Biostatistics
Week I

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ACIBADEM
MEHMET ALİ AYDINLAR
ÜNİVERSİTESİ

Statistics

- The study of data
- A discipline concerned with
  - **Collecting data** for a certain purpose
  - **Analysis** of the collected data
  - **Reaching conclusions** based on the analysis

Statistics

Collection

Organization

Analysis

Interpretation

Presentation

Biotatistics

- Does a novel drug affect survival in pancreatic cancer?
- Which mutation is most likely the cause of an inherited disease?
- Can health status of advanced AIDS patients be improved by a novel treatment?

Descriptive/Inferential Statistics

- Descriptive Statistics
  - Organization of collected data, calculation of mean and dispersion, presentation as tables, graphics, etc.
- Inferential Statistics
  - Building hypothesis concerning the population based on sample findings, hypothesis testing, interpretation.

Population vs. Sample

- Population
  - All subjects under consideration that have the same properties
  - E.g., everyone living in Istanbul

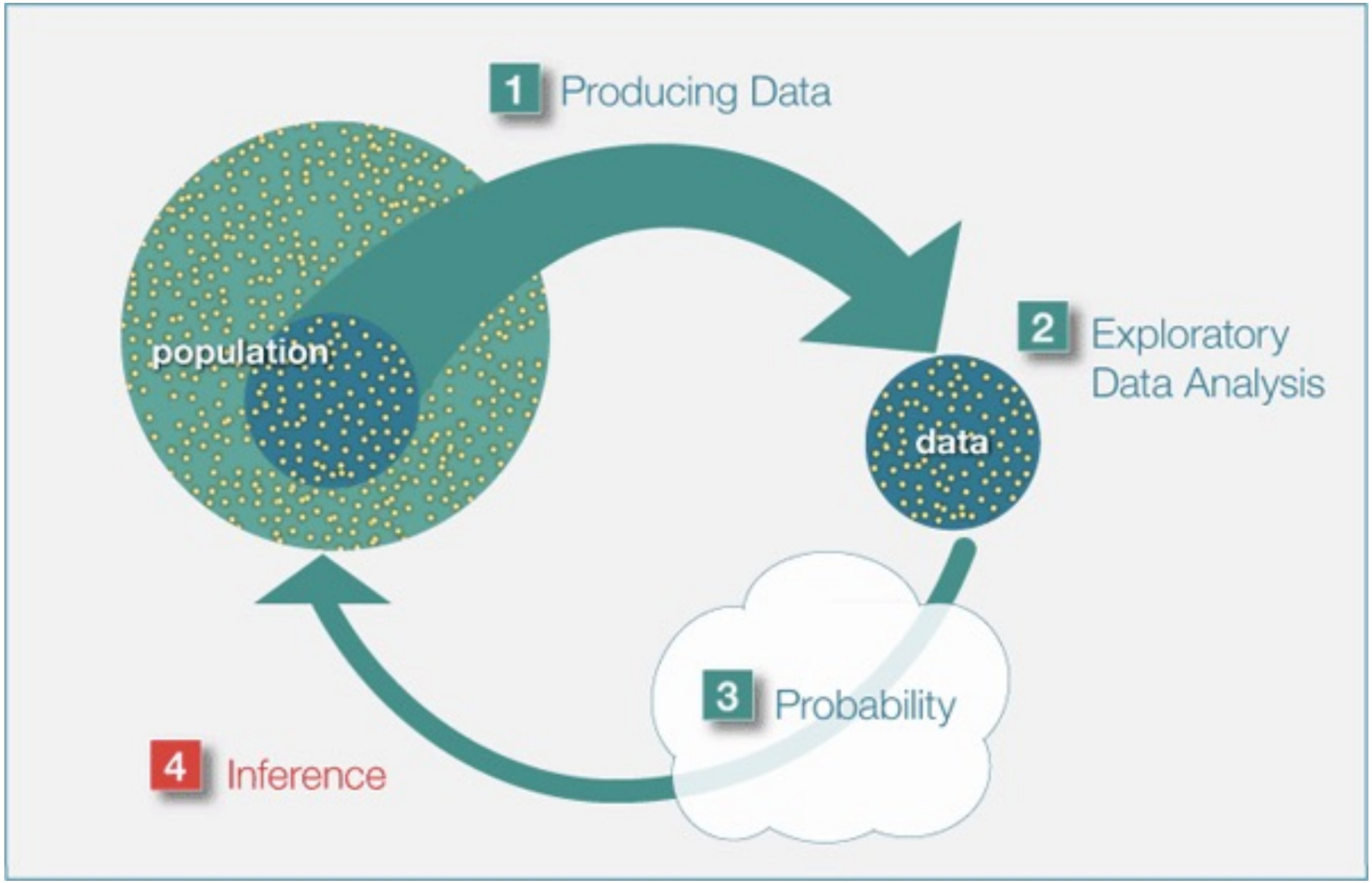
  N = 15.52 million (as of 31 Dec 2019)

- Sample
  - A proportion of the population (ideally randomly selected)
  - E.g., **n** = 500, 1000, 5000, …

  (n might be decided based on sample size calculations)

Terminology/Notation

	Sample Statistic	Population Parameter
Size	n	N
Mean	$\bar{x} = \frac{\sum x}{n}$	$\mu = \frac{\sum X}{N}$
Variance	$s^2 = \frac{\sum (x-\bar{x})^2}{n-1}$	$\sigma^2 = \frac{\sum (X-\mu)^2}{N}$
Standard Deviation	$s = \sqrt{s^2}$	$\sigma = \sqrt{\sigma^2}$
Proportion	$\hat{p} = \frac{n \text{ of successes}}{n \text{ of trials}}$	$p = \frac{N \text{ of successes}}{N \text{ of trials}}$



Unit 4a: introduction to statistical inference [Internet]. [cited 2021 Sep 27]. Available from: https://bolt.mph.ufl.edu/6050-6052/unit-4/

Data/Variable

- Items of information, often numeric, that are collected through observation
    - Age
    - Gender
    - Ethnicity
    - Systolic blood pressure
    - Treatment type

    …

Example Study

- Main question
  - Can the health status of advanced AIDS patients be improved by a novel drug treatment?

- Sub-questions
  - Are there differences between treatments in terms of health benefits?
  - Do health benefits differ with respect to gender?
  - Do health benefits differ with respect to age?

Example Study (cont.)

- Randomized clinical trial
- 1178 patients
  - 289, 288, 293, and 308 patients per treatment arm
- Data collection at baseline (week = 0)
- 5 more follow-ups with 8-week intervals

Example Study (cont.)

- Variables
  - Identification number
  - Treatment arm
  - Age
  - Gender
  - CD4 cell count at each follow-up
  - Time of follow-up (in weeks since baseline)

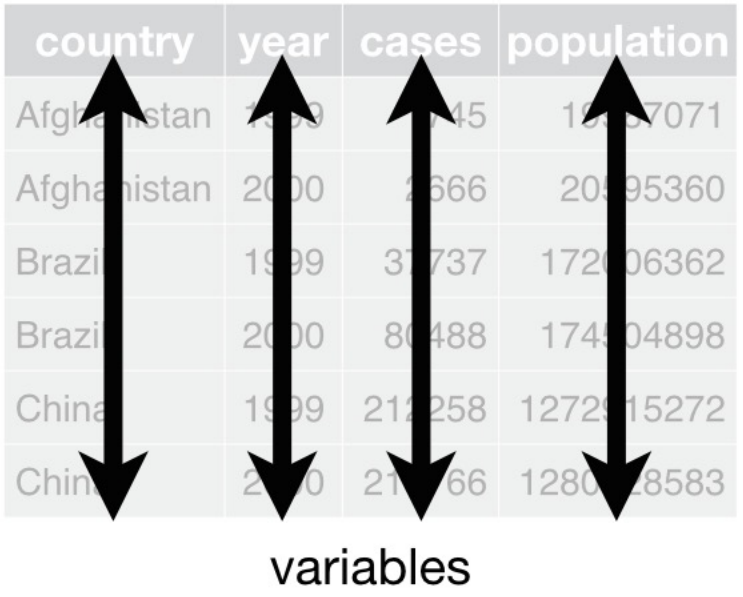
Example Study (cont.)

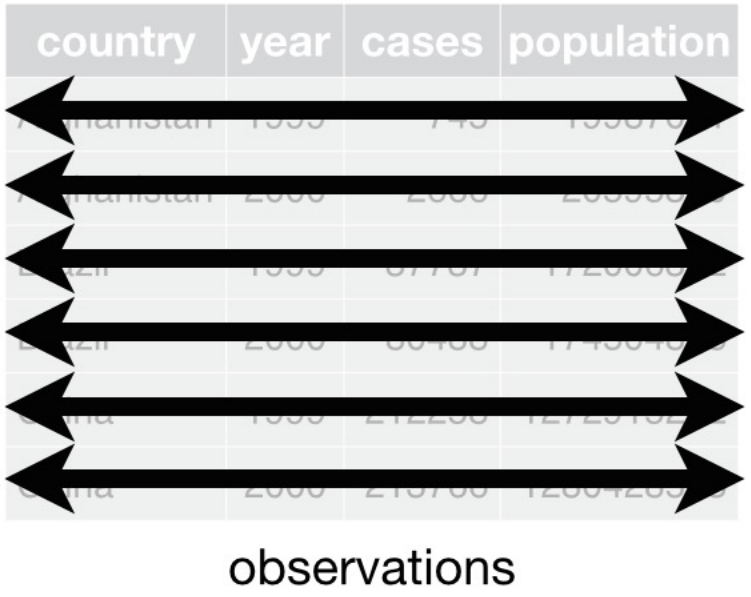
First 5 patients' data, out of 1,178 (only for the first two weeks)

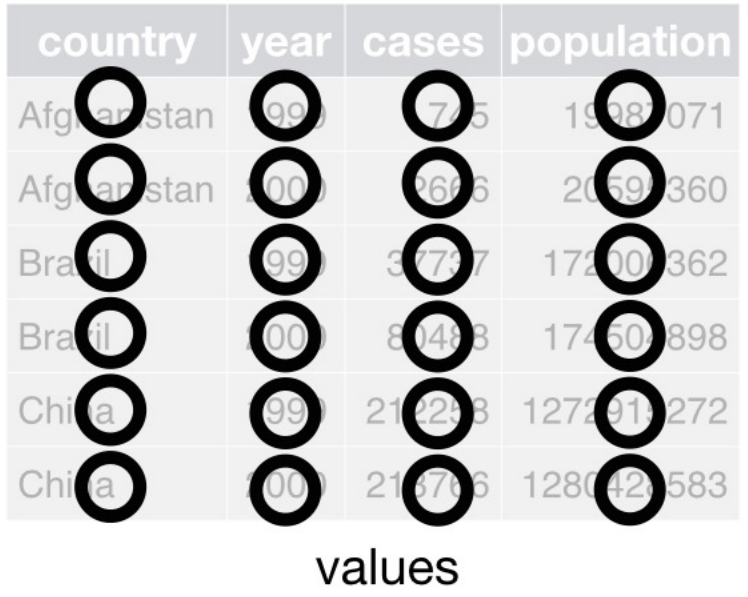
id	treatment	age	gender	week_1	cd4_1	week_2	cd4_2
1	trt2	36.43	male	0	22	7.57	20
2	trt4	47.85	male	0	21	8.00	48
4	trt3	36.60	male	0	61	7.14	60
5	trt1	35.95	male	0	35	8.00	30
6	trt2	38.40	male	0	10	7.29	10

Applied longitudinal analysis [Internet]. [cited 2021 Sep 27]. Available from: https://content.sph.harvard.edu/fitzmaur/ala2e/

«Clean» Data







12 tidy data | r for data science [Internet]. [cited 2021 Sep 27]. Available from: https://r4ds.had.co.nz/tidy-data.html

Variable Types

- **Discrete/Categorical/Qualitative**
  - Measured in a discrete manner

  - **Nominal**: no natural ordering. E.g., eye color, zip-code
  - **Dichotomous/binary**: only takes two values. E.g., dead/alive, female/male
  - **Ordinal**: natural ordering. E.g., agree/neutral/disagree, bad/fair/good
  - **Count**: counted values. E.g., number of tumor occurrences in one month

Variable Types

- **Continuous/Quantitative**
  - Measured in a continuous manner

  - **Interval:** real number (+/- including 0). E.g., temperature, location
  - **Ratio:** positive values (**0 indicates none**). E.g., height, age, daily calcium consumption (mg).

