VILNIAUS UNIVERSITETAS

Sandra
KUTKIENĖ

Dislipidemijų įvertinimo ir modifikavimo įtaka širdies ir kraujagyslių ligų etiopatogenezei bei prevencijai ir sąsajos su kitais aterosklerozę skatinančiais rizikos veiksniais

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The Assessment and Modification of Dyslipidemias: Effects on Etiopathogenesis, the Prevention of Cardiovascular Diseases and the Relationship with other Atherosclerotic Risk Factors

SUMMARY OF DOCTORAL DISSERTATION

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ABBREVIATIONS

ABP	–	arterial blood pressure
AD	–	atherogenic dyslipidemia
AH	–	arterial hypertension
AIxHR	–	heart rate adjusted augmentation index
Apo	–	apolipoprotein
BIA	–	bioelectrical impedance analysis
BMI	–	body mass index
CAC	–	Coronary artery Calcium
CAVI	–	cardio-ankle vascular index
CCA	–	common carotid artery
CHD	–	coronary heart disease
CI	–	confidence interval
CT	–	computed tomography
CVD	–	cardiovascular disease
DBP	–	diastolic blood pressure
DM	–	diabetes mellitus
EAS	–	European Atherosclerosis Society
ECG	–	electrocardiogram
ESC	–	European Society of Cardiology
FCH	–	Familial combined hyperlipidemia
FEM	–	femoral artery
FH	–	familial hypercholesterolemia
HDL	–	high-density lipoproteins
HDL-C	–	high-density lipoprotein cholesterol
HR	–	heart rate
IMT	–	intima-media thickness
LBM	–	lean body mass
LCCA	–	left common carotid artery
LDL	–	low-density lipoproteins
LDL-C	–	low-density lipoprotein cholesterol
LitHiR	–	Lithuanian High Cardiovascular Risk
Lp(a)	–	lipoprotein(a)

MetS	–	metabolic syndrome
OR	–	odds ratio
PBF	–	percentage body fat
PCSK9	–	Proprotein convertase subtilisin/kexin type 9
PH	–	Polygenic hypercholesterolemia
PWV	–	pulse wave velocity
RA	–	radial artery
RCCA	–	right common carotid artery
SBP	–	systolic blood pressure
SCORE	–	Systematic COronary Risk Evaluation
SD	–	standard deviation
SD	–	severe dyslipidemia
SH	–	severe hypercholesterolemia
TBW	–	total body water
TC	–	total cholesterol
TG	–	triglycerides
VFA	–	visceral fat area
vs.	–	against *(versus)*
VUH SK	–	Vilnius University Hospital Santaros Klinikos
WC	–	waist circumference
WHR	–	waist-hip ratio

SUMMARY

1. INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of death globally, with one-third of deaths attributed to CVD worldwide. Lithuania has the highest level of deaths from coronary heart disease (CHD) in Europe and is classified as a high-risk country in the 2016 European guidelines on CVD prevention. The main risk factors for CVD are elevated levels of blood lipids, high blood pressure, tobacco use, diabetes mellitus, unhealthy eating habits, a low level of physical activity, overweight and obesity. To tackle these risk factors is proven to be the key approach for lowering cardiovascular mortality.

Various genetic, pathological, observational and interventional studies have established the important role of dyslipidemia in the development of CVD. Dyslipidemia is a multifactorial disorder, which emerges due to an interplay between genetic, lifestyle and environmental factors and is defined as having an increased concentration of total cholesterol (TC) or an increased low-density lipoprotein cholesterol (LDL-C), or a high concentration of plasma triglycerides (TG), or low high-density lipoprotein cholesterol (HDL-C). A proper treatment of dyslipidemia has been shown to reduce the risk of CVD by 30% in a 5-year period. Also, dyslipidemia is often found together with multiple other cardiovascular risk factors, especially hypertension and obesity. It is well-known that coexisting multiple risk factors tend to increase the risk of CVD synergistically because of the additional adverse effects on the vascular endothelium.

The estimated prevalence of dyslipidemia among middle-aged Lithuanians is very high. An elevation of LDL-C, known as severe hypercholesterolemia (SH), is the most common type of dyslipidemia. It constitutes a major risk factor for the development of atherosclerosis and receives most attention as an established treatment goal. According to an analysis of data from the Lithuanian

High Cardiovascular Risk (LitHiR) program (hereinafter referred to as "the program"), elevated TC and increased LDL-C are the lipid abnormalities most commonly found among middle-aged Lithuanians without established CVD: 80.5% have an increased TC, and 75.7% – an increased LDL-C. Patients with severely elevated LDL-C might either have genetic disorders, such as Familial hypercholesterolemia (FH), Polygenic hypercholesterolemia (PH) and Familial combined hyperlipidemia (mixed hyperlipidemia) (FCH), or non-genetic explanations, including certain secondary causes of SH (e.g., the nephrotic syndrome, cholestasis or untreated hypothyroidism) as well as lifestyle factors. It is evident that only a small proportion of severely hypercholesterolemic subjects will have identified FH mutations, so the recognition of SH is important on the population-basis, as extremely elevated LDL-C levels drive the clinical risk for these patients. An analysis of the serum lipid profile could provide an initial approximate differentiation between various types of dyslipidemia and help distinguish subjects for further evaluation for the familial forms of dyslipidemia, as opportunistic screening in community laboratories for potential FH has been proven to be effective.

Epidemiological studies found low HDL-C to be a common lipid abnormality across European populations. Low HDL-C is not prevalent in Lithuania, as most people have increased TC or LDL-C concentrations, even though dyslipidemia is a very common risk factor in Lithuania. Although low levels of HDL-C have been proven to be a major risk factor for coronary heart disease (CHD) many decades ago, recent genetic studies suggest that the causal relationship is weak. Also, therapeutic interventions aimed at increasing plasma HDL-C levels showed no real benefits on CVD morbidity and mortality. These revelations highlight the fact that measuring plasma HDL-C concentration might not be enough and emphasize the importance of exploring lipoprotein quality and function.

1.1 Aim of the Research

The aim of this study is to evaluate the prevalence and trends in the morbidity of different types of dyslipidemia, as well as any associations with other cardiovascular risk factors, among middle-aged Lithuanians without any established cardiovascular diseases and to develop recommendations for evaluating and long-term monitoring of patients with severe dyslipidemia in Lithuania.

1.2 Objectives of the Research

1. To evaluate the prevalence, trends in morbidity, diagnosis and treatment of different types of dyslipidemia as well as its associations with other cardiovascular risk factors in the program's population.
2. To assess and compare the cardiovascular risk profiles of patients with dyslipidemia and those of the control group.
3. To assess and compare the cardiovascular risk profiles of different types of dyslipidemia.
4. To evaluate the prevalence and trends in morbidity of severe dyslipidemia as well as to assess and compare the cardiovascular risk profiles of patients with different types of severe dyslipidemia.
5. To evaluate the cardiovascular risk profile of patients with severe hypercholesterolemia and establish recommendations for evaluating and long-term monitoring of patients with severe dyslipidemia.
6. To assess the quality and function of high-density lipoproteins in patients with severe dyslipidemia and the control group.

1.3 Statements to Be Defended

1. Lithuanians have a distinct cardiovascular risk profile with dyslipidemia being one of the most important cardiovascular risk factors.

2. Dyslipidemia is often found together with multiple other cardiovascular risk factors.

3. A delayed diagnosis and poor control of dyslipidemia is one of the main problems in the treatment of middle-aged Lithuanians and should thus receive more attention.

4. The diagnosis, treatment and monitoring of severe, possibly familial, dyslipidemia is delayed and inadequate.

5. The HDL function is insufficient among middle-aged Lithuanians.

1.4 Scientific Novelty of the Research

More than ten years ago, in 2006, the LitHiR primary prevention program was started due to an unfavorable situation of cardiovascular morbidity and mortality in our country. The design of the program is compatible with the ESC/EAS Guidelines suggesting that risk-factor screening, including the lipid profile, may be considered in men ≥40 and women ≥50 years of age. The program includes men aged 40–54 and women aged 50–64 without overt CVD from all regions of Lithuania. Patients are evaluated in primary health care institutions, and high-risk subjects are reffered to specialized cardiovascular prevention units. The goals of this program are to decrease the prevalence of cardiovascular risk factors, reduce CVD-related morbidity and mortality as well as increase the early diagnosis of dyslipidemia, hypertension and other cardiovascular risk factors. Analysis of data from 23 204 patients evaluated in primary health care centers revealed that dyslipidemia was diagnosed for 89.7% of middle-aged adults without overt CVD, and severe dyslipidemia was determined for 12.1% of the program's population (Rinkūnienė, 2014).

Also, dyslipidemia remained a very prevalent and poorly controlled risk factor in Lithuania during the period of 2009–2012 (Rinkūnienė, 2014). While continuing and extending the work of E. Rinkūnienė, it was decided to focus on the early diagnosis and management of

dyslipidemia while also assessing the prevalence of severe dyslipidemia and its associations with other cardiovascular risk factors: arterial hypertension (AH), smoking, diabetes mellitus (DM), metabolic syndrome (MetS) and obesity. The aim was to evaluate and compare the cardiovascular risk profiles of different types of dyslipidemia. While focusing on severe dyslipidemia, it was intended to create recommendations for the evaluation and long-term monitoring of patients with severe dyslipidemia in Lithuania. The analysis of the program's population showed that only 16.7% of middle-aged subjects have decreased plasma HDL-C (Rinkūnienė, 2014). This revelation served as an encouragement for performing a quality evaluation of HDL particles in order to assess the function of HDL and possibly re-evaluate the causes of high cardiovascular morbidity in Lithuania.

Main Novelties of the Research:

- Retrospective data analysis for the period of 2009–2016;
- The sample of the restrospective data analysis consists of 92 373 forms;
- A detailed evaluation and comparison of cardiovascular risk profiles as well as associations with other cardiovascular risk factors of various types of dyslipidemia;
- Recommendations given for the evaluation and long-term monitoring of patients with severe dyslipidemia in Lithuania;
- The detection and evaluation of cases of familial hypercholesterolemia;
- An assessement of the quality of high-density lipoproteins in order to evaluate the function of HDL and help determine the reasons of high cardiovascular morbidity in Lithuania.

2. STUDY SUBJECTS AND METHODS

The study was conducted at Vilnius University Hospital (VUH) Santaros Klinikos during the period of 2014–2018. Permission No.

158200-15-816-329 was issued by the Vilnius Regional Biomedical Research Ethics Committee.

2.1 Retrospective Analysis of the Primary Prevention Program Electronic Database

2.1.1 Sample Size and the Selection of Participants

A retrospective study describes the analysis of the lipid profile in a randomly selected group of 92 373 subjects included in the electronic database of the primary prevention program during the period of 2009–2016. The LitHiR program is funded by the Ministry of Health and has obtained the Local Research Ethics Committee's approval. It includes men aged 40–54 and women aged 50–64 years without overt CVD from all regions of Lithuania. This program is conducted in 398 out of 420 (94.8%) primary health care centers, uniformly covering the whole country. In 2016, 256 625 adults were examined in the primary health care centers, covering about 37.5% of the whole target population. The program consists of subjects selected in three different ways: enlisting patients of proper age in primary health care centers, inviting patients who fit the program's enrollment criteria after looking at their existing medical histories and enrolling patients informed about the program via mass media. The exclusion criteria are: a) a proven (clinically evident) coronary heart disease (CHD); b) a proven (clinically evident) cerebrovascular disease; c) a proven (clinically evident) peripheral artery disease; d) an end-stage oncological disease; e) any other end-stage somatic disease.

2.1.2 Study Design and Methods

Primary care physicians filled specially designed protocols providing information about subjects included in the program. Each participant underwent a physical examination, which consisted of an anthropometry (height, weight, waist circumference, waist-to-hip

ratio and body mass index (BMI), defined as weight in kilograms divided by height (in meters squared)) as well as blood pressure and pulse readings. Histories of cardiovascular risk factors, other diseases and medications were obtained during interviews. Serum TC, HDL-C, TG and plasma glucose levels were evaluated by commercially available kits using venous blood samples at the standardized laboratories in the participating centers. LDL-C levels were calculated using the Friedewald formula for individuals with TG <4.5 mmol/l. Tests were performed in the morning, and it was suggested that the participants not to eat for at least 12 hours before the scheduled tests. Secondary causes of dyslipidemia were not ruled out. Less than 5% of subjects in the database were reported to use lipid-lowering medications. Metabolic syndrome (MetS) was assessed according to the National Cholesterol Education Program III modified criteria. Arterial hypertension (AH) was defined as systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg, or the diagnosis of hypertension was documented in a medical record. Obesity was identified whenever the BMI ≥30, and abdominal obesity was determined when waist circumference was >102 cm for men and >88 cm for women. The overall cardiovascular risk was calculated according to the risk estimation Systematic Coronary Risk Evaluation (SCORE) system.

2.1.3 Grouping of the Participants

Participants were divided into groups according to their lipidogram parameters, and different lipid profiles were distinguished. Dyslipidemia was considered if serum TC >5 mmol/l, or LDL-C >3 mmol/l, or HDL-C <1.0 mmol/l in men and <1.2 mmol/l in women, or TG >1.7 mmol/l. Severe dyslipidemia was described as TC ≥7.5 mmol/l, or LDL-C ≥6 mmol/l, or TG ≥4.5 mmol/l. Severe hypercholesterolemia was described as LDL-C ≥6 mmol/l, and severe hypertriglyceridemia was defined as TG ≥4.5 mmol/l. Atherogenic dyslipidemia (AD) was defined as TG >1.7 mmol/l and

HDL-C <1.2 mmol/l in women and <1.0 mmol/l in men. Low HDL-C was described as HDL-C <1.2 mmol/l in women and <1.0 mmol/l in men, normal HDL-C – from 1.2 mmol/l in men and 1.0 mmol/l for women to 1.55 mmol/l, high HDL-C – ≥1,55 mmol/l in both men and women. The control group was defined as TC<5mmol/l and LDL-C<3 mmol/l, HDL-C >1.0 mmol/l for men, >1.2 mmol/l for women, and TG <1.7 mmol/l for both men and women.

We performed a thorough analysis and comparison of selected dyslipidemia profiles as well as the trends of the prevalence of different dyslipidemias, for the period of 2009–2016. Study data has been further analyzed by dividing all subjects into appropriate groups based on age. Men: 40–44 years, 45–49 years, 50–54 years; women: 50–54 years, 55–59 years, 60–64 years.

2.2 Prospective Analysis of the Selected Group of Patients with Severe Dyslipidemia and the Control Group

2.2.1 The Selection and Grouping of Participants

A total of 213 participants were enrolled in the prospective study. It included men and women from 18 up to 60 years of age. The average age of subjects was 49.15 ± 8.01 years. We collected data from 110 (51.6%) patients (N=54 women and 56 men) with severe dyslipidemia and 103 (48.4%) controls (N=51 women and 52 men) without dyslipidemia or established CVD. Written informed consent was obtained from all participants before their inclusion in the study.

Severe dyslipidemia was considered as serum TC ≥7.5 mmol/L or LDL-C ≥6 mmol/L. Subjects with possible secondary causes of severe dyslipidemia (uncontrolled hypothyroidism, diabetes mellitus, nephrotic syndrome, renal insufficiency, cholestasis, viral hepatitis, liver cirrhosis, alcoholism, anorexia), pregnancy, terminal stage cancer and any terminal stage disease were excluded from this study.

Controlled thyroid dysfunction and diabetes mellitus diagnosed later than dyslipidemia were not considered as exclusion criteria.
Included in the control group of this study were only subjects without dyslipidemia, without any evident cardiovascular diseases (myocardial infarction, an unstable angina, a stable angina with a positive cardiac stress test, a coronary artery pathology identified during cardiac catheterization or a coronary computed tomography angiography, coronary artery bypass surgery, percutaneous coronary intervention), with no cerebrovascular disorders (a previous acute ischemic or hemorrhagic stroke, a diagnosed stenosis of carotid arteries), no peripheral artery diseases (acute ischemic syndromes, chronic limb ischemia, aortic aneurysm), no disorders that may impact the concentrations of blood lipids (an uncontrolled hypothyroidism, diabetes mellitus, a nephrotic syndrome, a renal insufficiency, cholestasis, viral hepatitis, liver cirrhosis, alcoholism, anorexia), pregnancy, terminal stage cancer and any terminal stage disease.

2.2.2 Study Design and Methods

Thorough cardiovascular disease risk estimations (history of smoking, arterial hypertension, physical activity, dietary habits, body composition analysis) were completed. Various diagnostic tests, including coronary artery calcium score evaluations, echocardiographies, abdominal ultrasounds and ultrasounds of the tendons, were performed. Anthropometric data (height, weight, waist circumference) were gathered, and the heart rate, arterial blood pressure were measured. Blood cholesterol, lipoprotein and apolipoprotein analyses was performed in the Center of Laboratory Medicine in VUH Santaros Klinikos. All the tests and procedures were carried out in the morning, and the participants were advised not to eat for at least 12 hours beforehand. The recommended values of measured lipids and lipoproteins are shown in Table 1.

Table 1. *Recommended values of measured lipids and lipoproteins.*

Measurement	Recommended value
Total cholesterol (mmol/l)	<5
Triglycerides (mmol/l)	≤1.7
HDL cholesterol (mmol/l)	>1 male, >1.2 female
LDL cholesterol (mmol/l)	<3
ApoA1 (g/l)	1.1–2.05 male, 1.25–2.15 female
ApoB (g/l)	0.55–1.40 male, 0.55–1.25 female
ApoA2 (g/l)	0.26–0.51
ApoE (mg/l)	23-63
ApoB/ApoA1	0.35–1.0 male, 0.3–0.9 female
Lipoprotein(a) (g/l)	<0.3

Abbrevations: HDL – high-density lipoprotein; LDL – low-density lipoprotein; Apo – apolipoprotein.

Arterial hypertension was considered as systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg, or the diagnosis of hypertension was documented in a medical record.

Different anthropometric parameters were measured by applying the required anthropometric tools and following the rules of accurate measurement. Abdominal obesity was determined as waist circumference >102 cm for men and >88 cm for women. The waist-hip ratio reference range was 0.75-0.9 for men and 0.70-0.85 for women. The BMI was calculated by dividing body weight (in kilograms) by height (in meters squared). While assessing the BMI, the following groups were distinguished: ideal – 22, normal – 20–25 for men and 18.5–24 for women, overweight – 25–29.9, obese – 30–40 and severely obese – >40. Bioelectrical impedance analyses were performed using a bioimpedance analyzer IOI353, using which the individual, dressed in light clothing, would stand barefoot on metal plates while the following parameters would be measured: lean body mass (LBM), skeletal muscle mass (SMM), mineral mass, body fat mass (BFM), percentage body fat (PBF), visceral fat area (VFA), total body water (TBW) and protein mass. Also, analyses of the

abdominal region were performed. The measurements were evaluated and grouped in accordance with the recommendations posed by manufacturers of the body composition analyzer.

Abdominal ultrasounds were performed using an abdominal transducer of 3.5 MHz. Patients were assessed lying in the supine position or on the left side. During the ultrasound examination, the presence of conditions associated with severe dyslipidemia were evaluated: atherosclerotic lesions of the abdominal aorta, fatty liver, pancreatic steatosis and gallstones.

Morphological assessments of the aortic valve were based on transthoracic echocardiography parasternal long and short axis view. We evaluated the number of cusps, cups mobility, thickness and calcification.

For the ultrasound examinations of the Achilles and wrist tendons, a linear transducer of 9 MHz was used. The Achilles tendons were accessed from a myotendinous junction to the site of the calcaneal insertion in sagittal and transverse planes. Patients were assessed lying in prone position with both feet hanging over the edge of the table. Measurements of the tendon thickness (anteroposterior diameter) were made at the level of the medial malleolus. The Achilles tendons were considered normal if their thickness and echogenicity was uniform in both planes and the AP diameter was less than 6.4 mm for females and 6.8 mm for males. Tendinosis was diagnosed if a fusiform thickening of the Achilles tendon without the disruption of tendon fibers was found with or without intratendinous hypoechoic foci.

Images for the CAC scoring were acquired following a standard protocol with 2.5 mm collimation, sequential acquisition and electrocardiographic gating. Imaging was performed with the 64 slice multidetector CT (GE LightSpeed VCT, Milwaukee, Wisconsin, US). Advantage Workstation (version 4.6, GE Healthcare, US) software was used for post processing of the images. The CAC scores were calculated according to the Agatston's method

and later with respect to age, sex and ethnicity converted to percentiles.

Arterial stiffness was evaluated using the applanation tonometry system SphygmoCor v.8.0, and the cardio-ankle vascular index (CAVI) technique using the VaSera VS 1000 device. Brachial blood pressure was recorded, and the distance between the surface markings of the sternal notch and the femoral artery was measured. The data and the simultaneously recorded ECG allowed the system to compute the main parameters of arterial stiffness: pulse wave velocity (PWV) and aortic augmentation index (AIxHR). PWV was measured in femoral (FEM) and radial (RA) arteries. Normal PWV was defined as <10 m/s. The cardio-ankle vascular index (CAVI) was calculated automatically using two main parameters: the β-parameter of arterial stiffness and the cardio-ankle index. Cuffs were applied bilaterally to the upper arms and ankles, and electrodes were fixed to each wrist, and a heart sound sensor was placed on the second intercostal sternum. The arteriosclerosis detector was equipped with both measurement and calculation systems to calculate the CAVI automatically: optimal <8.0, moderately increased – 8.0–9.0, severely increased – >9.0.

Duplex scannings of the carotid arteries for the assessment of the presence of atherosclerotic plaques and the measurement of carotid intima-media thickness (IMT) was performed using high-resolution echo-tracking technology (Logiq 700, General Electric). The following parameters were measured: right and left side common carotid artery (CCA) wall distention, CCA IMT, CCA stiffness and plaques in carotid arteries. A plaque was described as an intima-media thickness of more than 1.5 mm.

Additionally, for patients with a very high probability of familial hypercholesterolemia, genetic testing was performed. In the Center of Medical Genetics of VUH Santaros Klinikos, next-generation sequencing (NGS) analyses of genomic DNA, isolated from the patients' peripheral blood, were performed using the TruSight Cardio Sequecing panel (Illumina Inc., San Diego, CA) to identify the

known genes associated with inherited cardiac conditions.
A detailed evaluation of HDL-C quality and quantity was performed for 93 (48 women and 45 men) randomly selected participants. Cholesterol efflux capacity was measured using the Cholesterol efflux fluorometric assay kit (BioVision, Inc., CA, US) according to the manufacturer's protocol. HDL cholesterol efflux was calculated and categorized into tertiles – below average, average or above average.

