IM Journal Club

July 2018

What is Evidence Based Medicine?

The practice of EBM is the integration of

individual clinical expertise

with the

best available external clinical evidence from systematic research

and

patients' values and expectations

"The good physician treats the disease; the great physician treats the patient who has the disease." Sir William Osler

Observational

- Case Control
- Cross-sectional
- Cohort (retrospective, prospective)

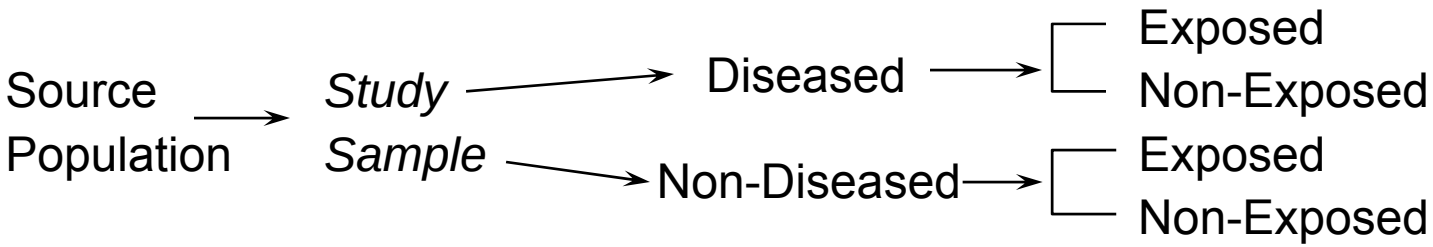
Interventional (clinical trial)

Cohort Studies

- Framingham
  - **Cardiovascular heart disease**
  - **Cohort I (1948): 5200**
  - **Cohort II (1972): 5100**
  - **Cohort III (2002): 4000**
- Nurses' Health Study (1976)
  - **Diet and Lifestyle and Cancer**
  - **120,000 female nurses aged 30-55**

Case-control Studies

Flow Chart:



Examples

- Reye's syndrome and medications
- Prenatal diethylstilbestrol (DES) exposure and cancer of the vagina
- Superabsorbent tampon use and toxic shock syndrome
- Sleeping position and SIDS

Prevalence

- Numerator
  - all those with the attribute at a particular time
- Denominator
  - the population at risk of having the attribute during that same time period

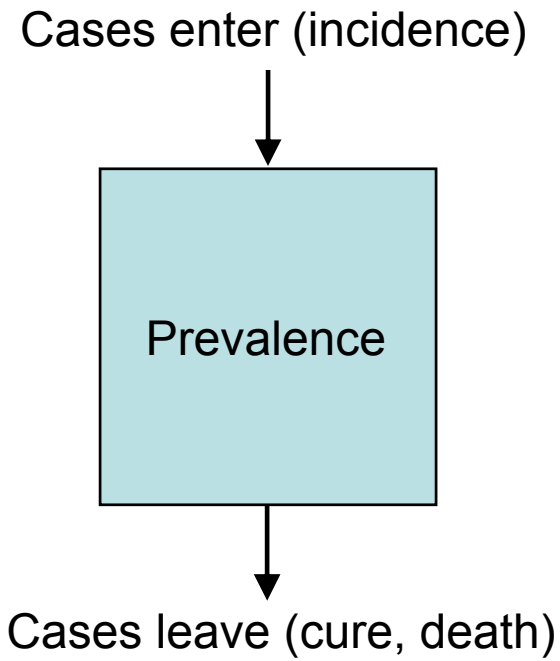
$$\text{Prevalence} = \frac{\text{Number of cases}}{\text{Number in population}}$$

Incidence

- **Cumulative Incidence:** the probability (risk) of an individual developing the disease (outcome) during a specific period of time.

$$\text{Incidence} = \frac{\text{New cases over a time period}}{\text{Population at risk}}$$

Prevalence = Incidence X Duration



AIDS: Early years: Incidence 1/1000 Duration: 1 yr Prevalence: 250,000

Now: : Incidence 1/1000 Duration: 30 yrs Prevalence: 9,900,000

In an RCT, aspirin was compared to placebo for prevention of stent restenosis. Aspirin was better, but the p value was 0.10. This means:

