 1)/RR
Attributable Fraction – Population = [p(RR -1)] / [p(RR – 1) + 1]

This quantity also can be estimated using the estimated risks (cumulative incidence) from population data and is referred to as the **Attributable Proportion** in the **Total Population** (Ashcengrau and Seage), **Attributable**

Fraction for the Population (Stata, Rothman), **Population Attributable Risk Percent** (Hennekens and Buring).

We use the same chart for Cumulative Incidence from the previous page to estimate Attributable Proportions as follows,

	Outcome			
Exposure	**D+ (Death)**	**D- (No death)**	**Total**	**Risk**
Smoker (E+)	**788**	1393	**2181**	(# exposed dead / # exposed) = **788/2181 = 0.36**
Non-Smoker (E-)	**762**	1491	**2253**	(# not exposed dead / # not exposed) = **762/2253 = 0.34**
Total	**1550**	2884	**4434**	(# total dead / # total) = **1550/4434 = 0.35**

Risk Ratio = RR = Risk of death being exposed / Risk of death being not exposed = 0.36/0.33 = 1.06

p = Prevalence of Smoking = # E+ / # total = 2181/4434 = 0.49

Attributable Fraction – Exposed = (RR – 1)/RR
= (1.0683 – 1)/1.0683 = 0.0639

Attributable Fraction – Population = [p(RR -1)] / [p(RR – 1) + 1]
= [0.4919(1.0683-1)]/ [0.4919(1.0683-1) +1] = 0.0325

Number needed to Harm and Number needed to Treat

	Outcome			
Exposure	**D+ (Death)**	**D- (No death)**	**Total**	**Risk**
Smoker (E+)	**788**	1393	**2181**	(# exposed dead / # exposed) = **788/2181 = 0.36**
Non-Smoker (E-)	**762**	1491	**2253**	(# not exposed dead / # not exposed) = **762/2253 = 0.34**

Risk Difference = RD = Risk of death being exposed - Risk of death being not exposed = 0.3613 - 0.3823 = 0.0231 = 231 / 10,000

Therefore, if 10,000 subjects smoked, rather than not smoking, then 231 extra deaths would have occurred, in other words,

231 extra deaths occurred if 10,000 subjects smoked
=> 1 extra death would have occurred if 10,000/231 = 43.29 subjects smoked

This is derived from –
231/10000 = (231/231 / 10,000/231) = 1/43.29 = 1/RD

The general formula for the

Number Needed to Harm (NNH) is

NNH = 1/RD

Similarly is an exposure (treatment) lowers the risk of developing an outcome ($R_1 < R_0$) then the

Number Needed to Treat (NNT) to prevent one case of disease is

NNT = $1/(R_0 - R_1)$ = $1/|RD|$

Regression Coefficients

The general formula for a straight line to describe linear relationship between two variables X and Y is

Y = mX +b, where
b = Y-intercept = value for Y when X=0
m = slope = change in Y when X changes by one unit

In epidemiology research, Y (dependent variable) represents a function of outcome measure and X (independent variable) represents an exposure (E) and the model is usually written as

f(outcome measure) = B_0 + B_1E, where
B_1 = slope = **change in f(outcome measure)/ unit change in E**

Logistic Regression

When the outcome is binary scale and the outcome measure is a proportion (P: prevalence, cumulative incidence) then the **logistic regression model** to describe the relationship between and exposure (E) and the outcome. The logistic regression model uses a function of P (logit: natural logarithm of the P/(1-P)) for Y, yielding the following formula

log(P/(1-P)) = B_0 + B_1E, where
B_1 = Δlog(P/(1-P)) / unit Δ in E

If the exposure is binary, labeled 1 for exposed subjects and 0 for non-exposed subjects, then

B_1 = $[\log(P_1/(1-P_1)) - \log(P_0/(1-P_0))] / (1-0)$
= $\log[P_1/(1-P_1)) / (P_0/(1-P_0))]$
= **log(OR)** , where
P_1 = outcome measure for exposed subjects; and
P_0 = outcome measure for non-exposed subjects.

Recall that Odds Ratio is defined as follows –

Odds = # with / # without

	Outcome			
Exposure	**D+ (Death)**	**D- (No death)**	**Total**	**Odds**
Smoker (E+)	**788**	**1393**	2181	For Exposed – (# dead) / (# not dead) = **788/1393 = 0.5657**
Non-Smoker (E-)	**762**	**1491**	2253	For not Exposed – (# dead) / (# not dead) = **762/1491 = 0.5111**

Therefore, Odds Ratio = 0.5657 / 0.5111 = 1.1068

If we were to fit a logistic regression model to the above data in the FHS dataset, we would have gotten,

log(P/(1-P)) = -0.6713 + **0.1015**(Smoker)
=> **B_1 = 0.1015 = log(OR)**
OR = e^(0.1015)) = 1.1068 …….. i.e., same as above

Week 5 – Study Designs

A study design is a plan (proposal) to enroll subjects, collect data, and analyze the data to draw inference. In epidemiology, studies can be characterized by their design. A commonly sited list of study designs that will be discussed in this course is

1. Case Reports
2. Ecological Studies
3. Cross Sectional Studies
4. Experimental Studies
5. Cohort Studies
6. Case Control Studies

5.1 Case Reports

Case Reports are detailed descriptions of unexpected and unusual symptoms, disease, treatments, and outcomes of individual patient(s). Because of the unexpected nature of their findings, case reports often serve as a basis for **hypothesis generation** and for springboards for future studies.

Examples of Case Reports

"In the period October 1980 – May 1981, 5 young men, all active homosexuals, were treated for biopsy-confirmed *Pneumocystis carinii* pneumonia at 3 different hospitals in Los Angeles, California"

Editorial Note: "*Pneumocystis* pneumonia in the United States is almost exclusively limited to severely immunosuppressed patients. The occurrence of Pneumocystis in these 5 previously healthy individuals without a clinically apparent underlying immunodeficiency is unusual"

CDC – MMWR June 5 1981 /30(21); 1-3
www.cdc.gov/hiv/resources/reports/mmwr.1981.htm

"During the past 30 months, Kaposi's Sarcoma (KS), an uncommonly reported malignancy in the United States, has been diagnosed in 26 homosexual men (20 in New York; 6 in California)."

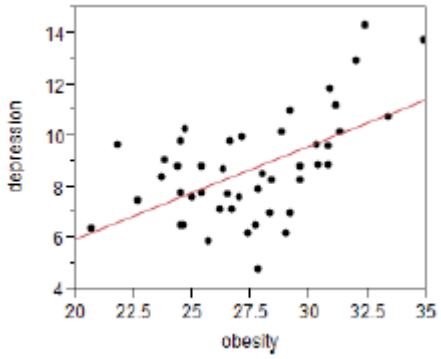
Editorial Note: … "The occurrence of this number of KS cases during a 30 month period among young homosexual men is considered highly unusual."

CDC – MMWR July 4;30:306-8

5.2 Ecologic Studies

Ecologic Studies (correlation studies) examine the relationship between two factors on a population level, rather than on an individual level. The unit of the analysis is a population, rather than an individual subject.

For example, the following figure shows the relationship between the prevalence of depression and the prevalence of obesity in the United States. Each point in the figure corresponds to the prevalence of these two characteristics for a particular state.



In general, states with higher prevalence of obesity tend to have higher prevalence of depression. However, does this imply that obesity causes depression or that depression causes obesity **in individuals**? The problem is that these data do not tell us if the inhabitants of a particular state who suffer from depression and the same individuals who are obese.

The **Ecologic Fallacy** refers to the potential for incorrectly assuming that an association that exists on a population level reflects an association on an individual.

In the above study, although, on the state level, we see a positive relationship between obesity and depression (as the prevalence of obesity increases over states, so does the prevalence of depression.However the opposite relationship is seen among individuals within states (obese individuals are less likely to be depressed).

5.3 Cross Sectional Studies (Prevalence)

Cross-Sectional Studies (Survey Studies) report the prevalence of an exposure and a disease in a population at a point in time. For example, the following table from the FHS teaching data set reports the cross-sectional relationship between smoking status and the existence of coronary heart disease at the 1956 examination.

	CHD		Total	Prevalence of CHD
	Yes	No		
Smokers	86	2095	2181	86/2181 = 0.0394
Non-Smokers	108	2145	2253	108/2253 = 0.0479

Cross Sectional studies report prevalence outcomes. These data show that the prevalence of CHD is lower among smokers compared to non-smokers. As noted in earlier lectures on prevalence, the challenge is with the interpretation of any association found in such studies. For example, since prevalence is a function of incidence and duration of disease, two possible explanations for this association are:

1. Smokers have lowers risk (incidence) of developing CHD (unlikely)
2. Smokers who develop CHD have shorter duration of survival

For, any association, there are three additional generic explanations to consider:

1. **Bias**
2. **Confounding**
3. **Chance**

Bias refers to a flaw in a study design that leads to an invalid result. Biases can be characterized into two major types: **selection bias** and **measurement bias**.

A **selection bias** may occur in a Cross-Sectional study when the disease of interest might differentially influence the selection exposed and non-exposed subjects (or the exposure might differentially influence the selection of diseased and non-disease individuals). For example, the Framingham Heart Study initially enrolled 5209 subjects but only 4434 of them are included in the above table. Perhaps the non-attending smokers had a higher prevalence of CHD and not attend the exam because of limitations due to the CHD.

A **measurement bias** pertains to the errors and measurement or classification of the exposure or the disease (or any other factor in a study). For example, perhaps smokers see their physicians less often and are tested less often for CHD. This might lead to an under-reporting of the true prevalence of CHD among smokers in a study. There are two general types of measurement bias:

1. **Random Misclassification** (non-differential misclassification) occurs when the errors in classification of disease are the same in the exposed and nonexposed groups

2. **Non-Random Misclassification** (differential misclassification) occurs when the errors in classification of disease are different in the exposed and nonexposed groups

Confounding refers to the existence of a third factor that has different distributions in the exposed and non-exposed groups and is also a risk factor (or a determinant) of the disease. For example suppose that the 2181 smokers in the above table are younger than the 2253 non-smokers. Younger people have lower risk (incidence) for developing CHD, leading to lower prevalence of CHD. Hence, the lower prevalence among the smokers in the table is not due to smoking but to the younger age of the smokers.

Chance refers to sampling variability in the selection of subjects for a study (a sample) from a larger population of potential subjects. For example, the 2181 smokers in this study can be considered as a sample of a larger population of smokers who could have enrolled in the Framingham Heart Study. Although we expect the prevalence of CHD within a sample of subjects will estimate the prevalence of CHD in the larger population, the estimate from one sample may overestimate or underestimate the prevalence of CHD in the population.

In addition to these potential reasons for the observed association, there is another possible explanation for an association like this in a Cross Sectional study:

6. The disease outcome may influence the incidence of the exposure (**reverse causation – only in Cross Sectional Study**).

Perhaps the most likely explanation for the lower prevalence of CHD among smokers, is the reason for the lower prevalence of smoking among cases of CHD, compared to non-cases. It is very likely that smokers who developed CHD stopped smoking soon after the disease was diagnosed.

Examples of Survey Data Sets

Cross Sectional studies are often based on routinely collected survey data. For example the **National Center for Health Statistics (NCHS)** is part of CDC and performs both annual and periodic survey in this country through personal interviews or examinations and by data collected from vital and medical records. Four major survey programs of the NCHS are

1. National Health and Nutrition Examination Survey (NHANES)
2. National Health Interview Survey (NHIS)

3. **National Health Care Surveys** (survey of health care providers and organizations
4. **National Vital Statistics System (NVSS)** (records information on births and deaths

Information and the National Health and Nutrition Examination Survey (NHANES) can be found at http://www.cdc.gov/nchs/nhanes/about_nhanes.htm

Information on the National Health Interview Survey (NHIS) can be found at http://www.cdc.gov/nchs/nhis.htm

Finally, the data used above to describe an ecologic study was obtained from reports for the **Behavioral Risk Factor Surveillance System (BRFSS).** Information about this survey can be found at http://www.cdc.gov/brfss/

5.4 Experimental Studies

Two major categories of epidemiologic studies are:

1. Experimental Studies
2. Observational (Non-Experimental Studies)

The key distinction between these two types of study designs is the role of the investigator. **In an experimental study, the investigator has the active role of assigning subjects to treatment (exposure) groups for the primary purpose of evaluating the effect of that treatment on an outcome**. On the other hand, in **observational studies exposures (including treatments) are self-selected or determined by someone else (e.g. one's physician) for a primary reason other than evaluating the effect of the treatment. The role of the investigator is passive, to observe outcomes and measure the association between an exposure and an outcome**.

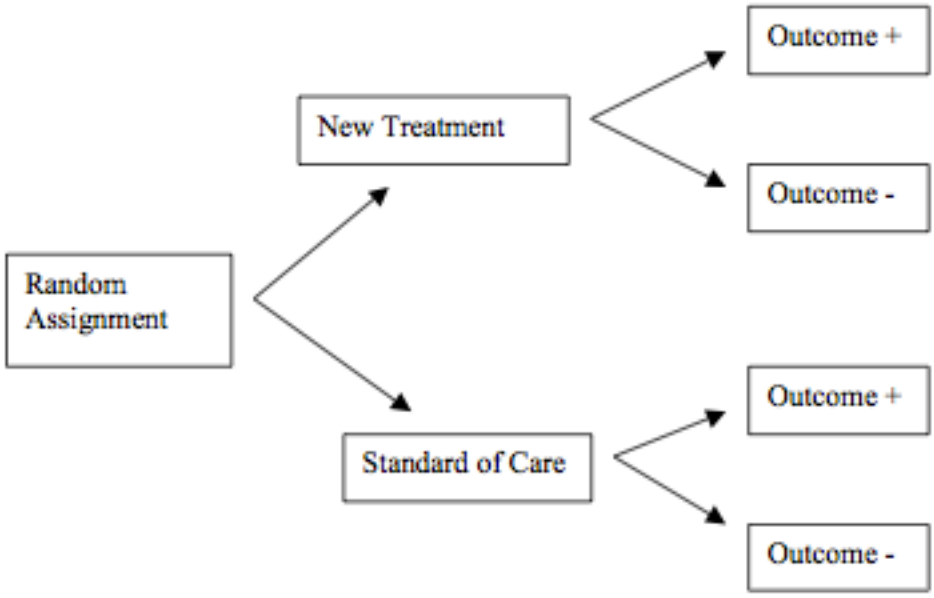
Experimental Study

For example, suppose and investigator wished to evaluate the effect of daily consumption of a low dose aspirin on the risk of developing a myocardial infarction (heart attack). **In an experimental study the investigator might assign some subjects to a regimen of daily low aspirin and assign others to a placebo drug**. Usually the assignment is dictated by some type of randomization, whereby each subject has an equal chance of assignment to either group. The use of a **placebo** and **randomization** will be discussed later in these lecture notes.

Observational Study

In an observational study the investigator might enroll a series of subjects who report taking daily aspirin and a comparison group of non-aspirin users. The reasons for aspirin use in the first group might because of a **personal decision** (subjects anticipating some benefit from daily aspirin use) or at the **recommendation** by one's physician (for disease prevention). One concern with such a study is the group taking aspirin might differ with respect to many indications (confounders) that are risk factors for the outcome.

The type of experimental study described above is often referred to a randomized controlled trial or a **randomized clinical trial (RCT)** if it performed in a clinical setting. The following figure describes the basic principles of a Randomized Clinical Trial comparing outcomes for patients who are randomized to receive a new treatment versus receiving standard of care.

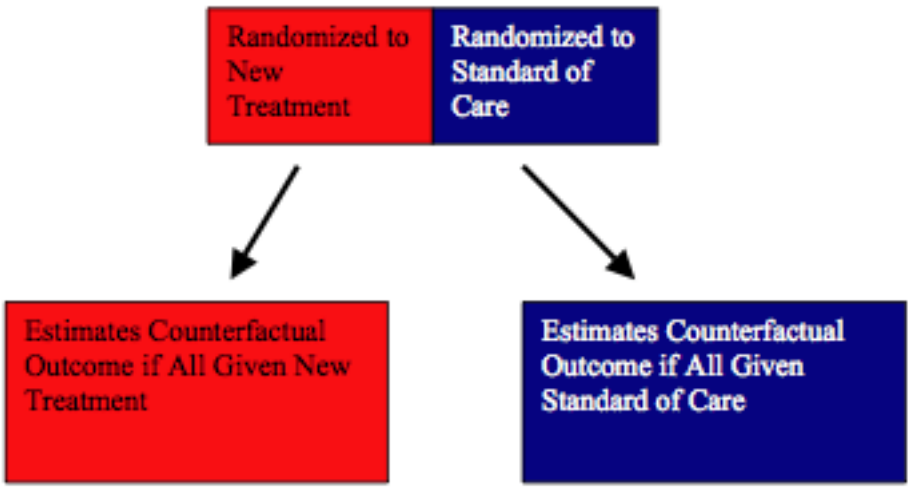


Why Randomization produces true factual and counterfactual estimates

As mentioned previously, the practical problem in measuring the causal effect of a treatment is that only one counterfactual outcome can be observed for any study participant. However, subjects who are randomized to receive the new treatment can be considered a **random sample** of all study subjects. **Therefore, their factual outcomes can estimate the counterfactual outcomes for all study subjects, if everyone received the new treatment.**

Similarly, the subgroup of subjects who are randomized to receive the standard of care can be considered a random sample of all study subjects, and their factual outcomes estimate the counterfactual outcomes of all study participants if none were received the new treatment (i.e. all received the standard of care).

This is depicted in the following figure



It follows that a Measure of Association comparing the actual (factual) outcomes in the two comparison groups will estimate the causal effect of the treatment, provided that

1. there is no confounding
2. there are no bias

Ethics: The State of Equipoise

Since the investigator assigns treatment, usually at random, in an experimental study, ethical issues are a major concern. If the assignment was based on a random coin flip then approximately half of subjects will receive the new treatment and the other half will receive the standard of care. Therefore, the investigator must have enough confidence in the new treatment to justify giving it to half of the study participants; while at the same time have enough confidence in the new treatment to withhold it from the other half of the patients. This balance opinion about the risk and benefits of a treatment is referred to **as equipoise.**

Imagine that you have just suffered a myocardial infarction and have been rushed to the emergency room of a nearby hospital. How would you react if you observed a physician reaching into his/her pocket and flipping a coin to make a treatment decision. One would hope that treatment decisions are grounded on solid clinical judgment; however a coin flip is a reasonable action to take when a treating physician is in a state of equipoise.

Randomization Methods

The main motivation for randomization is to remove the effect of participants and their physician in treatment decision. Random assignment is not influence by patients' characteristics. Therefore, especially in a large randomized trail, the investigator should expect the comparison groups to be comparable with respect to other factors that might influence the risk of developing the outcome. However, for small trials it is possible that some imbalance in the distribution of risk factors may occur and require adjustment in the analysis.

Simple Randomization

Simple randomization implies that the probability of treatment assignment for one study participant is not influenced by that of another participant. Although randomization is usually determined by a table of random number or a computer generated series of random numbers, simple randomization could be thought of as determined by a coin flip for each participant.

