Biostatistics
Week VI

Ege Ülgen, M.D.

18 November 2021

ACIBADEM
MEHMET ALİ AYDINLAR
ÜNİVERSİTESİ

Maximum Likelihood Estimation

- MLE selects the set of values of the parameters that maximizes the likelihood function
  - maximizes the "agreement" of the selected model with the observed data

MLE of λ for Poisson Distribution

Recall that the pmf for Poisson distribution is:

$$P(X = x) = \frac{e^{-\lambda}\lambda^{x}}{x!}$$

For observations $x_1, ..., x_N$ that are i.i.d. $\sim Pois(\lambda)$, the likelihood (L) of this observation is:

$$L = P((X_1 = x_1) \cap ... \cap (X_N = x_N)) = \prod_{i=1}^{N} P(X_i = x_i)$$

$$= \prod_{i=1}^{N} \frac{e^{-\lambda}\lambda^{x_i}}{x_i!} = \frac{e^{-N\lambda}\lambda^{\sum_{i=1}^{N} x_i}}{\prod_{i=1}^{N} x_i!}$$

MLE of λ for Poisson Distribution

Since the likelihood is monotonically increasing log-likelihood is then:

$$log(L) = -N\lambda + (\sum_{i=1}^{N} x_i) log(\lambda) - log(\prod_{i=1}^{N} x_i!)$$

MLE of λ for Poisson Distribution

$$log(L) = -N\lambda + (\sum_{i=1}^{N} x_i)log(\lambda) - log(\prod_{i=1}^{N} x_i!)$$

Under suitable regularity conditions, the maximum likelihood estimate (estimator) is defined as:

$$\hat{\lambda} = \underset{\lambda \in \mathbb{R}^+}{\operatorname{argmax}}\, log(L)$$

FOC:

$$\left.\frac{\partial log(L)}{\partial \lambda}\right|_{\hat{\lambda}} = -N + \frac{1}{\hat{\lambda}} \sum_{i=1}^{N} x_i = 0$$

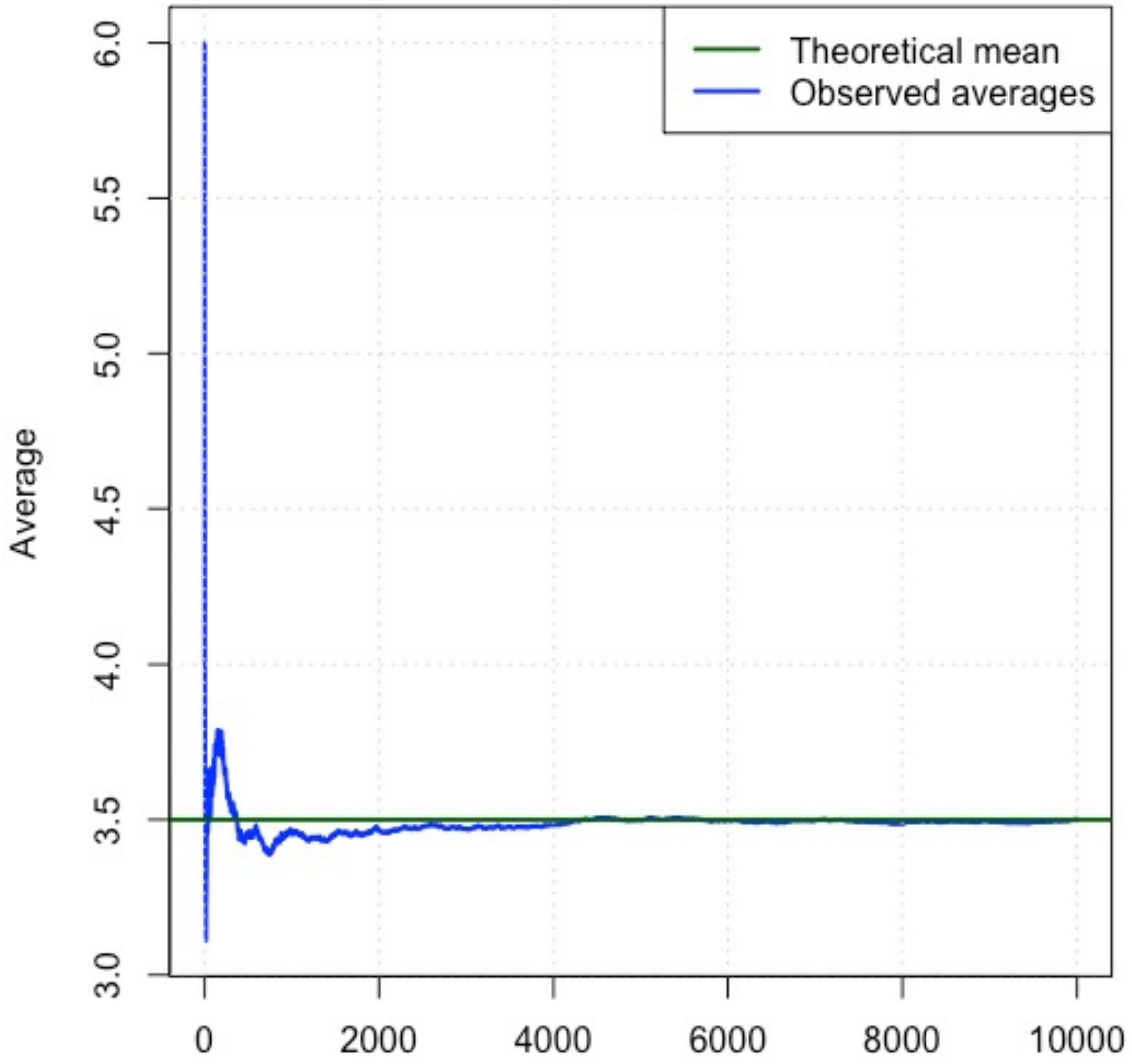
$$\iff \hat{\lambda} = \frac{1}{N} \sum_{i=1}^{N} x_i$$

Law of Large Numbers

- the average of the results obtained from a large number of trials should be close to the expected value and will tend to become closer to the expected value as more trials are performed

- e.g., if $X_1, \ldots, X_n$ are i.i.d. normal variables with mean μ and variance σ^2, then $\bar{X}$ converges to μ as *n* increases

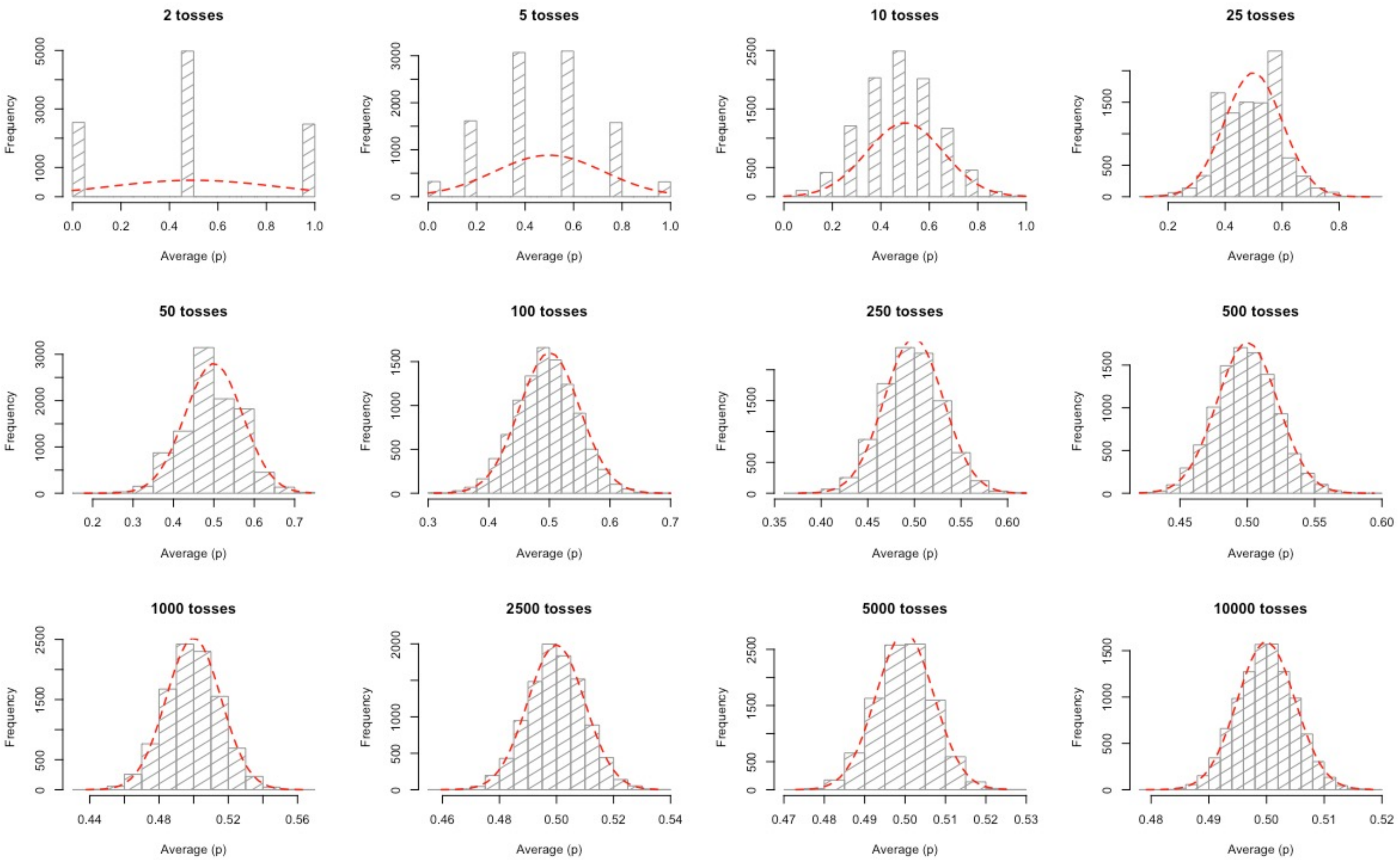
Law of Large Numbers



The Central Limit Theorem

- The central limit theorem (CLT) states that the distribution of sample means approximates a normal distribution as the sample size gets larger, regardless of the population's distribution

Tossing a coin n times (repeated for 10 000 times) – Distribution of sample means



The Central Limit Theorem

- A key aspect of CLT is that the average of the sample means and standard deviations will equal the population mean and standard deviation
- A sufficiently large sample size can predict the characteristics of a population more accurately

Sampling Distributions of Mean and Variance

- $\bar{X}$ and s^2 are **point estimates**

- If $X_1, \ldots, X_n$ are i.i.d. RVs $\sim N(\mu, \sigma^2)$
  1. $\bar{X} \sim N\left(\mu, \frac{\sigma^2}{n}\right)$
  2. $\frac{1}{\sigma^2} \sum_{i=1}^{n} (X_i - \bar{X})^2 = \frac{(n-1)s^2}{\sigma^2}$
  3. $\bar{X}$ *and* s^2 *are independent*

Brief Summary

- MLE is a useful approach for finding an estimator that maximizes the "agreement" of the selected model with the observed data
- CLT states that "the distribution of sample means approximates a normal distribution as the sample size gets larger"
- $\bar{X} \sim N\left(\mu, \frac{\sigma^2}{n}\right)$

Biostatistics
Week VII

Ege Ülgen, M.D.

