Cardiovascular risk factor profiles in familial hypercholesterolemia patients with and without genetic mutation compared to a nationally representative sample of adults in a high-risk European country

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Background There is a paucity of data on the distribution of cardiovascular risk factors in patients with familial hypercholesterolemia (FH) as compared to the general population. The aim of the study was to compare cardiovascular risk factors in a cohort of FH patients to the representative sample of adults in Poland who represent a high–cardiovascular risk European region.

Methods We compared the distribution of risk factors in 1,382 individuals with FH phenotype referred for genetic testing between 2006 and 2014 to the National Centre of Familial Hypercholesterolemia in Gdansk, Poland. The cohort was comprised of 637 positive FH(+) and 745 negative FH(–) patients who were compared to a nationally representative sample of 2,413 adults age 18-79, standardized by age and sex, from the NATPOL 2011 study (NATPOL). We analyzed patients' distribution of history of atherosclerotic cardiovascular disease (ASCVD) and standard risk factors including total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol, triglycerides, systolic and diastolic blood pressure (SBP, DBP), body mass index, smoking, and diabetes.

Results FH(+) patients (mean age 45.6 years) had the highest LDL-C of 241.7 mg/dL (95% CI 234.8-248.5) compared to 206.1 mg/dL (200.5-211.7) in FH(–) patients (mean age 48.2) and 126.2 mg/dL (124.8-127.6) in NATPOL. Mean SBP was the lowest in FH(+) patients at 128.7 mm Hg (126.7-130.7) compared to 133.4 mm Hg (132.6-134.3) in NATPOL and 134.4 mm Hg (132.3-136.5) in FH(–). No differences were found in the prevalence of diabetes and body mass index. Smoking was less common in FH(+) at 12.4% (9.4-15.4) compared to both FH(–) and NATPOL: 20.4% (16.6-24.1) and 28.4% (26.6-30.2), respectively. The prevalence of individuals with a history of ASCVD in both FH(+) and FH(–) was nearly 3-fold higher compared to NATPOL: 26% (21.8-30.1) and 26.6% (22.2-30.9) versus 9.5% (8.3-10.7), respectively.

Conclusions The FH(+) patients had significantly higher mean LDL-C, but the levels of nonlipid factors were lower or similar compared to the other groups. Both FH(+) and FH(–) were characterized by a heavy burden of ASCVD. This suggests that cholesterol, and no other risk factors, is a key contributor to cardiovascular risk in patients with FH, especially those with genetic mutation. (Am Heart J 2019;218:32-45.)

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Submitted September 13, 2019; accepted September 13, 2019.

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0002-8703

https://doi.org/10.1016/j.ahj.2019.09.007

Diagnosis of familial hypercholesterolemia (FH) is associated with a many-fold increase in mortality due to atherosclerotic cardiovascular disease (ASCVD),[1] but other risk factors are also likely to be at play. Although technical advances in genetic testing have significantly increased its effectiveness,[2,3] the proportion of patients with an appropriately made diagnosis of FH is still not optimal.[4] The FH population is still underdiagnosed,[4] but estimated numbers of FH patients are high (about 136,000 adults in Poland[5] and 834,500 in the United States[6]).

Table I. Characteristics of FH patients with positive and negative genetic test result compared to age- and sex-standardized nationally representative sample of the NATPOL 2011 survey

Parameters*	FH+ (95% CI)	FH– (95% CI)	NATPOL 2011 (95% CI)
Age (y)	45.6 (44.3-47.0)	48.2 (47.0-49.4)	46.4 (46.0-47.2)
Sex (% male)	37.4 (33.0-41.8)	41.9 (37.4-46.4)	39.6 (37.6-41.6)
TC (mg/dL)	325.9 (318.7-333.1)	296 (289.3-302.6)	201.2 (199.5-202.9)
HDL-C (mg/dL)	56.9 (55.4-58.4)	57.3 (55.7-58.8)	50.7 (50.2-51.3)
Non–HDL-C (mg/dL)	269.2 (261.7-276.7)	236.5 (229.9-243.1)	150.5 (148.9-152.1)
TGs (mg/dL)†	112 (80-155)	133 (97-185)	100 (74-141)
LDL-C (mg/dL)	241.7 (234.8v248.5)	206.1 (200.5-211.7)	126.2 (124.8-127.6)
SBP (mm Hg)	128.7 (126.7-130.7)	134.4 (132.3-136.5)	133.4 (132.6-134.3)
DBP (mm Hg)	78.4 (77.3-79.6)	81 (79.8-82.2)	81.9 (81.4-82.3)
BMI (kg/m^2)	26.1 (25.6-26.6)	26.7 (26.2-27.1)	26.6 (26.4v26.8)
Hypercholesterolemia (TC ≥ 190 mg/dL or statin)	100	100	64.2 (62.3-66.1)
Overweight (BMI ≥ 25 kg/m^2)	55 (50-59.9)	58.3 (53.5v63.2)	59.6 (57.6-61.6)
Obesity (BMI ≥ 30 kg/m^2)	19.1 (15.2v23)	21 (16.9v25)	22.4 (20.7v24.1)
Uncontrolled hypertension (mean SBP ≥ 140 mm Hg)	42 (37.4-46.6)	53.9 (49.2-58.6)	41.2 (39.2-43.2)
Diabetes mellitus (%)	5 (3-7)	8.6 (6v11.2)	4.8 (3.9-5.7)
Active smoking (%)	12.4 (9.4-15.4)	20.4 (16.6-24.1)	28.4 (26.6-30.2)
ASCVD (%)	26 (21.8-30.1)	26.6 (22.2-30.9)	9.5 (8.3-10.7)
% on hypolipemic treatment	28.3 (23.8-32.8)	22.3 (17.9-26.6)	11.7 (10.5-13.0)

* Numbers represent mean or percentage with a corresponding 95% CI.
† Median with 25th and 75th percentile.

Some data indicate that in FH patients with an identified mutation, the risk of premature coronary heart disease is higher compared to patients without a mutation.[7] However, no data are available regarding the levels of risk factors in patients with and without mutation compared to an adult cohort representing the general population.