A. The chances are that placebo is better than aspirin

B. The probability is 1 in 10 that these results occurred by chance

C. The chance is 90% that the study is correct

D. Aspirin is 10% better than placebo

Risks

- Cohort study:
  - (Absolute) Risk in group1 = 20%
  - Absolute Risk (AR) in Group 2 = 30%
  - Relative Risk (RR) of group1 to group 2 =
    - 20%/30% = 0.67
  - Absolute risk reduction = AR_2-AR_1 =
    - 30%-20% = 10% (0.10)
  - Number Needed to Treat = 1/ARR =
    - 1/(0.10) = 10

Risks

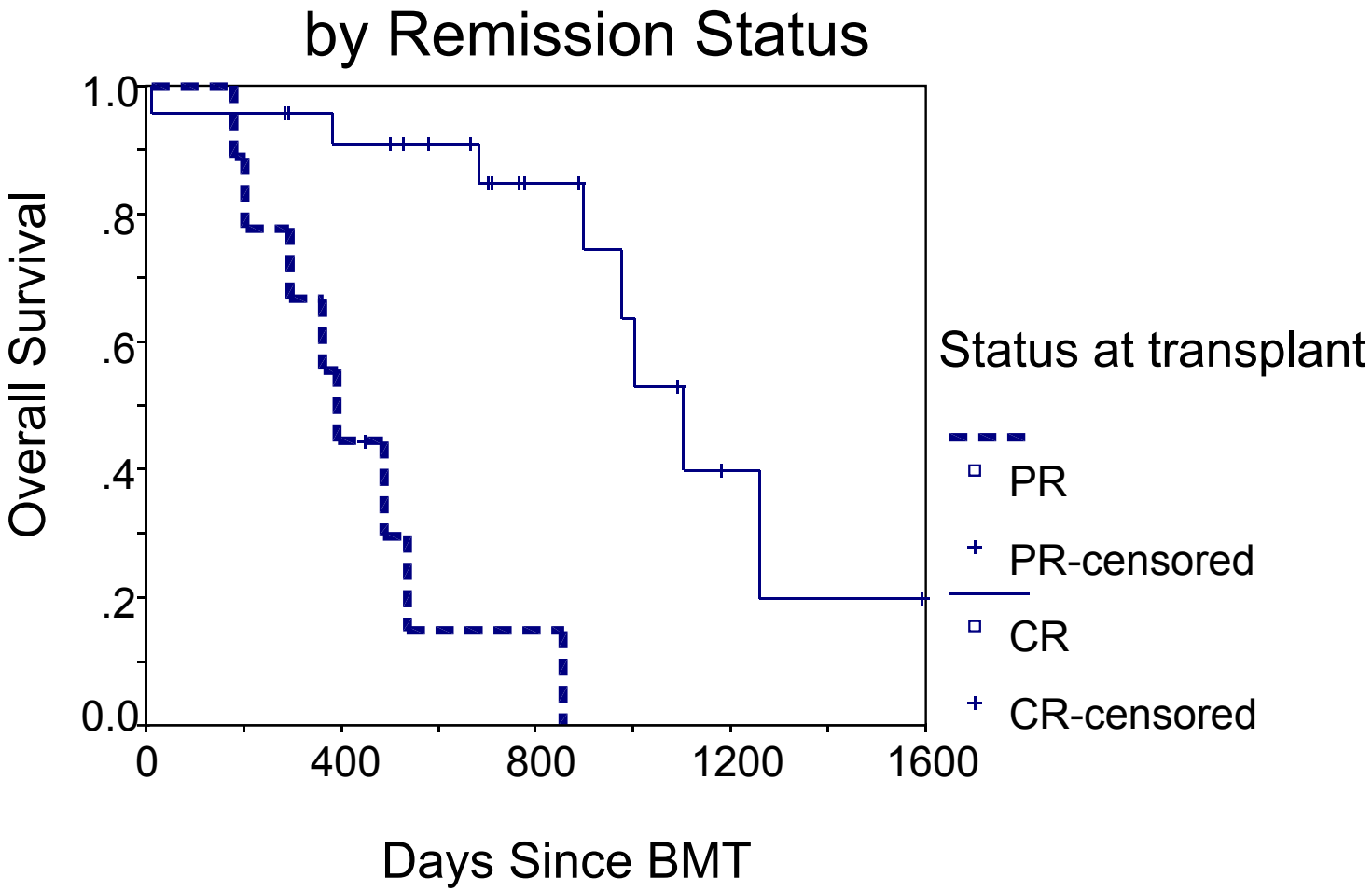
Case Control Study

Exposure	Disease	
	Cases	***Controls***
Exposure	**A**	**B**
No Exposure	**C**	**D**