18 November 2021

ACIBADEM
MEHMET ALİ AYDINLAR
ÜNİVERSİTESİ

Hypothesis Testing

- **Hypothesis**: an assumption that can be tested based on the evidence available
  - A novel drug is efficient in treating a certain disease
  - Regular smoking leads to lung cancer

  - Overweight individuals who (1) consume greasy food and (2) consume a low amount vegetables (1) have high levels of cholesterol and (2) have a higher risk of cardiovascular diseases

- **Hypothesis test**: investigation of the hypothesis using the sample
  - Assessing evidence provided by the data against the null claim (the claim which is to be assumed true unless enough evidence exists to reject it)

Null and Alternative Hypotheses

- H_0 – Null hypothesis
  - The mean of a variable is not different than *c*
  - There is no difference between the two groups' means
  - There is no difference compared to baseline
  - …
- H_a or H_1 – Alternative hypothesis
  - There is a difference between the two groups' means
  - The mean in group A is higher than group B
  - …

One- vs. Two-tailed Tests

- The coin is biased

Two-tailed

H_0: $p = 0.5$

H_a: $p \neq 0.5$

- The probability of heads is larger (or smaller) than 0.5

One-tailed

H_0: $p \leq 0.5$ (or $p \geq 0.5$)

H_a: $p > 0.5$ (or $p < 0.5$)

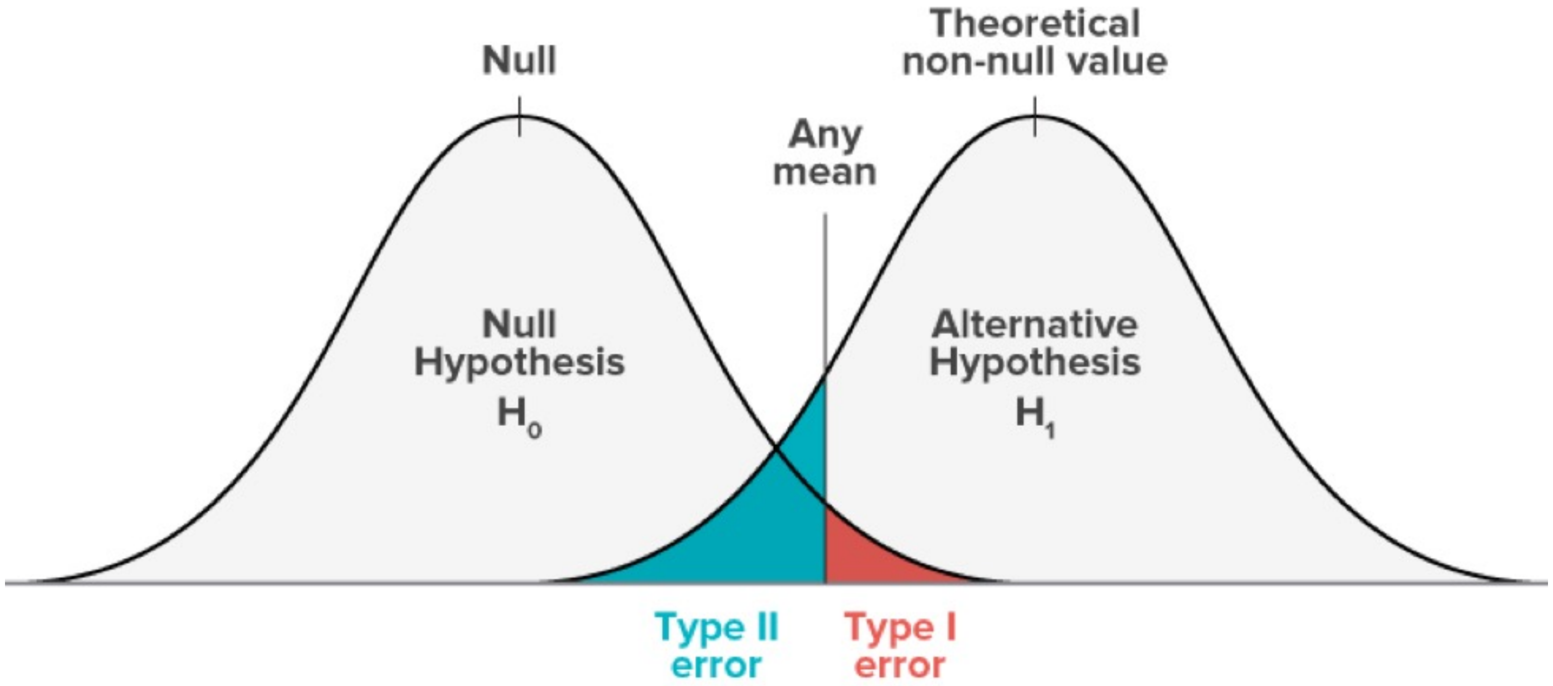
H_0	Decision	
	Fail to reject	Reject
True	Correct decision	**Type I Error** α
False	**Type II Error** β	Correct decision

Barai A. Hypothesis Testing | All a beginner needs to know [Internet]. Medium. 2020 [cited 2021 Oct 4]. Available from: https://medium.com/analytics-vidhya/hypothesis-testing-all-a-beginner-needs-to-know-dd1bdeebdbf1

Hypothesis Testing

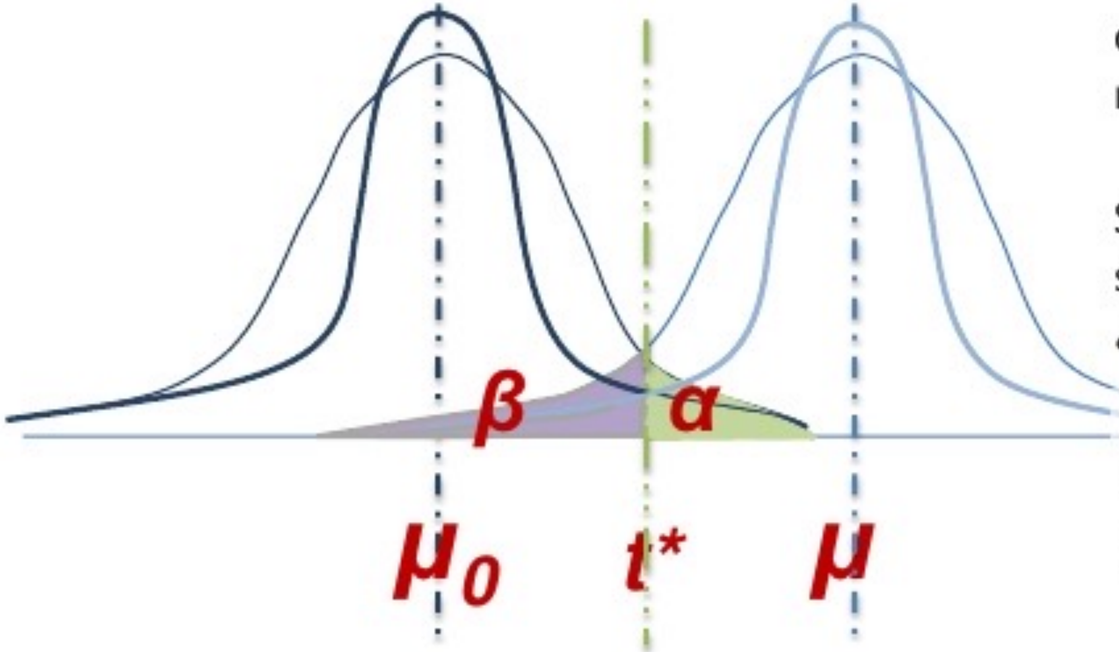
- P(Type 1 error) = α = P(reject H_0| H_0 is true)
- P(Type 2 error) = β = P(fail to reject H_0| H_0 is false)

- As α gets larger β gets smaller, vice versa
- As *n* gets large, both α and β get smaller



Reducing the probabilities of errors

- We control the **spread** of our normal curves.



CLT

If our sample size increases, the centers don't move, and we reduce variability…

So by increasing *n*, our sample size, we've reduced *both* α *and* β.

And if we've reduced β, we've increased the power (1 – β).

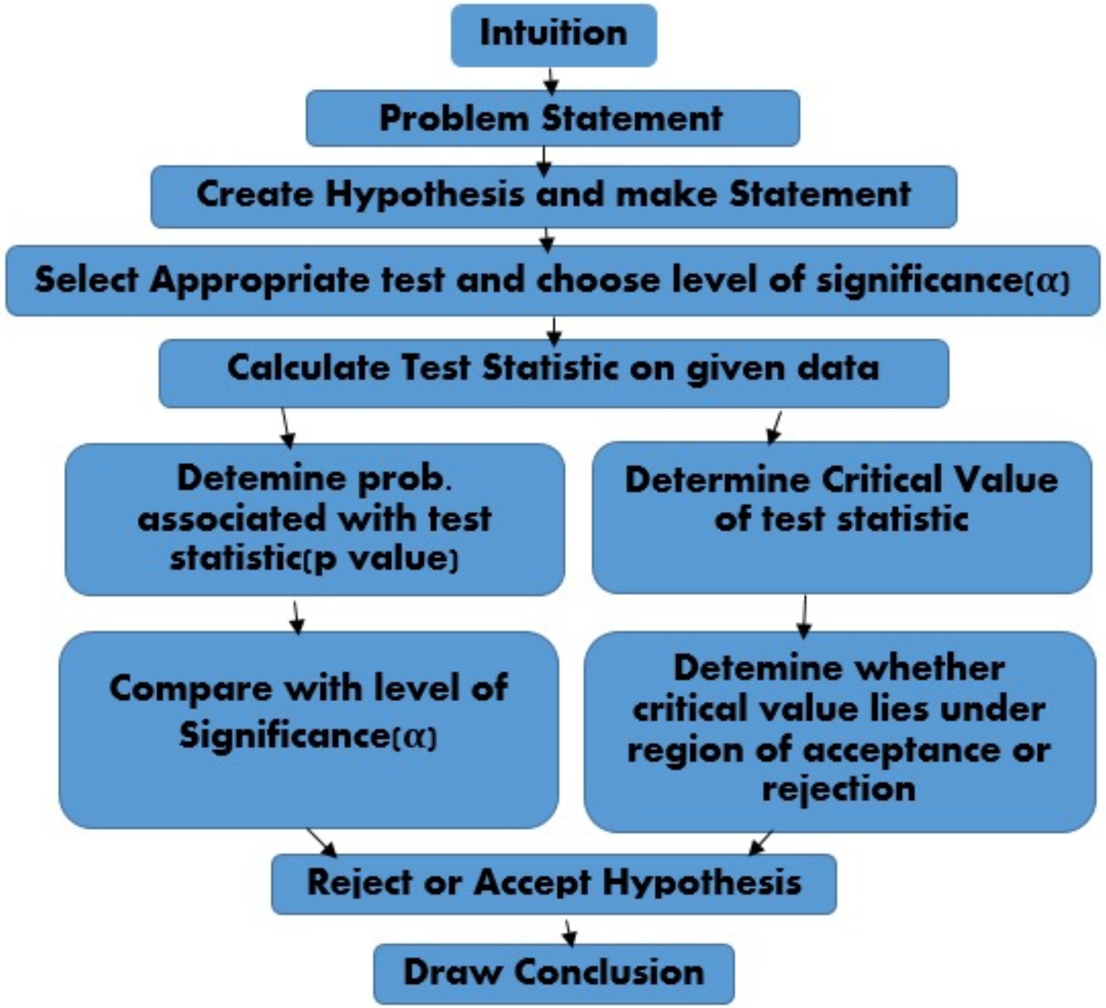
Hypothesis Testing

H_0	Decision	
	Fail to reject	Reject
True	Correct decision	**Type I Error** α
False	**Type II Error** **ß**	Correct decision

- **Confidence level** = 1 – α
  - P(fail to reject H_0| H_0 is true)
- **Statistical power** = 1 – β
  - P(reject H_0| H_0 is false)

Barai A. Hypothesis Testing | All a beginner needs to know [Internet]. Medium. 2020 [cited 2021 Oct 4]. Available from: https://medium.com/analytics-vidhya/hypothesis-testing-all-a-beginner-needs-to-know-dd1bdeebdbf1