Methods

The FH group for this analysis included 1,382 subjects aged 18-79 years referred from 2006 to 2014 to the National Centre of FH in Gdansk with a Dutch Lipid Clinic Network (DLCN) score of at least 3 who underwent genetic testing for FH mutation. In 637 patients (238 men, 399 women), the presence of LDRL, ApoB, or PCSK9 gene mutation was found (FH[+]: mean DLCN score 6.71 ± 3.21). In 745 patients (313 men, 432 women), genetic tests were negative (FH[−]: mean DLCN 5.05 ± 2.64). Blood pressure (BP) measurements were performed with the participant in a seated position, on the right upper arm, after rest and at 2-minute intervals; the average of 2 measurements constituted the result. BP readings were taken using fully automatic oscillometric BP measuring devices certified by the British Hypertension Society and the European Society of Hypertension. Lipid profile levels were determined using standardized laboratory methods. For consistency across cohorts, low-density lipoprotein cholesterol (LDL-C) was calculated using the Friedewald equation. Cigarette smoking status was ascertained by self-report. *Hypolipemic treatment* was defined, consistently with clinical practice in Poland at the time, as statin treatment with simvastatin, atorvastatin, or rosuvastatin. Antihypertensive treatment was ascertained based on a combination of medical record and self- report.

No meaningful differences in the distribution of standard ASCVD risk factors were found between men and women in the FH cohorts (histograms 1-9 in Appendix); therefore, for clarity of the presentation, we combined data for both sexes in the primary analysis.

The NATPOL 2011 survey was designed as a cross-sectional study of ASCVD risk factors and carried out on a representative sample of 2,413 Polish residents aged 18-79 years (1,168 men; 1,245 women). The biochemical methods for blood tests, as well as anthropometric and blood pressure measurements, were described in details elsewhere.[8]

Statistical analysis

In the FH(+) and FH(−) cohorts, the results are presented as means with 95% CIs for continuous variables. Proportions with 95% CIs are reported for categorical variables. These results are compared with the NATPOL cohort. To avoid differences in the sex and age structure, the NATPOL sample was standardized to the same structure as the combined FH(+) and FH(−) cohorts.

Table II. Characteristics of FH patients with genetic mutation and with or without ASCVD

Paremeters*	FH+ with ASCVD (95% CI)	FH+ without confirmed ASCVD (95% CI)
Age (y)	55.8 (53.8-57.8)	42.2 (40.5-43.9)
Sex (% male)	44 (34.7-53.4)	34.7 (29.4-40)
TC (mg/dL)	338.5 (321.6-355.3)	323 (314.6-331.4)
HDL-C (mg/dL)	51.5 (48.9-54.1)	59 (57-60.9)
Non–HDL-C (mg/dL)	289.8 (272.9-306.6)	263 (254.1-271.9)
LDL-C (mg/dL)	256.4 (240.8-272)	238.4 (230.2-246.6)
SBP (mm Hg)	130.8 (126.2-135.5)	128.5 (126.2-130.7)
DBP (mm Hg)	78.4 (75.8-81.1)	78.4 (77.2-79.7)
BMI (kg/m^2)	27.9 (27-28.7)	25.3 (24.8-25.8)
Overweight (BMI $\geq$ 25 kg/m^2)	70.8 (61.3-80.3)	49.1 (43.2-55)
Obesity (BMI $\geq$ 30 kg/m^2)	27 (17.7-36.2)	14.8 (10.6-19)
Uncontrolled hypertension (mean SBP $\geq$ 140 mm Hg)	67.3 (58.1-76.5)	33.2 (27.9-38.5)
Diabetes mellitus (%)	14.2 (7.5-20.8)	2.6 (0.8-4.4)
Active smoking (%)	12 (5.9-18.2)	12.6 (8.9-16.3)
ASCVD (%)	100	0
% on hypolipemic treatment	54.1 (42.6-65.5)	45.9 (34.5-57.4)

ASCVD: history of 1 or more of the following morbidities: myocardial infarction/ acute coronary syndrome, stable or unstable angina, coronary or other arterial revascularization, stroke, transient ischemic attack, or peripheral artery disease presumed to be of atherosclerotic origin.
*Reported numbers represent mean or percentage with a corresponding 95% CI.

Results

The mean LDL-C was the highest in FH(+) patients: 241.7 mg/dL (95% CI 234.8-248.5), followed by 206.1 mg/dL (200.5-211.7) in FH(−) and 126.2 mg/dL (124.8-127.6) in NATPOL. The differences in the mean total cholesterol (TC) level were similar (Table I). The high-density lipoprotein cholesterol (HDL-C) level was higher in both FH(+) and FH(−) compared to NATPOL; median triglyceride (TG) levels were the highest in FH(−) (Table I). Lipid-lowering treatment rates were the highest in FH(+): 28.3% (23.8%-32.8%), followed by 22.3% (17.9%-26.6%) in HF(−) and 11.7% (10.5%-13.0%) in NATPOL.

FH(+) patients had significantly lower mean systolic blood pressure (SBP) compared to the other 2 groups: 128.7 mm Hg (126.7-130.7) in FH(+) compared to 133.4 mm Hg (132.6-134.3) in NATPOL and 134.4 mm Hg (132.3-136.5) in FH(−). Similar differences were found for diastolic blood pressure (DBP) (Table I). No significant differences were found in mean body mass index (BMI) or the rates of overweight, obesity, and diabetes. Smoking was much less common among FH(+) patients: 12.4% (9.4-15.4) compared to both FH(−) and in particular NATPOL: 20.4% (16.6%-24.1%) and 28.4% (26.6%-30.2%), respectively.

The proportion of individuals with history of ASCVD was nearly 3-fold higher in both FH(+) and FH(−) compared to the general Polish population: 26.0% (21.8%-30.1%) and 26.6% (22.2%-30.9%) versus 9.5% (8.3-10.7), respectively. Among FH(+) patients, history of ASCVD was associated with higher levels of LDL-C, TC, blood pressure, and BMI and lower levels of HDL-C (Table II).