2.2.3 Statistical Analysis

Continuous variables were expressed by means and standard deviations (SD). Frequencies (%) are reported for categorical data. A Mantel-Haenszel chi-square test for trends was used to analyze the trends of the prevalence for categorical variables ("*p* for trend"). To evaluate linear associations between continuous variables, ANOVA for linear trends was used ("*p* for trend"). Continuous variables were compared using the Kruskal–Wallis univariate analysis of variance (ANOVA). Categorical variables were compared with the help of a Chi-square test or Fisher exact test.
Correlation analysis was performed to assess the linear association between characteristics, and a Spearman's correlation coefficient (r) was applied. Correlation was considered to be either weak ($r < 0.3$), moderate ($0.3 \leq r \leq 0.7$) or strong ($r > 0.7$). The impact of factors on the change of the likelihood of morbidity was defined by assessing the ratios of odds (OR) together with confidence intervals (CI). A p-value of <0.05 was considered significant. Statistical analyses were performed using SPSS 23.0 (SPSS Inc., Chicago, Illinois, US).

3. RESULTS

3.1 Results of the Retrospective Analysis

3.1.1 An Evaluation of the Prevalence, Trends in Morbidity, Diagnosis and Treatment of Dyslipidemia

The prevalence of any type of dyslipidemia remained stable and high, affecting 89.7% (n=82 893) (from 89.1% in 2009 to 89.5% in 2016) of middle-aged adults participating in the Primary Prevention Program. The tendencies of prevalence of any type of dyslipidemia in the program's population and in different gender and age groups during the period of 2009–2016 are shown in Figures 1–3.

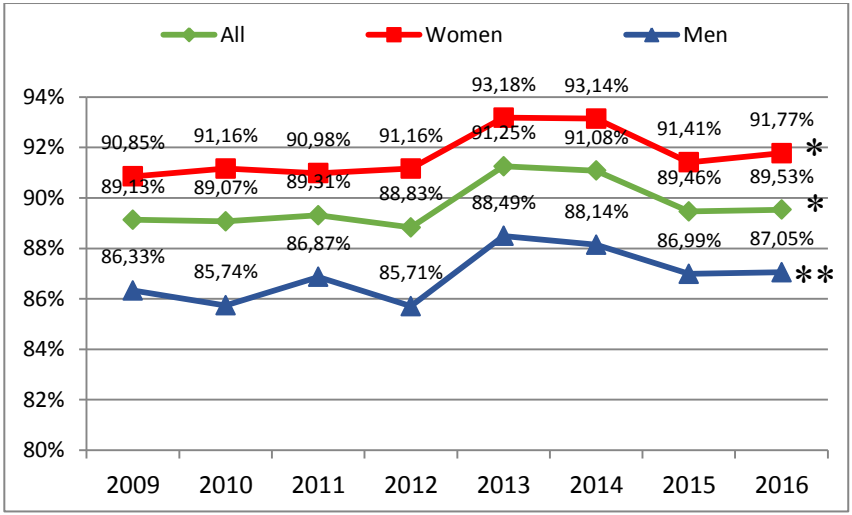


Figure 1. *Trends in the prevalence of any type of dyslipidemia among middle-aged Lithuanian adults from 2009 to 2016.*
* $p<0.001$; ** $p=0.005$.

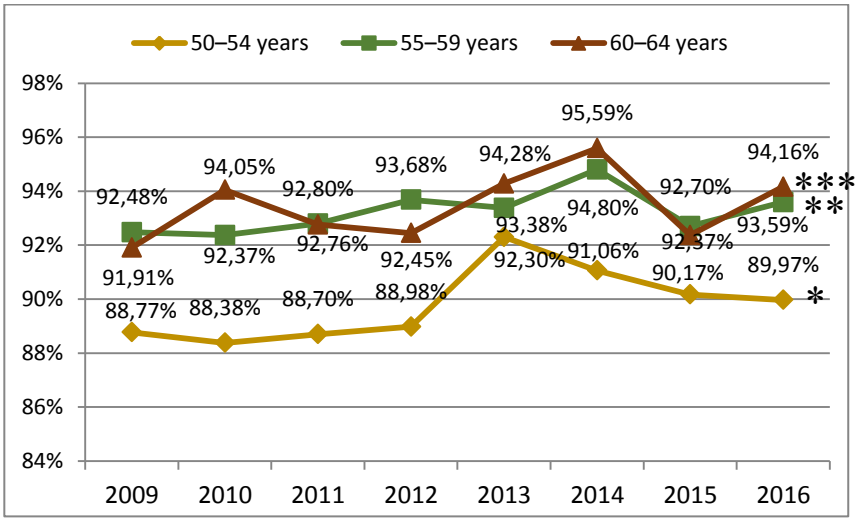


Figure 2. *Trends in the prevalence of any type of dyslipidemia among middle-aged Lithuanian women from 2009 to 2016.*
* $p<0.001$; ** $p=0.021$; *** $p=0.070$.

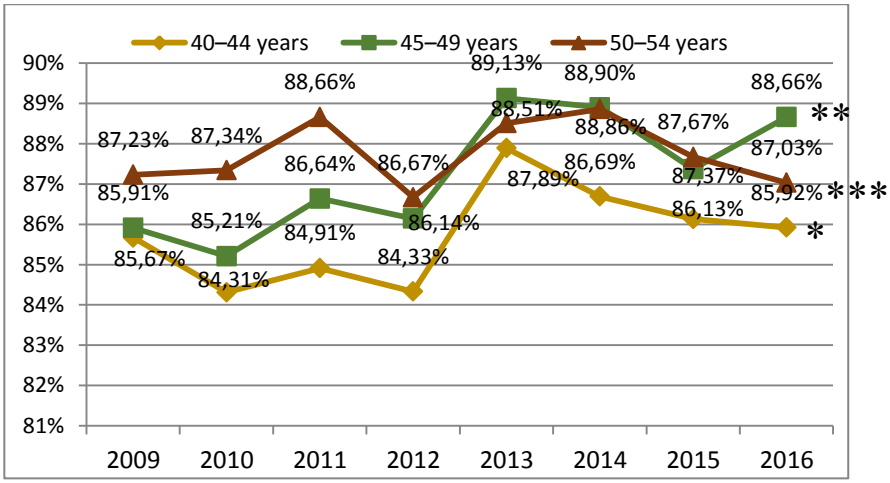


Figure 3. *Trends in the prevalence of any type of dyslipidemia among middle-aged Lithuanian men from 2009 to 2016.*
* $p=0.09$; ** $p<0.001$; *** $p=0.711$.

Based on the analysis of a digital database, primary care physicians diagnosed dyslipidemia for 66.5% (n=61 441) of the examined patients during the period of 2009–2016. The prevalence of dyslipidemia and the percentage of newly diagnosed dyslipidemia during the period of 2009–2016 are shown in Figure 4.

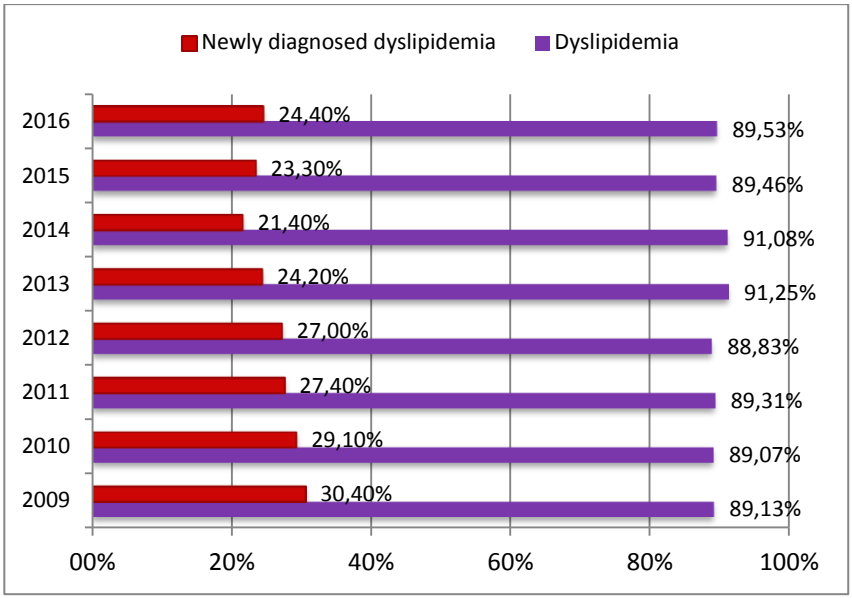


Figure 4. *The prevalence of dyslipidemia and the percentage of newly diagnosed dyslipidemia for 2009–2016.*

Lipid-lowering medications were prescribed to 15.9% of subjects with dyslipidemia. Of the patiens with the diagnosis of dyslipidemia, 58.3% did not receive any treatment. In this study, dyslipidemia was newly diagnosed for 25.9% of the participants according to the laboratory analysis. These patients did not receive lipid-lowering drugs, as they were not considered to have dyslipidemia by primary care physicians. An evaluation of dyslipidemia treatment in the program's population is presented in Figure 5. In the cohort

receiving lipid-lowering treatment, only 6.7% of the patients reached treatment goals (LDL-C <3 mmol/l). The achievement of treatment goals in middle-aged Lithuanians during the period of 2009–2016 is presented in Figure 6.

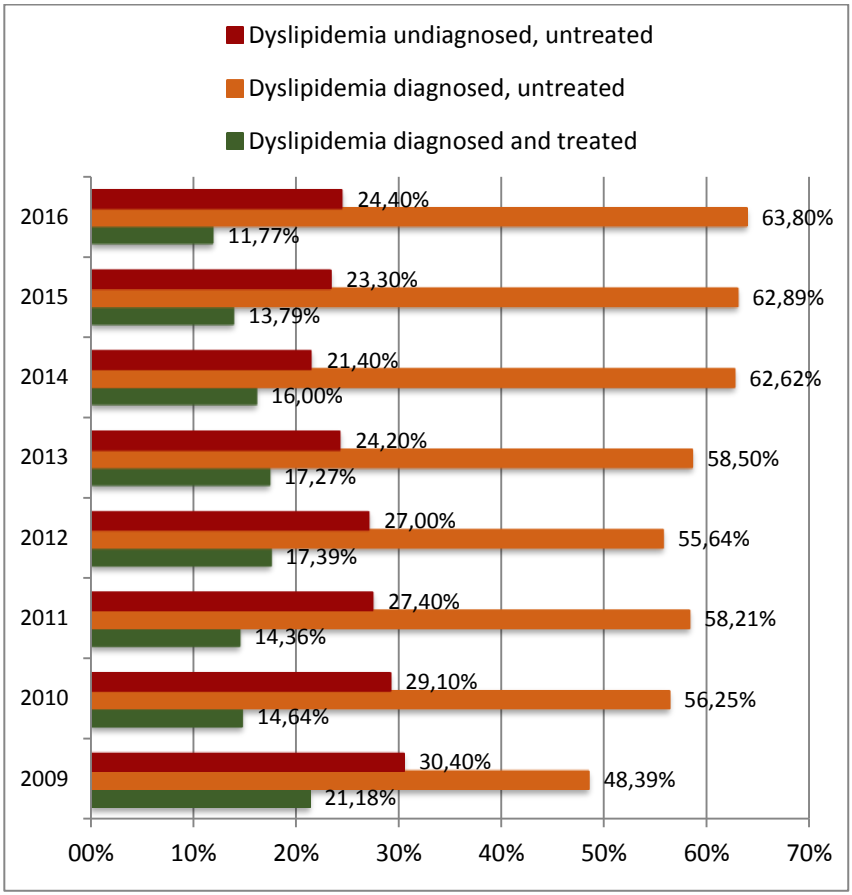
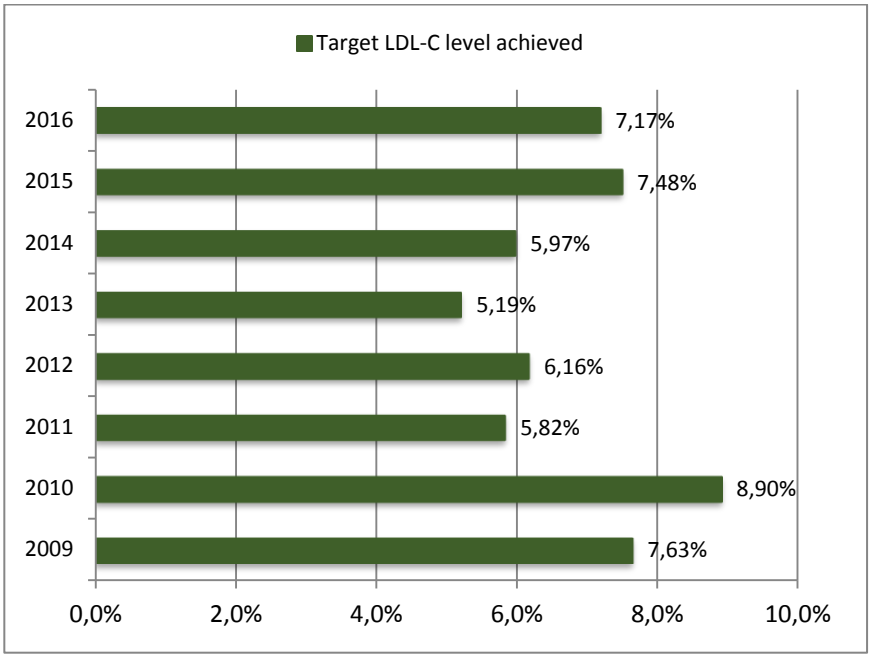


Figure 5. *Treatment of dyslipidemia in the program's population during the period of 2009–2016.*



Abbrevations: LDL-C – low-density lipoprotein cholesterol.

Figure 6. *The achievement of treatment goals (LDL-C < 3 mmol/l) in patients with dyslipidemia receiving lipid-lowering medications for 2009–2016.*

3.1.2 Basic Characteristics and Lipidogram Parameters of the Study Participants

This study included 92 373 adults without overt cardiovascular disease – 53 961 (58.4%) women and 38 412 (41.6%) men. The average age of the sample group was 52.15 (± 6.21) years. Women and men varied in age because of the different study enrollment criteria: the average age of men was 46.96 (± 4.39) years, and women – 55.85 (± 4.40) years. A larger part – 81.7% – of subjects had TC >5 mmol/L; 79.3% had LDL-C >3 mmol/L; 30.4% had TG >1.7 mmol/L, and 13.7% had low HDL-C (<1.0 mmol/L in men and <1.2 mmol/L in women). The distribution of the lipidogram

parameters among the studied population is shown in Figures 7–10. Any type of dyslipidemia was diagnosed in 89.7% of middle-aged adults without overt cardiovascular disease. When analyzing the prevalence of other major cardiovascular risk factors, the most frequent were arterial hypertension (AH) – 54.5%, abdominal obesity – 43.7%, metabolic syndrome (MetS) – 31.5% and obesity – 34.6%. Unhealthy dietary patterns were determined in 61.5% of the studied participants, while insufficient physical activity – in 51.2% of subjects. Baseline characteristics and the prevalence of cardiovascular risk factors of the whole study population are shown in Table 2.

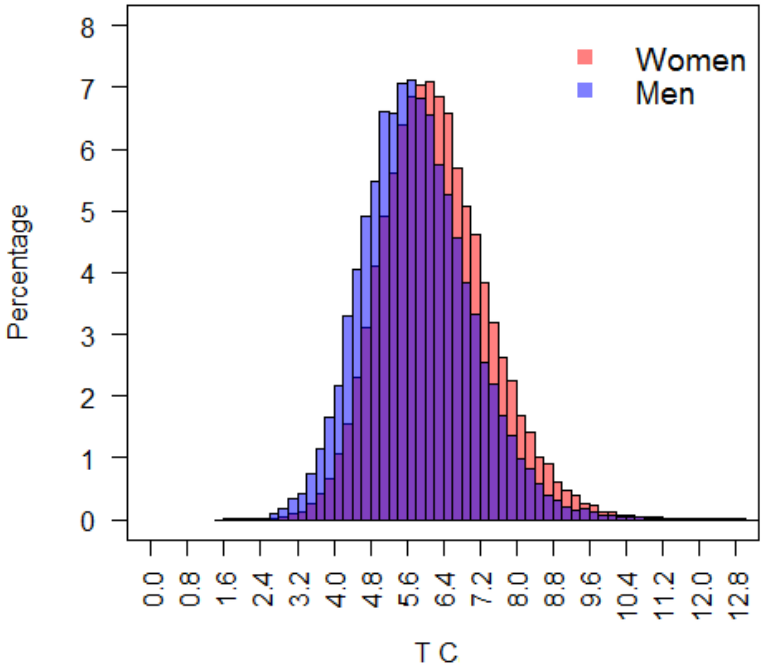


Figure 7. *The distribution of TC concentrations among the program's population during the period of 2009–2016 (n=92 373).*

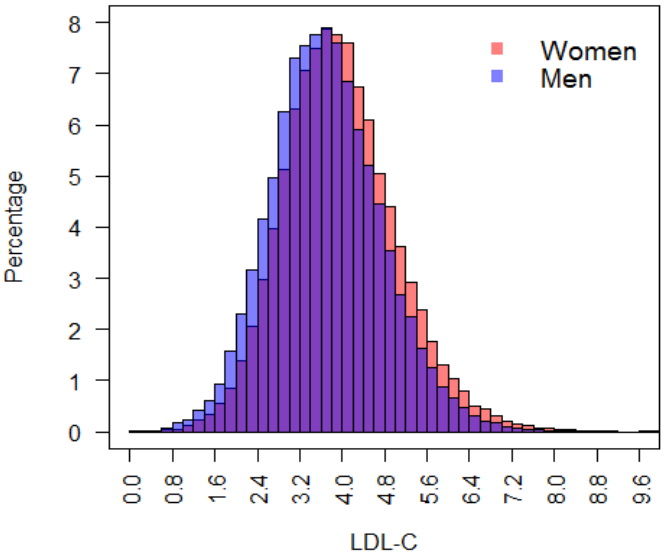
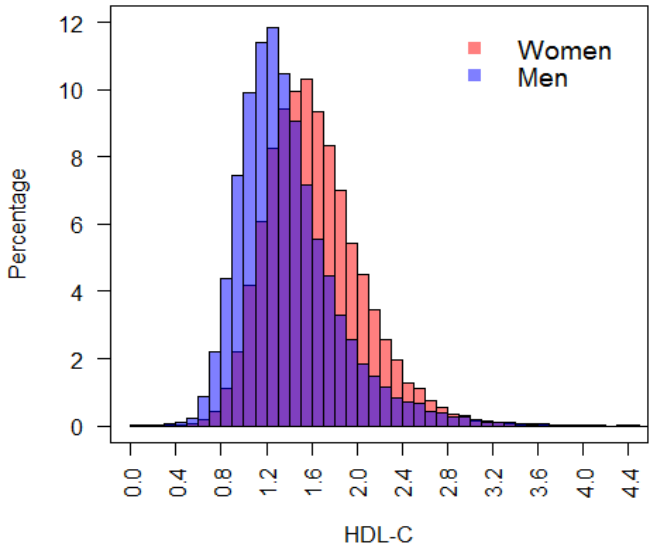


Figure 8. *The distribution of LDL-C concentrations among the*



program's population during the period of 2009–2016 (n=92 373).

Figure 9. *The distribution of HDL-C concentrations among the program's population during the period of 2009–2016 (n=92 373).*

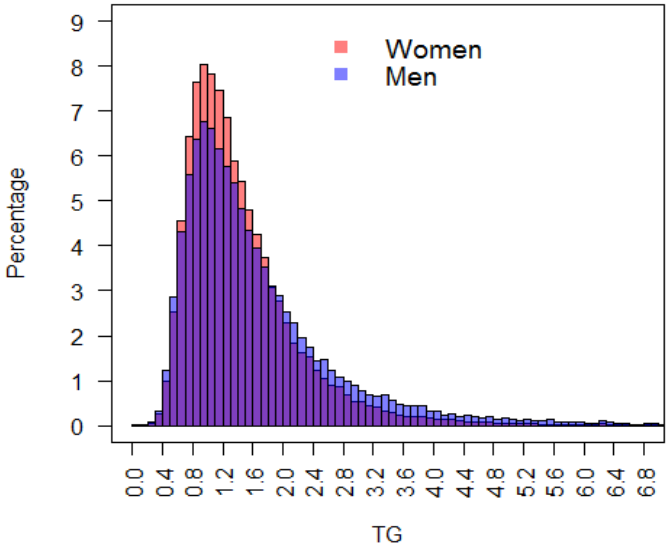


Figure 10. *The distribution of TG concentrations among the program's population during the period of 2009–2016 (n=92 373).*

3.1.3 Cardiovascular Risk Assessment in Middle-Aged Patients with and without Dyslipidemia

The group with dyslipidemia consisted of 82 893 (89.7%) subjects, and the group without dyslipidemia included 9 480 (10.3%) adults. All the major risk factors, including AH, abdominal obesity, MetS, diabetes mellitus (DM) and obesity, except for smoking, were more prevalent in patients with dyslipidemia compared to patients without it ($p < 0.001$) (Table 2). The average SCORE index of the whole study population was 1.87, while patients with dyslipidemia had a higher SCORE compared to the control group (Table 2).