Odds of Disease in Exposed = A/B
Odds of Disease in Unexposed = C/D
Odds Ratio = OR = (A/B)/(C/D) = AD/BC

Risks

Metastatic Breast Cancer



Survival Analysis: Hazard Ratio (HR)

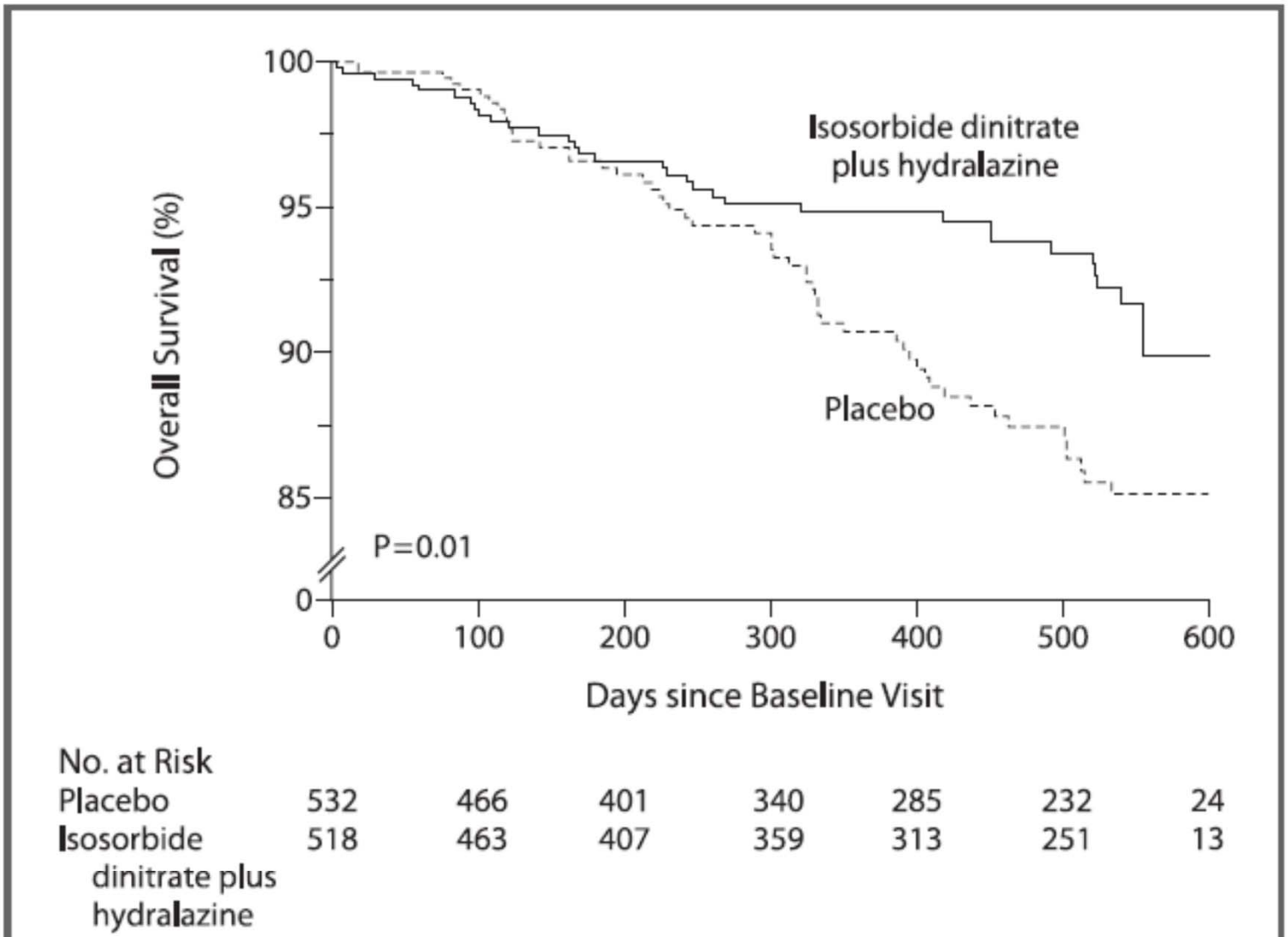


Figure 1. Kaplan–Meier Estimates of Overall Survival.

