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Preliminaries

Director:  Tatsuki Koyama, PhD

Schedule:  Monday, August 7th - Friday, August 11th from 1:00 PM - 4:00 PM

Description:  This course will introduce fundamental concepts and techniques for basic statistical analysis, including types of variables, data summary, hypothesis testing, simple linear regression, and power analysis.

- This course covers basic concepts in statistical data analysis.
- This course is not a tutorial on using a statistical software.

Learning objectives:  After participating in this activity, participants should be able to:

1. Critically read statistical analysis plans and analysis reports.
2. Identify study design appropriate for research question.
3. Select and perform simple statistical analysis for each study design.

Software:  We will use R, a programming language and software environment for statistical computing and graphics. R can be downloaded from www.r-project.org.
Chapter 1

Introduction

1.1 What is (bio)statistics?

**Biostatistics** The application of statistics to a wide range of topics in biology. (Wikipedia)

**Statistics** The study of the collection, analysis, interpretation, presentation, and organization of data. (The Oxford Dictionary of Statistical Terms)

When we have census data, interpretation of the data is straightforward. (A census is the procedure of systematically acquiring and recording information about the member of a given population.)

In medical research, it is almost always impossible to get the data on everyone in the population of interest. So we take a representative sample from the population and make inference about the population.

Samples vary from one another. Statistics allows us to make inference about the unknown population parameters using the data at hand (samples) and computing statistics.

The following definitions are from Freedman et. al.

**Population** A whole class of individuals on which we want to make a general statement.

**Parameters** Some numerical facts about the population.

---

**Sample** A part of population that can be examined.

**Statistics** Numbers which can be computed from a sample.

### 1.2 Example

#### 1.2.1 Prostate Cancer Intervention Versus Observation Trial (PIVOT)

"From November 1994 through January 2002, we randomly assigned 731 men with localized prostate cancer to radical prostatectomy or observation and followed them through January 2010. The primary outcome was all-cause mortality; the secondary outcome was prostate cancer mortality."

Inclusion criteria

1. 75 years or younger
2. Localized disease
3. PSA < 50mg/mL
4. Diagnosed within 12 months
5. Radical prostatectomy candidate

The following are the population of interest and the sample if we are to make an inference about all prostatectomy patients.

**Population** All prostate cancer patients meeting the inclusion criteria who receive radical prostatectomy.

**Sample** 364 patients in this study who were assigned to the radical prostatectomy group.

**Parameter** All-cause mortality in the population (% of the population who die).

**Statistic** All-cause mortality in the sample (% of $N = 364$ of the sample who die).

Conclusions: 171 of 364 (47.0%) men assigned to radical prostatectomy died.

The number, 47.0%, is specific to our sample, and if we had a different sample, the number probably would have been different. Using various techniques in statistics, we sort of understand how the samples (the corresponding statistics) vary. And that understanding allows us to say something about the unknown population parameter, the true all-cause mortality of the all prostate cancer patients meeting the inclusion criteria and received and will receive the radical prostatectomy.

An estimate of the all-cause mortality for the prostatectomy patients is 47.0% and its 95% confidence interval is (41.8%, 52.2%).

“We do not know the true all-cause mortality, but it is probably close to 47.0%. Perhaps between 41.8% and 52.2%.”

1.2.2 Example: Comparative Effectiveness Analysis of Surgery And Radiation (CEASAR)

CEASAR is an observational study which recruited men who were diagnosed with prostate cancer from 2011 to 2012.

- CEASAR enrolled 3,691 men.
• Two of the primary variables are sexual and urinary function scores (UCLA Prostate Cancer
  Index) based on quality of life survey.

• Quality of life score (QoL) ranges from 0 to 100.

• Majority of patients underwent surgery (radical prostatectomy), and other treatment options
  include radiation and active surveillance.

In this course, we use a small subset of the data as a practice data set. (This is from an ongoing
project, and data have been altered.)

```r
getwd()
[1] "/Users/tatsukikoyama/Dropbox/CQS/CqsSummerInstitute/2017Biostats1"

d <- read.csv("R/practiceCesarData.csv", header = TRUE, as.is = FALSE)
d$Race <- factor(d$Race, levels = c("White", "Black", "Other"))
d$Education <- factor(d$Education, levels = c("High school", "Some college", "College graduate", "Graduate school"))
d$Income <- factor(d$Income, levels = c("- 30K", "30K - 50K", "50K - 100K", "100K -"))
d$Gleason <- factor(d$Gleason, levels = c("6 or less", "3 + 4", "4 + 3", "8,9,10"))

names(d)  # Variable names
[1] "Risk" "Gleason" "PSA" "Age" "Race"
[6] "MaritalStatus" "Education" "Income" "QoL0" "QoL6"
[11] "Treatment" "HeartDisease" "Hypertension" "Athma" "Diabetes"

dim(d)  # Number of rows and columns
[1] 200  15
Table 1.1: Descriptive Statistics by Treatment

<table>
<thead>
<tr>
<th></th>
<th>Radiation</th>
<th>Surgery</th>
<th>Test Statistic</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$N = 70$</td>
<td>$N = 130$</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>200</td>
<td>63.0</td>
<td>67.0 73.0</td>
</tr>
<tr>
<td>Race: White</td>
<td>200</td>
<td>69% (48)</td>
<td>75% (97)</td>
</tr>
<tr>
<td>Black</td>
<td>10% (7)</td>
<td>10% (13)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>21% (15)</td>
<td>15% (20)</td>
<td></td>
</tr>
<tr>
<td>Marital Status: Not married</td>
<td>200</td>
<td>27% (19)</td>
<td>10% (13)</td>
</tr>
<tr>
<td>Education: High school</td>
<td>200</td>
<td>47% (33)</td>
<td>25% (33)</td>
</tr>
<tr>
<td>Some college</td>
<td>21% (15)</td>
<td>23% (30)</td>
<td></td>
</tr>
<tr>
<td>College graduate</td>
<td>20% (14)</td>
<td>26% (34)</td>
<td></td>
</tr>
<tr>
<td>Graduate school</td>
<td>11% (8)</td>
<td>25% (33)</td>
<td></td>
</tr>
<tr>
<td>Income: &lt; 30K</td>
<td>195</td>
<td>34% (23)</td>
<td>15% (19)</td>
</tr>
<tr>
<td>30K - 50K</td>
<td>24% (16)</td>
<td>20% (26)</td>
<td></td>
</tr>
<tr>
<td>50K - 100K</td>
<td>25% (17)</td>
<td>31% (40)</td>
<td></td>
</tr>
<tr>
<td>100K -</td>
<td>16% (11)</td>
<td>34% (43)</td>
<td></td>
</tr>
<tr>
<td>PSA</td>
<td>200</td>
<td>5.00</td>
<td>6.30 9.05</td>
</tr>
<tr>
<td>Gleason: 6 or less</td>
<td>200</td>
<td>46% (32)</td>
<td>47% (61)</td>
</tr>
<tr>
<td>3 + 4</td>
<td>44% (31)</td>
<td>34% (44)</td>
<td></td>
</tr>
<tr>
<td>4 + 3</td>
<td>4% (3)</td>
<td>7% (9)</td>
<td></td>
</tr>
<tr>
<td>8,9,10</td>
<td>6% (4)</td>
<td>12% (16)</td>
<td></td>
</tr>
<tr>
<td>Heart Disease: Yes</td>
<td>200</td>
<td>9% (6)</td>
<td>15% (19)</td>
</tr>
<tr>
<td>Hypertension: Yes</td>
<td>200</td>
<td>67% (47)</td>
<td>52% (68)</td>
</tr>
<tr>
<td>Diabetes: Yes</td>
<td>200</td>
<td>17% (12)</td>
<td>18% (24)</td>
</tr>
<tr>
<td>QoL0</td>
<td>200</td>
<td>32.6</td>
<td>51.9 68.2</td>
</tr>
<tr>
<td>QoL6</td>
<td>200</td>
<td>19.6</td>
<td>48.0 73.9</td>
</tr>
</tbody>
</table>

$^{ab}$ represent the lower quartile $a$, the median $b$, and the upper quartile $c$ for continuous variables. $N$ is the number of non–missing values. Numbers after percents are frequencies. Tests used:  
$^1$Wilcoxon test; $^2$Pearson test
Chapter 2

Basic Concepts

2.1 Types of data

Response variable ($Y$) (Outcome variable, Dependent variable) Clinical endpoint and lab measurements that represent an effect.

Explanatory variable ($X$) (Exposure variable, Independent variable) Something that may be associated with the response variable and of major interest.

Confounding variable (Confounder) (Adjustment variable, Effect modifier) A variable not of major interest but may be associated with response and/or independent variables.

A few example:

• Survival $\sim$ Breast Cancer Treatment
  Possible confounders: age, BMI, smoking history.

• Prostate Cancer Treatment $\sim$ Participatory decision making score
  Possible confounders: tumor stage, age, comorbidities.

2.1.1 Types of measurements

• Binary (Dichotomous): A variable with 2 possible categories.
• Categorical (Nominal): More than 2 categories that are not naturally ordered. e.g., Race, Location.

• Ordinal: A categorical variable with natural order. e.g., Income bracket

• Count: An ordinal variable with no upper limit.

• Continuous: A numeric variable having many possible values.

What type of variables are these?

1. Age: Younger than 65, 65 to 75, older than 75.

2. Education level.

3. Number of ER visits.


6. Number of stained cells.

7. Age: Younger than 65, 65 and older.

8. Age.

A continuous variable can always be categorized or dichotomized, but doing so is never a good idea. There is loss of information, and a larger sample size is required to yield the same statistical information (precision or power).

Random variable: A variable whose possible values are numerical outcomes of a random phenomenon. It is usually denoted by a capital alphabet $X$ and $Y$. And its values are usually denoted by $x$ and $y$.

Example:
• $X$ is systolic blood pressure of patients in a study. $x = 122, 124, 141, \ldots$

• $X$ is race of patients. $x = \text{white, black, Asian, \ldots}$

### 2.2 Distribution

The *distribution* of a random variable $X$ is a profile of its variability and other tendencies. A distribution is characterized by:

- Binary variable: the probability (proportion) of “yes” (or one of the categories).
- Categorical variable (more than 2 levels): the probability (proportion) of each category.
- Continuous variable: cumulative probability distribution. $P[X \leq x]$ for all values of $x$. (There are many other ways...) Sometimes, the *mean* and *standard deviation* are sufficient.

### 2.3 Descriptive statistics

- Categorical variables (including binary and ordinal variables) can be described by the proportion of each category.
  
  Because proportions add up to 1 (100%), we only need to report $K - 1$ proportions for a variable with $K$ categories.

```r
table(d$Race)  # Distribution of 'Race'

White Black Other
 145  20  35

prop.table(table(d$Race))  # Proportions of each category

White Black Other
0.725 0.100 0.175

table(d$Education)
```
• To represent (summarize) a continuous variable, a measure of central tendency and a measure of variation are often used.

  – Measure of central tendency
    Mean, median, geometric mean
  – Measure of variation
    Standard deviation, inter-quartile range (IQR)

2.3.1 Mean, median, geometric mean

Mean (aka “average”, arithmetic mean)

\[
\bar{x} = \frac{\sum_{i=1}^{n} x_i}{n}
\]

• Add all the numbers and divide by the number of items.

• Works well in general but not always.
  Grossly influenced by outliers.
  Grossly influenced by skewness.

Median: The middle value.

• Works well with outliers and skewness.

Geometric mean: Multiply all the numbers and take the \( n^{th} \) root.

• Works only for positive numbers.
- Works well with skewed data with outliers.

- Used often without being mentioned because it is antilog of the mean of log-transformed data.

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>Median</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symmetric data</td>
<td>25.0</td>
<td>24.7</td>
</tr>
<tr>
<td>With a few outliers</td>
<td>26.0</td>
<td>24.9</td>
</tr>
<tr>
<td>With a huge outlier</td>
<td>26.7</td>
<td>24.9</td>
</tr>
</tbody>
</table>
CHAPTER 2. BASIC CONCEPTS

Right skewed data

<table>
<thead>
<tr>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
</tr>
<tr>
<td>5</td>
</tr>
<tr>
<td>10</td>
</tr>
<tr>
<td>15</td>
</tr>
<tr>
<td>20</td>
</tr>
</tbody>
</table>

Log transformed

<table>
<thead>
<tr>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>3</td>
</tr>
<tr>
<td>4</td>
</tr>
</tbody>
</table>

Mean | Median | Geometric mean
---|---|---
Right skewed data | 32.4 | 23.8 | 23.1
Log transformed | 3.1 | 3.2 |

```r
x <- rnorm(n = 40, mean = 100, sd = 15)
## Generate 40 random numbers from Normal(100, 15) distribution.

mean(x) ## mean
[1] 101.3

median(x) ## median
[1] 101.17

prod(x)^(1/length(x)) ## geometric mean
[1] 100.38
```
2.3.2 Variance, standard deviation, standard error, IQR

Variance

$$s^2 = \frac{\sum_{i=1}^{n}(x_i - \bar{x})^2}{n - 1}$$

- Variance is average of squared-distance from the mean.
- Denominator is $n - 1$ instead of $n$ to make the value a little bigger to compensate for the fact we are estimating the mean. (i.e., more uncertainty)
- The more spread the data the bigger the variance.

Standard deviation ($s$) is the square root of variance.

- Standard deviation and the mean have the same units as the original data.
- Variance and standard deviation are always positive.
- Variance and standard deviation are 0 when all the data are the same (constant).
- Variance and standard deviation are grossly influenced by outliers.
- Variance and standard deviation are only useful for symmetric data.
Quantiles (percentiles): the $q$-th sample quantile is the value such that $q\%$ of the data fall below. For example, 20% of the data fall below the 20th percentile.

- 50th percentile is the median ($Q_2$).
- 25th quantile is the lower quartile ($Q_1$).
- 75th quantile is the upper quartile ($Q_3$).
• Interquartile range (IQR) is the difference of $Q_3$ and $Q_1$. (or $Q_1$ to $Q_3$).

  – IQR is the range such that the middle 50% of the data fall.
  
  – It is meaningful for any continuous data (skewed, outliers), perhaps except when there are a large number of ties.

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>Median</th>
<th>Variance</th>
<th>sd</th>
<th>$Q_1$</th>
<th>$Q_2$</th>
<th>$Q_3$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symmetric data</td>
<td>25.0</td>
<td>24.7</td>
<td>7.2</td>
<td>2.7</td>
<td>23.2</td>
<td>24.7</td>
<td>27.0</td>
</tr>
<tr>
<td>With a few outliers</td>
<td>26.0</td>
<td>24.9</td>
<td>22.9</td>
<td>4.8</td>
<td>23.2</td>
<td>24.9</td>
<td>27.2</td>
</tr>
<tr>
<td>With a huge outlier</td>
<td>26.7</td>
<td>24.9</td>
<td>59.2</td>
<td>7.7</td>
<td>23.3</td>
<td>24.9</td>
<td>27.2</td>
</tr>
</tbody>
</table>

2.3.3 CEASAR: summarizing continuous variables

Let’s look at age of the patients in the CEASAR data.