Block Randomization

An alternative to simple randomization is block randomization. Here subjects are assigned to treatment groups in blocks with the condition that equal numbers of participants within each block may be assigned to each treatment group. For example, if the treatments under consideration are labeled A and B, then possible sequences of treatment assignments with a block size of 4 are

AABB ABAB ABBA BBAA BABB BAAB

One potential drawback of block randomization is the potential to determine the treatment assignment of the next participant who enrolls in a study. This potential problem can be avoided by blinding everyone (except for the person performing the randomization) from the block size or by changing the block size during the enrollment period. Blocking is often used along with stratification to essentially guarantee the similarity of the distribution of a risk factor in the treatment groups. Suppose a study was performed at multiple sites and an investigator wished to have similar distribution of study site within each treatment group to balance the baseline care offered at each group. This can bed accomplished by using a separate block randomization within each site (stratum). For example the following table demonstrates the use of stratification and blocking in a study performed at three sites.

Study Site	Number of Participants	Selected Assignment Sequence
I	12	ABBA
		ABAB
		BABA
II	8	AABB
		ABBA
III	4	BBAA

Blinding

As mentioned above, a measure of association from a RCT estimates the causal effect of a treatment in the absence of confounding and bias. Randomization reduces the potential for confounding, especially in large trials.

However, post randomization selection-bias can still occur due to losses-to-follow-up. In addition, measurement bias can occur in a RCT because of non- compliance with treatment assignment or with outcome detection. **Blinding is one means for limiting the potential for these biases.**

Blinding refers to masking knowledge of the treatment assignment from individuals who might influence the compliance with treatment or the detection with the outcome.

Blinding the study subjects also eliminates the potential for errors in self-reported outcomes to be related to treatment assignments. In addition, a study subject with a preference for one of the treatment options might be less likely to comply with the assigned treatment is he/she knew that it was not the preferred treatment. This, blinding study subjects may also reduce the potential for non-compliance.

Blinding other physicians who are providing ancillary care to study subjects may also limit the potential prescription of other therapies that might influence compliance of assigned treatment by the study subjects.

In non-clinical trails examining the effect of a preventive agent, the comparison to treatment is often no treatment. In such instances, a placebo agent is often used to enhance the blinding of study subjects. A placebo may also be used in a clinical trial, *but a standard of care is typically chosen to evaluate the effect of a new treatment because of ethical considerations.*

Run-In Phase

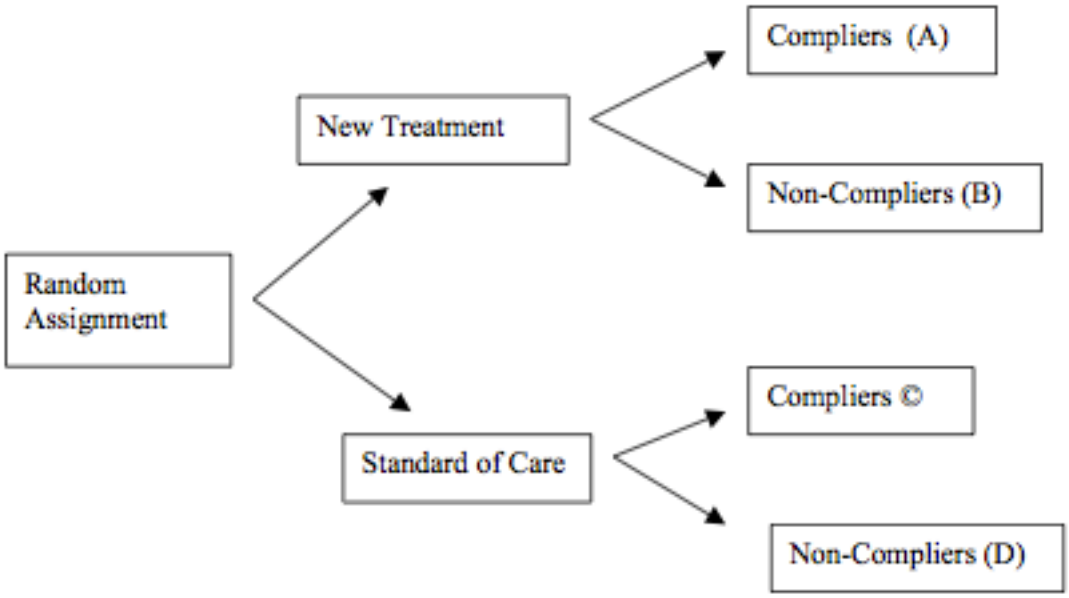
Another means to increase assigned treatment compliance is to enroll only participants who are likely to adhere to their assigned treatment. **The identification of such subjects might be accomplished during a pre-randomization trial period (Run-In Phase), where potential subjects are given a trial period of active or placebo treatment.** Non-compliers during this period would be likely to remain non-compliers after randomization, and therefore are not enrolled in the actual trial. The use of a Pun-In Phase will be discussed in more detail later in these notes when referring to the Physicians' Health Study.

Data Safety Monitoring Board

The role of a Data Safety Monitory Board (DSMB) in a RCT is to monitor and protect the safety of the study participants. This board is usually comprised of outside scientists who are not involved in the study at hand. The DSMB can recommend termination of the study when it is no longer in a state of equipoise and feels that the study participants would be better served with the superior treatment.

Analytic Issues

The following figure displays the potential comparison groups for evaluating the effect of a new treatment in a RCT.



An **Intention to Treat (ITT)** analysis **compares outcomes for subjects who are randomized to receive a new treatment (A+B) to those who are randomized to receive a standard of care (C+D)**. However, the presence of non-compliers in the treatment group (B), weakens the ability to detect an effect of the new treatment as not all subjects in the group who are assigned to the new treatment (A+B) will actually receive the benefit of the new treatment.

An **On-Treatment Analysis compares outcome only among those who comply with treatment assignment (i.e. compares outcomes in groups A versus C**). This analysis might have the advantage over the ITT analysis to detect an effect of the treatment since all subjects in this analysis are compliers. However, this analysis no longer has the advantage of randomization to provide comparison groups that are free of confounding.

Table 1 in a RCT typically displays the distribution of demographic features and potential risk factors for the outcome in the two treatment groups.

Table 2 of a RCT typically displays the overall effect of the treatment on the primary outcome(s). It is usually based on an Intention-to-Treat Analysis.

Physicians' Heath Study

The Physicians' Health Study (PHS) was a randomized prevention trial with the primary aims to examine if

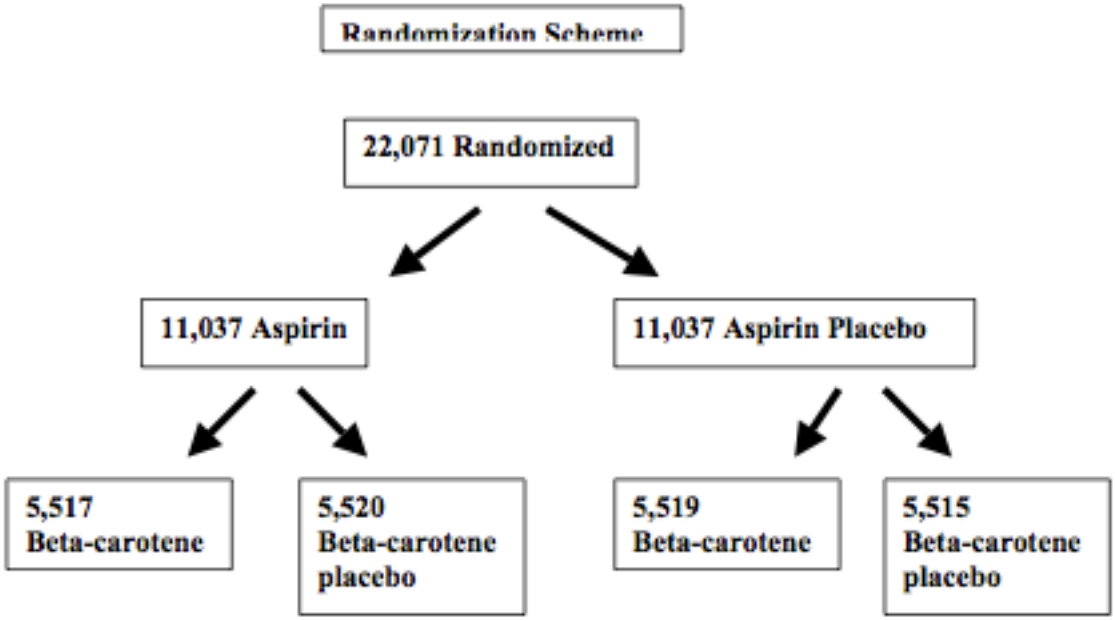
1. 325mg of aspirin taken every other day reduces cardiovascular disease mortality, and
2. 50 mg of beta carotene taken every other day reduces incidence of cancer

In 1981 the investigators sent invitation letters, consent forms, and enrollment questionnaires to 261,248 male physicians, 40 - 84 years of age, living in the US and registered with the American Medical Association. The following table (provided by Julie Buring) displays the final enrollment numbers in this trial
Only 112,528 physicians responded to the invitation, and 59,285 expressed a willingness to participate in the

study. However, 26,062 were ineligible because if a variety of reasons including a history of CVD or cancer; current renal or liver disease; peptic ulcer; gout; or contraindication to or current use of either aspirin or beta-carotene.

The remaining 33,223 were enrolled in a Run-In Phase during which all received active aspirin and placebo beta-carotene. After 18 weeks, participants were sent a questionnaire asking about their health status, side effects, compliance, and willingness to continue in the trial. 11,152 changed their minds, reported a reason for exclusion, or did not reliably take the study pills. This resulted in 22,871 remaining participants for randomization

The PHS uses a 2x2 factorial design whereby each subject underwent two levels of randomization as depicted by the following slide (provided by Julie Buring).



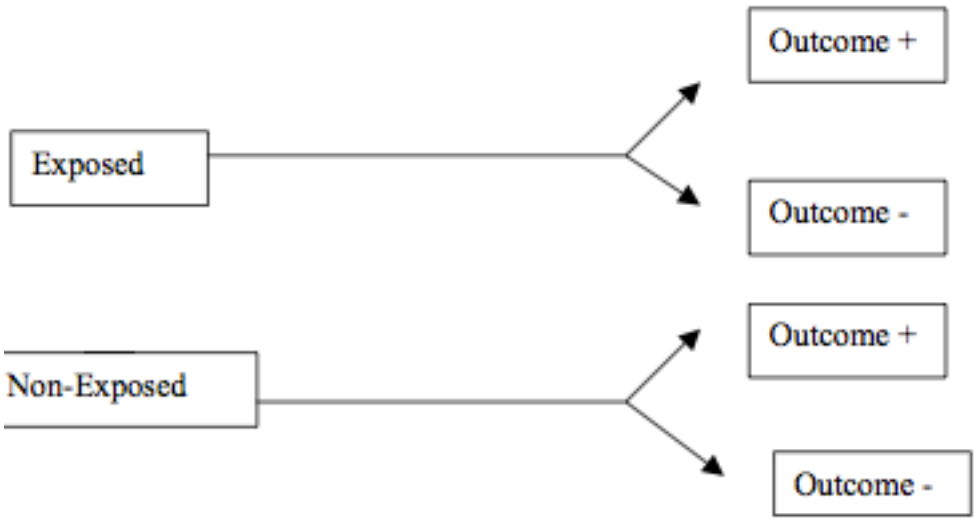
A factorial design allows for the estimation of multiple treatments on the same subjects in a single treatment. The following table displays the comparison groups to examining the two aims of the PHS.

Week 7 – Cohort Study Design

The basic components of a Cohort Study design include:

1. Enrolling subjects at-risk for developing the outcome
2. Measuring exposure status on study participants,
3. Following subjects over time, and
4. Recording outcomes.

This describes the same general features of randomized controlled trial (RCT) in the last series of lectures. The RCT is a special case of a cohort study with the defining feature that the investigator assigns exposure status, usually with a randomization device, for the purpose of evaluating the effect of the exposure on an outcome. In the general Cohort Study design, exposure is typically not determined otherwise by the investigator and not for the primary purpose of examining the effect of the exposure on some outcome. The general features of a cohort study are described by the following figure.



Suppose an investigator wished to study the association between smoking (exposure) and the incidence of a first CHD event. This would require enrolling subjects who are free of CHD and at risk for a first CHD event. There are numerous options for measuring the exposure of interest, smoking. Some are contained in the following list:

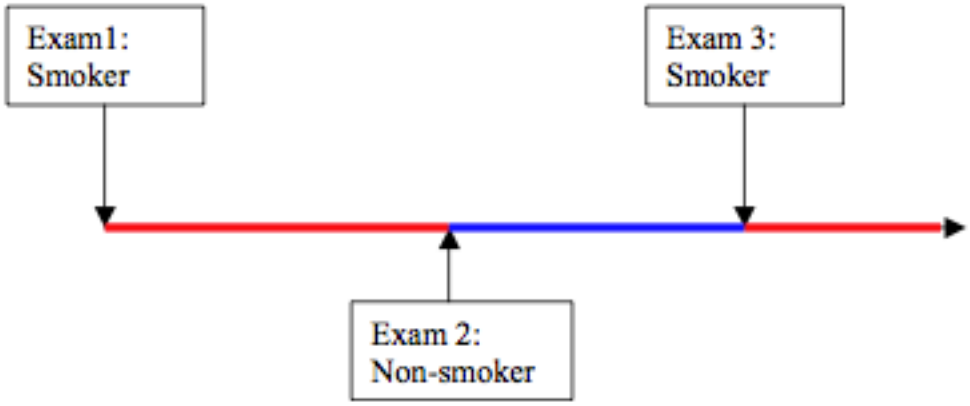
1. Smoking versus not smoking at baseline
2. Extent of smoking at baseline (non-smoker vs. light smoker vs. heavy smoker
3. Number of cigarettes smoked per day at baseline

...

One option is to classify subjects according to their baseline smoking status (static measurement) as smokers or non-smokers. This classification does not take into account any changes in smoking status that occurs during a follow-up period, meaning that some of the subjects classified as smokers at baseline might later become non-smokers and some of the non-smokers may become smokers. Baseline smoking also does not reflect the duration and extent of past smoking.

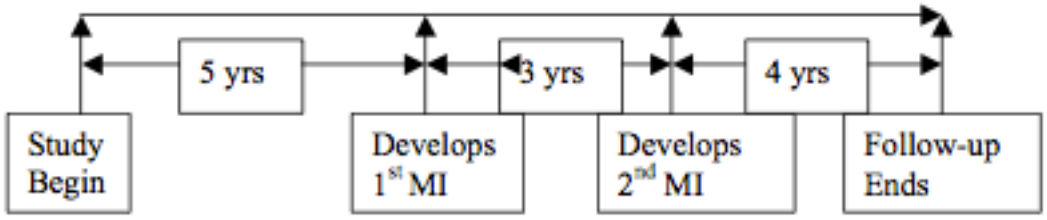
Having enrolled at-risk subjects and determined the appropriate method for measuring exposure, the investigator then needs to decide how to follow subjects over time and record outcomes. Follow-up is recorded in the Framingham Heart Study by having each subject return to an examination center every two years (biennial exams). In the Nurses Health Study follow-up questionnaires are sent by mail every two years. Alternatively, if the subjects are members of an insurance plan then follow-up information may be available through medical records or billing records.

If a person changes smoking status during a follow-up period then he/she can contribute person-years to the calculations of the CHD Incidence Rate for both the smoking and non-smoking group. In addition, if this person developed CHD during the follow-up period, then he/she will also contribute an outcome case to the calculation of one of these Incidence rates. For example, the following figure describes the person-years of follow-up for an individual in the FHS teaching data set who was a smoker at the first exam, a non-smoker at the second exam, and returned to be a smoker at the third exam. This person contributes person-time to both the smoking (red lines) and non-smoking group (blue lines).



Finally the investigator needs to determine which outcomes to record during the follow-up period. For non-fatal events, one question to address to how to handle repeated events. For example, a subject may develop and survive multiple myocardial infarctions (MI, heart attacks) during the follow-up period. A common practice is to focus on only the first of such multiple events and stop the follow-up period at the time of the first myocardial infarction. Once a person develops a myocardial infarction he/she is no longer at risk for developing a first myocardial infarction.

Alternatively, multiple events could be taken into account by dividing each subject's follow-up time into periods when he/she is at risk for different events. For example, the following figure describes the follow-up experience for a subject, who developed a first MI after 5 years of follow-up, second MI 3 later, and is followed for another 4 years until the study ends. This person would contribute 5 person-years of follow-up to the denominator and 1 case to the numerator for the calculation of the incidence rate for developing a first MI. He would contribute 3 person-years of follow-up to the denominator and 1 case to the numerator for the calculation the incidence rate for developing a second MI. He would also contribute 4 person-years of follow-up and nothing to the numerator for the calculation of the incidence rate of developing a third MI.



The incidence of developing an outcome in a cohort study potentially can be measured in two ways:

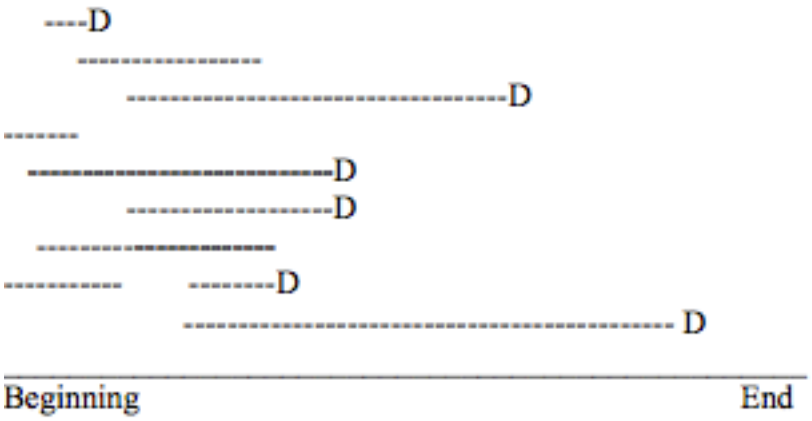
1. Cumulative Incidence
2. Incidence Rate

The Cumulative Incidence requires that all subjects be followed for a fixed period of time and that there be no losses-to-follow-up or losses due to no longer being at risk during the follow-up period because of a competing event (for example dying from another cause). The Incidence Rate requires that the reason for terminating follow-up not be related to the risk of developing the outcome.

Open vs. Closed Cohort

An Open Cohort is a dynamic population with migration into and out of the cohort occurring during the follow-up period. Exposure status may change over time so that the same subjects can contribute person-time to

different exposure groups. The outcome measure in an open cohort is the Incidence Rate. The following figure shows the general features of an open cohort study.



Closed Cohort - No losses to follow-up, Outcome Measure = Cumulative Incidence or Incidence Rate

A Closed Cohort has a common starting point and fixed potential period of follow-up for all subjects. For example, the Framingham Cohort Study started in 1948. It enrolled 5,209 subjects in 1948 with the plan to follow all subjects for 20 years. Exposure is defined at the start of the follow-up and does not change over time. There are no losses-to-follow-up.