Example Study (cont.)

id	treatment	age	gender	week_1	cd4_1	week_2	cd4_2
1	trt2	36.43	male	0	22	7.57	20
2	trt4	47.85	male	0	21	8.00	48
4	trt3	36.60	male	0	61	7.14	60
5	trt1	35.95	male	0	35	8.00	30
6	trt2	38.40	male	0	10	7.29	10

Discrete - nominal

Contin.- ratio

Discrete – nominal /binary

Discrete - count
Contin. - ratio

Applied longitudinal analysis [Internet]. [cited 2021 Sep 27]. Available from: https://content.sph.harvard.edu/fitzmaur/ala2e/

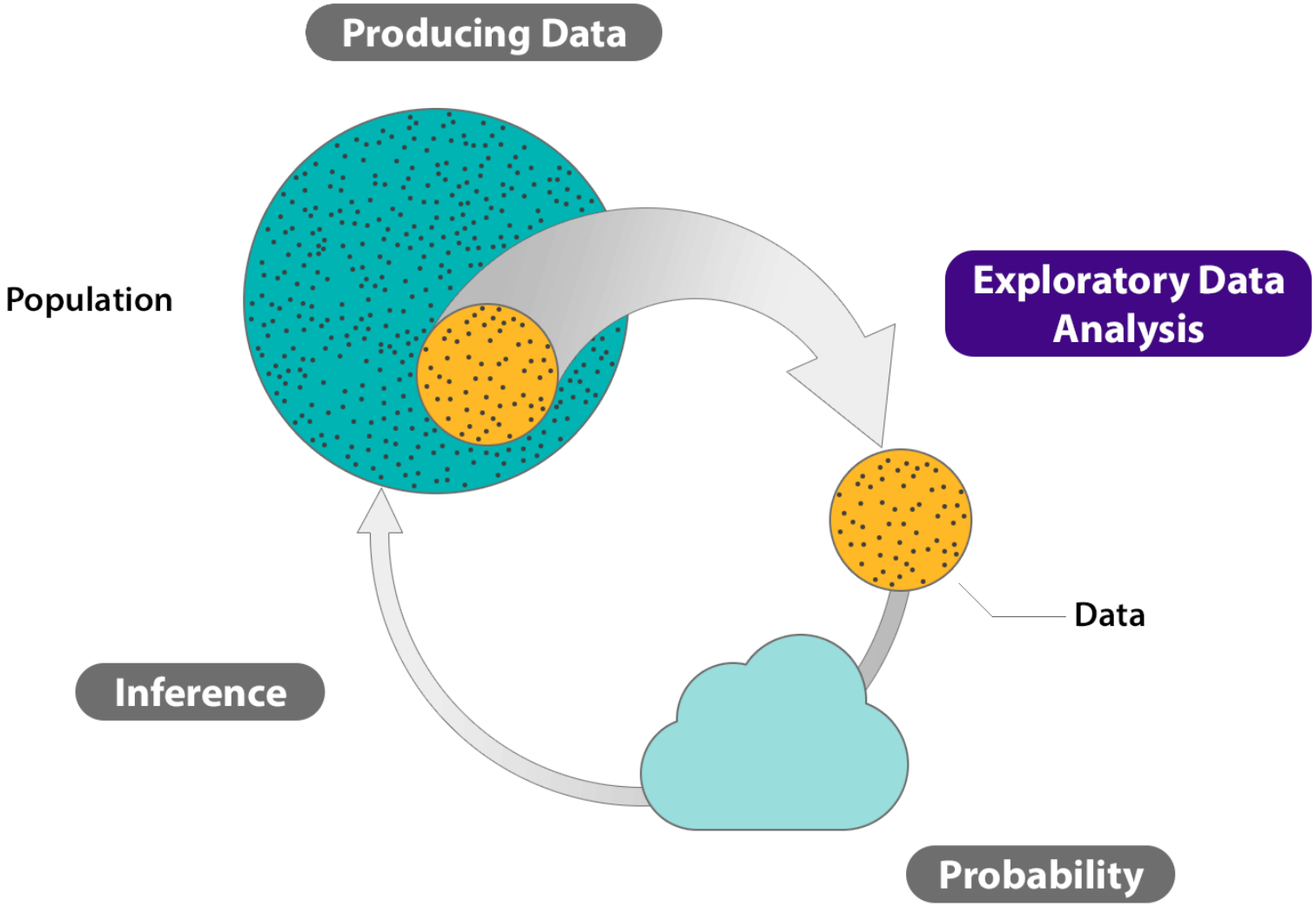
Same variable – different classifications

1. Time after study entry
   0, 1.2, 2.5, 3.1, 4.6, 5.2, 6.6, 7.1, 8 weeks
   Continuous - ratio
2. Time after study entry
   < 4 weeks, ≥ 4 weeks
   Categorical - binary
3. Time after study entry
   < 2 weeks, ≥ 2 and < 4 weeks, ≥ 4 weeks
   Categorical - ordinal
4. Time after study entry
   -4.6, -3.4, -2.1, -1.5, 0, 0.6, 2, 2.5, 3.4 weeks
   Continuous - interval

Brief Summary

- Statistics is a discipline concerned with collection, organization, analysis and interpretation of data
- The aim is to infer information regarding the population using sample data
- There are two kinds of variables:
  - Categorical – nominal, binary, ordinal, count
  - Continuous – interval, ratio

The Big Picture



Unit 1: exploratory data analysis [Internet]. [cited 2021 Sep 27]. Available from: https://bolt.mph.ufl.edu/6050-6052/unit-1/

Exploratory Data Analysis (EDA)

- Examining Distributions — exploring data **one variable at a time**
- Examining Relationships — exploring data **two variables at a time**

Frequency Tables – Categorical Variable

- Eye colors of 10 individuals:

  blue, green, brown, blue, brown, blue, blue, green, brown, brown

Frequency Tables – Categorical Variable

- Eye colors of 10 individuals:

  blue, green, brown, blue, brown, blue, blue, green, brown, brown

Eye Color	Frequency
Blue	4
Brown	4
Green	2

Frequency Tables – Categorical Variable

- Eye colors of 10 individuals:

  blue, green, brown, blue, brown, blue, blue, green, brown, brown

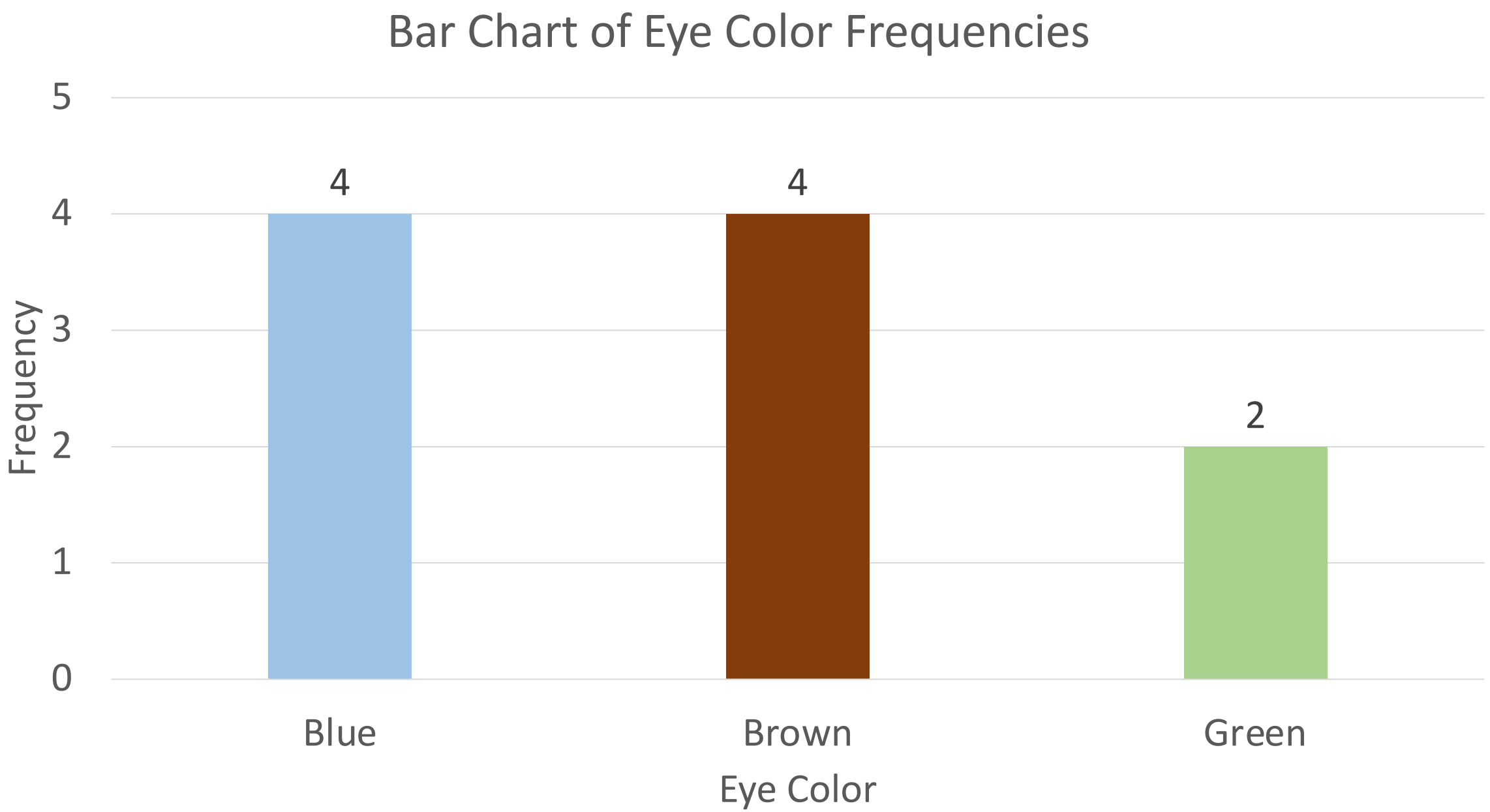
Eye Color	Frequency	Relative Freq.
Blue	4	4/10 = 0.4
Brown	4	4/10 = 0.4
Green	2	2/10 = 0.2

Frequency Tables – Categorical Variable

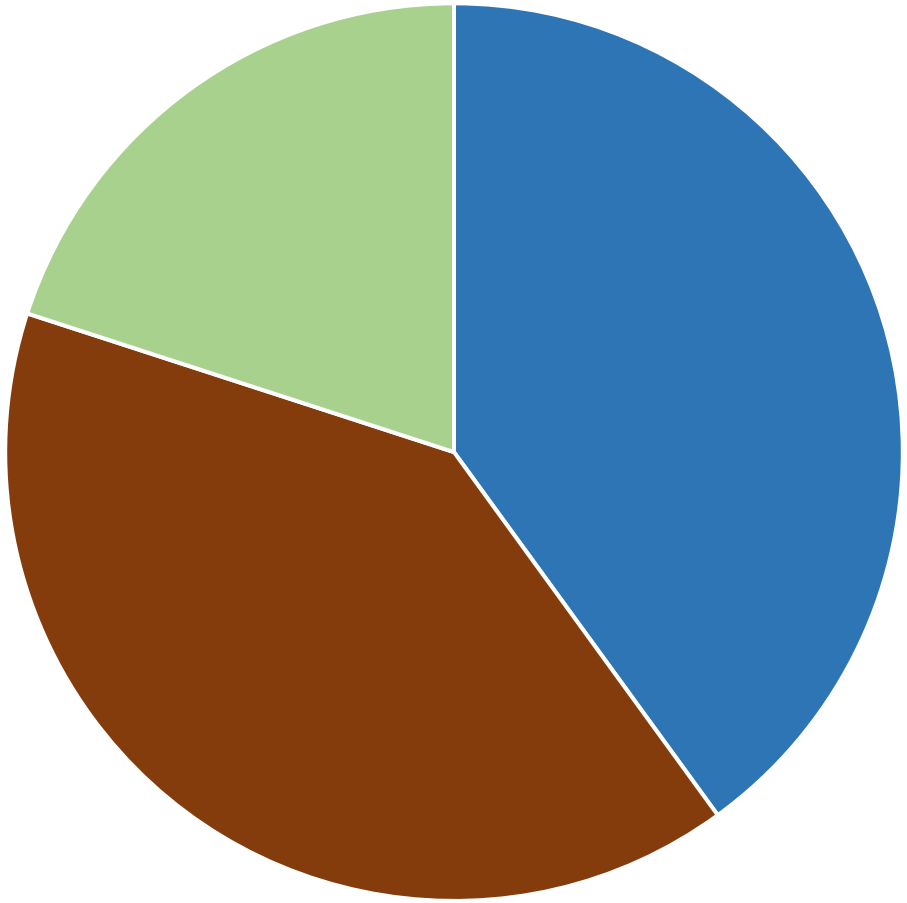
- Eye colors of 10 individuals:

  blue, green, brown, blue, brown, blue, blue, green, brown, brown

Eye Color	Frequency	Relative Freq.	%
Blue	4	4/10 = 0.4	40
Brown	4	4/10 = 0.4	40
Green	2	2/10 = 0.2	20


Bar Chart of Eye Color Frequencies
5
4
3
2
1
0
Frequency
4
4
2
Blue
Brown
Green
Eye Color

Avoid using pie charts!