Discussion

In this report, we compared the levels of cardiovascular risk factors among individuals with FH(+) and FH(−) to those in the general population of the same age and sex in Poland, a high–ASCVD risk region in Europe. We found that, as expected, the FH (+) individuals had significantly higher mean TC, non–HDL-C, and LDL-C levels but also significantly lower SBP, DBP, and smoking rates as well as similar other risk factor levels. These findings confirm the typical characteristics of FH(+), that is, high LDL-C levels but normal TG levels. Our study expands this by showing that the burden of other risk factors is not more than in the general population, highlighting the need for effective focus on lipids to prevent ASCVD in FH patients.

Indeed, history of ASCVD was nearly 3-fold more common in patients with FH(+) compared to the general population. The percentage of FH (+) individuals with cardiovascular disease (27%) was lower than in a Canadian cohort (38%),[9] although Polish FH(+) patients were older and more often had hypertension. Another FH (+) cohort from France with a similar age structure to ours had a similar prevalence of history of ASCVD. It differed from our cohort in the much higher prevalence of smoking (31% vs 12%) but lower prevalence of hypertension (15% vs 42%).[10]

Our sample was younger than the American patients enrolled in the CASCADE-FH registry[11] (mean age 46 vs 51). Only 5.7% of CASCADE-FH patients underwent genetic testing. Compared to our FH cohorts, they were characterized by higher prevalence of smoking, hypertension, diabetes, and confirmed ASCVD. In

contrast, there were only small differences in TC and LDL-C levels.

We found that FH(−) patients had a similar rate of ASCVD to FH(+) cohort and that lipid levels were intermediate between FH(+) and the general population. In addition, the FH(−) group had a significantly higher mean TG level compared to FH(+) and NATPOL. This indicates a possible contribution of patients with mixed hyperlipidemia, which, similarly to FH(+), results in frequent ASCVD events despite lower LDL-C levels. A similar effect may be related to the fact that hypertension was significantly more common in FH(−) compared to the other 2 groups.

A question arises whether lower SBP, DBP, and smoking rates are secondary to a relatively high rate of ASCVD, that is, results from secondary prevention. Data shown in Table II indicate that this may not be the case because rates of other risk factors (overweight, obesity, hypertension, and diabetes) were significantly more common in FH(+) patients with a history of ASCVD.

Conclusions

1. FH(+) patients with a genetic mutation have significantly higher cholesterol levels compared to patients with FH phenotype but no mutation and adults from the general Polish population. However, their levels of other risk factors were similar or significantly lower (SBP, DBP, smoking). Still, the prevalence of ASCVD history in FH(+) was almost 3 times that of the general Polish population. This highlights the need for effective lipid control in this population.
2. FH(−) patients had a similar rate of ASCVD to FH(+) cohort and lipid levels that were intermediate between FH(+) and the general population. In addition, the FH (−) group had the highest median TG level. This indicates a possible contribution of patients with mixed hyperlipidemia, which, similarly to FH(+), results in frequent ASCVD events despite lower LDL-C levels. This suggests the need for active management of both lipid and nonlipid risk factors in these patients.

Acknowledgements

Author contributions

All authors have been involved in the study design, analysis, and manuscript revision. All authors read and approved the final manuscript. We wish to acknowledge Seanna Horan for valuable input in the preparation and editing of this manuscript.

We wish also to acknowledge to Prof A. Rynkiewicz, MD, PhD, for initiation of research on FH in Medical University of Gdansk, members of FH team in National Centre of Familial Hypercholesterolemia in Gdansk: J. Borowiec, MD; N. Malinowska- Gillis, MD; and physicians of 1st Department of Cardiology Medical University of Gdansk: R. Nowak, MD; A. Mickiewicz, MD, PhD, for valuable work on database; and B. Wasąg, MD, PhD, Head of Department of Biology and Medical Genetics, Medical University of Gdansk, for genetic diagnostics.

Access to data

K. Chlebus had full access to all of the data in the study and takes responsibility for its integrity and the accuracy of the data analysis.

Concept and design: Chlebus, Zdrojewski, Pencina,

Acquisition, analysis, or interpretation of data: Chlebus, Pajkowski, Romanowska- Kocejko, Gałąska, Chmara, Gruchała, Zdrojewski, Pencina.

Drafting of the manuscript: Chlebus, Zdrojewski, Pencina,

Critical revision of the manuscript for important intellectual content: Zdrojewski, Pencina, Chlebus.

Statistical analysis: Pencina.

Supervision: Pencina, Zdrojewski, Chlebus.

Sources of funding

This study was supported internally by the Medical University of Gdansk.

Role of the sponsor

The funding source had no role in design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; or decision to submit the manuscript for publication.

Conflict of interest disclosures

All authors will complete the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf.

All authors reported no relevant disclosures.