Fixed Cohort - Possibility of loss to follow-up (eg, FHS combination of closed/fixed)

A Fixed Cohort is similar to a closed cohort with the exception that there are some subjects who are lost-to-follow-up. The Framingham Heart Study with the outcome of all-cause mortality and sex as an exposure is an example of a Closed Cohort as there is complete ascertainment of this outcome on all subjects. On the other hand, if the outcome is the development of CHD then it should be considered as a Fixed Cohort as some subjects are lost-to-follow-up and their subsequent development of CHD is unknown. Also, there are other subjects who die from non-CHD causes (competing risk) and therefore are no longer at risk for developing CHD.

Prospective versus Retrospective Cohort Studies

The distinction between a Prospective and Retrospective Cohort Study concerns the two time periods involved in a cohort study: the time period spent by the investigator to perform the study and the time period spent by the study subjects when they were followed and at-risk for developing the outcome. The Study Period is the time period spent by the investigator to perform the study. The Follow-up Period is the time period in which subjects at risk and followed to ascertain outcome of interest.

Prospective Cohort Study

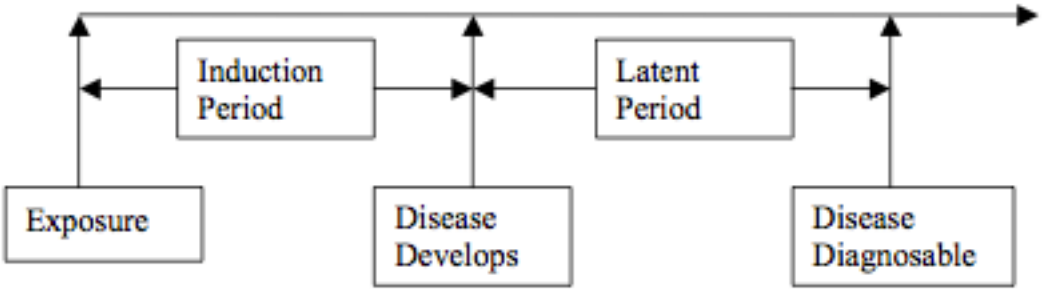
For example, suppose an investigator received grant funding and begins working on a study on 1/1/12, the start of the Study Period. If the investigator enrolls at risk subjects on that date and follows them for the next 5 years to record outcomes, then the Follow-up Period also begins on that date. This is an example of a Prospective Cohort Study. Under this design all outcome cases occur after the beginning of the Study Period.

Retrospective Cohort Study

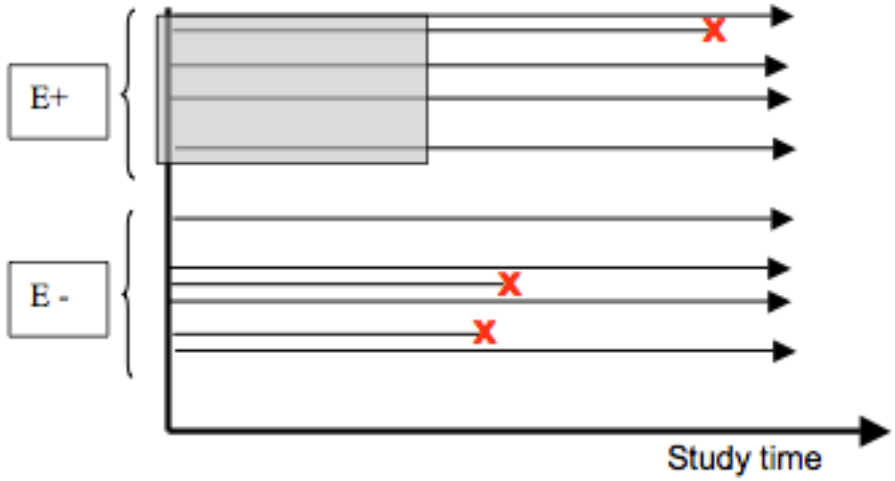
Suppose that, at the start of the Follow-up Period (1/1/12), the investigator began reviewing medical records to establish an at-risk cohort that existed 10 years ago and then followed that cohort through the medical records to see which of these subjects had developed outcome in the past 10 years. This is an example of a Retrospective Cohort Study. Under this design all outcome cases occur before the beginning of the Study Period.

Induction Period

The Induction Period is the time between the exposure to a risk factor and development of disease. For example, a woman might be exposed to radiation on a specific data and 3years later might develop the first evidence of leukemia. However, it may take additional time for the disease to reach a state where it can be diagnosed by current technology. The Latent Period is time period between disease development and the ability to detect it. Often these periods are combined and referred to as the Empirical Latent Period. These time periods are depicted in the following figure:



Suppose that Induction Period for a particular exposure to cause a disease is 3 years and the Latent Period to be able to detect this disease is another 2 years. Any disease outcome that occurs within 5 years of the exposure could not be caused by the exposure. This implies that person-time and outcomes that are observed during the Induction Period and Latent Period among exposed subjects should not contribute to the calculation of the Incidence Rate for the exposed group. The shaded area in the following graph (provided by Heather Baer – EPI208, 2012) pertains to person-time for the exposed group during the Induction and Latent Periods. This experience should not be included in the calculation of the Incidence Rate for the exposed group.



Bias

Measurement Bias can occur in a Cohort Study, as in any study. One example is if the detection of the outcome is performed differently for exposed and non-exposed groups, resulting in a potential for a non-differential misclassification (detection bias). For example, suppose an investigator wished to examine the relationship between Oral Contraceptive use and the incidence of Breast Cancer. If women or their physicians suspected a causal link between these factors, then women taking oral contraceptive might see their physicians more often and be tested more often for breast cancer, compared to women not taking oral contraceptives.

Another example of a measurement bias in a cohort study might occur when knowledge of the exposure status for an individual may influence (consciously or unconsciously) the classification of outcome status by an

interviewer. One method for avoiding this bias is by blinding the interviewer to the exposure status of the study subjects or, if this is not possible, blinding the interviewer to the study hypothesis.

Selection bias can also occur in a cohort study due to losses-to-follow-up. This may **occur if the reason for the loss if related to the risk of the developing the outcome and also to the exposure.**

Confounding

Confounding can occur in a Cohort Study if risk factors (determinants) of the disease are related to the exposure of interest. For example, the following table describes the age, blood pressure, and sex distribution among current smokers and non-smokers in the FHS teaching data set.

	Smokers	Non-Smokers
Mean Age	48.1	51.7
Mean SBP	129.8	135.9
% Male	53.9	34.1

Smokers are younger than non-smokers but also have higher average blood pressure and a great percentage of males than non-smokers. These imbalances provide alternative explanations for any difference in CHD outcomes that might be observed when comparing smokers to non-smokers.

Strengths and Limitations of Cohort Studies

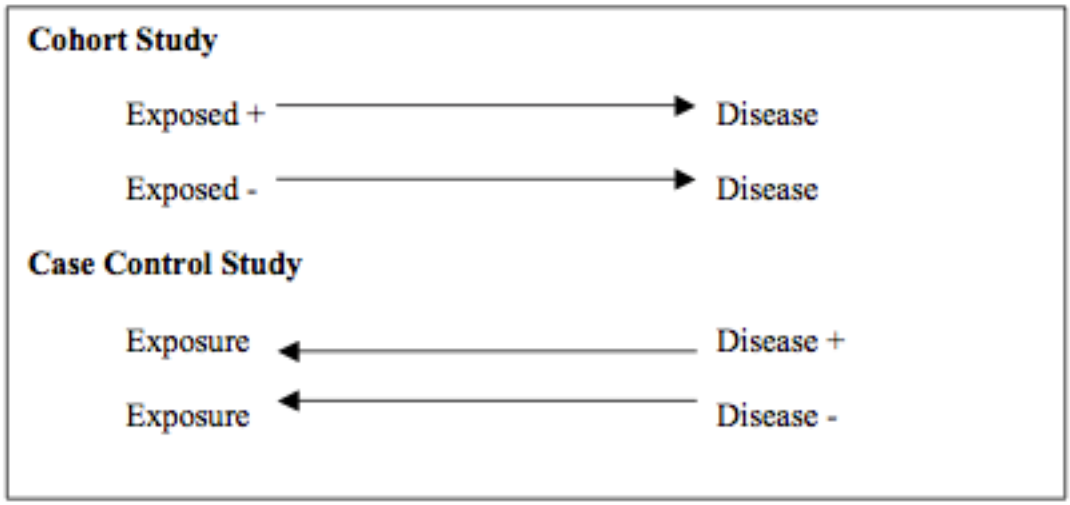
Cohort Studies can examine the effects of single exposure on multiple outcomes. Unlike Cross Sectional Studies, Cohort Studies can elucidate temporal relationship between exposure and disease. They allow direct measurement of incidence of disease in exposed and unexposed groups, as well as calculating various measures of association. Carefully planned and implemented Prospective Cohort Studies may reduce the potential for measurement and selection bias.

Other the other hand, **Cohort Studies may not be efficient for study rare diseases because of the need to enroll large number of subjects and follow them for long periods to time to record enough cases of the disease.** Prospective Cohort Studies can be expensive in terms of time and money. Retrospective Cohort Studies are more efficient but require the existence of previously collected data of adequate quantity and quality. Biases due to losses-to-follow-up are a potential problem to both Prospective and Retrospective Cohort Studies.

Week 8 – Case Control Studies

A Prospective Cohort Study is not efficient for investigating a rare disease outcome because of the large number of study subjects and/or the long period of follow- up that are needed to obtain a sufficient number of cases of disease. In this situation the Case Control Study is a more efficient alternative design to consider.

The classical description of a Case Control Study is a study that compares previous exposure histories among a group of study subjects who have the disease in question (cases) and a group of subjects who do not have the disease (controls). This description and its relationship to a Cohort Study are depicted in the following figure:



Two important questions related to this description of the Case Control Study design are:

1. What criteria should be used to select the controls?
2. Does comparing exposure history among cases and control result in a measure of association that estimates the causal effect of the exposure on the disease, as in a Cohort Study?

To address the first question, suppose an investigator wished to examine the effect of oral contraceptive use on the risk of breast cancer with a Case Control Study. According to the above description the investigation would enroll cases (women with breast cancer) and controls (women without breast cancer). Suppose the cases were women diagnosed with breast cancer at local hospitals and, for convenience, the investigator wanted to enroll controls from the same hospital. Would any group of women without breast cancer be appropriate controls? For example, would newborn baby girls in the nursery be an appropriate control group? They are free of breast cancer but almost everyone would agree that they are not appropriate for examining the effect of oral contraceptive use on the risk of developing breast cancer. Therefore, some other characteristic is needed to define an appropriate control group.

The answer to what is an appropriate control group lies with the link between Case Control Studies and Cohort Studies. This link is formed by considering the cases in a Case Control Study to be the outcomes from a corresponding Cohort Study. Sometimes this is true by definition, if the cases were taken from a registry of outcomes in a previously documented Cohort Study. However, in many situations the cases are selected from a hospital or health care plan and were not part of a previous performed Cohort Study. Nevertheless we can still entertain the notion that a cohort of subjects existed in the past and if it were followed over time, then its outcomes would be the cases in our Case Control study. Under this assumption, the role of the controls in a Case Control Study is to provide in estimate of the prevalence of exposure in that Cohort Study. If this holds, then comparing previous exposure history among cases and controls yields estimates of measures of association that were previously discussed for Cohort Study.

Exposure Odds Ratio

The link between the controls in a Case Control Study and a Cohort Study can be quantified as follows,

	Case (D+)	Control (D-)
Exposure + (E+)	a	b
Exposure – (E-)	c	d
Total	M_1	M_0

Exposure Odds Ratio is obtained by comparing the odds of D+ vs the odds of D-

Exposure Odds Ratio = EOR = (a/c) / (b/d)

Mathematically, many measures of association from Cohort Study can also be expressed as a ratio of exposure odds. For instance,

	Disease +	Disease -	Total
Exposure + (E+)	A	B	N_1
Exposure – (E-)	C	D	N_0

Risk Ratio = RR = (A/N1) / (C/N0)
= (**A/C**) / (N1/N0)

Disease Odds Ratio = DOR = (A/B) / (C/D)
= **(A/C) / (B/D)**

The second equation for the Risk Ratio (RR) demonstrates that is can also be calculated by dividing the odds of exposure among the cases of disease (A/C) by the odds of exposure in the source population (closed cohort) (N1/N0).

Also, by the symmetry of the odds ratio, the Disease Odds Ratio (DOR) is equal to the ratio of the odds of exposure among the cases (A/C) divided by the odds of exposure among the subjects who did not develop the disease (B/D).

Similarly the following table displays the results from an open cohort and the calculation for the Rate Ratio

	Disease +	Person-Time
Exposure + (E+)	A	K1
Exposure – (E-)	C	K0

Risk Ratio = RR = (A/K1) / (C/K0)
= (A/C) / (K1/K0)

The second equation for the Rate Ratio demonstrates that is can also be calculated by dividing the odds of exposure among the cases of disease (A/C) by the ratio of exposed to non-exposed person-time in source population.

Control Selection

The role of the controls in a Case Control Study is to estimate the prevalence of exposure in the Cohort Study whose outcomes would be the cases at hand. From the above formulas, this allows the Exposure Odds Ratio from a Case Control study to estimate common measures of association from the corresponding Cohort Study. This cohort could be closed or open.

Corresponding Cohort Study: Closed Cohort

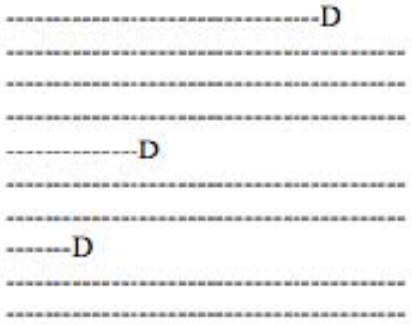
If the corresponding cohort is closed, then the selection of controls is often referred to as cumulative incidence sample and there are two options for selecting controls:

Classic Nested Case Control Study
Selecting controls from subjects in the cohort who did not develop the outcome during the period of follow-up

Case Cohort Study
Select controls from everyone in the cohort at the beginning of the follow-up

These options are describes in the following figure:

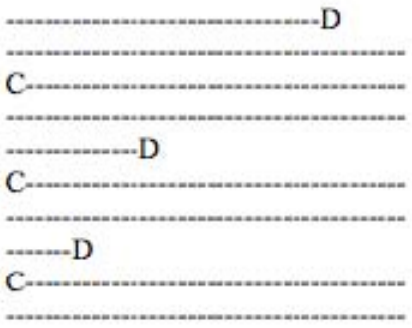
Closed Cohort (D indicates the development of disease)



Nested Case Control Study (C indicates Controls selected from non-disease group)

----C means Controls selected based on results at the end of the study. Controls = Non-Disease Group

Case Cohort Study (C indicates Controls selected from full cohort)



C--- means Controls selected based on classification at the beginning of study, i.e., from the full cohort

Classic Nested Case Control Study

The following example describes the classic Nested Case Control Study (Willett. Lancet 1983 Jul 16;2(8342):130-4). The study involves data from the Hypertension Detection and Follow-up Program (HDFP).

This was a previously performed randomized clinical trail that investigated different treatments for hypertension. However, 4480 participants in this RCT provided blood sample, which were frozen for future use. The RCT also created a registry that recorded the names of study subjects who developed cancer from 4480 participants. 111 of these subjects developed cancer and were chosen as the cases in a Case Control Study to examine the relationship between selenium levels and cancer. Controls should be chosen to reflect the prevalence of exposure in the in the corresponding cohort of 4480 subjects. However, in this classic Nested Case Control Study controls were selected from the members of the cohort who did not develop the disease (4480 – 111 = 4369 subjects). 210 controls were selected form these 4369 study subjects.

	Case	Control
Low Selenium	57	84
High Selenium	54	126
Total	111	210

EOR = [57/54] / [84/126] = 1.6

The following tables displays the results of the Cohort Study had the investigator measured the blood specimens for all 4480 study subjects.

The values for the Risk Ratio (RR) and Disease Odds Ratio (DOR) would require analyzing the blood specimen on the remaining 4369 subjects. If the selenium distribution of the 210 controls reflects the distribution of all 4369 potential controls then the Exposure Odds Ratio (EOR) from the Nested Case Control Study will estimate the Disease Odds Ratio from the Cohort Study as demonstrated in the following calculation:

$$\begin{aligned} \text{DOR} &= [(57/B)]/[(54/D)] \\ &= [57/54] / [B/D)] \\ &\approx [57/54] / [84/126] = 1.6 = \text{EOR} \end{aligned}$$

Furthermore, since the disease is rare, the number of potential controls (4369) is almost the same as the number of subjects in the cohort (4480). Therefore, the odds of exposure among the 4369 potential controls (B/D) should be similar to the odds of exposure in the full cohort (N1 / N0). Under this rare disease assumption, it follows that the Exposure Odds Ratio approximates the Risk Ratio from this Cohort Study.

$$\begin{aligned} \text{EOR} &= [57/54] / [84/126] = 1.6 \\ &\approx [57/54] / [B/D] = \text{DOR} \\ &\approx [57/54] / [N1 / N0\} = \text{RR} \end{aligned}$$

Case Cohort Study

In the classic Nested Case Control Study controls are chosen from subjects who did not develop the disease in the corresponding closed cohort (4,369 subjects in the previous example). The Exposure Odds Ratio from the Case Control Study estimates the Disease Odds Ratio from the corresponding Cohort Study, and under the rare disease assumption also estimates the Risk Ratio from the Cohort Study.

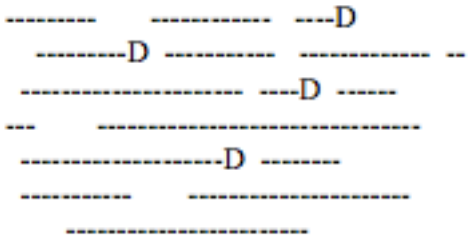
An alternative option is to select controls from the 4,480 members of the original cohort. The resulting Case Control Study is usually referred to as a Case Cohort Study. The exposure odds among the selected controls (b/d) should estimate the exposure odds in the full cohort (N1/N0). Furthermore, the Exposure Odds Ratio from the Case Cohort Study estimates the Risk Ratio from the Cohort Study without any assumption about the rarity of the disease.

Since the outcomes in a Cohort Study at part of the at-risk subjects at the start of a study, it is possible disease case might also be selected as a control in a Case Cohort Study. This presents some problems in performing tests of significance and confidence interval estimation, but does not invalidate the Exposure Odds Ratio from the Case Cohort Study estimating the Risk Ratio from the Cohort Study.

Corresponding Cohort Study: Open Cohort

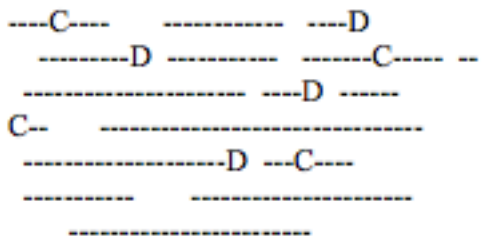
Returning to a previous example, suppose that an investigator plans a Case Control Study examining the relationship between oral contraceptive use and the risk of developing breast cancer. Furthermore, suppose that the cases are women diagnosed with breast cancer at a local hospital in the past two years. Since the purpose of the controls is to reflect the prevalence of exposure (oral contraceptive use) in the cohort study that gave rise to the cases, the challenge to the epidemiology is to formulate this cohort study and determine an appropriate control to describe the prevalence of exposure in that cohort.

