

Biostat 200

Lecture 6

Recap

- We calculate confidence intervals to give the most plausible values for the population mean or proportion – 95% of the time the interval contains the population mean
- We conduct hypothesis tests of a mean or a proportion to make a conclusion about how our sample mean or proportion compares with some hypothesized value for the population mean or proportion.

Recap

- You can use 95% confidence intervals to reach the same conclusions as hypothesis tests
 - If the null value of the mean is outside of the 95% confidence interval, that would be the same as rejecting the null of a two-sided hypothesis test at significance level 0.05.

Recap

- We make these conclusions based on what we observed in our sample -- we will never know the true population mean or proportion
 - If the data are very different from the hypothesized mean or proportion, we reject the null
 - Example: Phase I vaccine trial – does the candidate vaccine meet minimum thresholds for safety and efficacy?
 - Statistical significance can be driven by n , and does not equal clinical or biological significance
 - On the other hand, you might have a suggestive result but not statistical significance with a small sample that deserves a larger follow up study

Types of error

- Type I error = significance level of the test
 $\alpha = P(\text{reject } H_0 \mid H_0 \text{ is true})$
- Incorrectly reject the null
- We take a sample from the population, calculate the statistics, and make inference about the true population. If we did this repeatedly, we would incorrectly reject the null 5% of the time that it is true if α is set to 0.05.

Types of error

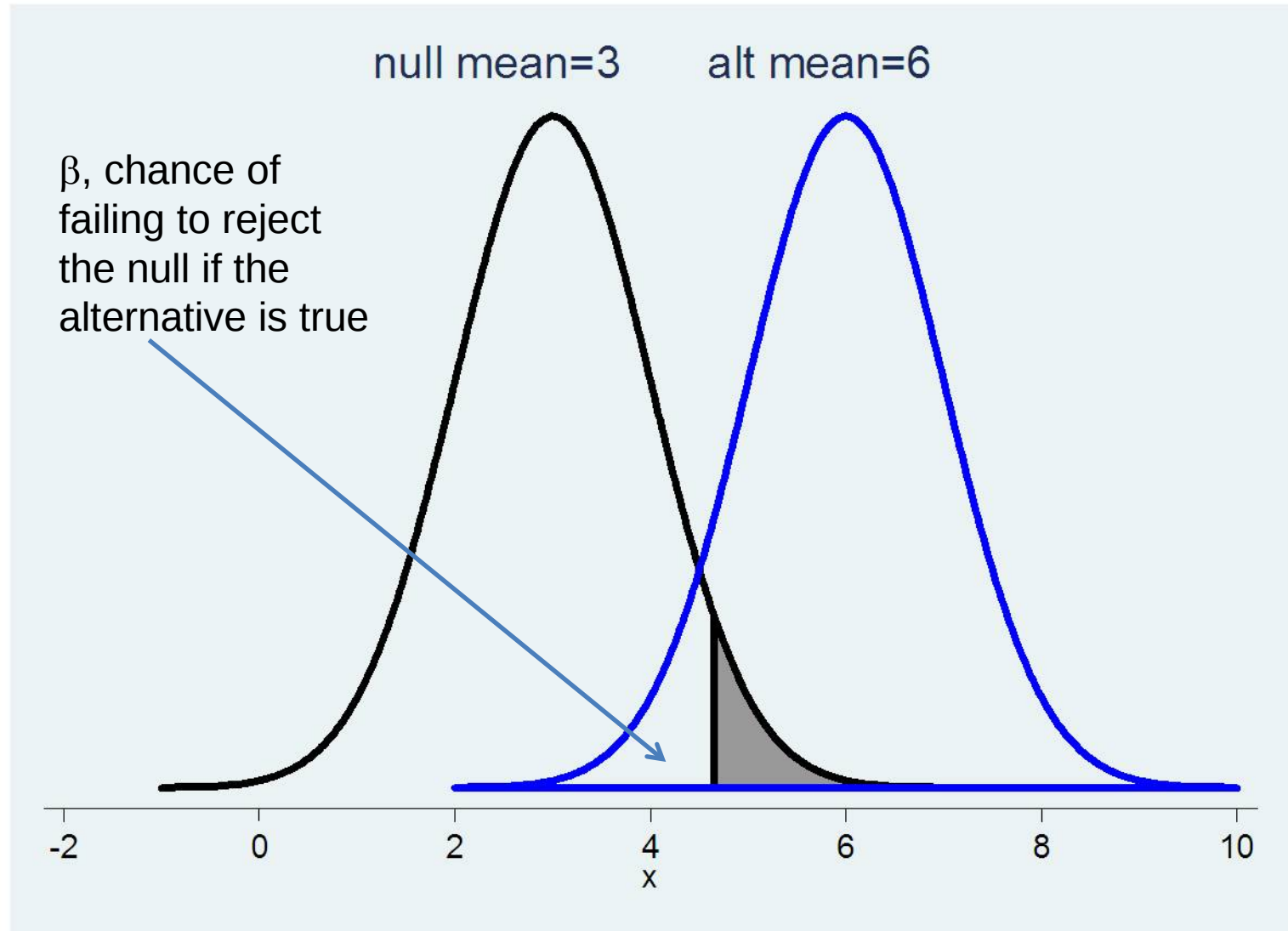
- Type II error –
 $\beta = P(\text{do not reject } H_0 \mid H_0 \text{ is false})$
- Incorrectly fail to reject the null
- This happens when the test statistic is not large enough, even if the underlying distribution is different