Contingency table/Cross tabulation/Crosstab

- Tables in which two categorical variables are investigated together

	Male	Female
No education	4	10
Primary school	3	5
High school	2	8
Bachelor’s degree	7	9

Frequency Tables – Continuous Variable

Cholesterol levels of 40 patients:

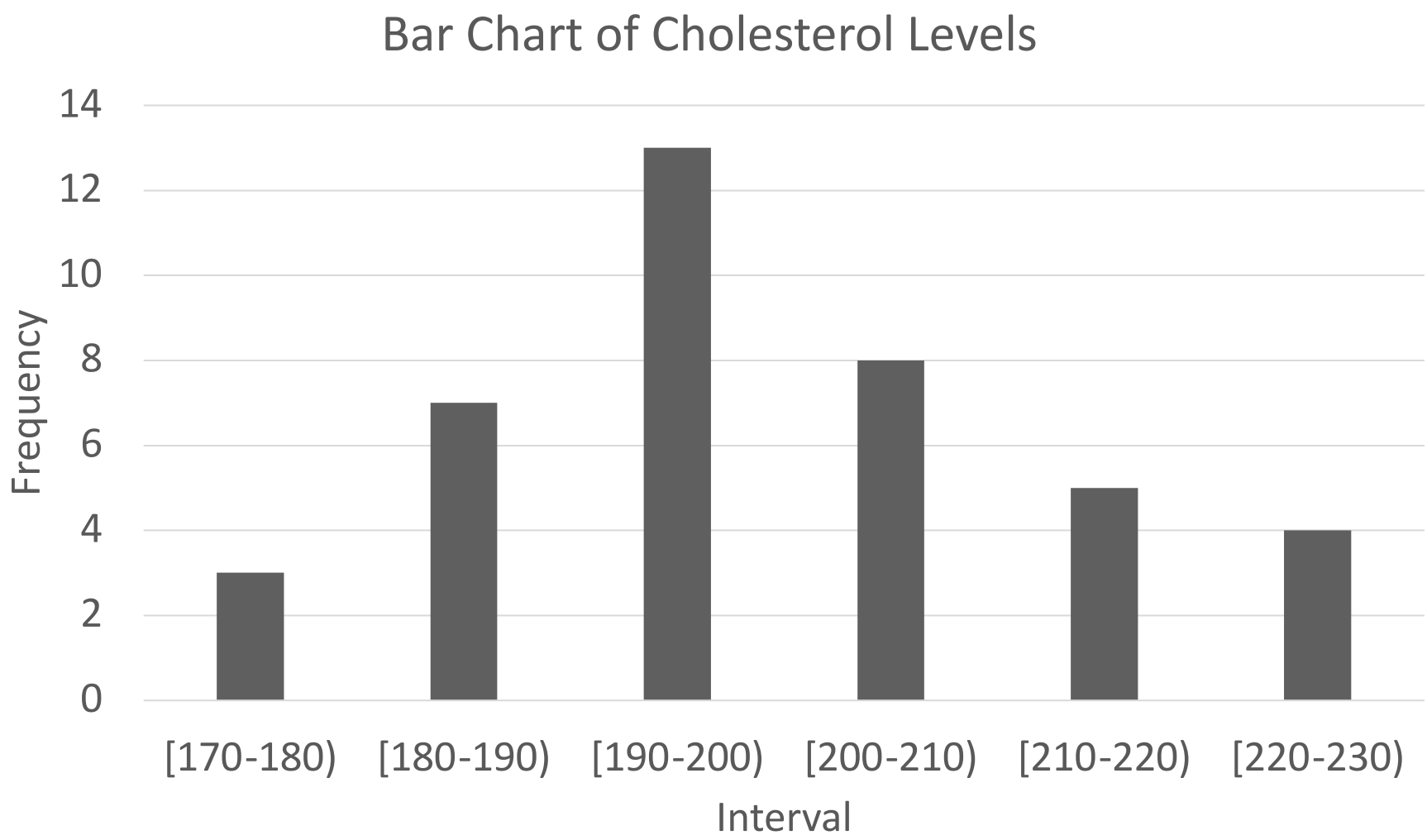
Original data

213, 174, 193, 196, 220, 183, 194, 200, 192, 200, 200, 199, 178, 183, 188, 193, 187, 181, 193, 205, 196, 211, 202, 213, 216, 206, 195, 191, 171, 194, 184, 191, 221, 212, 221, 204, 204, 191, 183, 227

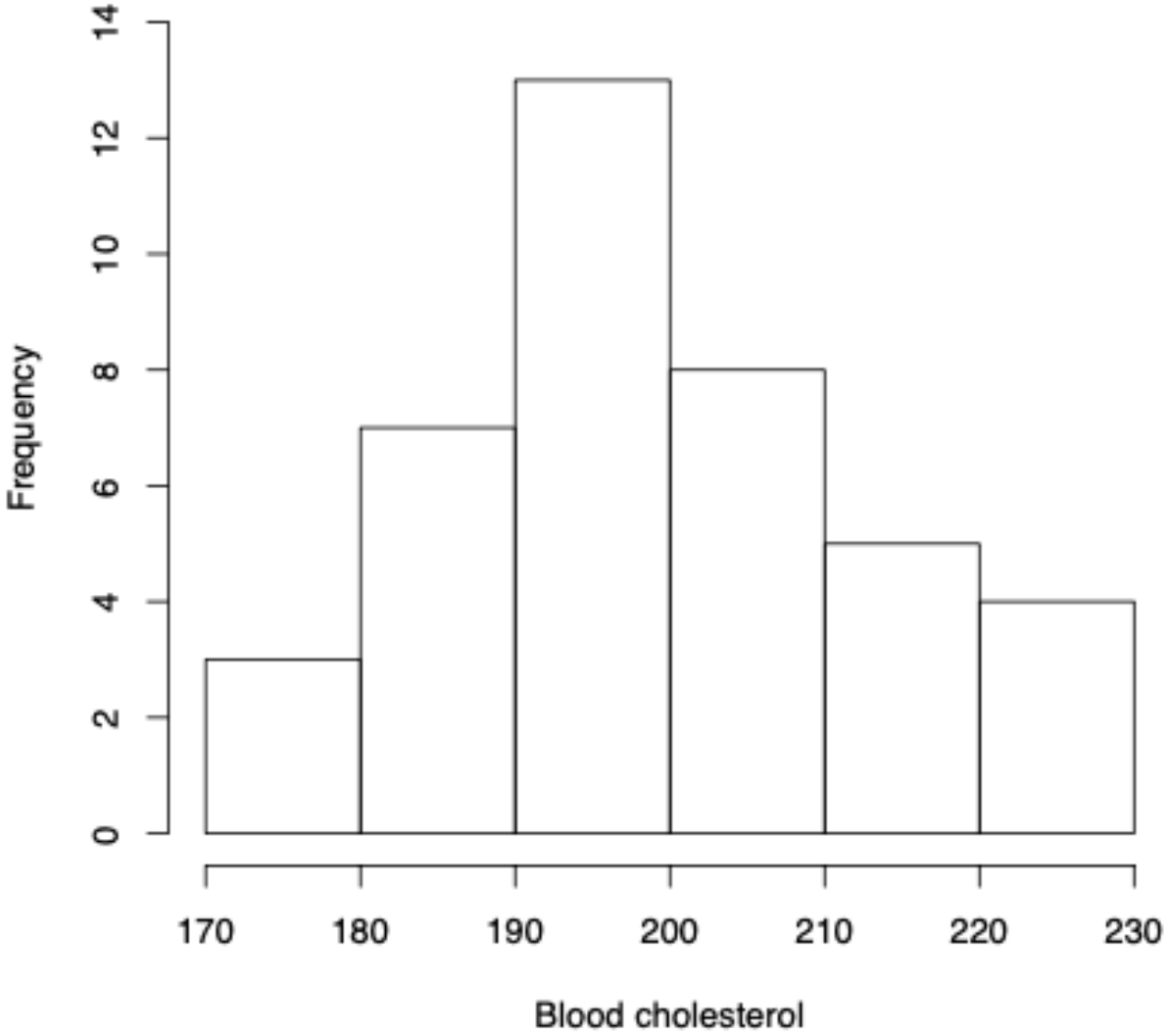
Sorted data

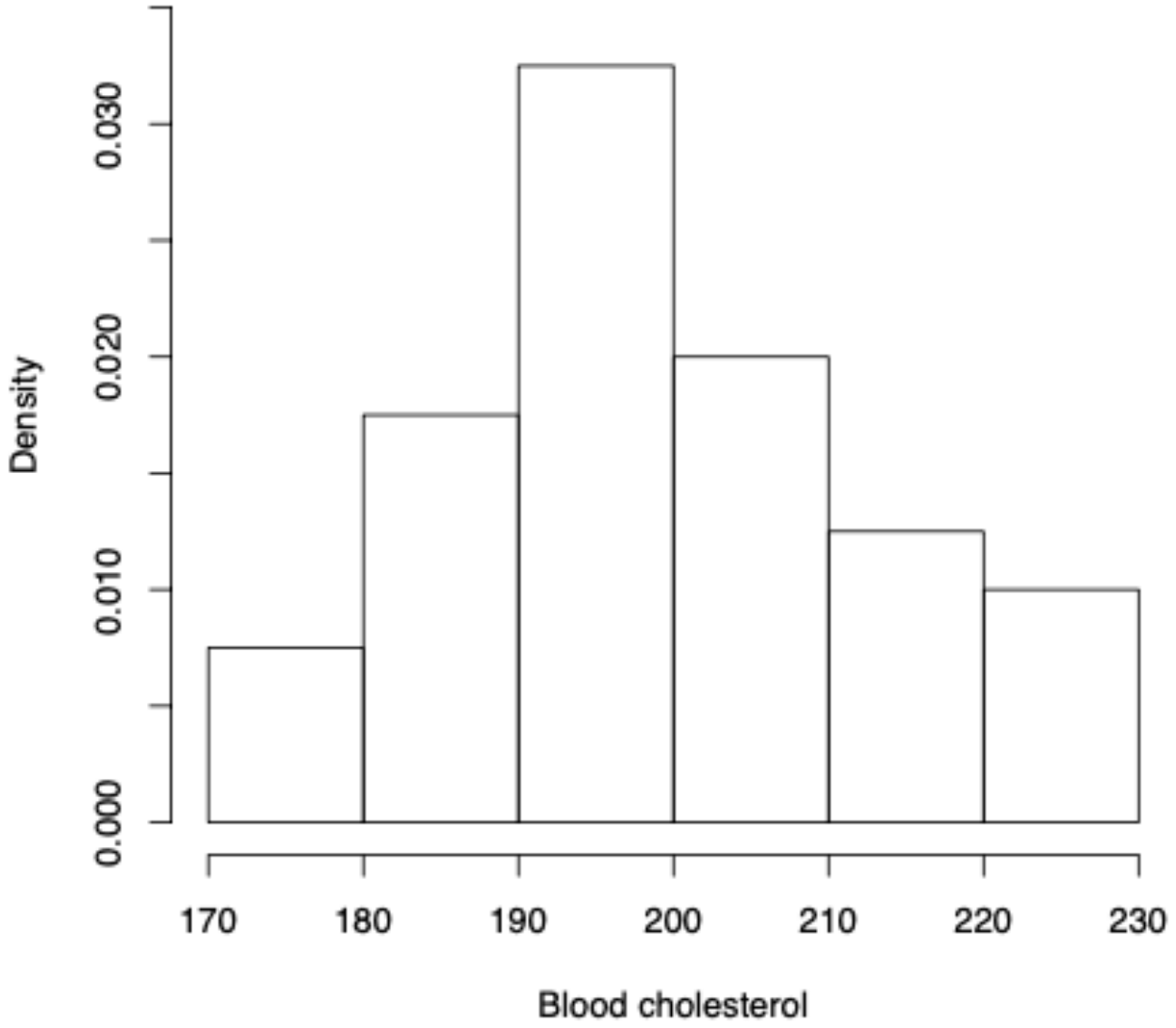
171, 174, 178, 181, 183, 183, 183, 184, 187, 188, 191, 191, 191, 192, 193, 193, 193, 194, 194, 195, 196, 196, 199, 200, 200, 200, 202, 204, 204, 205, 206, 211, 212, 213, 213, 216, 220, 221, 221, 227

