

Introduction to Medical Statistics II For Medical Students

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Class objectives

 After the end of this session, (hopefully) the students would be able to understand and correctly describe the concept of the following topics:

Topics outline

- Medical statistics II
 - Statistical inference
 - Hypothesis generation and testing
 - The alpha level and p value
 - Type I error and type II error
 - Test of statistical significance
 - Test of clinical importance
 - Confidence intervals
 - Impact (size of effect)

Inferential Statistics

Learning objectives

- Statistical inference
- Confidence intervals
- Hypothesis generation
- Hypothesis testing
- The alpha level and p value
- Type I error and type II error
- Test of statistical significance, clinical importance
- Impact (size of effect)

RS



If we want to know the birthweight of newborns from smoking mothers and nonsmoking mothers, how should we design and analyze our study?

Given that you are ...



So you just log-in to your infinite database...





If we want to know the birthweight of newborns from smoking mothers and nonsmoking mothers, how should we design and analyze our study?

But if you're not ... Then, what should you do?





Sample statistics





Statistical Inference Point estimate! Why is there a difference?? Δ= 2772-2600 BW smoking Smoking mothers Birthweight moms= 2600 2772±659 gm (n=74)Non-smoking Birthweight BW non-smoking mothers (n=115) 3055±752 gm moms = 3000 $\Delta = 3055 - 3000$

Point estimate! Difference between the point estimates and the unknown population mean is due to sampling error!

Δ= 2772-2600



Sampling error – error introduced because we are working with a sample and not the population itself.

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 $\Delta = 3055 - 3000$



Population parameter BW = 2600 gm??





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Sample statistics BW = 2772 gm





Population parameter BW = 2600 gm??





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Sample statistics BW = 2772 gm



Statistical Inference 2772 gm 2600 gm 2452 gm 2598 gm 2800 gm 2320 gm ??????



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 If the number of trials are large enough then the sample means will follow a Normal distribution because of the central limit theorem





2452 gm







2600 gm



2598 gm

2320 gm



Sampling Distribution of the Mean (SEM)

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Standard error

Standard error of the mean SD of the mean



As the sample size increases, the estimated standard error decreases. The bigger the sample, the smaller is the error in our estimate of population mean.

Standard error

- Standard error of the mean
 - Why divided by \sqrt{n} ?
 - Scenario 1: Mean 100 SD 10 N=10
 - Scenario 2: Mean 100 SD 10 N=100
 - Scenario 3: Mean 100 SD 10 N=1000
 - Scenario 4: Mean 100 SD 10 N=10000
 - Scenario 5: Mean 100 SD 10 N=100000
 - Calculate the SE for each scenario

Standard error

Standard error of the mean

- Why divided by \sqrt{n} ?
 - Scenario 1: Mean 100 SD 10 N=10
 - Scenario 2: Mean 100 SD 10 N=100
 - Scenario 3: Mean 100 SD 10 N=1000
 - Scenario 4: Mean 100 SD 10 N=10000
 - Scenario 5: Mean 100 SD 10 N=100000
 - Calculate the SE for each scenario

SE 3.16 SE 1.00 SE 0.32 SE 0.10 SE 0.03

As sample size increases, the standard error of the mean decreases and will continue to approach zero as your sample size increases infinitely (closer to the TRUE population size)

Confidence interval

- 95% confidence interval
 Upper bound Mean + 1.96 (SE)
 - Lower bound
 Mean 1.96 (SE)

95% Confidence interval



Confidence interval

Confidence Level	Critical Values (z)
80%	1.28
85%	1.44
90%	1.64
95%	1.96
99%	2.57







Variances

Standard deviation

Single sample variation

Descriptive statistics

Inferential statistics

Variation in all possible samples from a source population

Standard error

Confidence Interval

Calculate the 95%CI



95%CI

- Calculation formula
 - Mean±1.96(SE)
 - For smoking moms: SE=659/√74 = 76.6
 1.96xSE = 150.2 => 2621.8 to 2922.2
 - For non-smoking moms: SE=752/√115 = 70.1
 1.96xSE = 137.4 => 2917.6 to 3192.4

. tabstat birthwt,by(smoke) stat(mean sd n median p25 p75)

