Biostatistics

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Measures of Association

Based on two Principles about the distribution and determinants of disease (dz):

1) They can be described by comparing the rates of disease (*frequency*) in different populations.
2) Can be inferred from the **Relative Risk** or **Odds Ratio** (*likelihood*) of dz based on the group

Measures of Dz Frequency

- Incidence Rate (IR)
  - Rate of NEW cases in a population for a given time PERIOD
- Prevalence
  - Proportion of TOTAL cases in a population at ONE POINT in time

Incidence Rate (IR)

$$IR = \frac{\textbf{NEW Cases}}{\text{Population at risk per time period}}$$

Person years can take the place of the denominator

- In a **cohort** study, the time period is defined
  - Person years can be used as the denominator
- In a population that is
  - Free of dz AND
  - At risk of dz

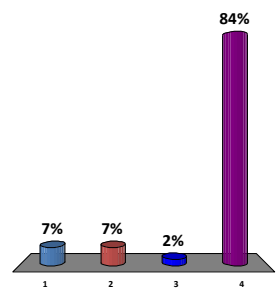
Incidence tells us the risk of acquiring the disease

Incidence Rate

- Sample of 100 premature children followed for development of myopia from birth to age 5.
- None had myopia at birth, next eye exam was done when they were 5 years old.
- 10 had myopia at the 5-yo eye exam.
- Assuming none were lost to follow up

What is the Incidence Rate of Myopia in this sample?

1. 10 %
2. 20 %
3. 1 %
4. 2 %



Incidence Rate of Myopia in this sample

IR= **NEW** Cases
Population at risk per time period

- 100 children x 5 years=500
- 10 had NEW myopia
- 10/500= 0.02 =2 % in 5 years

Mortality Rate

Mortality Rate is the Incidence Rate of death (Usually in deaths per 100,000 people per year)

i.e.:

The Collaborative Ocular Melanoma Study (COMS) compared preoperative external-beam radiation therapy plus enucleation to enucleation alone in patients with **large choroidal melanomas.** After 10 years of follow-up, the cumulative all-cause mortality rate for each treatment arm was 61%. In addition, the 10-year rates of death with histopathologically confirmed melanoma metastasis were not significantly different (45% in the pre-enucleation radiation arm and 40% in the enucleation-alone arm, *P* = .40)

Prevalence

- Prevalence= TOTAL number of cases
  Total population

Most useful in **Cross-Sectional** studies

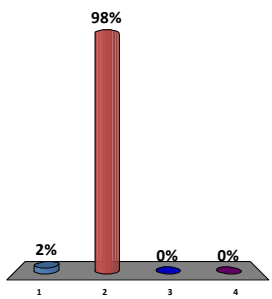
Prevalence tells us the frequency of a disease.

Prevalence

- In a study of 100 million adults in the US, that took two years, it was found that 10 million had cataracts.

What is the prevalence of cataracts in this group?

1. 5 %
2. 10 %
3. 20 %
4. 25 %



Prevalence of cataracts in this group

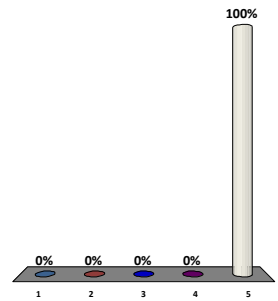
- Prevalence= TOTAL number of cases
  Total population
- P=10/100=0.1=10%

Risk

- Likelihood that people who are without a disease but exposed to certain risk factors acquire the disease

What risk factors can have an association with disease?

1. Physical
2. Behavioral
3. Inherited
4. Social stress
5. All of the above



Relative Risk (*likelihood*)

- The odds of contracting a disease based on group membership (personal characteristics)
- i.e. Risk of retinoblastoma in a child whose father had bilateral retinoblastoma is double the risk than that of a child whose father did not have retinoblastoma

Relative Risk

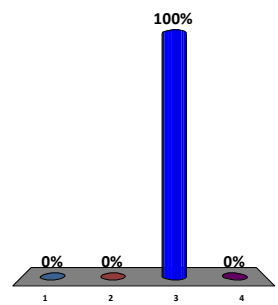
	Cataracts	No cataracts	Total
Smoking	30	70	100
No smoking	10	90	100
Total	40	160	200

RR

- IR exposed=30/100 =0.3
- IR unexposed=10/100=0.1
- RR= IR exposed/IR unexposed

What is the Relative Risk?