Data sharing

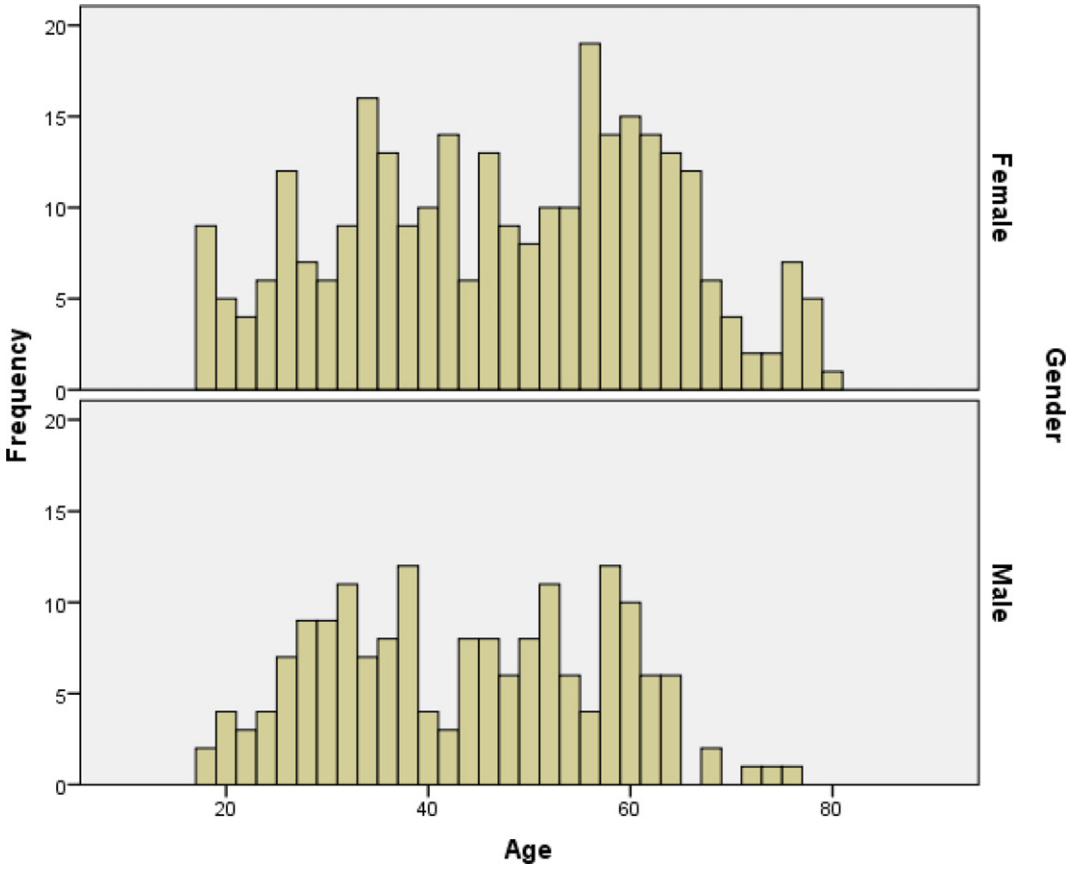
No additional data available.

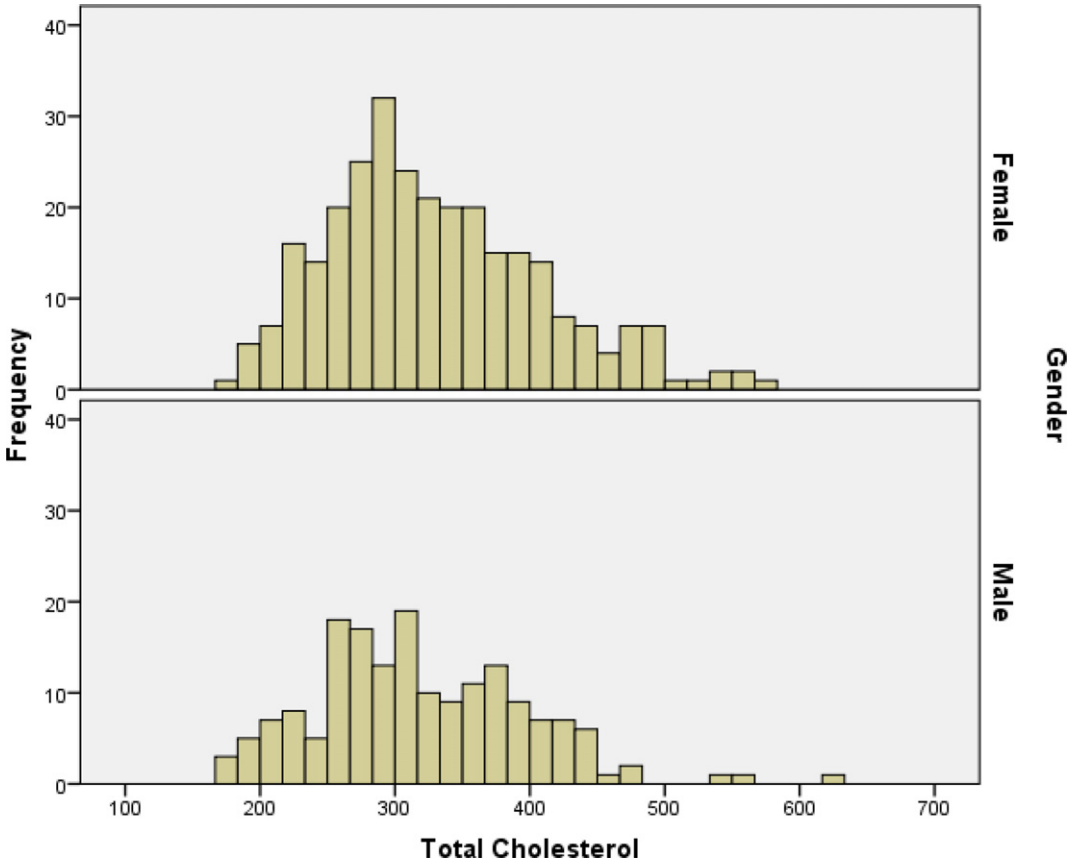
Transparency

The lead author affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

Appendix

Histograms (1-9) showing distribution of standard ASCVD risk factors in men and women.