Summary for variables: birthwt

by categories of: smoke (smoking during pregnancy: 0=no, 1=yes)

smoke	mean	sd	Ν	p50	p25	p75
0	3054.957	752.409	115	3100	2495	3629
1	2772.297	659.8075	74	2775.5	2367	3260
Total	2944.286	729.016	189	2977	2414	3475

. ci means birthwt if smoke==1

Variable	Obs	Mean	Std. Err.	[95% Conf.	Interval]
birthwt	74	2772.297	76.70106	2619.432	2925.162

. ci means birthwt if smoke==0

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Variable	Obs	Mean	Std. Err.	[95% Conf.	Interval]
birthwt	115	3054.957	70.1625	2915.965	3193.948

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Smoking mothers (n=74) Statistical inference [95% Conf. Interval] Birthweight 2772±659 gm

Source population of all mothers (n=unknown) Non-smoking mothers (n=115) Birthweight 3055±752 gn

The wider the CI, the lesser the precision The narrower the CI, the higher the precision

3055±752 gm

[95% Conf. Interval] 2915.965 3193.948



Comparative question

Are they <u>significantly different</u> from each other?

Are the mean birthweight different between the 2 groups?








Are they significantly different from each other??



Are they significantly different from each other??

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2915.965

3193.948

Mean difference of point estimates



Are they significantly different from each other??

Mean difference of point estimates



Are they significantly different from each other??

General concept

- 1. Making an initial assumption (hypothesis)
- 2. Collect the data (evidence)

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3. Based on the available data (evidence), decide whether to reject or not reject the initial assumption (hypothesis)





Criminal Trial Analogy

"the defendant is innocent until proven guilty by evidence"

Null hypothesis (H₀)

- Hypothesis of no difference (contradicts to the investigators' belief)
- Defendant is not guilty (innocent)

Alternative hypothesis (H_a)

- Hypothesis of difference (complies with the investigators' belief)
- Defendant is guilty (criminal)

Null hypothesis (H₀)

- Hypothesis of no difference (contradicts to the investigators' belief)
- Defendant is not guilty (innocent)

Alter No statistically testable!

- Hypothesis of difference (complies with the investigators' belief)
- Defendant is guilty (criminal)

Null hypothesis (H₀)

- Hypothesis of no difference (contradicts to the investigators' belief)
- Defendant was not at the crime scene

Alternative hypothesis (H_a)

- Hypothesis of difference (complies with the investigators' belief)
- Defendant was at the crime scene



In statistics, try to think of yourself (the investigators) as the jury. The jury makes a decision based on the available evidence (data).







Trial Pocult	Actual Truth		
	Drug works	Drug does not work	
Drug works	Correct	Type I error (False positive)	
Drug does not work	Type II error (False negative)	Correct	

Trial Pocult	Actual Truth		
mat kesutt	Drug works	Drug does not work	
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Trial Pocult	Actual Truth		
mai Kesuli	Drug works	Drug does not work	
Drug works	Correct	Type I error (False positive)	
Drug does not work	Type II error (False negative)	Correct	

Alpha error (type I error)

- When the investigators rejected the null hypothesis, when, in fact, the null hypothesis is TRUE.
- Accept: at critical value 0.05, 0.01
- Statistical power (type II error, Beta error)
 - When the investigators were not able to reject the null hypothesis, when, in fact, the null hypothesis is FALSE.
 - Accept: power 80-90%, Beta 10-20%

- To minimize the possibility of both type I and type II error, researchers calculate the appropriate study size for hypothesis testing!
- Factors that influence the study size
 - Statistical power
 - Alpha error
 - Variability
 - Effect size

- To minimize the possibility of both type I and type II error, researchers calculate the appropriate study size for hypothesis testing!
- Increase study size
 Increase statistical power
 Reduced type II error





- To minimize the possibility of both type I and type II error, researchers calculate the appropriate study size for hypothesis testing!
- Increase study size
- Reduce type I error
- 0.10 small study size
- 0.05 moderate study size
- 0.01 highest study size

To minimize the possibility of both type I and type II error, researchers calculate the appropriate study size for hypothesis testing!

Variability

- Large variability needs large study size
- Small variability needs small study size

medium variability





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To minimize the possibility of both type I and type II error, researchers calculate the appropriate study size for hypothesis testing!