Table 2. *The baseline characteristics and trends of cardiovascular risk factors in the study's population.*

Characteristics	**All patients**		**With dyslipidemia**		**Without dyslipidemia**		*p*
	n=92 373		n=82 893		n=9 480		
	Mean	SD	Mean	SD	Mean	SD	
Age (years)	52.15	6.21	52.34	6.20	50.54	6.05	<0.001
WC (cm)	93.72	13.5	94.07	13.5	90.64	13.08	<0.001
BMI (kg/m²)	28.60	5.41	28.78	5.39	27.04	5.38	<0.001
SBP (mmHg)	133.52	16.3	133.87	16.4	130.4	15.44	<0.001
DBP (mmHg)	82.76	9.48	82.95	9.50	81.15	9.14	<0.001
HR (bpm)	71.95	8.78	72.00	8.78	71.50	8.72	<0.001
Glucose(mmol/l)	5.52	1.22	5.54	1.23	5.35	1.08	<0.001
TC (mmol/l)	6.08	1.21	6.28	1.12	4.40	0.45	<0.001
LDL-C (mmol/l)	3.87	1.08	4.04	1.00	2.42	0.43	<0.001
HDL-C (mmol/l)	1.54	0.46	1.54	0.47	1.58	0.37	<0.001
TG (mmol/l)	1.59	1.16	1.66	1.19	0.93	0.31	<0.001
Non-HDL-C	4.54	1.21	4.74	1.11	2.83	0.48	<0.001
TG/HDL-C	1.22	1.55	1.29	1.62	0.63	0.28	<0.001
SCORE index	1.87	1.68	1.95	1.71	1.20	1.18	<0.001
Frequencies	n	%	n	%	n	%	*p*
DM (%)	9897	10.7	9207	11.1	690	7.3	<0.001
AH (%)	50317	54.5	46216	55.8	4101	43.3	<0.001
Abdominal obesity (%)	40408	43.7	37547	45.3	2861	30.2	<0.001
Smoking (%)	21218	23.0	18703	22.6	2515	26.5	<0.001
Metabolic syndrome (%)	29094	31.5	28219	34.0	875	9.2	<0.001
RF ≥3 (%)	53971	58.4	49819	60.1	4152	43.8	<0.001
CHD history (%)	24025	26.0	21837	26.3	2188	23.1	<0.001

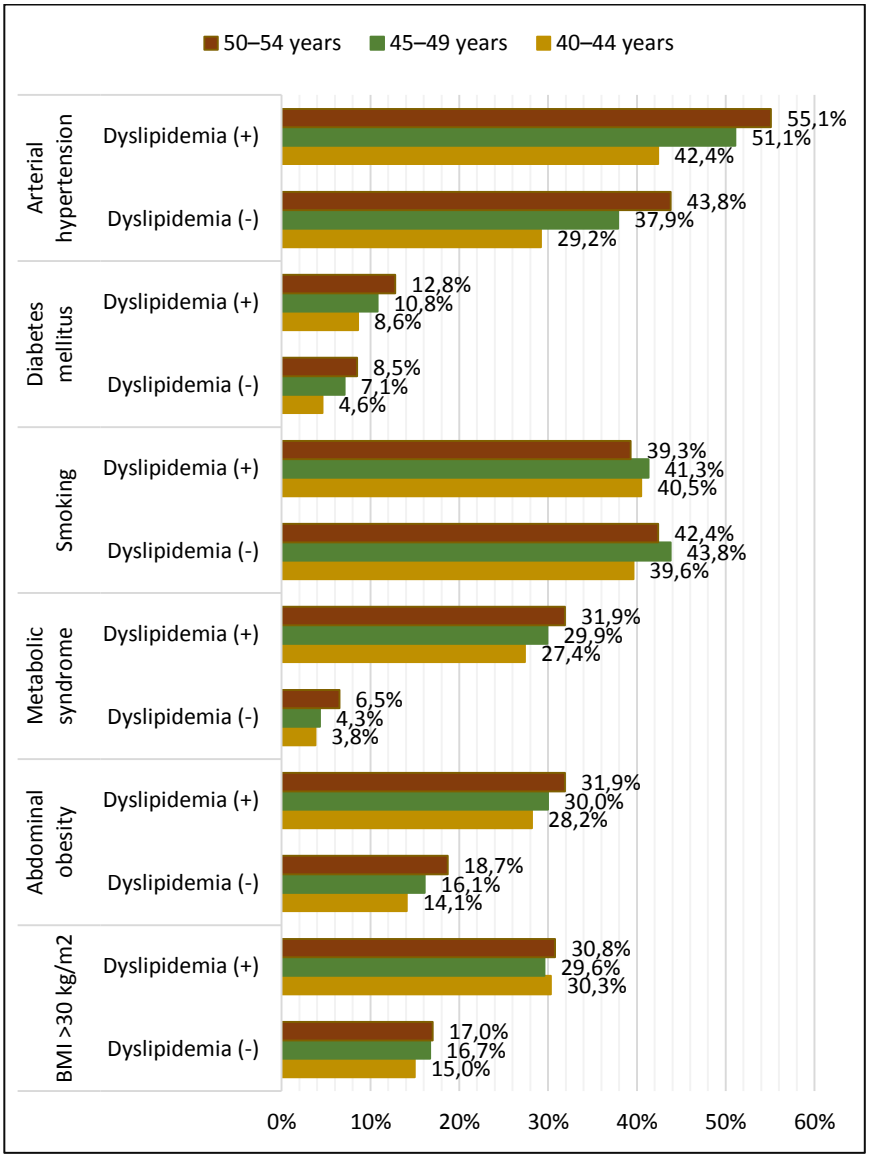
Diet (unbalanced) (%)	56800	61.5	51783	62.5	5017	52.9	<0.001
Physical activity (insufficient) (%)	47268	51.2	43074	52.0	4194	44.2	<0.001
BMI <25 (kg/m²) (%)	24891	26.9	21037	25.4	3854	40.7	<0.001
BMI 25-30 (kg/m²) (%)	35589	38.5	32209	38.9	3380	35.7	<0.001
BMI 30-40 (kg/m²) (%)	28778	31.2	26776	32.3	2002	21.1	<0.001
BMI >40 (kg/m²) (%)	3115	3.4	2871	3.5	244	2.6	<0.001

Abbreviations: SD – standard deviation; WC – waist circumference; BMI – body mass index; SBP – systolic blood pressure; DBP – diastolic blood pressure; HR – heart rate; TC – total cholesterol; LDL-C – low-density lipoprotein cholesterol; HDL-C – high-density lipoprotein cholesterol; TG – triglycerides; DM – diabetes mellitus; AH – arterial hypertension; RF – risk factors; CHD – coronary heart disease.

3.1.4 Cardiovascular Risk Assessment in Middle-Aged Men with and without Dyslipidemia

The study included 38 412 men aged 40–54 years: 33 403 (87.0%) with dyslipidemia and 5 009 (13.0%) without dyslipidemia. The mean value of TC in men was 6.07 ± 1.10mmol/l, LDL-C – 3.92 ± 0.98 mmol/l, HDL-C – 1.39 ± 0.47 mmol/l and TG – 1.86 ± 1.45 mmol/l. The prevalence of different cardiovascular risk factors in dyslipidemic and non-dyslipidemic men is presented in Figure 11. Men with dyslipidemia possessed all the main risk factors – except for smoking – significantly more often than the males without dyslipidemia: AH (49.6% vs. 36.6%, p<0.001), DM (10.8% vs. 6.6%, p<0.001), abdominal obesity (30.1% vs. 16.2%, p<0.001), MetS (29.8% vs. 4.8%, p<0.001) and obesity (30.3% vs. 16.1%, p<0.001). The prevalence of DM, AH, abdominal obesity, MetS and obesity increased with age in both dyslipidemic and non-

dyslipidemic men's groups. Males with dyslipidemia had a higher prevalence of DM, AH, abdominal obesity, MetS and obesity in all age groups in comparison with the control group (Figure 11). Smoking was more prevalent in men aged 40–54 without dyslipidemia compared to the group with dyslipidemia (41.8% vs. 40.3%, p <0.001). The highest frequency of smoking in males without dyslipidemia was observed in those aged 45–49 years (43.8%), followed by the groups of men aged 50–55 (42.4%) and 40–44 (39.6%). The prevalence of smoking was lower in men older than 50 years compared to younger males in both dyslipidemic and non-dyslipidemic groups (Figure 11). Also, men with dyslipidemia tended to have histories of CHD in their families, an unbalanced diet and insufficient physical activity more often than those without dyslipidemia (23.9% vs. 20.6%, p<0.001; 65.5% vs. 54.1%, p<0.001; 47.3% vs. 39.5%, p<0.001, respectively).

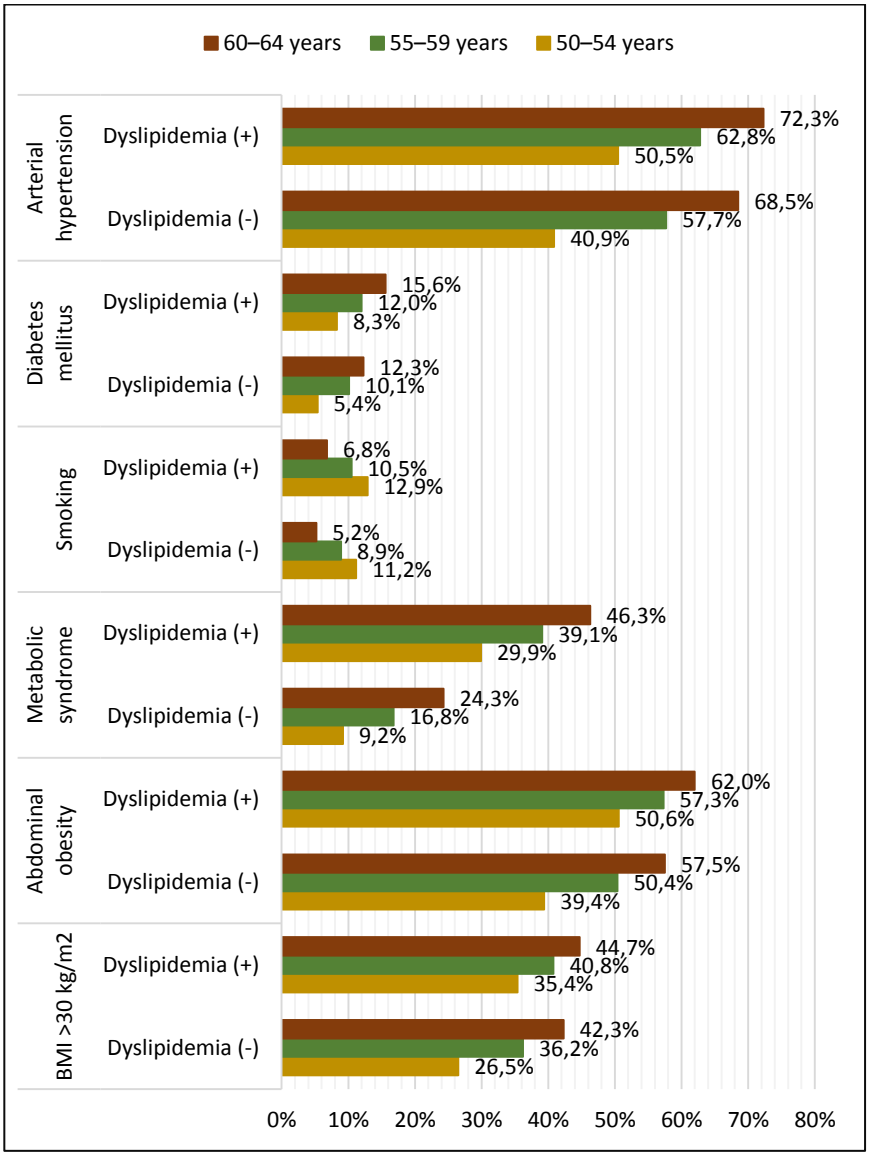


Abbrevations: BMI – body mass index.

Figure 11. *The prevalence of different cardiovascular risk factors in men of different ages with and without dyslipidemia.*

3.1.5 Cardiovascular Risk Assessment in Middle-Aged Women with and without Dyslipidemia

The study included 53 961 women aged 50–64: 49 490 (91.7 %) with dyslipidemia and 4 471 (8.3%) without dyslipidemia. The mean laboratory values of women were: TC – 6.41 ± 1.11 mmol/l, LDL-C – 4.12 ± 1.01 mmol/l HDL-C – 1.63 ± 0.45 mmol/l and TG – 1.53 ± 0.96 mmol/l. The prevalence of different cardiovascular risk factors in dyslipidemic and non-dyslipidemic women of different ages is shown in Figure 12. Women aged 50–64 with dyslipidemia had all the main cardiovascular risk factors significantly more frequently than females without dyslipidemia (DM (11.3% vs. 8.0%, $p<0.001$), AH (59.9% vs. 50.7%, $p<0.001$), abdominal obesity (55.6% vs. 45.8%, $p<0.001$), smoking (10.6% vs. 9.4%, $p<0.001$), MetS (36.9% vs. 14.2%, $p<0.05$) and obesity (39.5% vs. 32.1%, $p<0.001$)). The prevalence of DM, AH, abdominal obesity, MetS and obesity increased with age in both dyslipidemic and non-dyslipidemic groups (figure 12). Subjects with dyslipidemia had a higher prevalence of DM, AH, abdominal obesity, MetS and obesity in all age groups in comparison with the control group (Figure 12). Women with dyslipidemia reported smoking more often in all age groups compared to women without dyslipidemia ($p <0.001$). The frequency of smoking was lower in older women in both dyslipidemic and non-dyslipidemic groups compared to younger females (Figure 12).

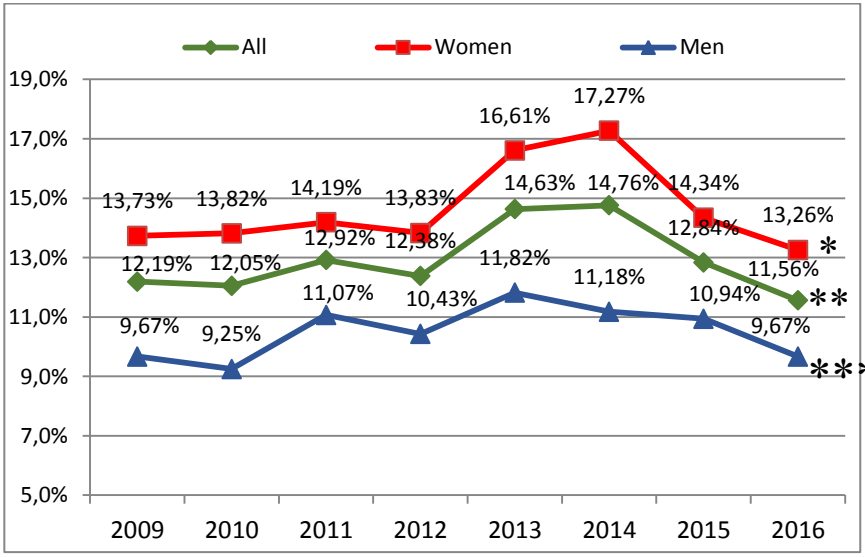


Abbrevations: BMI – body mass index.

Figure 12. *The prevalence of different cardiovascular risk factors in women of different ages with and without dyslipidemia.*

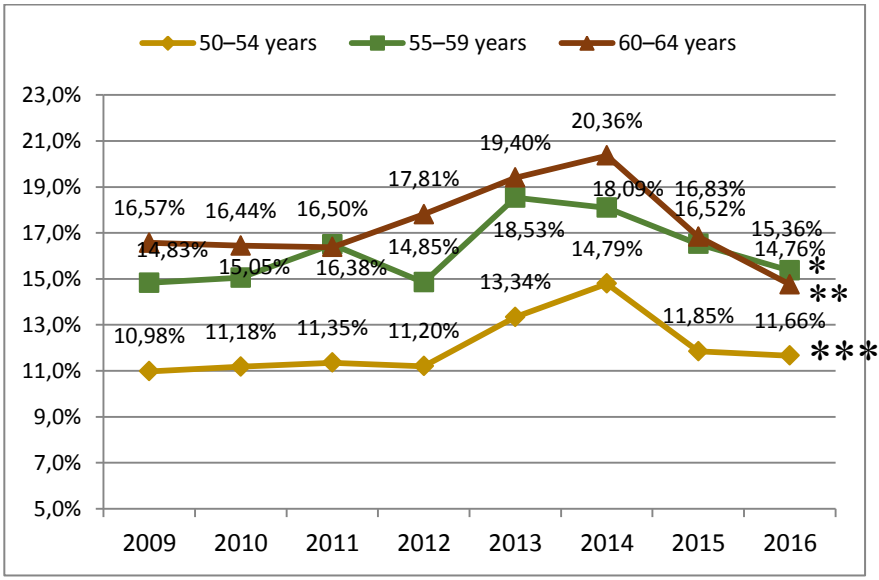
3.1.6 The Prevalence of Severe Dyslipidemia in the Study Population

Severe dyslipidemia was diagnosed for 13.4% (n=12 334) of study subjects (n=92 373). Severe dyslipidemia made up 14.9% (n=12 334) of the dyslipidemia cases (n=82 893). Severe dyslipidemia was more prevalent among women compared to men (14.63% vs. 10.5%, p <0,001, respectively). While assessing the trends of the prevalence of severe dyslipidemia from 2009 to 2016, the prevalance decreased from 12.2% in 2009 to 11.6% in 2016 (p <0.013). Trends in the prevalence of severe dyslipidemia among men and women in different age groups over the period of 2009–2016 are shown in Figures 13–15.



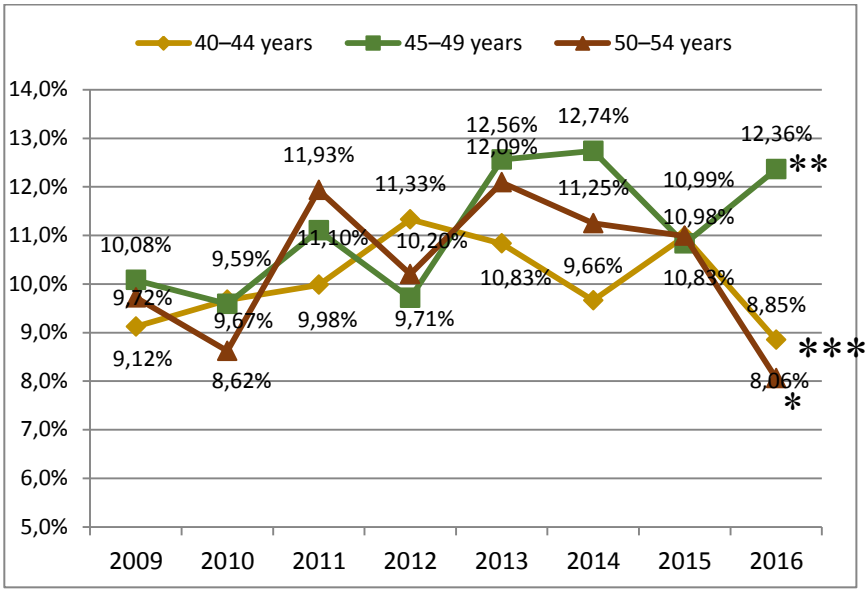
* p=0.004; ** p=0.013; *** p=0.078.

Figure 13. *Trends in the prevalence of any type of severe dyslipidemia among middle-aged Lithuanian adults from 2009 to 2016.*



* p=0.016; ** p=0.191; *** p=0.006.

Figure 14. *Trends in the prevalence of any type of severe dyslipidemia among middle-aged Lithuanian women (50–64 years) from 2009 to 2016.*



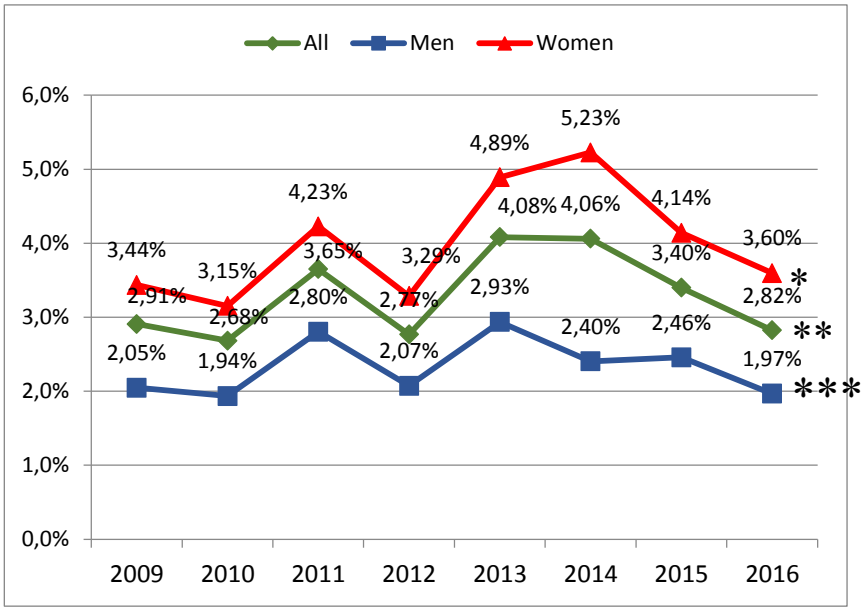
* p=0.005; ** p=0.894; *** p=0.679.

Figure 15. T*rends in the prevalence of any type of severe dyslipidemia among middle-aged Lithuanian men (40–54 years) from 2009 to 2016.*

3.1.7 The Prevalence of Severe Hypercholesterolemia and Severe Hypertriglyceridemia in the Study Population

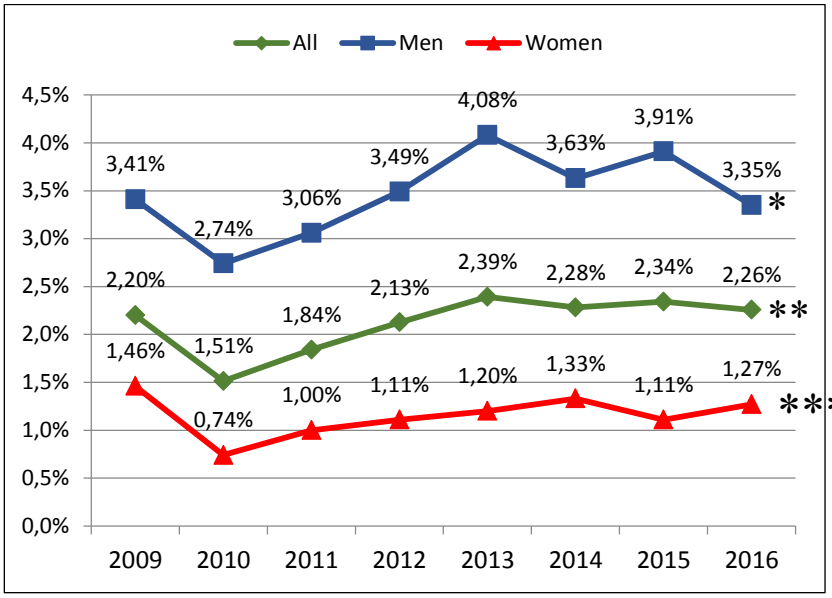
Severe hypercholesterolemia (LDL-C ≥ 6 mmol/l) was detected in 3.2% (2 956) of the subjects, while severe hypertriglyceridemia (TG ≥4.5 mmol/l) was observed in 2.0% (1 827) of the subjects. The prevalence of severe hypercholesterolemia in the overall population decreased from 2.91% to 2.82% (p=0.003), and the prevalence of severe hypertriglyceridemia increased from 2.20% to 2.26% (p= 0.001) in the overall population over the period of 2009–2016 (Figures 16, 17). Patients with severe hypercholesterolemia were significantly older in comparison with the severe hypertriglyceridemia group (54.14±6.22 years vs. 49.37±6.10 years,

p<0.001). There were no statistically significant changes in the prevalence of LDL-C ≥6 mmol/l or TG ≥4.5 mmol/l in different age groups.