Open Cohort (D represent the development of disease)



Since the cohort is open, the appropriate measure of disease incidence is the Incidence Rate. Another term for an Incidence Rate is the Incidence Density. (proposed by Olli Miettinen), and the corresponding Case Control Study is called a Density Type Case Control Study. **The controls are chosen so that their odds of exposure will reflect the ratio of the amount of person time in the open cohort that was contributed by oral contraceptive users to the amount of person time in the open cohort that was contributed by non-oral contraceptive users. Therefore controls should be selected from the person- years of the cohort study.** The following figure displays this type of density type sampling for controls:

Density Type Sampling of Controls (C represents a selected control)



The measure of association in an open cohort study is the Rate Ratio (RR) as described in the following table

	Cases of Disease	Person-Time
Exposed	A	K_1
Non-Exposed	C	K_0

$$RR = (A/K_1) / (C/K_0)$$
$$= (A/C) / (K_1/K_0)$$

The display of data from the corresponding Density Type Case Control Study is

	Case	Control
Exposure +	A	B
Exposure -	C	D
Total	M_1	M_0

$$EOR = (A/C) / (B/D)$$

If the exposure odds among the controls (B/D) estimates the amount of person time in the open cohort that was contributed by exposed subjects divided by the amount of person time in the open cohort that was contributed by non-exposed subjects (K1/K0), then is follows that the Exposure Odds Ratio from the Density Type Case Control Study estimates the Rate Ratio from the corresponding Open Cohort Study

$$EOR = (A/C) / (B/D)$$
$$\approx (A/C) / (K1 / K0) = RR$$

Sources of Controls

If the cases in a Density Type Case Control Study are a list of all cases that develop in a geographical population (e.g. state of Massachusetts) then the corresponding open cohort is a census of individuals living in that population in the past. Such cases are referred to as Population-Based Cases and the selected are referred to as Population- Based Controls.

If the cases are chosen from one (or more) hospitals with a specified diagnosis, then they are referred to as Hospital Based Cases. Controls selected from the same hospital as the cases are referred to as Hospital Based Controls.

Example: Density Type Case Control Study

The following results are from a hospital-based Density Case Control Study measuring the association between a series of potential risk factors and the development of Aortic Stenosis

The cases for this study were 105 subjects with Aortic Stenosis documented by cardiac catheterization (gold standard test).

1. **Group 1**: Patients who underwent cardiac catheterization, which showed no Aortic Stenosis but did show another type of valvular heart disease (n=110)
2. **Group 2**: Patients who underwent cardiac catheterization, which showed no Aortic Stenosis and no other type of valvular heart disease (n=170)
3. **Group 3**: Surgical patients whose reason for surgery was not known to be associated with risk factors of interest (n=269)

All data was obtained from medical record reviews. If no mention of a risk factor was indicated in the medical record, then it was assumed to be absent (i.e. non-exposed). This may results in a large potential for a misclassification bias.

The following table shows the relationship between hypertension and Aortic Stenosis using control Group 3.

	Case	Control
Hypertension	43	91
No Hypertension	62	178
Total	105	269

EOR = (43/62)/ (91/178)
= 1.4

One limitation of a Case Control Study is that it does not allow for the estimation of exposure-specific risks or rates for developing the outcome. Since the investigator usually determines the relative sizes of the case and control groups, it follows that the overall prevalence of disease in the data does not reflect the incidence of the disease in the corresponding cohort study. For example, the prevalence of disease, P(D), among the exposed and non-exposed groups from the previous table is

P(Aortic Stenosis| History of Hypertension) = 43/134 = .32
P(Aortic Stenosis| No History of hypertension) = 62/240 = .26

These proportions are somewhat arbitrary and do not reflect the risk of developing hypertension. To demonstrate this, suppose that the investigator selected twice as many controls for the study. The expected results from this study are shown in the following table:

	Case	Control
Hypertension	43	182
No Hypertension	62	356
Total	105	538

EOR = (43/62)/ (91/178)
= 1.4

The value for the Exposure Odds Ratio does not change but the prevalence of Aortic Stenosis in each group changes to –

P(Aortic Stenosis| History of Hypertension) = 43/225 = .19
P(Aortic Stenosis| No History of Hypertension) = 62/418= .15

Case Control Studies are sometimes referred to as “quick and dirty” studies. They are labeled as “quick” compared to prospective Cohort Studies in that the follow-up period for the study subjects has happened in the past. On the other hand, they are labeled as “dirty” in part because their potential for selection bias, due to the use of an incorrect control group. This may hold true for the first two control groups considered for this study. Control Group 1 included patients who underwent cardiac catheterization, which showed no Aortic Stenosis, but did show another type of valvular heart disease. It is very possible that the same risk factors, which cause Aortic Stenosis, may also cause these other types of valvular heart disease.

Therefore the exposure history in Control Group 1 may over estimate that for the source population. Control Group 2 included patients who underwent cardiac catheterization, which showed no Aortic Stenosis and no other type of valvular heart disease. It is very possible that the risk factors being considered as exposures in this study may have influenced the decision for cardiac catheterization for Control Group 2. If so, then the exposure history in Control Group 2 may over estimate that for the source population. This is demonstrated by the suggestion of a protective effect of hypertension in the following table that uses Control Group 2.

	Case	Control
Hypertension	43	89
No Hypertension	62	81
Total	105	170

EOR = (43/62) / (89/81)
= .63

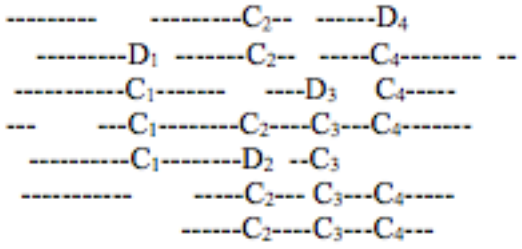
Measurement bias is a potential in any study but may be a particular problem in the study at hand. All exposure information was recorded from medical records. Control Group 3 included surgical patients whose reason for surgery was not known to be associated with the risk factors of interest. Exposure information on the Cases, members of Control Groups 1, and members of Control Group 2 where obtained from interview by cardiology fellows at the time of cardiac catheterization, which would include detailed questions on Coronary Heart Disease (CHD) risk factors. On the other hand, subjects in Control Group 3 were interviewed by different hospital staff prior to surgery and may have had less detailed questions on CHD risk factors. For, example, it may be that subjects in Control Group 3 were not asked detailed questions about family history of heart disease or such information was not completely recorded in their medical records. This might explain the possible protective effect of this factor that is shown in the following table.

	Case	Control
Family History	42	53
No Family History	63	216
Total	105	269

EOR = (42/63) / (53/216)
= 2.72

Risk Set Sampling

Risk Set Sampling is another option for selection controls, in which the selected controls are matched the follow-up times of cases. The risk-set for a case is the members of the cohort study who were also at risk for developing the disease at the time a case developed the disease. Risk-set sampling involves selecting one of more members of that set as controls. The resulting matched analysis is similar to a survival analysis that could be performed on the full cohort. Risk-set sampling is depicted in the following figure.
Risk-Set Sampling of Controls (Ci represents a potential control for Di)



Week 9 – Concept of Confounding

Suppose an investigator performed a Cohort Study to investigate the association between smoking and the risk of developing Coronary Heart Disease and found that the incidence of CHD among smokers was twice that of non-smokers (Risk Ratio = RR = 2.0). As noted previously before we can conclude that this measure of association reflects the causal effect of smoking, we need to rule out the alternative explanations of

1. Bias
2. Confounding
3. Chance

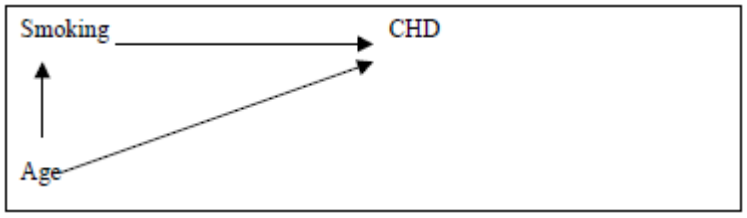
Suppose that the investigator is confident that there is little potential for bias in this study and that the large sample size limits the role of chance as possible reason for this association. However, a closer look at the data reveals that the smokers are much older than the non-smokers. Does the measure of association (RR = 2.0) reflect the effect of

1. Smoking ?
2. Older Age ?
3. Both ?

Recall that the causal effect of a risk factor for a person reflects the change in the outcome that is observed when that person is exposed to that risk factor and when that person is not exposed to that risk factor, under identical situations. These two outcomes are referred to as counterfactual outcomes.

If a person is a lifetime smoker then the observed CHD outcome (factual outcome) matches the counterfactual outcome following a lifetime of smoking. However, we are unable to observe the other CHD counterfactual outcome for that person had that person never smoked. Hence, it is not possible to measure the causal effect of a risk factor for a specific person. The average causal effect of a risk factor for a population is the difference in average counterfactual outcomes when all members of the population receive the risk factor and when none of the members of the population receive it.

Causal diagrams in epidemiology are called Directed Acyclic Graphs (DAGS). They are directed in that **they contain arrows that reflect causal assumptions between potential risk factors and outcomes and they acyclic in that the direction of the arrows do not contains loops from outcomes back to their causes. For example, the following DAG describes the Cohort Study mentioned above and shows two pathways (explanations) that could account for the crude association between smoking and CHD in a data set.**



The top arrow reflects of potential direct effect that smoking may have on the risk of developing CHD. However, the other two arrows suggest that there is also a second, backdoor pathway to explain this association. Smokers might be older than nonsmokers and older age also influences the risk of developing CHD. The existence of a backdoor pathway involving a third factor (e.g. age) provides a DAG-based

definition of confounding. A risk factor, whose control blocks a backdoor pathway, is a confounder (confounding factor).

Adjusted measures of association control for factors (confounders) that account for a difference in the factual outcomes in the non-exposed group and the counterfactual outcomes in the exposed group. The lack of exchangeability is the counterfactual based definition of confounding.

The existence of a backdoor pathway in a causal diagram, leading to a lack of exchangeability leads to a **commonly sited definition of confounding** –

1. **The confounder must be associated with the exposure** (in this example smokers have an older age distribution than non-smokers).
2. **The confounder must be associated with the disease**, independent of the exposure (in this example, older age increases the risk of disease among the non-smokers).
3. **The confounder must not be part of the causal pathway connecting the exposure to the disease**.

Suppose that the following data reflect the associations found in the Cohort Study mentioned above.

Crude Analysis

	CHD		
	+	-	Total
Smokers	240	760	1000
Non-Smokers	120	880	1000

Stratified analysis (by Age)

	Young			Old		
	CHD			CHD		
	+	-	Total	+	-	Total
Smokers	60	340	400	180	420	600
Non-Smokers	80	720	800	40	160	200

Do these data reflect confounding by age?

Criteria for Confounding

The first criterion for confounding states that the confounder must be associated with the exposure. This holds in these data as the prevalence of old age, P(old age), among smokers and non-smokers differ.

P(Old|Smoker) = 600/1000 = 60%
P(Old|Non-Smoker) = 200/1000 = 20%

The second criterion for confounding refers to the relationship between age and CHD, independent of smoking. This can be examined by examining the relationship between age and CHD among the non-smokers. The data support such a relationship as

P(CHD|Young Non-Smoker) = 80/800 = 10%
P(CHD|Old Non-Smoker) = 40/200 = 20%

The third criterion for a confounder states that age should not be in the causal pathway that link smoking with CHD. This criterion can not be examined by the data but can be logically ruled out as smoking does not cause old age.

When confounding exists, the causal graph implies that the value for the crude measure of the association reflects both the effect of the exposure and of the confounder (direct pathway and backdoor pathway). On the other hand, adjusting for a confounder blocks the backdoor pathway and the value for the adjusted measure of association reflects only the direct effect of the exposure. Therefore, when confounding exists, one would expect to observe different values for the crude and adjusted measures of association. This results in commonly used working definition of confounding:

A confounder is a factor that when adjusted in the analysis results in a value for the adjusted measure of association that is meaningfully different from the value for the crude measure of association.

Crude Analysis:

	CHD +	CHD -	Total
Smokers	240	760	1000
Non-Smokers	120	880	1000

$RR_{Crude} = (240/1000)/(120/1000)$
$= .24/.12$
$= 2.0$

Crude RR vs Stratified RR

Stratified analysis (by Age)

	Young CHD +	Young CHD -	Young Total	Old CHD +	Old CHD -	Old Total
Smk	60	340	400	180	420	600
Non-Smk	80	720	800	40	160	200

$RR_{Young} = (60/400)/(80/800)$
$= .15/.10$
$= 1.5$

$RR_{Old} = (180/600)/(40/200)$
$= .30/.20$
$= 1.5$

$RR_{adjusted} = RR_{Young} = RR_{Old} = 1.5$

The **change-in-estimate method is practical for detecting confounding and displays the "result" of confounding**, while the conceptual definition of confounding describes the "mechanism" for the change in estimates.

Stratification

The implication of confounding is that the crude measure of association reflects a mixture of the effect of the exposure and the effect of the confounding factor(s). When confounding exists in a data set, analytical methods of adjustment must be used to separate the effect of the exposure from the effect(s) of the confounding factor(s). There are two general approaches for adjusting for confounding factors in the analysis:

1. Stratification,
2. Regression Modeling.

Regression modeling is the more common method for controlling confounding and stratification can be considered as a special case of modeling. However, because of its intuitive appeal, controlling confounding by stratification will be discussed initially.

Stratification involves dividing the data set into disjoint subgroups (strata) based on categories/values of the confounder(s). There are two methods for adjustment based on stratification:

1. Pooling (weighted averaging)
2. Standardization.

Stratification with pooling involves the following steps:

1. **Create subgroups (strata) defined by categories** or sub-ranges of the confounding factor, which are free of residual confounding by that factor,
2. **Estimate the value for the measure of association within each stratum**, and
3. When appropriate, **average (pool) these estimates over strata to determine the adjusted measure of association**.

The justification for this method is reflected in its first step. If all subjects within a stratum possess (essentially) a common value for a risk factor, then that factor cannot satisfy either of the first two criteria for confounding defined above within that stratum. For a non-continuous confounder, strata defined by distinct categories of the confounder automatically satisfy this situation. For example, when stratifying by sex, the exposed subjects and the non-exposed subjects will have the same sex distribution within the male stratum (all will be males). However, stratification by a continuous confounder requires the specifications of sub-ranges of the confounder to define the strata.

Depending on how sub-ranges of a continuous are defined, there may still be residual confounding by the stratifying factor within a stratum. Suppose that age is a confounder in a study. On one hand, narrowly defined sub-ranges (for example, one-year age intervals) are more homogenous and are less prone to contain residual confounding, but this approach may result in a large number of strata, with little information (individuals) contained within each strata.

Given the creation of strata that are free of residual confounding by the stratifying factor, the second step in the stratification calls for estimating the chosen measure of association within each stratum. Averaging (when appropriate) the stratum-specific measures of association into a single number (adjusted measure of association) is usually not based on a simple arithmetic mean, but is based on a method of weighted averaging or pooling that takes into account the amount of information associated with each stratum-specific estimate. The most commonly used method for averaging stratum-specific estimates of effect is the method proposed by Mantel and Haenszel (JNCI 22:719-748, 1959).

Example 1

The following tables show the crude and age-adjusted measures of association between sex and mortality among patients diagnosed with trigeminal neuralgia.

Crude Analysis:

	Deaths	Person-yrs	Mort. Rate (per 100 py)
Males	90	2465	3.65
Females	131	3946	3.32

$RR_{Crude} = 3.65/3.32 = 1.10$

Stratified (by aged) Analysis

	age < 65		age 65+	
	Deaths	py	Deaths	py
Males	14	1516	76	949
Females	10	1701	121	2245
Total	24	3217	197	3194

$RR_{age<65} = (14/1516)/(10/1701) = 1.57$

$RR_{age65+} = (76/949)/(121/2245) = 1.49$

These data suggest that age is a confounder.

1. Age satisfies the **first criterion for confounding** (1516/2465 = 62% of the male person-years are in the younger group, compared to 1701/3946 = 43% of the female person-years).

2. Age also appear to satisfy the **second criterion for confounding** (the mortality rate among old females, 5.39 deaths/100py, is much greater than that for young females, .59 deaths/100py). This confounding by age is reflected be the difference between the crude (RRCrude = 1.10) and adjusted (RRMH = 1.50) measures of association.

Example 2

The following tables show the crude and age-adjusted association between smoking and the 24-year risk of death in the FHS teaching data set.

Crude Analysis

	Died	Survived	Total
Smokers	788	1393	2181
Non-Smokers	762	1491	2253
Total	1550	2884	4434

$RR_{Crude} = (788/2181) / (762/2253) = 1.07$

Stratified Analysis

Age ≤ 40	Died	Survived	Total
Smokers	67	385	452
Non-Smokers	25	277	302
Total	92	662	754

Smokers	266	689	955
Non-Smokers	110	574	684
Total	376	1263	1639

50 < Age ≤ 60	Died	Survived	Total
Smokers	286	281	567
Non-Smokers	312	500	812
Total	598	781	1379

Age > 60	Died	Survived	Total
Smokers	169	38	207
Non-Smokers	315	140	455
Total	484	178	662

$$RR_{MH} = [\sum(a_i)(N_{0i})/T_i] / [\sum (c_i)(N_{1i})/T_i]$$

$$= [(67)(302)/754 + (266)(684)/1639 + (286)(812)/1379 + (169)(455)/662] / [(25)(452)/754 + (110)(955)/1639 + (312)(567)/1379 + (315)(207)/662$$

$$= 1.38$$

vs RRcrude = 1.07

Age appears to be a confounder in these data. The following table shows that age satisfies the first criterion for confounding (associated with the exposure).

	Non-Smokers (N= 2253)		Smokers (N=2181)	
Age	N	%	N	%
Age ≤ 40	302	13.40	452	20.72
40 < Age ≤ 50	684	30.36	955	43.79
50 < Age ≤ 60	812	36.04	567	26.00
Age > 60	455	20.20	207	9.49

2253

= 302/2253

The following table suggests that age satisfies the second criterion for confounding (associated with the outcome independent of the exposure).

Age	Estimated Risk Among Females (Non-Exposed)
Age ≤ 40	25/302 = .0828
40 < Age ≤ 50	110/684 = .1608
50 < Age ≤ 60	312/812 = .3842
Age > 60	315/455 = .6923

non-exposed

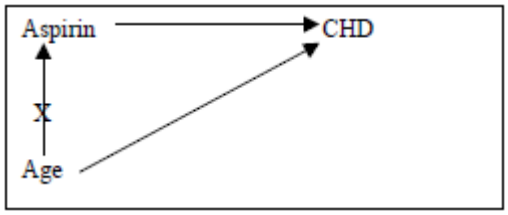
Confounding by age is reflected by the difference between the crude ($RR_{Crude} = 1.07$) and adjusted ($RR_{MH} = 1.38$) measures of association

Standardization

Standardization is a second method for adjusting for confounding through stratification. It is also used as a method for summarizing the effect of an exposure when there is **Effect Modification**.