1. 1
2. 2
3. 3
4. 30



Relative Risk

- A RR of 1 means that the exposure does not seem to increase the likelihood of the disease
- A RR <1 means that the exposure seems to decrease the likelihood of the disease
- A RR >1 means that the exposure seems to increase the likelihood of the disease

Measures of Stability

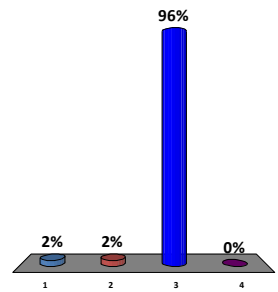
- The larger the Relative Risk, the stronger the association between exposure and disease
- But, need to evaluate the likelihood that the RR was affected by chance
- Confidence Intervals help us decide

Confidence Intervals

If the CI includes 1 in it, then we can conclude that that the RR finding was due to chance alone

Which of the following findings was due to chance alone?

1. RR=0.3 CI (0.16,0.5)
2. RR=5 CI (4.3,7)
3. RR=5 CI (0.9,6)
4. RR=0.8 CI (0.7,0.9)



Confidence Intervals

95% CI mean that we are 95% sure that the value of the RR is between the given bracket:

- **RR= 4** of PDR (proliferative diabetic retinopathy) after 10 years of type II DM compared to those people who have only had diabetes for one year
- **CI=(1.5,7.5)**
- Can conclude that you are 95 % sure there is an increased risk (4 times higher) because 1 is not included in the CI bracket

Odds Ratio(*likelihood*)

- In follow-up studies RR=IR exposed/IR control (not exposed)
- In **case control** and cross sectional studies

RR=Odds Ratio

OR = odds that a case is exposed

odds that a control is exposed

When OR is 1, then the disease and exposure are unrelated

Two by two table for OR

	Case	Non case
Exposed	a	b
Not Exposed	c	d

$$OR=\frac{ad}{bc}$$

Odds Ratio

	Chlamydia Conjunctivitis	No Chlamydia Conjunctivitis
Multiple Sexual partners	100	100
NO Multiple Sexual partners	20	180

- OR=100*180/20*100=9
- cases are 9 times more likely to have multiple partners

Variability

- When an estimate is presented as a single value (ie OR=9), we call it a *Point Estimate*
- To indicate the precision of that Point Estimate, we use a *Confidence Interval (CI)*
- We need CIs because a Point Estimate by itself cannot express *statistical variation or random error*
- A wide CI indicates low precision and a narrow CI indicates high precision

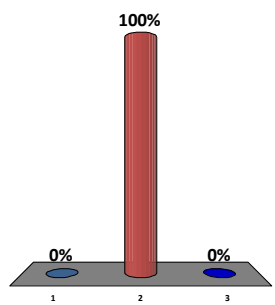
Variability

For the previous example:

- OR=100*180/20*100=9
- cases are 9 times more likely to have multiple partners

Which CI more precise?

1. CI (0,10)
2. CI (7.5,9.5)
3. CI (2,10)



Variability

From Harding Et al. Diabetes, glaucoma, sex, and cataract: analysis of combined data from two case control studies. Br J Ophthalmol. 1993 January; 77(1): 2–6:

The relative risk of glaucoma as a risk factor for cataract was 3.96 with 95% confidence interval from 2.35 to 6.68

What can you conclude?

Error

- Systematic Error=Bias
  - The result of any process that causes observations to differ systematically from the true values
    - i.e. a tonometer (or a clinician) that obtains consistently high readings for intraocular pressures
- Random Error=Chance
  - Normal in all observations

Chance

- Likely to result in observed values being on one side of the true values as on the other
- Reported as p Value and/or CI

Hypothesis Testing

- Asking whether an effect is present or not by using statistical tests
- The principal conclusion is stated in two terms:
  - Is there a relationship between exposure and disease?
  - Are the results statistically significant?
- The null hypothesis H_o states that there is no relationship between exposure and disease.
  (IR among Exposed=IR among unexposed RR=1; or that the OR=1 in a Case-control study))
- The alternative hypothesis H_1states that there is a relationship between exposure and disease

5 Steps in Hypothesis Testing

- State the Hypothesis
- Select the Sample and collect the data
- Calculate the test statistic
- Evaluate the evidence against the null hypothesis
- State the conclusion

Test Statistics

- Different for parametric data and non parametric data
- Parametric
  - z Test: Two group comparison
  - t Test: Two group comparison
  - Analysis of Variance (ANOVA): two or more groups
  - Regression
- Non Parametric
  - Wilcoxon's Rank sum test: two groups
  - Chi squared test: two or more groups
  - Mantel-Hanszel test : two or more groups

Statistical Significance

- The p (probability) Value is used for hypothesis testing
- The p Value represents the probability, assuming that the null hypothesis is true, that the results obtained would have occurred by chance
- The smaller the p Value, the more evidence you have against the null hypothesis
- The standard significance levels (α) for rejecting the null hypothesis are 0.05 (95%) or 0.1(90%)

Statistical Significance

- If α=0.05, then we reject the null hypothesis when p<0.05
- Reject H_o if the test statistic has a p Value< α
- Fail to Reject H_o if the test statistic has a p Value> α