* $p<0.001$; ** $p=0.003$; *** $p=0.574$.

Figure 16. *Trends of the prevalence of severe hypercholesterolemia (LDL-C ≥6.0 mmol/l) among middle-aged Lithuanians from 2009 to 2016.*



* p=0.017; ** p<0.001; *** p=0.358.

Figure 17. *Trends of the prevalence of severe triglyceridemia (TG ≥4.5 mmol/l) among middle-aged Lithuanians from 2009 to 2016.*

3.1.8 An Analysis and Comparison of the Cardiovascular Risk Profiles of Patients with Severe Hypercholesterolemia and Severe Hypertriglyceridemia

This study included 2 956 patients with severe hypercholesterolemia and 1 827 subjects with severe hypertriglyceridemia (a total of 4 783). The two groups were compared by demographic characteristics, laboratory parameters and the frequency of cardiovascular risk factors (Table 3). Patients with severe hypercholesterolemia were older compared to severe triglyceridemia group (54.14 years vs. 49.37 years, p <0,001). While assessing the prevalence of major CVD risk factors, all cardiovascular risk factors, except the family history of CHD, were more prevalent among

patients with severe hypertriglyceridemia compared with subjects with severe hypercholesterolemia (Table 3).

Table 3. *The comparison of baseline characteristics and the cardiovascular risk profile of patients with severe hypercholesterolemia and severe hypertriglyeridemia.*

Characteristics	Total		LDL-C ≥6 mmol/l		TG ≥4.5 mmol/l		*p-value*
	n=4 783		n=2 956		n=1 827		
	Mean	SD	Mean	SD	Mean	SD	
Age (years)	52.32	6.60	54.14	6.22	49.37	6.10	<0.001
WC (cm)	96.91	13.24	93.04	11.98	103.18	12.77	<0.001
BMI (kg/m²)	29.65	5.07	28.61	4.69	31.34	5.22	<0.001
SBP (mmHg)	136.68	17.17	135.14	16.78	139.17	17.50	<0.001
DBP (mmHg)	84.51	9.95	83.51	9.58	86.12	10.31	<0.001
HR (bpm)	72.87	8.94	72.33	8.80	73.75	9.11	<0.001
Glucose (mmol/l)	5.92	1.84	5.54	1.06	6.54	2.54	<0.001
TC (mmol/l)	8.22	1.44	8.89	0.91	7.14	1.47	<0.001
LDL-C (mmol/l)	5.43	1.76	6.61	0.65	3.52	1.25	<0.001
HDL-C (mmol/l)	1.39	0.46	1.57	0.40	1.12	0.40	<0.001
TG (mmol/l)	3.78	3.18	1.92	0.78	6.79	3.29	<0.001
Non-HDL-C	6.83	1.30	7.33	0.87	6.02	1.46	<0.001
SCORE index	2.82	2.34	2.99	2.35	2.55	2.30	<0.001
Frequencies	n	%	n	%	n	%	
DM (%)	851	17.8	335	11.3	516	28.2	<0.001
AH (%)	3065	64.1	1801	60.9	1264	69.2	<0.001
Abdominal obesity (%)	2537	53.0	1425	48.2	1112	60.9	<0.001
Smoking (%)	1351	28.2	675	22.8	676	37.0	<0.001
Metabolic syndrome (%)	2665	55.7	1270	43.0	1395	76.4	<0.001
RF ≥3 (%)	3490	73.0	1957	66.2	1533	83.9	<0.001

CHD history (%)	1436	30.0	902	30.5	534	29.2	0.346
Diet (unbalanced) (%)	3272	68.4	1903	64.4	1369	74.9	<0.001
Physical activity (insufficient) (%)	2769	57.9	1614	54.6	1155	63.2	<0.001
BMI <25 (kg/m²) (%)	795	16.6	643	21.8	152	8.3	<0.001
BMI 25-30 (kg/m²) (%)	1972	41.2	1321	44.7	651	35.6	<0.001
BMI 30-40 (kg/m²) (%)	1859	38.9	929	31.4	930	50.9	<0.001
BMI >40 (kg/m²) (%)	157	3.3	63	2.1	94	5.1	<0.001

Abbreviations: SD – standard deviation; WC – waist circumference; BMI – body mass index; SBP – systolic blood pressure; DBP – diastolic blood pressure; HR – heart rate; TC – total cholesterol; LDL-C – low-density lipoprotein cholesterol; HDL-C – high-density lipoprotein cholesterol; TG – triglycerides; DM – diabetes mellitus; AH – arterial hypertension; RF – risk factors; CHD – coronary heart disease.

3.1.9 The Characteristics of Subjects with Different Low-Density Lipoprotein Cholesterol Levels

According to our database, 19.8% of subjects without overt cardiovascular disease (n=18 290, 49.6% women and 50.4% men, p<0.01) had LDL-C less than 3 mmol/l. From 2009 to 2016 a significant decrease in number of subjects with normal LDL-C (<3 mmol/l) levels was observed in the whole study population (from 21.9% to 19.3%, p=0.001) and both gender groups (men's group from 25.5% to 22.9%, p=0.001, women's group from 19.7% to 16.1%, p=0.001). The distribution of LDL-C levels in the middle-aged Lithuanian adults over the period of 2009-2016 is shown in figure 18. In the study population, LDL-C >3 mmol/l was more frequently determined in women compared to men (Figure 19). We additionally evaluated TG levels for patients with elevated LDL-C. 1.4% (n=1293) of adults with disregarded TG levels had LDL-C 6.5–8.49 mmol/l, while both LDL-C 6.5–8.49 mmol/l and TG ≤1.7 mmol/l were found in 0.6% (n=554) of the subjects (Figure 20).

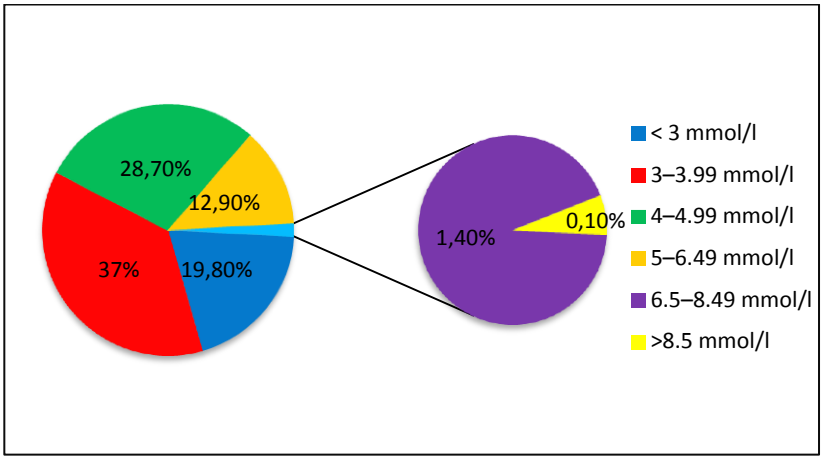


Figure 18. *The distribution of LDL-C levels in middle-aged Lithuanian adults during the period 2009–2016.*

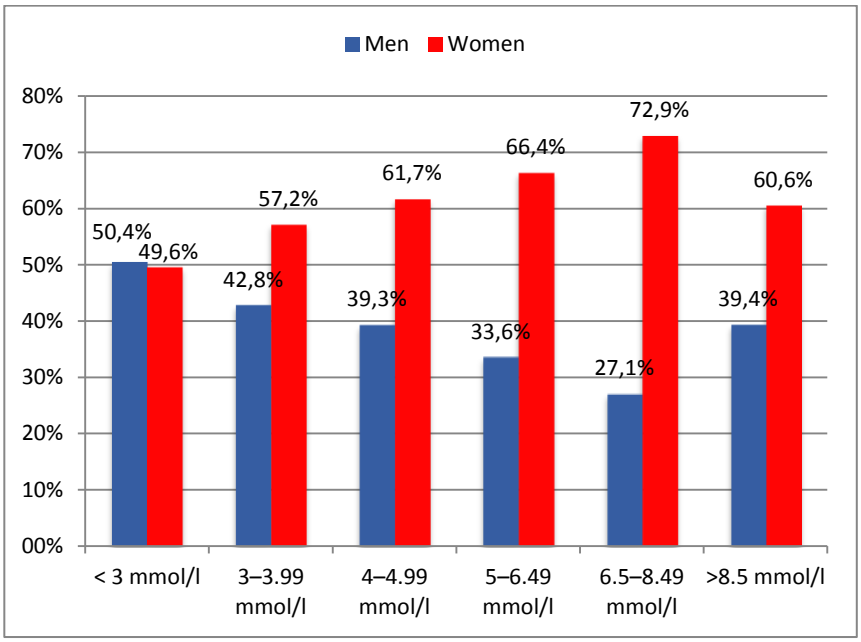
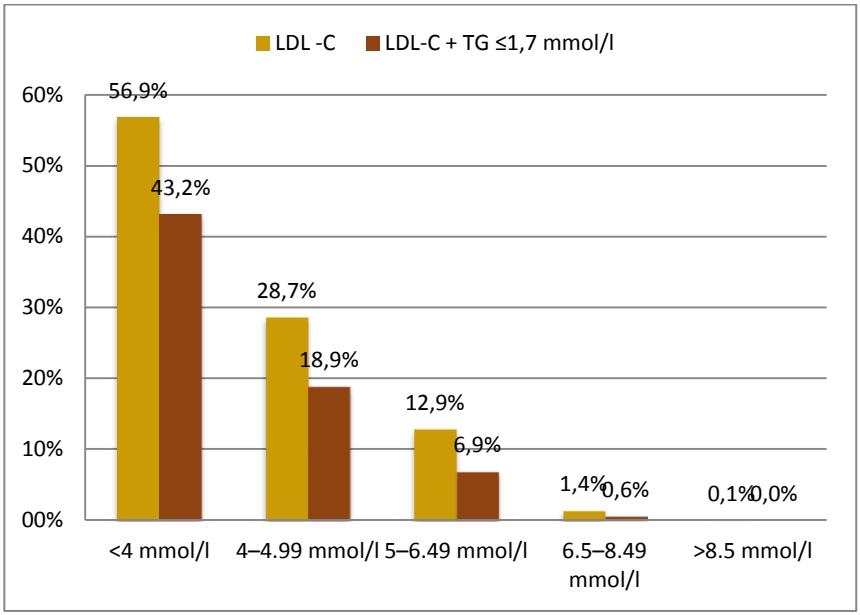


Figure 19. *The differences in LDL-C levels in middle-aged Lithuanian men and women during the period 2009–2016.*



Abbrevations: LDL-C – low-density lipoprotein cholesterol; TG – triglycerides.

Figure 20. *The distribution of LDL-C levels and LDL-C levels with normal TG levels in middle-aged Lithuanian adults during the period of 2009–2016.*

3.1.10 The Characteristics of Subjects with Different Triglycerides Levels

Of all subjects, 68.9% (n=63 644, 61.4% women and 38.6% men, p<0.01) had the concentration of triglycerides that amounted to less than 1.7 mmol/l. During the period of 2009–2016, the prevalence of normal TG levels (<1.7 mmol/l) decreased from 69.69% to 69.09% (p <0.001) in all study participants. This pattern was also seen in men (from 64.31% to 63.63%, p=0.002), but the mean TG values remained consistent in women (from 73.0% to 74.0%, p=0.778). The distribution of different TG levels in the middle-aged Lithuanian population over the period of 2009–2016 is shown in Figure 21. The

TG levels of <2.3 mmol/l were more commonly found in women, while the TG levels of >11.2 mmol/l were more common among men (Figure 22).

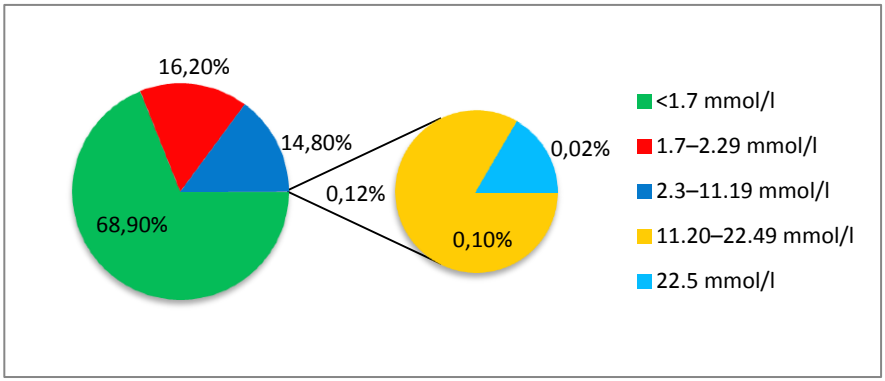


Figure 21. *The distribution of TG levels in middle-aged Lithuanian adults during the period of 2009–2016.*

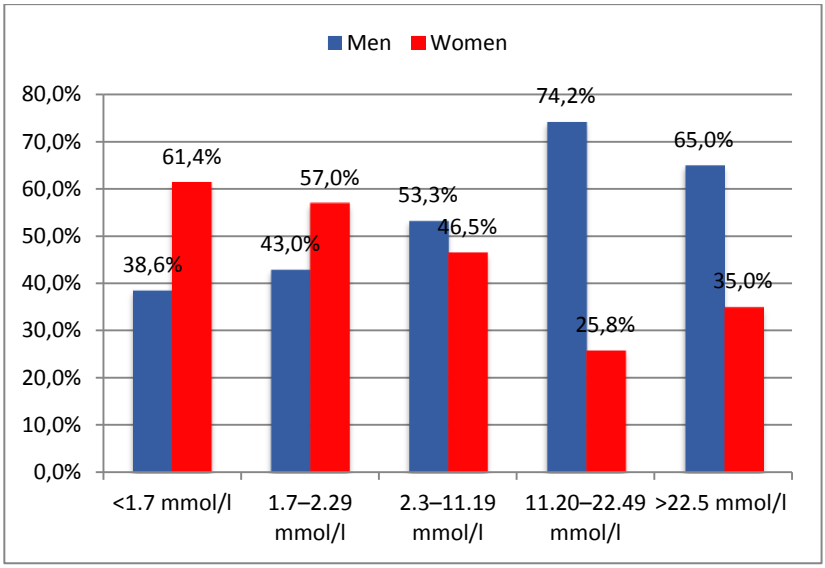


Figure 22. *The differences in TG levels in middle-aged Lithuanian men and women during the period of 2009–2016.*

3.1.11 The Cardiovascular Risk Profile of Patients with Atherogenic Dyslipidemia, Hypertriglyceridemia and Low HDL-C

In the program's population, 8.1% (n=7 489) of subjects had atherogenic dyslipidemia (54.5% of them were women and 45.5% men). Isolated high TG (>1.7 mmol/l) was observed in 22.3% of adults, and the prevalence of isolated low HDL-C (<1.2 mmol/l in women and <1.0 mmol/l in men) was 5.6%. The mean age in the atherogenic dyslipidemia group was 52.03 ± 6.60 years. The average values of triglycerides were lower in the older men and women with atherogenic dyslipidemia compared to younger subjects.

Demographic, anthropometric and laboratory characteristics of participants with AD, hypertriglyceridemia and low-HDL-C levels groups are shown in Table 4. Participants in the low-HDL-C group were statistically significantly older (52.41 ± 6.33 years) in comparison with other groups. Participants with AD tended to have higher prevalences of AH (69.0%), DM (22.6%), abdominal obesity (67.6%), MetS (88.9%), an unbalanced diet (71.0%), low physical activity (64.2%) and the percentage of people having more than 3 risk factors (86.1%). In addition, the prevalence of smoking (26.1%) and CHD in the first degree relatives (29.1%) was higher in the AD group than in the low-HDL-C group. Participants in low-HDL group had a more favorable risk profile: a lower prevalence of DM (12.5%), AH (56.9%), MetS (52.7%), smoking (22.3%), an unbalanced diet (62.2%) and low physical activity (56.5%). Participants in the hypertriglyceridemia group had higher values of total cholesterol (6.74 ± 1.24mmol/l), LDL-C (4.28 ± 1.16mmol/l), HDL-C (1.45 ± 0.34mmol/l), non-HDL cholesterol (5.29 ± 1.22mmol/l) and the SCORE index (2.27 ± 1.94) in comparison with other groups.

Table 4. *A comparison of demographic characteristics, laboratory parameters and the cardiovascular risk factors of participants with atherogenic dyslipidemia, hypertriglyceridemia and low HDL-C.*

Characteristics	Atherogenic dyslipidemia		Hyper-triglyceridemia		Low HDL-C		*p-value*	*p-value* (AD vs. HTG)	*p-value* (AD vs. HDL-C)	*p-value* (HTG vs. HDL-C)
	n=7 489		n=20 593		n=5 153					
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**				
Age (years)	52.03	6.6	51.71	6.44	52.41	6.33	<0.001	0.001	0.004	<0.001
BMI (kg/m²)	31.91	5.63	30.21	5.30	29.99	5.95	<0.001	<0.001	<0.001	0.027
SBP (mmHg)	137.61	16.95	136.85	16.79	133.87	16.36	<0.001	0.002	<0.001	<0.001
DBP (mmHg)	84.93	9.71	84.66	9.73	82.87	9.31	<0.001	0.093	<0.001	<0.001
HR (bpm)	73.02	8.70	72.67	8.77	72.52	8.88	0.002	0.009	0.005	0.519
Glucose (mmol/l)	6.06	1.90	5.76	1.47	5.55	1.27	<0.001	<0.001	<0.001	<0.001
TC (mmol/l)	6.16	1.25	6.74	1.24	5.10	1.05	<0.001	<0.001	<0.001	<0.001
LDL-C (mmol/l)	3.89	1.12	4.28	1.16	3.53	0.97	<0.001	<0.001	<0.001	<0.001
HDL-C (mmol/l)	0.95	0.15	1.45	0.34	0.98	0.15	<0.001	<0.001	<0.001	<0.001

TG (mmol/l)	3.16	2.09	2.55	1.22	1.24	0.29	<0.001	<0.001	<0.001	<0.001
Non-HDL-C (mmol/l)	5.20	1.23	5.29	1.22	4.11	1.02	<0.001	<0.001	<0.001	<0.001
TG/HDL-C ratio	3.58	4.11	1.86	1.04	1.32	0.55	<0.001	<0.001	<0.001	<0.001
SCORE index	2.19	1.95	2.27	1.94	1.63	1.45	<0.001	0.008	<0.001	<0.001
Atherogenic index (log (TG/HDL-C))	0.48	0.22	0.23	0.17	0.10	0.14	<0.001	<0.001	<0.001	<0.001
Frequencies	**n**	**%**	**n**	**%**	**n**	**%**	***p***	***p***	***p***	***p***
DM (%)	1696	22.6	3258	15.8	644	12.5	<0.001	<0.001	<0.001	<0.001
AH (%)	5170	69.0	13373	64.9	2934	56.9	<0.001	<0.001	<0.001	<0.001
Abdominal obesity (%)	5062	67.6	11485	55.8	2764	53.6	<0.001	<0.001	<0.001	0.018
Smoking(%)	1953	26.1	5319	25.8	1148	22.3	<0.001	<0.001	<0.001	<0.001
MetS (%)	6657	88.9	11809	57.3	2714	52.7	<0.001	<0.001	<0.001	<0.001
RF ≥3 (%)	6448	86.1	15051	73.1	3473	67.4	<0.001	<0.001	<0.001	<0.001
CHD history (%)	2176	29.1	5716	27.8	1311	25.4	<0.001	<0.001	<0.001	0.003
Diet (unbalanced) (%)	5319	71.0	14086	68.4	3204	62.2	<0.001	<0.001	<0.001	<0.001
Physical activity	4811	64.2	11737	57.0	2910	56.5	<0.001	<0.001	<0.001	<0.001

(insufficient) (%)										
BMI <25 (kg/m²) (%)	591	7.9	2996	14.5	1001	19.4	<0.001	<0.001	<0.001	<0.001
BMI 25-30 (kg/m²) (%)	2451	32.7	7950	38.6	1877	36.4	<0.001	<0.001	<0.001	<0.001
BMI 25-30 (kg/m²) (%)	3844	51.3	8706	42.3	1952	37.9	<0.001	<0.001	<0.001	<0.001
BMI 25-30 (kg/m²) (%)	603	8.1	941	4.6	323	6.3	<0.001	<0.001	<0.001	<0.001

Abbreviations: HDL-C – high-density lipoprotein cholesterol; SD – standard deviation; AD – atherogenic dyslipidemia; HTG – hypertrygliceridemia; WC – waist circumference; BMI – body mass index; SBP – systolic blood pressure; DBP – diastolic blood pressure; HR – heart rate; TC – total cholesterol; LDL-C – low-density lipoprotein cholesterol; TG – triglycerides; DM – diabetes mellitus; AH – arterial hypertension; MS – metabolic syndrome; RF – risk factors; CHD – coronary heart disease.

3.1.12 The Associations of Cardiovascular Risk Factors with Different Types of Dyslipidemia (Atherogenic Dyslipidemia, Hypertriglyceridemia and Low HDL-C)

According to the program's database, all analyzed risk factors, including the main risk factors, such as DM (OR: 2.74, 95% CI: 2.58-2.90), AH (OR: 1.96, 95% CI 1.87-2.01), obesity (OR: 2.92, 95% CI: 2.78-3.10) and smoking (OR: 2.74, 95% CI: 2.58-2.90), were significantly associated with AD and hypertriglyceridemia (Table 5). There was no association between isolated low HDL-C levels and smoking, CHD history in first-degree relatives and an unbalanced diet.