N Engl J Med. 2004;351(20):2049-2057.

- A study is a sample
- The sample is from an underlying population
- The study (however small) hopes to infer something about the population
  - e.g. What is the difference between two treatments?

Confidence Intervals

- We are 95% sure that the true value (of the underlying population) lies within this interval
- OR 2.1 (95% CI 1.2-3.3)
- Null hypothesis:
  - OR, RR HR 1.0
  - Treatment Difference 0.0

Question 2

A study looks at two treatments of hypertension. The outcome is change in SBP. Which of these differences between treatment A and B is significant?

A. 4.1 mm (95% CI 0.9-7.3)
B. 5.2 mm (95% CI 1.0-9.4)
C. 3.6 mm (95% CI -1.0-8.2)
D. A and B
E. I am 95% confident that I don’t know

Errors in Making Decisions

- **Type I Error**
  - **Reject True Null Hypothesis (“False positive”)**
  - **Has Serious Consequences**
  - **Probability of Type I Error Is α**
    - **Called Level of Significance**
- **Type II Error**
  - **Do Not Reject False Null Hypothesis (“False negative”)**
  - **Probability of Type II Error Is β (Beta)**

Type I and II Errors

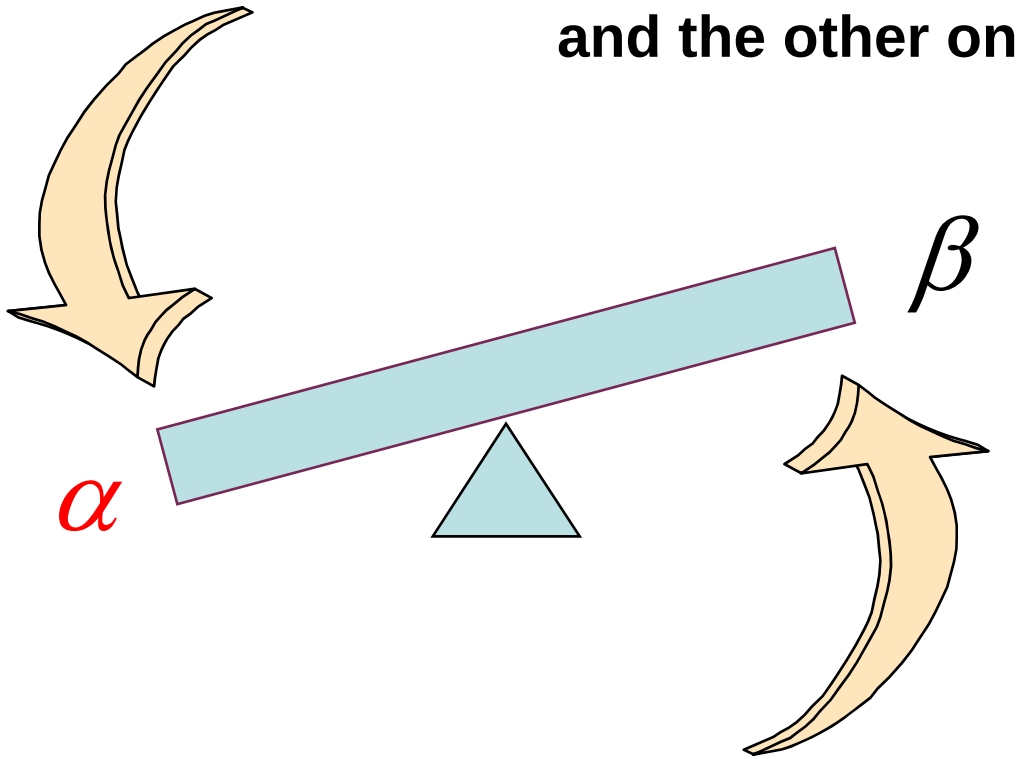
Jury Trial		
	Actual Situation	
Verdict	Innocent	Guilty
Innocent	**Correct**	**Error**
Guilty	**Error**	**Correct**