Types of error

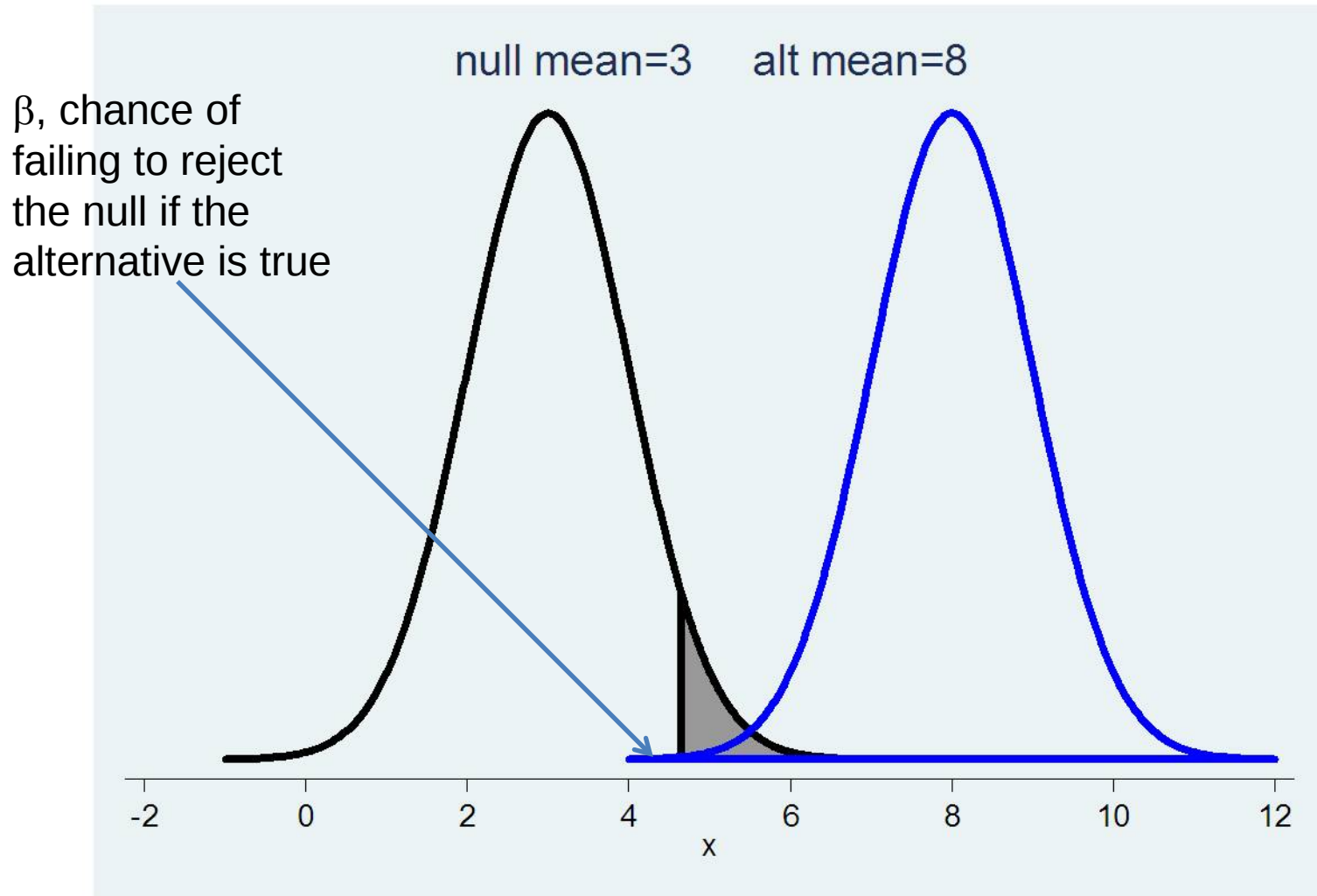
- Remember, H_0 is a statement about the population and is either true or false
- We take a sample and use the information in the sample to try to determine the answer
- Whether we make a Type I error or a Type II error depends on whether H_0 is true or false
- We set α , the chance of a Type I error, and we can design our study to minimize the chance of a Type II error

	True state	
<u>Decision</u>	<u>H_0 is true</u>	<u>H_0 is false</u>
Do not reject H_0	Correct	Type II error= β
Reject H_0	Type I error= α	Correct