```r
range(d$Age)
[1] 42 79
mean(d$Age)
[1] 63.92
median(d$Age)
[1] 65
var(d$Age)
[1] 70.92
sd(d$Age)
[1] 8.422
quantile(d$Age, c(0.25, 0.5, 0.75))
25% 50% 75%  
 58 65 70
```

And PSA.
range(d$PSA)
[1]  0.9 48.2

mean(d$PSA)
[1]  7.099

median(d$PSA)
[1]   6.05

var(d$PSA)
[1]  24.46

sd(d$PSA)
[1]  4.946

quantile(d$PSA, c(0.25, 0.5, 0.75))
25% 50% 75%
4.80  6.05  8.10
Summary

- For symmetric data, mean and standard deviation are good summaries of the distribution.

- For any data, median and quartiles are good summaries of the distribution.

So why do we even compute the mean and standard deviation? They are very useful when they are useful! (More about this later: Normal, Central Limit Theorem)
Chapter 3

Normal Distribution

Many random variables (are assumed to) have a Normal distribution. A normal distribution is symmetric and is bell-shaped.
This is a Normal distribution with mean $= 100$ and sd $= 15$. $X \sim \text{Normal}(100, 15)$ or $X \sim \text{Normal}(100, 15^2)$.

- A normal distribution can be uniquely specified by the mean and standard deviation.
- 50% of the data are above (below) the mean.
- About 2.5% of the data are above 2 standard deviations above (below) the mean.
- About 15% of the data are above 1 standard deviation above (below) the mean.

```
> pnorm(85, mean = 100, sd = 15, lower.tail = TRUE)
[1] 0.1587
> pnorm(130, mean = 100, sd = 15, lower.tail = FALSE)
[1] 0.02275
```
Normal distribution is very useful because ...

• when the data come from a normal distribution the distribution of *sample means* is normal.

• the distribution of *sample means* is normal even when the data do not come from a normal distribution.

  There are exceptions.
  
  True only when *sample size* is large.

A (made-up) example:

Suppose that a psychological test score has the true (unknown) distribution shown below.

![True unknown distribution of Test Scores](image-url)
<table>
<thead>
<tr>
<th>mean</th>
<th>sd</th>
<th>Q1</th>
<th>median</th>
<th>Q3</th>
</tr>
</thead>
<tbody>
<tr>
<td>42.35</td>
<td>30.17</td>
<td>14.26</td>
<td>37.88</td>
<td>68.66</td>
</tr>
</tbody>
</table>

Because the data are not normally distributed, it would be incorrect to say things like “2.275% of the data are 2 standard deviations above the mean.” (This is only true for normal distributions.) It is still correct to say 25% of the data are above the third quartile (68.66). (This is always true.)

Now suppose that we took a sample of size $n = 225$ from this distribution and compute the sample mean. And it was 41.5. If we take a different sample of size $n = 225$, the new sample mean will be different from 41.5. In reality, we only take one sample, but here, let’s say we keep taking samples of size $n = 225$ and keep computing the sample means. And the first 10 are:

```r
sampleMeans[1:10]
```

```
[1] 41.45 43.78 42.70 38.99 41.35 42.06 42.92 39.93 40.69 44.04
```

The distribution of 1,000 sample means looks like:
CHAPTER 3. NORMAL DISTRIBUTION

Histogram of sample means

<table>
<thead>
<tr>
<th></th>
<th>mean</th>
<th>sd</th>
<th>Q1</th>
<th>median</th>
<th>Q3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test Score</td>
<td>42.35</td>
<td>30.17</td>
<td>14.26</td>
<td>37.88</td>
<td>68.66</td>
</tr>
<tr>
<td>Sample Average</td>
<td>42.35</td>
<td>2.04</td>
<td>40.99</td>
<td>42.30</td>
<td>43.70</td>
</tr>
</tbody>
</table>

If the data come from a distribution with mean $\mu$ and sd $\sigma$, the sample means have $Normal(\mu, \sigma/\sqrt{n})$ distribution, where $n$ is the sample size. This is the Central Limit Theorem.

$30.17/\sqrt{225} = 2.01$.

- When making an inference about the population mean, we can assume that its distribution follow $Normal(\mu, \sigma/\sqrt{n})$ regardless of the underlying (true) distribution of the data.

- The quantity $\sigma/\sqrt{n}$ is standard error = standard deviation of the sample mean.

- The mean of a skewed data may not be that interesting because it is not a good measure of central tendency.
Standard deviation or standard error?

- A distribution can be summarized with “mean & standard deviation” or “mean & standard error”.

- With standard deviation, you can compute “mean + sd” and say, “Ok about 15% of the data are above this number.”

- With standard error, you can compute “mean + se” and say, “...” You can’t say much. “mean + se” is an important number when making an inference (later), but as a summary of a distribution, there isn’t much use.

- “median & quartile” is a better combination to report, anyway.

So far, we have always assumed that the true distribution to be known, but obviously, it is not the case in reality. What we want to do is to make an inference about the unknown population using the information from samples. The 2 key components in statistical inference are estimation and hypothesis testing. Perhaps the former is a little bit more important, but we’ll talk about hypothesis testing because it’s easier to explain!
Chapter 4

Hypothesis Testing

4.1 Fundamentals

**Hypothesis** Usually a statement about the population parameters (such as the population mean, difference of the population means, and the population proportions). Note that the population parameters are the unknown truth.

- $\mu = 100$ (The population mean is 100.)
- $\pi = 0.2$ (The population proportion is 20%.)
- $\mu_1 - \mu_0 = 0$ (The mean of population 1 is the same as the mean of population 0.)

It can be about population distributions, but that is rare. (e.g., The true distribution is Normal.)

**Null hypothesis** is the statement you hope to reject/dismiss. ($H_0$)

- “Probability of success is 20%.” when you want to say that the probability of success is *greater than* 20%.
- “There is no difference in the group means.” when you want to say that the true means are different.

**Alternative hypothesis** is the statement you want to use as a conclusion. ($H_1$ or $H_a$)
• $H_0 : \pi = 0.2$
  $H_1 : \pi > 0.2$

  This is an example of one-sided alternative.

• $H_0 : \mu_1 = \mu_2$
  $H_a : \mu_1 \neq \mu_2$

  This is an example of two-sided alternative.

How we think when we conduct a hypothesis testing.

1. Compute the probability of acquiring the data we actually acquired assuming that $H_0$ is true.

   Strictly speaking, “acquiring the data we actually acquired or something more extreme.

2. If that probability (p-value) is small, we say that something is wrong...

3. The data we have cannot be wrong, so what's wrong must be our assumption (i.e., $H_0$).

**P-value** is the probability of observing the data actually observed or something more extreme under $H_0$.

• Note that a p-value can be computed without ever referring to the alternative hypothesis.

• We can just compute the p-value, but a lot of times, we are required to make a go/no-go decision. So using the data, we decide to either “reject $H_0$” or “not reject $H_0$”.

• The null hypothesis is a statement about (true but unknown) population parameter, and it can be either true or false. $H_1$ is a complement of $H_0$, and it can be either true or false.

• Sometimes rejecting $H_0$ is correct, and sometimes it is not. The following table summarizes what happens when we reject or fail to reject $H_0$.

<table>
<thead>
<tr>
<th>Conclusion</th>
<th>Truth</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Reject $H_0$</td>
<td>$H_0$ is true.</td>
<td>Type I error</td>
</tr>
<tr>
<td>Fail to reject $H_0$</td>
<td>$H_0$ is not true.</td>
<td>Correct</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Type II error</td>
</tr>
</tbody>
</table>
Type I error is an error of rejecting a true $H_0$. We use $\alpha$ to denote the probability of such an error.

Type II error is an error of failing to reject a false $H_0$. We use $\beta$ to denote the probability of such an error.

Power is $1 - \beta$: probability of correctly rejecting a false $H_0$.

- Customarily, we set $\alpha$ to 5%.
- Note that we can reject $H_0$ when the p-value is less than 5%. That is, if the probability of observing what we observed (or something more extreme) is less than 5% that is an evidence against $H_0$.
- **Warning**: $H_0$ can never be shown to be true (believable), i.e., even a p-value of 95% does not allow us to say “$H_0$ is shown to be true”. Not even “$H_0$ seems to be true/believable/credible.”

### 4.2 SPADI example

After the rotator cuff repair surgery using a new technique, the Shoulder Pain and Disability Index (SPADI) is measured on each patient. We would like to test the average SPADI is higher than 72, which is the known average for the conventional surgical technique. We also know (or assume) that the true standard deviation is 8.

Let $\mu$ be the true (but unknown) mean SPADI for the new technique. We’d like to test

$H_0 : \mu = 72$

$H_1 : \mu > 72$

Note: Perhaps it is more appropriate to write $H_0 : \mu \leq 72$. Either is acceptable for a one-sided alternative hypothesis.

To test these hypotheses, a random sample of size 16 was taken from the population of patients. We know that the sample average $\bar{X}$ has the null distribution,

$$\bar{X} \sim \text{Normal} \left( 72, \frac{8}{\sqrt{16}} \right).$$
This is the distribution of $\bar{X}$ assuming that the null hypothesis is true. Suppose that the observed sample mean was 75.

P-value is 0.067, and it is not smaller than 5%, so we do not have strong enough evidence to conclude that the true average SPADI for the new technique is higher than 72.

- Can we say the true average is 72? -No.

- Can we say the true average is lower than 72? -No.

- So what can we say? -Nothing.
When we do not reject $H_0$, we cannot conclude anything other than “The sample size was too small.” or “We didn’t do the experiment right.” More on this later.

Now suppose that the sample size is 36. The sample average was still 75.

```r
## p-value ##
pnorm(75, mean = 72, sd = 8/sqrt(36), lower.tail = FALSE)
[1] 0.01222
```

With these data, we reject $H_0$. We have enough evidence to claim that the true mean is greater than 72 (with type I error rate of 5%).
Statistical hypothesis testing
Q: Is the true mean less than 72?
A: If the true mean is less than 72, then the probability of observing what we observed is very small (0.012).
Q: So are you saying that the true mean is less than 72?
A: No.

So what is the true mean? That is a more interesting research question than “Is the true mean greater than 72?”

⇒ Estimation

4.3 Multiplicity

- When type I error rate is controlled at 5%, we conduct a hypothesis test with a 5% probability of making an erroneous conclusion (reject \( H_0 \) that is true).
- If we conduct more than one hypothesis test, the probability of making at least one erroneous conclusion becomes more than 5%.

When we test \( K \) (independent) hypotheses, probability of rejecting at least one true null hypothesis is

\[
P[\text{At least one type I error}] = 1 - (1 - 0.05)^K
\]

<table>
<thead>
<tr>
<th>( K )</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>10</th>
<th>20</th>
<th>50</th>
</tr>
</thead>
<tbody>
<tr>
<td>P[At least one type I error]</td>
<td>5%</td>
<td>9.75%</td>
<td>14.26%</td>
<td>18.55%</td>
<td>40.13%</td>
<td>64.15%</td>
<td>92.31%</td>
</tr>
<tr>
<td>To make P[family-wise error] = 5%</td>
<td>5%</td>
<td>2.53%</td>
<td>1.70%</td>
<td>1.27%</td>
<td>0.51%</td>
<td>0.26%</td>
<td>0.01%</td>
</tr>
</tbody>
</table>

So if we want to make P[at least one error] controlled at 5%, we need to make each test more
stringent. Solve

\[ 0.05 = 1 - (1 - \alpha)^K \]

for \( \alpha \). This is controlling \textit{family-wise} type I error rate, and it is a general but conservative multiplicity control.

\textbf{Analysis of Variance} A generalization of two group comparison to comparisons of more than 2 groups. Sometimes, all pair-wise comparisons are of interest; however, oftentimes, you can pre-specify comparisons of interest.

\textbf{Kruskal Wallis test} The non-parametric counterpart to ANOVA.

\textbf{Multiple comparison procedures}

\textbf{Bonferroni} Very general; applicable to many situations but conservative (not very powerful). Holm’s procedure is uniformly better than Bonferroni.

\textbf{Dunnett} Applicable when multiple groups are compared to a common control group.

\textbf{Tukey-Kramer} Applicable when all pair-wise comparisons are sought.

\textbf{Scheffé} Applicable with general contrasts (e.g., \( \mu_1 - (\mu_2 + \mu_3)/2 = 0 \), i.e., “The mean of groups 2 and 3 is equal to the mean of group 1.”)

- If only pair-wise comparisons are of interest, Tukey-Kramer is preferred.

\textbf{Holm} Applicable in general.

- Suppose that there are \( K \) comparisons of interest. Compute p-value for each comparison.
- Compare the smallest p-value to \( \alpha/K \). If the p-value is smaller, reject the corresponding \( H_0 \) and continue. Otherwise end.
- Compare the second smallest p-value to \( \alpha/(K - 1) \). Continue in the same manner as long as \( H_0 \)'s are getting rejected.
• The largest p-value is compared $\alpha$ if all other p-values are smaller than the respective threshold.

**FDR** A different concept. Popular method when testing many, many hypotheses.

• Benjamini-Hochberg

• Benjamini-Hochberg-Yekutieli

• Bonferroni, Tukey-Kramer, and Scheffé are used as post-hoc tests for ANOVA, which tests an *overall* hypothesis. $H_0 : \mu_1 = \mu_2 = \cdots = \mu_K$ (All the means are the same.); $H_1 : \text{At least one mean is different.}$

• If the overall test is not significant, no group-wise comparisons are granted.

```r
p.values <- c(0.002, 0.58, 0.0015, 0.077, 0.002, 0.14, 0.0014, 0.33)
pv.ordered <- sort(p.values)
Bonf <- p.adjust(pv.ordered, method = "bonferroni")
Holm <- p.adjust(pv.ordered, method = "holm")
Bh <- p.adjust(pv.ordered, method = "BH")
Bhy <- p.adjust(pv.ordered, method = "BY")
data.frame(pv = pv.ordered, Bonf, Holm, Bh, Bhy)
```

<table>
<thead>
<tr>
<th>pv</th>
<th>Bonf</th>
<th>Holm</th>
<th>Bh</th>
<th>Bhy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.0014</td>
<td>0.0112</td>
<td>0.0112</td>
<td>0.0040</td>
</tr>
<tr>
<td>2</td>
<td>0.0015</td>
<td>0.0120</td>
<td>0.0112</td>
<td>0.0040</td>
</tr>
<tr>
<td>3</td>
<td>0.0020</td>
<td>0.0160</td>
<td>0.0120</td>
<td>0.0040</td>
</tr>
<tr>
<td>4</td>
<td>0.0020</td>
<td>0.0160</td>
<td>0.0120</td>
<td>0.0040</td>
</tr>
<tr>
<td>5</td>
<td>0.0770</td>
<td>0.6160</td>
<td>0.3080</td>
<td>0.1232</td>
</tr>
<tr>
<td>6</td>
<td>0.1400</td>
<td>1.0000</td>
<td>0.4200</td>
<td>0.1867</td>
</tr>
<tr>
<td>7</td>
<td>0.3300</td>
<td>1.0000</td>
<td>0.6600</td>
<td>0.3771</td>
</tr>
<tr>
<td>8</td>
<td>0.5800</td>
<td>1.0000</td>
<td>0.6600</td>
<td>0.5800</td>
</tr>
</tbody>
</table>
Chapter 5

Estimation

5.1 Point estimates

When we want to make inference about the population parameters, we take a (representative) sample from the population and compute a statistic using the data from the sample. Using the sample statistic, we estimate the population parameter.

- Sample mean to estimate the population mean.
- Sample proportion to estimate the population proportion.
- Sample correlation to estimate the population correlation.
- Sample difference of means/proportions to estimate the population difference.

5.2 Confidence intervals

SPADI example

Recall that the sample mean was 75 from a sample of size 16. The population standard deviation was known to be 8. We estimate the population mean to be 75 (sample mean).
If the true (unknown) mean is 71.08, observing a sample mean of 75 is barely plausible. And if the true mean is 78.92, observing a sample mean of 75 is barely plausible. Any values between these 2 numbers would make observing $\bar{x} = 75$ not very unusual. Let’s call this interval $(71.08, 78.92)$ a 95% confidence interval.

Interpreting a 95% confidence interval.

• “Probability that the true mean is between 71.08 and 78.92 is 95%” is wrong.
  The true mean is unknown but a constant. It is a regular number, so it is either in an interval or it is not. There is no probability (randomness) about it.

• Remember that the numbers, 71.08 and 78.92, are specific to the particular samples we observed. With different samples we will get a different confidence interval.

• If we imagine repeating this experiment many times, each sample will give us a different
confidence interval. Most of (95% of) these confidence intervals contain the true, unknown mean, but some of them (5%) do not.

“We don’t know if the true mean is in (71.08, 78.92). But we are using a process that produces intervals, 95% of which include the true mean. (We don’t know if the one that we have is one of them...)