Effect size

- Large effect needs small study size
- Small effect needs large study size

Hypothesis generation MISS * UNIVERSE



Smoking moms

Non-smoking moms



Testing association between maternal smoking and neonatal birthweight

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Null hypothesis (H₀)

- Hypothesis of no difference (contradicts to the investigators' belief)
- BW in smokers = BW in non-smokers

Alternative hypothesis (H_a)

- Hypothesis of difference (complies with the investigators' belief)
- BW in smokers ≠ BW in non-smokers

Null hypothesis (H₀)

- Hypothesis of no difference (contradicts to the investigators' belief)
- BW in smokers = BW in non-smokers
- BW difference = 0
- Alternative hypothesis (H_a)
 - Hypothesis of difference (complies with the investigators' belief)
 - BW in smokers ≠ BW in non-smokers
 - BW difference $\neq 0$



Smoking moms		Non-smoking moms		
[95% Conf. In	terval]	[95% Conf. Interval]		
2619.432 2	925.162	2915.965 3193.948		

Find the statistical testing to compare two independent mean

Independent or two-sample t-test

Hypothesis testing with t-test

. ttest birthwt,by(smoke)

Two-sample t test with equal variances

Group	Obs	Mean	Std. Err.	Std. Dev.	[95% Conf.	Interval]
0	115	3054.957	70.1625	752.409	2915.965	3193.948
1	74	2772.297	76.70106	659.8075	2619.432	2925.162
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diff		282.6592	106.9544		71.66693	493.6515
diff = m	ean(0) -	mean(1)			t :	2.6428
Ho: diff = 0				degrees	of freedom =	= 187
Ha: diff	< 0		Ha: diff !=	0	Ha: d	iff > 0
Pr(T < t) =	0.9955	Pr(T > t = 0	0.0089	Pr(T > t)	= 0.0045

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Hypothesis testing with t-test

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diff = 1	mean(0) -	mean(1)		dogrados	t of freedom	= 2.6428
HO: $aTTT = 0$	0			aegrees	of freedom	= 10/
Ha: dif	f < 0		Ha: diff !=	0	Ha: d	iff > 0
Pr(T < t) :	0.9955	Pr(T > t) =	0.0089	Pr(T > t) = 0.0045
			P-value			
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P stands for probability.

- Thus, P-value is the probability value.
- It expresses the weight of evidence in favor of against the stated null hypothesis.
- Precise definition: P value is the probability, given the null hypothesis is true, of obtaining the data as extreme or more extreme than that of the observed.

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โอกาสพบความแตกต่างบนสมมติฐานของความไม่แตกต่าง



- Suppose we want to test the efficacy of the 2 drugs
- Outcomes = success rate of something
- Given the null hypothesis is really TRUE.
- H0: success rate in drug A = success rate in drug B



- Suppose we want to test the efficacy of the 2 drugs
- Outcomes = success rate of something
- Given the null hypothesis is really TRUE.
- H0: success rate in drug A = success rate in drug B



Success rate 50%

Success rate 50%

Diff=0, p-value=1.000

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- Suppose we want to test the efficacy of the 2 drugs
- Outcomes = success rate of something
- Given the null hypothesis is really TRUE.
- H0: success rate in drug A = success rate in drug B



Success rate 45%

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Success rate 55%

Diff=10, p-value=0.200


- Suppose we want to test the efficacy of the 2 drugs
- Outcomes = success rate of something
- Given the null hypothesis is really TRUE.
- H0: success rate in drug A = success rate in drug B



Success rate 55%

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Success rate 45%

Diff=10, p-value=0.200



- Suppose we want to test the efficacy of the 2 drugs
- Outcomes = success rate of something
- Given the null hypothesis is really TRUE.
- H0: success rate in drug A = success rate in drug B



Success rate 60%

Success rate 40%

Diff=20, p-value=0.100

Introduction To Medical Statistics

- Suppose we want to test the efficacy of the 2 drugs
- Outcomes = success rate of something
- Given the null hypothesis is really TRUE.
- H0: success rate in drug A = success rate in drug B



Success rate 40%

Success rate 60%

Diff=20, p-value=0.100

Introduction To Medical Statistics

- Suppose we want to test the efficacy of the 2 drugs
- Outcomes = success rate of something
- Given the null hypothesis is really TRUE.
- H0: success rate in drug A = success rate in drug B



- Observed difference = 40%
- What are the chances to get a result like this, when the null hypothesis is TRUE?
- P-value < 0.05 means?</p>



Success rate 70%

Success rate 30%

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 P-value <0.05 means there is less than 5% chance to identify the difference of 40% or more in any sample if the null hypothesis is TRUE.