Design methods of avoiding confounding

Randomization in experimental studies reduces for the potential for confounding. For example, in a large RCT examining the effect of aspirin on the risk of Coronary Heart Disease, age should not be a confounder as it would be expected to have very similar distributions in the aspirin and non-aspirin groups as depicted by the following DAG



Restriction is one way to avoid confounding in observational studies. For example, enrolling only subjects of a certain narrow age range in a Cohort Study would avoid confounding by age in a study comparing the incidence of CHD among aspirin and non-aspirin users. However, it may be difficult to generalize the result of this study to other age groups.

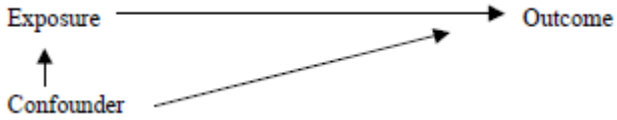
Matching is a less rigid for of restriction and may avoid confounding in a Cohort Study. For example, suppose for every aspirin user enrolled in the study, the investigator enrolled a non-aspirin user of the same age. As a result of this matching, the age distribution of the aspirin users would be identical to that of the non-aspirin users and age would not satisfy the first criterion for confounding (as depicted in the DAG above). The topic of matching will be covered in the next sequence of lecture notes.

Week 10 – Matching and Effect Modification

Matching in a cohort study usually involves selecting non-exposed subjects to have the same the distribution of the matching factor that exists in the exposed group. For example, matching by age may involve selecting a non-exposed subject with the same age as each exposed subject in the study. If the same number of matched non-exposed subjects is enrolled for each enrolled exposed subject (fixed matching ratio), then the distribution of the matching factor among the non-exposed will be identical to that of the exposed subjects.

Matching in a case control study involves selecting a control with the same value for the matching factor as each case. If the same number of matched controls is enrolled for each case, then the distribution of the matching factor among the controls will be identical to that of the cases.

Directed Acyclic Graph (DAG) reflecting the relationship between a confounder and the exposure and the outcome in the absence of matching in a study.



Matching -> Number of Cases = Number of Controls in each strata

Matching in Cohort Studies with a fixed matching ratio guarantees that the matching factor will have identical distribution among the exposed and among the nonexposed subjects in the data. This entails eliminating the arrow from the confounder (matching factor) and the exposure in this figure

Matching with a fixed matching ratio in case control studies forces cases and controls to have the same distribution of the matching factor. For example, matching on age would mean that the percentage of elderly people would be the same for cases and controls. However, the causal diagram shows that there are two factors that influence the age distribution of the cases: the direct influence of age (depicted by the arrow connect age with the outcome) and the direct influence of the exposure (which is related to age). Therefore, matching in a case control study does not directly relate to only the pathway from the confounding factor to the outcome. As a result, matching in a Case Control Study does not block the backdoor pathway and avoid confounding by the matching factor.

Matching by a confounder in a Case Control Study builds similar distributions of the matching factor among the cases and among the matched controls. It will also build similar distributions of other factors that are correlated with the matching factor, including the exposure of interest. Therefore, matching in a Case Control Study tends bias the value for the crude Odds Ratio by towards its null value (1.0). This is demonstrated in the following example.

Example (Large Population)

Large Population:

A. Sex distribution among exposed and among non-exposed subjects in the source population

	Exposed	Non-exposed
Males	8,000 (80%)	2,000 (20%)
Females	2,000 (20%)	8,000 (80%)
Total	10,000	10,000

here net number of exposed males is NOT = number of unexposed males and similarly for females = non-matched

B. Exposure and sex-specific risks of outcome

	Exposed	Non-exposed
Males	.06	.02
Females	.03	.01

C. Expected number of outcomes cases (# subject x risk)

	Exposed	Non-exposed
Males	480	40
Females	60	80
Total	540	120

D. Expected sex-specific data

Males

	Outcome +	-	Total
Exposed	480	7520	8000
Non-exposed	40	1960	2000

RR = 3.0

Females

	Outcome +	-	Total
Exposed	60	1960	2000
Non-exposed	80	7920	8000

RR = 3.0

E. Expected crude data

	Outcome +	-	Total
Exposed	540	9460	10000
Non-exposed	120	9880	10000

RR = 4.5

In these data, sex is a confounder since it is associated with the exposure in the source population (Panel A) and is an independent determinant of the outcome (Panel B). Moreover, the common stratum-specific value for the Risk Ratio (RR = 3.0, Panel D) differs from the crude value of the Risk Ratio (RR = 4.5, Panel E).

Matched Cohort Study

A Cohort Study that matches on sex with a fixed matching ratio will enroll a sample of exposed subjects and a sample of non-exposed subjects whose sex distributions are identical. The following table presents the expected results from a matched cohort study that enrolled 1000 exposed subjects selected at random from all exposed subjects in the original large population described in Panel A of the original data. These data also contain 1000 non-exposed subjects who are matched by sex to the exposed subjects.

A. Sex distribution among exposed and among matched non-exposed subjects

	Exposed	Non-exposed
Males	800 (80%)	800 (80%)
Females	200 (20%)	200 (20%)
Total	1000	1000

here net number of exposed males = number of unexposed males and similarly for females

B. Exposure and sex-specific risks of outcome

	Exposed	Non-exposed
Males	.06	.02
Females	.03	.01

then calculate the risks of outcome

C. Expected number of outcomes cases

	Exposed	Non-exposed
Males	48	16
Females	6	2
Total	54	18

D. Expected sex-specific data

Males	Outcome +	-	Total
Exposed	48	752	800
Non-exposed	16	784	800

RR = 3.0

Females	Outcome +	-	Total
Exposed	6	184	200
Non-exposed	2	198	200

RR = 3.0

E. Expected crude data

	Outcome +	-	Total
Exposed	54	946	1000
Non-exposed	18	982	1000

RR = 3.0

Panel A of this table shows that the impact of matching in a cohort study is to create a study population to one that cannot support confounding due to the lack of association between the matching factor and the exposure. As a result, the crude Risk Ratio (3.0 from Panel E) is equal to the adjusted values (from Panel D).

Matched Case Control Study

Matching in a Case Control Study impacts the selection of controls. Although a fixed matching ratio will guarantee the lack of a crude association between the matching factor and the outcome, unless the exposure has no effect on the outcome (Odds Ratio =1.0), matching on a confounder will not result in the lack of a conditional association between the matching factor and the outcome. This is demonstrated by the example in the following table. The data are from matched (by sex) case control study based on all 660 outcome cases that developed from the original large population and 660 sexmatched controls.

A. Sex distribution among cases and matched controls

	Cases	Controls
Males	520 (79%)	520 (79%)
Females	140 (21%)	140 (21%)
Total	660	660

Male cases = Male Controls

B. Prevalence of exposure among cases and matched controls

Cases (Panel C of table for original large population):

	Exposed	Non-exposed	Total
Males	480 (92%)	40 (8%)	520
Females	60 (43%)	80 (57%)	140
Total	540 (82%)	120 (18%)	660

Control (Based on Panel A for original large population):

	Exposed	Non-exposed	Total
Males	416 (80%)	104 (20%)	520
Females	28 (20%)	12 (80%)	140
Total	444 (67%)	216 (33%)	660

C. Expected sex-specific data

	Males Exposure +	-	Total
Case	480	40	520
Control	416	104	520

OR = 3.0

	Females Exposure +	-	Total
Case	60	80	140
Control	28	112	140

OR = 3.0

D. Expected crude data

	Exposure +	-	Total
Case	540	120	660
Control	444	216	660

OR = 2.2

E. Expected exposure-specific data:

exposed m vs f

	Exposed Male Sex +	-	Total
Case	480	60	540
Control	416	28	444

OR = .54

	Non-exposed Male Sex +	-	Total
Case	40	80	120
Control	104	112	216

OR = .54

non-exposed m vs f

This example demonstrates that matching by sex in this case control study did not avoid confounding. The association between sex and exposure among the controls in Panel B suggests that the matching factor (sex) satisfies the first criterion for confounding. More importantly, Panel E demonstrates that despite the equal sex distribution among cases and controls caused by matching, conditional on exposure status sex remains an independent determinant of the outcome, although its measure of effect, OR = .54, is different from that suggested in the original large population, RR = 2.0). Therefore by the results of Panels B and E, sex satisfies the two criteria for confounding. In addition, the stratum-specific measure of the effect of the exposure in Panel C (OR=3.0) is different from the crude measure in Panel D (OR = 2.2), suggesting that sex is a confounder by the change-in-estimate criterion for confounding. Because of its independent relationship to the outcome, stratifying by a confounder in an unmatched Case Control Study would show varying ratios of cases to controls over the strata. If the factor is a strong determinant of the outcome, then some of these strata may contain many cases but few controls (or vice versa), suggesting an inefficient basis to try to measure the effect of the exposure.

Matched Analysis

The basic principle that underlies a matched analysis is that the association between the exposure and the outcome is first performed within each matched group and then pooled over groups to obtain a summary average. As an example of a matched analysis, the following table presents the basic layout of the results from a Case Control study with a one-one matching design.

		Exposure Status of Control	
		+	-
Exposure Status of Case	+	A	B
	-	C	D

IMPORTANT

Matched pairs (A and D) with identical exposure status for both the case and the matched control are referred to as concordant pairs. These pairs provide no information on the relationship between exposure and outcome. Matched pairs (B and C) show different exposure status for the case and the matched control, and thus provide information about the relationship between the exposure and the outcome. These matched pairs are referred to as discordant pairs and are the basis for estimates of the effect of the exposure on the outcome and for tests of significance concerning this effect.

The relative sizes of the two types of discordant pairs provide the basis for the measure of the effect of the exposure. An estimate for the odds ratio (OR) from 1-1 match data is

OR = B/C

This estimate is identical to the Mantel-Haenszel estimator from a stratified analysis with each stratum corresponding to a separate matched group containing one case and 1 control.

The data for this analysis pertain to 56 matched pairs. Each matched pair contained one case (low birth weight infant) and one control (normal birth weight infant), with the controls matched by the age of mothers of the cases.

		Maternal Smoking of Control	
		+	-
Maternal Smoking of Case	+	8	22
	-	8	18

OR = 22/8 = 2.75

The following table displays the stratified analysis from the 56 strata.

Strata		Frequency	AD/T	BC/T
	D+ D-			
E+ 1	1	8	0	0
E- 0	0			
E+ 1	0	22	1/2	0
E- 0	1			
E+ 0	1	8	0	1/2
E- 1	0			
E+ 0	0	18	0	0
E- 1	1			

$OR_{MH} = 22(1/2) / 8(1/2) = 22/8 = 2.75$

Effect Modification

Effect Modification refers to the situation where the effect of the exposure is modified or changed according to the value or level of another factor. Effect Modification is detected by examining sub-group analyses, examining the association between and exposure and an outcome with sub-groups defines by categories of the candidate effect modifier.

For example, the following data are from a Retrospective Cohort Study examining the relationship between perioperative beta-blocker use and in-hospital mortality among 663,535 patients undergoing non-cardiac surgery at 329 Hospitals (Lindenauer et al: N Engl J Med 2005;353:349-61) The data are stratified by the Revised Cardiac Risk Index Score (RCRI), a measure of a patient's risk of developing a cardiac complication during surgery.

RCRI Score	Odds Ratio	Confidence Interval
0	1.36	(1.27,1.45)
1	1.09	(1.01,1.19)
2	0.88	(0.80,0.98)
3	0.71	(0.63,0.80)
≥ 4	0.58	(0.50,0.67)

These data shows the effect of beta-blocker use on mortality depends on the level of the RCRI. Among patients with low risk of a cardiac complication (RCRI scores of 0 or 1), beta-blocker use tends to increase the risk of in-hospital death (RR = 1.36 for patients with RCRI=0 and RR= 1.09 for patients with RCRI=1). On the other hand, for patients with higher values of RCRI, beta-blocker use tends to decrease the risk of inhospital death (RR= 0.88 for patients with RCRI=2, RR= 0.71 for patients with RCRI=3 and RR= 0.58 for patients with RCRI > 3).

The detection of Effect Modification is challenging. Before concluding that results like those presented in the previous numerical example reflect the presence of effect modification, an investigator must rule out the roles of

1. Bias
2. Confounding
3. Chance

Presenting the Effect of an Exposure in the Presence of Effect Modification

When effect modification exists, the single average measures of association cannot be expected to estimate the differing values for the measure of association that exist in the various strata. In this situation, the presentation of stratum-specific results or a method of standardization is superior to the method of weighted averaging (Mantel- Haenszel Estimate) as described in the previous lecture notes.

When effect modification exists, probably the best manner to present the effect of the exposure is by displaying the different measures of association for different subgroups or strata of the effect modifier. For example, if age is an effect modifier, then one might display the separate effects of the exposure for young, middle-aged, and old subjects.

An alternative to presenting stratum-specific estimates of effect is to present a summary (average) measure of association that is linked to a specified population with a known distribution of the effect modifier. This involves the method of direct standardization and compares two standardized measures of disease frequency: one under the assumption that everyone in the standard population has the stratum-specific risks of the exposed subjects, and the other under the assumption that everyone in the standard population has the stratum-specific risks of the non-exposed subjects. Therefore, standardization estimates the counterfactual outcomes that were described in the previous series of lecture and estimates the average causal effect of the exposure in the standard population.

In this special case where the exposed subjects are taken as the standard population, the standardized risk ratio becomes the ratio of the observed number of exposed cases to the expected number of exposed cases. This ratio is usually referred to as the SMR (standardized mortality ratio or standardized morbidity ratio) and is a component of the method of indirect standardization.

A standardized risk ratio reflects the overall, unconfounded effect of the exposure in a specific population (the chosen standard) with a specific distribution for the effect modifier. Choosing a different standard with a different distribution for the effect modifier should result in a different value for the standardized risk ratio, reflecting the overall effect of the exposure in the new standard population.

Example

The following data can be used estimate the age-standardized risks of death among smokers and non-smokers in the FHS teaching data set. The standard population is the total number of study subjects (4434) in the data and the age strata are the same that were used in the previous lecture notes to describe stratification.

Age ≤ 40	Died	Survived	Total
Smokers	67	385	452
Non-Smokers	25	277	302
Total	92	662	754

40 < Age ≤ 50	Died	Survived	Total
Smokers	266	689	955
Non-Smokers	110	574	684
Total	376	1263	1639

50 < Age ≤ 60	Died	Survived	Total
Smokers	286	281	567
Non-Smokers	312	500	812
Total	598	781	1379

Age > 60	Died	Survived	Total
Smokers	169	38	207
Non-Smokers	315	140	455
Total	484	178	662

The following table displays the calculation of the expected number of deaths under the two scenarios that all members of the population smoked and that none of the members of the population smoked. The expected number of deaths for each age group (columns 4 and 6) are estimated by multiplying the number of subjects in the standard population who are in that age group by the correspond risk of dying for that age group.

Standard Population(Age Group)	Number	Risk if all were Exposed (Smoker)	Expected. # Cases	Risk if all Non-Exposed (Non-Smoker)	Expected # of Cases
≤ 40	754	67/452 = .1482	754(.1482) = 111.74	25/302 = .0828	754(.0828) = 62.43
(40, 50]	1639	266/955 = .2785	1639(.2785) = 456.46	110/684 = .1608	1639(.1608) =263.55
(50, 60]	1379	286/567 = .5044	1379(.5044) = 695.57	312/812 = .3842	1379(.3842) = 529.82
> 60	662	169/207 = .8164	662(.8164) = 540.52	315/455= .6923	662(.6923) = 458.30
Total	4434		1804.29		1314.10

IMPORTANT TECHNIQUE

The Standardized Risks of Death (estimated counterfactual outcomes) and Standardized Risk Ratio from this table are

Smokers: 1804.29/4434 = 0.4069
Non-Smokers: 1314.10/4434 = 0.2964
Standardized Risk Ratio: .4069/.2964 = 1.37

Inverse Probability Weighting

Standardization involves inverse probably weighting. For example, the previous table shows that the expected number of deaths in the youngest age group if all 754 subjects smoked is111.74. The following calculation shows two formulas for the calculation of this value.

111.74 = (smokers risk) x (size of standard population)
= (67/452) x (754)
= (67/452) x (452) x (754/452)
= (smokers risk) x [(# smokers) x (weight)]

The bottom equation implies that the expected number of death can be obtained by multiplying the number of young smokers by a weight and then multiplying this value by the risk of death among the young smokers. The weight (754/452) equals

754/452 = 1/P(Smoking| Age < 40)
= 1/P(Exposure| Age < 40)
= 1/P(Exposure|Confounder)

The P(Exposure | Confounder(s)) is called the **Propensity Score.** This topic will be discussed in the next series of lecture notes. The previous calculation demonstrated that the estimation of the number of deaths if everyone in the standard population has the exposure involves weighting the exposed subjects by the inverse of their propensity scores. Similarly, the estimation of the number of deaths if no one in the standard population has the exposure involves weighting the non-exposed subjects by the inverse of (1- propensity score).

Week 11 – Regression Models

Role of Regression Models in Clinical Research:

The practical goal of epidemiology is to measure and interpret associations between suspected risk factors and outcomes. For causal research, the usual measurement goal of the investigation is to quantifying the effect of a single risk factor of interest (exposure) on the outcome while controlling for confounding by other factors (explanation). However, a second measurement goal of epidemiology (especially of clinical epidemiology) may be to quantify the joint effect of many risk factors to estimate an individual's risk of developing or possessing an outcome (prediction). Regression Models are commonly used to achieve either of these goals. However, the steps used to develop these models and the focus on their results depends on whether explanation or prediction is the goal of the analysis.

Regression Coefficients

Regression coefficients can be interpreted as slope coefficients, reflecting the change in an outcome, per unit chance in a risk factor. For example, the following data show the relationship between smoking (measured in packs smoked per day) and the log(odds of dying), the logit, during the 24 years of follow-up in the Framingham Heart Study (FHS) Teaching Data Set. (N.B. 32 of the 4434 participants have missing values for cigpday1 and therefore have missing values for packs smoked per day.)