```r
## Recall that the population standard deviation is 8.
sig <- 8
## Sample mean is 75.
x.bar <- 75
## Sample size is 16.
n <- 16

## 2.5% of the data will fall below this number.
qnorm(p = 0.025, mean = x.bar, sd = sig/sqrt(n))

[1] 71.08

qnorm(p = 0.975, mean = x.bar, sd = sig/sqrt(n))

[1] 78.92
```
Chapter 6

Comparing Means

6.1 One sample test for mean

In CEASAR data, first we will look at the Surgery group, and we want to test if the true baseline QoL is 55. $\sigma$ is assumed to be 35.

```r
table(d$Treatment)

<table>
<thead>
<tr>
<th>Radiation</th>
<th>Surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>70</td>
<td>130</td>
</tr>
</tbody>
</table>

surgery <- subset(d, Treatment == "Surgery")
# surgery <- d[ d$Treatment == 'Surgery', ]
dim(surgery)
[1] 130 15

• Because we want to see if the mean is different from 55. This is a 2-sided test.
  
  $H_0 : \mu = 55$
  
  $H_1 : \mu \neq 55$

• We want to limit the type I error rate to 5%. But now this is a 2-sided test, we can make type I error rate on the upper side and lower side, ($H_0$ will be rejected if $\bar{X}$ is much bigger and much
smaller than 55.) and 5% needs to be split into two. 2.5% each. So if the p-value is less than 2.5%, we will reject $H_0$.

- Do we have a normally distributed data? Maybe not. But we are not that concerned because we are pretty sure that $X$ is normally distributed.

![Baseline QoL](image)

```r
(msq0 <- mean(surgery$QoL))
[1] 61.35
(n <- nrow(surgery))
[1] 130
```

- The following is the distribution of $\bar{x}$ under $H_0$. 
The shaded area is the p-value. How do we compute this?

We use the standard normal distribution, which is \( \text{Normal}(0, 1) \). We can convert any normal distribution to the standard normal by

\[
    z = \frac{\bar{X} - \mu_0}{\sigma/\sqrt{n}}.
\]

And we know \( \bar{X} \sim \text{Normal}(55, \frac{35}{\sqrt{130}}) \), so

\[
    z = \frac{61.35 - 55}{\frac{35}{\sqrt{130}}} = \frac{6.35}{3.07} = 2.068
\]
Once we compute a $Z$ value, we can look up the table of standard normal probabilities. Or

\[
(z.\text{value} \leftarrow (msq0 - 55)/(35/\text{sqrt}(n)))
\]

\[
[1] 2.068
\]

\[
\text{pnorm}(z.\text{value}, \text{lower.tail} = \text{FALSE})
\]

\[
[1] 0.0193
\]

Or we can use `pnorm` function without standardizing the value.

\[
(pval \leftarrow \text{pnorm}(msq0, \text{mean} = 55, \text{sd} = 35/\text{sqrt}(n), \text{lower.tail} = \text{FALSE}))
\]

\[
[1] 0.0193
\]

So the shaded area is 0.0193, which is smaller than 2.5%. So we reject $H_0$ and conclude that the we have enough evidence to claim that the true mean is different from 55. Can we say “bigger”? Probably. With this hypothesis testing, strictly speaking all we can claim is difference, but we can estimate the true mean and see if it is bigger than 55.

**Confidence interval.** A 95% confidence interval is an interval centered at the observed sample mean. Its width depends on the standard error ($\sigma/\sqrt{n}$).

\[
\bar{X} \pm Z_{0.975} \times \frac{\sigma}{\sqrt{n}},
\]

where $Z_{0.975}$ is the $z$ value (from the standard normal distribution), and we know it is 1.96.

\[
\text{qnorm}(0.975)
\]

\[
[1] 1.96
\]

If we want different value from 95% (confidence limit), we can compute the corresponding $z$ value using `qnorm` function. For example, for a 90% confidence interval, we’d use 1.645.

\[
\text{qnorm}(0.95)
\]

\[
[1] 1.645
\]
For the current problem, a 95% confidence interval is

\[
\bar{X} \pm Z_{0.975} \times \frac{\sigma}{\sqrt{n}}
\]

\[
= 61.35 \pm 1.96 \times 3.07
\]

\[
= 61.35 \pm 6.02
\]

\[
= (55.33, 67.37)
\]

So we think that the true mean is somewhere between 55.33 and 67.37.

### 6.2 Unknown variance

So far, we have assumed that the (unknown, true) population variance (and standard deviation) to be known. It is rare that we know the population standard deviation. When we don’t know the population standard deviation, we substitute it with the sample standard deviation. Instead of

\[
z = \frac{\bar{X} - \mu}{\sigma/\sqrt{n}},
\]

we use

\[
t = \frac{\bar{X} - \mu}{s/\sqrt{n}},
\]

where \(s\) is an estimate of the true standard deviation from the sample. \(t\) does not have a normal distribution any more. Instead, its distribution is a Student's \(t\) distribution.

- developed by William Gossett, who used the pen name “Student”.
• It is centered at 0.

• It is symmetric around 0.

• It looks a lot like a normal distribution but has heavier tails.

• Its shape depends on the degree of freedom, which depends on the sample size. For a simple one-sample problem, the degree of freedom is \( n - 1 \), which comes from the fact

\[
\sigma^2 = \frac{\sum_{i=1}^{n} (x_i - \bar{x})^2}{n - 1}.
\]

• As the degree of freedom increases, t distributions start to look a lot like the standard normal distribution.
97.5 percentiles (to form a 95% confidence interval)

```r
qnorm(0.975)
```

[1] 1.96

```r
qt(0.975, df = c(5, 10, 15, 20, 25, 30))
```

[1] 2.571 2.228 2.131 2.086 2.060 2.042

### 6.2.1 CEASAR example: revisited

Now we repeat the last example (beginning of Chapter 6) without assuming that the standard deviation is 35. Sample standard deviation is
(s <- sd(surgery$QoL0))
[1] 22.78

\[
t = \frac{\bar{x} - \mu_0}{s/\sqrt{n}} = \frac{61.35 - 55}{22.78/\sqrt{130}} = \frac{6.35}{2.00} = 3.178
\]

P-value is

(t.value <- (msq0 - 55)/(s/sqrt(n)))
[1] 3.178

pt(t.value, df = n - 1, lower = FALSE)
[1] 0.0009273

To compute a confidence interval, we replace \(Z_{0.975}\) with \(t_{0.975, df}\). For degree of freedom 129 (\(n = 130\)), we have

(t975 <- qt(0.975, df = n - 1))
[1] 1.979

so that

\[
\bar{X} \pm t_{0.975,129} \times \frac{s}{\sqrt{n}} = 61.35 \pm 1.979 \times 2.00 = 61.35 \pm 3.95 = (57.40, 65.30)
\]
Using R.

```r
\texttt{t.test(surgery$QoL0, mu = 55, alternative = "two.sided")}
```

One Sample t-test
data: surgery$QoL0
t = 3.2, df = 129, p-value = 0.002
alternative hypothesis: true mean is not equal to 55
95 percent confidence interval:
57.4 65.3
sample estimates:
mean of x
61.35

- Why is this p-value different? My way is to divide $\alpha = 5\%$ by 2 and compare the p-value to $2.5\%$. Their way is to multiply the p-value by 2 and compare it with $\alpha = 5\%$.

- Why is this degree of freedom 130 instead of 129. After $df = 100$, R rounds $df$ to the nearest 10.

### 6.3 Paired t test

Paired data arise when two observations are made on the same individual. Or more generally, two \textit{correlated} data are analyzed.

- Observations before and after treatment.

- Same individuals taking two drugs (cross-over clinical trial).

- Experiments involving siblings (one acting as a control).

The biggest advantage of an experiment utilizing paired data is reduced variance.

$$Var(X - Y) = Var(X) + Var(Y) - 2Cov(X,Y)$$

$$= Var(X) + Var(Y) - 2Cor(X,Y) \sqrt{Var(X)Var(Y)}$$
So as long as the correlation is greater than 0, variance of $X - Y$ is smaller than $\text{Var}(X) + \text{Var}(Y)$, which is the variance of $X - Y$ when they are uncorrelated.

Generally, we would like to test hypotheses about difference of the averages. We often write $\mu_1$ and $\mu_2$ to denote the population means at time 1 and 2, respectively, and use $\mu_d$ to denote $\mu_2 - \mu_1$. So to test there is no difference between two time points (two drugs, two siblings), we write

$$H_0 : \mu_d = 0$$
$$H_1 : \mu_d > 0$$

if what we want to say is $\mu_2 > \mu_1$.

Even though there are two groups of data (time 1 and time 2), we compute their differences and treat the whole problem as one-sample problem. Paired t test is one-sample t test on differences!

Let’s see if the QoL scores decreased for the radiation group. Our hypotheses are:

$$H_0 : \mu_d = 0$$
$$H_1 : \mu_d < 0$$

First we compute the difference of QoL for everyone in the radiation group.

```r
radiation <- subset(d, Treatment == "Radiation")
qol <- subset(radiation, select = c("QoL0", "QoL6"))
qol$Diff <- qol$QoL6 - qol$QoL0
head(qol, 20)
```

<table>
<thead>
<tr>
<th>QoL0</th>
<th>QoL6</th>
<th>Diff</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>35.0</td>
<td>34.7</td>
</tr>
<tr>
<td>12</td>
<td>79.4</td>
<td>93.6</td>
</tr>
<tr>
<td>15</td>
<td>60.0</td>
<td>71.8</td>
</tr>
<tr>
<td>16</td>
<td>28.0</td>
<td>3.6</td>
</tr>
<tr>
<td>19</td>
<td>62.1</td>
<td>18.6</td>
</tr>
<tr>
<td>21</td>
<td>67.0</td>
<td>80.7</td>
</tr>
<tr>
<td>22</td>
<td>78.3</td>
<td>76.3</td>
</tr>
<tr>
<td>24</td>
<td>87.0</td>
<td>72.8</td>
</tr>
<tr>
<td>25</td>
<td>63.6</td>
<td>53.9</td>
</tr>
<tr>
<td>27</td>
<td>68.9</td>
<td>59.1</td>
</tr>
<tr>
<td>28</td>
<td>31.7</td>
<td>13.6</td>
</tr>
</tbody>
</table>
30 64.4 75.9  11.5
32  80.0 77.4  -2.6
34  33.2  0.8 -32.4
37  67.8  73.0   5.2
39  18.9  23.2   4.3
40  88.4  71.7 -16.7
51  38.6  20.6 -18.0
54  28.8  42.5  13.7
58  32.6  11.1 -21.5

Change in QoL: Radiation group

```
t.test(qol$Diff, mu = 0, alternative = "less", conf.level = 0.95)
```

One Sample t-test

data:  qol$Diff
t = -1.8, df = 69, p-value = 0.04
alternative hypothesis: true mean is less than 0
95 percent confidence interval:
  -Inf -0.4041
sample estimates:
mean of x
  -4.416

t.test(qol$QoL6, qol$QoL0, alternative = "less", paired = TRUE)

Paired t-test
data: qol$QoL6 and qol$QoL0
t = -1.8, df = 69, p-value = 0.04
alternative hypothesis: true difference in means is less than 0
95 percent confidence interval:
   -Inf -0.4041
sample estimates:
mean of the differences
  -4.416

A one-sided confidence interval is given for a one-sided test. Sometimes, we want a two-sided confidence interval. To make a confidence interval and a one-sided test consistent, we can compute 90% confidence interval for one-sided test with $\alpha = 5\%$.

t.test(qol$Diff, mu = 0, alternative = "two.sided", conf.level = 0.9)

One Sample t-test
data: qol$Diff
t = -1.8, df = 69, p-value = 0.07
alternative hypothesis: true mean is not equal to 0
90 percent confidence interval:
  -8.4274 -0.4041
sample estimates:
mean of x
  -4.416
What happens if we cannot assume that $X$ follows a normal distribution even approximately? This happens when the underlying distribution of $X$ is not normal and sample size is small. We’ll have to use a nonparametric method, which does not require normality. (Later!)

### 6.4 Two sample data - Equal variance

Now we consider comparing two means from two groups of data (unpaired).

- There are two populations; one with mean $\mu_1$ and variance $\sigma_1^2$, and another one with mean $\mu_2$ and variance $\sigma_2^2$. 

![Radiation Group](image_url)
• First we assume $\sigma_1^2 = \sigma_2^2$ (Equal variance) and test

$$H_0 : \mu_1 = \mu_2$$

$$H_1 : \mu_1 \neq \mu_2$$

• Sample sizes are $n_1$ and $n_2$.

• Test statistic is

$$t = \frac{\bar{x}_1 - \bar{x}_2}{\text{se of numerator}}$$

• If we know the true variance $\sigma^2$, the variance of $\bar{x}_1 - \bar{x}_2$ is

$$\frac{\sigma^2}{n_1} + \frac{\sigma^2}{n_2} = \sigma^2 \left( \frac{1}{n_1} + \frac{1}{n_2} \right)$$

• We need to estimate $\sigma_2$ from the two samples.

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

This is called “pooled variance”.

• The true standard error of the difference of the sample means is

$$\sigma \sqrt{\frac{1}{n_1} + \frac{1}{n_2}}.$$  

and its estimate is

$$s \sqrt{\frac{1}{n_1} + \frac{1}{n_2}},.$$
and

\[ t = \frac{\bar{x}_1 - \bar{x}_2}{s\sqrt{\frac{1}{n_1} + \frac{1}{n_2}}}. \]

- Degree of freedom is the sum of the individual d.f., \( n_1 - 1 + n_2 - 1 = n_1 + n_2 - 2 \), which is the denominator of \( s^2 \). −2 comes from having to estimate two sample means.