Type I and II Errors

Jury Trial			**Hypothesis Test**		
	Actual Situation			Actual Situation	
Verdict	Innocent	Guilty	**Decision**	H_0 True	H_0 False
Innocent	**Correct**	**Error**	Do Not Reject H_0	1- α	**Type II Error** β
Guilty	**Error**	**Correct**	Reject H_0	**Type I Error** α	**Power** 1- β

α & β Have an Inverse Relationship

Reduce probability of one error and the other one goes up.



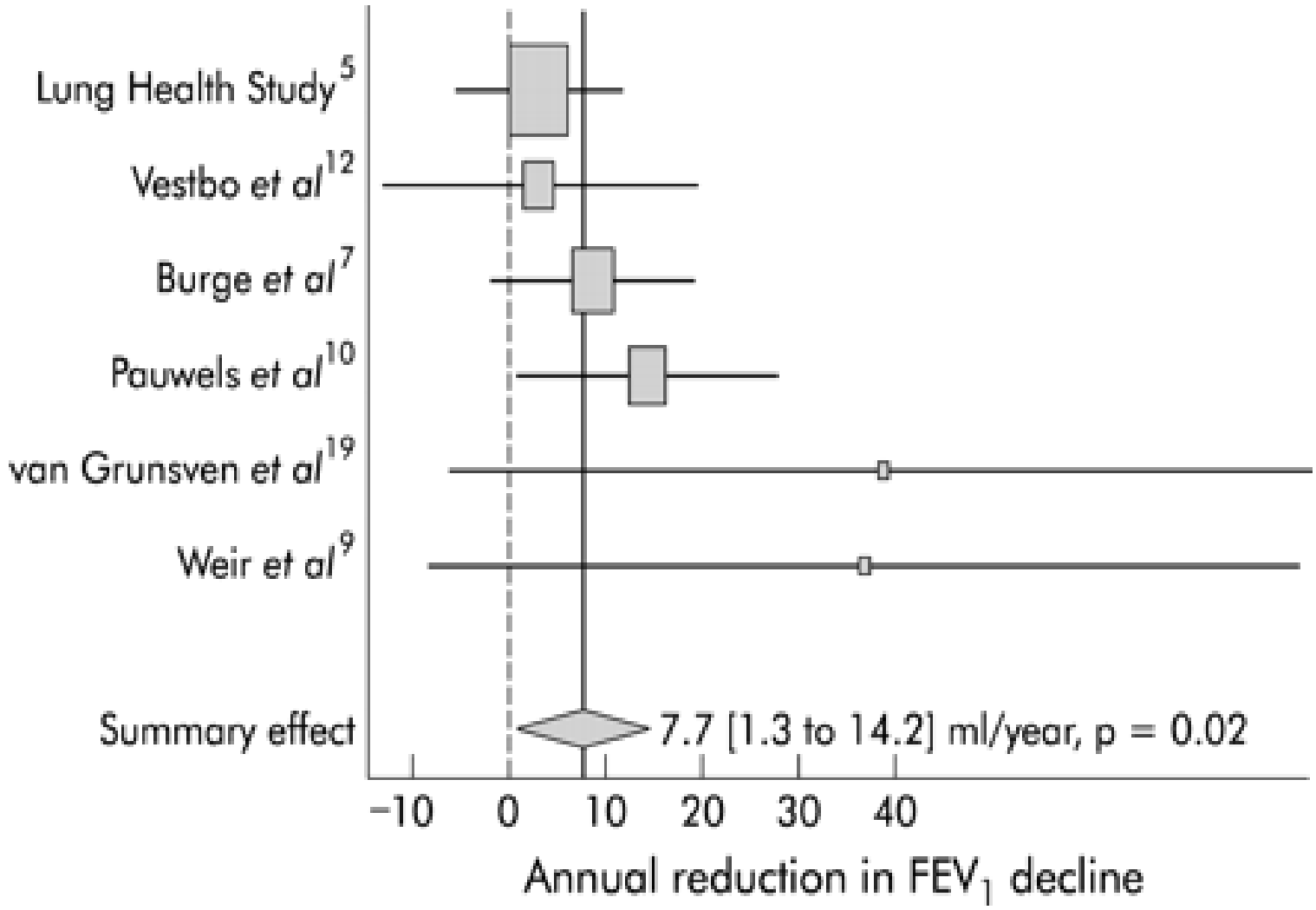
Why $p < 0.05$

- It is arbitrary (R.A. Fisher)
- Should it be lowered to 0.005?