Packs Smoked Per Day	Number at Risk	Number of Deaths	Estimated Risk	Logit
0	2253	762	762/2253 = .34	log(.34/.66) = -.66
1	1671	573	573/1671 = .34	log(.34/.66) = -.66
2	398	169	169/398 = .42	log(.42/.58) = -.32
3+	80	36	36/80 = .45	log(.45/.55) = -.20

The data in this table shows evidence of an increasing log(odds of death) with increasing number of packs of cigarettes smoked, which might be approximated by the following linear equation

$$\log(\text{Odds of Death}) = B_0 + B_1(\text{Packs})$$

A regression equation that describes the relationship between the log(odds of an outcome) as function of one or more risk factors is called a Logistic Regression Model. The slope of this linear equation (B1) measures the change in the log(Odds of Death) per smoking one additional pack of cigarettes per day. For example, if Px is the risk of death when smoking "x" packs of cigarettes per day then

$$\begin{aligned} B_1 &= \log(P_{x+1}/(1-P_{x+1})) - \log(P_x/(1-P_x)) \\ &= \log[(P_{x+1}/(1-P_{x+1})) / \log(P_x/(1-P_x))] \\ &= \log(\text{Odds Ratio}) \end{aligned}$$

The last equation shows that regression coefficients for a logistic regression model can be interpreted as the logarithm of a common measure of association, the Odds Ratio. In addition if the logistic regression model contains multiple risk factors, the coefficient for any risk factor has the interpretation as the log(Odds Ratio), measuring the association between that risk factor and the outcome, conditional on all other risk factors in the model.

For example, the following formula describes the risk (P) of death during 24 years of follow-up in the FHS Teaching Data Set as a function of five risk factors: current smoking status (CURSMOK1: 1=yes, 0=no), age in years (AGE), male sex (MALE: 1= yes, 0=no), hypertension (HIGHBP1: 1 if sysbp1 > 140 or diabp1 > 90, 0 otherwise) and diabetes (DIABETES1: 1=yes, 0=no).

$$\log(P/(1-P)) = B_0 + B_1\text{CURSMOK1} + B_2\text{AGE} + B_3\text{MALE} + B_4\text{HIGHBP1} + B_5\text{DIABETES1}$$

When fit to the FHS teaching data set, the fitted model becomes

$$\log(P/(1-P)) = -7.5869 + 0.5522(\text{CURSMOK1}) + 0.1181(\text{AGE}) + 0.7759(\text{MALE}) + 0.6386(\text{HIGHBP1}) + 1.5834(\text{DIABETES1})$$

If this model correctly describes the relationship between the 5 risk factors and the risk of death, then it follows that the 24-year risk of death for a 50-year-old female, without hypertension and without diabetes is

$$\begin{aligned} \log(P/(1-P)) &= -7.5869 + 0.5522(\text{CURSMOK1}) + 0.1181(50) + 0.7759(0) + 0.6386(0) + 1.5834(0) \\ &= -1.6819 + 0.5522(\text{CURSMOK1}) \end{aligned}$$

This equation resembles the linear equation presented above. Therefore, the coefficient of CURSMOK1 (0.5522) is the log(Odds Ratio) describing the relationship between smoking and death, for a 50-year-old female, without hypertension and without diabetes and

$$OR = e^{0.5522} = 1.74$$

On the other hand, the 24-year risk of death for a male, 50-year-old male with hypertension and with diabetes is

$$\begin{aligned} \log(P/(1-P)) &= -7.5869 + 0.5522(\text{CURSMOK1}) + 0.1181(50) + 0.7759(1) + 0.6386(1) + 1.5834(1) \\ &= 1.3160 + 0.5522(\text{CURSMOK1}) \end{aligned}$$

The coefficient of CURSMOK1 (0.5522) again is the log(Odds Ratio) describing the relationship between smoking and death, but now for a 50-year-old male, with hypertension and without diabetes and

OR = $e^{0.5522} = 1.74$

In summary, for any combination of (AGE, MALE, HIGHBP1, and DIABETES1), the model's estimate of the effect of CURSMOKE1 is OR = 1.74.

In general, a regression coefficient estimates the effect of a predictor on the outcome, controlling for all other factors in the model.

Multiple Regression Models

A multiple regression model is a mathematical expression that postulates a relationship between an outcome and a set of predictors. Typically the predictors in the model represent the exposure of interest, potential confounders, and possibly effect modifiers. Perhaps the most commonly used model in epidemiologic research is the **logistic regression model**. This model is appropriate for a **binary outcome** (e.g. dead versus alive) and describes the risk (P) of developing the outcome as a function of the predictors (X_1, X_2, … , X_n) by the following formula:

$$\log(P/(1-P)) = B_0 + B_1X_1 + B_2X_2 + \ldots. + B_nX_n$$

logistic regression model -
for binary outcome (y variable)

The unknown coefficients in this model are the intercept term (B_0) and the coefficients (B_i) of the predictors (X_i). The intercept term (B_0) specifies the value for the outcome (log(P/(1-P))) when all predictors are set equal to zero (i.e. $X_i = 0$, i = 1,2, …., n). More importantly, each coefficient (B_i) is a slope coefficient, describing the change in log(P/(1-P)) per unit change in X_i (log(OR)) when all other predictors are fixed. This coefficient is often interpreted as an estimate of the "effect" of the corresponding predictor, controlling for all of the other factors in the model.

Another multivariable model often used in clinical research is the **linear regression model**, which describes the relationship between a **continuous outcome** (Y) and a set of predictors. This model assumes that the average outcome (expected value, E(Y)) is related to the predictors according to the following formula

$$E(Y) = B_0 + B_1X_1 + B_2X_2 + \ldots. + B_nX_n$$

Other models that are sometimes used in clinical research are the **Cox Regression Model** for survival time outcomes with censoring and the **Poisson Regression Model** for count outcomes. The main differences in these models are the type of outcome (binary outcome, continuous outcome, survival time outcome, and count outcome) and the method for fitting a model to a data set. However, all model share many principles in common, including the interpretation of any regression coefficient as representing the change in the outcome per unit change in a predictor, controlling for all other predictors in the model.

Model Assumptions

The following table shows the equation for the Mortality Prediction Model (MPM_0)

Table. Model predicting the risk of hospital mortality (P) for patients admitted to an intensive care unit based on a logistic regression model containing seven predictors

Predictors

CONS : level of consciousness (1 if coma or deep stupor, 0 otherwise)
TYPE : type of admission (1 if emergent, 0 if elective)
CANCER : cancer as part of present problem (1 if yes, 0 if no)
CPR : prior CPR (1 if yes, 0 if no)
INFECT : infection (1 if probable, 0 otherwise)
AGE : age in ten year increments
SBP : systolic blood pressure
SBP2 : SBP squared.

Model :

log(P/(1-P)) = -1.370 + 2.44(CONS) + 1.81(TYPE) + 1.49(CANCER) + .974(CPR) + .965(INFECT) + .0368(AGE) -.0606(SBP) + .000175(SBP2)

Most of the factors in the MPM model are binary predictors, each representing the presence or absence of a risk factor. However, the model also contains terms for two continuous risk factors: age and systolic blood pressure.

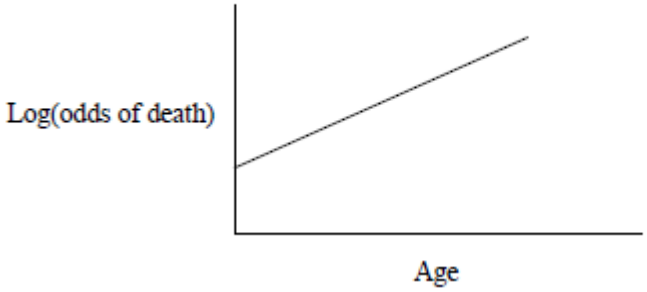
The model assumes that each predictor has a single effect on the outcome as measured by its coefficient and that this effect holds over all subgroups of subjects that are defined by the other predictors in the model. For example, this model assumes that the effect prior CPR (as estimated by its regression coefficient (0.974) is not modified by any of the other predictors in the model. This condition is known as the **assumption of additivity**.

The model in this table also contains a single term for the age of each subject. If we fix the values for the other predictors, then this model assumes that the conditional linear relationship between age and the log odds of dying, which is described by the following equation and represented by a straight line as depicted in the following figure.

$\log(P/(1-P)) = B_0^* + .0368(AGE)$

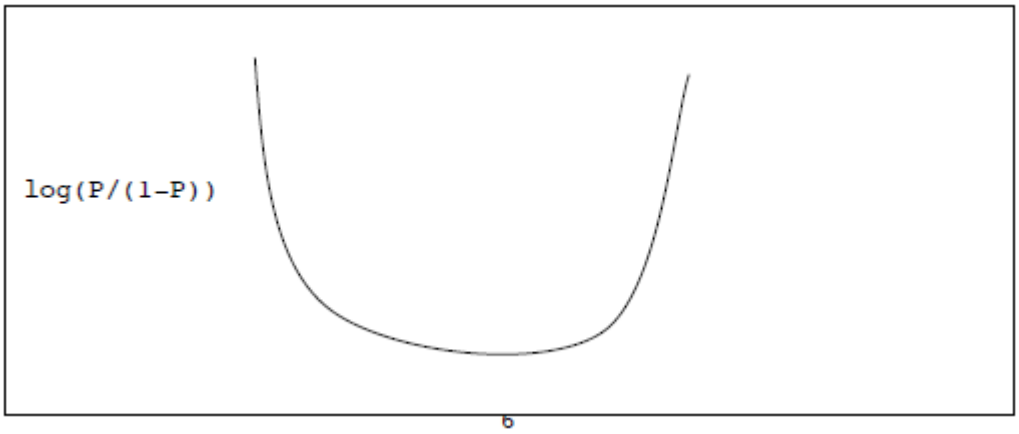
where the value for B_0^* depends on the fixed values for the other predictors in the model.

Figure Assumed conditional linear relation between age and Log(odds of deaths)



The relationship displayed in this figure refers to an **assumption of linearity**. The slope of the line reflects the increase in the outcome (log odds of dying) per unit increase in the age. For example, the model presented in previous table assumes that the log odds of death increases by 0.0368 for every increase in the year of age. This corresponds to an odds ratio of $e^{.0368} = 1.04$ for each one-year increase in of age.

It is important that the model's assumption properly reflect the true relationship between a continuous predictor and the outcome. If the relationship between a continuous predictor and an outcome is not linear, then the model may need to contain additional terms to reflect its nonlinear relationship to the outcome. For example, one might expect that the risk of death might be high for patients with very high blood pressure (hypertension), but also be high for patients with very low blood pressure (hypotension). Thus one might expect a U-shape relationship between blood pressure and the log(odds of death as shown in the following figure:



Fixing the values of the other predictors, the MPM_0 simplifies to the following quadratic equation to describe the conditional association between systolic blood pressure (SBP) and the log(odds of death):

$$\log(P/(1-P)) = B_{0*} - .0606(SBP) + .000175(SBP_2)$$

where the value for B_{0*} depends on the fixed values for the other predictors in the model.

Relationship Between Stratification and Regression for Controlling Confounding

The simplest method for controlling a confounder is through stratification according to categories or sub-ranges of the confounder. Strata are sub-groups of patients with common values for the confounder. Since the value for the confounding factor is constant (or nearly constant) within a stratum, all subjects with a stratum should have homogeneous risk of developing the outcome as influenced by the confounder. For example, stratifying by sex will create two strata, one containing only males and the other only females. Even if males may have higher risk for developing the outcome than females, comparing males who received the exposure to males who did not receive the exposure will provide an estimate for the effect of the intervention that is free of confounding by sex.

Control of Multiple Confounders

Potentially stratification can adjust for the joint confounding by a set of factors through multiple levels of stratification. For example, if age is divided into three age groups (young, middle-aged, and old), then the joint stratification by age and sex will result in six strata (young men, young women, middle-aged men, middle-aged women, old men, and old women). Although simple and straightforward, this method is not practical for adjusting for many confounders. For example, simultaneous stratification by only six binary confounders results in 64 strata, which may be too many for most data sets. Therefore alternative adjustment strategies must be considered. A regression model is the most commonly method for controlling multiple confounders. This is accomplished by fitting a model containing a term for the intervention/exposure and additional terms for the confounding factors.

If age is treated as a categorical variable (as in the previous paragraph) then controlling for age and sex in a model is analogous to stratification if the model contains separate terms to represent the 6 strata defined by age

and sex. However, if age possesses a linear relationship with the log(odds of death) and the effect of age is not modified by sex, then the following simple model may provide a better control of confounding by age and sex than stratification.

$$\text{Log}(P/(1-P)) = B_0 + B_1(\text{Exposure}) + B_2(\text{Age}) + B_3(\text{Sex})$$

A regression model that controls for many confounders would be very large and complex. Fixing large models to small or moderate sized data sets is a challenge. One way to resolve this problem is to summarize the confounders into a single score. For example, the following section provides another methods for controlling confounding, not by including terms for the individual confounders in the model, but by summarizing the confounders into summary score, a **propensity score**.

Propensity Scores

Typically observational studies (i.e. non-randomized trials) that investigate the effect of clinical interventions (treatments or triage decisions) are characterized by a large number of factors that influence both the choice of the intervention and the outcome. This problem is labeled as confounding by indication by epidemiologists, and is demonstrated by the following examples.

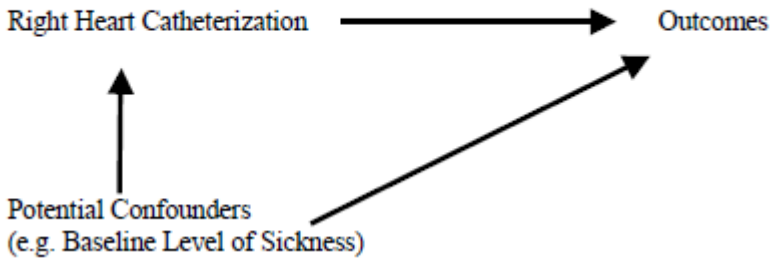
Example # 1: Measuring the Effect of Right Heart Catheterization (SUPPORT) Connors et al examined effect of right heart catheterization in the care of critically ill patients (Connors et al. The effectiveness of right heart catheterization in the initial care of critically ill patients. JAMA. 1996;276:889-897.).

This study examined the survival and health care utilization outcomes for 5735 ICU patients. 2184 of these patients received a right heart catheter (RHC) during the first 24 hours of care in an ICU and another 3551 ICU patients did not receive a RHC. The following table displays the distributions for a sample of patient characteristics.

Patient Characteristics	Received (RHC) (n=2184)	Did Not Receive RHC (n= 3551)
Percent over 80 Years of Age	8%	14%
Mean SBP	68	85
Mean Heart Rate	119	112
Mean Creatinine	221	168
Mean of Apache Score (Measure of Disease Severity)	61	51
Mean Albumin	29	32
Mean of Estimate for 2-Month Survival from Prediction Rule	56	61

This table demonstrates that RHC patients differed from the non-RHC patients on a number of factors that can influence outcomes. Therefore, any difference in the outcomes for the two groups of patients might be attributed to the effect of the right heart catheter and/or to the effects of these other factors. This potential for confounding is depicted by the following causal graph (Directed Acyclic Graph, DAG).

Figure: Directed Acyclic Graph (DAG) displaying potential for confounding in the study by Connors et al.



The following table shows the outcomes (6 month survival, mean total cost, and mean ICU Length of Stay (LOS)) for these patients. Although RHC patients showed worse outcomes, the potential for confounding by the patient characteristics in the previous table raises the question about whether the worse outcomes for the RHC patients reflects the effect of RHC or the type of patient who is given a RHC.

Outcome	Received (RHC) (n=2184)	Did Not Receive RHC (n= 3551)	P-Value
6-Month Survival Probability	53.7%	46.3%	< 0.001
Mean Total Cost	$131,900	$74,300	< 0.001
Mean ICU LOS (days)	15.5	10.3	< 0.001

The following table displays the same patient characteristics for a sample of 1008 RHC and 1008 non-RHC patients who were matched by a propensity score (to be defined later in these notes). Contrary to the previous table for all 2187 RHC patients and 3551 non-RHC patients, the following table shows near identical distributions of these characteristics, suggesting less potential for confounding.

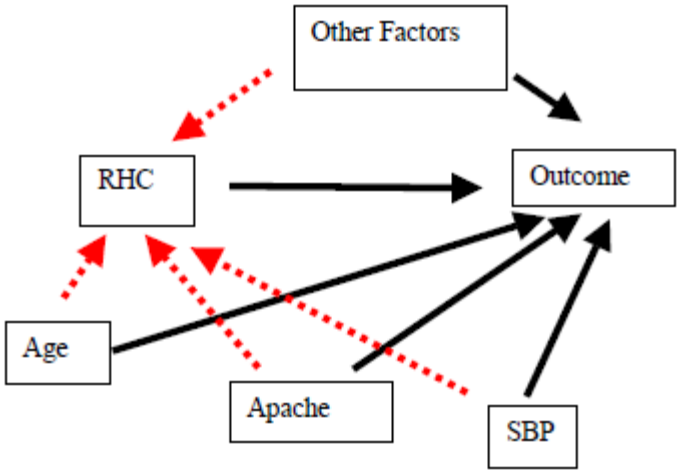
Patient Characteristics	Received (RHC) (n=2184)	Did Not Receive RHC (n= 3551)
Mean Age	60	60
Percent Male	59%	54%
Mean SBP	71	73
Mean Heart Rate	111	111
Mean Creatinine	203	203
Mean of Apache Score (Measure of Disease Severity)	57	57
Mean Albumin	30	30
Mean of Estimate for 2-Month Survival from Prediction Rule	.59	.58

The following table displays the outcomes for the 1008 RHC patients and the 1008 non- RHC patients who were matched by the propensity score. Although the difference in outcomes are attenuated compared to those for all 5735 patients, the outcome for the RHC group remain worse than those for the non-RHC group. These may reflect the true effect of Right Catheterization or possibly confounding by other factors.

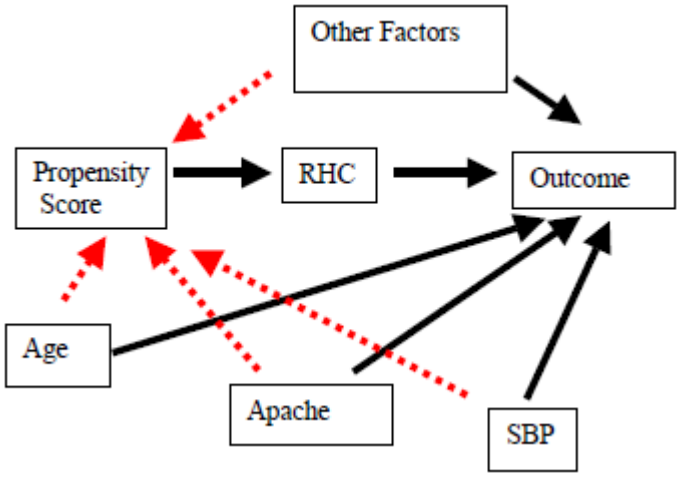
Outcome	Received (RHC) (n=1008)	Did Not Receive RHC (n= 1008)	P-Value
6-Month Survival Probability	51.2%	46.0%	< 0.001
Mean Total Cost	$49,300	$35,700	< 0.001
Mean ICU LOS (days)	14.8	13.0	< 0.001

The motivation for a Propensity Score Analysis is to control for a large number of confounders by combining them into a single summary score. Although the theory of propensity scores was developed over 30 years, their use to control confounding was seldom used until recently.

The Propensity Score is the probability of receiving the exposure as a function of the confounders. The following causal diagram (DAG) displays the anticipated relationship for the factors mentioned in the previous example. The solid arrows connect the suspected confounders and the exposure to the outcome. These arrows reflect the regression coefficients for these predictors in a regression model that predicts the outcome, like the models mentioned earlier in these notes.