Interval	Frequency	Relative Freq.	%
[170-180)	3	3/40 = 0.075	7.5
[180-190)	7	7/40 = 0.175	17.5
[190-200)	13	13/40 = 0.325	32.5
[200-210)	8	8/40 = 0.200	20.0
[210-220)	5	5/40 = 0.125	12.5
[220-230)	4	4/40 = 0.100	10.0

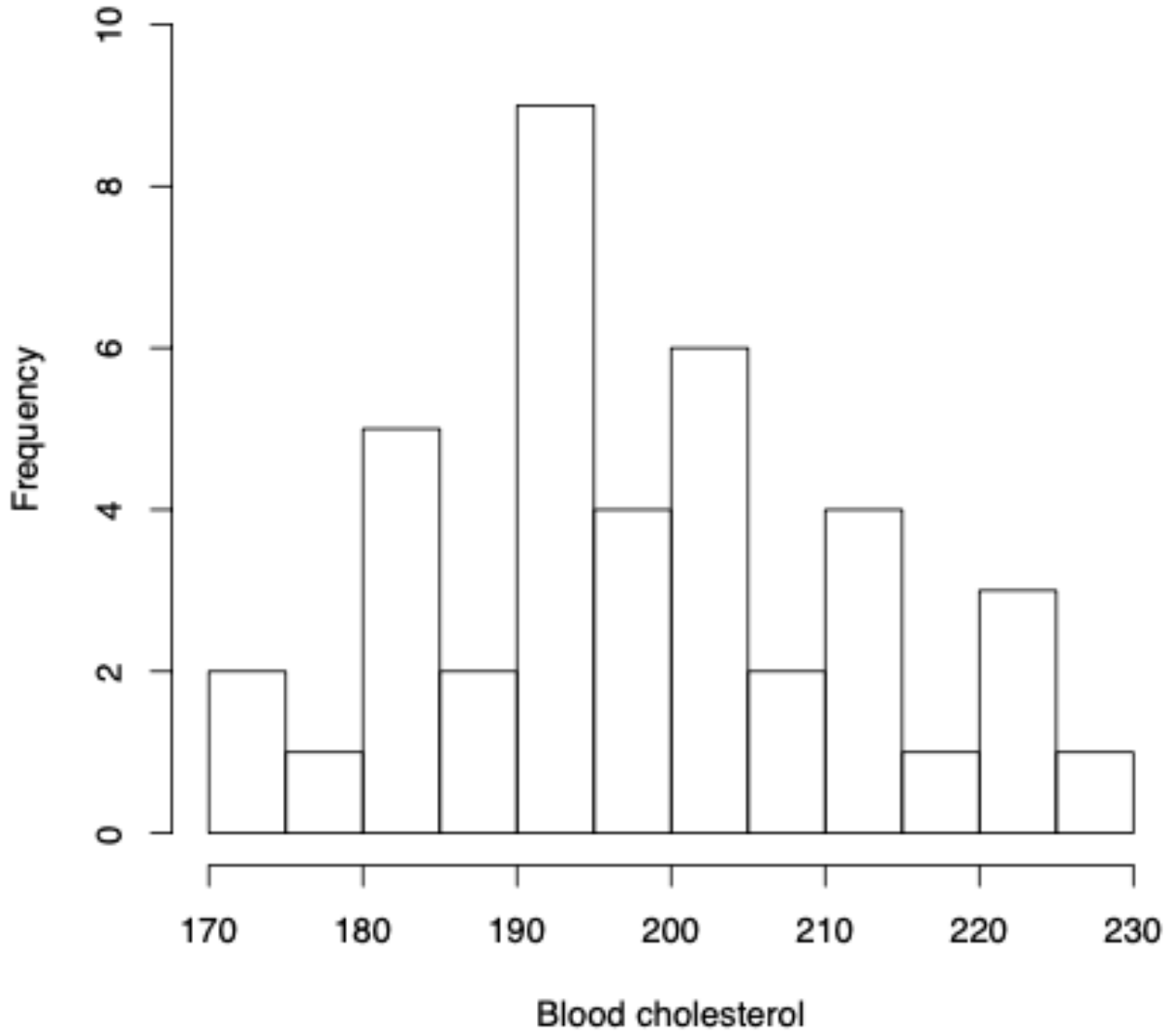

Bar Chart of Cholesterol Levels
14
12
10
8
6
4
2
0
Frequency
[170-180)
[180-190)
[190-200)
[200-210)
[210-220)
[220-230)
Interval

Histogram


Frequency
0
2
4
6
8
10
12
14
170
180
190
200
210
220
230
Blood cholesterol


Density
0.000
0.010
0.020
0.030
170
180
190
200
210
220
230
Blood cholesterol

Histogram


Frequency
0
2
4
6
8
10
170
180
190
200
210
220
230
Blood cholesterol

Ross, S. M. (2017). Introductory statistics. Amsterdam: Elsevier/AP.

Histogram

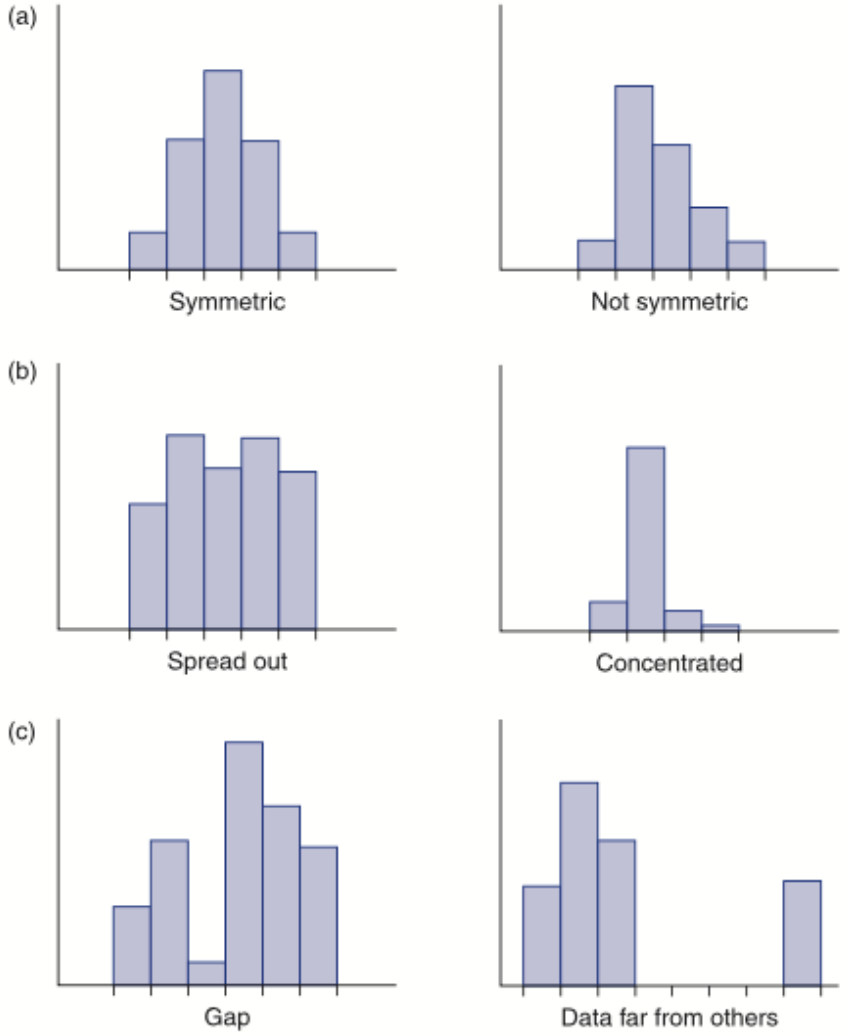


FIGURE 2.8

Characteristics of data detected by histograms. (a) symmetry, (b) degree of spread and where values are concentrated, and (c) gaps in data and data far from others.

Table 2.9 Class Frequencies of Systolic Blood Pressure of Two Groups of Male Workers

Blood pressure	Number of workers	
	Aged 30–40	Aged 50–60
Less than 90	3	1
90–100	17	2
100–110	118	23
110–120	460	57
120–130	768	122
130–140	675	149
140–150	312	167
150–160	120	73
160–170	45	62
170–180	18	35
180–190	3	20
190–200	1	9
200–210		3
210–220		5
220–230		2
230–240		1
Total	**2540**	**731**

Table 2.10 Relative Class Frequencies of Blood Pressures

Blood pressure	Percentage of workers	
	Aged 30–40	Aged 50–60
Less than 90	0.12	0.14
90–100	0.67	0.27
100–110	4.65	3.15
110–120	18.11	7.80
120–130	30.24	16.69
130–140	26.57	20.38
140–150	12.28	22.84
150–160	4.72	9.99
160–170	1.77	8.48
170–180	0.71	4.79
180–190	0.12	2.74
190–200	0.04	1.23
200–210		0.41
210–220		0.68
220–230		0.27
230–240		0.14
Total	**100.00**	**100.00**

Ross, S. M. (2017). Introductory statistics. Amsterdam: Elsevier/AP.