Meta-analysis

- Combine similar studies with same defined outcome in order to gain power
- Weighted average of the studies is calculated

Tree Plots


Lung Health Study[5]
Vestbo et al[12]
Burge et al[7]
Pauwels et al[10]
van Grunsven et al[19]
Weir et al[9]
Summary effect
7.7 [1.3 to 14.2] ml/year, p = 0.02
−10
0
10
20
30
40
Annual reduction in FEV1 decline

RCT Analysis

- Intent-to-treat = as randomized
  - If not all randomized subjects are counted, those not counted may be different from those included in the analysis

A test has a sensitivity of 70% and a specificity of 90%. If the prevalence of disease is 20%, what is the PPV?

	Disease +	Disease -	
Test +			Total with Test +
Test -			Total with Test -
	Total with Disease	Total without Disease	Total patients

	Disease +	Disease -	
Test +			Total with Test +
Test -			Total with Test -
	Total with Disease	Total without Disease	1000

	Disease +	Disease -	
Test +			Total with Test +
Test -			Total with Test -
	200	Total without Disease	1000

	Disease +	Disease -	
Test +			Total with Test +
Test -			Total with Test -
	200	800	1000

	Disease +	Disease -	
Test +	140		Total with Test +
Test -			Total with Test -
	200	800	1000

	Disease +	Disease -	
Test +	140		Total with Test +
Test -	60		Total with Test -
	200	800	1000

	Disease +	Disease -	
Test +	140		Total with Test +
Test -	60	720	Total with Test -
	200	800	1000

	Disease +	Disease -	
Test +	140	80	Total with Test +
Test -	60	720	Total with Test -
	200	800	1000

	Disease +	Disease -	
Test +	140	80	220
Test -	60	720	Total with Test -
	200	800	1000