Frequency
20
15
10
5
0
Female
Male
Gender
20
40
60
80
Age


Frequency
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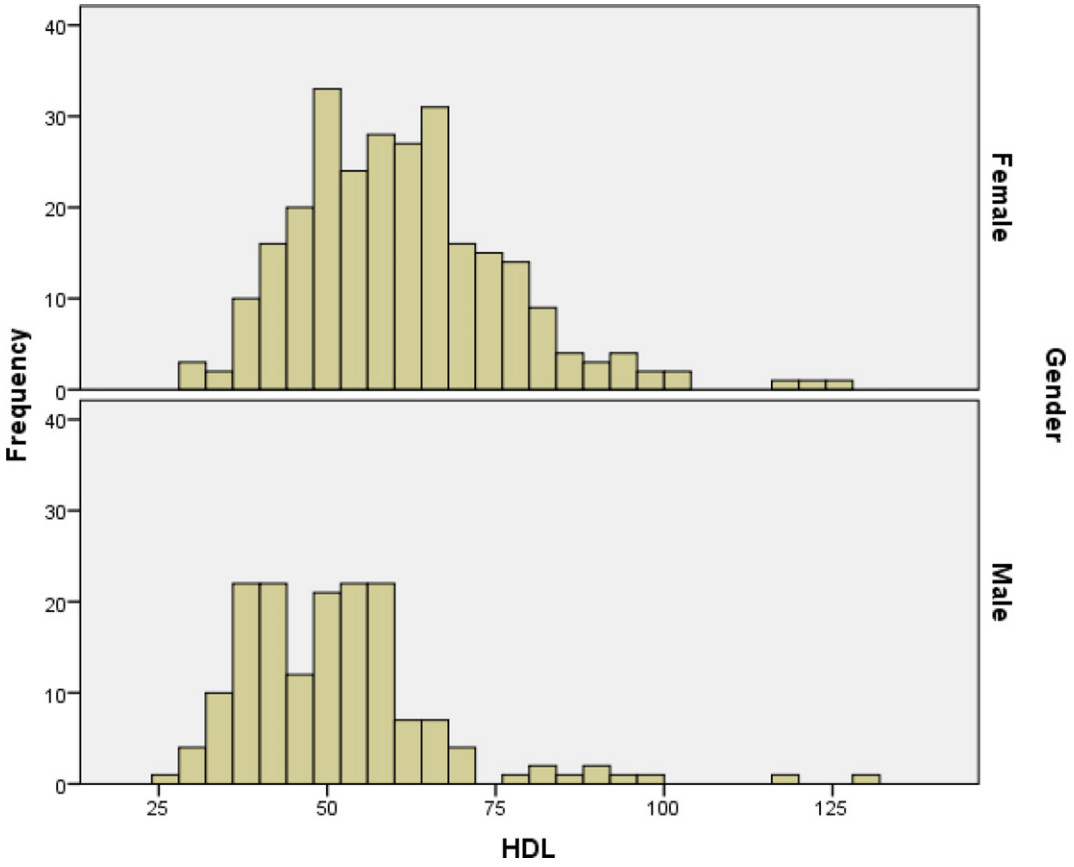
30
20
10
0
Female
Male
Gender
100
200
300
400
500
600
700
Total Cholesterol