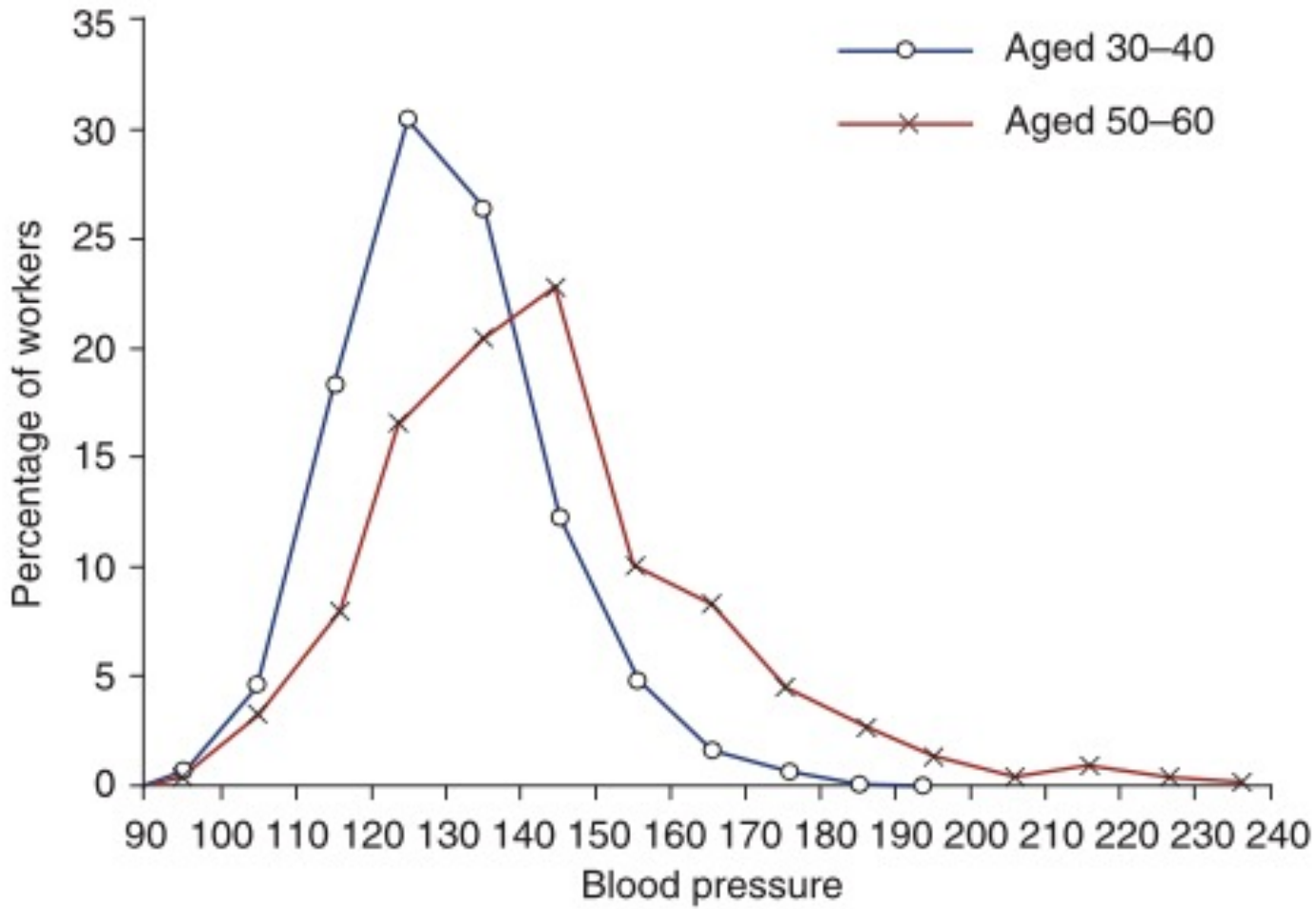


FIGURE 2.10

Relative frequency polygons for the data of Table 2.10.

Brief Summary

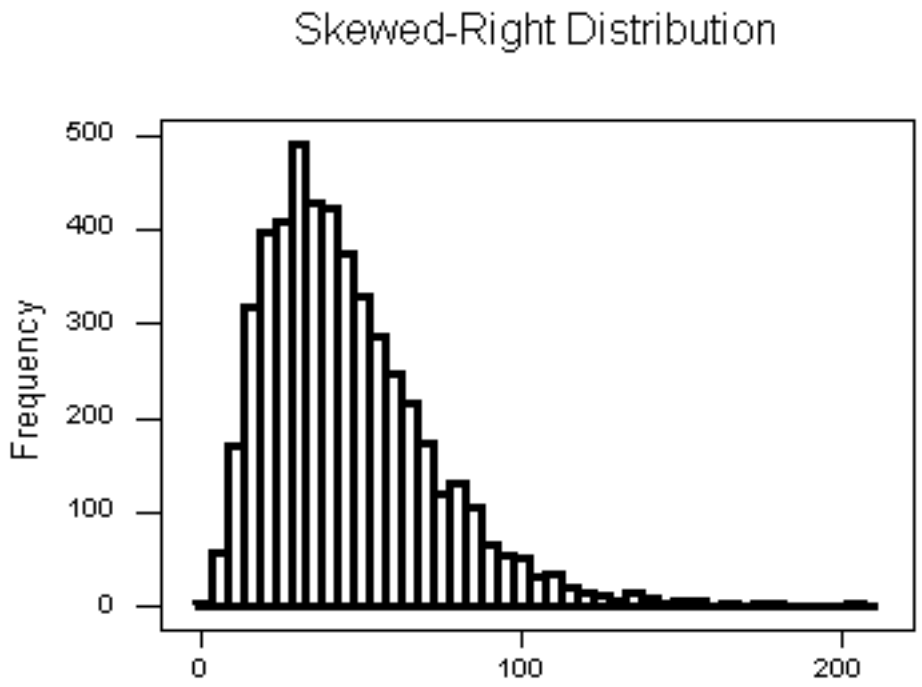
- In one-variable EDA,
  - We may summarize a categorical variable using frequency, relative frequency and/or percentage tables
  - We may visually display a categorical variable using bar charts, etc.

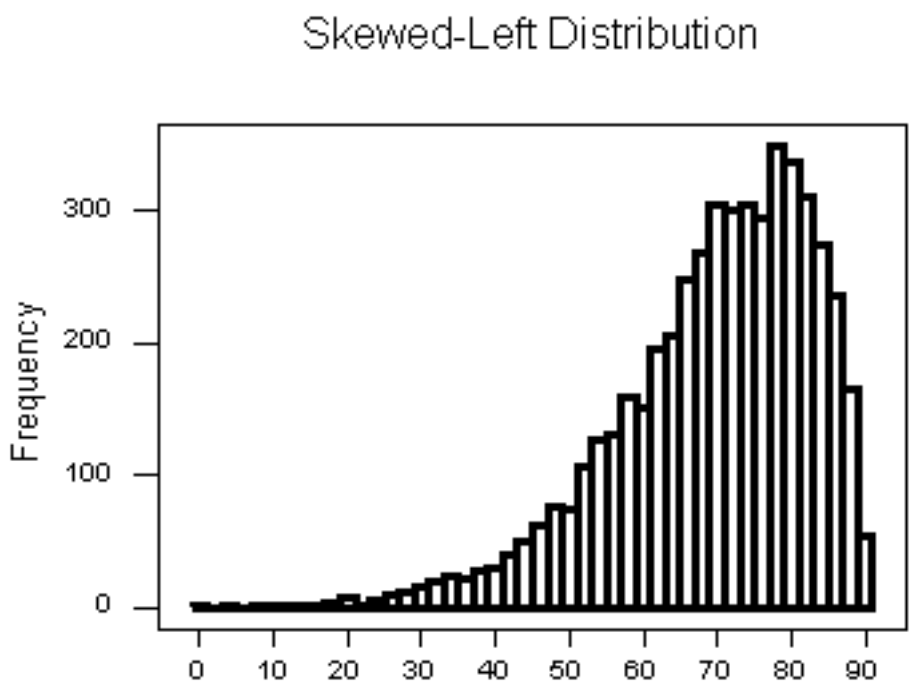
Describing a Dataset

- **Shape**
- Center
- Spread
- Outliers

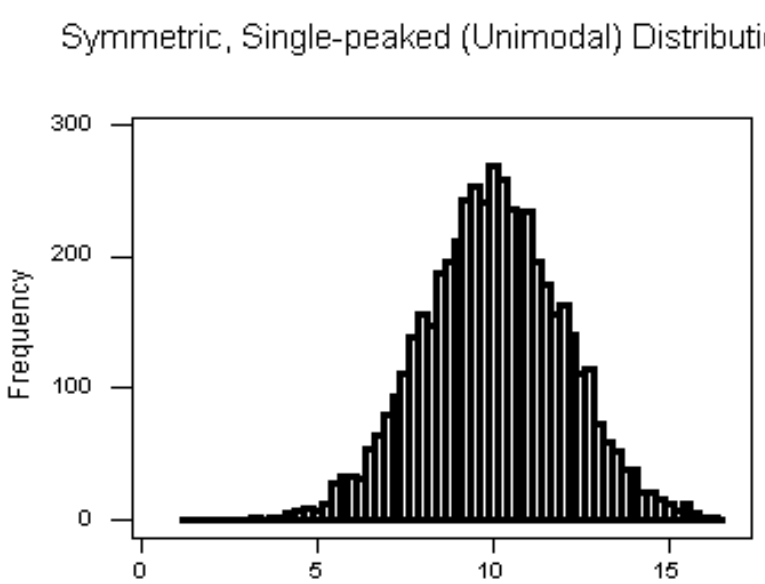
Shape

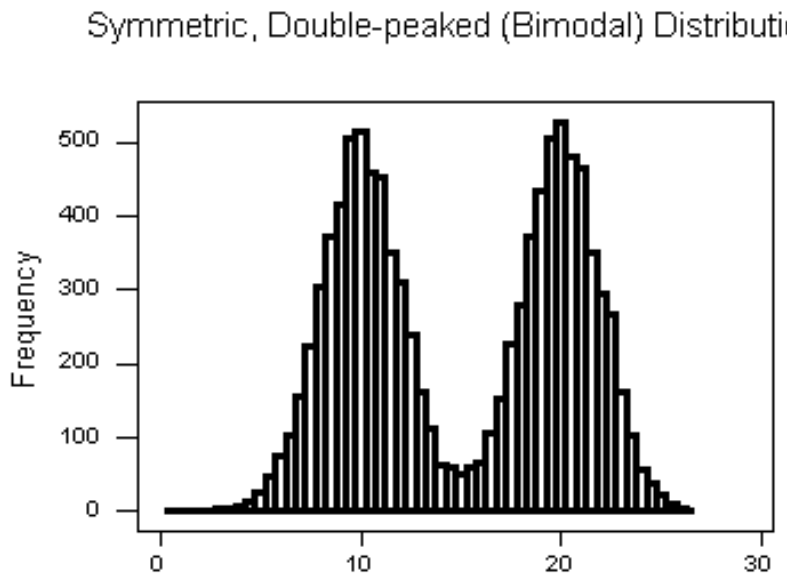
- **Symmetry/Skewness** of the distribution
- **Peakedness (modality)**
  - The number of peaks (modes) the distribution has

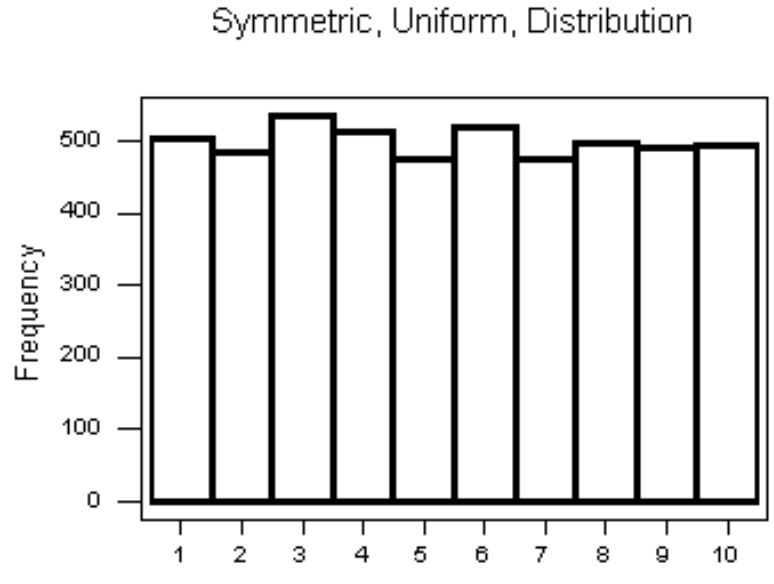




Describing distributions [Internet]. [cited 2021 Oct 1]. Available from: https://bolt.mph.ufl.edu/6050-6052/unit-1/one-quantitative-variable-introduction/describing-distributions/







Describing distributions [Internet]. [cited 2021 Oct 1]. Available from: https://bolt.mph.ufl.edu/6050-6052/unit-1/one-quantitative-variable-introduction/describing-distributions/

Describing Distributions

- Shape
- **Center**
- Spread
- Outliers

Center

- Mean
- Median
- Mode

Center - Mean

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

Cholesterol levels of 40 patients:

213, 174, 193, 196, 220, 183, 194, 200, 192, 200, 200, 199, 178, 183, 188, 193, 187, 181, 193, 205, 196, 211, 202, 213, 216, 206, 195, 191, 171, 194, 184, 191, 221, 212, 221, 204, 204, 191, 183, 227

$$\bar{x} = \frac{213+174+\ldots+227}{40} = 197.625$$

Mean

If $y_i = x_i + c$ (c is a constant) $\bar{y} = \bar{x} + c$

$$\bar{x} = \frac{213+174+...+227}{40} = 197.625$$

$$\bar{y} = \frac{(213+5)+(174+5)+...+(227+5)}{40} = 202.625$$

Mean

If $y_i = x_i \; x \; c$ (c is a constant) $\quad \bar{y} = \bar{x} \; x \; c$

x: 1, 2, 3, 4, 5

y: 3 (1 * 3), 6 (2 * 3), 9 (3 * 3), 12 (4 * 3), 15 (5 * 3)
$\Rightarrow c = 3$

$\bar{x} = 3, \; \bar{y} = 9 \Rightarrow \bar{y} = 3 * \bar{x}$

Mean

- Even a small change in a single value affects the mean

213, 174, 193, 196, 220, 183, 194, 200, 192, 200, 200, 199, 178, 183, 188, 193, 187, 181, 193, 205, 196, 211, 202, 213, 216, 206, 195, 191, 171, 194, 184, 191, 221, 212, 221, 204, 204, 191, 183, 227

- If the maximal value was 700 (instead of 227), the mean would be 209.45 (instead of 197.625)

Median

- It is calculated as the:
  - middle value of the sorted values (if n is odd)
  - average of two middle values of the sorted values (if n is even)

2, 5, 3, 10, 4

2, 3, 4, 5, 10 => median = 4

5, 3, 10, 4

3, 4, 5, 10 => median = 4.5

Median

Cholesterol levels of 40 patients:

Original data

213, 174, 193, 196, 220, 183, 194, 200, 192, 200, 200, 199, 178, 183, 188, 193, 187, 181, 193, 205, 196, 211, 202, 213, 216, 206, 195, 191, 171, 194, 184, 191, 221, 212, 221, 204, 204, 191, 183, 227

Sorted dataa

171, 174, 178, 181, 183, 183, 183, 184, 187, 188, 191, 191, 191, 192, 193, 193, 193, 194, 194, 195, 196, 196, 199, 200, 200, 200, 202, 204, 204, 205, 206, 211, 212, 213, 213, 216, 220, 221, 221, 227

Mean = 197.625

Median = 195.5

Median

171, 174, 178, 181, 183, 183, 183, 184, 187, 188, 191, 191, 191, 192, 193, 193, 193, 194, 194, 195, 196, 196, 199, 200, 200, 200, 202, 204, 204, 205, 206, 211, 212, 213, 213, 216, 220, 221, 221, **227**

Mean = 197.625

Median = 195.5

171, 174, 178, 181, 183, 183, 183, 184, 187, 188, 191, 191, 191, 192, 193, 193, 193, 194, 194, 195, 196, 196, 199, 200, 200, 200, 202, 204, 204, 205, 206, 211, 212, 213, 213, 216, 220, 221, 221, **700**

Mean = 209.45

Median = 195.5

Mode

- The mode is the value that appears most often in a set of data values

- Systolic blood pressures of 12 patients:

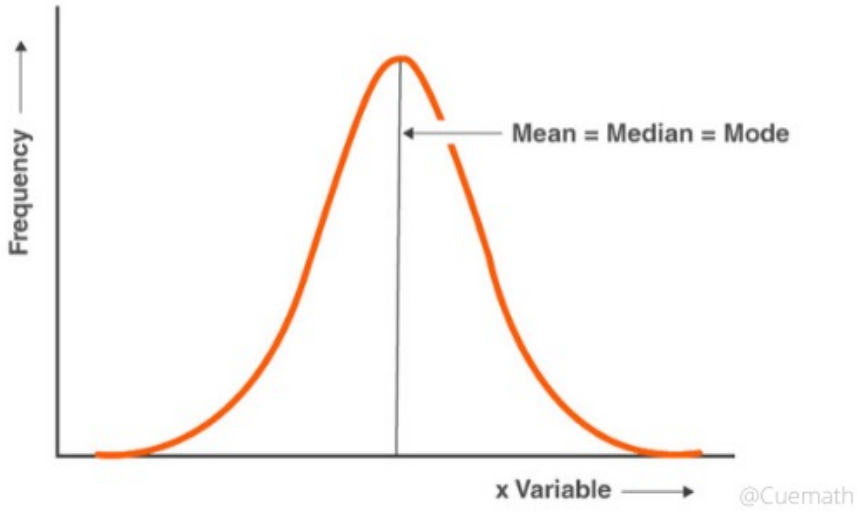
90, 80, **100**, 110, **100**, 120, **100**, 90, **100**, 110, 120, 110

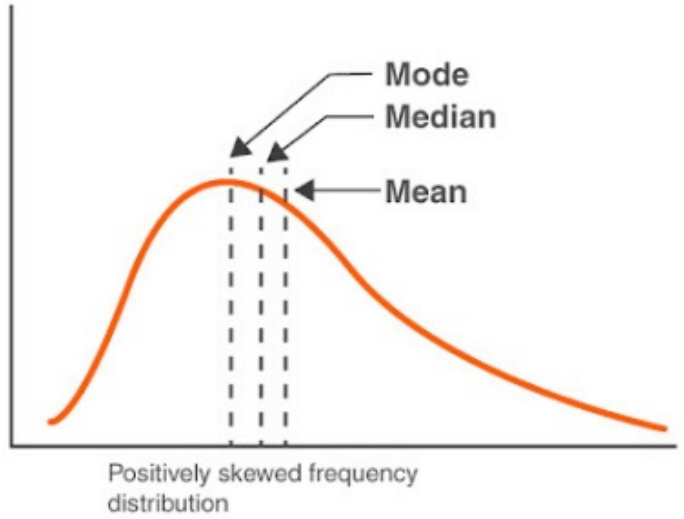
Mode = 100

Mean = 102.5

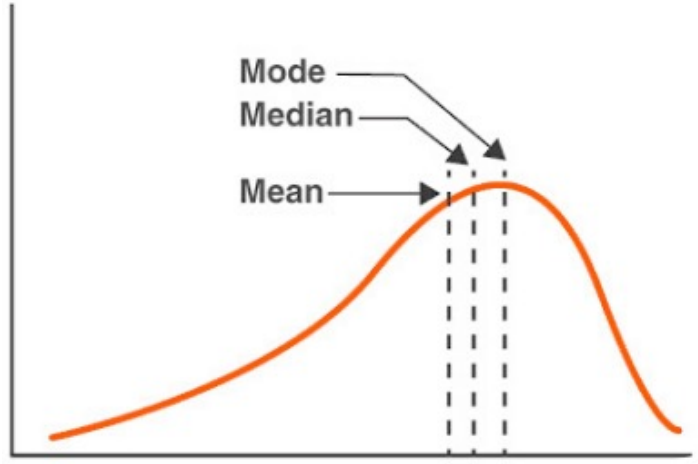
Median = 100

Mean – Median – Mode Relationship





Positively skewed frequency distribution

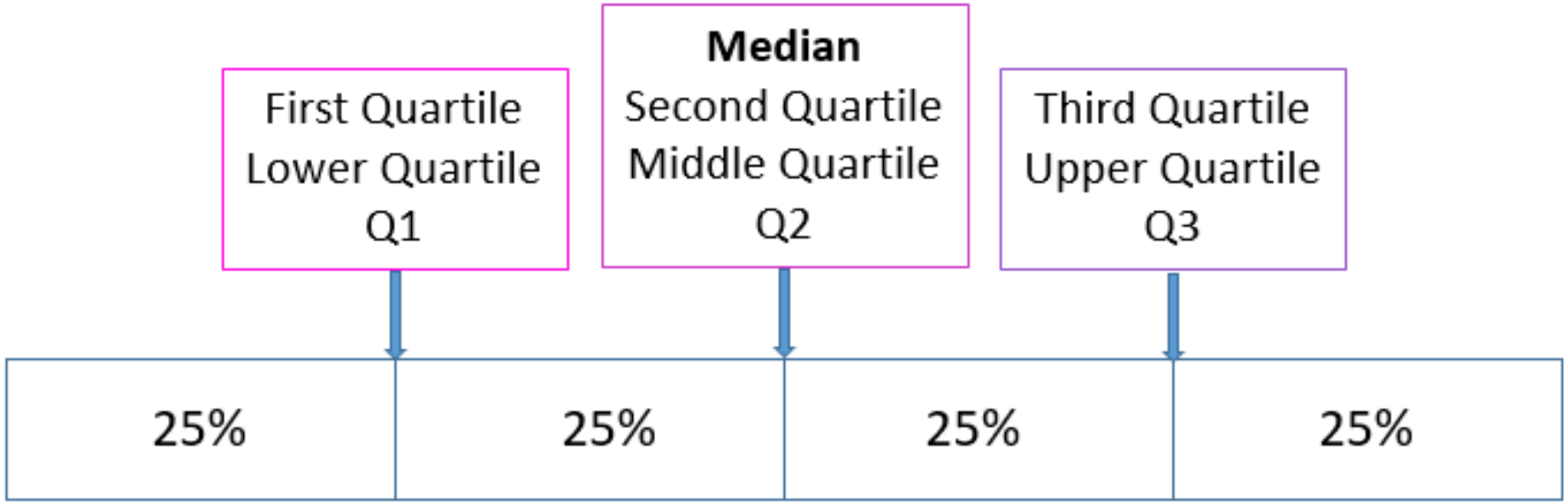


Negatively skewed frequency distribution

Describing Distributions

- Shape
- Center
- **(Measures of position)**
- Spread
- Outliers

Quartiles



Median, quartiles, percentiles(Video lessons, examples, solutions) [Internet]. www.onlinemathlearning.com. [cited 2021 Oct 4]. Available from: https://www.onlinemathlearning.com/quartile.html

Quartiles

- Recovery duration of 8 patients treated with a novel drug:

30, 20, 24, 40, 65, 70, 10, 62

10, 20, 24, 30, 40, 62, 65, 70

$Q_2 = 35$

x_1	x_2	x_3	x_4	x_5	x_6	x_7	x_8
10	20	24	30	40	62	65	70

$$Q_1 = \frac{20+24}{2} = 22$$

$$Q_3 = \frac{62+65}{2} = 63.5$$

Quartiles

- Systolic blood pressure measurements of 9 patients:

151, 124, 132, 170, 146, 124, 113, 111, 134

x_1	x_2	x_3	x_4	x_5	x_6	x_7	x_8	x_9
111	113	124	124	132	134	146	151	170

Q_2

$$Q_1 = \frac{113 + 124}{2} = 118.5 \qquad Q_3 = \frac{146 + 151}{2} = 148.5$$

Percentiles - Definition

$100 * p$ percentile ($0 \leq p \leq 1$) is the data value for which:

- at least $100 * p$ of the data values are less than or equal to it
- at least $100 * (1 - p)$ of the data values are greater than or equal to it

* If there are two values that satisfy the above conditions, the average of these values is taken as the $100 * p$ percentile

Percentiles - Algorithm

- Sort values in ascending order
- Calculate n * p
  - If n * p is not an integer, take the smallest integer greater than n * p
  - If n * p is an integer take the average of n * p^{th} and $(n * p + 1)^{th}$ values

Percentiles - Example

- Sorted data: 171, 174, 178, 181, 183, 183, 183, 184, 187, 188, 191, 191, 191, 192, 193, 193, 193, 194, 194, 195, 196, 196, 199, 200, 200, 200, 202, 204, 204, 205, 206, 211, 212, 213, 213, 216, 220, 221, 221, 227