Hypothesis Testing - Steps



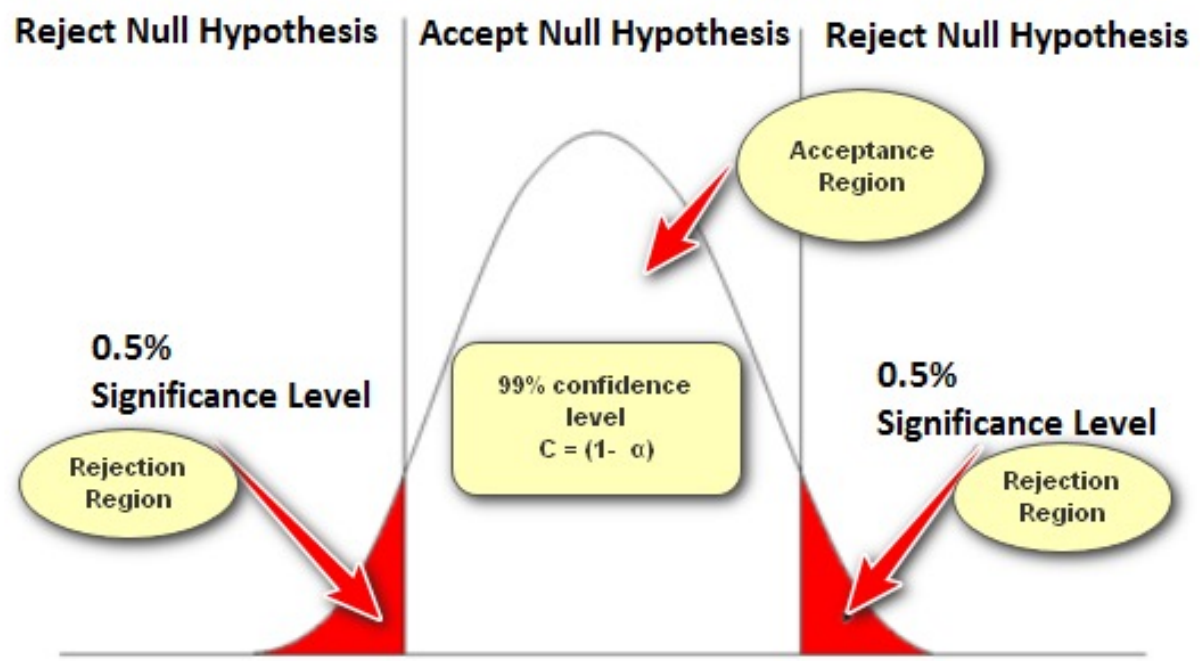
Hypothesis Testing - Steps

1. **Check assumptions, determine H_0 and H_a, choose α**
    - Assumptions differ based on the test
    - The null hypothesis always contains equality (=)
2. **Calculate the appropriate test statistic**
    - z, t, χ^2, …
3. **Calculate critical values/p value**
    - With the aid of precalculated tables/software
4. **Decide whether to reject/fail to reject H_0**
    - Reject if the statistic is within the critical region/$p \leq \alpha$

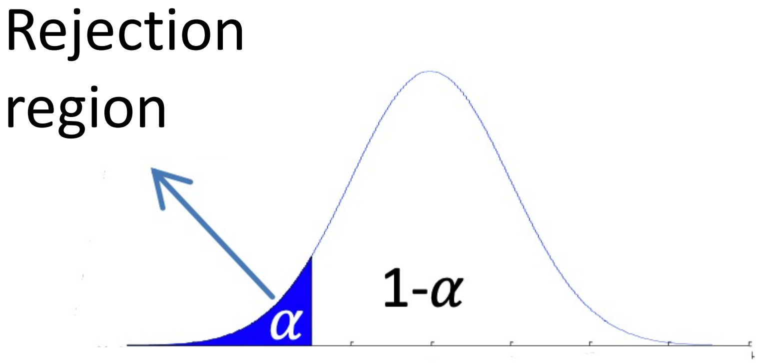
Barai A. Hypothesis Testing | All a beginner needs to know [Internet]. Medium. 2020 [cited 2021 Oct 4]. Available from: https://medium.com/analytics-vidhya/hypothesis-testing-all-a-beginner-needs-to-know-dd1bdeebdbf1

Critical Value/Rejection Region

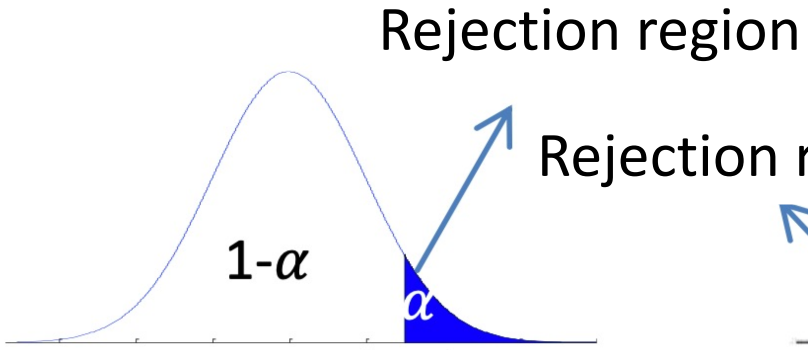
- We select α (**significance level**) prior to performing a hypothesis test
  - Some common values for α are 0.01, **0.05** an 0.10
- Based on the selected α, the critical values are calculated, and the rejection region is determined
  - the region where the null hypothesis is rejected



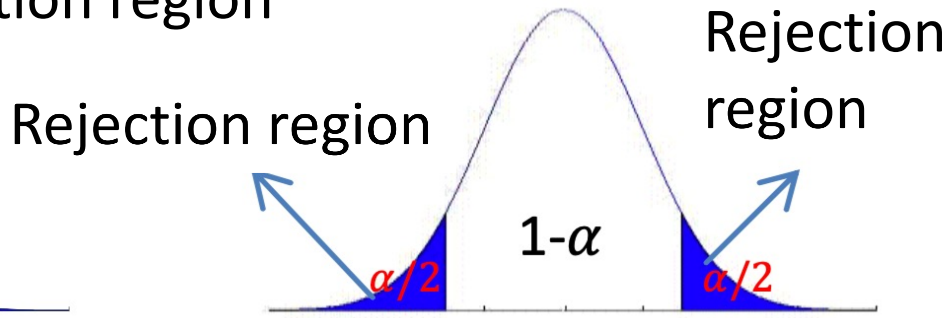
$$H_0: \mu = \mu_0$$
$$H_1: \mu < \mu_0$$



$$H_0: \mu = \mu_0$$
$$H_1: \mu > \mu_0$$



$$H_0: \mu = \mu_0$$
$$H_1: \mu \neq \mu_0$$



Test Statistic

$$\text{test statistic} = \frac{\text{estimator} - \text{null value}}{\text{standard error of estimator}}$$

$$t = \frac{\boxed{\bar{X} - \mu}}{\boxed{s/\sqrt{n}}}$$

Commonly Used Hypothesis Tests

- Continuous (comparing means)
  - One sample
    - z-Test
    - Student's t-Test
  - Two samples
    - Student's t-Test
      - Equal variance
      - Unequal variance
    - Paired t-Test
  - >2 samples
    - Analysis of Variance (ANOVA)
- Categorical
  - Chi-squared (χ^2) Test

One-sample z-Test for μ

- **Assuming we know the true value of the population variance σ^2**

- If $X_1, \dots, X_n$ are i.i.d. RVs $\sim N(\mu, \sigma^2)$, then:

$$\bar{X} \sim N(\mu, \frac{\sigma^2}{n})$$

$$z = \frac{\bar{X} - \mu}{\sigma/\sqrt{n}} \sim N(0,1)$$

One-Sample z-Test for μ – Example

- It is claimed that the post-treatment tumor volume of glioblastoma patients subject to a novel treatment is different than 5 cm^3
- The mean tumor volume of 41 randomly-selected patients is 5.9 cm^3
- **Population standard deviation** is 1.74

One-Sample z-Test for μ – Example (cont.)

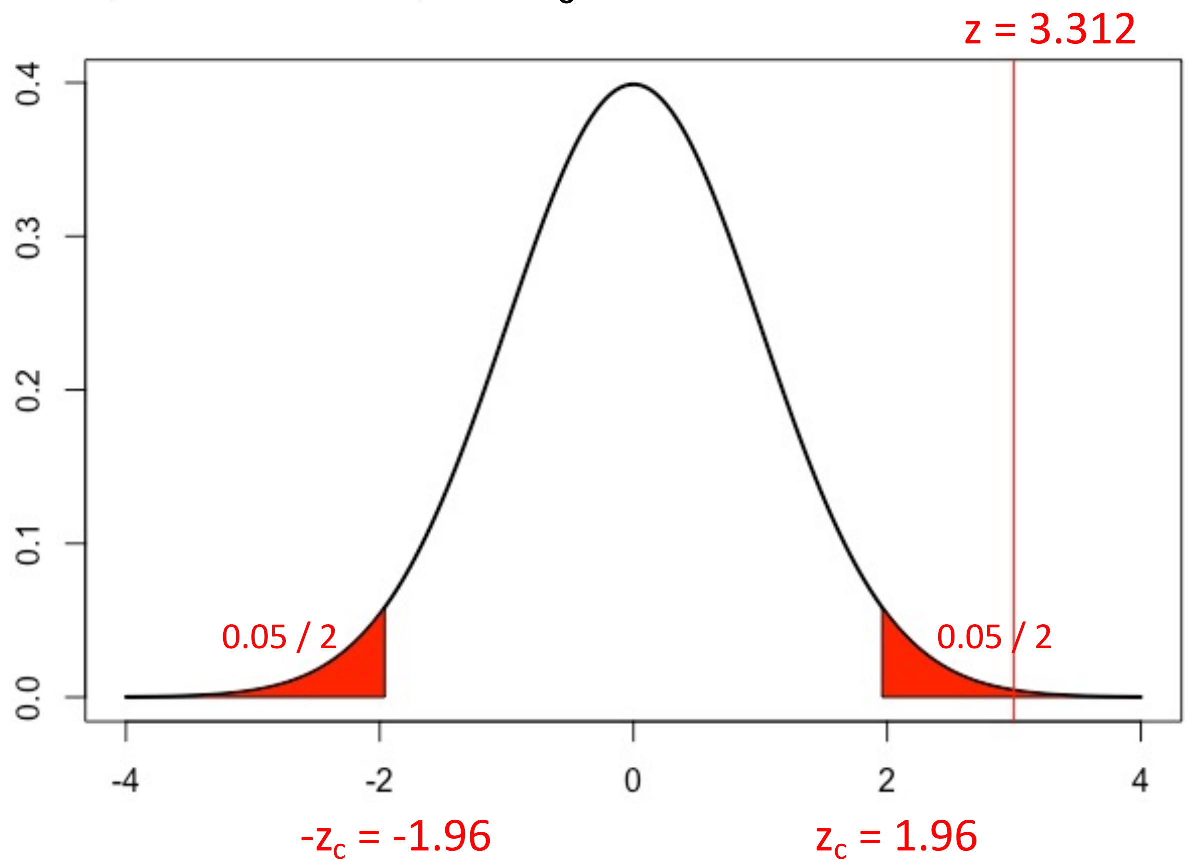
1. Check assumptions, determine H_0 and H_a, choose α
   - Normality of the variable is checked, **Population variance is known**
   - H_0: $\mu = 5$ H_a: $\mu \neq 5$
   - $\alpha = 0.05$

2. Calculate the appropriate test statistic

$$z = \frac{\bar{X} - \mu}{\sigma/\sqrt{n}} = \frac{5.9 - 5}{1.74/\sqrt{41}} = 3.312$$

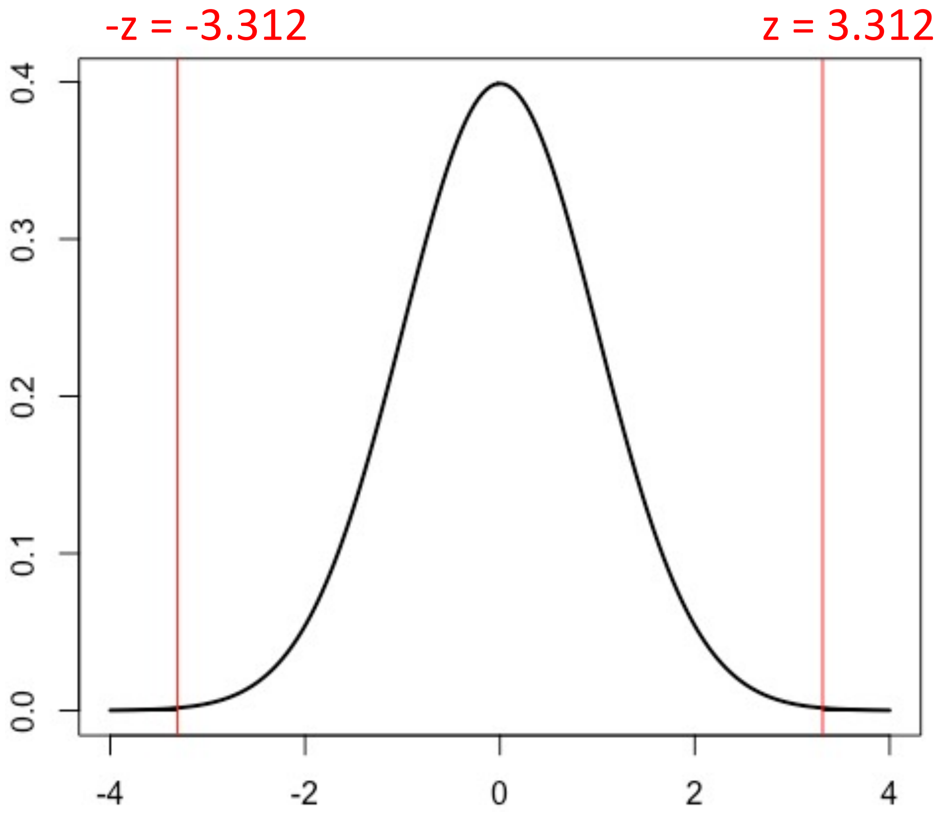
One-Sample z-Test for μ – Example (cont.)