- If \( H_0 \) is true, \( t \) has the \( t_{n_1+n_2-2} \) distribution.

### 6.4.1 CEASAR example: two-sample t test

We think that younger patients are more likely to receive surgery. Let’s confirm this. Let \( \mu_s \) and \( \mu_r \) be the average ages of the surgery and radiation groups, respectively. We are to test

\[ H_0 : \mu_s - \mu_r = 0 \]
\[ H_1 : \mu_s - \mu_r < 0. \]

Let’s use \( \alpha = 5\% \).

Here are some information about age of the patients.

```r
mean(surgery$Age)
[1] 62.56
sd(surgery$Age)
[1] 8.242
mean(radiation$Age)
[1] 66.46
sd(radiation$Age)
[1] 8.217
```

The pooled variance is:
\[ s_p^2 = \frac{(n_s - 1)s_s^2 + (n_r - 1)s_r^2}{n_s + n_r - 2} \]
\[ = \frac{(129)(8.24^2) + (69)(8.22^2)}{198} \]
\[ = 67.795. \]
\[ s_p = \sqrt{67.795} \]
\[ = 8.234 \]

And t statistic is

\[ t = \frac{x_r - x_s}{s_p \sqrt{1/n_s + 1/n_r}} \]
\[ = \frac{62.56 - 66.46}{8.23 \sqrt{1/130 + 1/70}} \]
\[ = -3.19. \]

And p-value is

\[
\text{pt}(-3.19, \text{df} = 198, \text{lower.tail} = \text{TRUE})
\]

[1] 0.0008272

We can do this using `t.test` function.

\[
\text{t.test}(\text{surgery$Age, radiation$Age, alternative = "less", paired = FALSE, var.equal = TRUE})
\]

Two Sample t-test
data: surgery$Age and radiation$Age
t = -3.2, df = 198, p-value = 0.0008
alternative hypothesis: true difference in means is less than 0
95 percent confidence interval:  
-Inf -1.878  
sample estimates:  
mean of x mean of y  
62.56  66.46  

A 95% confidence interval for the difference of the means has the form:  
\[ \bar{x}_2 - \bar{x}_1 \pm t_{0.975, df} \times s_p \sqrt{1/n_1 + 1/n_2} \]

For the current problem (for \( \mu_s - \mu_r \))  
\[ 62.56 - 66.46 \pm t_{0.975, 198} 8.23 \sqrt{0.022} \]

\( t_{0.975, 198} \) is 1.972, and  
\[ -3.90 \pm 2.41 = (-6.303, -1.488) \]

Using R, we get the same answer:  
```r  
t.test(surgery$Age, radiation$Age, alternative = "two.side", paired = FALSE, var.equal = TRUE, conf.level = 0.95)  
```

Two Sample t-test  
data:  surgery$Age and radiation$Age  
t = -3.2, df = 198, p-value = 0.002  
alternative hypothesis: true difference in means is not equal to 0  
95 percent confidence interval:  
-6.303 -1.488  
sample estimates:  
mean of x mean of y  
62.56  66.46  
```

With such large sample sizes, the answers would not differ much if we used a normal distribution instead.
6.5 Two sample data - Unequal variances

- When the true group variances are not assumed to be the same, we cannot combine two samples to estimate the true variance. (We cannot use the pooled variance.)

- This case the test statistic is

\[ t = \frac{\bar{x}_1 - \bar{x}_2}{\sqrt{\frac{s_1^2}{n_1} + \frac{s_2^2}{n_2}}} \]

```r
(tt <- t.test(surgery$Age, radiation$Age, alternative = "less", paired = FALSE, var.equal = FALSE))
```

Welch Two Sample t-test

data: surgery$Age and radiation$Age
t = -3.2, df = 142, p-value = 0.0009
alternative hypothesis: true difference in means is less than 0
95 percent confidence interval:
 -Inf -1.876
sample estimates:
mean of x mean of y
 62.56 66.46

- Where does df 140 come from? (Note: Newer version of R gives a right df.)

- The Satterthwaite approximation is a formula to calculate an “effective” degrees of freedom
in a two-sample t test.

\[ df = \frac{\left( \frac{s_1^2}{n_1} + \frac{s_2^2}{n_2} \right)^2}{\frac{1}{n_1 - 1} \left( \frac{s_1^2}{n_1} \right)^2 + \frac{1}{n_2 - 1} \left( \frac{s_2^2}{n_2} \right)^2} = 141.8. \]

- In the old days, we used \( df = \text{smaller } n - 1. \)
Chapter 7

Nonparametric Methods

When the underlying distribution is not normal and we don’t have large enough samples to apply the Central Limit Theorem, we cannot use the methods based on normal approximation (parametric methods). In such a case, a non-parametric method may be useful.

<table>
<thead>
<tr>
<th>Parametric test</th>
<th>Nonparametric test</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 sample $t$</td>
<td>Wilcoxon signed-rank</td>
</tr>
<tr>
<td>2 sample $t$</td>
<td>Wilcoxon rank sum</td>
</tr>
<tr>
<td>ANOVA</td>
<td>Kruskal-Wallis</td>
</tr>
<tr>
<td>Pearson’s correlation</td>
<td>Spearman’s rank correlation</td>
</tr>
</tbody>
</table>

Example: Suppose that we have the following samples from Group A and Group B.

```r
(A0 <- c(8, 7, 4, 9, 11, 12, 5, 13, 12))
[1]  8  7  4  9 11 12  5 13 12
(B <- c(3, 4, 2, 6, 9, 4, 2))
[1]  3  4  2  6  9  4  2
t.test(A0, B, paired = FALSE, var.equal = FALSE)

Welch Two Sample t-test
data:  A0 and B
```
$t = 3.3, \ df = 14, \ p\text{-value} = 0.005$

alternative hypothesis: true difference in means is not equal to 0

95 percent confidence interval:
\[1.638, 7.791\]

sample estimates:
mean of x mean of y
\[9.000, 4.286\]

With addition of just one large number, \texttt{t.test} looks very different.

\begin{verbatim}
(A1 <- c(8, 7, 4, 9, 11, 12, 5, 13, 12, 100))
[1] 8 7 4 9 11 12 5 13 12 100

(B <- c(3, 4, 2, 6, 9, 4, 2))
[1] 3 4 2 6 9 4 2

t.test(A1, B, paired = FALSE, var.equal = FALSE)

Welch Two Sample t-test
data: A1 and B
t = 1.5, df = 9.2, p-value = 0.2
alternative hypothesis: true difference in means is not equal to 0
95 percent confidence interval:
\[-6.931, 34.560\]
sample estimates:
mean of x mean of y
\[18.100, 4.286\]
\end{verbatim}

The non-significant result is due to increased standard deviation, which is particularly not robust to outliers.

\begin{verbatim}
sd(A0)
[1] 3.24

sd(A1)
[1] 28.94
\end{verbatim}

• Non-parametric methods are not heavily influenced by outliers or skewness.

They do not use the means or standard deviations. Instead they transform the data to ranks.
• What are the hypotheses about? (They are not about the means.)
  Loosely speaking these tests are about the population medians.

• The confidence interval and the test may not correspond to each other.

**One sample test**

First let’s see if the median of the population $A_1$ is not equal to 6. We use a Wilcoxon signed rank test.

```r
wilcox.test(A1, mu = 6, alternative = "two.sided", conf.int = TRUE)
```

```
Warning in wilcox.test.default(A1, mu = 6, alternative = "two.sided", conf.int = TRUE): cannot compute exact p-value with ties
Warning in wilcox.test.default(A1, mu = 6, alternative = "two.sided", conf.int = TRUE): cannot compute exact confidence interval with ties

Wilcoxon signed rank test with continuity correction
data:  A1
V = 50, p-value = 0.02
alternative hypothesis: true location is not equal to 6
95 percent confidence interval:
  6.5 53.5
sample estimates:
(pseudo)median
  10
```

If we use a t test,

```r
t.test(A1, mu = 6, alternative = "two.sided", conf.int = TRUE)
```

```
One Sample t-test
data:  A1
t = 1.3, df = 9, p-value = 0.2
alternative hypothesis: true mean is not equal to 6
95 percent confidence interval:
  -2.601 38.801
sample estimates:
mean of x
  18.1
```
CHAPTER 7. NONPARAMETRIC METHODS

Two sample test

Now test if the medians of the population $A_1$ and $B$ are the same. For this 2 sample test, we use a Wilcoxon rank-sum test (aka Mann-Whitney U test).

```r
dx <- data.frame(y = c(A1, B), g = rep(c("A", "B"), c(length(A1), length(B))))
dx$r <- rank(dx$y)
dx
```

```r
wilcox.test(A1, B, alternative = "two.sided", conf.int = TRUE)

Warning in wilcox.test.default(A1, B, alternative = "two.sided", conf.int = TRUE): cannot compute exact p-value with ties
Warning in wilcox.test.default(A1, B, alternative = "two.sided", conf.int = TRUE): cannot compute exact confidence intervals with ties

Wilcoxon rank sum test with continuity correction
data:  A1 and B
W = 62, p-value = 0.008
alternative hypothesis: true location shift is not equal to 0
95 percent confidence interval:
 2 9
sample estimates:
difference in location
 5.25
```

The corresponding t test is:

```r
t.test(A1, B, alternative = "two.sided", conf.int = TRUE)

Welch Two Sample t-test
data:  A1 and B
t = 1.5, df = 9.2, p-value = 0.2
alternative hypothesis: true difference in means is not equal to 0
95 percent confidence interval:
-6.931 34.560
sample estimates:
mean of x mean of y
18.100 4.286
```

Rank-based tests like Wilcoxon rank-sum are about the same as t test on ranks.
<table>
<thead>
<tr>
<th>y</th>
<th>g</th>
<th>r</th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td>A</td>
<td>10.0</td>
</tr>
<tr>
<td>7</td>
<td>A</td>
<td>9.0</td>
</tr>
<tr>
<td>4</td>
<td>A</td>
<td>5.0</td>
</tr>
<tr>
<td>9</td>
<td>A</td>
<td>11.5</td>
</tr>
<tr>
<td>11</td>
<td>A</td>
<td>13.0</td>
</tr>
<tr>
<td>12</td>
<td>A</td>
<td>14.5</td>
</tr>
<tr>
<td>5</td>
<td>A</td>
<td>7.0</td>
</tr>
<tr>
<td>13</td>
<td>A</td>
<td>16.0</td>
</tr>
<tr>
<td>12</td>
<td>A</td>
<td>14.5</td>
</tr>
<tr>
<td>100</td>
<td>A</td>
<td>17.0</td>
</tr>
<tr>
<td>3</td>
<td>B</td>
<td>3.0</td>
</tr>
<tr>
<td>4</td>
<td>B</td>
<td>5.0</td>
</tr>
<tr>
<td>2</td>
<td>B</td>
<td>1.5</td>
</tr>
<tr>
<td>6</td>
<td>B</td>
<td>8.0</td>
</tr>
<tr>
<td>9</td>
<td>B</td>
<td>11.5</td>
</tr>
<tr>
<td>4</td>
<td>B</td>
<td>5.0</td>
</tr>
<tr>
<td>2</td>
<td>B</td>
<td>1.5</td>
</tr>
</tbody>
</table>

```r
t.test(r ~ g, data = dx, alternative = "two.sided")
```

Welch Two Sample t-test
data:  r by g
t = 3.6, df = 14, p-value = 0.003 alternative hypothesis: true difference in means is not equal to 0
95 percent confidence interval:
  2.679 10.678
sample estimates:
mean in group A  mean in group B
  11.750        5.071

Perhaps, these non-parametric tests should be our default choice...
Chapter 8

Proportions

8.1 One proportion

When outcome is binary (Yes/No; Success/Failure), we count the number of 'successes' \( X \) out of \( n \). The number of successes has \( \text{Binomial}(n, p) \) distribution, where \( p \) is the true (unknown) probability of success. We are interested in estimating this \( p \). (population proportion)

- Given that \( X \sim \text{Binomial}(n, p) \), the mean is \( np \) and variance is \( np(1 - p) \). And standard deviation is \( \sqrt{np(1 - p)} \).

- The sample proportion, \( \hat{p} = X/n \), has the mean \( p \) and standard deviation \( p(1 - p)/n \).

- To make an inference about \( p \), we either use an approximate method (normal approximation) or an exact method.

- When sample size is large \( (X \geq 30) \), normal approximation is good.

Approximate 95% confidence interval for \( p \) is

\[
\hat{p} \pm 1.96 \sqrt{\frac{\hat{p}(1 - \hat{p})}{n}}
\]
To test $H_0: p = p_0$, use

$$z = \frac{\hat{p} - p_0}{\sqrt{p_0(1 - p_0)/n}},$$

which is approximately Normal$(0, 1)$ under $H_0$. When estimating $p$, we never use a t distribution.

Example: Using the CEASAR data, estimate the proportion of the radiation patients who had diabetes, and test if it is different from 20%, and give a 95% confidence interval.

```r
table(radiation$Diabetes)
```

<table>
<thead>
<tr>
<th></th>
<th>No</th>
<th>Yes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>58</td>
<td>12</td>
</tr>
</tbody>
</table>

```r
prop.table(table(radiation$Diabetes))
```

<table>
<thead>
<tr>
<th></th>
<th>No</th>
<th>Yes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.8286</td>
<td>0.1714</td>
</tr>
</tbody>
</table>

From this, we get $\hat{p} = 0.1714$. The null value, $p_0 = 0.20$. So we have

$$z = \frac{0.1714 - 0.20}{\sqrt{0.20(1 - 0.20)/70}} = -0.5976$$
Sampling distribution of \( p \)

P-value is

\[
\text{pnorm}(-0.5976)
\]

[1] 0.2751

and this is compared to \( 5\% / 2 \). We do not have enough evidence to reject \( p = 0.20 \).

To compute a 95\% confidence interval, we use

\[
\text{qnorm}(0.975)
\]

[1] 1.96

so that it is \( \hat{p} \pm 1.96 \sqrt{(\hat{p}(1 - \hat{p}))/n} \)

\[
\text{phat} <- 12/70
\text{margin} <- \text{qnorm}(0.975) * \text{sqrt}(\text{phat} * (1 - \text{phat})/70)
\text{phat + c(-1, 1) * margin}
\]
Thus, a 95% confidence interval is (0.0831, 0.2597).

We can use `binconf` function in `Hmisc` library to get the same answer.