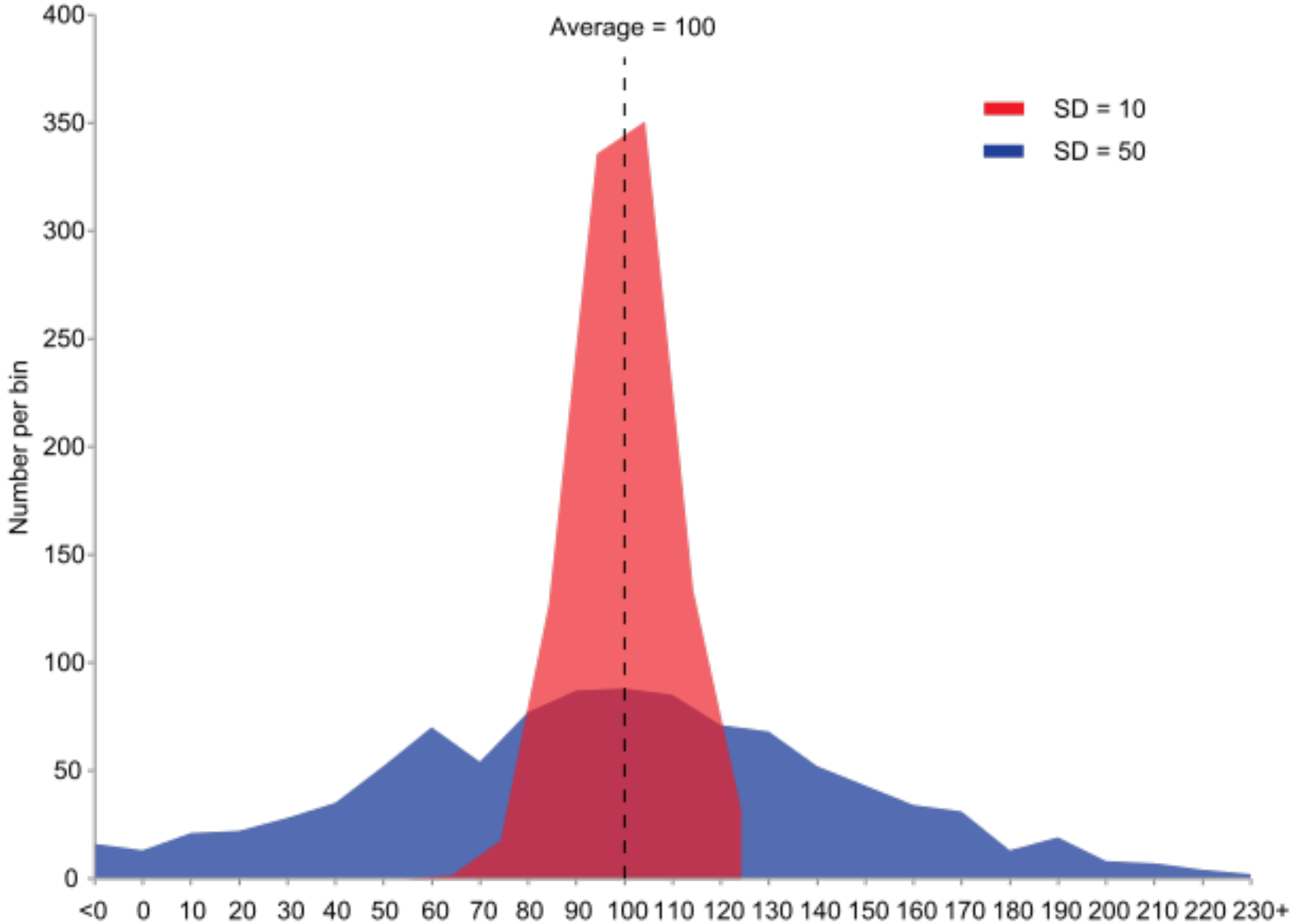
- 25th percentile (1st quartile, Q1): 189.5 (40 * 0.25 = 10)
- 50th percentile (median, Q2): 195.5 (40 * 0.5 = 20)
- 75th percentile (3rd quartile, Q3): 205.5 (40 * 0.75 = 30)
- 90th percentile : 218 (40 * 0.9 = 36)
- 95th percentile: 221 (40 * 0.95 = 38)
- 97.5th percentile: 224 (40 * 0.975 = 39)

Describing Distributions

- Shape
- Center
- **Spread**
- Outliers

Measures of Spread

- The distances of the values to the center differ
  - The degree of these differences constitute the spread of the distribution
- Two distributions may have the same mean/median/mode and differ in terms of spread


Average = 100
SD = 10
SD = 50
Number per bin
400
350
300
250
200
150
100
50
0
<0 0 10 20 30 40 50 60 70 80 90 100 110 120 130 140 150 160 170 180 190 200 210 220 230+

Range

- The difference between the maximal and minimal value

$$R = maximum - minimum$$

e.g., The ages of 12 arthritis patients:

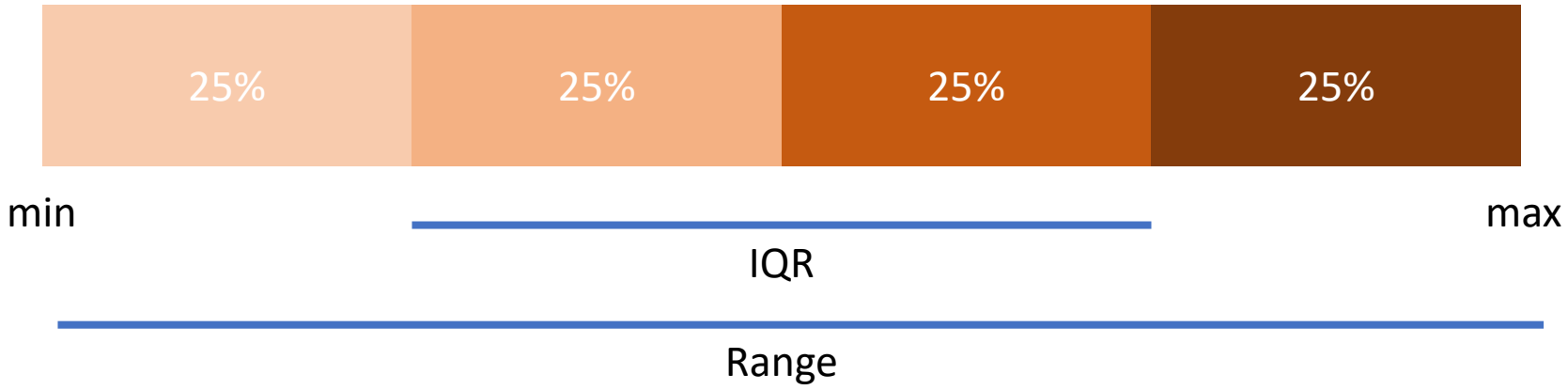
30, 12, 15, 22, 40, 55, 20, 58, 25, 60, 23, 72

$$R = 72 - 12 = 60$$

Inter-Quartile Range

- The range quantifies the variability by using the range covered by **all** the data
- the **Inter-Quartile Range (IQR)** measures the spread of a distribution by describing the range covered **by the middle 50%** of the data

$$\boldsymbol{IQR} = Q3 - Q1$$



Inter-Quartile Range

- Recovery durations of 8 patients in days:

  30, 20, 24, 40, 65, 70, 10, 62

  10, 20, 24, 30, 40, 62, 65, 70

x_1	x_2	x_3	x_4	x_5	x_6	x_7	x_8
10	20	24	30	40	62	65	70

$$Q_1 = \frac{20+24}{2} = 22 \qquad Q_3 = \frac{62+65}{2} = 63.5$$

$$\text{IQR} = 63.5 - 22 = 41.5$$

Variance and Standard Deviation

- Variance
  - A measure of how distant observations are from the mean
  - Population variance: σ^2
  - Sample variance: s^2
- Because **the unit of variance is quadratic**, standard deviation is more widely used

- Standard deviation (sd)
  - Defined as the square-root of variance
  - Population sd: σ
  - Sample sd: s

Sample Variance and Standard Deviation

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

Variance and Standard Deviation

Ages of 6 patients in a study:

10, 15, 22, 26, 31, 40

$\bar{x}$ = (10 + 15 + 22 + 26 + 31 + 40) / 6 = 24

$$s^2 = \frac{(10-24)^2+(15-24)^2+(22-24)^2+(26-24)^2+(31-24)^2+(40-24)^2}{6-1} = 118$$

$$s = \sqrt{s^2} = \sqrt{118} = 10.863$$

Units

- Mean: same unit with the data
- Median: same unit with the data
- Mode: same unit with the data
- Quartiles: same unit with the data
- Percentiles: same unit with the data
- Variance: square of the unit of the data
- Standard deviation: same unit with the data

Describing Distributions

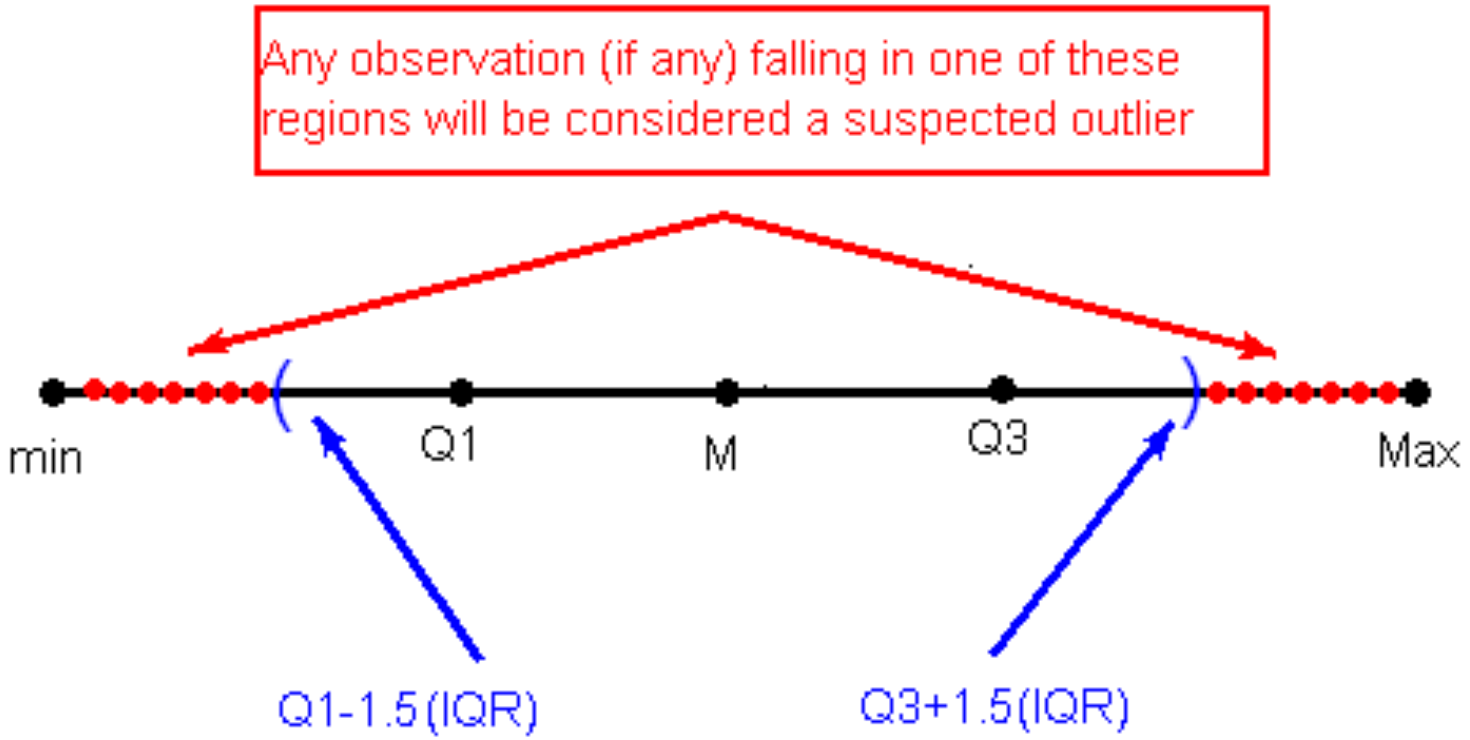
- Shape
- Center
- Spread
- **Outliers**

Outliers

- Extreme observations that are distant from the rest of the data

- For
  - Lower Limit = Q_1 - 1.5 * IQR
  - Upper Limit = Q_3 + 1.5 * IQR
- Outliers are defined as any value(s) larger than the upper limit or smaller than the lower limit

Outliers



Outliers [Internet]. [cited 2021 Oct 4]. Available from: https://bolt.mph.ufl.edu/6050-6052/unit-1/one-quantitative-variable-introduction/understanding-outliers/

Outliers – Cholesterol Level Example

- Sorted data: 171, 174, 178, 181, 183, 183, 183, 184, 187, 188, 191, 191, 191, 192, 193, 193, 193, 194, 194, 195, 196, 196, 199, 200, 200, 200, 202, 204, 204, 205, 206, 211, 212, 213, 213, 216, 220, 221, 221, 227

- 25^{th} percentile (1st quartile, Q_1): 189.5 (40 * 0.25 = 10)
- 75th percentile (3rd quartile, Q_3): 205.5 (40 * 0.75 = 30)
- IQR = 205.5 - 189.5 = 16

- LL = Q_1 - 1.5 * IQR = 189.5 - 1.5 * 16 = 165.5
- UL = Q_3 + 1.5 * IQR = 205.5 + 1.5 * 16 = 229.5

- **No outliers**

Outliers – Cholesterol Level Example (cont.)