3. Calculate **critical values**/p value
4. Decide whether to reject/fail to reject H_0



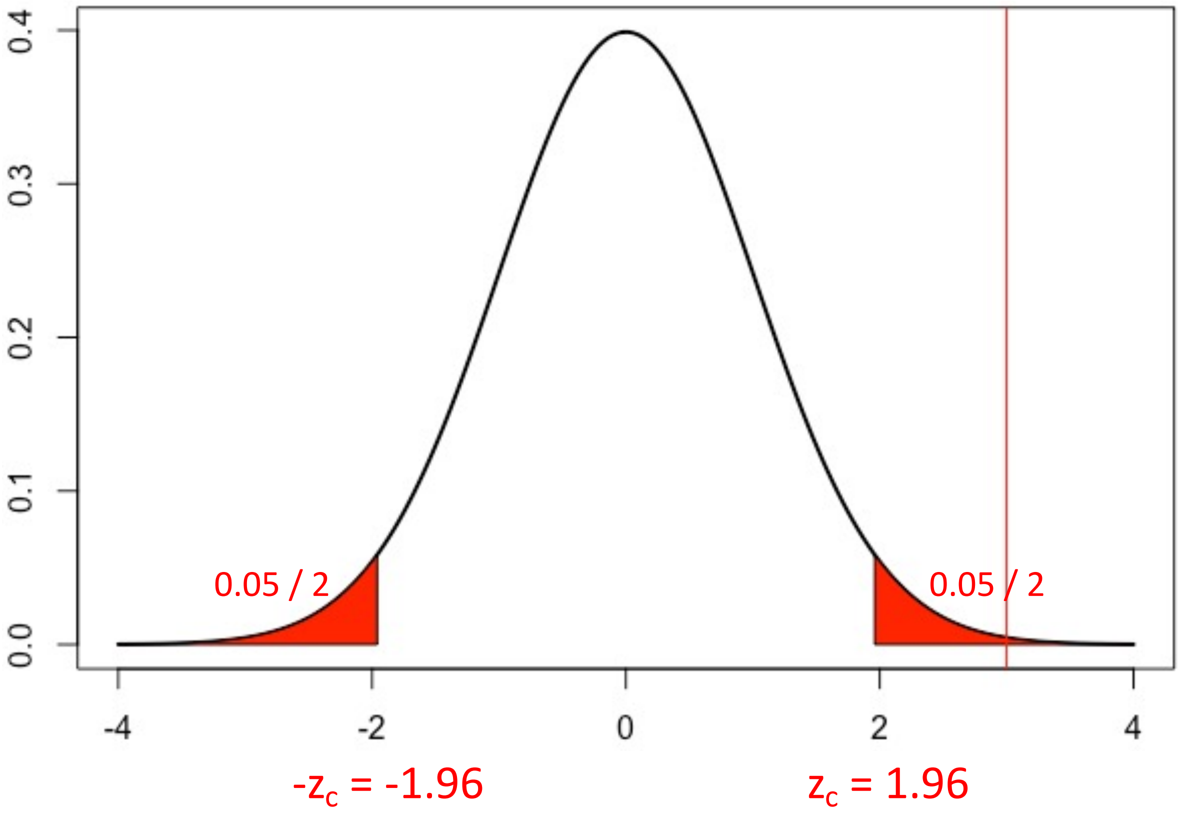
One-Sample z-Test for μ – Example (cont.)

3. Calculate critical values/**p value**
4. Decide whether to reject/fail to reject H_0



$p < 0.001$

Confidence Interval



$$P\left(\bar{X} - Z_c\frac{\sigma}{\sqrt{n}} \le \mu \le \bar{X} + Z_c\frac{\sigma}{\sqrt{n}}\right) = 0.95$$

$$\bar{X} \mp Z_c\frac{\sigma}{\sqrt{n}} = 5.9 \mp 1.96\frac{1.74}{\sqrt{41}}$$

95% Confidence Interval for μ

[5.367, 6.433]

One-Sample z-Test for μ – Example (cont.)

5. State a conclusion:

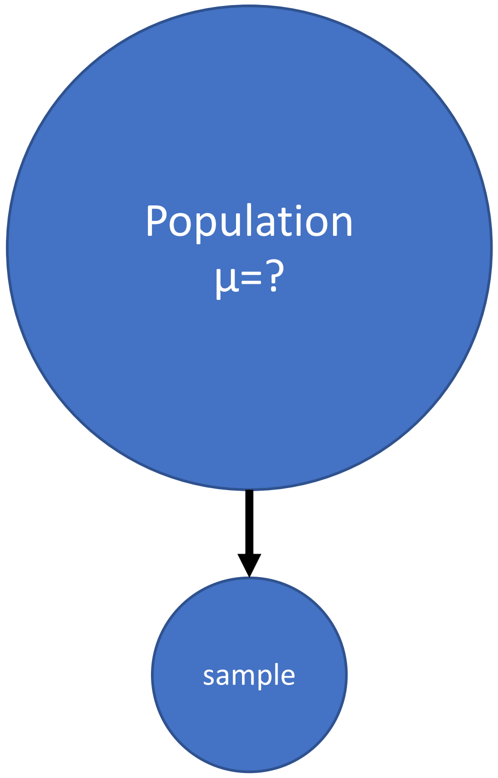
With 95% confidence, we can conclude that there is enough evidence to say that post-treatment tumor volume of glioblastoma patients subject to a novel treatment is different than 5 cm^3

Post-treatment tumor volume of glioblastoma patients subject to a novel treatment was found to be different than 5 cm^3 (z-test, $p < 0.001$)

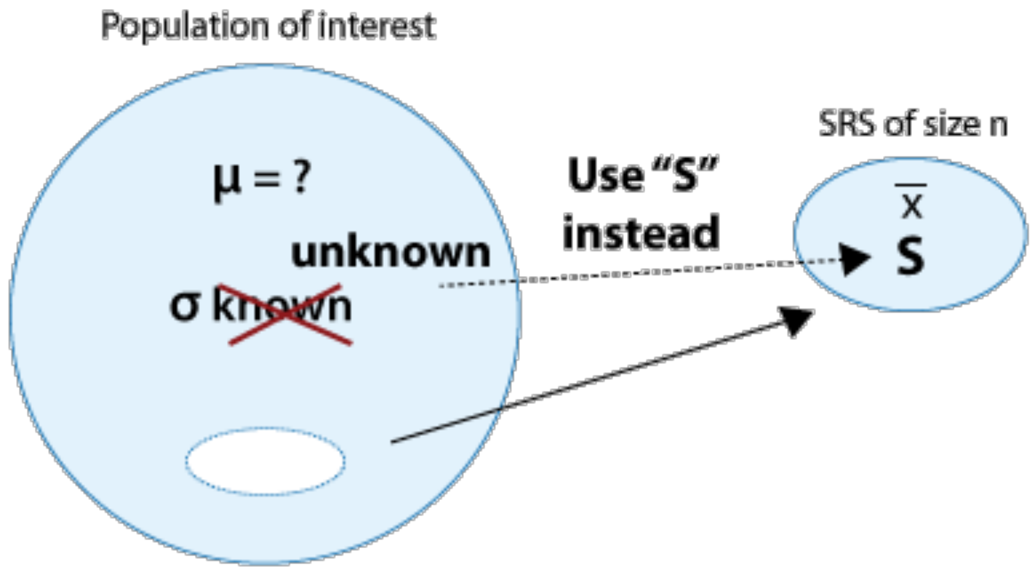
Post-treatment tumor volume of glioblastoma patients subject to a novel treatment was found to be different than 5 cm^3 (z-test, 95% CI = 5.367-6.433)

One-Sample t-Test

- a statistical hypothesis test used to determine whether an unknown population mean is different from a specific value



One-Sample t-Test



Means(All steps) [Internet]. [cited 2021 Oct 6]. Available from: https://bolt.mph.ufl.edu/6050-6052/unit-4/module-12/means-all-steps/

One-Sample t-Test – Example I

- It is claimed that the post-treatment tumor volume of glioblastoma patients subject to a novel treatment is different than 5 cm^3
- The mean tumor volume of 41 randomly-selected patients is 5.9 cm^3
- **Population variance is unknown**
- Sample standard deviation is 1.74

One-Sample t-Test – Example I (cont.)

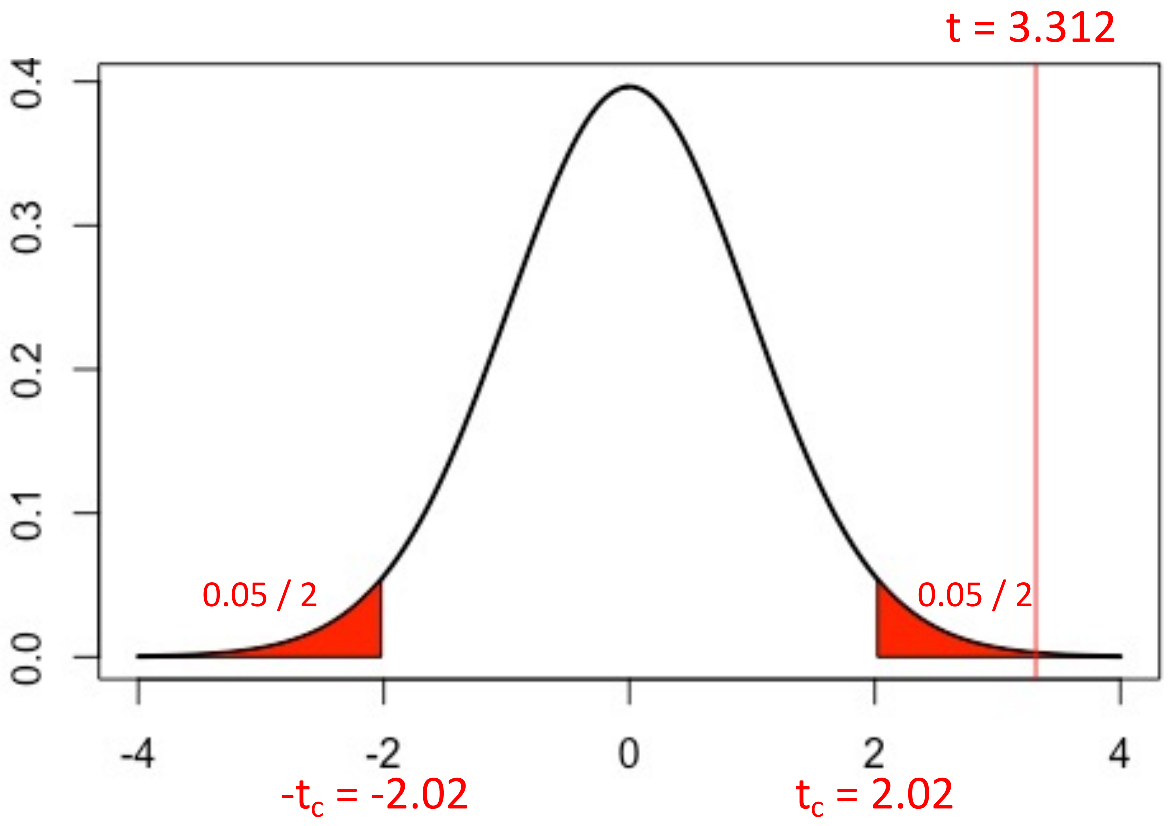
1. Check assumptions, determine H_0 and H_a, choose α
   - Normality of the variable is checked
   - H_0: $\mu = 5$ H_a: $\mu \neq 5$
   - $\alpha = 0.05$

2. Calculate the appropriate test statistic

$$t = \frac{\bar{X} - \mu}{s/\sqrt{n}} = \frac{5.9 - 5}{1.74/\sqrt{41}} = 3.312 \qquad (\sim t_{n-1} = t_{40})$$

One-Sample t-Test – Example I (cont.)

3. Calculate **critical values**/p value
4. Decide whether to reject/fail to reject H_0



One-Sample t-Test – Example II (cont.)

5. **State a conclusion:**

With 95% confidence, we can conclude that there is enough evidence to say that post-treatment tumor volume of glioblastoma patients subject to a novel treatment is different than 5 cm^3.