```r
library(Hmisc)
binconf(x = 12, n = 70, method = "all", include.x = TRUE, include.n = TRUE, alpha = 0.05)
```

<table>
<thead>
<tr>
<th></th>
<th>X</th>
<th>N</th>
<th>PointEst</th>
<th>Lower</th>
<th>Upper</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exact</td>
<td>12</td>
<td>70</td>
<td>0.1714</td>
<td>0.09184</td>
<td>0.2803</td>
</tr>
<tr>
<td>Wilson</td>
<td>12</td>
<td>70</td>
<td>0.1714</td>
<td>0.10088</td>
<td>0.2762</td>
</tr>
<tr>
<td>Asymptotic</td>
<td>12</td>
<td>70</td>
<td>0.1714</td>
<td>0.08314</td>
<td>0.2597</td>
</tr>
</tbody>
</table>

Because the “Asymptotic” method only works well as $n$ gets large, sometimes it does not give a confidence interval with a specified confidence level (95% in this example). Wilson score interval (1927) has an improved coverage probability and is often preferred.

### 8.2 Two proportions

Now we are concerned with the problem of comparing two proportions. Data are often tabulated in a 2 by 2 table.

Let's test if the probabilities of success are the same for treatment 1 and 2 given the following data.

<table>
<thead>
<tr>
<th></th>
<th>Success</th>
<th>Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment 1</td>
<td>7</td>
<td>13</td>
</tr>
<tr>
<td>Treatment 2</td>
<td>3</td>
<td>22</td>
</tr>
</tbody>
</table>

```r
# Set up the data
trt <- rep(c("Trt.1", "Trt.2"), c(7 + 13, 3 + 22))
outcome <- rep(rep(c("Success", "Failure"), 2), c(7, 13, 3, 22))
outcome <- factor(outcome, levels = c("Success", "Failure"))
(dat <- data.frame(trt, outcome))
```

```
   trt outcome
1  Trt.1   Success
2  Trt.1   Success
```
3 Trt.1 Success
4 Trt.1 Success
5 Trt.1 Success
6 Trt.1 Success
7 Trt.1 Success
8 Trt.1 Failure
9 Trt.1 Failure
10 Trt.1 Failure
11 Trt.1 Failure
12 Trt.1 Failure
13 Trt.1 Failure
14 Trt.1 Failure
15 Trt.1 Failure
16 Trt.1 Failure
17 Trt.1 Failure
18 Trt.1 Failure
19 Trt.1 Failure
20 Trt.1 Failure
21 Trt.2 Success
22 Trt.2 Success
23 Trt.2 Success
24 Trt.2 Failure
25 Trt.2 Failure
26 Trt.2 Failure
27 Trt.2 Failure
28 Trt.2 Failure
29 Trt.2 Failure
30 Trt.2 Failure
31 Trt.2 Failure
32 Trt.2 Failure
33 Trt.2 Failure
34 Trt.2 Failure
35 Trt.2 Failure
36 Trt.2 Failure
37 Trt.2 Failure
38 Trt.2 Failure
39 Trt.2 Failure
40 Trt.2 Failure
41 Trt.2 Failure
42 Trt.2 Failure
43 Trt.2 Failure
44 Trt.2 Failure
45 Trt.2 Failure
8.2.1 Fisher's exact test

- First we fix both margins.

<table>
<thead>
<tr>
<th></th>
<th>Success</th>
<th>Failure</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment 1</td>
<td></td>
<td></td>
<td>20</td>
</tr>
<tr>
<td>Treatment 2</td>
<td></td>
<td></td>
<td>25</td>
</tr>
<tr>
<td>Total</td>
<td>10</td>
<td>35</td>
<td>45</td>
</tr>
</tbody>
</table>

- Then if we fix 1 of the 4 cells (Treatment 1, Success), we have a complete table.

- We can determine which of the tables are “more extreme” than observed for each table.

Below is an example of an “extreme” table under the null (no difference between treatments).

<table>
<thead>
<tr>
<th></th>
<th>Success</th>
<th>Failure</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment 1</td>
<td>10</td>
<td>10</td>
<td>20</td>
</tr>
<tr>
<td>Treatment 2</td>
<td>0</td>
<td>25</td>
<td>25</td>
</tr>
<tr>
<td>Total</td>
<td>10</td>
<td>35</td>
<td>45</td>
</tr>
</tbody>
</table>

- We know how to compute the probability of each table (using a hypergeometric distribution), and we also have a way to order all the tables from “least extreme under null” to “most extreme”.

- Sum of the probabilities that correspond to “more extreme than observed” is the p-value.

- This is called “exact” because we don’t use large-sample approximation.

```
fisher.test(table(dat))
```

Fisher's Exact Test for Count Data

data:  table(dat)
p-value = 0.08
alternative hypothesis: true odds ratio is not equal to 1
95 percent confidence interval:
  0.7172 26.9850
sample estimates:
  odds ratio
  3.825
8.2.2 Odds ratio

- The summary statistic often used for a 2 by 2 table is an odds ratio.

- Odds of Success = # Success / # Failure
  Contrast it with Probability of Success = # Success / (# Success + # Failure)

- Equivalent to $p/(1-p)$ if $p$ is the probability of success.

- Odds range from 0 to $\infty$.

- To compare two groups (treatments), we compute the odds for each group and compute the ratio. (Odds ratio)

  $\text{Odds ratio (OR)} = \frac{p_1}{1-p_1} / \frac{p_2}{1-p_2}$.

- Odds ratio ranges from 0 to $\infty$, and $\text{OR} = 1$ means $p_1 = p_2$.

For the current example, odds ratio is:

\[
\frac{7/13}{(3/22)} \quad [1] \quad 3.949
\]

It’s slightly different from fisher.test output as it uses a slightly different method. We read the R output as “Odds of success for Treatment 1 is 3.8 times (95% CI: 0.72 to 27.0) as big as the odds for Treatment 2.”

8.2.3 $\chi^2$ test

We can use a $\chi^2$ test to test the same hypothesis $p_1 = p_2$.

<table>
<thead>
<tr>
<th></th>
<th>Success</th>
<th>Failure</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment 1</td>
<td>20</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment 2</td>
<td></td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>10</td>
<td>35</td>
<td>45</td>
</tr>
</tbody>
</table>
• If we assume $p_1 = p_2$, then we’d expect $10/45 (22.2\%)$ of 20 Treatment 1 data to be success.

• We can compute the expected cell count for each cell to get:

<table>
<thead>
<tr>
<th></th>
<th>Success</th>
<th>Failure</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment 1</td>
<td>4.4</td>
<td>15.6</td>
<td>20</td>
</tr>
<tr>
<td>Treatment 2</td>
<td>5.6</td>
<td>19.4</td>
<td>25</td>
</tr>
<tr>
<td>Total</td>
<td>10</td>
<td>35</td>
<td>45</td>
</tr>
</tbody>
</table>

• We use how far the actual data are from this expected cell counts to test the hypotheses.

• "\[ \sum (\text{Observed} - \text{Expected})^2 / \text{Expected} \]" follows a $\chi^2$ distribution.

```r
chisq.test(table(dat), correct = FALSE)
```

Warning in chisq.test(table(dat), correct = FALSE): Chi-squared approximation may be incorrect

Pearson's Chi-squared test

data: table(dat)
X-squared = 3.4, df = 1, p-value = 0.07

• $\chi^2$ test uses asymptotic theory and works when $n$ is large.

• There is a popular belief that $\chi^2$ should be used only all the cell counts are 5 or larger. (and Fisher’s test should be used for small data set.)

• $\chi^2$ test actually works fine with small cell counts.

• We don’t use Yates’ continuity correction because it is an overly conservative test.

### 8.2.4 Normal theory

• Recall that the null hypothesis is $H_0: p_1 = p_2$. This does not specify what value these two population proportions are equal to.
• Sample proportions are $\hat{p}_1$ and $\hat{p}_2$.

• The z value is

$$z = \frac{\hat{p}_1 - \hat{p}_2}{\sqrt{\hat{p}(1 - \hat{p})\left(\frac{1}{n_1} + \frac{1}{n_2}\right)}}$$

• $\hat{p}$ are from combined data. $(x_1 + x_2)/(n_1 + n_2)$.

• We can combine the groups because $p_1 = p_2$ under the null.

• For a confidence interval, such an assumption is not applicable, and we use

$$\hat{p}_1 - \hat{p}_2 \pm z \times \sqrt{\frac{\hat{p}_1(1 - \hat{p}_1)}{n_1} + \frac{\hat{p}_2(1 - \hat{p}_2)}{n_2}}$$

$z$ is 1.96 for a 95% confidence interval.

Back to example:

```r
x1 <- 7
n1 <- 20
x2 <- 3
n2 <- 25
(p1 <- x1/n1)
[1] 0.35
(p2 <- x2/n2)
[1] 0.12
(p.hat <- (x1 + x2)/(n1 + n2))
[1] 0.2222

# Z-value
(z <- (p1 - p2)/sqrt(p.hat * (1 - p.hat) * (1/n1 + 1/n2)))
[1] 1.844

# P-value
pnorm(z, lower.tail = FALSE)
```
There is not enough evidence that the two treatments’ probabilities of success are different. Estimate of the difference of the probabilities (Treatment 1 − Treatment 2) is 0.23 and its confidence interval is (−0.015, 0.47).

We can use the following function à la me to do the same test:

twoSamplePropTest <- function(x, n, confLimit = 0.95) {
  # This will test if proportions are equal. x and n are vectors of length 2.
  pObs <- x/n
  phat0 <- sum(x)/sum(n)

  zValue <- -diff(pObs)/sqrt(phat0 * (1 - phat0) * sum(1/n))
  pValue <- pnorm(abs(zValue), lower.tail = FALSE)
  ci <- -diff(pObs) + c(-1, 1) * qnorm(1 - (1 - confLimit)/2) * sqrt(sum(pObs * (1 - pObs)/n))

  list(estimate = pObs, z = zValue, oneSided.p = pValue, conf.int = ci)
}

twoSamplePropTest(x = c(7, 3), n = c(20, 25), confLimit = 0.95)
Chapter 9

Sample Size and Power

When we cannot reject $H_0$ (or when our confidence interval contains the null value), we are left with no conclusion. We can never say that we show that there is no difference. The only thing we can say is that we didn’t plan our study well and the sample size was too small.

- Tacking on new samples after concluding “sample size was too small” is also problematic because it inflates type I error rate.

- So it is critical that we start an experiment with the right sample size.

- In general, we compute the sample size so that the hypothesis test has enough power, which is the probability of rejecting $H_0$ under $H_1$.

- Example: We want to say that the baseline QoL is higher for the surgery group.
  
  $H_0 : \mu_s = \mu_r$  
  $H_1 : \mu_s > \mu_r$.

  And we want to make sure that we reject $H_0$ when the true difference is at least 10.

  We say, we want power to be 90% when $\mu_s - \mu_r = 10$.

  - Power is usually set at 90% or 80%.

What’s wrong with the sample size being too large?
Factors that affect sample size and power.

Everything being equal...

- Sample size ↑ ... Power ↑
- Type I error rate (α) ↓ ... Power ↓
- Difference to detect ↑ ... Power ↑
- Standard deviation ↑ ... Power ↓

9.1 Continuous random variables

For continuous outcome (t test), we need to know the standard deviation to perform sample size computation! Let’s compute the sample size needed to detect a difference of 10 in the baseline QoL between two groups. We set $\alpha = 0.025$. (equivalent to 5% two-sided test). Assume that $\sigma = 30$.

```r
power.t.test(n = NULL, delta = 10, sd = 30, sig.level = 0.025, power = 0.9, alternative = "one")
```

Two-sample t test power calculation

n = 190.1
delta = 10
sd = 30
sig.level = 0.025
power = 0.9
alternative = one.sided

NOTE: n is number in *each* group

```r
power.t.test(n = NULL, delta = 10, sd = 30, sig.level = 0.025, power = 0.8, alternative = "one")
```

Two-sample t test power calculation

n = 142.2
delta = 10
sd = 30
CHAPTER 9. SAMPLE SIZE AND POWER

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```
sig.level = 0.025
delta = 10
sd = 20
power = 0.8
alternative = one.sided
```

NOTE: n is number in *each* group

If we assume that $\sigma = 20$.

```
power.t.test(n = NULL, delta = 10, sd = 20, sig.level = 0.025, power = 0.9, alternative = "one")
```

Two-sample t test power calculation

```
n = 85.03
delta = 10
sd = 20
sig.level = 0.025
power = 0.9
alternative = one.sided
```

NOTE: n is number in *each* group

```
power.t.test(n = NULL, delta = 10, sd = 20, sig.level = 0.025, power = 0.8, alternative = "one")
```

Two-sample t test power calculation

```
n = 63.77
delta = 10
sd = 20
sig.level = 0.025
power = 0.8
alternative = one.sided
```

NOTE: n is number in *each* group

9.2 Binary random variables

To test $p_1 = p_2$ against $p_1 > p_2$ with a one-sided $\alpha = 0.025$, power=90% when $p_1 - p_2 = 0.10$.

- Even though the null and alternative hypotheses do not specify $p_1$ and $p_2$ separately, the power calculation requires setting $p_1$ and $p_2$. 
require(Hmisc)
bsamsize(p1 = 0.1, p2 = 0.2, fraction = 0.5, alpha = 0.05, power = 0.8)
   n1 n2
199 199

bsamsize(p1 = 0.2, p2 = 0.3, fraction = 0.5, alpha = 0.05, power = 0.8)
   n1 n2
293.2 293.2

bsamsize(p1 = 0.3, p2 = 0.4, fraction = 0.5, alpha = 0.05, power = 0.8)
   n1 n2
355.9 355.9

This example shows, even though the detectable difference is the same (10 percentage difference), the sample sizes differ much depending on the location of $p_1$ and $p_2$. Larger sample size is required near 0.5.

9.3 Additional topics on sample size and power

9.3.1 Continuous endpoint

- If $\sigma$ is doubled, $n$ is 4 times bigger.

power.t.test(n = NULL, delta = 10, sd = 20, sig.level = 0.025, power = 0.9, alternative = "one")

    Two-sample t test power calculation

    n = 85.03
delta = 10
    sd = 20
    sig.level = 0.025
    power = 0.9
    alternative = one.sided

NOTE: n is number in *each* group

power.t.test(n = NULL, delta = 10, sd = 40, sig.level = 0.025, power = 0.9, alternative = "one")
Two-sample t test power calculation

\begin{verbatim}
 n = 337.2
delta = 10
sd = 40
sig.level = 0.025
power = 0.9
alternative = one.sided
\end{verbatim}

NOTE: n is number in *each* group

• \( N \) for two-sided test with type I error = \( \alpha \) is the same for \( N \) for one-sided test with \( \alpha/2 \).

\begin{verbatim}
power.t.test(n = NULL, delta = 10, sd = 20, sig.level = 0.05, power = 0.9, alternative = "two")
\end{verbatim}

Two-sample t test power calculation

\begin{verbatim}
 n = 85.03
delta = 10
sd = 20
sig.level = 0.05
power = 0.9
alternative = two.sided
\end{verbatim}

NOTE: n is number in *each* group

\begin{verbatim}
power.t.test(n = NULL, delta = 10, sd = 20, sig.level = 0.025, power = 0.9, alternative = "one")
\end{verbatim}

Two-sample t test power calculation

\begin{verbatim}
 n = 85.03
delta = 10
sd = 20
sig.level = 0.025
power = 0.9
alternative = one.sided
\end{verbatim}

NOTE: n is number in *each* group

• 2 sample tests require larger sample sizes than 2 times \( n \) for 1 sample test.
CHAPTER 9. SAMPLE SIZE AND POWER

\[
\text{power.t.test}(n = \text{NULL}, \ delta = 10, \ sd = 20, \ \text{sig.level} = 0.05, \ \text{power} = 0.9, \ \text{alternative} = \text{"two"}, \ \text{type} = \text{"one"})
\]

One-sample t test power calculation

\[
\begin{align*}
n &= 44 \\
delta &= 10 \\
sd &= 20 \\
s\text{ig.level} &= 0.05 \\
p\text{ower} &= 0.9 \\
alternative &= \text{two.sided}
\end{align*}
\]

\[
\text{power.t.test}(n = \text{NULL}, \ delta = 10, \ sd = 20, \ \text{sig.level} = 0.05, \ \text{power} = 0.9, \ \text{alternative} = \text{"two"}, \ \text{type} = \text{"two"})
\]

Two-sample t test power calculation

\[
\begin{align*}
n &= 85.03 \\
delta &= 10 \\
sd &= 20 \\
s\text{ig.level} &= 0.05 \\
p\text{ower} &= 0.9 \\
alternative &= \text{two.sided}
\end{align*}
\]

NOTE: \(n\) is number in *each* group

- The sample size given above is for each group.