Frequency
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10
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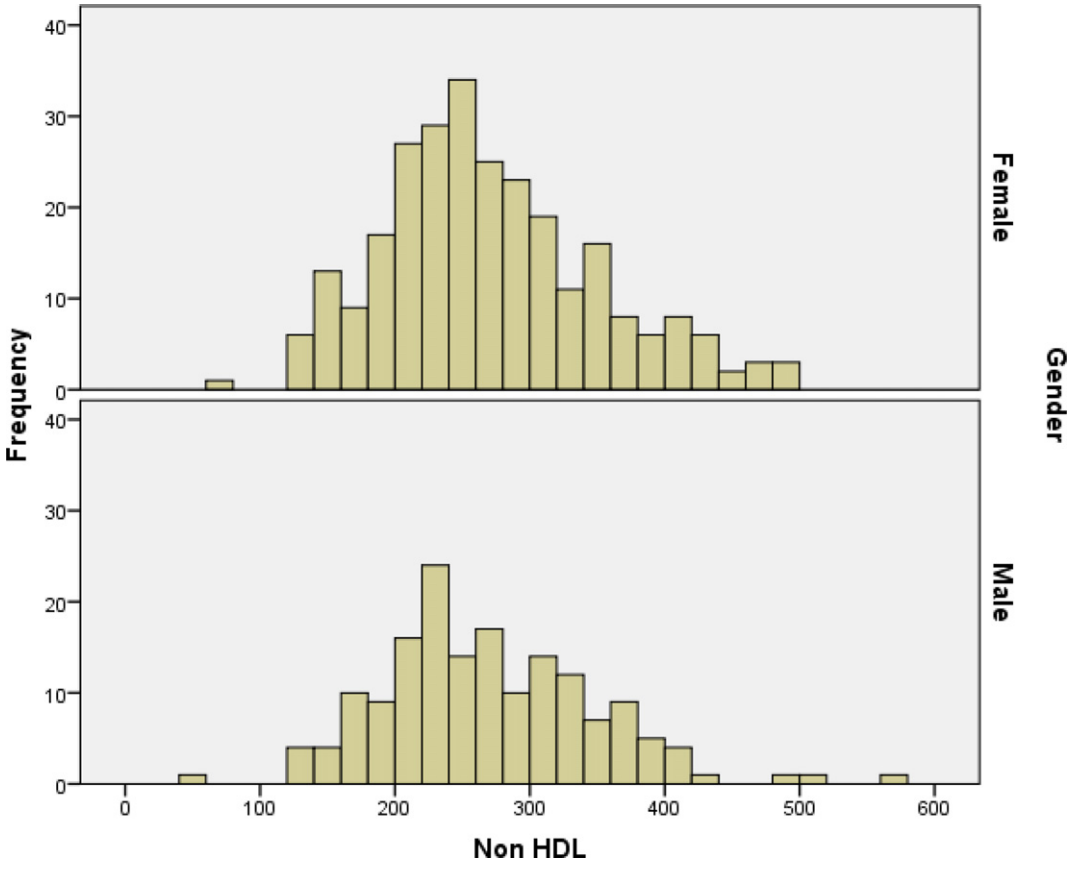
Female
Male
Gender
25
50
75
100
125
HDL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30
20
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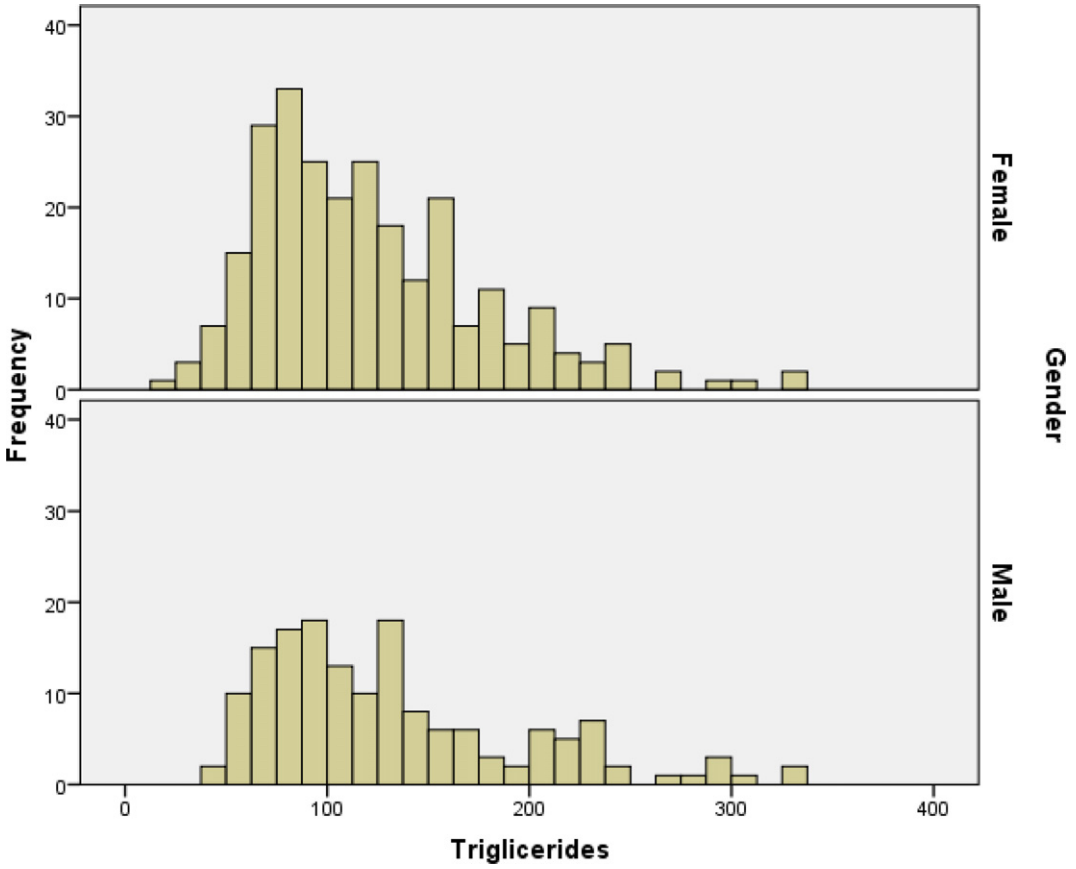
Female
Male
Gender
0
100
200
300
400
500
600
Non HDL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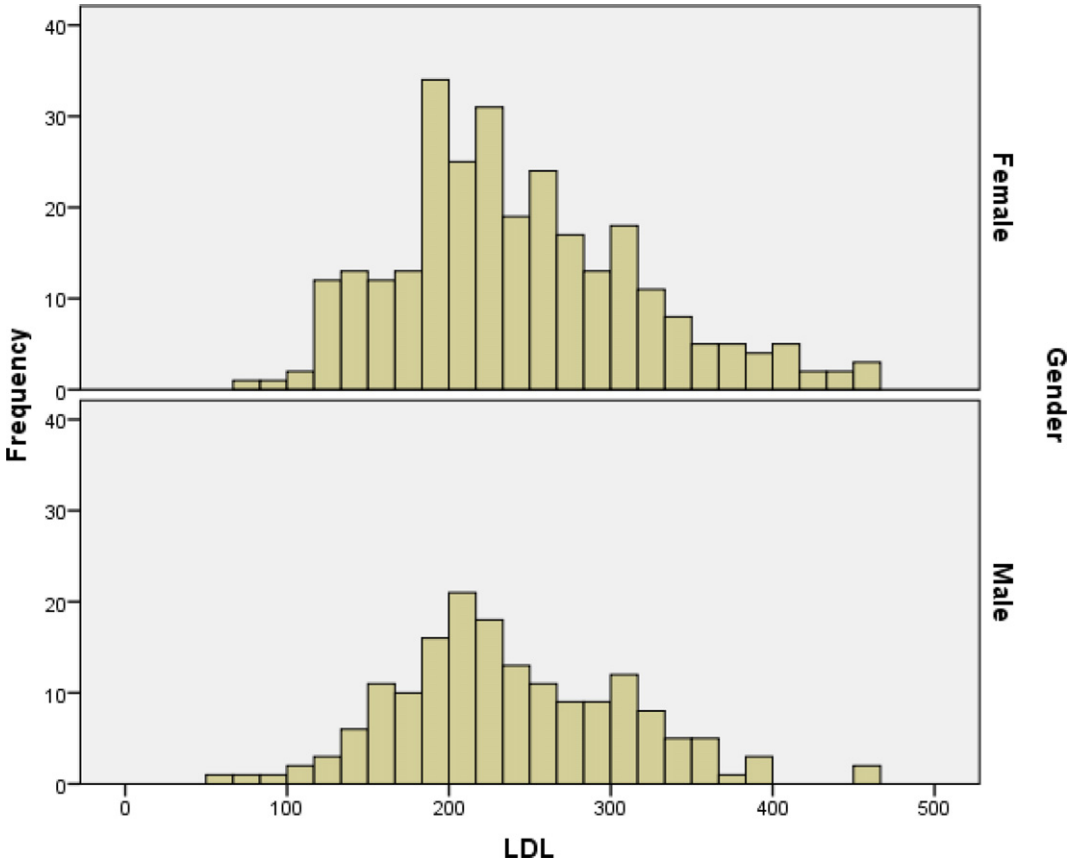
Female
Male
Gender
0
100
200
300
400
Triglicerides