On the other hand, the dashed arrows connecting the suspected confounders to the exposure are the basis for the propensity score. The role of the propensity score is to summarize the role of the individual confounders in influencing the treatment decision as shown the following DAG. If the propensity score captures the influence of all of the individual confounders on the treatment decision, then controlling for the propensity score will block the backdoor pathways through the individual factors to the outcome, thereby controlling for any confounding attributed to them.



Example # 2: Effect of Hypertension Treatment

The following analyses examine the association between hypertension treatment (BPMEDS1) at the 1956 exam and the 24-year risk of death in the FHS teaching data set. The analysis is restricted to 1372 participants with a diagnosis of hypertension at the 1956 exam. The following table shows the crude association between hypertension medication use and death

	Died	Survived	Total
BPMEDS1=1	91	48	139
BPMEDS1=0	627	606	1233
Total	718	654	1372

$OR_{Crude} = (91/48) / (627/606) = \mathbf{1.83}$

These results suggest a somewhat surprising harmful effect from hypertension medication use. However the following table displays the imbalance of the distribution for 10 potential confounders.

TABLE	On Hypertension Medication (N=139)	Not on Hypertension Medication (N=1233)
Male (%)	30%	47%
Age (Mean)	56.29	53.55
Cholesterol (Mean)	257.43	246.34
SBP (Mean)	165.08	154.26
DBP (Mean)	96.45	93.43
Obese/Overweight (%)	73%	72%
Smoker (%)	35%	42%
Diabetes (%)	6%	4%
Prevalence of CHD (%)	14%	7%
Prevalence of Stroke(%)	5%	1%

The table shows that participants taking hypertension medication have greater average Age, SBP, DBP, Total Cholesterol, Diabetes, History of CHD and Stroke. Participants not on hypertension medication have a higher percentage of Males and Smokers. As mentioned above, the usual method for controlling multiple confounders is by an outcome regression model that contains terms for the individual confounders. For example, the following logistic regression model depicts the risk of death, P, as a function of the exposure (BPMEDS1) and the 10 potential confounding factors

$$\log(P/(1-P)) = -9.4873 + 0.3405(\text{BPMED1}) + 0.1117(\text{AGE1}) + 0.000239(\text{TOTCHOL1}) + 0.0232(\text{SYSBP1}) - 0.00894(\text{DIABP1}) + 1.2178(\text{MALE}) + 0.4763(\text{CURSMOKE1}) + 1.6317(\text{DIABETES1}) + 1.0511(\text{PRECCHD1}) + 0.9972(\text{PREVSTRK1}) + 1.3087(\text{UNDERWT}) - 0.3166(\text{OVERWT}) + 0.0301(\text{OBESE})$$

As described earlier, the coefficient of BPMED1 (0.3405) is the log(Odds Ratio) measuring the association between medication use and death, controlling for the other factors in the model. It follows that the adjusted Odds Ratio is

$$OR_{Logistic} = e^{0.3405} = 1.41$$

An alternative method to control for the potential confounders in this model is by an analysis based on a propensity score, reflecting their relationship of the confounders with the exposure (BPMEDS1). The following logistic regression model describes the risk of hypertension medication use, PS, as a function of the potential confounders

$$\log(PS/(1-PS)) = -7.0445 + 0.0207(\text{AGE1}) + 0.00347(\text{TOTCHOL1}) + 0.0145(\text{SYSBP1}) + 0.00592(\text{DIABP1}) - 0.4586(\text{MALE}) - 0.0289(\text{CURSMOKE1}) + 0.0697(\text{DIABETES1}) + 0.5283(\text{PRECCHD1}) + .3750(\text{PREVSTRK1}) + 0.8119(\text{UNDERWT}) + 0.0849(\text{OVERWT}) + 0.1080(\text{OBESE})$$

The propensity score is a balancing score. If it captures the relationship between the potential confounders and the exposure, then conditioning on it should eliminate any association between the individual confounders and the exposure. The following table shows the adjusted relationship between the individual confounders and hypertension medication use after adjusting for the propensity score. The first two columns repeat the crude imbalance of the confounders shown in a previously presented table. The last two columns show the balance of the same potential confounders in an analysis that adjusts for the propensity score by we-weighting the data by a function of the propensity score (as demonstrated in the last series of lecture notes). This table demonstrates very similar distributions of the confounders (better balance) after adjusting by the propensity score.

TABLE	Crude		Propensity Score Adjusted	
	Meds	No Meds	Meds	No Meds
Male (%)	30%	47%	43%	45%
Age (Mean)	56.29	53.55	53.91	53.83
Cholesterol (Mean)	257.43	246.34	245.77	247.43
SBP (Mean)	165.08	154.26	153.86	155.37
DBP (Mean)	96.45	93.43	92.66	93.73
Obese/Overweight (%)	73%	72%	71%	66%
Smoker (%)	35%	42%	41%	41%
Diabetes (%)	6%	4%	4%	5%
Prevalence of CHD (%)	14%	7%	9%	8%
Prevalence of Stroke(%)	5%	1%	2%	2%

Confounding can be controlled with a propensity score by the following methods

1. Matching by the propensity score (as in the RHC analysis above)
2. Stratifying by ranges of the propensity score
3. Including the propensity score in an outcome regression model in place of individual confounders
4. Re-weight the data by a function of the propensity score (similar to standardization as described in the previous lecture notes)

The following analysis uses stratification by ranges of the propensity score (second option) to control for confounding in the problem at hand. The following table shows the distribution of the propensity score in seven strata defined by ranges of the propensity score. Not surprising, 33.81% of the participants taking hypertension medication belong to the last four strata, compared to only 12.90% of the participants not on medication.

Propensity Score	BPMEDS=1	BPMEDS=0
$0 \leq PS \leq 0.05$	12 (8.63%)	234 (18.98%)
$0.05 < PS \leq 0.10$	43 (30.94%)	574 (46.55%)
$0.10 < PS \leq 0.15$	37 (26.62%)	266 (21.57%)
$0.15 < PS \leq 0.20$	20 (14.39%)	82 (6.65%)
$0.20 < PS \leq 0.25$	9 (6.47%)	32 (2.60%)
$0.25 < PS \leq 0.30$	8 (5.76%)	28 (2.27%)
$PS > 0.30$	10 (7.19%)	17 (1.38%)

Creating seven strata (defined by ranges of the propensity score), measuring the association between hypertension medication use and death within each stratum, and average these results over the strata using the Mantel-Haenszel formula (presented in the previous series of lecture notes), yields an adjusted Odds Ratio

$$OR_{MH} = 1.37$$

This value for the Odds Ratio from stratifying by the propensity score ($OR_{MH} = 1.37$) is very similar to the adjusted Odds Ratio that was obtained from the outcome logistic regression model ($OR_{Logistic} = 1.41$). The similarity of results is not surprising as both methods are valid options for controlling confounding.

In general, a correctly specified outcome model and an appropriately performed propensity score analysis should result in similar adjusted measures of association to estimate the effect of the exposure. Both methods use regression models, either to prediction the outcome (outcome regression model) or to predict the exposure (propensity score). Using computer simulations, Drake (*Effects of misspecification of the propensity score on estimators of treatment effects. Biometrics, 1993;49:1231-1236*) and Cepeda et al. (*Comparison of logistic regression versus propensity score when the number of events is low and there are multiple confounders. Am J Epidemiol 2003;158:280-287.*) demonstrated that incorrect modeling assumption may have less influence in a propensity score analysis. Cepeda et al. also suggested that a propensity score analysis is superior to an outcome model analysis when the number of outcome events per confounder is small (< 7 events/confounder).

Propensity score analyses are used more frequently that in the past and provide an alternative method for controlling confounding, compared to the commonly used outcome regression model. However, the propensity score analysis (nor the traditional analysis) controls for unmeasured confounders, unless they tend to be highly correlated with those measured confounders present in the model. Even after correctly controlling for multiple confounders by a propensity score analysis (or by an outcome model), the reported adjusted measure of association can still be confounded by other unknown or unmeasured confounders (as might be the case withthe adjusted measures of association for the RHC example).

Week 12 – Screening

Screening

The goal of a screening program is to apply a simple and inexpensive test to a large number of persons in order to classify them as likely or unlikely to have a disease of interest.

Time Periods / Factors influencing the decision to begin a screening programme or otherwise

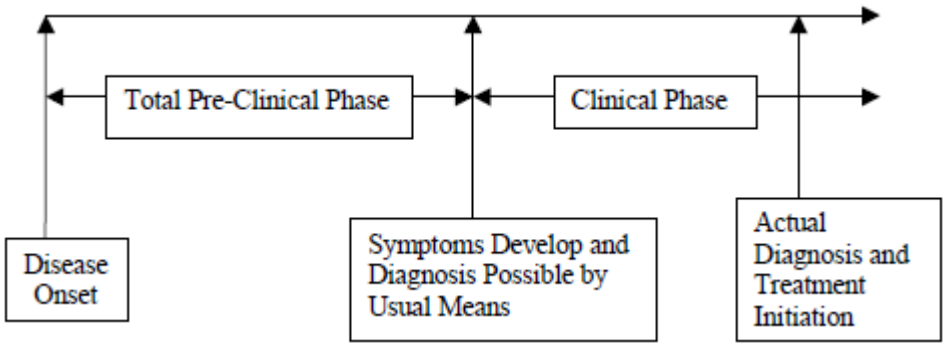
1. **A disease that is suitable for a screening program should have serious consequences** (e.g. fatal or severe/prolonged morbidity) to merit the time and cost as the target of a screening program.

2. **It must have a treatment that, when applied to a case of disease that is detected by screening**, is more effective than treatment applied after symptoms when the case is detected by usual means.

3. **Finally, the disease should have a high prevalence in the Detectable Preclinical Phase (DPCP)**.

Clinical disease begins with the development of signs or symptoms that would lead to a diagnosis of that disease through usual means. Pre-Clinical Disease refers to the existence of disease that has not advanced to a stage where it could be detected by usual means. The Total Preclinical Phase begins with the first

development of disease (biologic onset) and ends with the development of signs/symptoms and the diagnosis of disease by usual means. These time periods are depicted in the following figure:



The **Detectable Preclinical Phase (DPCP)** refers to a portion of the TCPP and begins when the disease can be detected by the screening test. The length of the DPCP depends on the screening test's ability to detect the disease before signs and symptoms develop.

Screening Test

A suitable screening test is one that accurately detects the presence of absence of pre-clinical disease. This is usually measured by two performance measure,

1. Sensitivity = P(Test + | Pre-Clinical Disease Exists)
2. Specificity = P(Test - | Pre-Clinical Disease Does Not Exist)

These measures can be estimated from the following 2x2 table

	Pre-Clinical Disease		
	Present	Absent	Total
Test +	A (True Positives)	B (False Positives)	A+B
Test -	C (False Negatives)	D (True Negatives)	C+D
Total	A+C	B +D	

Sensitivity = A/(A+C)
Specificity = D/(B+D)

As an example, shows the performance of a screening test of physical examination and mammography for the detection of breast cancer from the Health Insurance Plan (HIP) of Greater New York

	Pre-Clinical Disease		
	Present	Absent	Total
Test +	132	983	1115
Test -	45	63650	63695
Total	177	64633	64810

Sensitivity = 132/177 = 0.75
Specificity = 63650/64633 = 0.98

The Sensitivity and Specificity of a Test are characteristics of the screening test. Therefore, one might expect that these values would not change is a screening test were applied to different populations.

Screening Program

A Screening Program involves using a particular screening test in a particular population of asymptomatic individuals. Process measures that reflect the suitability of a screening program include process measures of the screening test (Sensitivity and Specificity) as well as the following

1. Number of people examined
2. Detected prevalence of disease in DPCP
3. Cost
4. Follow-up treatment and outcome

The **Positive (PV+) and Negative (PV-) Predictive Values** of a test refer to the tests ability to predict the presence and absence of the disease. These measures are defined as

Positive Predictive Value = P(Pre-Clinical Disease Present| Test +)
Negative Predictive Value = P(Pre-Clinical Disease Absent| Test -)

The following table shows these values for the HIP data shown above

	Pre-Clinical Disease		
	Present	Absent	Total
Test +	132	983	1115
Test -	45	63650	63695
Total	177	64633	64810

The Positive and Negative Predictive Values are posterior probabilities. They are predictions of an outcome (pre-clinical disease) that take data (test results) into account. They also depend on the base prevalence of disease in the screened population (prior probability).

These dependencies are demonstrated by the following expression of Bays Theorem.

(PV+)/(1-(PV+))= [P(D)/(1-P(D))] [sensitivity/(1-specificity)]
(PV-)/(1-(PV-)) = [(1-P(D))/P(D)][specificity/(1-sensitivity)]

Posterior Odds = (Prior Odds)(Likelihood Ratio)

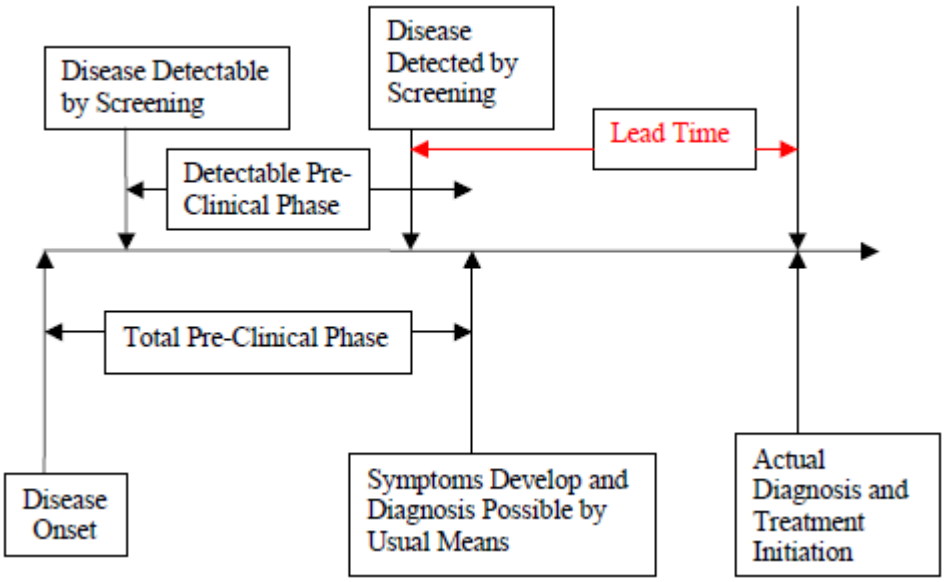
These formulas demonstrate that Positive Predictive of Test depends on prevalence of preclinical disease in a population. Screening in a high risk population will results in higher PV+ and enhanced the suitability of a screening program. One means to increase the prevalence of pre-clinical disease in DPCP of a population is to restrict enrollment of participants in the screening program to those with one of more risk factors for the disease. Another option is to screen a population at an optimum frequency. An initial screen of a population will remove prevalent cases of detectable pre-clinical disease. Sufficient time should elapse for incident cases of pre-clinical disease to develop in that population before it re-screened.

Evaluation

The ultimate goal of a screening program is to reduce the morbidity and mortality from that disease in the persons that are screened by detecting disease at an earlier stage, where a treatment might have a more beneficial effect. Therefore, the effect of a screening program can be detected by comparing outcomes from participants in a screening program to similar other individuals who were not part of a screening program. This can be done using the study design options that were discussed in previous lecture notes. For example, with an experimental design, study participants can be randomized to participate in a screening program or to usual care, then mortality rates in each group can be compared from the point of randomization.

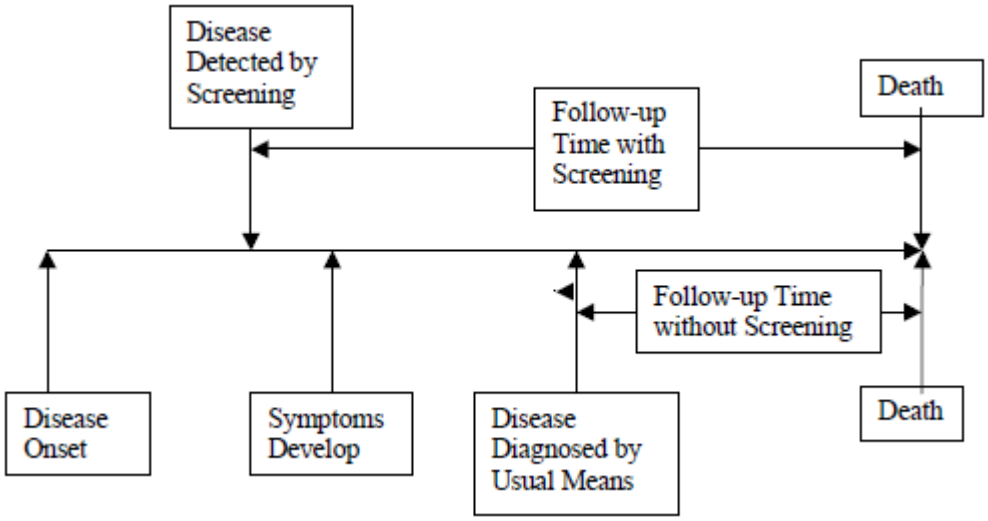
On the other hand, evaluation a screening program with a non-experimental Cohort Study has some potential problems. Individuals who agree to participate in a screening program may not be comparable to those who refuse to participate, providing a potential for confounding. In addition the potential for Lead Time Bias and Length Bias can be considered.

Lead Time is the additional time an individual lives with knowledge of disease because of earlier diagnosis from screening. A long Lead Time is desirable property for a screening program if early treatment results in better outcomes. The following figure depicts the lead time from a screening program.



Lead Time Bias occurs when the follow-up time for the screened participants does not account for the Lead Time, since individuals in the comparison group will not benefit from a lead time.

This is depicted in the following figure. The bottom part of the figure describes the life course of an individual without screening.



Length Bias occurs when evaluating a screening program because of the expectation that screening may detect prevalent cases of disease in the Detectable Pre- Clinical Phase that have a favorable prognosis. Since prevalence is a function of incidence and duration, an initial screening in a population may detect cases of preclinical disease with a long duration. Some of these cases may never develop into clinical cases of disease. Cases of disease detected from a screening program may have better prognosis that those detected by usual means. Therefore, better outcomes in the screened groups may not reflect the effect of the screening program but rather the types of cases that are detected by screening.

Ethical issues may also be important to consider when implementing a screening program. For example, screen-detected cases are often subjected to more invasive diagnostic tests or might be treated with therapies with potential serious side-effects.

Clinical Prediction Rules

Prediction is an integral part of clinical medicine. Prognostic models quantify the likelihood of developing (prognosis) or possessing (diagnosis) an outcome of interest. A prediction rule is an algorithm for estimating this likelihood based on values of selected predictors for this outcome.

Examples of Clinical Prediction Rules Although a clinical prediction rule could be based on expert opinion, usually these rules are based on empirical relationships (associations in a data set) between other identified predictors and the outcome. Some Common types of clinical prediction rules include:

1. Stratification Patterns
2. Regression Models
3. Point Scoring Systems
4. Neural Networks
5. Other Data Mining Methods

Stratification Patterns involves grouping the subjects into subgroups (strata) defined by combinations of categories of categorical predictors. The stratum-specific cumulative incidence or the prevalence of the outcome is used as the estimated risk for all patients within that stratum.