Further statistical analysis according to gender revealed that arterial hypertension, diabetes mellitus, obesity, metabolic syndrome, an unbalanced diet and CHD history in first-degree relatives were significantly associated with AD and isolated hypertriglyceridemia in both men and women. An unbalanced diet was significantly associated with low-HDL in men; however, smoking did not show any significant association with AD and low-HDL in men. There was a significant association between an unbalanced diet and low-HDL in women (OR: 1.09, 95% CI 1.01-1.17).

Table 5. *The associations of cardiovascular risk factors with different types of dyslipidemia (atherogenic dyslipidemia, hypertriglyceridemia and low HDL-C).*

Risk factor	Group	Atherogenic dyslipidemia		Hypertriglyceridemia		Low HDL-C	
		OR (95 % CI)	*p-value*	OR (95 % CI)	*p-value*	OR (95 % CI)	*p-value*
DM	Total	2.74 (2.58-2.90)	<0.001	1.84 (1.76-1.93)	<0.001	1.20 (1.11-1.31)	0.001
	Men	2.13 (1.94-2.34)	<0.001	1.69 (1.57-1.81)	<0.001	1.08 (0.94-1.25)	0.293
	Women	3.29 (3.05-3.55)	<0.001	2.02 (1.90-2.15)	<0.001	1.28 (1.15-1.42)	0.001
AH	Total	1.96 (1.87-2.01)	<0.001	1.75 (1.69-1.80)	<0.001	1.11 (1.05-1.18)	0.001
	Men	1.70 (1.59-1.83)	<0.001	1.78 (1.70-1.87)	<0.001	0.89 (0.82-0.98)	0.014
	Women	2.40 (2.23-2.59)	<0.001	1.92 (1.84-2.02)	<0.001	1.27 (1.18-1.37)	0.001
Smoking	Total	1.20 (1.14-1.27)	<0.001	1.22 (1.18-1.27)	<0.001	0.96 (0.90-1.03)	0.225
	Men	1.07 (0.99-1.14)	0.081	0.95 (0.91-0.99)	0.043	1.04 (0.95-1.14)	0.378
	Women	1.29 (1.17-1.42)	<0.001	1.27 (1.19-1.36)	<0.001	0.94 (0.83-1.06)	0.296
Obesity	Total	2.92 (2.78-3.10)	<0.001	1.87 (1.81-1.93)	<0.001	1.52 (1.44-1.61)	0.001
	Men	3.09 (2.88-3.32)	<0.001	2.19 (2.09-2.30)	<0.001	1.34 (1.22-1.47)	0.001
	Women	3.75 (3.46-4.06)	<0.001	2.29 (2.19-2.40)	<0.001	1.67 (1.54-1.80)	0.001
MetS	Total	22.27 (20.69-23.97)	<0.001	4.24 (4.10-4.38)	<0.001	2.57 (2.43-2.72)	0.001
	Men	17.51 (15.97-19.19)	<0.001	3.97 (3.78-4.17)	<0.001	1.72 (1.57-1.89)	0.001
	Women	38.52 (33.68-44.04)	<0.001	5.23 (5.00-5.48)	<0.001	3.31 (3.07-3.57)	0.001

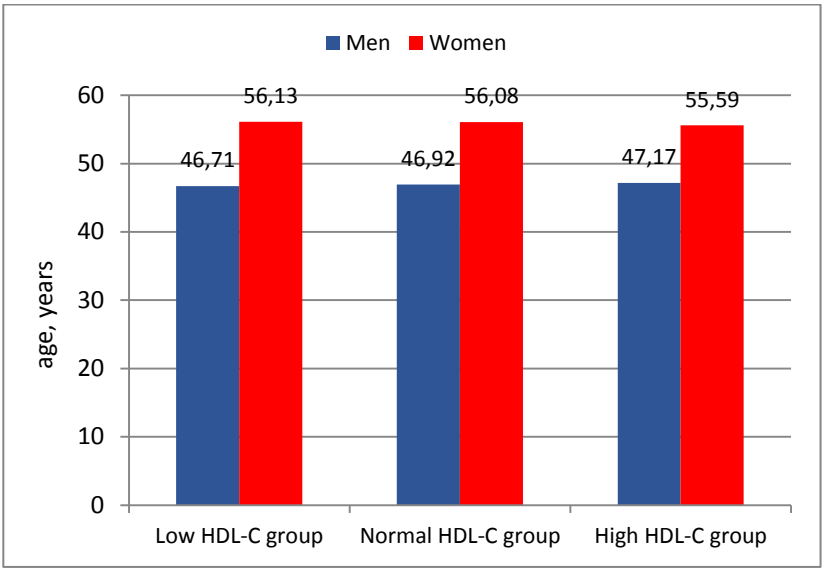
CHD history	Total	1.18 (1.12-1.25)	<0.001	1.12 (1.08-1.16)	<0.001	0.97 (0.90-1.03)	0.340
	Men	1.30 (1.20-1.40)	<0.001	1.20 (1.14-1.26)	<0.001	0.96 (0.86-1.07)	0.427
	Women	1.13 (1.05-1.21)	<0.001	1.11 (1.06-1.16)	<0.001	0.97 (0.89-1.05)	0.414
Diet (unbalanced) (%)	Total	1.59 (1.51-1.68)	<0.001	1.47 (1.43-1.52)	<0.001	1.03 (0.97-1.09)	0.297
	Men	1.47 (1.36-1.58)	<0.001	1.49 (1.42-1.56)	<0.001	0.96 (0.88-1.06)	0.407
	Women	1.68 (1.56-1.80)	<0.001	1.42 (1.36-1.49)	<0.001	1.09 (1.01-1.17)	0.029
Physical activity (insufficient)	Total	1.80 (1.71-1.89)	<0.001	1.35 (1.31-1.40)	<0.001	1.25 (1.19-1.33)	<0.001
	Men	1.79 (1.67-1.92)	<0.001	1.42 (1.35-1.48)	<0.001	1.13 (1.04-1.24)	0.007
	Women	1.87 (1.74-1.99)	<0.001	1.40 (1.34-1.46)	<0.001	1.33 (1.23-1.43)	0.001
RF ≥3	Total	1.47 (1.38-1.57)	<0.001	1.58 (1.51-1.64)	<0.001	0.90 (0.84-0.96)	0.002
	Men	1.99 (1.76-2.25)	<0.001	1.56 (1.46-1.67)	<0.001	1.19 (1.04-1.36)	0.011
	Women	1.26 (1.16-1.36)	<0.001	1.45 (1.37-1.52)	<0.001	0.82 (0.76-0.89)	0.001

Abbreviations: OR – odds ratio; HDL-C – high-density lipoprotein cholesterol; DM – diabetes mellitus; AH – arterial hypertension; MetS – metabolic syndrome; RF – risk factors; CHD – coronary heart disease.

3.1.13 The Distribution of High-Density Lipoprotein Cholesterol Levels among Study Population and Associations with Other Cardiovascular Risk Factors

Of all subjects, 42.8% (n=39 496) had normal levels of HDL-C, 43.6% (n=40 235) – high concentrations of HDL-C, and 13.7% (n=12 642) of the population had low HDL-C. The mean age in the low HDL-C group was 52.19 ± 6.49 years, in the normal HDL-C group – 51.00 ± 6.34, and 53.27 ± 5.76 years ($p < 0.001$) in the high HDL-C group (Table 6). Men in the high HDL-C group were older compared to men with low or normal HDL-C ($p<0.001$). In contrast, women with low HDL-C were older than women with normal or high HDL-C ($p<0.001$) (Figure 23).

The baseline characteristics and comparison of cardiovascular risk profiles of patients with low, normal and high HDL-C levels are shown in Table 6. The mean concentration of TC was the highest (6.31 ± 1.18) in patients with high HDL-C compared to subjects with low or normal HDL-C, $p<0.001$. Mean levels of LDL-C were the highest in patients with normal HDL-C (3.95 ± 1.04, $p<0.001$), while the highest mean concentration of TG was found in subjects with low HDL-C (2.38 ± 1.87, $p<0.001$). All cardiovascular risk factors, except for smoking, were most prevalent among the patients with low HDL-C ($p<0.001$): AH (64.1%), DM (18.5%), abdominal obesity (61.9%), MetS (74.1%), family history of CHD (27.6%), an unhealthy diet (67.4%), insufficient physical activity (61.1%) and a BMI of 30–40 (kg/m²) (45.8%). Smoking was most prevalent among subjects with normal HDL-C (25.1%), followed by low HDL-C (24.5%) and high HDL-C (20.4%) ($p<0.001$) (Table 6).



Abbreviations: HDL-C – high-density lipoprotein cholesterol.

Figure 23. *Age differences (in years) between the analyzed groups of HDL-C levels (p=0.001).*

Table 6. *A comparison of baseline characteristics and the cardiovascular risk profiles of patients with low, normal and high HDL-C levels.*

Characteristics	Low HDL-C		Normal HDL-C		High HDL-C		*p*	*p* (1 gr. vs. 2 gr.)	*p* (1 gr. vs. 3 gr.)	*p* (2 gr. vs. 3 gr.)
	n=12642		n=39496		n=40235					
	Mean	SD	Mean	SD	Mean	SD				
Age (years)	52.19	6.49	51.00	6.34	53.27	5.76	<0.001	<0.001	<0.001	<0.001
WC (cm)	99.99	13.96	96.23	13.01	89.28	12.42	<0.001	<0.001	<0.001	<0.001
BMI (kg/m²)	31.12	5.84	29.20	5.29	27.22	4.98	<0.001	<0.001	<0.001	<0.001
SBP (mmHg)	136.08	16.81	133.97	16.11	132.27	16.27	<0.001	<0.001	<0.001	<0.001
DBP (mmHg)	84.09	9.60	83.26	9.51	81.86	9.33	<0.001	<0.001	<0.001	<0.001
HR (bpm)	72.81	8.78	71.84	9.10	71.78	8.44	<0.001	<0.001	<0.001	0.579
Glucose (mmol/l)	5.85	1.69	5.57	1.24	5.36	0.97	<0.001	<0.001	<0.001	<0.001
TC (mmol/l)	5.72	1.28	5.97	1.19	6.31	1.18	<0.001	<0.001	<0.001	<0.001
LDL-C (mmol/l)	3.75	1.08	3.95	1.04	3.84	1.10	<0.001	<0.001	<0.001	<0.001

HDL-C (mmol/l)	0.97	0.15	1.31	0.14	1.94	0.38	<0.001	<0.001	<0.001	<0.001
TG (mmol/l)	2.38	1.87	1.70	1.06	1.23	0.72	<0.001	<0.001	<0.001	<0.001
Non-HDL-C	4.76	1.27	4.66	1.18	4.36	1.20	<0.001	<0.001	<0.001	<0.001
TG/HDL-C	2.66	3.37	1.33	0.91	0.66	0.42	<0.001	<0.001	<0.001	<0.001
SCORE index	1.96	1.78	1.88	1.69	1.84	1.63	<0.001	<0.001	<0.001	0.001
Atherogenic index (log (TG/HDL-C))	0.32	0.27	0.06	0.23	-0.24	0.22	<0.001	<0.001	<0.001	<0.001
Frequencies	n	%	n	%	n	%				
DM (%)	2340	18.5	4559	11.5	2998	7.5	<0.001	<0.001	<0.001	<0.001
AH (%)	8104	64.1	22058	55.8	20155	50.1	<0.001	<0.001	<0.001	<0.001
Abdominal obesity (%)	7826	61.9	17998	45.6	14584	36.2	<0.001	<0.001	<0.001	<0.001
Smoking (%)	3101	24.5	9917	25.1	8200	20.4	<0.001	0.582	<0.001	<0.001
MetS (%)	9371	74.1	12356	31.3	7367	18.3	<0.001	<0.001	<0.001	<0.001
RF ≥3 (%)	9921	78.5	23879	60.5	20171	50.1	<0.001	<0.001	<0.001	<0.001
CHD history (%)	3487	27.6	10243	25.9	10295	25.6	<0.001	0.001	<0.001	0.798

Diet (unbalanced) (%)	8523	67.4	24982	63.3	23295	57.9	<0.001	<0.001	<0.001	<0.001
Physical activity (insufficient) (%)	7721	61.1	20620	52.2	18927	47.0	<0.001	<0.001	<0.001	<0.001
BMI <25 (kg/m²) (%)	1592	12.6	8391	21.2	14908	37.1	<0.001	<0.001	<0.001	<0.001
BMI 25-30 (kg/m²) (%)	4328	34.2	15915	40.3	15346	38.1	<0.001	<0.001	<0.001	<0.001
BMI 30-40 (kg/m²) (%)	5796	45.8	13742	34.8	9240	23.0	<0.001	<0.001	<0.001	<0.001
BMI >40 (kg/m²) (%)	926	7.3%	1448	3.7	741	1.8	<0.001	<0.001	<0.001	<0.001

Abbreviations: HDL-C – high-density lipoprotein cholesterol; SD – standard deviation; WC – waist circumference; BMI – body mass index; SBP – systolic blood pressure; DBP – diastolic blood pressure; HR – heart rate; TC – total cholesterol; LDL-C – low-density lipoprotein cholesterol; TG – triglycerides; DM –diabetes mellitus; AH – arterial hypertension; MetS – metabolic syndrome; RF – risk factors; CHD – coronary heart disease.

3.1.14 The Associations of Cardiovascular Risk Factors with Lipidogram Parameters

All analyzed cardiovascular risk factors, except for DM, were associated with increased and severely increased levels of TC and LDL-C (Tables 7, 8). DM was significantly related only to severely increased concentration of TC (OR: 1.317, 95% CI: 1.227-1.414). Smoking was determined less frequently together with moderate hypercholesterolemia (OR: 0.895, 95% CI: 0.86-0.93) while more frequently with severe hypercholesterolemia (OR: 1.213, 95% CI: 1.1-1.337) (Table 8). All evaluated CVD risk factors were associated with increased and severely increased levels of triglycerides (Table 9). All analyzed CVD risk factors, including DM (OR: 1.68, 95% CI: 1.59-1.775), AH (OR: 1.311, 95% CI 1.257-1.368), obesity (OR: 1.744, 95% CI: 1.67-1.821) and smoking (OR: 1.202, 95% CI: 1.144-1.264), were significantly related to low levels of HDL-C (Table 10).

Table 7. *The associations of cardiovascular risk factors with different total cholesterol concentrations.*

Risk factor	Group	5.2 mmol/l> TC <7.5 mmol/l			TC ≥7.5 mmol/l		
		OR (CI)	*p-value*	**p-value*	OR (CI)	*p-value*	**p-value*
Insufficient physical activity	Women	1.04 (0.995;1.088)	0.079	<0.001	1.119 (1.054;1.187)	<0.001	<0.001
	Men	1.174 (1.123;1.228)	<0.001		1.39 (1.287;1.502)	<0.001	
	Total	1.105 (1.071;1.14)	<0.001		1.214 (1.159;1.273)	<0.001	
Unbalanced diet	Women	1.243 (1.189;1.299)	<0.001	0.001	1.388 (1.307;1.474)	<0.001	<0.001
	Men	1.381 (1.32;1.445)	<0.001		1.772 (1.63;1.927)	<0.001	

	Total	1.309 (1.268;1.351)	<0.001		1.515 (1.443;1.59)	<0.001	
DM	**Women**	0.915 (0.853;0.981)	0.013	<0.001	1.14 (1.042;1.248)	0.004	<0.001
	Men	1.134 (1.051;1.222)	0.001		1.714 (1.529;1.923)	<0.001	
	Total	1.012 (0.962;1.066)	0.643		1.317 (1.227;1.414)	<0.001	
AH	**Women**	1.086 (1.038;1.135)	<0.001	<0.001	1.365 (1.285;1.451)	<0.001	<0.001
	Men	1.384 (1.324;1.447)	<0.001		1.867 (1.727;2.018)	<0.001	
	Total	1.227 (1.189;1.266)	<0.001		1.537 (1.466;1.612)	<0.001	
Smoking	**Women**	1.12 (1.039;1.207)	0.003	0.086	1.385 (1.26;1.523)	<0.001	0.011
	Men	1.037 (0.992;1.085)	0.111		1.185 (1.096;1.281)	<0.001	
	Total	1.059 (1.019;1.101)	0.004		1.257 (1.184;1.335)	<0.001	
Obesity	**Women**	1.013 (0.97;1.059)	0.554	<0.001	1.067 (1.005;1.132)	0.033	<0.001
	Men	1.267 (1.205;1.332)	<0.001		1.599 (1.472;1.737)	<0.001	
	Total	1.118 (1.082;1.156)	<0.001		1.217 (1.16;1.277)	<0.001	
CHD history	**Women**	1.07 (1.018;1.125)	0.008	0.106	1.274 (1.193;1.36)	<0.001	0.959
	Men	1.136 (1.078;1.198)	<0.001		1.279 (1.171;1.398)	<0.001	
	Total	1.101 (1.061;1.141)	<0.001		1.277 (1.212;1.345)	<0.001	
MetS	**Women**	1.178 (1.123;1.236)	<0.001	<0.001	1.83 (1.721;1.946)	<0.001	<0.001
	Men	1.637 (1.551;1.727)	<0.001		3.001 (2.763;3.26)	<0.001	
	Total	1.365 (1.317;1.415)	<0.001		2.164 (2.06;2.273)	<0.001	

BMI >30	**Women**	0.948 (0.907;0.992)	0.021	<0.001	0.891 (0.839;0.947)	<0.001	<0.001
	Men	1.298 (1.234;1.365)	<0.001		1.583 (1.456;1.72)	<0.001	
	Total	1.093 (1.057;1.13)	<0.001		1.079 (1.028;1.133)	0.002	
RF >=3	**Women**	1.901 (1.807;2)	<0.001	<0.001	2.555 (2.369;2.755)	<0.001	<0.001
	Men	2.321 (2.206;2.442)	<0.001		3.627 (3.26;4.035)	<0.001	
	Total	2.103 (2.029;2.179)	<0.001		2.906 (2.734;3.089)	<0.001	

* *p* – homogeneity of variance
Abbreviations: TC – total cholesterol; OR – odds ratio; DM – diabetes mellitus; AH – arterial hypertension; CHD – coronary heart disease; MetS – metabolic syndrome; BMI – body mass index; RF – risk factors.

Table 8. *The associations of cardiovascular risk factors with different low-density lipoprotein cholesterol concentrations.*

Risk factors	**Group**	**3mmol/l > LDL-C< 6 mmol/l**			**LDL-C ≥6 mmol/l**		
		OR (CI)	**p-value**	***p-value**	**OR (CI)**	**p-value**	***p-value**
Insufficient physical activity	**Women**	1.118 (1.069;1.169)	<0.001	0.578	1.219 (1.11;1.339)	<0.001	0.953
	Men	1.138 (1.086;1.193)	<0.001		1.225 (1.069;1.404)	0.004	
	Total	1.128 (1.092;1.164)	<0.001		1.221 (1.13;1.319)	<0.001	
Unbalanced diet	**Women**	1.305 (1.248;1.364)	<0.001	0.834	1.414 (1.285;1.556)	<0.001	0.234
	Men	1.296 (1.235;1.359)	<0.001		1.573 (1.358;1.824)	<0.001	
	Total	1.3 (1.259;1.344)	<0.001		1.461 (1.348;1.583)	<0.001	
DM	**Women**	0.987	0.718	0.573	1.027	0.722	0.039

		(0.92;1.059)			(0.887;1.189)		
	Men	1.017 (0.942;1.099)	0.665		1.339 (1.091;1.643)	0.005	
	Total	1.001 (0.95;1.054)	0.978		1.118 (0.992;1.26)	0.067	
AH	**Women**	1.2 (1.147;1.255)	<0.001	0.029	1.457 (1.323;1.604)	<0.001	0.561
	Men	1.289 (1.23;1.351)	<0.001		1.531 (1.335;1.755)	<0.001	
	Total	1.242 (1.203;1.283)	<0.001		1.48 (1.368;1.602)	<0.001	
Smoking	**Women**	0.975 (0.907;1.048)	0.494	0.005	1.375 (1.198;1.578)	<0.001	0.015
	Men	0.863 (0.823;0.904)	<0.001		1.08 (0.942;1.239)	0.271	
	Total	0.895 (0.86;0.93)	<0.001		1.213 (1.1;1.337)	<0.001	
Obesity	**Women**	1.257 (1.203;1.315)	<0.001	0.012	1.315 (1.198;1.445)	<0.001	0.652
	Men	1.376 (1.304;1.451)	<0.001		1.37 (1.179;1.592)	<0.001	
	Total	1.305 (1.262;1.351)	<0.001		1.33 (1.228;1.44)	<0.001	
CHD history	**Women**	1.082 (1.029;1.137)	0.002	0.087	1.351 (1.221;1.493)	<0.001	0.655
	Men	1.155 (1.092;1.222)	<0.001		1.295 (1.108;1.513)	0.001	
	Total	1.114 (1.073;1.156)	<0.001		1.334 (1.226;1.452)	<0.001	
MetS	**Women**	1.447 (1.378;1.519)	<0.001	0.539	2.266 (2.06;2.493)	<0.001	0.974
	Men	1.481 (1.4;1.565)	<0.001		2.26 (1.958;2.608)	<0.001	
	Total	1.461 (1.409;1.516)	<0.001		2.264 (2.091;2.451)	<0.001	

BMI>30	**Women**	1.182 (1.129;1.238)	<0.001	<0.001	1.023 (0.928;1.127)	<0.001	0.005
	Men	1.391 (1.318;1.468)	<0.001		1.323 (1.137;1.539)	<0.001	
	Total	1.268 (1.224;1.313)	<0.001		1.099 (1.013;1.193)	0.023	
RF >=3	**Women**	2.212 (2.104;2.326)	<0.001	0.061	2.955 (2.603;3.355)	<0.001	0.613
	Men	2.371 (2.25;2.498)	<0.001		3.129 (2.607;3.756)	<0.001	
	Total	2.288 (2.206;2.372)	<0.001		3.011 (2.713;3.342)	<0.001	

* *p* – homogeneity of variance

Abbreviations: LDL-C – low-density lipoprotein cholesterol; OR – odds ratio; DM – diabetes mellitus; AH – arterial hypertension; CHD – coronary heart disease; MetS – metabolic syndrome; BMI – body mass index; RF – risk factors.