Frequency
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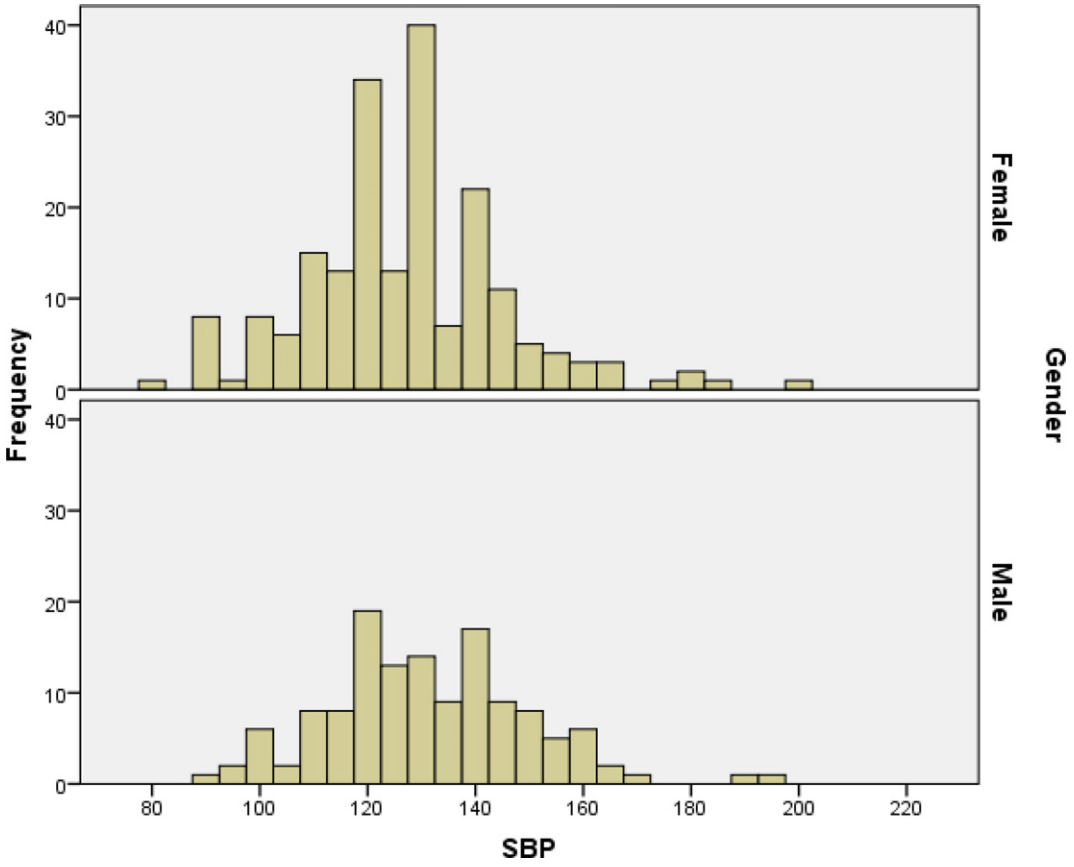
20
10
0
Female
Male
Gender
0
100
200
300
400
500
LDL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Gender
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100
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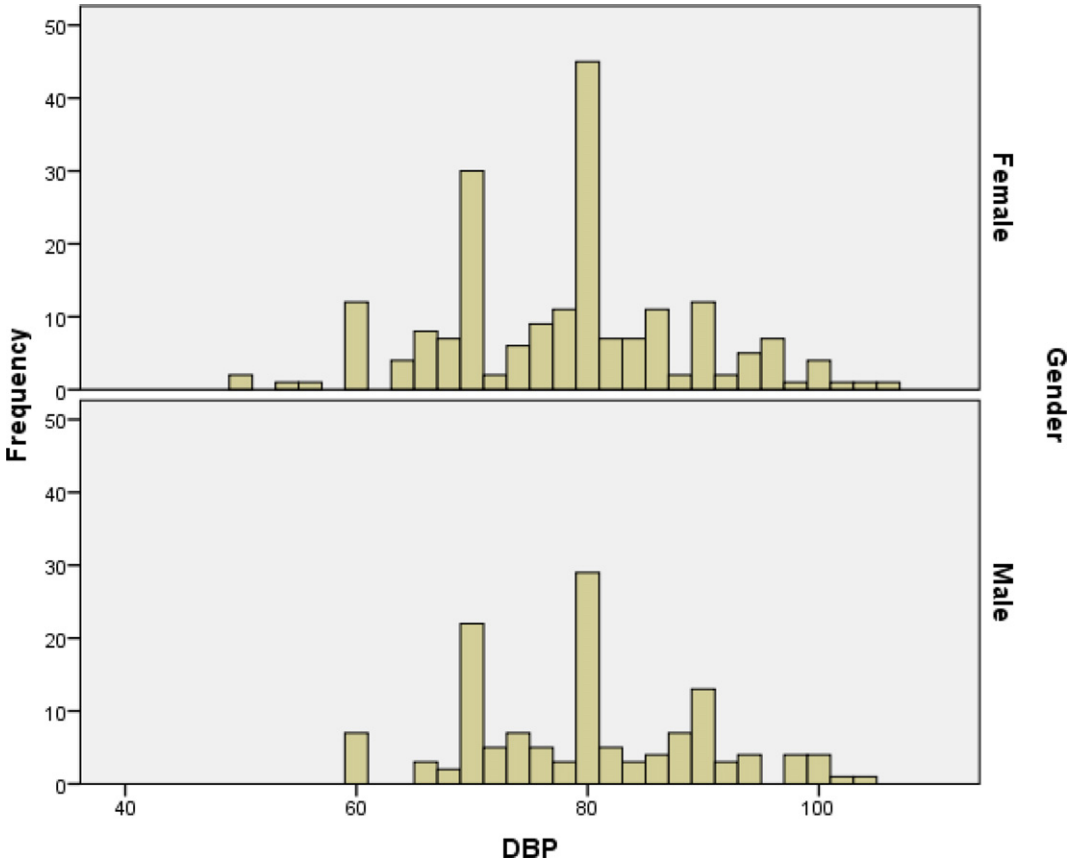
140
160
180
200
220
SBP