Success rate 70%

Success rate 30%

Diff=40, p-value=0.020



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P-value < 0.05 means there is less than 5% chance that a difference this large or more could occur by chance (random error) alone.



Success rate 30%

Diff=40, p-value=0.020

Introduction To Medical Statistics

P-value <0.05 means there is less than 5% chance that a difference this large or more could occur by chance (random error) alone.



 P-value <0.05 means there is less than 5% chance to identify the difference of 40% or more in any sample if the null hypothesis is TRUE.



- 0.05 or 5% is commonly used as a cut-off.
- P <0.05 is commonly described as statistically significant difference.
- P ≥0.05 is commonly described as not statistically significant difference.

Common misconception about the P-value

- A P-value is the probability that the null hypothesis is TRUE.
- A P-value quantifies the probability to falsely reject the null hypothesis.
- The smaller the P-value, the larger or the more importance is the clinical effect.

Common misconception about the P-value

The null hypothesis is already and always TRUE based on P-value definition!

A P-value quantifies the statistical evidence that the results identified in the sample are different from the null hypothesis (in population) or not?

The smaller the P-value, the more statistical evidence to reject the null hypothesis.

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Hypothesis testing with t-test

. ttest birthwt,by(smoke)

Two-sample t test with equal variances

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			P-value?	?		
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Hypothesis testing with t-test

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Two-sample t test with equal variances

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Ha: dif	f < 0		Ha: diff !=	0	Ha: d	iff > 0
Pr(T < t)	= 0.9955	Pr(T > t =	0.0089	Pr(T > t) = 0.0045

The probability is less than 1 in 100 that a difference this large could be due to chance (random error) alone (there must be some effect from smoking on birthweight for sure).

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Hypothesis testing Comparative questions Compare different between groups (independent group) = อิสระต่อกัน

 Compare different within groups (dependent group) = ไม่อิสระต่อกัน

- Comparative questions
 เปรียบเทียบระดับน้ำตาลในเลือดที่ 3 เดือนระหว่าง ผู้ป่วยที่ได้รับการรักษาด้วยยาเบาหวานใหม่ กับ ผู้ป่วยที่ได้รับการรักษาด้วยยาเบาหวานแบบเดิม
 - Two independent groups (ใหม่ vs. เดิม)
 Mean FBS in ใหม่ vs. Mean FBS in เดิม
 Compare two independent means

Comparative questions เปรียบเทียบระดับน้ำตาลในเลือดที่ 3 เดือนระหว่าง ้ผู้ป่วยที่ได้รับการรักษาด้วยยาเบาหวานใหม่ กับ ้ผู้ป่วยที่ได้รับการรักษาด้วยยาเบาหวานแบบเดิม Compare two independent means Null hypothesis Mean FBS in ใหม่ = Mean FBS in เก่า Alternative hypothesis ■ Mean FBS in ใหม่ ≠ Mean FBS in เก่า

Hypothesis testing Continuous variables 2 Types of statistics Parametric statistics Based on normal distribution Based on parameters Non-parametric statistics Not based on distribution Based on rank and order

Two independent: numerical

Normal di	stribution?
Yes	No
Parametric statistics	Nonparametric statistics
Independent t-test Two-sample t-test	Wilcoxon (Mann-Whitney) Rank sum test
Dependent t-test Paired t-test	Wilcoxon (Mann-Whitney) <mark>Sign rank test</mark>

t-test

Independent t-test

- Compares two independent means
- Based on normal distribution
- Null hypothesis: Mean 1 = Mean 2

(Two sample come from population with the same mean)

- Assumption
 - Continuous data, normally distributed
 - Variances are the same

Ranksum test

Rationale of test

- It is the analogue of t-test
- It is based on the ranks of the data
- Suitable for larger samples
- Does not test the medians, it tests the whole distribution
- Assumption
 - The data are in two groups and can be ranked