Example 1 of Hypothesis Testing

- H_o=There is no association between contact lens wear and bacterial keratitis
- H_1= There is an association between contact lens wear and bacterial keratitis
- Selected the sample and collected case-control data:

	bacterial keratitis	No bacterial keratitis
CL wearer	13	5
Not wearer	38	56

Example 1 of Hypothesis Testing

- The significance level was set at α=0.05
- Test Statistic formula was applied and the p value was found to be p=0.03
- We would reject the null hypothesis
- Conclusion: There is a statistically significant association between contact lens wear and bacterial keratitis

Example 2 of Hypothesis Testing

- H_o=There is no association between Crystalens and Cystoid Macular Edema
- H_1= There is an association between Crystalens and Cystoid Macular Edema

Selected the sample and collected case-control data:

	Cystoid Macular Edema	NO Cystoid Macular Edema
Crystalens	28	25
Other IOL	26	30

Example 2 of Hypothesis Testing

- The significance level was set at α=0.05
- Test Statistic formula was applied and the p value was found to be p>0.2
- We would fail to reject the null hypothesis
- There is not a statistically significant association between Crystalens and Cystoid Macular Edema

Can second eye cataract extraction be justified?

- From Laidlaw and Harrad article on Eye (1993) 7, 680–686;
- A prospective study was carried out to **test the null hypothesis** that there is no additional benefit to be gained from second eye cataract extraction.
- Twenty-nine patients with unilateral cataract but contralateral pseudophakia completed a questionnaire enquiring into their visual disability and underwent testing of monocular and binocular visual acuity, contrast sensitivity, glare disability, fusion and stereopsis. These tests were repeated 4 months after second eye cataract extraction and lens implantation.
- Patients universally considered their vision to have been improved by second eye surgery and the prevalence of all symptoms were significantly reduced by this procedure. Normal binocular summation and stereopsis were restored following second eye cataract extraction.
- The average number of symptoms elicited from the ten standard questions pre-operatively was 4.6 (range 2-8). Post-operatively this was reduced to 1.6 (range 1-3). Each elicited symptom was significantly less prevalent following second eye surgery (p<0.0l).
- Conclusion: Symptomatic patients may benefit from second eye cataract extraction with lens implantation.

Statistical Power (1 – beta)

- Power is the probability that you will find ***as statistically significant***, a given RR that you hypothesize, if you do your study with a stated number of subjects
- Power increases when you add subjects to your study. But time and cost increase as subjects are added
- Power also increases if the RR is very high (say, RR = 10) because it is "easy" to detect a RR far from the null than it is to detect a RR closer to the null (say, RR = 2)
- When planning a study we want to maximize power but typically 80% power is acceptable and higher power can require ***MANY*** more subjects

The "Power" of A Study

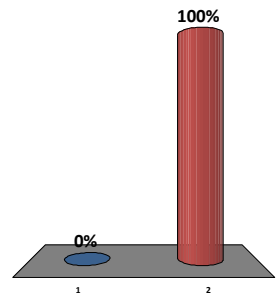
- By the "***power***" of a study design, we mean its capacity to furnish ***strong evidence of cause-and-effect*** when the results are positive.
- For the ***less powerful*** designs, even if the study is conducted appropriately and the results seem positive, concluding "***cause and effect***" is "going out on a limb" due to the type of data collected or due to the small sample size.

Statistical vs Clinical Significance/importance

- A statistically significant difference (no matter how low the p value is) does not mean that the difference is clinically important.
- The IOP lowering efficacy of drug A was statistically significantly better ($p<0.0001$) than that of drug B. The mean IOP reduction from drug A was lower by 1 mmHg.

Is this clinically important?

1. Agree
2. Disagree



Clinical significance

The COMET study evaluated 469 children 462 (98.5%) completed the 3-year visit. Mean (+/- SE) 3-year increases in myopia (spherical equivalent) were:

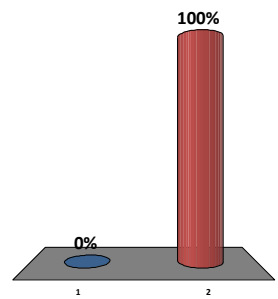
-1.28 +/- 0.06 D in the PAL group

-1.48 +/- 0.06 D in the SVL group.

The 3-year difference in progression of 0.20 +/- 0.08 D between the two groups was statistically significant (P = 0.004).

Is this clinically important?

1. Agree
2. Disagree



Validity

- Accuracy
- The degree to which the data measure what they were intended to measure
- Freedom from bias or ***systematic*** error (including confounding)
- Internal Validity and External Validity

Internal Validity

- Study is properly done
- No major methodological problems
- Means that the samples you studied are comparable to the populations from which you selected them

External Validity

- Generalizability based on a study results to all patients with the disease in ***other*** populations

Reliability

- Repeatability
- Precision
- The extent to which repeated measurements of a stable phenomenon by different people and instruments at different times and places get the same results