Frequency
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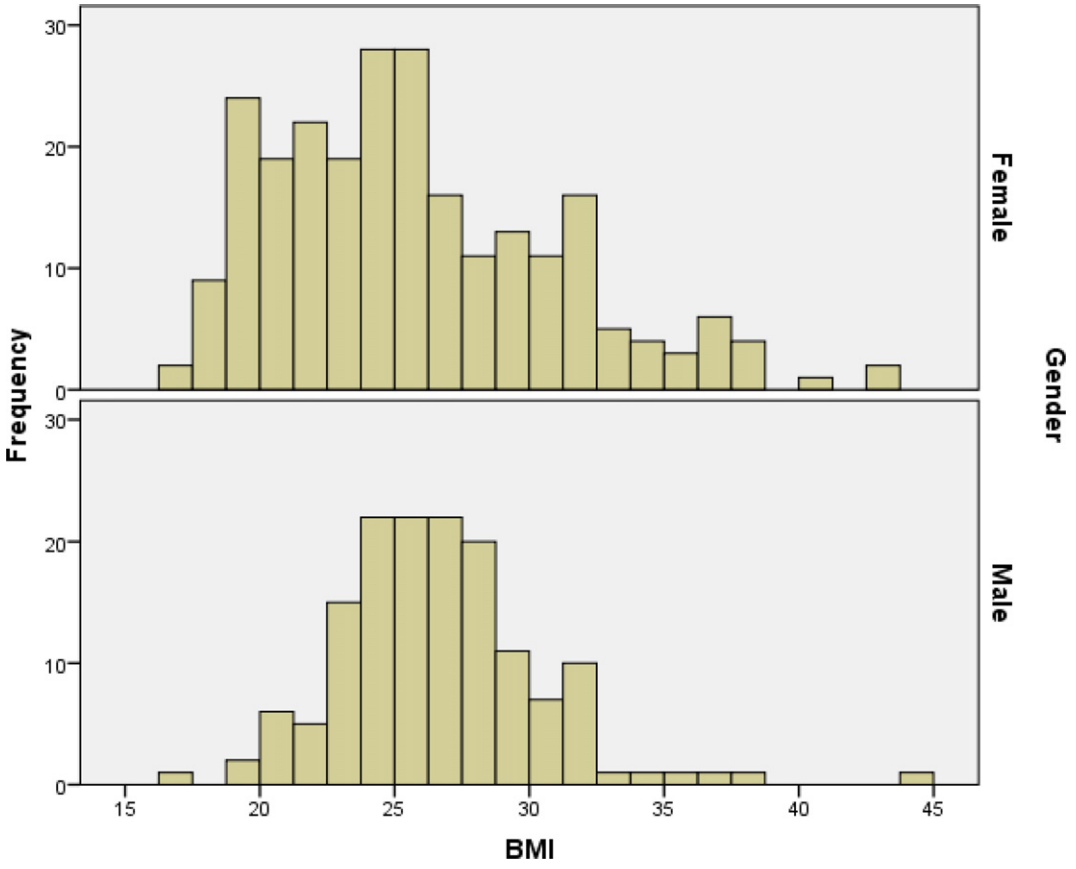
40
30
20
10
0
Female
Male
Gender
40
60
80
100
DBP


Frequency
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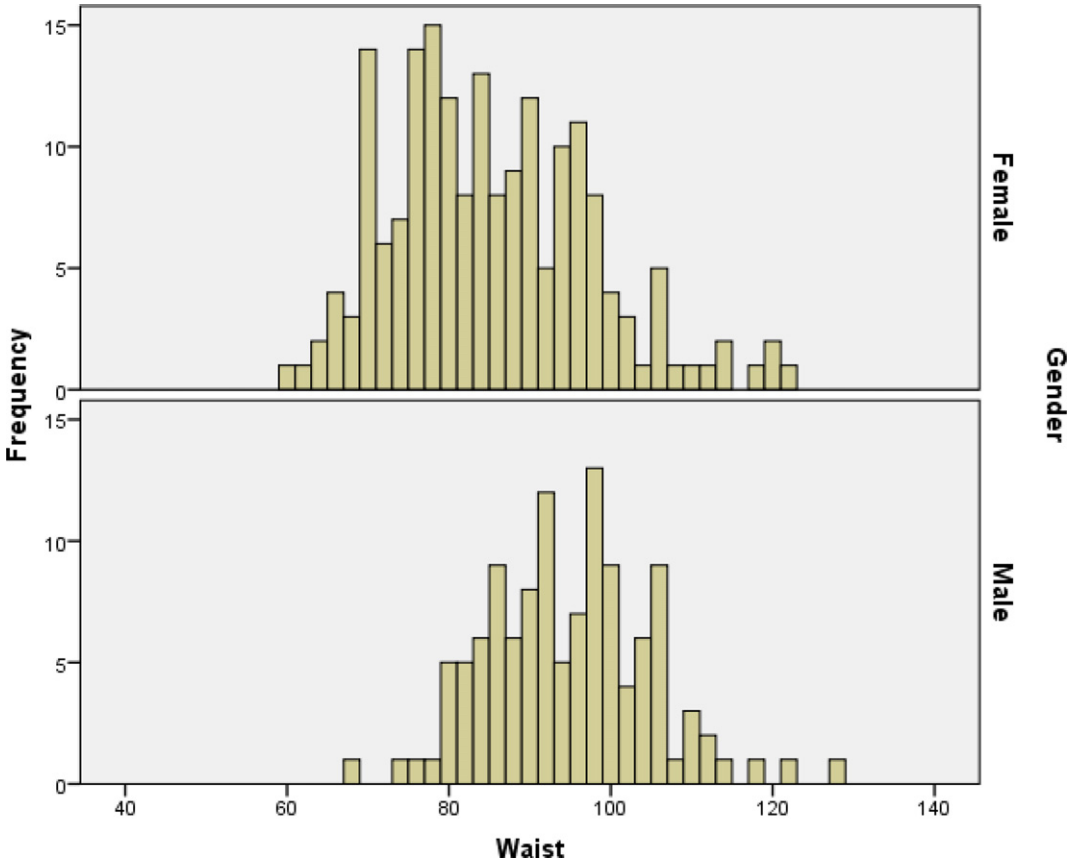
10
0
Female
Male
Gender
15
20
25
30
35
40
45
BMI



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