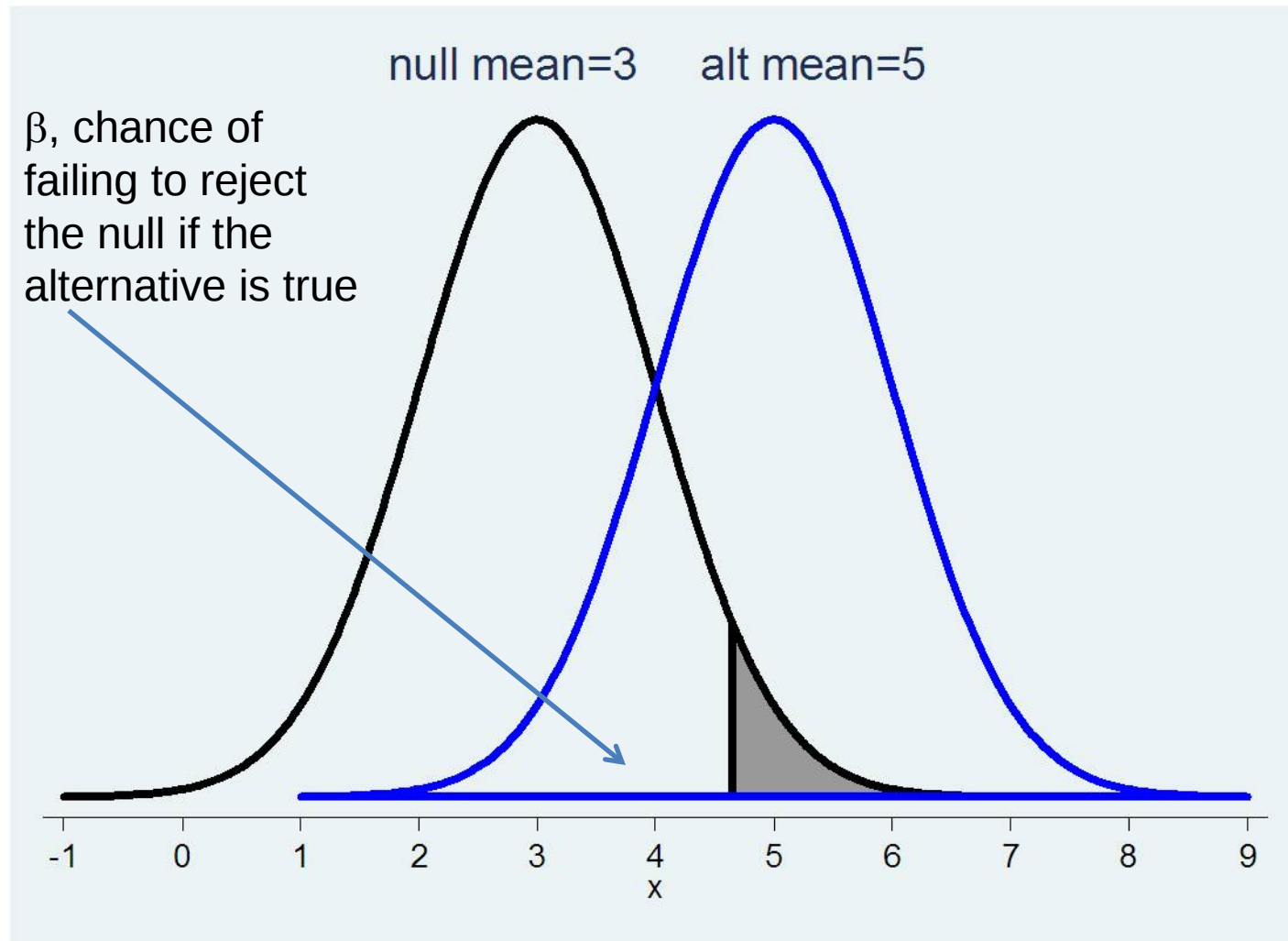
Chance of a type II error



If the alternative is very different from the null, the chance of a Type II error is low