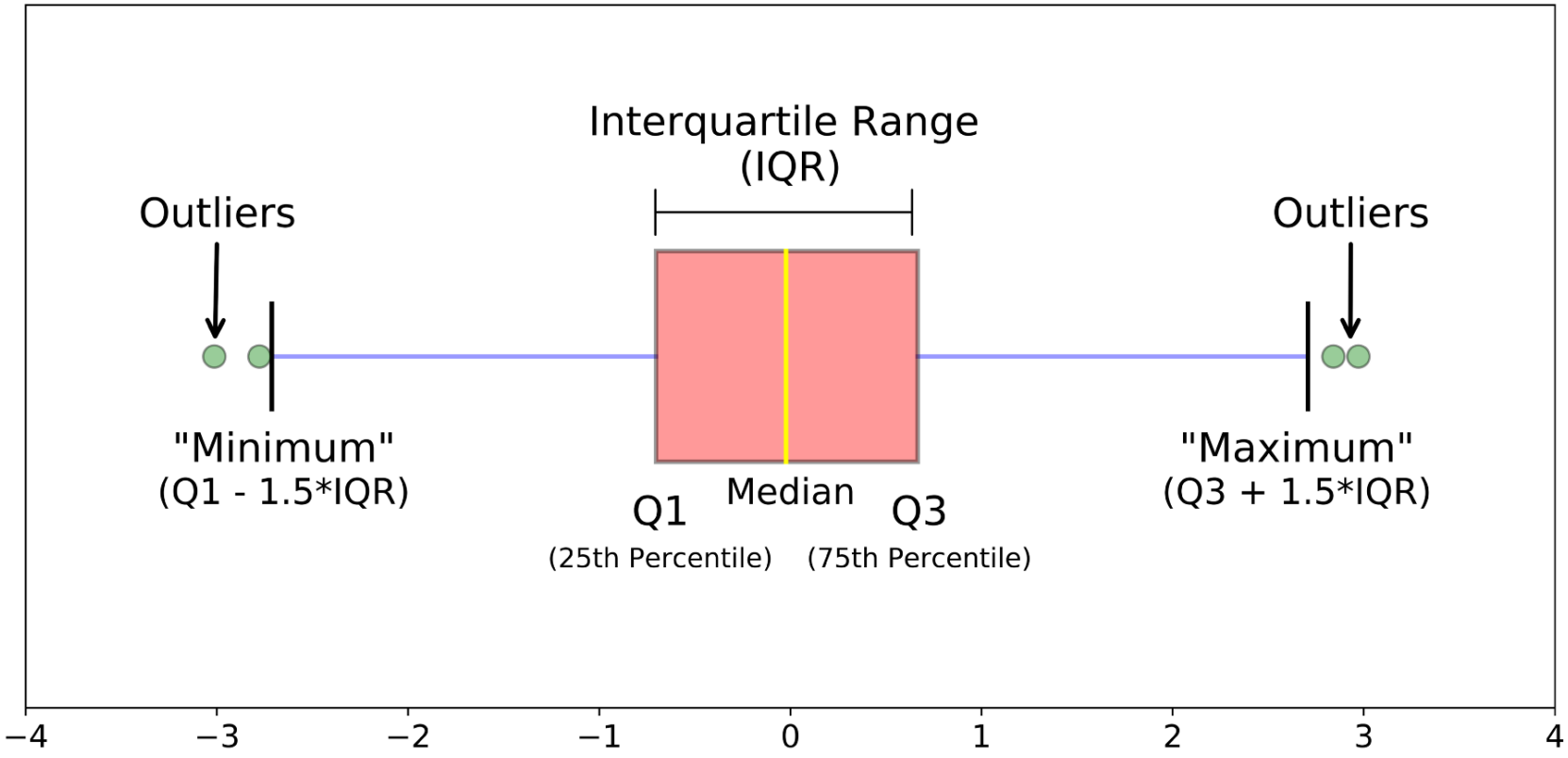
- Sorted data: 171, 174, 178, 181, 183, 183, 183, 184, 187, 188, 191, 191, 191, 192, 193, 193, 193, 194, 194, 195, 196, 196, 199, 200, 200, 200, 202, 204, 204, 205, 206, 211, 212, 213, 213, 216, 220, 221, 221, **300**

- 25^{th} percentile (1st quartile, Q_1): 189.5 (40 * 0.25 = 10)
- 75th percentile (3rd quartile, Q_3): 205.5 (40 * 0.75 = 30)
- IQR = 205.5 - 189.5 = 16

- LL = Q_1 - 1.5 * IQR = 189.5 - 1.5 * 16 = 165.5
- UL = Q_3 + 1.5 * IQR = 205.5 + 1.5 * 16 = 229.5

- **300 > UL => outlier**

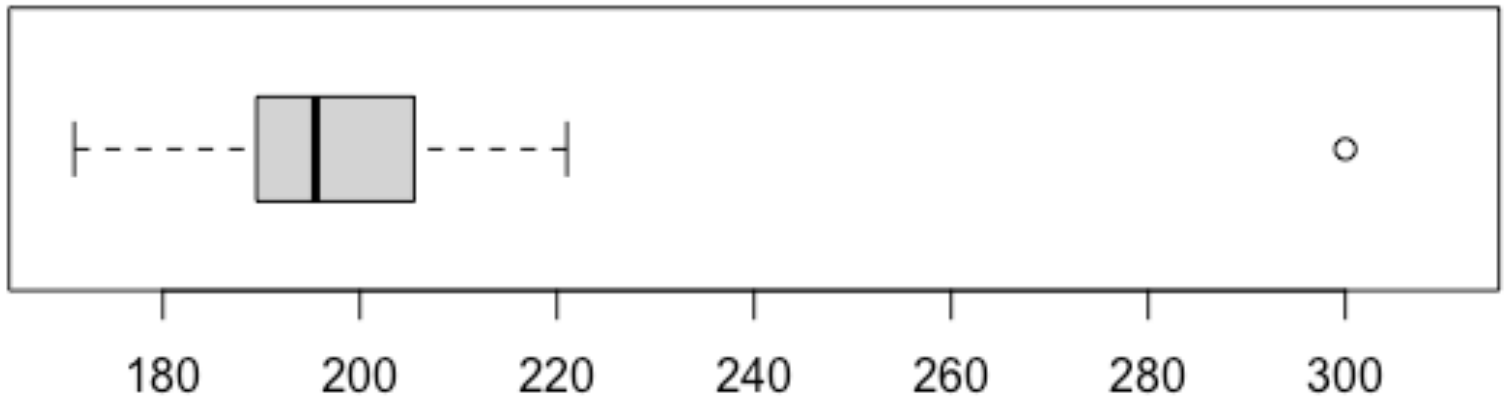
Box Plot

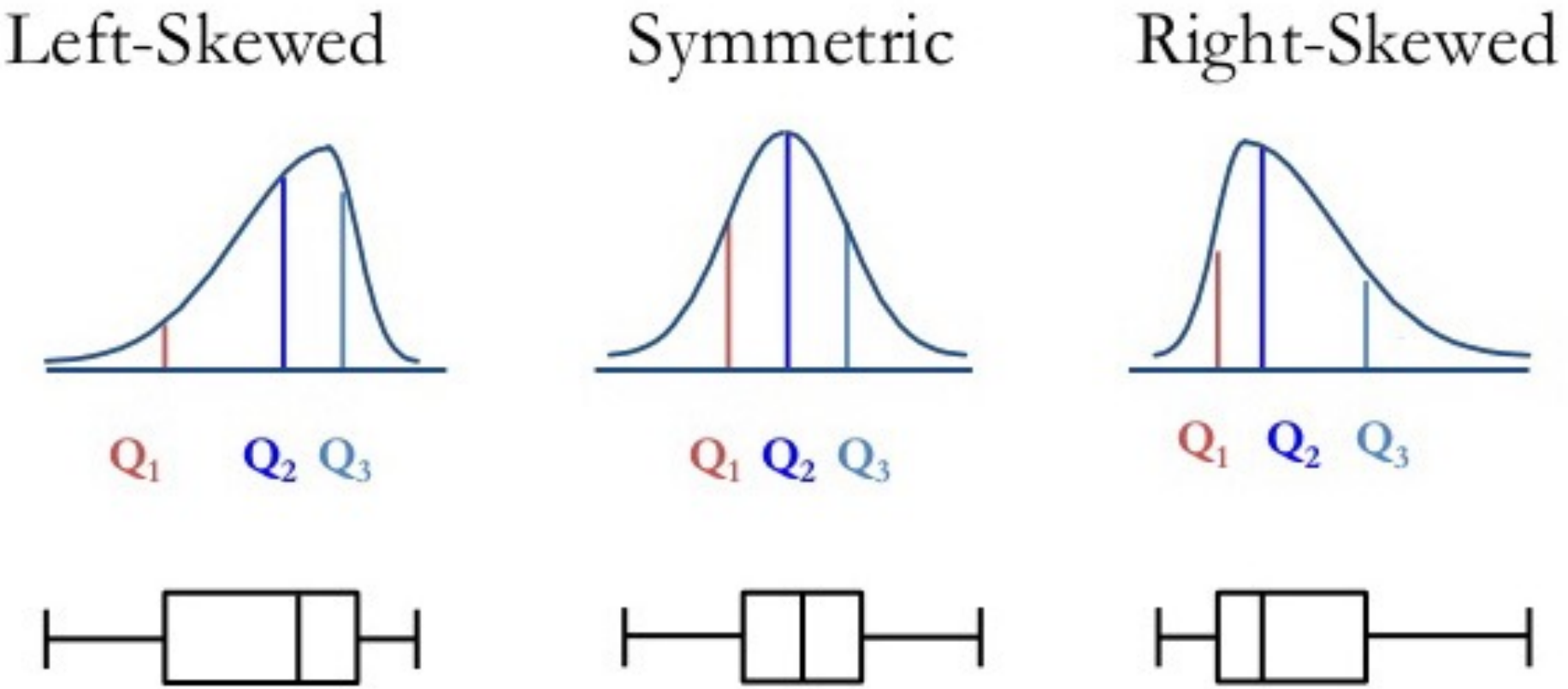


Galarnyk M. Understanding boxplots [Internet]. Medium. 2020 [cited 2021 Oct 4]. Available from: https://towardsdatascience.com/understanding-boxplots-5e2df7bcbd51

Box Plot – Example

- 171, 174, 178, 181, 183, 183, 183, 184, 187, 188, 191, 191, 191, 192, 193, 193, 193, 194, 194, 195, 196, 196, 199, 200, 200, 200, 202, 204, 204, 205, 206, 211, 212, 213, 213, 216, 220, 221, 221, **300**





Box plot | simply psychology [Internet]. [cited 2021 Oct 4]. Available from: https://www.simplypsychology.org/boxplots.html

Five-number Summary

1. the sample minimum (smallest observation)
2. the lower quartile or first quartile
3. the median (the middle value)
4. the upper quartile or third quartile
5. the sample maximum (largest observation)

Brief Summary

- Shape of a distribution can be described using skewness and modality
- Center of a distribution can be described using mean, median, mode
  - Median is more robust to outliers
- Quartiles and percentiles can be used to partition the data
- Variance and standard deviation are the most frequently used measures of spread
- Outliers can be defined based on Q1, Q3 and IQR
- Box plots can be used to display the distribution of a continuous variable
  - displays Q1, median, Q3, outliers