One-Sample t-Test – Example II

id	week_1	cd4_1	week_2	cd4_2	perc_benefit
361	0	26	7.43	3	-11.905994
1017	0	13	7.00	10	-3.296703
519	0	3	8.14	5	8.190008
1147	0	65	33.00	97	1.491841
1216	0	36	8.00	31	-1.736111
52	0	16	9.43	31	9.941676
660	0	34	8.43	32	-0.697788
1145	0	41	8.00	71	9.146341
697	0	33	8.00	45	4.545455
560	0	21	8.00	27	3.571429

- Mean percentage benefit is 1.925015
- Is it due to chance? Or does it indicate positive impact of the novel treatment?
    - What would be the value of mean percentage benefit what if you selected another set of 10 patients?

One-Sample t-Test – Example II (cont.)

1. Check assumptions, determine H_0 and H_a, choose α
   - Normality of the variable is checked (Quantile-quantile plot)
   - H_0: $\mu = 0$ H_a: $\mu \neq 0$
   - $\alpha = 0.05$

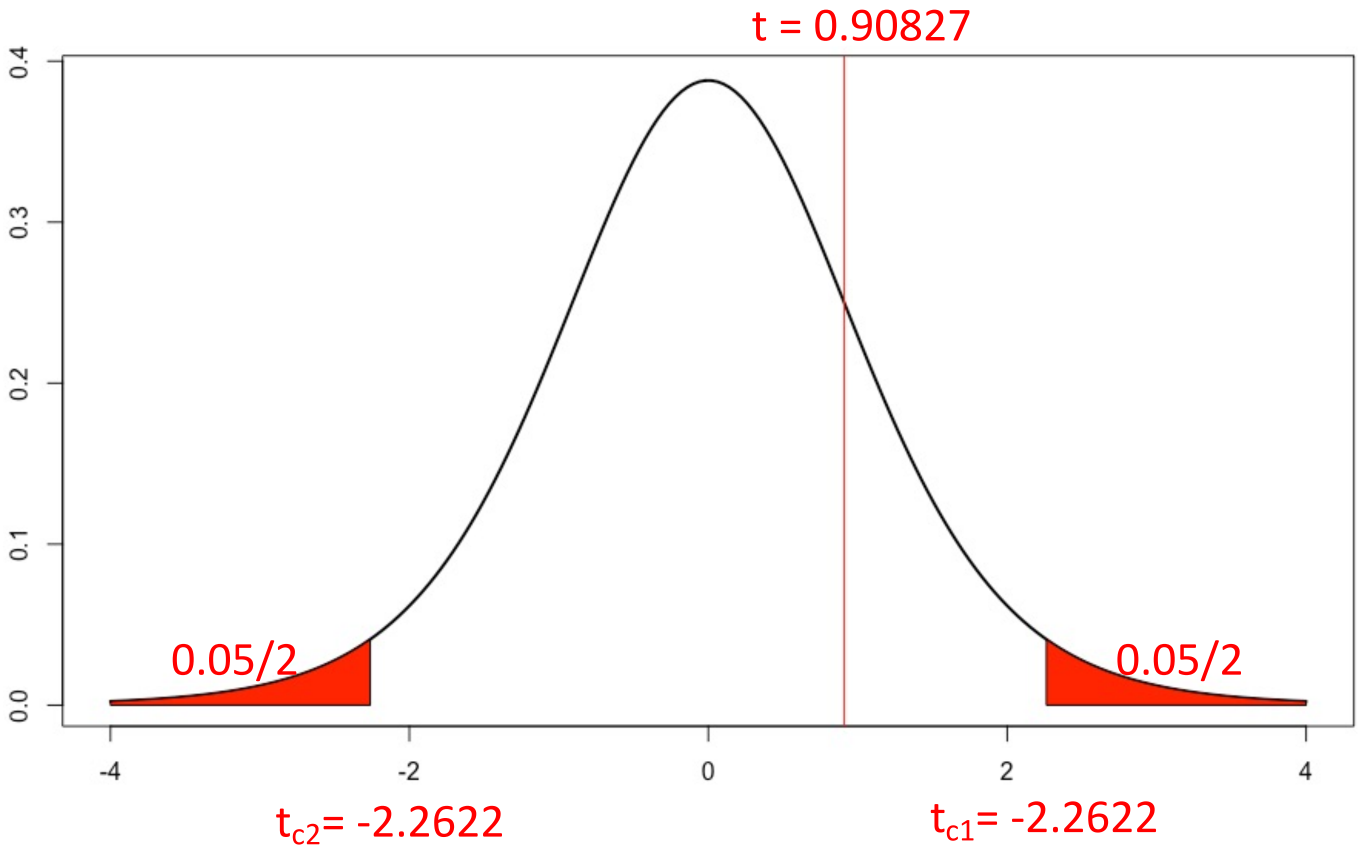
One-Sample t-Test – Example II (cont.)

2. Calculate the appropriate test statistic
   - Mean percentage benefit is 1.925015
   - Standard deviation is 6.702202
   - Sample size is 10

$$t = \frac{\bar{X} - \mu}{s/\sqrt{n}} = \frac{1.925015 - 0}{6.702202/\sqrt{10}} = 0.9082736 \quad (\sim t_{n-1} = t_9)$$

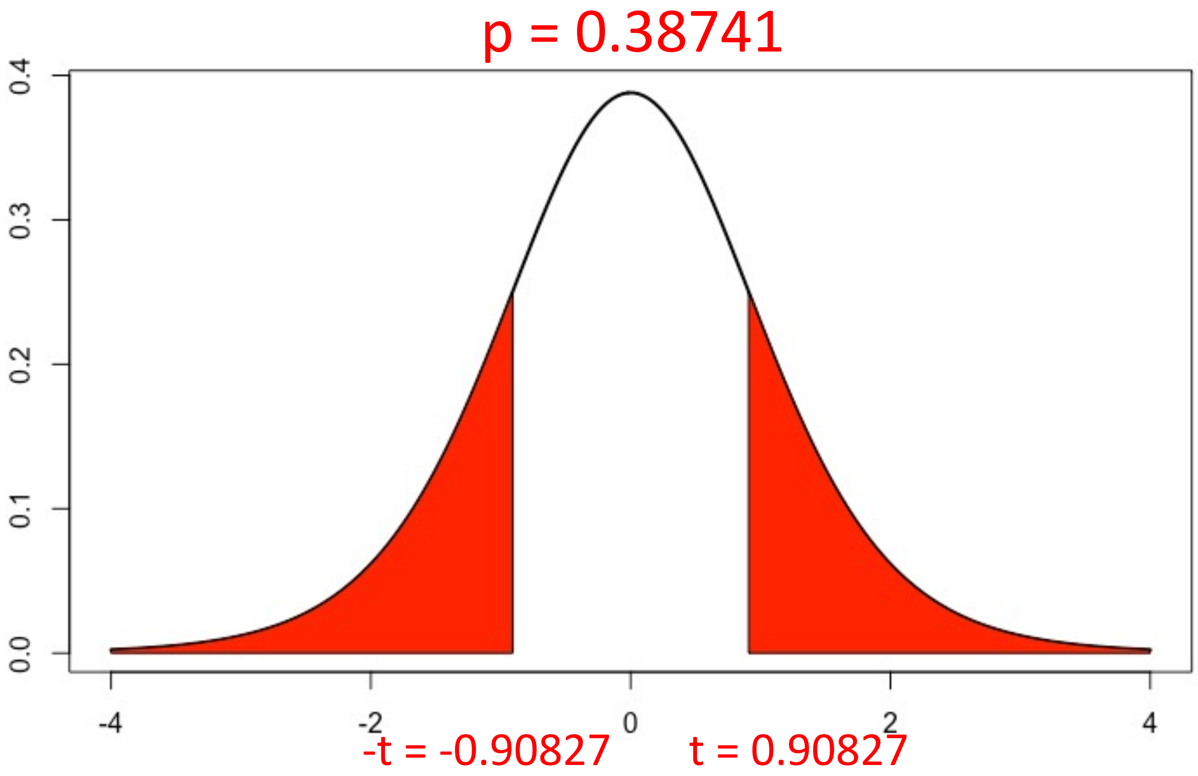
One-Sample t-Test – Example II (cont.)

3. Calculate **critical values**/p value
4. Decide whether to reject/fail to reject H_0



One-Sample t-Test – Example II (cont.)

3. Calculate critical values/**p value**
4. Decide whether to reject/fail to reject H_0



One-Sample t-Test – Example III

- It is claimed that:
- A novel drug reduces the recovery time of patients to less than 10 days
- Recovery time for 7 randomly-selected patients:

  2, 4, 11, 3, 4, 6, 8 ($\bar{X}$ = 5.43, s = 3.15)

- Test the hypothesis using $\alpha = 0.01$

One-Sample t-Test – Example III((cont.)

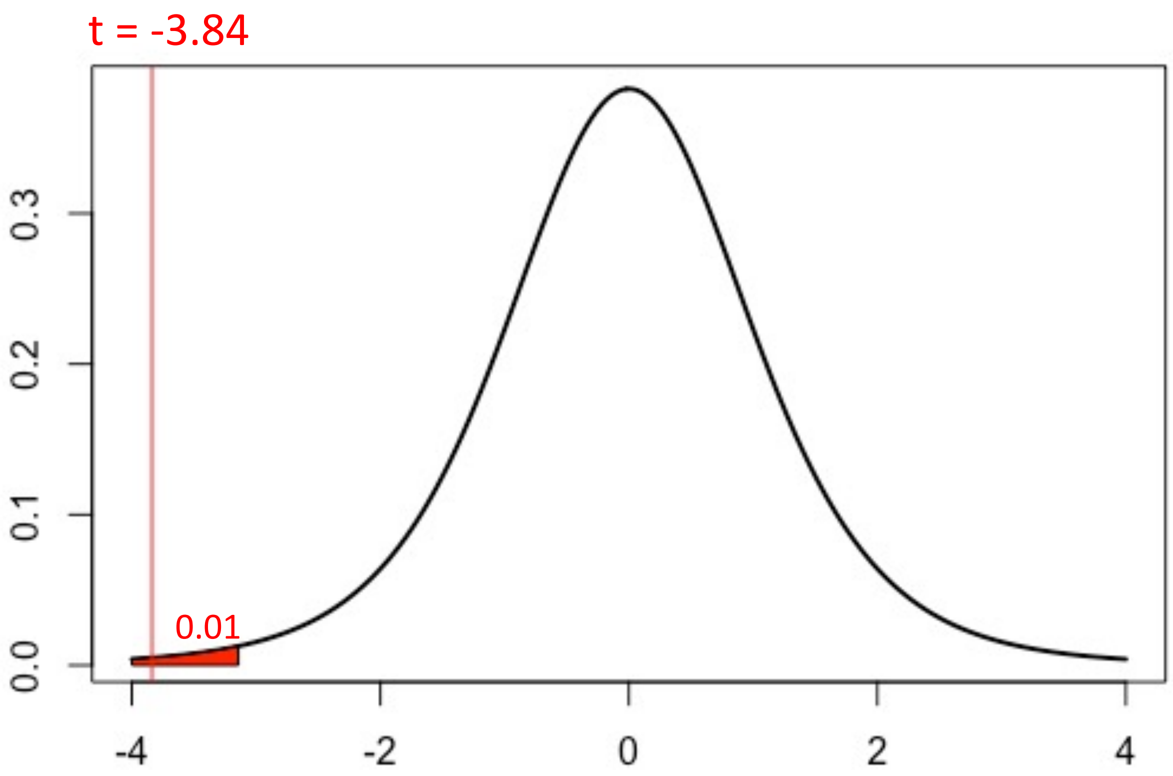
1. Check assumptions, determine H_0 and H_a, choose α
   - Normality of the variable is checked
   - H_0: $\mu \geq 10$ H_a: $\mu < 10$
   - $\alpha = 0.01$

2. Calculate the appropriate test statistic

$$t = \frac{\bar{X} - \mu}{s/\sqrt{n}} = \frac{5.43 - 10}{3.15/\sqrt{7}} = -3.84 \qquad (\sim t_{n-1} = t_6)$$