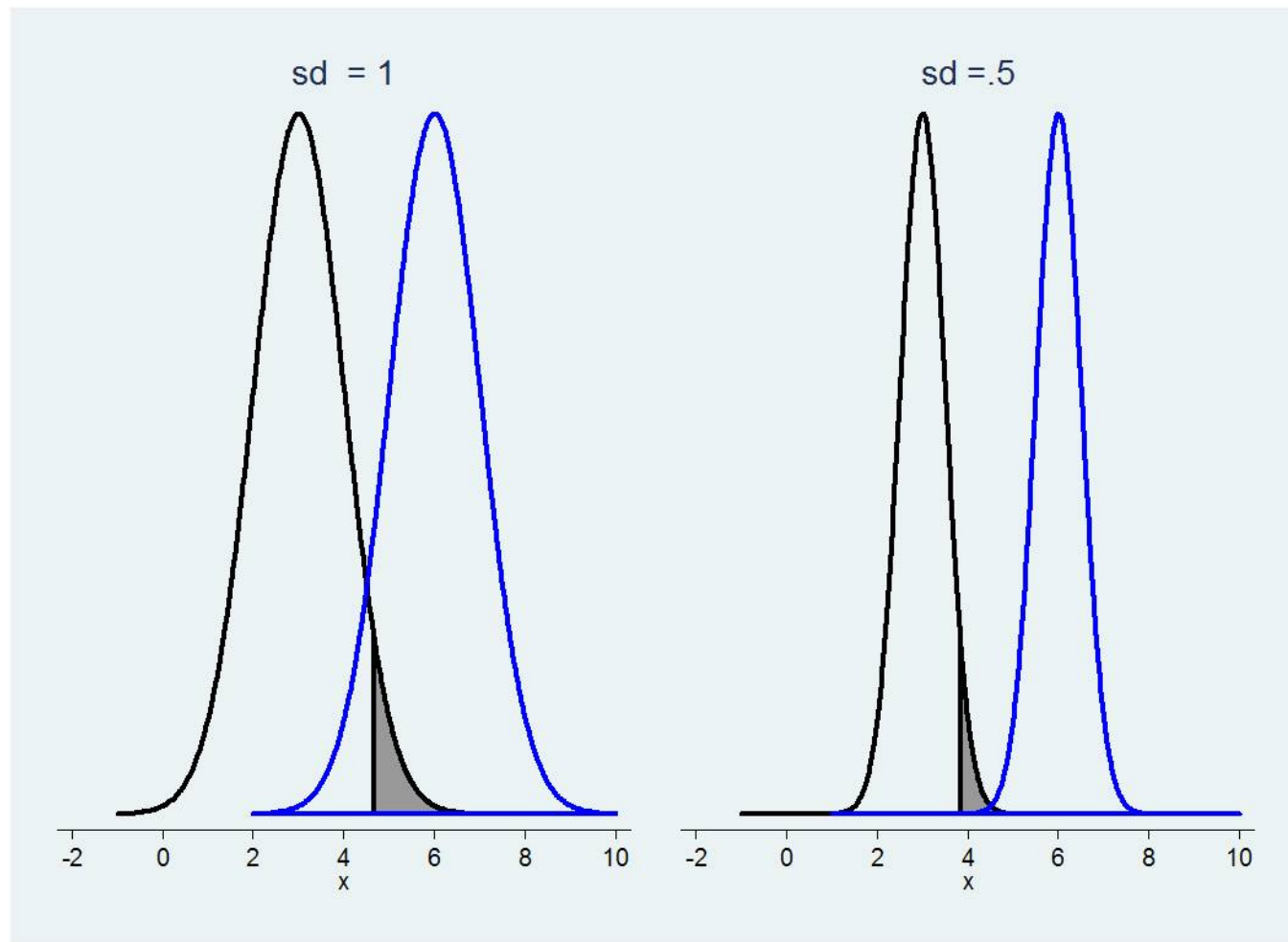


If the alternative is not very different from the null, the chance of a Type II error is high





Chance of a Type II error is lower if the SEM is smaller



This is relevant because the SD for the distribution of a sample mean is $\sigma/\sqrt{n}$
So increasing n decreases the SD of the mean

Finding β , P(Type II error)

- Find the critical value for your test
 - At what $\bar{x}$ will z_{stat} be greater than 1.96 (or 1.645 for a one-sided test) ?
 - This depends on n , σ , and α
- What is the probability of getting a sample mean less extreme than the critical value if the true mean is the alternate mean? This is β .

Power

- The power of a statistical test is lower for alternative values that are closer to the null value (the chance of a Type II error is higher) and higher for more extreme alternative values.
- It is standard to fix $\alpha=0.05$ and $\beta=0.20$ (for 80% power) and determine n for various alternative hypotheses

Sample size calculations

- In practice, you often have your n fixed by cost
- Then you can calculate how big the alternative has to be to reject the null with 80% probability assuming the alternative is true
- The difference between this alternative and the null is called the minimum detectable difference
 - In epidemiology when wanting to estimate an odds ratio it is called the minimum detectable odds ratio
- So if the minimum detectable difference is large, that is a bad thing – you will only have statistical significance if the alternative is very far from the null (very large effect sizes)

Comparison of two means: the paired t-test

- Paired samples, numerical variables
 - Two determinations on the same person (before and after)
 - e.g. before and after intervention
 - Matched samples – measurement on pairs of persons similar in some characteristics, i.e. identical twins (matching is on genetics)
 - Matching or pairing is performed to control for extraneous factors
- Each person or pair has 2 data points, and we calculate the difference for each
- Then we can use our one-sample methods to test hypotheses about the value of the difference

Example: BREATH Study

- We have found that self-reported alcohol consumption decreases after ART initiation, however we suspect a high degree of under-report. We use the biomarker PEth to obtain a biological measure of alcohol use in a one-year prospective study. Looking at baseline and 3 months...

Paired data – PEth at 0 and 3 months

** print out 1st 10 observations

```
. list studyid peth0_log10 peth3_log10 peth_diff in 1/10
```

```
+-----+
| studyid    peth0_log10    peth3_log10    peth_diff |
+-----+
1. | MBB2001    2.054766    1.950681    - .104085 |
2. | MBB2002     .30103     .30103         0 |
3. | MBB2006     .30103     .30103         0 |
4. | MBB2007     .30103     .30103         0 |
5. | MBB2008    1.388012    1.575477    .1874642 |
+-----+
6. | MBB2011     .30103     .30103         0 |
7. | MBB2013     .30103     .30103         0 |
8. | MBB2016    2.122216     .30103    -1.821186 |
9. | MBB2021    1.341533    1.348207    .0066741 |
10. | MBB2022     .30103    1.111766    .8107364 |
+-----+
```