- Variance of difference is large when the data are uncorrelated.

\[
\text{Var}(X - Y) = \text{Var}(X) + \text{Var}(Y)
\]

- For paired test, we need the standard deviation of differences.

\[
\text{power.t.test}(n = \text{NULL}, \ delta = 10, \ sd = 20, \ \text{sig.level} = 0.05, \ \text{power} = 0.9, \ \text{alternative} = \text{"two"}, \ \text{type} = \text{"paired"})
\]

## sd for difference is not 20 if sd for X and for Y are 20.
Paired t test power calculation

\[
\begin{align*}
n &= 44 \\
delta &= 10 \\
sd &= 20 \\
sig.level &= 0.05 \\
power &= 0.9 \\
alternative &= \text{two.sided}
\end{align*}
\]

NOTE: n is number of *pairs*, sd is std.dev. of *differences* within pairs

- We need an additional assumption about \( \rho \), correlation of \( X \) and \( Y \). Then we can compute

\[
\text{Var}(X - Y) = \text{Var}(X) + \text{Var}(Y) - 2\rho \sqrt{\text{Var}(X)\text{Var}(Y)}
\]

\[
(sdd \leftarrow \text{sqrt}(20^2 + 20^2 - 2 \times 0.8 \times 20 \times 20))
\]

\[1\]

\[
power.t.test(n = \text{NULL}, \ delta = 10, \ sd = sdd, \ sig.level = 0.05, \ power = 0.9, \ alternative = \text{"two"}, \ type = \text{"paired"})
\]

Paired t test power calculation

\[
\begin{align*}
n &= 18.84 \\
delta &= 10 \\
sd &= 12.65 \\
sig.level &= 0.05 \\
power &= 0.9 \\
alternative &= \text{two.sided}
\end{align*}
\]

NOTE: n is number of *pairs*, sd is std.dev. of *differences* within pairs

- Sample size computation for odds ratio uses the same formula for difference of proportions.

- Given \( p_1 \) and an odds ratio (to detect) \( \psi \), we can compute \( p_2 \).
\[ \psi = \frac{p_1/(1 - p_1)}{p_2/(1 - p_2)} \]

\[ p_2 = \frac{\psi p_2}{\psi p_2 + 1 - p_2} \]

```
find.p2 <- function(p1, odds.ratio) {
  odds.ratio * p1/(odds.ratio * p1 + 1 - p1)
}

(p2x <- find.p2(0.3, 1.8))
[1] 0.4355

bpower(p1 = 0.3, p2 = p2x, n1 = 200, n2 = 200, alpha = 0.05)
  Power
0.8046

(p2y <- find.p2(0.1, 1.8))
[1] 0.1667

bpower(p1 = 0.1, p2 = p2y, n1 = 200, n2 = 200, alpha = 0.05)
  Power
0.5005
```
Chapter 10

Regression Analysis

10.1 Correlation

- Correlation is the measure of linear association between two (continuous) random variables. The most popular statistic is Pearson’s correlation ($\rho$). It is a parametric statistic, and all the cautions as before apply, i.e., it doesn’t work well with outliers and skewness.

- $\rho$ ranges from $-1$ to $1$. $\rho = 0$ means that the two random variables are uncorrelated. $\rho$ near 1 is strong positive correlation, and near $-1$ is strong negative correlation.
A simple linear regression would make sense in B and C.

We can test for significant association by testing if the population correlation is 0.

\[ t = \frac{r \sqrt{n - 2}}{\sqrt{1 - r^2}} \] 

has \( t \) distribution with \( df = n - 2 \) under the null \( (\rho = 0) \).

Confidence interval is a little complex...

cor.test(x, y0, alternative = "two.sided", method = "pearson", conf.level = 0.95)

Pearson's product-moment correlation

data:  x and y0
A popular nonparametric correlation measure is Spearman’s correlation ($\rho$). This is Pearson’s correlation on ranks.

- Spearman’s correlation is also a measure of linear association. It does not work with a non-linear association.

10.2 Simple regression

A regression analysis fits a line that describes the relationship between two continuous variables. Let’s see the CEASAR example: The following scatter plot shows QoL0 (baseline) on the x-axis and QoL6 (6 months) on the y-axis for the radiation group.
library(rms)
## To use regression functions in rms package.
ddist <- datadist(d)
options(datadist = "ddist")

This line is fit with the Ordinary Least Squares (OLS) method, and it is the best in the sense that
sum of \( (vertical \ distance \ to \ the \ line)^2 \) is minimized.
• The vertical distance is $|\hat{y}_i - y_i|$, where $\hat{y}_i$ is the fitted value (predicted value) for the $i^{th}$ observation.

• The vertical distances are called residuals.

• This line is written as

$$y_i = \beta_0 + \beta_1 x_i + \varepsilon_i,$$

where $y_i$ is follow-up QoL, $x_i$ is baseline QoL, $\beta_0$ is the intercept, $\beta_1$ is the slope, and $\varepsilon_i$ is the residuals. Because we estimate the slope and intercept using the observed sample, we write:

$$y_i = \hat{\beta}_0 + \hat{\beta}_1 x_i + \varepsilon_i.$$
For the current example, we have:

\[ \hat{y} = -4.835 + 1.008x. \]

• What do these regression coefficients mean?

  – \( \beta_0 \) is the intercept, which is the value of \( y \) when \( x = 0 \). Sometimes, it does not have a good interpretation; e.g., when \( x \) is BMI, height, or weight. In this example, because nobody had \( QoL = 0 \), \( \hat{\beta}_0 = -4.835 \) is probably meaningless. It is outside of range!

  – \( \beta_1 \) is the slope, which is increment in \( y \) corresponding to a unit increment in \( x \). QoL6 increases by 1.008 when QoL0 is increased by 1.

Let’s look at the \( R \) output.

```r
(mod.rad <- ols(QoL6 ~ QoL0, data = radiation))
```

Linear Regression Model

```r
ols(formula = QoL6 ~ QoL0, data = radiation)
```

<table>
<thead>
<tr>
<th>Model Likelihood Discrimination</th>
<th>Indexes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ratio Test</td>
<td>Indexes</td>
</tr>
<tr>
<td>Obs 70</td>
<td>LR chi2 55.93</td>
</tr>
<tr>
<td>sigma20.2780</td>
<td>R2 0.550</td>
</tr>
<tr>
<td>d.f. 68</td>
<td>Pr(&gt; chi2) 0.0000</td>
</tr>
</tbody>
</table>

Residuals

<table>
<thead>
<tr>
<th>Min</th>
<th>1Q</th>
<th>Median</th>
<th>3Q</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>-39.171</td>
<td>-13.228</td>
<td>1.046</td>
<td>11.262</td>
<td>73.590</td>
</tr>
</tbody>
</table>

| Coef | S.E. | t     | Pr(>|t|) |
|------|------|-------|----------|
| Intercept | -4.8350 | 6.1817 | -0.78 | 0.4368 |
| QoL0   | 1.0082 | 0.1105 | 9.12   | <0.0001 |

• Coefficients, standard errors, t values, and p-values.
• $R^2$ (in this example, 0.550)
  
  55.0% of variation in $Y$ is explained by $X$. $R^2$ is square of $r$ (Pearson’s correlation of $X$ and $Y$)

\[
\text{cor(radiation$\$QoL0, radiation$\$QoL6)}
\]

[1] 0.7418

\[
\text{cor(radiation$\$QoL0, radiation$\$QoL6)^2}
\]

[1] 0.5502

### 10.2.1 Model diagnostics

Not all regression models are good.
Linear Regression Model

```r
ols(formula = yb1 ~ xb1)
```

<table>
<thead>
<tr>
<th>Model Likelihood Ratio Test</th>
<th>Discrimination Indexes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obs 20</td>
<td>LR chi2 56.92</td>
</tr>
<tr>
<td>sigma 0.0104</td>
<td>d.f. 1</td>
</tr>
<tr>
<td>d.f. 18</td>
<td>Pr(&gt; chi2) 0.0000</td>
</tr>
</tbody>
</table>

Residuals

<table>
<thead>
<tr>
<th>Min</th>
<th>1Q</th>
<th>Median</th>
<th>3Q</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>-82.87</td>
<td>-64.41</td>
<td>-28.85</td>
<td>56.31</td>
<td>208.35</td>
</tr>
</tbody>
</table>

| Coef         | S.E.     | t       | Pr(>|t|) |
|--------------|----------|---------|---------|
| Intercept    | -261.0750| 42.9050 | <0.0001 |
| xb1          | 37.3278  | 2.1846  | 17.09   | <0.0001  |
mod.bad2

Linear Regression Model

\[
\text{ols(formula = yb2 ~ xb2)}
\]

<table>
<thead>
<tr>
<th>Model Likelihood</th>
<th>Discrimination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ratio Test</td>
<td>Indexes</td>
</tr>
<tr>
<td>Obs 50</td>
<td>LR chi2 = 81.54</td>
</tr>
<tr>
<td>sigma4.2336</td>
<td>d.f. = 1</td>
</tr>
<tr>
<td>d.f. 48</td>
<td>Pr(&gt; chi2) = 0.0000</td>
</tr>
</tbody>
</table>

Residuals

<table>
<thead>
<tr>
<th>Min</th>
<th>1Q</th>
<th>Median</th>
<th>3Q</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>-13.7445</td>
<td>-2.3158</td>
<td>-0.4114</td>
<td>2.7599</td>
<td>12.8026</td>
</tr>
</tbody>
</table>

| Coef   | S.E.   | t      | Pr(>|t|) |
|--------|--------|--------|---------|
| Intercept | 1.3329 | 1.2339 | 1.08    | 0.2855  |
| xb2     | 0.8610 | 0.0613 | 14.04   | <0.0001 |
Assumptions for regression analysis

- Observations are independent. (Single observation from an individual)

- Residuals ($\varepsilon$) are $\text{Normal}(0, \sigma^2)$. Mean 0 with a constant variance for all values of $X$.
  
  - Note that $y$ does not have to be normally distributed. (only $y - \hat{y}$)
  
  - Heteroskedasticity refers to the situation where variance increases as $x$ increases.
  
  - We use a residual plot to examine this assumption.
    
    A plot of residuals against $x$ or $\hat{y}$.

- When these assumptions are not met, inference (on coefficients and predicted values) will be wrong.
10.2.2 CEASAR example

QoL model for CEASAR radiation group.

```r
(mod1 <- ols(QoL6 ~ QoL0, data = radiation, x = TRUE))
```

Linear Regression Model

```r
ols(formula = QoL6 ~ QoL0, data = radiation, x = TRUE)
```

<table>
<thead>
<tr>
<th>Model Likelihood</th>
<th>Discrimination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ratio Test</td>
<td>Indexes</td>
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<tr>
<td>Obs</td>
<td>70</td>
</tr>
<tr>
<td>LR chi2</td>
<td>55.93</td>
</tr>
<tr>
<td>R2</td>
<td>0.550</td>
</tr>
<tr>
<td>sigma2</td>
<td>0.2780</td>
</tr>
<tr>
<td>d.f.</td>
<td>68</td>
</tr>
<tr>
<td>Pr(&gt; chi2)</td>
<td>0.0000</td>
</tr>
<tr>
<td>g</td>
<td>25.750</td>
</tr>
</tbody>
</table>

Residuals

<table>
<thead>
<tr>
<th>Min</th>
<th>1Q</th>
<th>Median</th>
<th>3Q</th>
<th>Max</th>
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<tbody>
<tr>
<td>-39.171</td>
<td>-13.228</td>
<td>1.046</td>
<td>11.262</td>
<td>73.590</td>
</tr>
</tbody>
</table>

| Coef | S.E.  | t     | Pr(>|t|) |
|------|-------|-------|----------|
| Intercept | -4.8350 | 6.1817 | -0.78 | 0.4368 |
| QoL0 | 1.0082 | 0.1105 | 9.12 | <0.0001 |

Model diagnosis

```r
par(mfrow = c(2, 2), las = 1, family = "serif", bty = "L", tcl = -0.2)
plot(radiation$QoL0, radiation$QoL6, xlim = c(0, 100), ylim = c(0, 100), xlab = "Baseline QoL", ylab = "Follow-up QoL", main = "QoL Radiation Group")
abline(mod1, col = "red", lwd = 2)
plot(mod1$fitted, mod1$residuals, xlab = "Fitted values", ylab = "Residuals", main = "Radiation group")
abline(h = 0, col = 8)
qqnorm(mod1$fitted)
qqline(mod1$fitted)
```
Prediction intervals

```r
newX <- seq(10, 90)
pred1 <- predict(mod1, newdata = data.frame(QoL0 = newX), conf.int = 0.95, conf.type = "mean")
pred2 <- predict(mod1, newdata = data.frame(QoL0 = newX), conf.int = 0.95, conf.type = "individual")

par(mfrow = c(1, 1), las = 1, family = "serif", bty = "L", tcl = -0.2)
plot(radiation$QoL0, radiation$QoL6, xlim = c(0, 100), ylim = c(0, 100), col = "grey", xlab = "Baseline QoL", ylab = "Follow-up QoL", main = "QoL Radiation Group")
abline(mod1, col = "blue", lwd = 2)

lines(newX, pred1$lower, col = "royalblue")
lines(newX, pred1$upper, col = "royalblue")

par(mfrow = c(1, 1), las = 1, family = "serif", bty = "L", tcl = -0.2)
plot(radiation$QoL0, radiation$QoL6, xlim = c(0, 100), ylim = c(0, 100), col = "grey", xlab = "Baseline QoL", ylab = "Follow-up QoL", main = "QoL Radiation Group")
abline(mod1, col = "blue", lwd = 2)
```
lines(newX, pred2$lower, col = "royalblue")
lines(newX, pred2$upper, col = "royalblue")

QoL Radiation Group

Baseline QoL
Follow-up QoL

0 20 40 60 80 100
0 20 40 60 80 100

CHAPTER 10. REGRESSION ANALYSIS
CHAPTER 10. REGRESSION ANALYSIS

END of BIOSTATISTICS I
10.3 ANOVA as a regression analysis

- To compare 3 or more groups on a continuous variable, analysis of variance (ANOVA) is used.