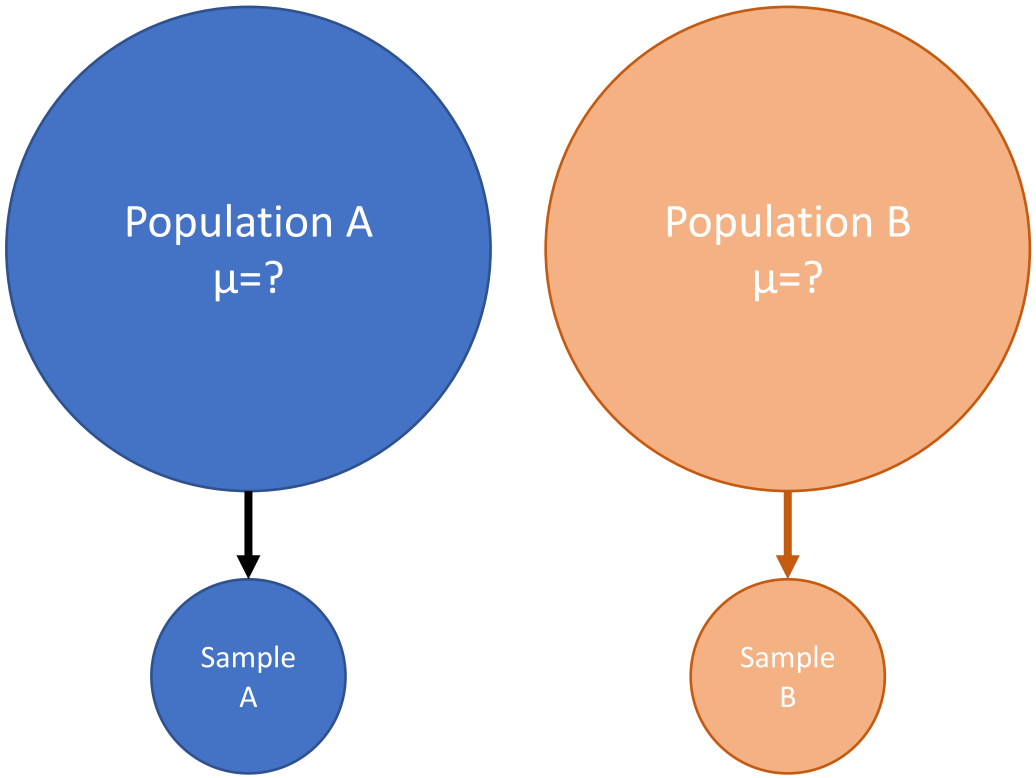
One-Sample t-Test – Example III (cont.)

3. Calculate **critical values**/p value
4. Decide whether to reject/fail to reject H_0



Two-Sample t-Test

- The **two-sample t-test** (also known as the **independent samples t-test**) is a method used to test whether the unknown population means of two groups are equal or not



Two-sample t-Test

$H_0: \mu_X = \mu_Y$

$H_a: \mu_X \neq \mu_Y$

or

$\mathbf{H_0: \mu_X - \mu_Y = 0}$

$\mathbf{H_a: \mu_X - \mu_Y \neq 0}$

Two-sample t-Test

$$\boldsymbol{\sigma_X^2 = \sigma_Y^2}$$

$$T = \frac{\bar{X} - \bar{Y}}{s_P\sqrt{\frac{1}{n_X} + \frac{1}{n_Y}}} \sim \mathrm{t}(\mathrm{n_X} + \mathrm{n_Y} - 2)$$

$$s_P = \frac{(n_X - 1)s_x^2 + (n_Y - 1)s_Y^2}{n_X + n_Y - 2}.$$

$$\boldsymbol{\sigma_X^2 \neq \sigma_Y^2}$$

$$T = \frac{\bar{X} - \bar{Y}}{\sqrt{\frac{s_X^2}{n_X} + \frac{s_Y^2}{n_Y}}} \sim \mathrm{t(m)},$$

$$m = \frac{(w_X + w_Y)^2}{\left(\frac{w_X^2}{n_X - 1} + \frac{w_Y^2}{n_Y - 1}\right)}$$

$$w_X = s_X^2/n_X, \quad w_Y = s_Y^2/n_Y$$

Can be checked via F-test

Two-sample t-Test – Example I

id	treatment	perc_benefit
158	trt1	37.2549020
392	trt1	-4.3864459
457	trt1	-5.1075269
487	trt1	36.7043369
723	trt1	5.1303099
832	trt1	3.1806616
894	trt1	-3.9062500
1104	trt1	5.9443608
1283	trt1	-0.8601855
1288	trt1	-3.1674208

id	treatment	perc_benefit
15	trt2	10.0978368
143	trt2	0.5048635
470	trt2	-0.8156940
536	trt2	50.0000000
549	trt2	-3.0303030
750	trt2	-2.8977108
891	trt2	26.3872135
997	trt2	4.3651179
1000	trt2	2.3582125
1209	trt2	8.9702189

- Mean percentage benefit is 7.0787 for treatment arm 1, and 9.5940 for treatment arm 2
- Is the difference a significant one?

F-test for Variance Equality

$$H_0 \colon \sigma_X^2 = \sigma_Y^2$$
$$H_1 \colon \sigma_X^2 \neq \sigma_Y^2$$

or

$$H_0 \colon \frac{\sigma_X^2}{\sigma_Y^2} = 1$$

F-test (cont.)

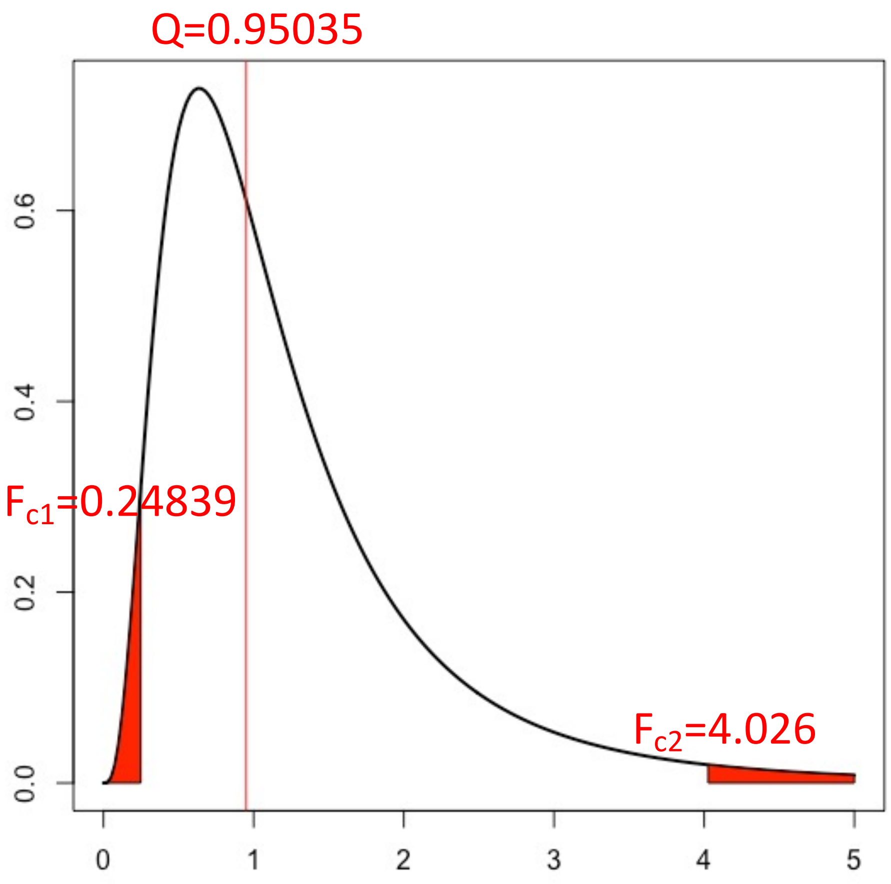
1. Check assumptions, determine H_0 and H_1, choose α
   - H_0: $\frac{\sigma_X^2}{\sigma_Y^2} = 1$ H_a: $\frac{\sigma_X^2}{\sigma_Y^2} \neq 1$
   - $\alpha = 0.05$

2. Calculate the appropriate test statistic

$$Q = \frac{s_X^2}{s_Y^2} = \frac{264.13}{277.93} = 0.95035 \quad \sim F_{n_X-1,n_Y-1} = F_{9,9}$$

F-test (cont.)

3. Calculate **critical region**/p value
4. Decide whether to reject/fail to reject H_0



Two-sample t-Test - Example I (cont.)

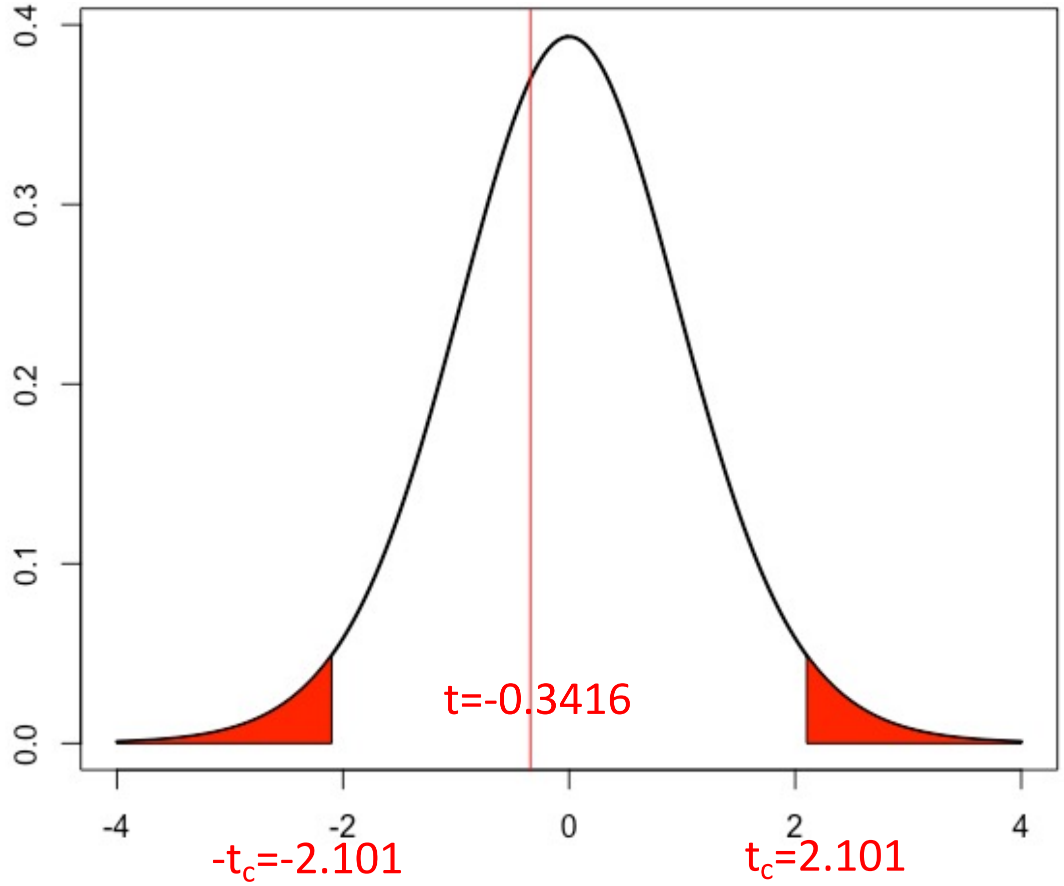
1. Check assumptions, determine H0 and Ha, choose α
   - We check that the variables are normally distributed
   - We have decided that the variances are equal
   - H_0: $\mu_1 = \mu_2$ H_a: $\mu_1 \neq \mu_2$
   - $\alpha = 0.05$

2. Calculate the appropriate test statistic

   $$t = -0.3416(\sim t_{17.98834})$$

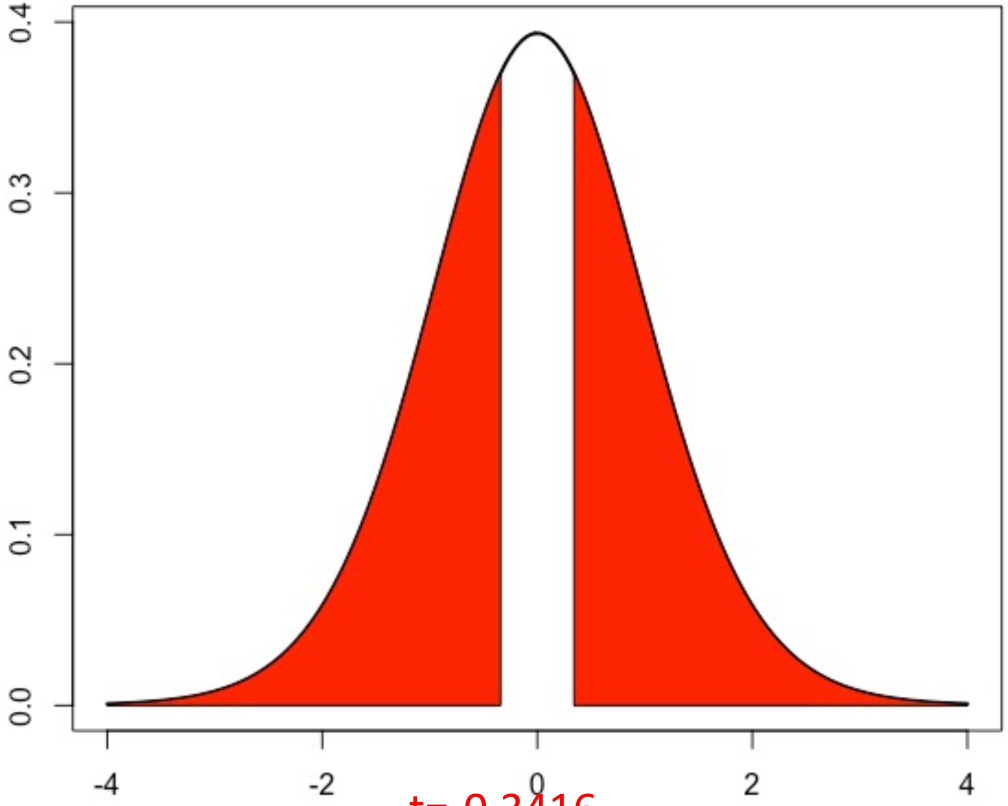
Two-sample t-Test - Example I (cont.)