These data from BREATH study_pethwide_2013_1020.dta"

Comparison of two means: *paired* t-test

- Step 1: The hypotheses (two sided)

- Generically $H_0: \mu_1 - \mu_2 = \delta$

$$H_A: \mu_1 - \mu_2 \neq \delta$$

- Often $\delta=0$, no difference

So $H_0: \mu_1 - \mu_2 = 0$, i.e. $H_0: \mu_1 = \mu_2$

$$H_A: \mu_1 - \mu_2 \neq 0, \text{ i.e. } H_A: \mu_1 \neq \mu_2$$

Comparison of two means: *paired* t-test

- Step 1: The hypotheses (one sided)
- Generically $H_0: \mu_1 - \mu_2 \geq \delta$ or $H_0: \mu_1 - \mu_2 \leq \delta$
 $H_A: \mu_1 - \mu_2 < \delta$ $H_0: \mu_1 - \mu_2 < \delta$
- Often $\delta=0$, no difference
So $H_0: \mu_1 \geq \mu_2$ or $H_0: \mu_1 \leq \mu_2$
 $H_A: \mu_1 < \mu_2$ $H_A: \mu_1 > \mu_2$

Comparison of two means: *paired* t-test

- Step 2: Calculate the test statistic

$$t_{stat} = \frac{\bar{d} - \delta}{s_d / \sqrt{n}} \text{ where}$$

$\bar{d}$ is the average difference between the pairs

$$s_d = \sqrt{\frac{\sum_{i=1}^n (d_i - \bar{d})^2}{n - 1}}$$

δ is the hypothesized difference between the means

Comparison of two means: *paired* t-test

- If $\delta=0$, the formula for t_{stat} is

$$t_{\text{stat}} = \frac{\bar{d}}{s_d / \sqrt{n}} \text{ where}$$

$$s_d = \sqrt{\frac{\sum_{i=1}^n (d_i - \bar{d})^2}{n-1}}$$

Comparison of two means: *paired* t-test

- Step 3: Reject or fail to reject the null
 - Is the p-value (the probability of observing a difference as large or larger, under the null hypothesis) greater than or less than the significance level, α ?

Example

- We think participants may be decreasing their alcohol use over time. The null hypothesis is that they are drinking the same amount.

$$H_0: \mu_2 - \mu_1 = 0 \rightarrow \mu_2 = \mu_1$$

$$H_A: \mu_1 - \mu_2 \neq 0 \rightarrow \mu_2 \neq \mu_1$$

- Significance level=0.05



```
. . summ peth_diff
```

Variable	Obs	Mean	Std. Dev.	Min	Max
peth_diff	177	-.101553	.5782935	-1.929419	1.685742

```
*** calculate the t statistic
di -.101553/.5782935*sqrt(177)
-2.3363133
```

```
*** calculate the p-value
. di 2*ttail(176,2.336133)
.02061082
```

```
. di 2*(1-ttail(176, -2.336133))
.02061082
```

→ So we reject the null

$$t_{stat} = \frac{\bar{d}}{s_d / \sqrt{n}} \text{ where}$$

$$s_d = \sqrt{\frac{\sum_{i=1}^n (d_i - \bar{d})^2}{n-1}}$$

These data from auditc_2studies.dta

Using the ttest command

```
. . ttest peth_diff==0
```

One-sample t test

Variable	Obs	Mean	Std. Err.	Std. Dev.	[95% Conf. Interval]	
peth_d~f	177	-.101553	.0434672	.5782935	-.187337	-.015769

mean = mean(peth_diff) t = -2.3363
Ho: mean = 0 degrees of freedom = 176

Ha: mean < 0
Pr(T < t) = 0.0103

Ha: mean != 0
Pr(|T| > |t|) = 0.0206

Ha: mean > 0
Pr(T > t) = 0.9897

Note that mean>0 here is *mean difference*

Another way without calculating the difference

The command is

```
ttest var1==var2
```

```
. . ttest peth3_log10==peth0_log10
```

Paired t test

Variable	Obs	Mean	Std. Err.	Std. Dev.	[95% Conf. Interval]	
peth3~10	177	1.426734	.0686534	.9133744	1.291244	1.562224
peth0~10	177	1.528287	.0690468	.9186077	1.392021	1.664553
diff	177	-.101553	.0434672	.5782935	-.187337	-.015769

mean(diff) = mean(peth3_log10 - peth0_log10) t = -2.3363
Ho: mean(diff) = 0 degrees of freedom = 176

Ha: mean(diff) < 0
Pr(T < t) = 0.0103

Ha: mean(diff) != 0
Pr(|T| > |t|) = 0.0206

Ha: mean(diff) > 0
Pr(T > t) = 0.9897

Comparison of two means: t-test

- The goal is to compare means from two independent samples
- Two different populations
 - E.g. vaccine versus placebo group
 - E.g. women with adequate versus inadequate micronutrient levels