Table 9. *The associations of cardiovascular risk factors with different triglycerides levels.*

Risk factor	Group	1,7 mmol/l < TG < 4,5 mmol/l			TG ≥ 4,5mmol/l		
		OR (CI)	p	*p	OR (CI)	p	*p
Insufficient physical activity	**Women**	1.601 (1.539;1.666)	<0.001	0.851	2.041 (1.72;2.421)	<0.001	0.732
	Men	1.61 (1.541;1.682)	<0.001		2.115 (1.89;2.367)	<0.001	
	Total	1.605 (1.559;1.653)	<0.001		2.091 (1.903;2.297)	<0.001	
Unbalanced diet	**Women**	1.564 (1.502;1.629)	<0.001	0.827	1.958 (1.641;2.336)	<0.001	0.558
	Men	1.553 (1.483;1.627)	<0.001		2.09 (1.838;2.376)	<0.001	
	Total	1.559 (1.512;1.608)	<0.001		2.044 (1.842;2.268)	<0.001	
DM	**Women**	2.868 (2.712;3.033)	<0.001	<0.001	5.694 (4.791;6.766)	<0.001	0.010
	Men	1.976 (1.844;2.118)	<0.001		4.282 (3.756;4.881)	<0.001	
	Total	2.463 (2.358;2.572)	<0.001		4.719 (4.252;5.239)	<0.001	
AH	**Women**	2.241 (2.149;2.338)	<0.001	<0.001	2.741 (2.275;3.304)	<0.001	0.745
	Men	1.919 (1.836;2.005)	<0.001		2.643 (2.354;2.968)	<0.001	
	Total	2.085 (2.022;2.149)	<0.001		2.673 (2.422;2.949)	<0.001	
Smoking	**Women**	1.303 (1.226;1.384)	<0.001	<0.001	1.921 (1.555;2.374)	<0.001	<0.001
	Vyras	0.959 (0.918;1.003)	0.066		1.211 (1.084;1.352)	0.001	
	Total	1.064 (1.026;1.102)	0.001		1.316 (1.192;1.453)	<0.001	
Obesity	**Women**	2.949 (2.826;3.076)	<0.001	0.885	3.999 (3.295;4.852)	<0.001	0.268

	Men	2.962 (2.825;3.106)	<0.001		4.527 (4.047;5.063)	<0.001	
	Total	2.954 (2.862;3.049)	<0.001		4.345 (3.936;4.797)	<0.001	
CHD history	**Women**	1.131 (1.083;1.18)	<0.001	0.001	1.201 (1.011;1.427)	<0.001	0.069
	Men	1.264 (1.202;1.33)	<0.001		1.461 (1.293;1.651)	<0.001	
	Total	1.185 (1.147;1.224)	<0.001		1.366 (1.236;1.508)	<0.001	
MetS	**Women**	10.946 (10.463;11.45)	<0.001	0.703	18.426 (14.939;22.727)	<0.001	0.035
	Men	10.796 (10.223;11.401)	<0.001		23.895 (21.034;27.146)	<0.001	
	Total	10.885 (10.514;11.27)	<0.001		21.792 (19.49;24.366)	<0.001	
BMI >30	**Moteris**	2.559 (2.46;2.662)	<0.001	<0.001	3.07 (2.61;3.61)	<0.001	<0.001
	Vyras	3.121 (2.976;3.273)	<0.001		4.691 (4.193;5.247)	<0.001	
	Total	2.772 (2.689;2.857)	<0.001		4.029 (3.673;4.421)	<0.001	
RF >=3	**Moteris**	3.925 (3.679;4.186)	<0.001	<0.001	6.454 (4.514;9.229)	<0.001	0.983
	Vyras	3.081 (2.901;3.273)	<0.001		6.483 (5.214;8.06)	<0.001	
	Total	3.478 (3.328;3.634)	<0.001		6.475 (5.375;7.8)	<0,001	

* *p* – homogeneity of variance

Abbreviations: TG – triglycerides; OR – odds ratio; DM – diabetes mellitus; AH – arterial hypertension; CHD – coronary heart disease; MetS – metabolic syndrome; BMI – body mass index; RF – risk factors.

Table 10. *The associations of cardiovascular risk factors with different high-density lipoprotein cholesterol levels.*

Risk factor	Group	HDL-C < 1mmol/l; HDL-C <1,2 mmol/l			HDL-C ≥1,55 mmol/l		
		OR (CI)	p-value	*p-value	OR (CI)	p-value	*p-value
Insufficient physical activity	Women	1.324 (1.251;1.402)	<0.001	0.144	0.699 (0.673;0.726)	<0.001	0.017
	Men	1.408 (1.326;1.495)	<0.001		0.751 (0.717;0.787)	<0.001	
	Total	1.363 (1.308;1.421)	<0.001		0.719 (0.699;0.741)	<0.001	
Unbalanced diet	Women	1.21 (1.142;1.281)	<0.001	0.842	0.785 (0.755;0.815)	<0.001	<0.001
	Men	1.22 (1.145;1.3)	<0.001		0.91 (0.868;0.954)	<0.001	
	Total	1.214 (1.164;1.267)	<0.001		0.832 (0.807;0.857)	<0.001	
DM	Women	1.729 (1.61;1.858)	<0.001	0.21	0.525 (0.493;0.558)	<0.001	<0.001
	Men	1.61 (1.478;1.754)	<0.001		0.729 (0.672;0.792)	<0.001	
	Total	1.68 (1.59;1.775)	<0.001		0.595 (0.566;0.625)	<0.001	
AH	Women	1.376 (1.297;1.461)	<0.001	0.022	0.622 (0.598;0.646)	<0.001	<0.001
	Men	1.248 (1.176;1.324)	<0.001		0.777 (0.742;0.813)	<0.001	
	Total	1.311 (1.257;1.368)	<0.001		0.681 (0.661;0.701)	<0.001	
Smoking	Women	1.227 (1.123;1.339)	<0.001	0.59	1.124 (1.056;1.196)	<0.001	<0.001
	Men	1.191 (1.121;1.265)	<0.001		1.401 (1.338;1.467)	<0.001	
	Total	1.202 (1.144;1.264)	<0.001		1.294 (1.247;1.343)	<0.001	
Obesity	Women	1.641 (1.544;1.745)	<0.001	0.004	0.452 (0.435;0.47)	<0.001	<0.001

	Men	1.861 (1.751;1.977)	<0.001		0.391 (0.368;0.415)	<0.001	
	Total	1.744 (1.67;1.821)	<0.001		0.432 (0.418;0.446)	<0.001	
CHD anamnesis	Women	1.043 (0.982;1.109)	0.17	0.337	0.978 (0.938;1.02)	0.304	<0.001
	Men	1.091 (1.019;1.168)	0.012		0.806 (0.762;0.852)	<0.001	
	Total	1.064 (1.017;1.113)	0.007		0.911 (0.881;0.942)	<0.001	
MetS	Women	6.297 (5.897;6.723)	<0.001	0.124	0.409 (0.392;0.426)	<0.001	0.056
	Men	5.861 (5.498;6.248)	<0.001		0.379 (0.354;0.405)	<0.001	
	Total	6.087 (5.814;6.373)	<0.001		0.399 (0.385;0.413)	<0.001	
BMI>30	Women	1.572 (1.487;1.661)	<0.001	<0.001	0.456 (0.438;0.474)	<0.001	<0.001
	Men	1.881 (1.771;1.999)	<0.001		0.353 (0.332;0.375)	<0.001	
	Total	1.703 (1.634;1.774)	<0.001		0.42 (0.406;0.433)	<0.001	
RF>=3	Women	2.452 (2.231;2.696)	<0.001	0.748	0.561 (0.535;0.588)	<0.001	<0.001
	Men	2.4 (2.195;2.624)	<0.001		0.74 (0.702;0.78)	<0.001	
	Total	2.424 (2.272;2.587)	<0.001		0.633 (0.611;0.656)	<0.001	

* *p-value* – homogeneity of variance

Abbreviations: HDL-C – high-density lipoprotein cholesterol; OR – odds ratio; DM – diabetes mellitus; AH – arterial hypertension; CHD – coronary heart disease; MetS – metabolic syndrome; BMI – body mass index; RF – risk factors.

3.2 Results of the Prospective Analysis

3.2.1 A Comparison of the Baseline Characteristics of Patients with and without Severe Dyslipidemia

The group with severe dyslipidemia consisted of 110 (51.6%) patients, while the control group comprised 103 (48.4%) participants. The study included a total of 105 (49.3%) women and 108 (50.7%) men. Patients with and without SD did not differ significantly in age (48.75 ± 9.07 vs. 49.57 ± 6.71, p=0.453, respectively). After assesing the gender aspect, women with SD were the same age as women in the control group (53.28 ± 6.79 vs. 52.12 ± 6.24, p=0.365) as well as men in the control group (44.39 ± 8.89 vs. 47.08 ± 6.24, p=0.074). Among subjects with SD, women were older compared to men (53.28 ± 6.79 vs. 44.39 ± 8.89, p<0.001), and, likewise, women in the control group were older than men without SD (52.12 ± 6.24 vs. 47.08 ± 6.24, p<0.001). In the study population, levels of TC, LDL-C and TG were higher in subjects with SD compared to the controls, while patients without SD had higher levels of HDL-C (Table 11).
In men and women without SD, their levels of TG (0.93 ± 0.37 vs. 0.99 ± 0.35, p=0.40) and LDL-C (2.71 ± 0.44 vs. 2.87 ± 0.50, p=0.094) did not differ significantly between genders, while in the control group, women had higher TC (4.88 ± 0.64 vs. 4.42 ± 0.50,p <0.001) and HDL-C (1.56 ± 0.31 vs. 1.28 ± 0.30, p<0.001) than to men. Among subjects with SD, men and women had similar levels of TC (7.41 ± 2.14 vs. 8.10 ± 2.04, p=0.083), LDL-C (5.04 ± 2.15 vs. 5.72 ± 2.02, p=0.089) and TG (2.56 ± 1.98 vs. 2.06 ± 1.60, p=0.146), while women with SD had higher mean concentrations of HDL-C compared to men with SD (1.46 ± 0.36 vs. 1.09 ± 0.24, p<0.001) (Table 11).

Table 11. *The baseline characteristics of subjects with and without severe dyslipidemia (n=213).*

Characteristics	**Group**	**Severe dyslipidemia group**		**Control group**		*p-value*
		n=110		n=103		
		Mean	SD	Mean	SD	
Age (years)	Total	48.75	9.07	49.57	6.71	0.453
	Men	44.39	8.89	47.08	6.24	0.074
	Women	53.28	6.79	52.12	6.24	0.365
TC (mmol/l)	Total	7.75	2.11	4.65	0.62	<0.001
	Men	7.41	2.14	4.42	0.50	<0.001
	Women	8.10	2.04	4.88	0.64	<0.001
LDL-C (mmol/l)	Total	5.37	2.10	2.79	0.48	<0.001
	Men	5.04	2.15	2.71	0.44	<0.001
	Women	5.72	2.02	2.87	0.50	<0.001
HDL-C (mmol/l)	Total	1.27	0.36	1.42	0.33	0.002
	Men	1.09	0.24	1.28	0.30	<0.001
	Women	1.46	0.36	1.56	0.31	0.125
TG (mmol/l)	Total	2.32	1.81	0.96	0.36	<0.001
	Men	2.56	1.98	0.93	0.37	<0.001
	Women	2.06	1.60	0.99	0.35	<0.001
ApoA1 (mmol/l)	Total	1.64	0.30	1.71	0.32	0.116
	Men	1.52	0.27	1.60	0.25	0.109
	Women	1.76	0.29	1.82	0.35	0.390
ApoA2	Total	0.36	0.18	0.32	0.06	0.047

(mmol/l)	Men	0.35	0.08	0.31	0.05	0.017
	Women	0.38	0.24	0.34	0.07	0.236
ApoB (mmol/l)	Total	1.50	0.48	0.76	0.18	<0.001
	Men	1.44	0.51	0.73	0.13	<0.001
	Women	1.55	0.44	0.78	0.23	<0.001
ApoB/ApoA1	Total	0.93	0.32	0.45	0.14	<0.001
	Men	0.96	0.34	0.47	0.12	<0.001
	Women	0.89	0.28	0.43	0.15	<0.001
ApoE (mg/l)	Total	67.58	27.95	43.33	13.55	<0.001
	Men	67.39	34.00	39.17	11.03	<0.001
	Women	67.77	20.33	47.66	14.65	<0.001
Lp(a) (g/l)	Total	0.25	0.37	0.13	0.19	0.006
	Men	0.23	0.35	0.14	0.18	0.095
	Women	0.26	0.39	0.13	0.20	0.034

Abbreviations: SD – standard deviation; TC – total cholesterol; LDL-C – low-density lipoprotein cholesterol; HDL-C – high-density lipoprotein cholesterol; TG – triglycerides; Apo – apolipoprotein; Lp(a) – lipoprotein(a).

Of all subjects with severe dyslipidemia, 8.2% (n=9) were diagnosed with SD for the first time. Of all patients with SD, 29.1% (n=32) received lipid-lowering treatment before the study (25.9% (n=14) women and 32.1% (n=18) men), although their SD was not controlled. The use of lipid-lowering medications in the study population with SD is presented in Figure 24.

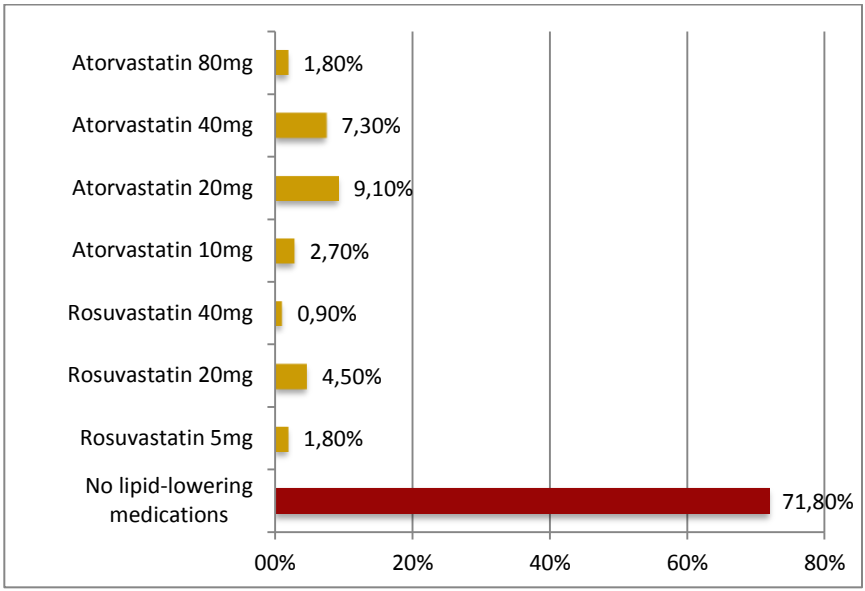
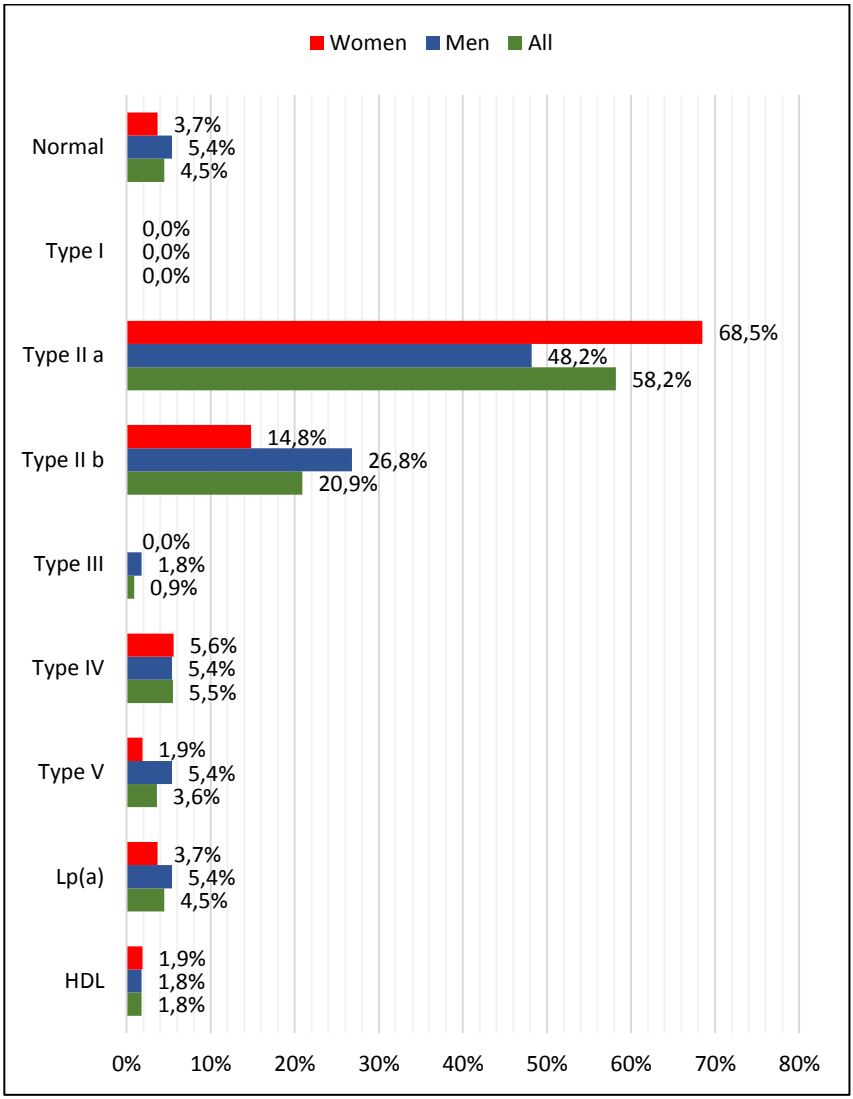


Figure 24. *Use of lipid-lowering drugs in the study group with SD.*

3.2.2 Types of Hyperlipoproteinemia in Patients with Severe Dyslipidemia

According to the Frederickson Classification of Lipid Disorders, most of the study participants with SD had hyperlipoproteinemia type II a (58.2%), followed by type II b (20.9%) and type IV (5%). None of the examined patients had hyperlipoproteinemia type I. The tendency of women having hyperlipoproteinemia type II a more frequently compared to men was observed (68.5% vs. 48.2%), while type II b was more prevalent among men (26.8% vs. 14.8%). The distribution of the types of hyperlipoproteinemia in patients with SD is shown in Figure 25.



Abbreviations: HDL – high-density lipoproteins; Lp(a) – lipoprotein(a).

Figure 25. *The distribution of the types of hyperlipoproteinemia in patients with severe dyslipidemia, p=0.533 (n=110).*

3.2.3 A Comparison of the Cardiovascular Risk Profiles of Patients with and without Severe Dyslipidemia

While assessing the frequency of cardiovascular risk factors in the study population, the prevalence of the following risk factors was such: AH – 38.5% (n=82), smoking – 24.9% (n=53), alcohol consumption – 71.4% (n=152), insufficient physical activity – 49.3% (n=105), family history of CHD – 43.2% (n=92). The comparison of the prevalence of CVD risk factors in the study groups is presented in Table 12. Patients with SD more frequently had AH, a family history of CHD and insufficient physical activity compared to subjects in the control group. Alcohol consumption was more prevalent among patients without SD, while smoking showed no significant difference between the groups (Table 12).

Table 12. *A comparison of the prevalence of cardiovascular risk factors in patients with and without severe dyslipidemia (n=213).*

Characteristics	**Group**	**Severe dyslipidemia group**		**Control group**		**p-value**
		n=110		n=103		
		n	%	n	%	
AH (%)	Total	52	47.3	30	29.1	0.007
	Men	19	33.9	11	21.2	0.139
	Women	33	61.1	19	37.3	0.015
Smoking (%)	Total	30	27.3	23	22.3	0.404
	Men	17	30.4	15	28.8	0.864
	Women	13	24.1	8	15.7	0.283
Alcohol consumption (%)	Total	68	61.8	84	81.6	0.001
	Men	40	71.4	42	80.8	0.257
	Women	28	51.9	42	82.4	0.001
Family history of CHD (%)	Total	71	64.5	21	20.4	<0.001

	Men	38	67.9	8	15.4	<0.001
	Women	33	61.1	13	25.5	<0.001
Insufficient physical activity (%)	Total	65	59.1	40	38.8	0.003
	Men	31	55.4	18	34.6	0.031
	Women	34	63.0	22	43.1	0.042
Family history of DM (%)	Total	18	16.4	16	15.5	0.869
	Men	9	16.1	7	13.5	0.703
	Women	9	16.7	9	17.6	0.894

Abbreviations: AH – arterial hypertension; CHD – coronary heart disease; DM – diabetes mellitus.

3.2.3.1 The Associations between Arterial Hypertension and Severe Dyslipidemia

AH was more prevalent among patients with SD compared to subjects in the control group (47.3% vs. 29.1%, p = 0,007, respectively) (Table 12). Subjects with SD were diagnosed with AH for approximately 8.9 years (8.9 ± 8.05), while patients without SD – for 7.5 years (7.5 ± 6.83), p=0.425. Patients with SD used antihypertensive drugs less frequently compared to the control group (73.1% (n=38) vs. 96.7% (n=29), p=0.008, respectively). The control of arterial hypertension was achieved in 55.8% (n=29) of subjects with severe dyslipidemia, and in70.0 % (n=21) of patients without SD, p=0.203. The chances of having severe dyslipidemia were two times higher among patients with AH (OR=2.18; 1.24-3.84; p=0.007). Subjects with AH more frequently had TC >5mmol/l, (75.6% vs. 55.0%, p=0.002), LDL-C >3 mmol/l (70.7% vs. 55.0%, p=0.022) and TG >1.7mmol/l (46.3% vs. 26.0%, p=0.002) compared to participants without AH.

3.2.3.2 The Associations between Smoking and Severe Dyslipidemia

The prevalence of smoking was similar in both SD and control groups (27.3% (n=30) vs. 22.3% (n=23), p=0.404, respectively). The average time of smoking was 19.08 (± 9.09) years in the SD group and 18.62 years (± 8.75) in the control group, p=0.836. The mean number of cigarettes smoked per day was 10.53 ± 6.10 in patients with SD and 10.28 ± 6.06 in the control group, p=0.867.