3. Calculate **critical values**/p value
4. Decide whether to reject/fail to reject H_0



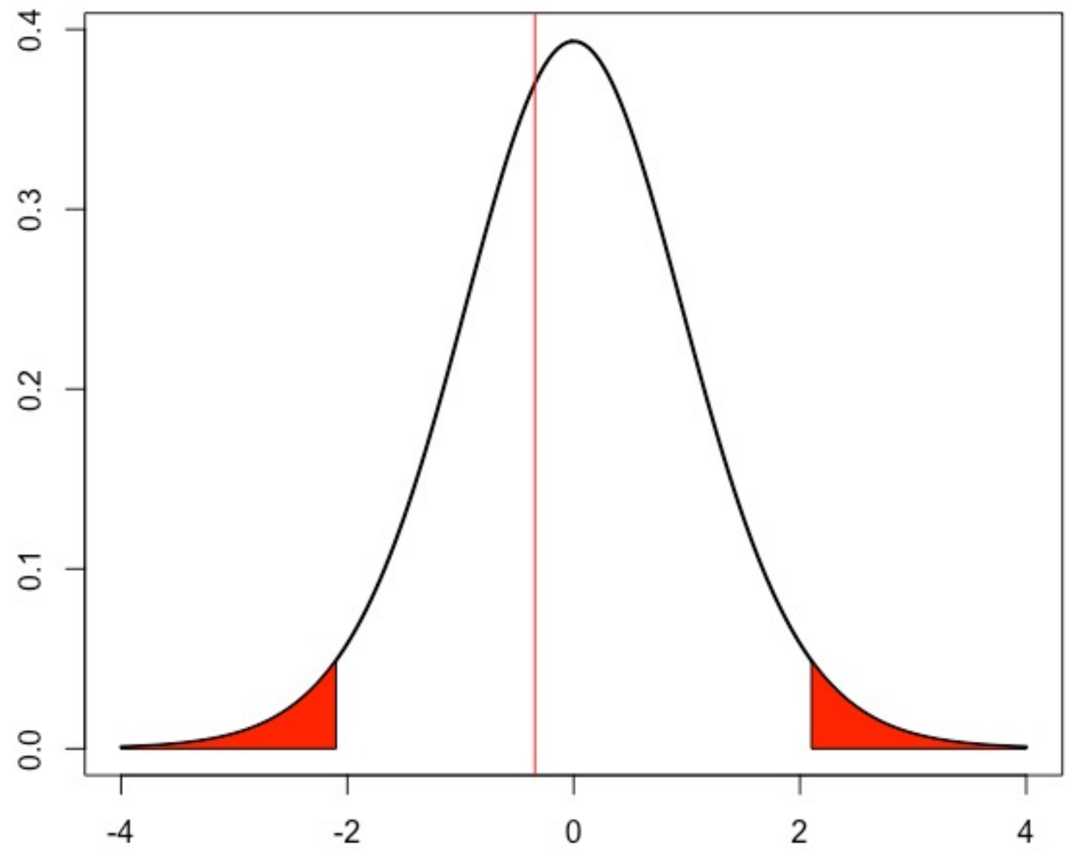
Two-sample t-Test - Example I (cont.)

3. Calculate critical values/**p value**
4. Decide whether to reject/fail to reject H_0



t=-0.3416

Two-sample t-Test - Example I (cont.)



95% confidence interval for $\mu_1 - \mu_2$ = [-17.98 , 12.95]

Two-sample t-Test - Example I (cont.)

- there is not enough evidence to say mean percentage benefit for treatment 1 and treatment 2 are significantly different

Two-sample t-Test - Example II

- In a study,
  - The sedimentation rate of 12 arthritis patients was measured: $\bar{X}_1 = 82.79$ mm and $s_1 = 18.4$ mm
  - The sedimentation rate of 15 healthy controls was measured: $\bar{X}_2 = 69.03$ mm and $s_2 = 21.4$ mm
- Is there a difference between the mean sedimentation rates of the two groups?

Two-sample t-Test - Example II (cont.)

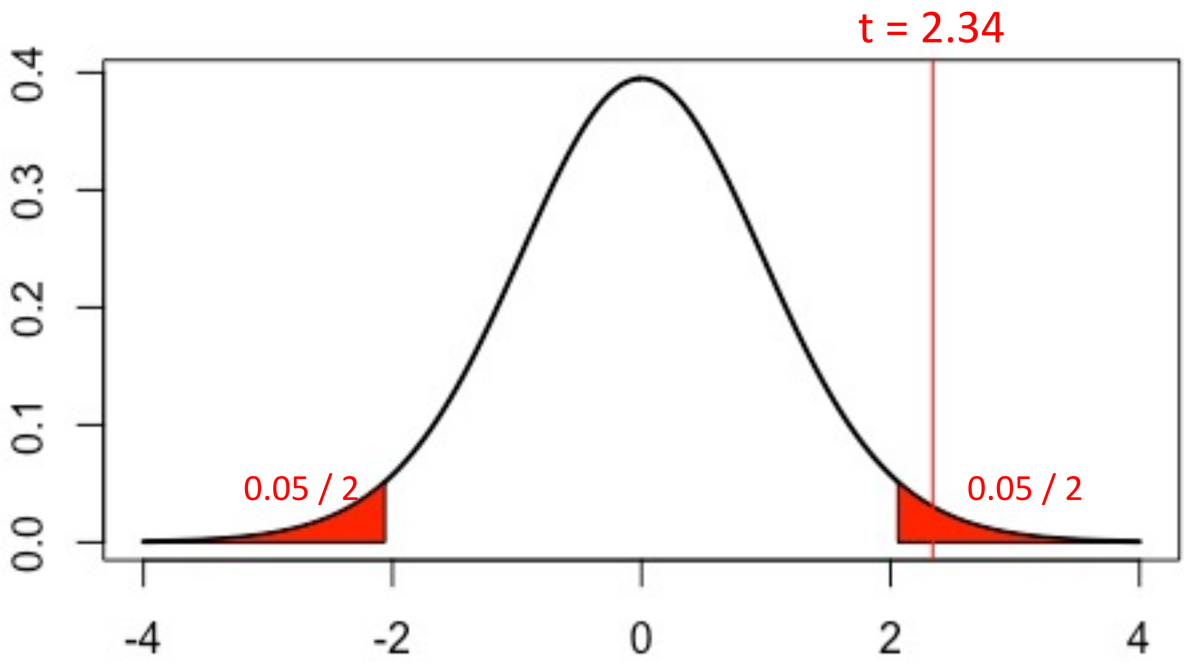
1. Check assumptions, determine H0 and Ha, choose α
   - We check that the variables are normally distributed
   - H_0: $\mu_1 = \mu_2$ H_a: $\mu_1 \neq \mu_2$
   - $\alpha = 0.05$

2. Calculate the appropriate test statistic

$$t = 2.34 \qquad (\sim t_{25})$$

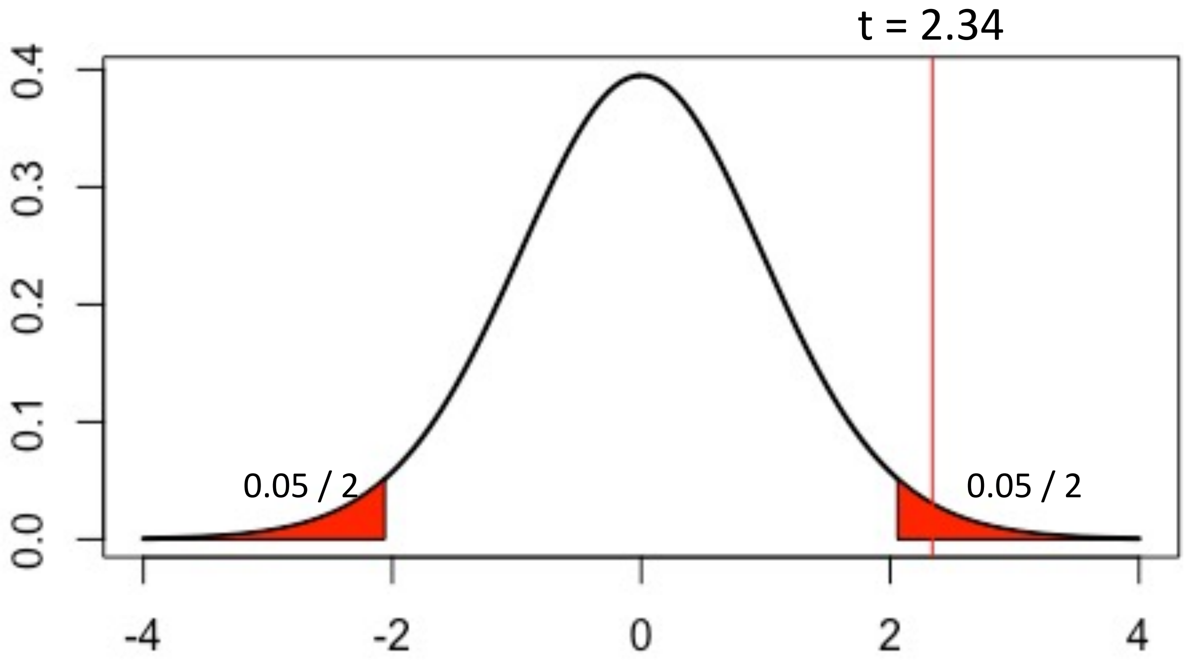
Two-sample t-Test - Example II (cont.)

3. Calculate critical values/p value
4. Decide whether to reject/fail to reject H_0



p = 0.027568

Two-sample t-Test - Example II (cont.)



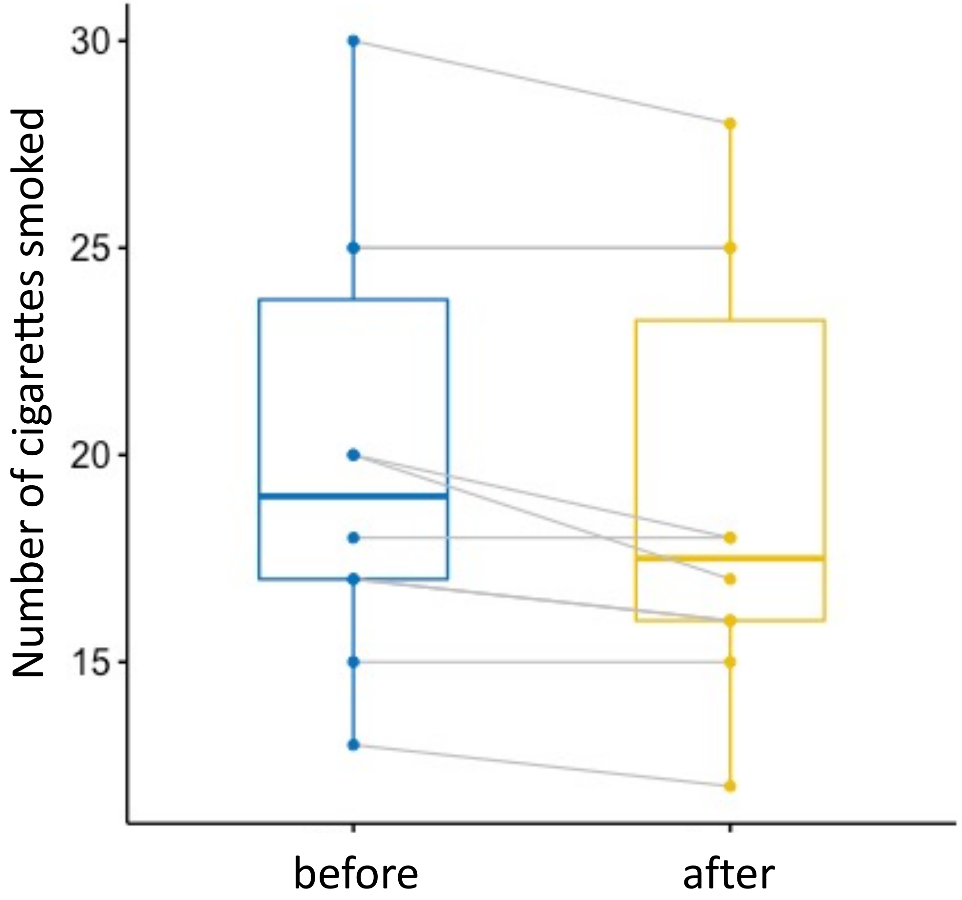
p = 0.027568

95% confidence interval for $\mu_1 - \mu_2$ = [3.52, 33]

Two-sample t-Test - Example II (cont.)