Ranksum test

124	A	В	С	D	E	F	G	н	1
1	Wilcoxon	Rank-Sum	rest						
2									
3	Original da	ata		Ranks					
4								Control	Drug
5	Control	Drug		Control	Drug		count	12	12
6	11	34		4	22.5		rank sum	119.5	180.5
7	15	31		10	20.5				
8	9	35		2	24		α	0.05	
9	4	29		1	17.5		tails	2	
10	34	28		22.5	16		W	119.5	
11	17	12		11	5.5		W-crit	115	
12	18	18		12.5	12.5		sig	no	
13	14	30		8.5	19		1005		
14	12	14		5.5	8.5				
15	13	22		7	14				
16	26	10		15	3				
17	31	29		20.5	17.5				
18	17	24.33333		119.5	180.5				

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	Group A (n=XX)	Group B (n=YY)	P-value	Statistical Test used
Age	50±10	40±10	0.030	
Parity	1±1	3±2	0.045	
Gestational age	32±3	36±3	0.005	
Hemoglobin	10.2±1.6	12.5±1.8	0.009	
Creatinine	2±1.5	0.7±1.1	0.067	
Blood loss	352±250	658±387	0.042	
Length of stay	5±10	2±5	0.033	

Fictitious data

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	Group A (n=XX)	Group B (n=YY)	P-value	Statistical Test used
Age	50±10	40±10	0.030	Independent t-test
Parity	1±1	3±2	0.045	Rank sum test
Gestational age	32±3	36±3	0.005	Independent t-test
Hemoglobin	10.2±1.6	12.5±1.8	0.009	Independent t-test
Creatinine	2±1.5	0.7±1.1	0.067	Rank sum test
Blood loss	352±250	658±387	0.042	Rank sum test
Length of stay	5±10	2±5	0.033	Rank sum test

Fictitious data

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Hypothesis testing Continuous variables Comparing >2 groups Multiple pairwise t-test Oneway ANOVA Kruskal-Wallis rank test

>2 independent: numerical



Hypothesis testing
Categorical variables
Comparing ≥2 groups
Chi-squared test
Fisher's exact probability test

Chi-squared test

Rationale of test

- Calculated the expected frequencies if there were no association.
- Null Hypothesis: No association
 Expected freq = Observed freq
- If observed frequencies are very different to the expected values, there is high possibility of association.

Hypothesis-driven question?

Does obese people carry higher risk of coronary heart disease than non-obese people?

Obese, category [yes, no] = [0,1]CHD, category [yes, no] = [0,1]

Hypothesis testing Comparative questions เปรียบเหียบสัดส่วนของการเกิดโรคหลอดเลือด หัวใจในคนที่ตุ้ยนุ้ยกับคนที่ไม่ตุ้ยนุ้ยว่าแตกต่างกัน หรือไม่?

Two independent groups (ตุ้ยนุ้ย vs. ไม่ตุ้ย)
 %CHD in obese vs. %CHD in non-obese
 Compare two independent proportions
 %CHD (event of CHD/total at risk)

Example

- Null hypothesis
 Proportion CHD in obese =
 Proportion CHD in non-obese
- Alternative hypothesis
 Proportion CHD in obese ≠
 Proportion CHD in non-obese

	CHD+ve	CHD-ve	Total
Obese	50 (0.5)	50 (0.5)	100
Non-obese	50 (0.5)	50 (0.5)	100
Total	100	100	200

	CHD+ve	CHD-ve	Total
Obese	70 (0.7)	30 (0.3)	100
Non-obese	30 (0.3)	70 (0.7)	100
Total	100	100	200

. tabi 70 30 \ 30 70, chi 2

	col		
row	1	2	Tot al
1 2	70 30	30 70	100 100
Tot al	100	100	200
P	earson chi 2(1) =	32 0000	Pr = 0.00

Fisher's exact test

- Exact probability test
- Complex calculation
- It is useful for small samples
- Used for only 2x2 tables
- Based on exact probabilities
- Tests the same null hypothesis as Chi2
- Assumption of test: None

. tabi 70 30 \ 30 70, chi2 exact

	col		
row	1	2	Total
1	70	30	100
2	30	70	100
Total	100	100	200
P	earson chi2(1) =	32.0000	Pr = 0.000
	Fisher's exact =		0.000
1-sided	Fisher's exact =		0.000
Take Home Knowledge

What's inferential statistics?

- What's the difference between SD, SE, and Confidence interval?
- What's hypothesis testing?
- What's null and alternative hypothesis?

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Take Home Knowledge

The importance of study size estimation?

Factors that influence study size?

Take Home Knowledge

 Compare two normally distributed numerical data?

 Compare two non-normally distributed numerical data?

 Compare two or more independent categorical data?