3.2.3.3 The Associations between Alcohol Consumption and Severe Dyslipidemia

The prevalence of alcohol consumption was lower in patients with severe dyslipidemia compared to the control group (61.8% (n=68) vs. 81.6% (n=84), p=0,001, respectively). A significant difference was not found between men with and without severe dyslipidemia (71.4% (n=40) vs. 80.8% (n=42), p=0.257), while women with severe dyslipidemia had a lower prevalence of alcohol consumption in comparison with healthy women (51.9% (n=28) vs. 82.4% (n=42), p=0.001). Patients who consume alcohol had smaller chances of having severe dyslipidemia (OR=0.37; 0.20-0.69; p=0.002).

3.2.3.4 The Associations between Menopause and Severe Dyslipidemia

The prevalence of menopause was higher in women with severe dyslipidemia compared to women in the control group (81.1% (n=43) vs. 58.8% (n=30), p=0.013, respectively). The average time of menopause was similar in both groups (SD+: 5.58 ± 3.20 years, SD-: 6.97 ±4.12 years, p=0.129). Menopause was associated with a greater chance of having severe dyslipidemia (OR=3.010; 1.24-7.30; p=0.015). Patients with menopause more frequently had TC >5mmol/l (75.3% vs. 51.6%, p=0.017), LDL-C >3 mmol/l (70.7% vs. 55.0%, p=0.022), TG >1,7mmol/l (39.7% vs. 12.9%, p=0.007), ApoE >63 mg/l (36.6% vs. 16.1%, p=0.039).

3.2.3.5 Associations between Family History of CHD and Severe Dyslipidemia

Family history of CHD was more prevalent among subjects with severe dyslipidemia compared to the control group (64.5 % (n=71) vs. 20.4 % (n=21), p<0.001). Family history of CHD was related to an approximately seven times higher probability of having severe dyslipidemia (OR=7.109; 3.83-13.19; p<0.001). Patients with histories of CHD in their families more frequently had TC >5mmol/l (82.6 % vs. 47.9 %, p <0.001), LDL-C >3 mmol/l (78.3 % vs. 47.9 %, p<0.001), TG >1,7mmol/l. (51.1 % vs. 20.7 %, p<0.001), ApoE >63 mg/l (42.7 % vs. 20.8 %, p=0.001).

3.2.3.6 The Associations between Physical Activity and Severe Dyslipidemia

Of all patients with severe dyslipidemia, 59.1% (n=65) had insufficient or no physical activity in comparison with the 38.8% (n=40) in the control group (p=0,003). Insufficient physical activity more than twice increases the chances of having SD (OR=2.28; 1.31-3.94; p=0.003).

3.2.3.7 The Associations between Dietary Patterns and Severe Dyslipidemia

In the severe dyslipidemia group, less subjects ate fruit 1–2 times per day compared to the control group (53.6% vs. 70.9%, p=0.035). Men with SD chose to eat pickled vegetables 1–2 times per day (28.6% vs. 42.3%, p=0.026) and grains 1–2 times per day (17.9% vs. 35.3%, p=0.041) less frequently than those in the control group. Patients with SD consumed more eggs per week compared to subjects without SD (Figure 26). The consumption of dairy products, bread, fish products, fresh and pickled vegetables, grains and fat, as well as salt intake, were similar in both groups. Also, the frequency of eating, regular eating patterns, snacking, use of food supplements

and vitamins were similar in both groups. Men in the control group tended to read specialized literature about nutrition and health more frequently than men with SD (23.3% vs. 12.7%, p=0.044), while women with SD consumed less food high in saturated fat and cholesterol compared to the control group (1.9% vs. 13.7%, p=0.022). Men with SD were more likely to use iodised salt in order to prevent Iodine deficiency compared to men in the control group (64.3% vs. 42.3%, p=0.022).

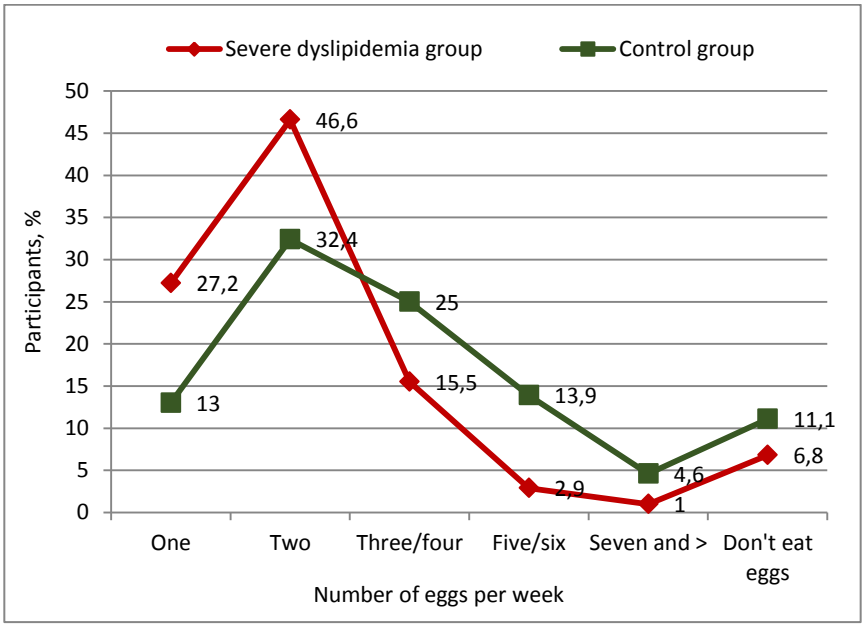


Figure 26. *Number of eggs consumed per week (p=0.001).*

3.2.4 The Associations of Anthropometric Measurements and Severe Dyslipidemia

A detailed analysis of the parameters of body composition analysis in patients with and without severe dyslipidemia is presented in Table 13. After comparing the assessments of LBM (%), SMM (%),

protein mass (%) and BFM (%) between men and women with SD, significant differences were not found. More men with severe dyslipidemia had decreased mineral mass in comparison with women with severe dyslipidemia (53.6% vs. 3.7%, <0.001).

Table 13. *An assessment of the parameters of body composition analysis in patients with and without severe dyslipidemia.*

Characteristics	Group	Under	Optimal	Over	*p*-value
BFM (%)	SD+	1.80	12.70	85.50	**<0.001**
	SD–	8.70	30.10	61.20	
LBM (%)	SD+	84.40	13.80	1.80	**0.001**
	SD–	62.10	29.10	8.80	
SMM (%)	SD+	84.50	13.60	1.90	**0.001**
	SD–	62.10	31.10	6.80	
Protein (%)	SD+	80.90	17.30	1.80	**<0.001**
	SD–	47.60	44.70	7.70	
Minerals (%)	SD+	29.10	70.90	0.00	0.142
	SD–	20.40	79.60	0.00	
TBW (%)	SD+	18.20	81.80	0.00	0.121
	SD–	10.70	89.30	0.00	

Abbreviations: SD+ – with severe dyslipidemia; SD– – without severe dyslipidemia; BFM – Body Fat Mass; LBM – Lean Body Mass; SMM – Sceletal Muscle Mass; TBW – Total Body Water.

After evaluating the abdominal region with a body composition analyzer, significant differences in the distribution of fat in the abdomen in study groups were not found (p=0.078) (Figure 27).

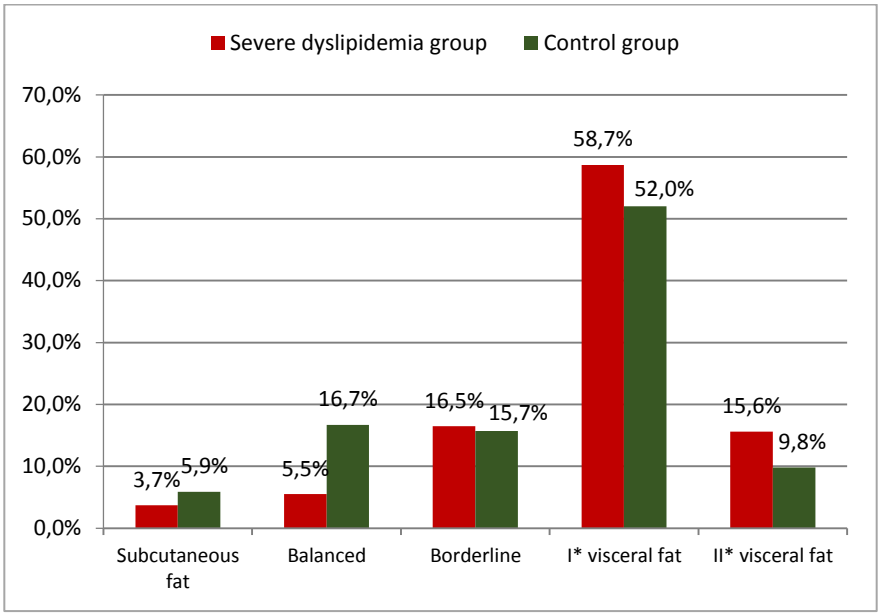


Figure 27. *A comparison of abdominal region analysis in study groups (p=0.078).*

After assessing fat distribution in the abdominal region in men and women, significant differences were found between genders (p=0.017) (Figure 28).

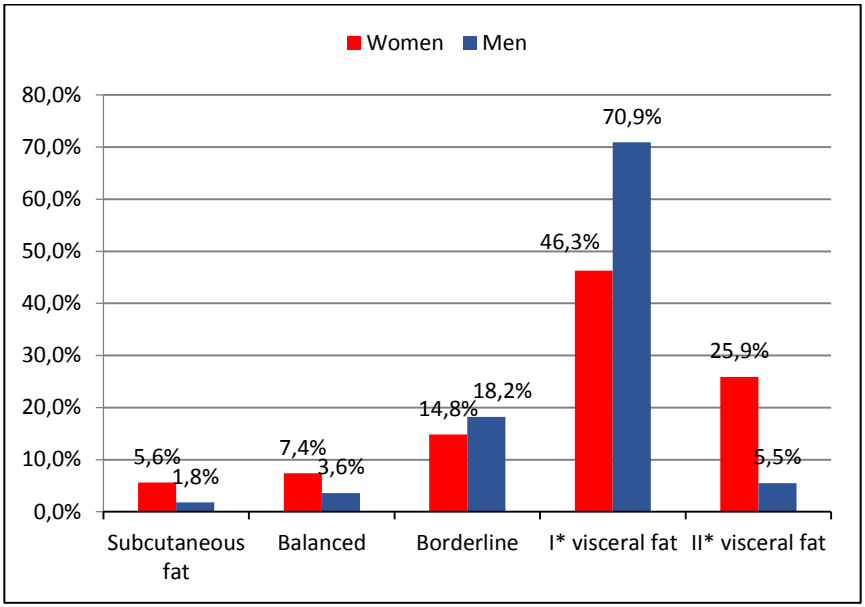


Figure 28. *A comparison of the abdominal region analysis in different genders (p=0.017).*

The distribution of visceral fat was similar in both the severe dyslipidemia and control groups (p=0.141) (Figure 29). Also, no differences were found between men and women (p=0.817). The prevalence of increased WHR was similar in study groups (67.3% vs. 68.9%, *p*=0.795), but increased WC was more frequently found among subjects with severe dyslipidemia compared to the control group (57.3% vs. 40.8%, p=0.016). Among patients with severe dyslipidemia, more women had increased WC compared to men (68.5% vs. 46.4%, p=0.019).

The evaluation of BMI in both study groups is presented in Figure 30 (p=0.002). No significant differences between women and men with SD were determined.

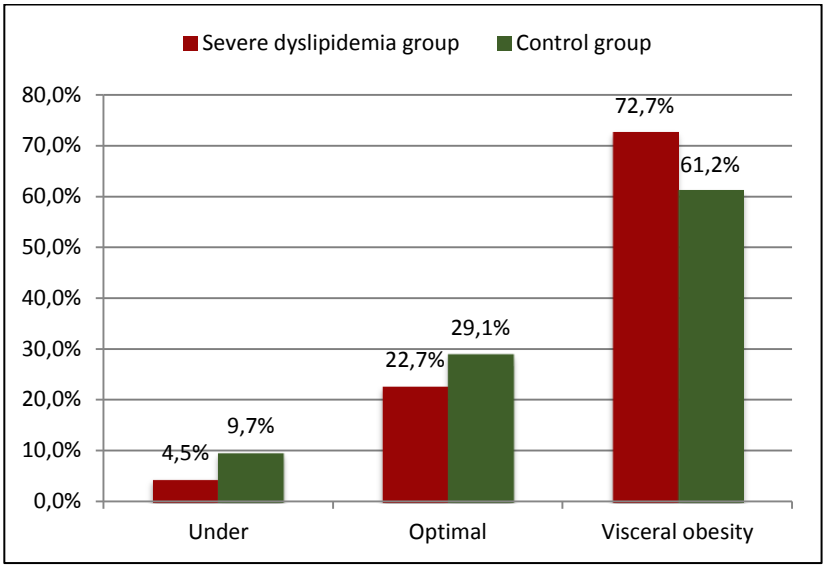


Figure 29. *Visceral fat evaluation in the study population (p=0.141).*

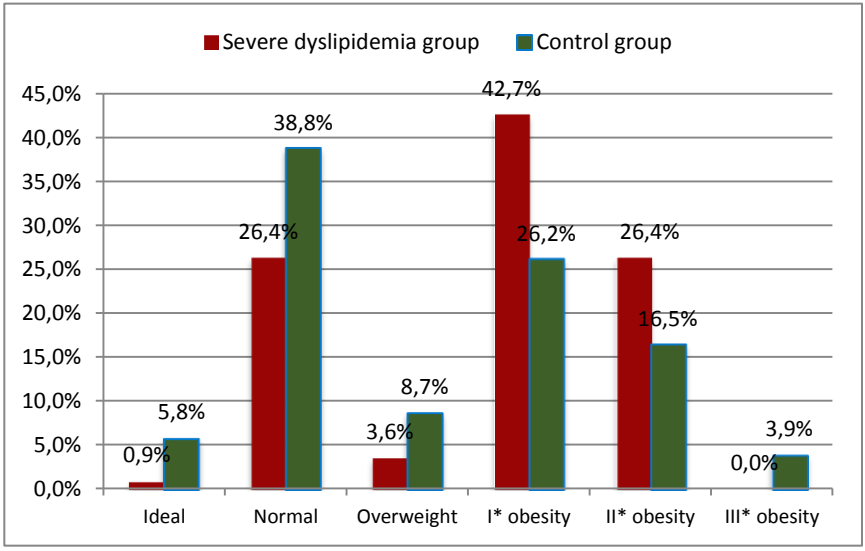


Figure 30. *The distribution of BMI values in the study population (p=0.002).*

An assessment of the body fat percentage (PBF) in patients with and without severe dyslipidemia is shown in Figure 31, p=0.008. Significant differences in the distribution of PBF categories were found between men and women (Figure 32, p=0.011).

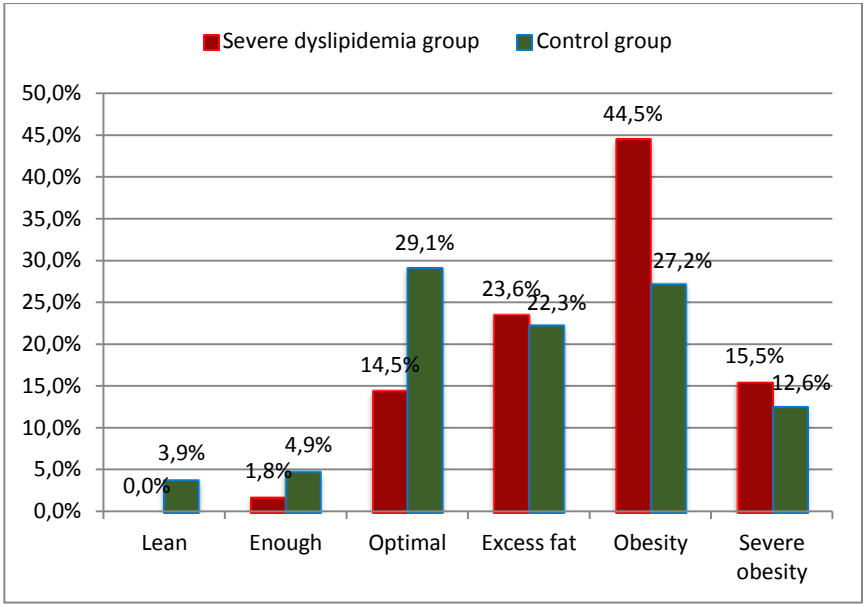


Figure 31. *The assessment of the percentage of body fat in patients with and without severe dyslipidemia (p=0.008).*

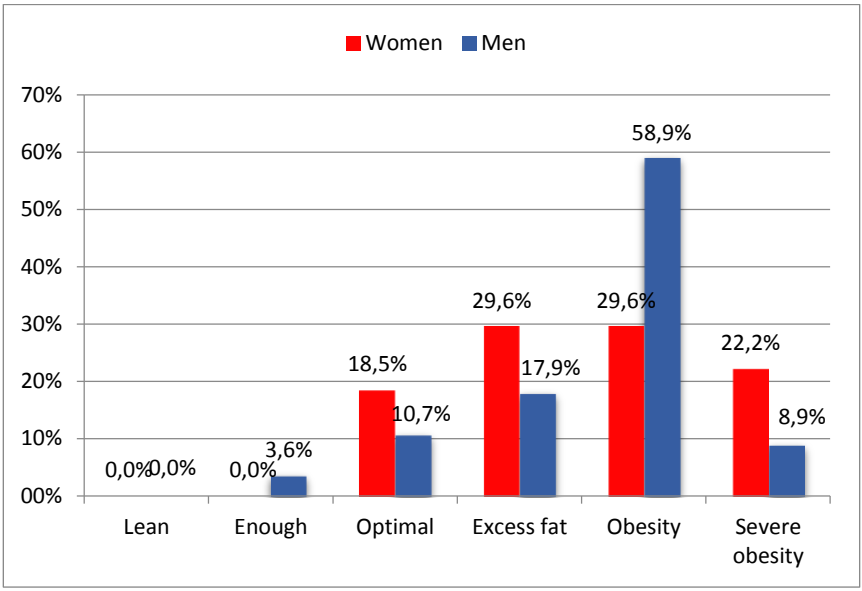


Figure 32. *The assessment of the percentage of body fat in men and women with severe dyslipidemia (p=0.011).*

Results of the correlation analysis between plasma lipid concentration and anthropometric measurements indicated that the TC level was significantly related to the parameters of the body composition analysis – body fat mass (BFM) and PBF (Table 14). Also, a moderate correlation was observed between LDL-C concentration and body fat mass (BFM), and a weak relation was found between LDL-C and PBF. No significant associations were found between TC or LDL-C and traditional anthropometric parameters (BMI, WC, WHR) (Table 14). Negative correlations were determined between most of the analyzed parameters and HDL-C levels, the strongest of them being HDL-C to WHR (r=-0.442, p<0.001). TG levels were associated with BMI, WC, WHR, BFM, PBF, visceral fat analysis (VFA) and body fat distribution; the strongest relation was observed between TG and BMI (r=0.402, p<0.001) as well as TG and PBF (r=0.402, p<0.001). Lp(a)

concentration was not related to any of the analyzed anthropometric parameters (Table 14). Lipid measurements showed most correlations with BFM or PBF (7 out of 10 parameters). Out of the traditional anthropometric parameters, most correlations were found between BMI and measured lipids (6 out of 10). The ApoB/apoA1 ratio, as well as ApoA1, were associated with most anthropometric measurements (11 out of 12), followed by HDL-C (10 out of 12). Spearman's correlation coefficients between anthropometric measurements or body composition analysis parameters and plasma lipid concentration are presented in Table 14.

Table 14. *Spearman's correlation coefficients between anthropometric measurements or body composition analysis parameters and plasma lipid concentration.*

Characteristics	TC	LDL-C	HDL-C	TG	Apo A1	Apo B	Apo A2	Apo E	Apo B/ apo A1	Lp(a)
BMI	0.099	0.094	**-0.331****	**0.402****	**-0.224****	**0.191****	0.030	**0.195****	**0.242****	0.094
WC	0.039	0.014	**-0.373****	**0.383****	**-0.269****	0.132	0.071	0.126	**0.211****	0.004
WHR	-0.037	0.000	**-0.442****	**0.301****	**-0.317****	0.086	0.018	0.058	**0.183****	0.003
PBF	**0.239****	**0.208****	0.131	**0.241****	**0.153***	**0.240****	**0.138***	**0.317****	0.132	0.060
BFM	**0.382****	**0.370****	-0.059	**0.402****	-0.017	**0.424****	**0.152***	**0.365****	**0.369****	0.124
LBM	-0.022	0.014	**-0.275****	0.024	**-0.259****	0.015	-0.071	**-0.157***	**0.140***	0.044
Muscle	-0.027	0.009	**-0.291****	0.025	**-0.265****	0.010	-0.077	**-0.155***	**0.137***	0.035
Protein	-0.026	0.010	**-0.275****	0.018	**-0.263****	0.010	-0.068	**-0.163***	**0.136***	0.045
Minerals	0.026	0.051	**-0.184****	0.046	**-0.215****	0.044	-0.019	-0.087	**0.138***	0.062
TBW	-0.026	0.011	**-0.281****	0.016	**-0.272****	0.009	-0.073	**-0.164***	**0.140***	0.041
Body fat distribution	0.100	0.122	**-0.270****	**0.310****	**-0.179****	**0.192****	0.060	**0.194****	**0.220****	0.017
VFA	0.035	0.077	**-0.374****	**0.311****	**-0.264****	**0.149***	0.034	0.129	**0.217****	-0.001

*** statistically significant as p<0.05; ** statistically significant as p<0.01;Abbreviations:** TC – total cholesterol; LDL-C – low-density lipoprotein cholesterol; HDL-C – high-density lipoprotein cholesterol; TG – triglycerides; Apo – apolipoprotein; Lp(a) – lipoprotein(a); BMI – body mass index; WC – waist circumference; WHR – waist-hip ratio; PBF – percent body fat; BFM – body fat mass; LBM – lean body mass; TBW – total body water; VFA – visceral fat analysis.3.2.5

The Usefulness of the Ultrasonographic Evaluation in Patients with Severe Dyslipidemia

An ultrasonographic evaluation revealed that an Achilles tendon pathology was present in 42.7% of subjects with severe dyslipidemia and in 29.1% of healthy controls (p=0.039, Table 15). A more pronounced association was present in women, where the frequency of Achilles tendinopathy (AT) reached 24.1% among SD patients and only 2.0% in controls (p=0.001, Table 15). Severe dyslipidemia increased the odds of AT by 1.815 (95% CI, 1.028-3.206). Wrist tendon pathologies in those with severe hypercholesterolemia were comparable to the controls (p=0.366, Table 15). Neither the aortic valve nor mitral valve pathology were associated with SD (p=0.856, p=0.300 respectively, Table 15). The frequency of liver steatosis (p=0.457), pancreatic steatosis (p=0.852) and gall bladder stones (p=0.056) differed slightly among groups but did not reach any statistical significance (Table 15).
Table 16 represents the ultrasonographic differences according to gender. The prevalence of the Achilles tendon pathology was higher in males despite the presence (SD^+) or absence (SD^-) of severe hypercholesterolemia (SD^+ 60.7% vs. 24.1%, SD^- 55.8% vs. 2.0%, p<0.001). Furthermore, men showed a higher proportion of subjects with wrist tendon pathologies (SD^+ 17.9% vs. 0%, p<0.001, SD^- 11.5 % vs. 0 %, p=0.012) and aortic valve atherosclerotic lesions (SD^+ 25.0 % vs. 5.6 %, p=0,005, SD^- 26.9 % vs. 2.0 %, p<0.001).