Recursive Partitioning (Classification Trees) creates an asymmetric stratification pattern by applying a step-wise stratification algorithm to sequential divide subgroups of subjects into smaller subgroups with different estimated outcome risks. This method initially divides the data into two subsets by the single "best" predictor.

Each subset in then divided into two additional subsets by the best predictor for that subgroup. The process continues in a recursive manner until there is no evidence that further division of each existing subset would improve prediction.

The most common method for developing clinical prediction is a Regression Model, describing the risk (P) of being in the outcome category of interest as a function of the predictors.

An example of a prediction rule based on a logistic regression model is the Mortality Prediction Model (MPM). This rule predicts the risk of in-hospital death for patients admitted to an intensive care unit

Panel A of the following table displays the seven predictors that are used in this rule.

Table Mortality Prediction Model (MPM) for Predicting In-Hospital Mortality among Patients admitted to an Intensive Care Unit

.

A. Predictors

CONS Level of Consciousness (1 if coma or deep stupor, 0 otherwise)
TYPE Type of Admission (1 if emergent, 0 if elective)
CANCER Cancer as Part of Present Problem (1 if yes, 0 if no)
CPR Prior CPR (1 if yes, 0 if no)
INFECT Infection (1 if probable, 0 otherwise)
AGE Age in Years
SBP Systolic Blood Pressure
SBP2 SBP squared.

Panel B of this table displays the formula for the Logistic Regression Model that defines this prediction rule.

B. Prediction Rule

$$\log(P/(1-P)) = -1.370 + 2.44(CONS) + 1.81(TYPE) + 1.49(CANCER) + .974(CPR) + .965(INFECT) + .0368(AGE) -.0606(SBP) + .000175(SBP2)$$

Panel C demonstrates the amount of calculations needed to obtain risk estimates from a logistic regression model. Although easy to program on a computer, the amount of calculations may limit the use of such a model in actual practice.

C. Sample Estimated Risk Calculation

CONS = 1 (patient has coma or deep stupor)
TYPE = 1 (emergent admission)
CANCER = 0 (cancer part of present problem
CPR = 0 (no prior CPR)
INFECT = 0 (no probable infection)
AGE = 50 (50 years of age)
SBP = 150 (systolic blood pressure = 150)
SBP2 = 22500 (SBP squared)

$$\log(P/(1-P)) = -.1370 + 2.44 + 1.81 + .0368(50) - .0606(150) + .000175(22500) = .8005$$

$$P/(1-P) = \exp(.8005) = 2.227$$
$$P = 2.227/3.227 = 0.69$$

As an example of a scoring system, Panel A of the following table displays the predictors that were chosen for a logistic regression model to predict the probability of bacteremia in blood samples of 1007 hospitalized patients

Table Scoring System to Predict the Risk of Bacteremia among Blood Tests.

A. Predictors

TEMP Indicator variable for having a maximum temperature > 38.3 C (1 = yes, 0 = no)
DCLASS2 Indicator variable specifying that a subject's diagnosis falls in a predefined category of rapidly fatal diseases (1 = yes, 0 = no)
DCLASS3 Indicator variable specifying that a subject's diagnosis falls in a predefined category of ultimately fatal diseases (1 = yes, 0 = no)
CHILLS Indicator variable for the presence of chills (1 = yes, 0 = no)
DRUG Indicator variable for intravenous drug abuse (1 = yes, 0 = no)
POSEXAM Indicator variable for a positive focal abdomen examination (1 = yes, 0 = no)
COMORB Indicator variable for a having one of a specified set of comorbid conditions (1 = yes, 0 = no)

B. Prediction Rule

$$\log(P/(1-P)) = -4.14 + .91*TEMP + 1.40*DCLASS1 + .65*DCLASS2 + .96*CHILLS + .287*DRUG + 1.03*POSEXAM + .96*COMORB$$

C. Scoring System

$$\text{Number of Points} = 3*TEMP + 4*DCLASS1 + 2*DCLASS2 + 3*CHILLS + 4*DRUG + 3*POSEXAM + 3*COMORB$$

The intercept term in the original regression model (Panel B of the previous table) is not included in the scoring system, since this would only add a constant to the total number of points calculated for any subject. The scoring system was used to develop a classification rule (shown the following table) based on ranges of points.

Table: Classification rule based on an Integer-Based Scoring System for predicting the presence of bacteremia among hospitalized patients.

	Risk Score			
	0-2 Points	3 Points	4-5 Points	≥ 6 Points
Training Set (n=1007)	4/303= 0.01	11/236 = 0.05	18/204 = 0.09	41/264=0.16
Testing Set (n=509)	3/155=0.02	8/121=0.07	9/88=0.10	21/145=0.14

An examination of the results for the Training Set in this table shows that the risk of bacteremia ranges from 1% (4/303) in patients with 0-2 points to 16% (41/264) in patients with > 6 points. However, as mentioned previously the performance of the prediction rule in these patients may be optimistic and over-estimate the performance in future patients. This is seen measuring the performance of the rule in a Testing Set of 509 different patients. The estimated risk of patients with 0-2 points is low (3/155 = 2%), but not as low as in the Training Set. Similarly, the estimated risk of patients with > points is high (21/145 = 14%), but not as high as in the Training Set.

Evaluation of a Clinical Prediction Rule

Performance Measures

The validity of a prediction rule is often quantified by various performance measured by how well its estimates agree with the actual outcomes of subjects. Measures of discrimination refer to the ability of the prediction rule to separate subjects with different outcomes into categories according to their values for the prediction rule. Measures of calibration refer to the ability of the model's estimated risk to agree with actual outcomes within groups of subjects.

Measures of Discrimination

One common method for assessing a prediction rule's ability to discriminate between the categories of a binary outcome is to determine the distribution of the outcome categories when subjects are ranked by their estimated risks. Ideally, cases of the outcome will tend to have high ranks of estimated risk, while non-cases will ten to have low ranks. The most common way to display the separation of outcome positive subjects from outcome negative subjects in this ranking is to calculate the ROC curve (Receiver Operating Characteristic). This curve is created by defining a classification rule based on a threshold of estimated risk. Subjects above that threshold are classified as "high risk" subjects and subjects below that threshold are classified as "low risk" subjects. A classification table can then be displayed comparing the categories of the classification rule to those of the actual outcome. The following table displays the format of a confusion matrix along with the formulas for the sensitivity and specificity of the classification.

Table: 2x2 Table Displaying the Validity of a Binary Classification Rule.

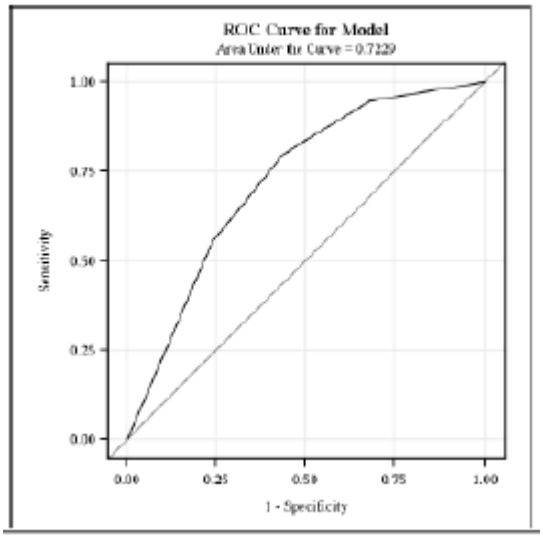
	Outcome +	Outcome -
High-Risk	A	B
Low-Risk	C	D
Total	A+C	B+D

Sensitivity =	A/(A+C)
Specificity =	D/(B+D)

Varying the threshold for defining high risk generates a series of tables like that displayed in the previous table, with corresponding values for sensitivity and specificity. The ROC curve depicts the overall relationship between the prediction rule and the outcome by graphing the value for the sensitivity from each classification table on the vertical axis and for (1-specificity) on the horizontal axis. An ideal curve is one with points in the top left-hand region of the graph, reflecting a classification rule with high sensitivity and high specificity. Since an axis of the ROC curve ranges from 0.0 to 1.0, the total area in a box bounded by these axes is 1.0. Therefore, the ideal curve is one whose area under the curve (AUC) is close to 1.0.

Table: Classification tables showing the risk of bacteremia according to different definitions of high risk for the data

	Bacteremia +	Bacteremia -	Sensitivity	Specificity
High Risk (3 + points)	70	634		
Low Risk (0-2 points)	4	299		
Total	74	933	70/74=0.95	299/933=0.32
High Risk (4 + points)	59	409		
Low Risk (0-3 points)	15	524		
Total	74	933	59/74=0.80	524/933=0.56
High Risk (6 + points)	41	264		
Low Risk (0-5 points)	33	669		
Total	74	933	41/74=0.55	669/933=0.72



Measures of Calibration

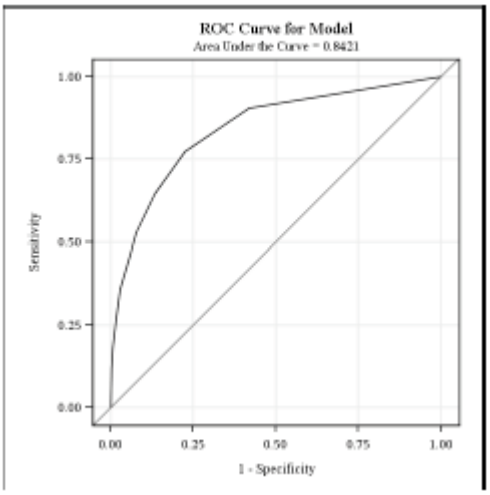
Calibration refers to the degree of agreement between a subject's estimated outcome from a prediction rule and the subject's actual outcome. Measures of the degree of calibration commonly take on the form of "observed versus expected" comparisons of the outcome. A common approach is to assign subjects to risk categories according to sub-ranges of predicted risk. Within each risk category, the average predicted risk is compared to the observed cumulative incidence of the outcome. Alternatively, the sum of the predicted risks in a category provides an estimate of the expected number of outcomes for that category (E), which can be compared to the actual number of outcomes for that category (O).

Table :. Calibration of the Mortality Prediction Model (MPM) in 1997 patients admitted to an intensive care unit.

Range of MPM P(Dying)	Number of Subjects (N)	Deaths Observed	Deaths Expected
.00 - .09	967	38	41.9
.10 - .19	365	52	52.2
.20 - .29	194	50	48.2
.30 - .39	139	47	48.8
.40 - .49	88	41	39.0
.50 - .59	56	26	30.0
.60 - .69	56	35	35.9
.70 - .79	48	35	36.0
.80 - .89	35	26	29.5
.90 - 1.0	49	46	46.7
Total	1997	396	408.2

$X^2_{HL} = 4.94, p = .90$

In general, the previous table shows good agreement between expected and observed outcomes for each risk category, suggesting good calibration of risk estimates. Furthermore, the following ROC curve and its corresponding AUC show good discriminating ability of the risk estimates.



Determining the Predictors to Include in a Prediction Rule

Often the pool of potential predictors is large and the choice is to include all or a representative subject of the predictors in a model. The optimal number of predictors to include in a rule should be guided by the amount of information that is contained in the data set. For a binary outcome, a very rough rule of thumb for model stability is to require a minimum number of subjects in each outcome category for every predictor considered for the analysis. The suggested minimum number of subjects has ranged from 5 to 10 (Wasson JH, et al. Clinical prediction rule: application and methodologic standards. N Engl J Med 1985;313:793-799.). For continuous outcomes, the suggested rule of thumb is to require 10 subjects for every candidate predictor

When the number of potential predictors exceeds the limit suggested by these guidelines then a model based on all predictors is not only unstable and complex but is also likely to be optimistic and not generalize to other data sets.

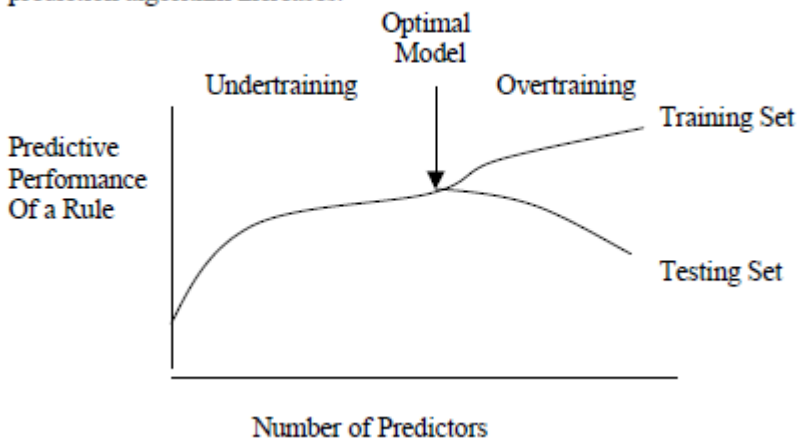
Parsimony

Parsimony pertains to the number of predictors to include in a prediction rule. Occam's Razor (William of Occam) states that "Pluralitas non est ponenda sine neccesitate" (plurality should not be posited without necessity). Albert Einstein stated a similar theme when saying “Everything should be made as simple as possible, but no simpler”.

For model building, parsimony implies including only those factors that are true predictors, not only in the data on which the model is created (training set) but also on other data sets on which it is to be applied (testing sets). This has direct relevance to models that are created by variable selection algorithms. A forward selection algorithm builds a model in steps, each time adding a factor that adds the more statistically significant, incremental predictive information to the model. A backwards elimination algorithm builds a model by starting with a large model that contains all of the factors and then reduces the model in steps, each time eliminating the least statistically significant factor.

Parsimony suggests that the model building process should cease at the point when selected factors would not be true predictors in other data sets. This is demonstrated by following figure showing the expected pattern of performance of series models created by a forward selection algorithm in training data set and evaluated in a testing data set. Models created in the early stage of the selection process tend to be based on predictors whose strong associations tend to generalize to other data sets. Therefore, the performance of these models in the training set also reflects the expected performance in other data sets. However, because of the search to identify factors related to the outcome in the training set, a point is often reached where factors are selected based on associations that are particular to the training set and are not repeated in a testing set. Including such factors in the model results in worse performance in a testing set. This process is often labeled as overtraining or overfitting. The challenge when using variable selection algorithms is to determine the optimal stopping point to avoid both problems.

Figure Expected change in predictive accuracy as the number of predictors in a prediction algorithm increases.



Validation

Validation of a clinical prediction rule involves obtaining "honest" estimates of the rule's performance in actual practice. Perhaps the simplest means for assessing the validity of a prediction rule is by examining its performance in an independent testing set. This is often implemented by randomly splitting a data set into a training data set and a testing data set. The prediction rule is developed in the training set and validated in the testing data set.

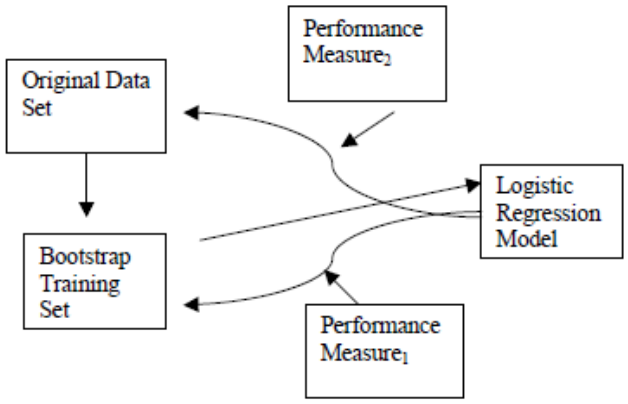
Alternatively, cross-validation divides the data set into a series of (usually disjoint but exhaustive) testing sets. For example, 10-fold cross-validation divides the data set into 10 mutually exclusive testing sets with each

subject in only one of these sets. A prediction rule is fit in the complement of each of these testing sets (90% of the data) and then evaluated in the corresponding testing set. Finally, the performances of the 10 prediction rules in the 10 testing sets are averaged and used as an estimate of the performance of the single prediction rule built on the entire data set. The following figure presents a graphical display of this method.

Subset #1	Subset #2	Subset #3	Subset #4	Subset #5	Subset #6	Subset #7	Subset #8	Subset #9	Subset #10
Test Set # 1	Train Set # 1	Train Set # 1	Train Set # 1	Train Set # 1	Train Set # 1	Train Set # 1	Train Set # 1	Train Set # 1	Train Set # 1
Train Set # 2	**Test Set # 2**	Train Set # 2	Train Set # 2	Train Set # 2	Train Set # 2	Train Set # 2	Train Set # 2	Train Set # 2	Train Set # 2
Train Set # 3	Train Set # 3	**Test Set # 3**	Train Set # 3	Train Set # 3	Train Set # 3	Train Set # 3	Train Set # 3	Train Set # 3	Train Set # 3
Train Set # 4	Train Set # 4	Train Set # 4	**Test Set # 4**	Train Set # 4	Train Set # 4	Train Set # 4	Train Set # 4	Train Set # 4	Train Set # 4
Train Set # 5	Train Set # 5	Train Set # 5	Train Set # 5	**Test Set # 5**	Train Set # 5	Train Set # 5	Train Set # 5	Train Set # 5	Train Set # 5
Train Set # 6	Train Set # 6	Train Set # 6	Train Set # 6	Train Set # 6	**Test Set # 6**	Train Set # 6	Train Set # 6	Train Set # 6	Train Set # 6
Train Set # 7	Train Set # 7	Train Set # 7	Train Set # 7	Train Set # 7	Train Set # 7	**Test Set # 7**	Train Set # 7	Train Set # 7	Train Set # 7
Train Set # 8	Train Set # 8	Train Set # 8	Train Set # 8	Train Set # 8	Train Set # 8	Train Set # 8	**Test Set # 8**	Train Set # 8	Train Set # 8
Train Set # 9	Train Set # 9	Train Set # 9	Train Set # 9	Train Set # 9	Train Set # 9	Train Set # 9	Train Set # 9	**Test Set # 9**	Train Set # 9
Train Set # 10	Train Set # 10	Train Set # 10	Train Set # 10	Train Set # 10	Train Set # 10	Train Set # 10	Train Set # 10	Train Set # 10	**Test Set # 10**

Bootstrapping is another method for estimating the validity of a prediction rule in the absence of an independent testing set. It involves re-sampling the original data set with replacement in order to obtain a new "bootstrap" training set of the same size as the original data set. A prediction rule is then developed on the bootstrap training set and a measure of its performance is calculated both on that data set and on the original data set, using the original data set as a testing set for the prediction rule developing on the bootstrap training set. The difference a performance measure on the two data set provides an estimate of the optimism of the performance of the prediction rule on the bootstrap training set. This process is then repeated multiple times and the average of the optimism values is used as an estimate of the optimism of a single prediction rule that is developed on the full data set. The following figure presents a graphical display of this method.

Figure Bootstrap estimate of the optimism of the Area of the ROC Curve (AUC) from a logistic regression model.



Optimism = (Performance Measure)$_1$ – (Performance Measure)$_2$