Question 4

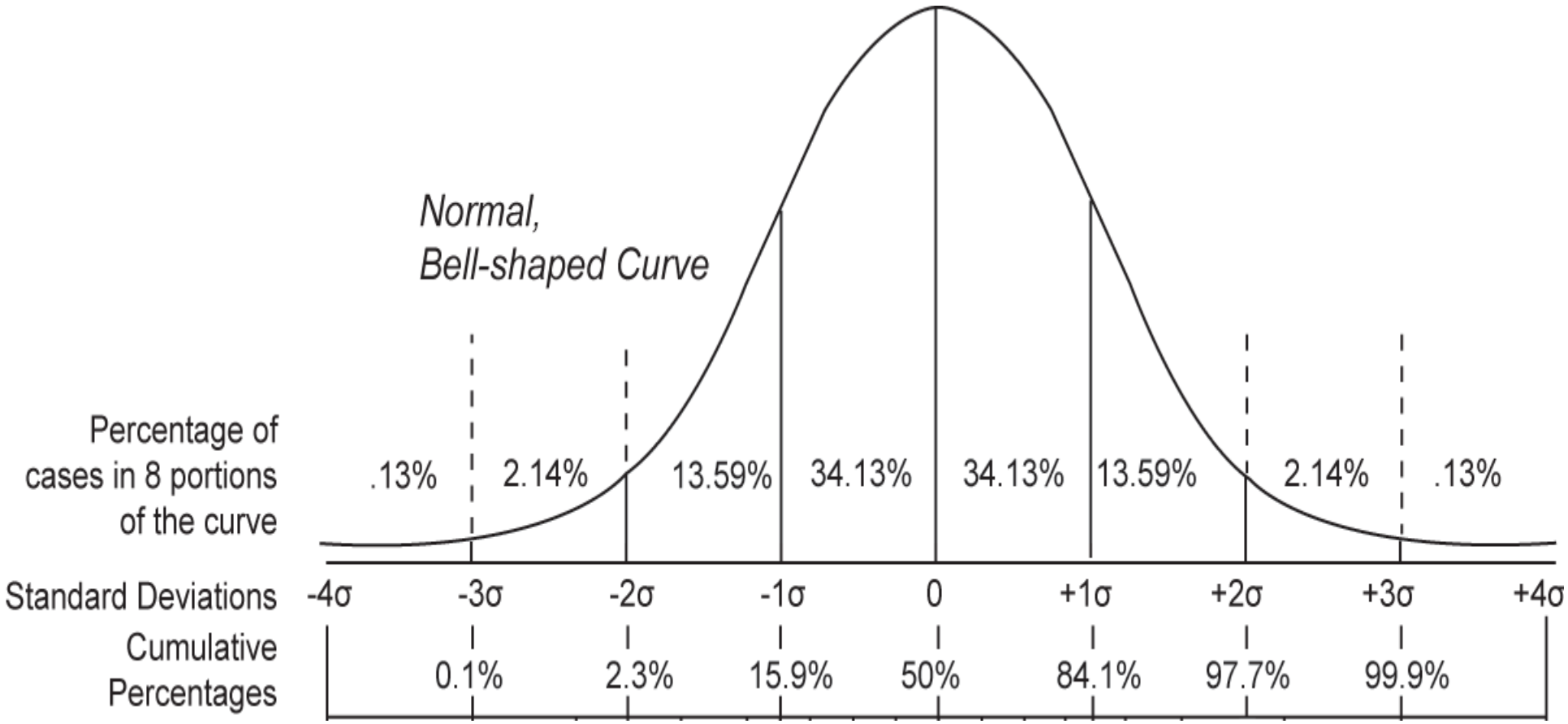
- PPV = 140/220 = 63.6%

2. To determine if fasting is associated with dengue fever, data from 40 patients with dengue fever were collected. These patients were matched for age, sex, and race to 40 patients without dengue fever. The hospital charts of these patients were then reviewed to determine whether they also fasted prior to their illness. This study type is known as:
   a. Cross-sectional study
   b. Concurrent cohort study
   c. Case-control study
   d. Retrospective cohort study
   e. Randomized clinical trial

3. The purpose of a double-blind or double-masked study is to:
   a. Achieve comparability of treated and untreated subjects
   b. Reduce the effects of sampling variation
   c. Avoid observer and subject bias
   d. Avoid observer bias and sampling variation

5. Any systematic error in the design, conduct, or analysis of a study that results in a mistaken estimate of an exposure's effect on the risk of disease is called:
   a. Confounding
   b. Bias
   c. Interaction
   d. Stratification

What next?


Normal,
Bell-shaped Curve
Percentage of cases in 8 portions of the curve
.13%
2.14%
13.59%
34.13%
34.13%
13.59%
2.14%
.13%
Standard Deviations
-4σ
-3σ
-2σ
-1σ
0
+1σ
+2σ
+3σ
+4σ
Cumulative Percentages
0.1%
2.3%
15.9%
50%
84.1%
97.7%
99.9%

T-test

- Tests difference between two means
- Requires approximately normal distribution in both groups

Who is this man?

- He is not Mr. T
- His name is not Student
- His name is W. S. Gossett

THE PROBABLE ERROR OF A MEAN

By STUDENT

Introduction

Any experiment may he regarded as forming an individual of a "population" of experiments which might he performed under the same conditions. A series of experiments is a sample drawn from this population.

Now any series of experiments is only of value in so far as it enables us to form a judgment as to the statistical constants of the population to which the experiments belong. In a greater number of cases the question finally turns on the value of a mean, either directly, or as the mean difference between the two quantities.

If the number of experiments be very large, we may have precise information as to the value of the mean, but if our sample be small, we have two sources of uncertainty: (1) owing to the "error of random sampling" the mean of our series of experiments deviates more or less widely from the mean of the population, and (2) the sample is not sufficiently large to determine what is the law of distribution of individuals. It is usual, however, to assume a normal distribution, because, in a very large number of cases, this gives an approximation so close that a small sample will give no real information as to the manner in which the population deviates from normality: since some law of distribution must he assumed it is better to work with a curve whose area and ordinates are tabled, and whose properties are well known. This assumption is accordingly made in the present paper, so that its conclusions are not strictly applicable to populations known not to be normally distributed; yet it appears probable that