Comparison of two means: t-test

- Two sided hypothesis

$$H_0: \mu_1 = \mu_2$$

$$H_A: \mu_1 \neq \mu_2$$

- One sided hypothesis

$$H_0: \mu_1 \geq \mu_2$$

$$H_A: \mu_1 < \mu_2$$

- One sided hypothesis

$$H_0: \mu_1 \leq \mu_2$$

$$H_A: \mu_1 > \mu_2$$

Comparison of two means: t-test

- Even though the null and alternative hypotheses are the same as for the paired t-test, the test is different, it is wrong to use a paired t-test with independent samples and vice versa

Comparison of two means: t-test

- By the CLT, if X_1 and X_2 are normally distributed, then $\bar{X}_1 - \bar{X}_2$ is normally distributed with mean $\mu_1 - \mu_2$ and standard deviation $\sqrt{\sigma_1^2 / n_1 + \sigma_2^2 / n_2}$
- In one version of the t-test, we assume that the population standard deviations are equal, so $\sigma_1 = \sigma_2 = \sigma$
- Substituting, the standard deviation for the distribution of the difference of two sample means is $\sqrt{\sigma^2 (1/n_1 + 1/n_2)}$

Comparison of two means: t-test

- So we can calculate a z-score for the difference in the means and compare it to the standard normal distribution. The test statistic is

$$z_{stat} = \frac{(\bar{x}_1 - \bar{x}_2) - (\mu_1 - \mu_2)}{\sqrt{\sigma^2(1/n_1 + 1/n_2)}}$$

Comparison of two means: t-test when σ is unknown

- T-test test statistic

$$t_{stat} = \frac{(\bar{x}_1 - \bar{x}_2) - (\mu_1 - \mu_2)}{\sqrt{s_p^2 (1/n_1 + 1/n_2)}} \text{ where}$$

$$s_p^2 = \frac{(n_1 - 1)s_1^2 + (n_2 - 1)s_2^2}{n_1 + n_2 - 2}$$

- The formula for the pooled SD is a weighted average of the individual sample SDs
- The degrees of freedom for the test are $n_1 + n_2 - 2$

Comparison of two means: t-test

- As in our other hypothesis tests, compare the t statistic to the t-distribution to determine the probability of obtaining a mean difference as large or larger as the observed difference
- Reject the null if the probability, the p-value, is less than α , the significance level
- Fail to reject the null if $p \geq \alpha$

Comparison of two means, example

- Study of non-pneumatic anti-shock garment (Miller et al)
- Two groups – pre-intervention received usual treatment, intervention group received NASG
- Comparison of hemorrhaging in the two groups
- Null hypothesis: The hemorrhaging is the same in the two groups
 $H_0: \mu_1 = \mu_2$
 $H_A: \mu_1 \neq \mu_2$
- The data:
- External blood loss after entry:
 - Pre-intervention group (n=83) mean blood loss =340.4 SD=248.2
 - Intervention group (n=83) mean blood loss =73.5 SD=93.9

Calculating by hand

- External blood loss:
 - Pre-intervention group (n=83) mean=340.4 SD=248.2
 - Intervention group (n=83) mean=73.5 SD=93.9

- First calculate s_p^2

$$s_p^2 = (82 * 248.2^2 + 82 * 93.9^2) / (83 + 83 - 2) \\ = 35210.2$$

$$t_{\text{stat}} = (340.4 - 73.5) / \sqrt{35210.2 * (2/83)} \\ = 9.16$$

$$df = 83 + 83 - 2 = 164$$

```
. di 2*ttail(164, 9.16)
2.041e-16
```

$$t_{\text{stat}} = \frac{(\bar{x}_1 - \bar{x}_2) - (\mu_1 - \mu_2)}{\sqrt{s_p^2 (1/n_1 + 1/n_2)}} \text{ where} \\ s_p^2 = \frac{(n_1 - 1)s_1^2 + (n_2 - 1)s_2^2}{n_1 + n_2 - 2}$$

Comparison of two means, example

```
* ttesti  n1 mean1  sd1  n2 mean2 sd2
```

```
ttesti 83 340.4 248.2 83 73.5 93.9
```

Two-sample t test with equal variances

	Obs	Mean	Std. Err.	Std. Dev.	[95% Conf. Interval]	
x	83	340.4	27.24349	248.2	286.204	394.596
y	83	73.5	10.30686	93.9	52.99636	94.00364
combined	166	206.95	17.85377	230.0297	171.6987	242.2013
diff		266.9	29.12798		209.3858	324.4142

diff = mean(x) - mean(y) t = 9.1630
Ho: diff = 0 degrees of freedom = 164

Ha: diff < 0
Pr(T < t) = 1.0000

Ha: diff != 0
Pr(|T| > |t|) = 0.0000

Ha: diff > 0
Pr(T > t) = 0.0000

- Remember that when conducting a hypothesis test that a mean is equal to or less than or greater than some value (a one-sample t-test), use

```
.ttesti  n mean sd hypothesizedmean
```

- When testing the equality of 2 means, use

```
ttesti  n1 mean1 sd1  n2 mean2 sd2
```

- Stata will know which one based on how many numbers you enter (4 vs. 6)