- A regression model with indicator variables (dummy variables) can accomplish the same goal.

- Indicator variable takes either 1 or 0.

Example: Is the baseline PSA different across different risk groups?

```R
# Data example
mean(d$PSA[d$Risk == "High Risk"])
[1] 9.697

mean(d$PSA[d$Risk == "Intermediate Risk"])
[1] 7.58

mean(d$PSA[d$Risk == "Low Risk"])
[1] 5.552
```

```R
source("http://biostat.mc.vanderbilt.edu/wiki/pub/Main/TatsukiRcode/RFunctions0.R")

par(las = 1, family = "serif", bty = "L", tcl = -0.2)
tplot(PSA ~ Risk, data = d, type = "b", jit = 0.01)
```
(anv <- ols(PSA ~ Risk, data = d))

Linear Regression Model

ols(formula = PSA ~ Risk, data = d)

Model Likelihood Discrimination

<table>
<thead>
<tr>
<th></th>
<th>Ratio Test</th>
<th>Indexes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obs</td>
<td>200</td>
<td>19.67</td>
</tr>
<tr>
<td>sigma</td>
<td>4.7322</td>
<td>d.f. 2</td>
</tr>
<tr>
<td>d.f.</td>
<td>197</td>
<td>Pr(&gt; chi2) 0.0001</td>
</tr>
</tbody>
</table>

Residuals

<table>
<thead>
<tr>
<th>Min</th>
<th>1Q</th>
<th>Median</th>
<th>3Q</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>-8.1971</td>
<td>-2.2802</td>
<td>-0.8163</td>
<td>0.9517</td>
<td>38.5029</td>
</tr>
</tbody>
</table>

Coef    S.E.    t    Pr(|t|)
Intercept 9.6971 0.7999 12.12 <0.0001
Risk=Intermediate Risk -2.1169 0.9572 -2.21 0.0282
$E[y] = \beta_0 + \beta_{\text{Int}} X_{\text{Int}} + \beta_{\text{Low}} X_{\text{Low}},$

where

$X_{\text{Int}} = 1$ if Risk = Intermediate Risk, 0 otherwise.

$X_{\text{Low}} = 1$ if Risk = Low Risk, 0 otherwise.

so that

$E[y] = \beta_0$ if Risk = High.

$E[y] = \beta_0 + \beta_{\text{Int}}$ if Risk = Intermediate.

$E[y] = \beta_0 + \beta_{\text{Low}}$ if Risk = Low.

The High risk group’s mean is $\hat{\beta}_0 = 9.70$. The Intermediate group’s mean is $\hat{\beta}_0 + \hat{\beta}_1 = 7.58$. The Low risk group’s mean is $\hat{\beta}_0 + \hat{\beta}_2 = 5.55$. Confidence intervals are:

<table>
<thead>
<tr>
<th></th>
<th>2.5%</th>
<th>97.5%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>8.120</td>
<td>11.2746</td>
</tr>
<tr>
<td>Risk=Intermediate</td>
<td>-4.005</td>
<td>-0.2292</td>
</tr>
<tr>
<td>Risk=Low Risk</td>
<td>-6.022</td>
<td>-2.2672</td>
</tr>
</tbody>
</table>

- Both $\beta_{\text{Int}}$ and $\beta_{\text{Low}}$ are significantly different from 0, which means that the respective group averages are different from High-Risk group’s average.

- How about Intermediate vs. Low?

$H_0 : \beta_{\text{Int}} = \beta_{\text{Low}}$

Another way of testing group differences are:
CHAPTER 10. REGRESSION ANALYSIS

```r
summary(anv, Risk = "High Risk")  ## only works with 'rms' functions. (ols)

<table>
<thead>
<tr>
<th>Factor</th>
<th>Low</th>
<th>High</th>
<th>Diff. Effect</th>
<th>S.E.</th>
<th>Lower 0.95</th>
<th>Upper 0.95</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk - Intermediate Risk:High Risk</td>
<td>1</td>
<td>2</td>
<td>-2.117</td>
<td>0.9572</td>
<td>-4.005</td>
<td>-0.2292</td>
</tr>
<tr>
<td>Risk - Low Risk:High Risk</td>
<td>1</td>
<td>3</td>
<td>-4.145</td>
<td>0.9520</td>
<td>-6.022</td>
<td>-2.2672</td>
</tr>
</tbody>
</table>
```

```r
summary(anv, Risk = "Low Risk")  ## Now reference group = 'Low Risk'

<table>
<thead>
<tr>
<th>Factor</th>
<th>Low</th>
<th>High</th>
<th>Diff. Effect</th>
<th>S.E.</th>
<th>Lower 0.95</th>
<th>Upper 0.95</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk - High Risk:Low Risk</td>
<td>3</td>
<td>1</td>
<td>4.145</td>
<td>0.9520</td>
<td>2.2672</td>
<td>6.022</td>
</tr>
<tr>
<td>Risk - Intermediate Risk:Low Risk</td>
<td>3</td>
<td>2</td>
<td>2.028</td>
<td>0.7369</td>
<td>0.5746</td>
<td>3.481</td>
</tr>
</tbody>
</table>
```

- How about the model assumptions, i.e., residuals are \( \text{Normal}(0, \sigma) \).
  
  In ANOVA, this is equivalent to the data are normal with constant variance.
  
  For these data, the assumptions are probably not met.

To alleviate some problems with data distribution, a simple transformation (e.g., \( \log(\cdot) \) and \( \sqrt{\cdot} \)) sometimes works.

```r
par(las = 1, family = "serif", tcl = -0.2, bty = "L")
tplot(log(PSA) ~ Risk, data = d, type = "b")
```
(anv2 <- ols(log(PSA) ~ Risk, data = d))

Linear Regression Model

```r
ols(formula = log(PSA) ~ Risk, data = d)
```

<table>
<thead>
<tr>
<th>Model Likelihood</th>
<th>Discrimination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ratio Test</td>
<td>Indexes</td>
</tr>
<tr>
<td>Obs: 200</td>
<td>sigma: 0.5038</td>
</tr>
<tr>
<td>LR chi2: 20.96</td>
<td>d.f.: 2</td>
</tr>
<tr>
<td>R2: 0.099</td>
<td>Pr(&gt; chi2): 0.0000</td>
</tr>
<tr>
<td>d.f.: 197</td>
<td>g: 0.172</td>
</tr>
</tbody>
</table>

Residuals

<table>
<thead>
<tr>
<th>Min</th>
<th>1Q</th>
<th>Median</th>
<th>3Q</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>-1.72588</td>
<td>-0.27281</td>
<td>-0.04169</td>
<td>0.27133</td>
<td>1.87864</td>
</tr>
</tbody>
</table>

| Coef | S.E. | t     | Pr(>|t|) |
|------|------|-------|----------|
| Intercept | 1.9967 | 0.0852 | 23.45 <0.0001 |
| Risk = Intermediate Risk | -0.0604 | 0.1019 | -0.59 0.5538 |
10.4 Multivariable regression models

10.4.1 Confounding

- Recall that a confounder is a variable that is not of major interest but may be associated with response and/or independent variables.

- When there are confounders, the true association between $X$ (Explanatory variable) and $Y$ (Response) may not be analyzed properly without accounting for the confounders.

- A multivariable (multiple) regression model is a very effective method to account for confounders.

- We will be able to say, "effect of $X$ on $Y$ is this adjusting for this, that, and that."

CEASAR Example: Comparing the follow-up QoL between the treatments.

- We would like to compare the follow-up QoL score between Surgery and Radiation group.

- We think (know by now) that many baseline characteristics are different between groups, so not adjusting for them will lead to biased conclusions.
(q6 <- aggregate(d$QoL6, by = list(d$Treatment), FUN = summary))

  Group.1 x.Min. x.1st Qu. x.Median x.Mean x.3rd Qu. x.Max.
1 Radiation 0.80   19.62   47.95   47.03   73.90  98.90
2 Surgery  0.70   10.80   24.70   36.30   59.20  96.30

(q0 <- aggregate(d$QoL0, by = list(d$Treatment), FUN = summary))

  Group.1 x.Min. x.1st Qu. x.Median x.Mean x.3rd Qu. x.Max.
1 Radiation 11.90  32.60   51.90   51.44   68.20  90.90
2 Surgery  15.50  41.47   64.25   61.35   81.77  94.90

(qd <- aggregate(d$QoL6 - d$QoL0, by = list(d$Treatment), FUN = summary))

  Group.1 x.Min. x.1st Qu. x.Median x.Mean x.3rd Qu. x.Max.
1 Radiation -43.500 -17.700  -3.250  -4.416   7.050  68.900
10.4.2 Multivariable linear regression

aka Multiple linear regression.

Don’t say “multivariate”.

- \( p \) independent variables, \( x_1, x_2, \ldots, x_p \).

- Model: \( y = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \cdots \beta_p x_p + \epsilon \)

- Estimated equation: \( \hat{y} = \hat{\beta}_0 + \hat{\beta}_1 x_1 + \hat{\beta}_2 x_2 + \cdots \hat{\beta}_p x_p \)

- Assume that the difference variables act in an additive fashion (later interaction).

- Each \( \beta \) represents an effect of increasing a variable by one unit, holding all others constant.

Example:

\[
Y = \beta_0 + \beta_1 X_{age} + \beta_2 X_{sex} + \epsilon,
\]

where \( X_{sex} = 0 \) if male, 1 if female.

- \( \beta_1 \) represents the change in the mean of \( Y \) for males when ages increases by 1 year. It is also the change in the mean of \( Y \) for females.

- \( \beta_2 \) is the “female effect”. The difference in the means of \( Y \) for two subjects of the same age. (Any age).

\[
E[Y|x_1, x_2] = \beta_0 + \beta_1 x_1 \text{ for male.}
\]
\[
E[Y|x_1, x_2] = \beta_0 + \beta_2 + \beta_1 x_1 \text{ for female.}
\]

CEASAR example:

- We will analyze association between QoL6 (Y) and Treatment (X).
• We will adjust for the following baseline variables.
  QoL0, Age, PSA, Race, HeartDisease, Hypertension, Diabetes.

Variables to include

• The number of variables that can be included in a multivariable regression model depends on sample size.

• The rule of thumb is \( n = 15 \) is required for 1 degree of freedom.
  – A continuous variable uses 1 degree of freedom.
  – A categorical variable uses \( C - 1 \) degree of freedom, where \( C \) is number of categories.
  – Flexible form (spline) and interactions need additional df.

• Important: We need to specify which variables to include in the model a priori.
  – We cannot look at a “Table 1” to decide which variables to account for. (univariate screening)
  – Doing so will inflate type I error rate and will result in overstating the association between \( X \) and \( Y \).

```r
latex(summary(Treatment ~ Age + Race + MaritalStatus + Education + Income + PSA + Gleason + HeartDisease + Hypertension + Diabetes + QoL0 + QoL6, method = "reverse", overall = !TRUE, test = !FALSE, data = d), file = "")
```

Warning in chisq.test(tab, correct = FALSE): Chi-squared approximation may be incorrect

```r
(qoLM <- ols(QoL6 ~ Treatment + QoL0 + Age + Race + PSA + HeartDisease + Hypertension + Diabetes, data = d))
```

Linear Regression Model

```r
ols(formula = QoL6 ~ Treatment + QoL0 + Age + Race + PSA + HeartDisease + Hypertension + Diabetes, data = d)
```

Table 10.1: Descriptive Statistics by Treatment

<table>
<thead>
<tr>
<th></th>
<th>Radiation</th>
<th>Surgery</th>
<th>Test Statistic</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 70</td>
<td>N = 130</td>
<td></td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td>200</td>
<td>63.0 67.0 73.0</td>
<td>56.0 63.5 68.0</td>
</tr>
<tr>
<td>Race : White</td>
<td>200</td>
<td>69% (48)</td>
<td>75% (97)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10% (7)</td>
<td>10% (13)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>21% (15)</td>
<td>15% (20)</td>
</tr>
<tr>
<td>MaritalStatus : Not married</td>
<td>200</td>
<td>27% (19)</td>
<td>10% (13)</td>
</tr>
<tr>
<td>Education : High school</td>
<td>200</td>
<td>47% (33)</td>
<td>25% (33)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>21% (15)</td>
<td>23% (30)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>20% (14)</td>
<td>26% (34)</td>
</tr>
<tr>
<td>Income : - 30K</td>
<td>195</td>
<td>34% (23)</td>
<td>15% (19)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>24% (16)</td>
<td>20% (26)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>25% (17)</td>
<td>31% (40)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>16% (11)</td>
<td>34% (43)</td>
</tr>
<tr>
<td>PSA</td>
<td>200</td>
<td>5.00 6.30 9.05</td>
<td>4.70 5.80 7.45</td>
</tr>
<tr>
<td>Gleason : 6 or less</td>
<td>200</td>
<td>46% (32)</td>
<td>47% (61)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>44% (31)</td>
<td>34% (44)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4% (3)</td>
<td>7% (9)</td>
</tr>
<tr>
<td>HeartDisease : Yes</td>
<td>200</td>
<td>9% (6)</td>
<td>15% (19)</td>
</tr>
<tr>
<td>Hypertension : Yes</td>
<td>200</td>
<td>67% (47)</td>
<td>52% (68)</td>
</tr>
<tr>
<td>Diabetes : Yes</td>
<td>200</td>
<td>17% (12)</td>
<td>18% (24)</td>
</tr>
<tr>
<td>QoL</td>
<td>200</td>
<td>32.60 51.90 68.20</td>
<td>41.47 64.25 81.77</td>
</tr>
<tr>
<td>QoL6</td>
<td>200</td>
<td>19.62 47.95 73.90</td>
<td>10.80 24.70 59.20</td>
</tr>
</tbody>
</table>

\( a, b, c \) represent the lower quartile \( a \), the median \( b \), and the upper quartile \( c \) for continuous variables. 
\( N \) is the number of non–missing values. Numbers after percents are frequencies. Tests used: 
\(^1\)Wilcoxon test; \(^2\)Pearson test


### Model Likelihood Discrimination

<table>
<thead>
<tr>
<th>Obs</th>
<th>200</th>
<th>LR chi2</th>
<th>101.45</th>
<th>R2</th>
<th>0.398</th>
</tr>
</thead>
<tbody>
<tr>
<td>sigma</td>
<td>23.7485</td>
<td>d.f.</td>
<td>9</td>
<td>R2 adj</td>
<td>0.369</td>
</tr>
<tr>
<td>d.f.</td>
<td>190</td>
<td>Pr(&gt; chi2)</td>
<td>0.0000</td>
<td>g</td>
<td>21.676</td>
</tr>
</tbody>
</table>

### Residuals

| Min | -51.839 | 1Q | -15.005 | Median | -3.115 | 3Q | 17.023 | Max | 73.087 |

| Coef            | S.E. | t     | Pr(>|t|) |
|-----------------|------|-------|---------|
| Intercept       | 32.1713 | 17.0368 | 1.89 | 0.0605 |
| Treatment=Surgery | -18.2629 | 3.7140 | -4.92 | <0.0001 |
| QoL0            | 0.7244 | 0.0794 | 9.13 | <0.0001 |
| Age             | -0.3901 | 0.2215 | -1.76 | 0.0798 |
| Race=Black      | 9.4428 | 5.7491 | 1.64 | 0.1021 |
| Race=Other      | -2.7699 | 4.5562 | -0.61 | 0.5440 |
| PSA             | 0.5166 | 0.3516 | 1.47 | 0.1434 |
| HeartDisease=Yes | -7.3865 | 5.1523 | -1.43 | 0.1533 |
| Hypertension=Yes | 1.2876 | 3.5585 | 0.36 | 0.7179 |
| Diabetes=Yes    | -6.5694 | 4.4583 | -1.47 | 0.1423 |

- Overall significance?
- $R^2$
- Significant Treatment effect?
- Other significant covariates?
- On average, QoL6 is higher for Radiation group by ...?
- Compared to a white person, a black person’s QoL6 is higher by ....?
- Compared to a 75 years old, an 85 years old’s QoL6 is ...?
"QoL6 for Surgery group is, on average, 18.3 points lower (95% CI: 10.9 to 25.6) compared to Radiation group."

summary(qolM)
### Chapter 10. Regression Analysis

#### 10.4.3 Interactions

- In the last model, we assumed that the effect of Treatment is the same for everybody regardless of their baseline characteristics.
A model with an interaction allows an effect of one $X$ vary depending the value of another $X$.