- With 95% confidence, there is enough evidence to say that there is a difference between the mean sedimentation rates of the two groups

Paired t-test



$$t_h = \frac{\bar{D} - \mu_D}{S_D / \sqrt{n}} \sim t_{n-1}$$

$$D = (X_{11} - X_{21}), (X_{12} - X_{22}), \dots, (X_{1n} - X_{2n})$$

$$\bar{D} = \frac{\sum_{i=1}^{n} D_i}{n}, S_D = \sqrt{\frac{\sum_{i=1}^{n} D_i^2 - \frac{\left(\sum_{i=1}^{n} D_i\right)^2}{n}}{n-1}}$$

Paired t-test

- In a study investigates a seminar that aims to reduce the number of cigarettes smoked
- For 10 randomly-selected smokers,
  - The number of cigarettes smoked per day before the seminar (X_1)
  - The number of cigarettes smoked per day after the seminar (X_2)

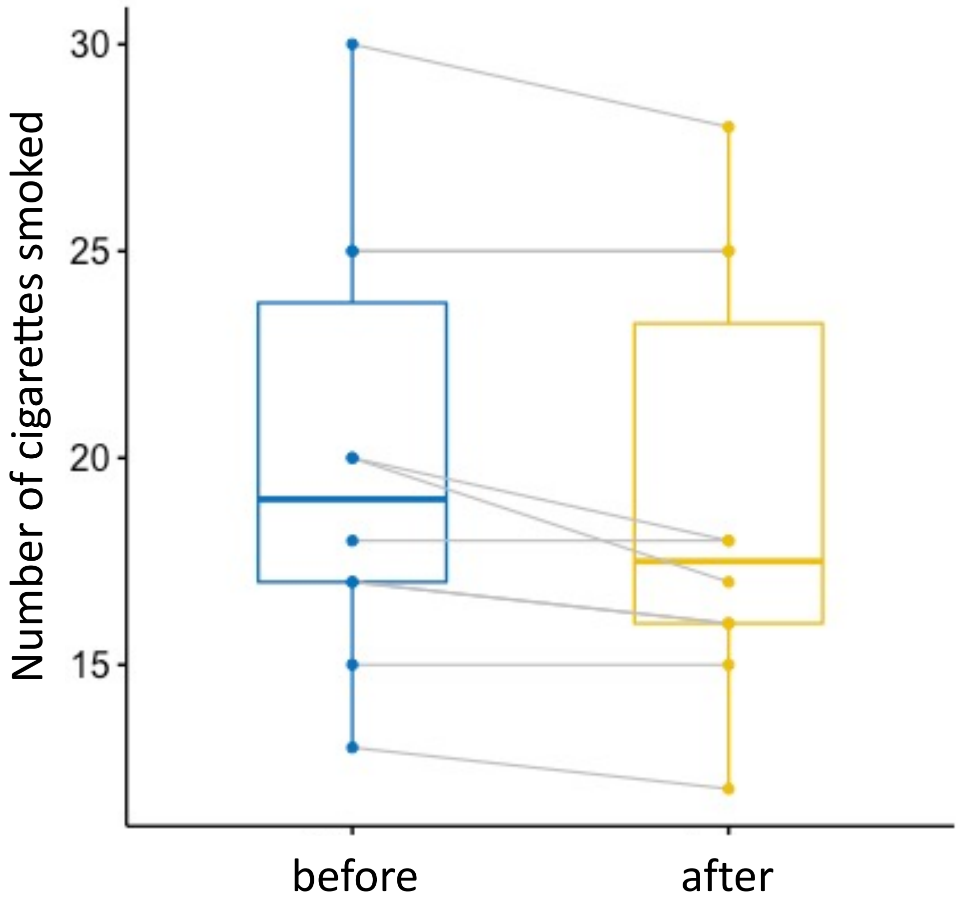
  are recorded

- Can it be claimed that the seminar reduces the number of cigarettes smoked per day?

Paired t-test

$D = X_1 - X_2$

X_{1i}	X_{2i}	D_j
30	28	2
25	25	0
25	25	0
20	18	2
20	17	3
18	18	0
17	16	1
17	16	1
15	15	0
13	12	1



Paired t-test

1. Check assumptions, determine H_0 and H_a, choose α
   - H_0: $\mu_D \leq 0$ H_a: $\mu_D > 0$ $D = X_1 - X_2$
   - $\alpha = 0.05$

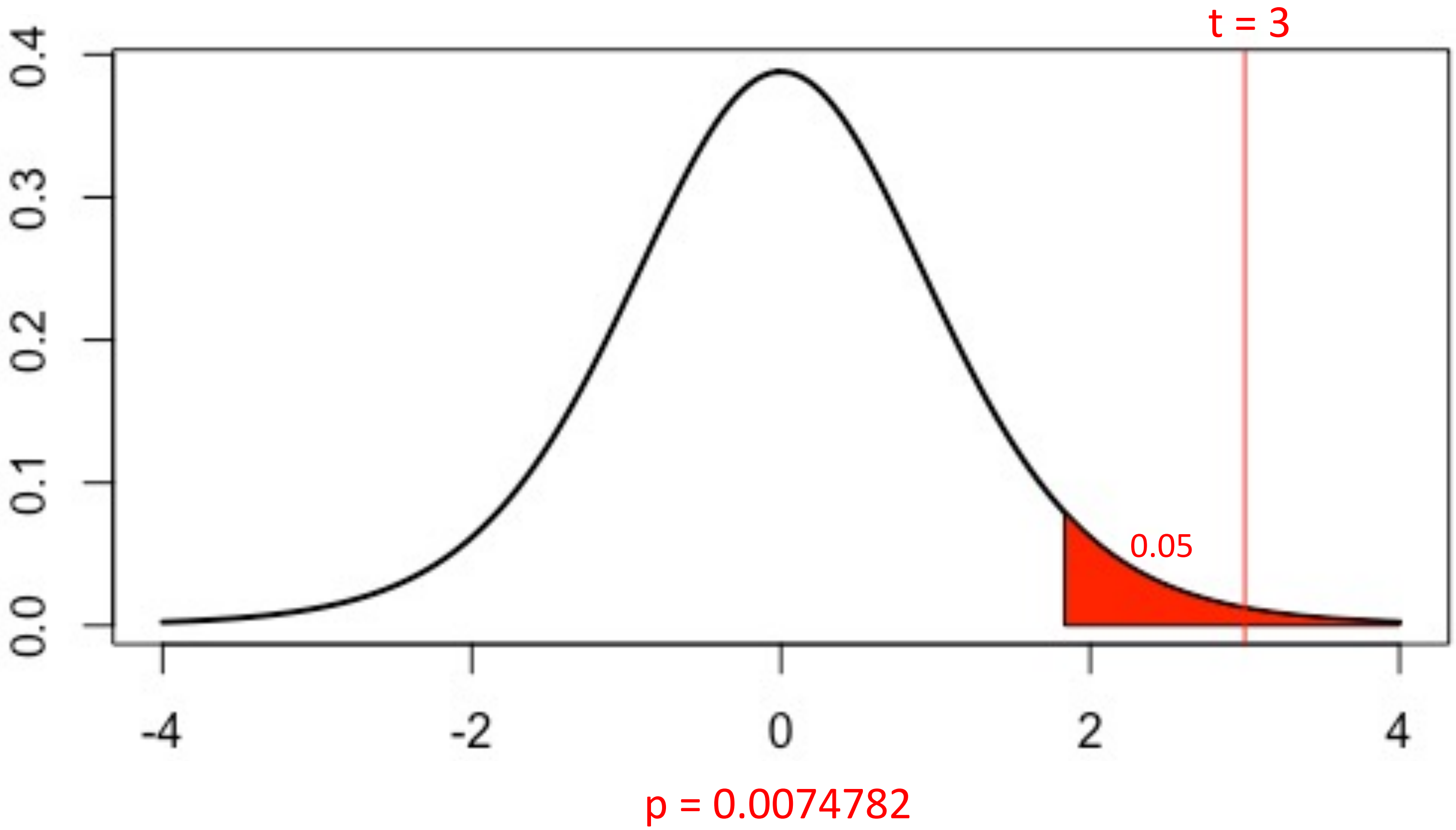
2. Calculate the appropriate test statistic

$$t = 3 \quad (\sim t_9)$$

$D = X_1 - X_2$

Paired t-test

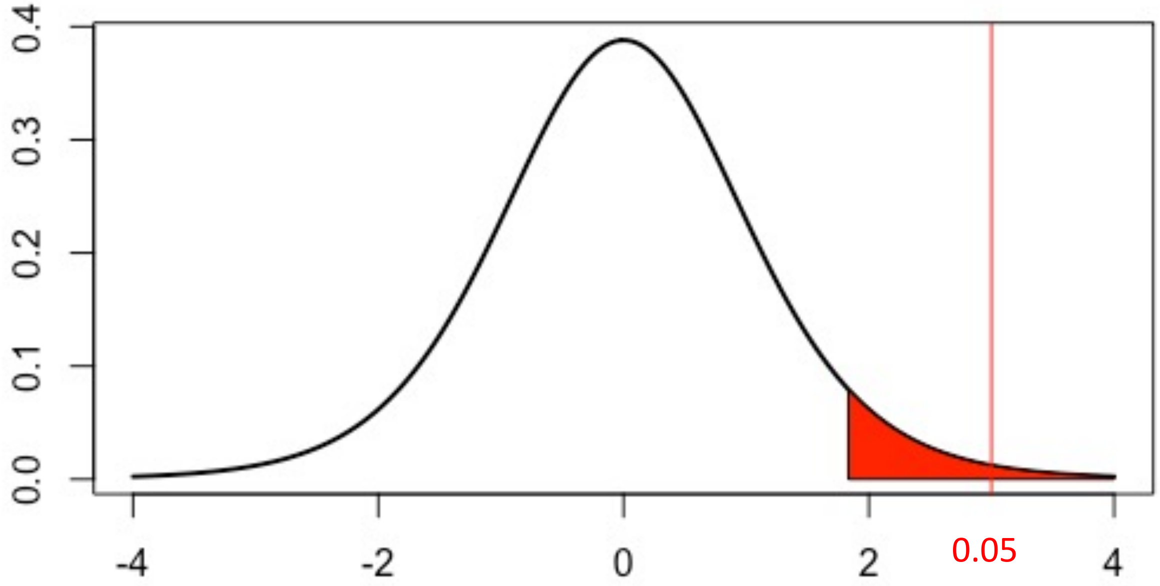
3. Determine the **critical region** / calculate the **p value** / calculate the confidence interval
4. Decide whether the null hypothesis can be rejected or not



$D = X_1 - X_2$

Paired t-test

3. Determine the critical region / calculate the p value / calculate **the confidence interval**
4. Decide whether the null hypothesis can be rejected or not



95% confidence interval for $\bar{D}$ = [0.246, ∞]

Barai A. Hypothesis Testing | All a beginner needs to know [Internet]. Medium. 2020 [cited 2021 Oct 4]. Available from: https://medium.com/analytics-vidhya/hypothesis-testing-all-a-beginner-needs-to-know-dd1bdeebdbf1

Brief Summary