- You can calculate a 95% confidence interval for the difference between the 2 means

$$\text{Lower bound : } (\bar{x}_1 - \bar{x}_2) - t_{df, .025} \sqrt{s_p^2 \left[\frac{1}{n_1} + \frac{1}{n_2} \right]}$$

$$\text{Upper bound : } (\bar{x}_1 - \bar{x}_2) + t_{df, .025} \sqrt{s_p^2 \left[\frac{1}{n_1} + \frac{1}{n_2} \right]}$$

- If the confidence interval for the difference does not include 0, then you can reject the null hypothesis of no difference

This is NOT equivalent to calculating separate confidence intervals for each mean and determining whether they overlap

Comparison of two means: t-test

- This t-test assumes equal variances in the two underlying populations
- If we do not assume equal variances we use a slightly different test statistic
 - Variances not assumed to be equal, so you do not use a pooled estimate
 - There is another formula for degrees of freedom
- Often the two different t-tests yield the same answer, but you should not assume equivalence unless you have a good reason for it
 - If the sample sizes are equal, you will get the same test statistic, just the df changes

The t statistic is

$$t_{stat} = \frac{(\bar{x}_1 - \bar{x}_2) - (\mu_1 - \mu_2)}{\sqrt{(s_1^2 / n_1) + (s_2^2 / n_2)}}$$

with degrees of freedom ν (pronounced "nu")

$$\nu = \frac{\left[(s_1^2 / n_1) + (s_2^2 / n_2) \right]^2}{\left[(s_1^2 / n_1)^2 / (n_1 - 1) + (s_2^2 / n_2)^2 / (n_2 - 1) \right]}$$

Round up to the nearest integer to get the degrees of freedom

Comparison of two means, example

```
ttesti 83 340.4 248.2 83 73.5 93.9, unequal
```

Two-sample t test with unequal variances

	Obs	Mean	Std. Err.	Std. Dev.	[95% Conf. Interval]	
x	83	340.4	27.24349	248.2	286.204	394.596
y	83	73.5	10.30686	93.9	52.99636	94.00364
combined	166	206.95	17.85377	230.0297	171.6987	242.2013
diff		266.9	29.12798		209.1446	324.6554

diff = mean(x) - mean(y)

t = 9.1630

Ho: diff = 0

Satterthwaite's degrees of freedom = 105.002

Ha: diff < 0

Pr(T < t) = 1.0000

Ha: diff != 0

Pr(|T| > |t|) = 0.0000

Ha: diff > 0

Pr(T > t) = 0.0000

Test of the means of independent samples

- When you have the data in Stata, with the different groups in different columns, use
 `ttest var1==var2, unpaired`
or
 `ttest var1==var2, unpaired unequal`

Test of the means of independent samples

- More commonly you will have the data all in one variable, and the grouping in another variable. Then use

`ttest var, by(groupvar)`

or `ttest var, by(groupvar) unequal`

Alcohol study example

Testing whether log PEth at baseline differs by sex

Null hypothesis: Log PEth for females = Log PEth for males

```
. ttest peth0_log10, by(sex)
```

Two-sample t test with equal variances

Group	Obs	Mean	Std. Err.	Std. Dev.	[95% Conf. Interval]	
Female	71	1.106233	.0995942	.8391959	.9075982	1.304867
Male	106	1.810984	.0837679	.8624433	1.644888	1.97708
combined	177	1.528287	.0690468	.9186077	1.392021	1.664553
diff		-.7047514	.1308476		-.9629938	-.446509
diff = mean(Female) - mean(Male)				t = -5.3860		
Ho: diff = 0				degrees of freedom = 175		
Ha: diff < 0		Ha: diff != 0		Ha: diff > 0		
Pr(T < t) = 0.0000		Pr(T > t) = 0.0000		Pr(T > t) = 1.0000		

.

```
. ttest peth0_log10, by(sex) unequal
```

Two-sample t test with unequal variances

Group	Obs	Mean	Std. Err.	Std. Dev.	[95% Conf. Interval]	
Female	71	1.106233	.0995942	.8391959	.9075982	1.304867
Male	106	1.810984	.0837679	.8624433	1.644888	1.97708
combined	177	1.528287	.0690468	.9186077	1.392021	1.664553
diff		-.7047514	.1301387		-.9618518	-.447651

diff = mean(Female) - mean(Male) t = -5.4154
Ho: diff = 0 Satterthwaite's degrees of freedom = 153.02

Ha: diff < 0 Ha: diff != 0 Ha: diff > 0
Pr(T < t) = 0.0000 Pr(|T| > |t|) = 0.0000 Pr(T > t) = 1.0000

- Confidence interval for the difference of two means from independent samples, when unequal variances are assumed

$$\text{Lower bound : } (\bar{x}_1 - \bar{x}_2) - t_{v,.025} \sqrt{\left[\frac{s_1^2}{n_1} + \frac{s_2^2}{n_2} \right]}$$

$$\text{Upper bound : } (\bar{x}_1 - \bar{x}_2) + t_{v,.025} \sqrt{\left[\frac{s_1^2}{n_1} + \frac{s_2^2}{n_2} \right]}$$

Comparison of two proportions

- Similar to comparing two means
- Null hypothesis about two proportions, p_1 and p_2 ,
$$H_0: p_1 = p_2$$
$$H_A: p_1 \neq p_2$$
- If n_1 and n_2 are sufficiently large, the difference between the two proportions follows a normal distribution.