Subgroup analysis can be conducted using interactions.

A simple example.

$$Y = \beta_0 + \beta_1 X_{\text{age}} + \beta_2 X_{\text{sex}} + \beta_{12} X_{\text{age}} X_{\text{sex}} + \epsilon,$$

where $X_{\text{sex}} = 0$ if male, 1 if female.

• For male ($X_{\text{sex}} = 0$), we have $Y = \beta_0 + \beta_1 X_{\text{age}} + \epsilon$.

• For female ($X_{\text{sex}} = 1$), we have $Y = \beta_0 + \beta_2 + (\beta_1 + \beta_{12}) X_{\text{age}} + \epsilon$.

• Thus, $\beta_1$ is the age effect for male.

• $\beta_{12}$ is the additional age effect for female.

• $\beta_0$ is average $Y$ when $X_{\text{age}} = 0$ for male.

• $\beta_2$ is difference of average $Y$’s when $X_{\text{age}} = 0$ between male and female.

• We can test whether the age effect is the same for male and female by testing $\beta_{12} = 0$.

A new CEASAR model.

Now we consider the interactions between Treatment and the following variables: QoL0, Age, Race.

The reasons for including these interactions is:

• We think that the Treatment effect on QoL6 is different according to the values of QoL0, Age, and Race.

• We would like to analyze (investigate) the Treatment effect for, e.g., blacks and whites separately.
Do we have enough data to include all these interactions? Degrees of freedoms spent:
Treatment (1), QoL0 (1), Age (1), Race (2), PSA (1), HeartDisease (1), Hypertension (1), Diabetes (1)
Treatment - QoL0 (1), Treatment - Age (1), Treatment - Race (2) So the total df is 13. We probably need about \( n = 13 \times 15 = 195 \).

(qolM.int <- ols(QoL6 ~ Treatment * (QoL0 + Age + Race) + PSA + HeartDisease + Hypertension + Diabetes, data = d))

Linear Regression Model

| Coef  | S.E.  | t     | Pr(>|t|) |
|-------|-------|-------|----------|
| Intercept | -5.0609 | 24.9680 | -0.20 | 0.8396 |
| Treatment=Surgery | 56.4236 | 32.4887 | 1.74 | 0.0841 |
| QoL0 | 1.0042 | 0.1334 | 7.53 | <0.0001 |
| Age | -0.0031 | 0.3478 | -0.01 | 0.9929 |
| Race=Black | 4.8575 | 9.7740 | 0.50 | 0.6198 |
| Race=Other | -1.7489 | 7.0026 | -0.25 | 0.8031 |
| PSA | 0.4048 | 0.3489 | 1.16 | 0.2474 |
| HeartDisease=Yes | -8.7150 | 5.1224 | -1.70 | 0.0905 |
| Hypertension=Yes | -1.6532 | 3.6611 | -0.45 | 0.6521 |
| Diabetes=Yes | -4.6510 | 4.4403 | -1.05 | 0.2963 |
| Treatment=Surgery * QoL0 | -0.4977 | 0.1716 | -2.90 | 0.0042 |
| Treatment=Surgery * Age | -0.7457 | 0.4439 | -1.68 | 0.0946 |
| Treatment=Surgery * Race=Black | 9.5978 | 12.1310 | 0.79 | 0.4298 |
| Treatment=Surgery * Race=Other | -1.1382 | 9.1542 | -0.12 | 0.9012 |

- With an interaction, interpreting the coefficients gets complicated.
• Even though changing models based on the results of model fit is not recommended (it would increase type I error rate in inference.), we can check if the interaction terms were necessary.

```
anova(qolM.int)
```

```
Analysis of Variance Response: QoL6

<table>
<thead>
<tr>
<th>Factor</th>
<th>d.f.</th>
<th>Partial SS</th>
<th>MS</th>
<th>F</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment (Factor+Higher Order Factors)</td>
<td>5</td>
<td>19569.7</td>
<td>3913.9</td>
<td>7.19</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>All Interactions</td>
<td>4</td>
<td>5932.6</td>
<td>1483.2</td>
<td>2.73</td>
<td>0.0308</td>
</tr>
<tr>
<td>QoL0 (Factor+Higher Order Factors)</td>
<td>2</td>
<td>45435.6</td>
<td>22717.8</td>
<td>41.74</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>All Interactions</td>
<td>1</td>
<td>4579.7</td>
<td>4579.7</td>
<td>8.42</td>
<td>0.0042</td>
</tr>
<tr>
<td>Age (Factor+Higher Order Factors)</td>
<td>2</td>
<td>3842.2</td>
<td>1921.1</td>
<td>3.53</td>
<td>0.0313</td>
</tr>
<tr>
<td>All Interactions</td>
<td>1</td>
<td>1535.9</td>
<td>1535.9</td>
<td>2.82</td>
<td>0.0946</td>
</tr>
<tr>
<td>Race (Factor+Higher Order Factors)</td>
<td>4</td>
<td>2807.0</td>
<td>701.8</td>
<td>1.29</td>
<td>0.2757</td>
</tr>
<tr>
<td>All Interactions</td>
<td>2</td>
<td>375.1</td>
<td>187.6</td>
<td>0.34</td>
<td>0.7089</td>
</tr>
<tr>
<td>PSA</td>
<td>1</td>
<td>732.7</td>
<td>732.7</td>
<td>1.35</td>
<td>0.2474</td>
</tr>
<tr>
<td>HeartDisease</td>
<td>1</td>
<td>1575.3</td>
<td>1575.3</td>
<td>2.89</td>
<td>0.0905</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1</td>
<td>111.0</td>
<td>111.0</td>
<td>0.20</td>
<td>0.6521</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1</td>
<td>597.1</td>
<td>597.1</td>
<td>1.10</td>
<td>0.2963</td>
</tr>
<tr>
<td>Treatment * QoL0 (Factor+Higher Order Factors)</td>
<td>1</td>
<td>4579.7</td>
<td>4579.7</td>
<td>8.42</td>
<td>0.0042</td>
</tr>
<tr>
<td>Treatment * Age (Factor+Higher Order Factors)</td>
<td>1</td>
<td>1535.9</td>
<td>1535.9</td>
<td>2.82</td>
<td>0.0946</td>
</tr>
<tr>
<td>Treatment * Race (Factor+Higher Order Factors)</td>
<td>2</td>
<td>375.1</td>
<td>187.6</td>
<td>0.34</td>
<td>0.7089</td>
</tr>
<tr>
<td>TOTAL INTERACTION</td>
<td>4</td>
<td>5932.6</td>
<td>1483.2</td>
<td>2.73</td>
<td>0.0308</td>
</tr>
<tr>
<td>REGRESSION</td>
<td>13</td>
<td>76736.7</td>
<td>5902.8</td>
<td>10.85</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>ERROR</td>
<td>186</td>
<td>101225.4</td>
<td>544.2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
```

Also a likelihood ratio test can be used to see if a bigger model is better than a smaller (nested) model significantly.

```
lrtest(qolM, qolM.int)
```

```
Model 1: QoL6 ~ Treatment + QoL0 + Age + Race + PSA + HeartDisease + Hypertension + Diabetes
Model 2: QoL6 ~ Treatment * (QoL0 + Age + Race) + PSA + HeartDisease + Hypertension + Diabetes

L.R. Chisq   d.f.   P
11.3909     4.0000  0.0225
```

It looks like including these interactions are not a bad idea.
resid <- qolM.int$residuals
fitted <- qolM.int$fitted
par(mfrow = c(2, 2), las = 1, family = "serif", bty = "L", tcl = -0.2)
plot(fitted, resid, main = "", xlab = "Fitted values", ylab = "Residuals")
abline(h = 0, col = 8)
qqnorm(qolM.int$residuals)
qqline(qolM.int$residuals)

How to read / report this model.

- The variables not involved in any interactions can be interpreted in the same way as before:
  e.g.,
  - “On average, QoL6 increases by 0.4048 with unit increment in PSA.”
  - “On average, QoL6 is lower by 8.72 for a patient with HeartDisease at baseline compared with a patient without.”
• Use `summary()`

For Surgery group:

```r
summary(qolM.int, Treatment = "Surgery", QoL0 = c(30, 60, 80), Age = c(60, 65, 70))
```

<table>
<thead>
<tr>
<th>Effects</th>
<th>Low</th>
<th>High</th>
<th>Diff.</th>
<th>Effect</th>
<th>S.E.</th>
<th>Lower 0.95</th>
<th>Upper 0.95</th>
</tr>
</thead>
<tbody>
<tr>
<td>QoL0</td>
<td>30.0</td>
<td>80.0</td>
<td>50.0</td>
<td>25.322</td>
<td>5.162</td>
<td>15.1370</td>
<td>35.506</td>
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<tr>
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<td>70.0</td>
<td>10.0</td>
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<td>2.818</td>
<td>-13.0480</td>
<td>-1.928</td>
</tr>
<tr>
<td>PSA</td>
<td>4.8</td>
<td>8.1</td>
<td>3.3</td>
<td>1.336</td>
<td>1.151</td>
<td>-0.9354</td>
<td>3.607</td>
</tr>
<tr>
<td>Treatment</td>
<td>Radiation:Surgery</td>
<td>2.0</td>
<td>1.0</td>
<td>NA</td>
<td>21.908</td>
<td>4.326</td>
<td>13.374</td>
</tr>
<tr>
<td>Race</td>
<td>Black:White</td>
<td>1.0</td>
<td>2.0</td>
<td>NA</td>
<td>14.455</td>
<td>7.112</td>
<td>-0.4240</td>
</tr>
<tr>
<td>HeartDisease</td>
<td>Yes:No</td>
<td>1.0</td>
<td>2.0</td>
<td>NA</td>
<td>-8.715</td>
<td>5.122</td>
<td>-18.8200</td>
</tr>
<tr>
<td>Hypertension</td>
<td>No:Yes</td>
<td>2.0</td>
<td>1.0</td>
<td>NA</td>
<td>1.653</td>
<td>3.661</td>
<td>-5.5693</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Yes:No</td>
<td>1.0</td>
<td>2.0</td>
<td>NA</td>
<td>-4.651</td>
<td>4.440</td>
<td>-13.4110</td>
</tr>
</tbody>
</table>
```

Adjusted to: Treatment=Surgery QoL0=60 Age=65 Race=White

For Radiation group:

```r
summary(qolM.int, Treatment = "Radiation", QoL0 = c(30, 60, 80), Age = c(60, 65, 70))
```

<table>
<thead>
<tr>
<th>Effects</th>
<th>Low</th>
<th>High</th>
<th>Diff.</th>
<th>Effect</th>
<th>S.E.</th>
<th>Lower 0.95</th>
<th>Upper 0.95</th>
</tr>
</thead>
<tbody>
<tr>
<td>QoL0</td>
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<td>80.0</td>
<td>50.0</td>
<td>50.208</td>
<td>6.669</td>
<td>37.0510</td>
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<tr>
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<tr>
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<td>8.1</td>
<td>3.3</td>
<td>1.336</td>
<td>1.151</td>
<td>-0.9354</td>
<td>3.607</td>
</tr>
<tr>
<td>Treatment</td>
<td>Surgery:Radiation</td>
<td>1.0</td>
<td>2.0</td>
<td>NA</td>
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<tr>
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<td>2.0</td>
<td>NA</td>
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<tr>
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<td>Yes:No</td>
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<td>2.0</td>
<td>NA</td>
<td>-8.715</td>
<td>5.122</td>
<td>-18.8200</td>
</tr>
<tr>
<td>Hypertension</td>
<td>No:Yes</td>
<td>2.0</td>
<td>1.0</td>
<td>NA</td>
<td>1.653</td>
<td>3.661</td>
<td>-5.5693</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Yes:No</td>
<td>1.0</td>
<td>2.0</td>
<td>NA</td>
<td>-4.651</td>
<td>4.440</td>
<td>-13.4110</td>
</tr>
</tbody>
</table>
```

Adjusted to: Treatment=Radiation QoL0=60 Age=65 Race=White

The Surgery effect is $-21.9(-30.4, -13.4)$ for a 65-year old white patient with $QoL0 = 60$. 

```r
summary(qolM.int, Treatment = "Radiation", QoL0 = c(30, 40, 80), Age = c(60, 75, 80), est.all = FALSE)
```
The Surgery effect is $-19.4 (-31.5, -7.4)$ for a 75-year old white patient with $QoL_0 = 40$. And finally, we can estimate the treatment effects for different values of age / baseline QoL / Race and show them in a plot.

```r
extract.effect <- function(qol0, age, race='White', m=qolM.int)
  s <- summary(m, QoL0=qol0, Age=age, Race=race, Treatment='Radiation')
  out <- s[grep('Treatment', row.names(s)), c(4,6,7)]

QoL0 <- seq(20,90) ; L <- length(QoL0)
Age <- 65
out <- matrix(0, ncol=3, nrow=L)
for(i in 1:L){
  out[i,] <- extract.effect(qol0=QoL0[i], age=Age)
}

par(las=1, family='serif', bty='L', tcl=-0.2)
plot(0,0, type='n', xlim=c(0,100), ylim=range(out), xlab='Baseline QoL',
     ylab='Difference in follow-up QoL', main=''
)
title(main='Surgery - Radiation', adj=0)
abline(h=0, col=8)
lines(QoL0, out[,1], col='blue')
lines(QoL0, out[,2], col='royalblue')
lines(QoL0, out[,3], col='royalblue')
```
CHAPTER 10. REGRESSION ANALYSIS

Surgery – Radiation

Baseline QoL

Difference in follow-up QoL

0 20 40 60 80 100

−50
−40
−30
−20
−10
0
10

0 20 40 60 80 100

Baseline QoL

Difference in follow-up QoL

0 10 20 30 40 50

−50
−40
−30
−20
−10
0
10