Comparison of two proportions

- So we can use the z statistic

$$z = \frac{(\hat{p}_1 - \hat{p}_2) - (p_1 - p_2)}{\sqrt{\hat{p}(1 - \hat{p})[1/n_1 + 1/n_2]}}$$

$$\text{where } \hat{p} = \frac{x_1 + x_2}{n_1 + n_2}$$

to find the probability of observing a difference as large as we do, under the null hypothesis of no difference

Comparison of two proportions

- Example: Going on antiretroviral therapy in the first 2 months of HIV care in the BREATH study.

```
. tab art3
```

3 art	Freq.	Percent	Cum.
0	87	49.15	49.15
1	90	50.85	100.00
Total	177	100.00	

```
. tab art3 if sex==2
```

3 art	Freq.	Percent	Cum.
0	50	47.17	47.17
1	56	52.83	100.00
Total	106	100.00	

```
. tab art3 if sex==1
```

3 art	Freq.	Percent	Cum.
0	37	52.11	52.11
1	34	47.89	100.00
Total	71	100.00	

Comparison of two proportions

- Null hypothesis: The rate of going on ART in males and females is the same

$$H_0: p_1 = p_2 \text{ (so } p_1 - p_2 = 0)$$

- Z statistic is calculated:

$$\hat{p} = 90/177 = 0.509$$

$$z_{\text{stat}} = (.528 - .479) / \sqrt{.509 * (1 - .509) * (1/106 + 1/71)} \\ = 0.639$$

$$\text{. di 2*normal(- .639)} \\ \text{.52282293}$$

$$z = \frac{(\hat{p}_1 - \hat{p}_2) - (p_1 - p_2)}{\sqrt{\hat{p}(1 - \hat{p})[1/n_1 + 1/n_2]}}$$

$$\text{where } \hat{p} = \frac{x_1 + x_2}{n_1 + n_2}$$

Comparison of two proportions

```
prtesti      n1  p1  n2   p2
```

```
. prtesti 106 .528 71 .479
```

Two-sample test of proportion

x: Number of obs = 106

y: Number of obs = 71

Variable	Mean	Std. Err.	z	P> z	[95% Conf. Interval]	
x	.528	.0484881			.4329651	.6230349
y	.479	.0592867			.3628002	.5951998
diff	.049	.0765899			-.1011134	.1991134
	under Ho:	.076668	0.64	0.523		

diff = prop(x) - prop(y)

z = 0.6391

Ho: diff = 0

Ha: diff < 0

Pr(Z < z) = 0.7386

Ha: diff != 0

Pr(|Z| < |z|) = 0.5227

Ha: diff > 0

Pr(Z > z) = 0.2614

Comparison of two proportions

```
. . prtest art3, by(sex)
```

Two-sample test of proportion

Female: Number of obs = 71
Male: Number of obs = 106

Variable	Mean	Std. Err.	z	P> z	[95% Conf. Interval]	
Female	.4788732	.0592861			.3626746	.5950718
Male	.5283019	.0484864			.4332702	.6233335
diff	-.0494286	.0765883			-.199539	.1006817
	under Ho:	.0766676	-0.64	0.519		

diff = prop(Female) - prop(Male) z = -0.6447
Ho: diff = 0

Ha: diff < 0
Pr(Z < z) = 0.2596

Ha: diff != 0
Pr(|Z| < |z|) = 0.5191

Ha: diff > 0
Pr(Z > z) = 0.7404

Statistical hypothesis tests

Data and comparison type	Alternative hypotheses	Parametric test Stata command
Numerical; One mean	$H_a: \mu \neq \mu_a$ (two-sided) $H_a: \mu > \mu_a$ or $\mu < \mu_a$ (one-sided)	Z or t-test • <code>ttest var1=hypoth val.*</code>
Numerical; Two means, <u>paired data</u>	$H_a: \mu_1 \neq \mu_2$ (two-sided) $H_a: \mu_1 > \mu_2$ or $\mu < \mu_a$ (one-sided)	Paired t-test • <code>ttest var1=var2*</code>
Numerical; Two means, independent data	$H_a: \mu_1 \neq \mu_2$ (two-sided) $H_a: \mu_1 > \mu_2$ or $\mu < \mu_a$ (one-sided)	T-test (equal or unequal variance) • <code>ttest var1, by(byvar)</code> • <code>ttest var1, by(byvar) unequal</code>
Numerical, Two or more means, independent data		
Dichotomous; One proportion	$H_a: p \neq p_a$ (two-sided) $H_a: p > p_a$ or $p < p_a$ (one-sided)	Proportion test • <code>prtest var1=hypoth value*</code> • <code>bitest var1=hypoth value</code>
Dichotomous; two proportions	$H_a: p_1 \neq p_2$ (two-sided) $H_a: p_1 > p_2$ (one-sided)	Proportion test (z-test) • <code>prtest var1, by(byvar)</code>
Categorical by categorical (nxk)		

In class problem

For next time

- Read Pagano and Gauvreau
 - Pagano and Gavreau Chapters 11, and 14 (pages 332-338)
 - Pagano and Gavreau Chapter 12-13