Table 15. *The ultrasonographic characteristics of the study population.*

Characteristics	**SD+** (n=110)	**SD–** (n=103)	p-value
Achilles tendon lesions			
Total	47 (42.7%)	30 (29.1%)	**0.039**
Women	13 (24.1%)	1 (2.0%)	**0.001**
Men	34 (60.7%)	29 (55.8%)	0.602
Wrist tendon lesions			
Total	10 (9.1%)	6 (5.8%)	0.366

Women	0 (0%)	0 (0%)	
Men	10 (17.9%)	6 (11.5%)	0.356
Atherosclerotic lesions of *abdominal* aorta			
Total	37 (33.6%)	40 (39.2%)	0.399
Women	17 (31.5%)	11 (22.0%)	0.276
Men	20 (35.7%)	29 (55.8%)	**0.036**
Fatty liver			
Total	32 (29.1%)	25 (24.3%)	0.457
Women	14 (25.9%)	7 (13.7%)	0.407
Men	18 (32.1%)	18 (34.6%)	0.534
Pancreatic steatosis			
Total	29 (26.4%)	26 (25.2%)	0.852
Women	11 (20.4%)	9 (17.6%)	0.722
Men	18 (32.1%)	17 (32.7%)	0.951
Gall bladder stones			
Total	7 (6.4%)	9 (8.7%)	0.056
Women	3 (5.6%)	4 (7.8%)	0.277
Men	4 (7.1%)	5 (9.6%)	0.292
Aortic valve lesions			
Total	17 (15.5%)	15 (14.6%)	0.856
Women	3 (5.6%)	1 (2.0%)	0.336
Men	14 (25.0%)	14 (26.9%)	0.820

Abbreviations: SD+ – severe dyslipidemia positive; SD– – severe dyslipidemia negative.

Table 16. *The differences of ultrasonographic characteristics according to gender.*

Characteristics	**Women** (n=105)	**Men** (n=108)	p-value
Achilles tendon lesions			
SD+	13 (24.1%)	34 (60.7%)	<0.001
SD–	1 (2.0%)	29 (55.8%)	<0.001
Total	14 (13.3%)	63 (58.3%)	<0.001
Wrist tendon lesions			
SD+	0%	10 (17.9%)	<0.001

SD–	0%	6 (11.5%)	0.012
Total	0%	16 (14.8%)	<0.001
Atherosclerotic lesions of *abdominal* aorta			
SD+	17 (31.5%)	20 (35.7%)	0.639
SD–	11 (22.0%)	29 (55.8%)	<0.001
Total	28 (26.9%)	49 (45.4%)	0.005
Fatty liver			
SD+	14 (25.9%)	18 (32.1%)	0.788
SD–	7 (13.7%)	18 (34.6%)	0.075
Total	21 (20.0%)	36 (33.3%)	0.153
Pancreatic steatosis			
SD+	11 (20.4%)	18 (32.1%)	0.161
SD–	9 (17.6%)	17 (32.7%)	0.079
Total	20 (19.0%)	35 (32.4%)	0.026
Gall bladder stones			
SD^{+}	3 (5.6%)	4 (7.1%)	0.794
SD–	4 (7.8%)	5 (9.6%)	0.977
Total	7 (6.7%)	9 (8.3%)	0.888
Aortic valve lesions			
SD+	3 (5.6%)	14 (25.0%)	0.005
SD–	1 (2.0%)	14 (26.9%)	<0.001
Total	4 (3.8%)	28 (25.9%)	<0.001

Abbreviations: SD+ – severe dyslipidemia positive; SD– – severe dyslipidemia negative.

3.2.4. The Usefulness of Vascular Imaging and the Indices of Arterial Stiffness in the Evaluation of Patients with Severe Dyslipidemia

Changes in the vascular ultrasound, such as atherosclerotic plaques or increased IMT, were found in the carotid arteries of 59.6% (n=127) of all patients. Carotid plaques were determined for 50.7% (n=108), while increased IMT was discovered in 34.3% (n=73) of subjects. Changes in carotid arteries were more prevalent among patients with severe dyslipidemia – 74.1% (atherosclerotic plaques: 66.4% vs. 33.0%, p<0,0001; increased IMT: 44.5% vs. 23.3%, p=0.001) compared to the

43.1% in the control group, p<0.001. The parameters of carotid arteries are presented in Table 17. SD was significantly related to the presence of atherosclerotic plaques (OR=4.00; 2.264-7.081, p<0.001) and increased IMT (OR=2.64;1.463-4.778, p=0.001) in the carotid arteries.
Severe dyslipidemia was associated with a decreased distention (OR=0.99; 0.995-0.999; p=0.004) and increased stiffness (OR=1.56; 1.242-1.967, p<0.001) of the right common carotid artery (CCA) as well as increased IMT (OR=1.00; 1.002-1.006; p=0.001), decreased distention (OR=0.99; 0.996-1.000, p=0.05) and increased stiffness (OR=1.30; 1.070-1.584, p=0.008) of the left CCA.
The possibility of having SD was three times higher (OR=2.98; 1.710-5.219; p<0.001), when the right CCA distention was <402 mm, three times higher (OR=3.03; 1.730-5.296; p<0.001), when the right CCA stiffness was >3.25 mm, 2.5 times higher (OR=2.54; 1.460-4.421; p=0.001), when the left CCA IMT was >601.5 μm, three times higher (OR=2.845; 1.576-5.137; p=0.001), when the left CCA stiffness was >3.75 mm and almost three times higher (OR=2.69; 1.449-4.997, p=0.002), when the left CCA distention was <478.5 mm.

Table 17. *A comparison of the parameters of the carotid arteries of both study groups.*

Characteristics	Group	**SD+**		**SD-**		p-value
		n=110		n=103		
		Mean	SD	Mean	SD	
RCCA IMT (μm)						
	Total	626.3	131.7	623.0	123.8	0.849
	Men	600.6	24.3	636.2	114.6	0.126
	Women	652.5	134.9	609.4	132.3	0.102
RCCA stiffness (mm)						
	Total	3.8	1.6	3.0	1.1	<0.001
	Men	3.4	1.6	2.7	0.9	0.008

	Women	4.2	1.5	3.3	1.3	0.001
RCCA distention (mm)						
	Total	393.5	160.5	459.2	154.1	0.003
	Men	441.0	188.9	517.7	163.6	0.027
	Women	344.2	105.2	399.6	118.1	0.012
LCCA IMT (µm)						
	Total	676.5	147.4	607	130.2	<0.001
	Men	650.2	149.5	603.0	128.1	0.082
	Women	703.8	142.1	611.2	133.5	0.001
LCCA stiffness (mm)						
	Total	3.8	1.5	3.2	1.4	0.007
	Men	3.6	1.4	3.0	1.4	0.036
	Women	4.0	1.6	3.5	1.3	0.078
LCCA distention (mm)						
	Total	390.1	147.6	430.7	148.3	0.046
	Men	421.5	172.0	497.2	146.2	0.016
	Women	357.4	109.5	362.8	117.4	0.807

Abbreviations: SD – standard deviation; SD+ – severe dyslipidemia positive; SD– – severe dyslipidemia negative; LCCA – left common carotid artery; RCCA – right common carotid artery; IMT – intima–media thickness.

After evaluating other parameters of vascular stiffness, instances of a higher PWV in the femoral artery was more frequently found in the severe dyslipidemia group compared to the control group (8.09 ± 1.36 m/s vs. 7.36 ± 1.29 m/s, $p<0.001$) (Table 18). Patients with SD had higher AIxHR than healthy controls (26.34 ± 10.01 vs. 12.53 ± 10.97, $p<0.001$) (table 18). Chances of having SD were more than 13 times higher (OR=13.508; 6.936-26.307; $p<0.001$) when AIxHR was <22.5%, and chances of having SD were 3.5 times higher (OR=3.578; 1.885-6.791; $p<0.001$) when PWV in the femoral artery was >8.35 m/s.

Table 18. *A comparison of the parameters of the arterial stiffness of both study groups.*

Characteristics		SD+		SD-		p-value
		n=110		n=103		
		Mean	SD	Mean	SD	
AIx/HR (%)						
	Total	12.53	10.97	26.34	10.01	<0.001
	Men	12.63	10.24	27.83	10.06	<0.001
	Women	12.07	11.77	24.80	9.81	<0.001
FEM (m/s)						
	Total	7.36	1.29	8.09	1.36	<0.001
	Men	7.33	1.02	8.23	1.44	<0.001
	Women	7.39	1.53	7.96	1.27	0.044
RA (m/s)						
	Total	8.58	1.04	8.48	0.99	0.507
	Men	8.69	1.06	8.59	0.80	0.608
	Women	8.47	1.01	8.37	1.16	0.658
R-CAVI						
	Total	7.67	1.59	7.70	1.39	0.871
	Men	7.29	1.69	7.60	1.40	0.303
	Women	8.05	1.40	7.80	1.38	0.348
L-CAVI						
	Total	7.54	1.49	7.49	1.53	0.822
	Men	7.23	1.65	7.52	1.70	0.363
	Women	7.86	1.23	7.46	1.34	0.114

Abbreviations: SD – standard deviation; SD+ – severe dyslipidemia positive; SD– – severe dyslipidemia negative; Aix/HR – heart rate adjusted augmentation index; FEM – pulse wave velocity in femoral artery; RA – pulse

wave velocity in radial artery; R-CAVI – right cardio-ankle vascular index; L-CAVI – left cardio-ankle vascular index.

3.2.6 The Usefulness of Evaluating the Coronary Artery Calcium Score in Patients with Severe Dyslipidemia

Figure 33 demonstrates the distribution of participants according to their CAC score percentiles. Table 19 represents the baseline lipid profile and the apolipoproteins of subjects with a CAC score ≥25th percentile. There were no significant correlations between the biochemical parameters and CAC percentiles except for lipoprotein(a). An increase in lipoprotein(a) was associated with CAC score percentiles (p=0.038) (Table 19).

TC and LDL-C demonstrated a tendency to increase as the percentiles of CAC score increased; however, this was not statistically significant (p=0.704 and p=0.667, respectively) (Figure 2). Concentrations of HDL-C and TG did not correlate with the percentiles either (p=0.443 and p=0.773, respectively) (Figure 34).

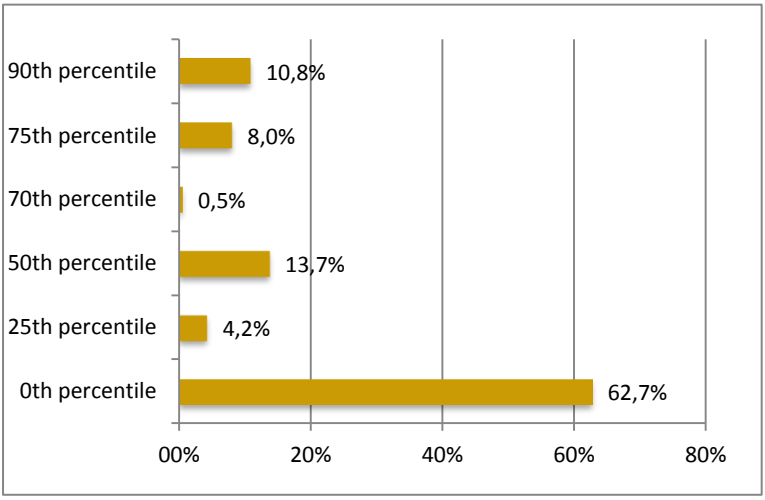
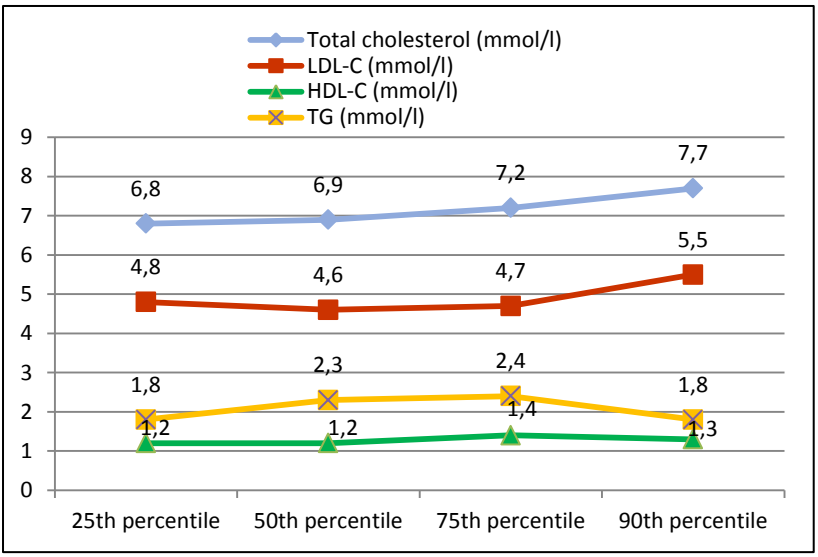


Figure 33. *The distribution of all participants according to their CAC score percentiles.*

Table 19. *The associations between CAC percentiles and lipid profile components.*

Characteristics	25th percentile (%)	50th percentile (%)	75th percentile (%)	90th percentile (%)	*p-value*	Chi-square
ApoA1 F <1.25 g/l; M <1.1 g/l	0	6.9	11.8	13.0	0.775	1.787
ApoA2 <0.26 g/l	33.3	6.9	0	13.0	0.095	7.901
ApoB/ApoA1 F >0.9; M >1.0	25.0	34.5	47.1	52.2	0.479	3.495
ApoB F >1.25 g/l; M >1.4 g/l	33.3	41.4	64.7	52.2	0.371	4.268
ApoE >63 mg/l	25.0	46.4	41.2	59.1	0.413	3.950
TC >5 mmol/L	66.7	86.2	82.4	78.3	0.219	5.743
Lp(a) >0.3 g/l	11.1	31.0	0	39.1	0.038	10.163
LDL-C >3 mmol/l	55.6	75.9	70.6	69.6	0.772	1.804
Low HDL-C F <1.2 mmol/l; M <1.0 mmol/l	33.3	37.9	17.6	21.7	0.258	5.294
TG >1.7 mmol/l	44.4	51.7	41.2	52.2	0.808	1.607

Abbreviations: Apo – apolipoprotein; TC – total cholesterol; Lp(a) – lipoprotein(a); LDL-C – low-density lipoprotein cholesterol; HDL-C – high-density lipoprotein cholesterol; TG – triglycerides; F – female; M – male.



Abbreviations: LDL-C – low-density lipoprotein cholesterol; HDL-C – high-density lipoprotein cholesterol; TG – triglycerides.

Figure 34. *Blood lipid components and their association with the CAC score ≥25th percentile, TC (p=0.704), LDL-C (p=0.667), HDL-C (p=0.443), TG (p=0.773).*

In 0th CAC percentiles group, 62 (47%) subjects out of 133 had severe hypercholesterolemia. In total, there were 79 (37.2%) subjects with elevated (≥25th) CAC percentiles. Out of them, 47 (59.5%) had severe dyslipidemia and 32 (40.5%) did not. However, the CAC score did not differ between the groups (severe dyslipidemia (+) 140.30 ± 185.72 vs. severe dyslipidemia (–) 87.84 ± 140.65, p=0.146). There was a comparable difference in how the participants of these groups were distributed among different percentile groups (p=0.044) according to their age, gender, race/ethnicity (Figure 35). Eigtheen women and 61 men had elevated CAC percentiles; however, the percentiles did not differ significantly between the genders either (p=0.075). Neither women nor men demonstrated percentile differences between severe dyslipidemia and control groups (women p=0.272, men p=0.706). There

were no gender differences in the severe dyslipidemia group separately as well (p=0.238).

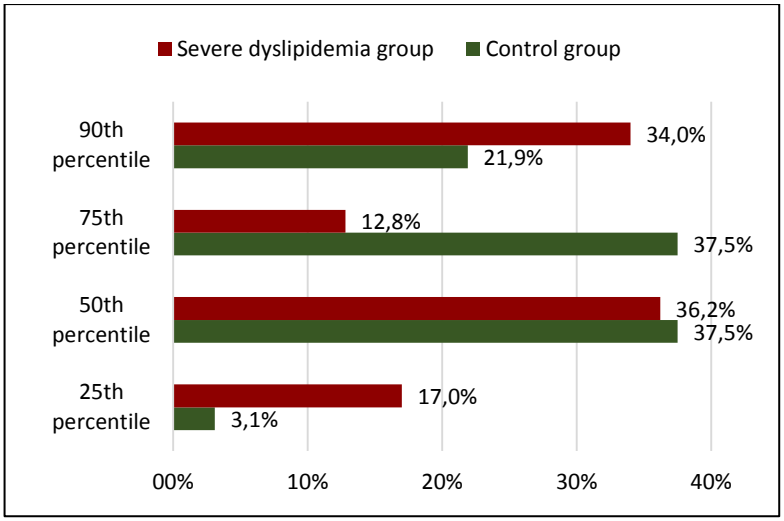


Figure 35. *The distribution of the CAC score's ≥25th percentile in severe hypercholesterolemia and control groups, p=0.044.*

The CAC percentiles did not differ between hypertensive and normotensive patients (p=0.875), smokers and non-smokers (p=0.083), subjects with and without any family history of CHD (p=0.576). CAC percentiles were not associated with physical activity (insufficient physical activity group p=0.512) or any family history of DM (p=0.219) as well. The CAC percentiles did not differ between subjects with and without ultrasonographically evident Achilles tendinopathies (p=0.480). Furthermore, the body composition analysis did not reveal any significant association between the CAC percentiles and visceral obesity (p=0.17), body mass index (p=0.20) or an increased waist-hip ratio (p=0.25) as well.

3.2.6. The Evaluation of the Quality and Quantity of HDL-C and Use in Clinical Practice

3.2.6.1 The Evaluation of HDL-C Concentration in the Study Population

A detailed examination of the quality and quantity of HDL-C was performed on 93 randomly selected participants from both study groups. We found 70.2 % (n=33) of decreased HDL-C concentrations in the SD group. Patients with SD more frequently had decreased levels of HDL-C (30%, n=33) compared to healthy controls (13.6%, n=14), p=0.004. If assessed in terms of gender, more men with SD had decreased HDL-C (33.9%, n=19) compared to the control group (13.5%, n=7), p=0.013. No significant difference in HDL-C levels between women with SD (25.9%, n=14) and healthy women (13.7%, n=7) was found (p=0.118). A weak but significant association was found between age and HDL-C concentration (r=0.180, p=0.008). Chances of having severe dyslipidemia are approximately two times higher (OR 2.433, CI:1.366-4.334), when HDL-C <1.19 mmol/l (sensivity – 46.4%, specifity – 73.8%, area under the curve – 2.6%). In order to define the increased, normal and decreased HDL-C concentration, in this study, we calculated the 33th percentiles, which divide all measurements in three equal parts (Table 20).

Table 20. *The descriptive statistics of HDL-C (n=93).*

Characteristics		HDL-C (mmol/l)
Mean		1.28
Median		1.27
Standard deviation		0.32
Smallest observation		0.75
Largest observation		2.16
Percentiles	33.33	1.08
	66.66	1.40

Abbreviations: HDL-C – high-density lipoprotein cholesterol.

A normal concentration of HDL-C was determined for most of the evaluated men and women, irrespective of the severe dyslipidemia status (Figure 36). While analyzing the group with increased HDL-C, more women had increased HDL-C compared to men (13 vs. 4; p=0.015) (Figure 37). After evaluating the different age groups of study population, significant differences in HDL-C levels were not found (Figure 38).

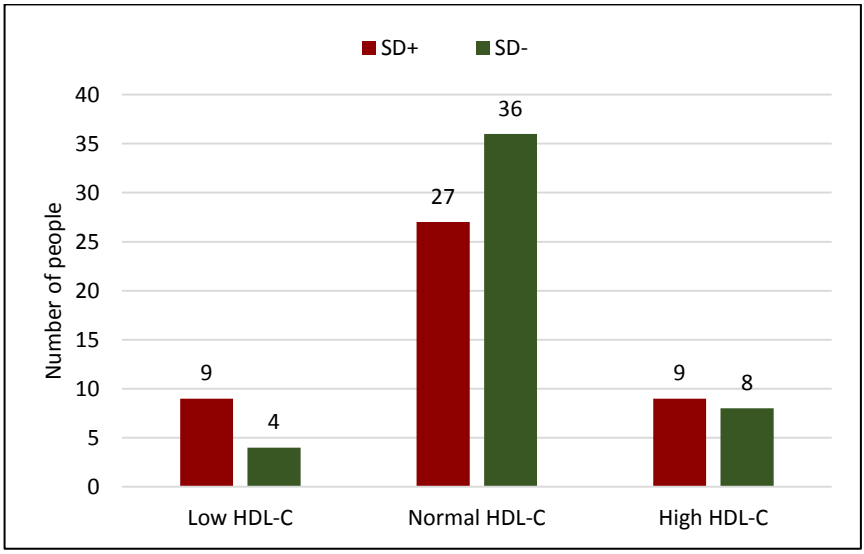


Figure 36. *The associations between HDL-C concentration and severe dyslipidemia in the study population, p=0.205 (n=93).*
Abbreviations: SD+ – patients with severe dyslipidemia; SD – – patients without severe dyslipidemia

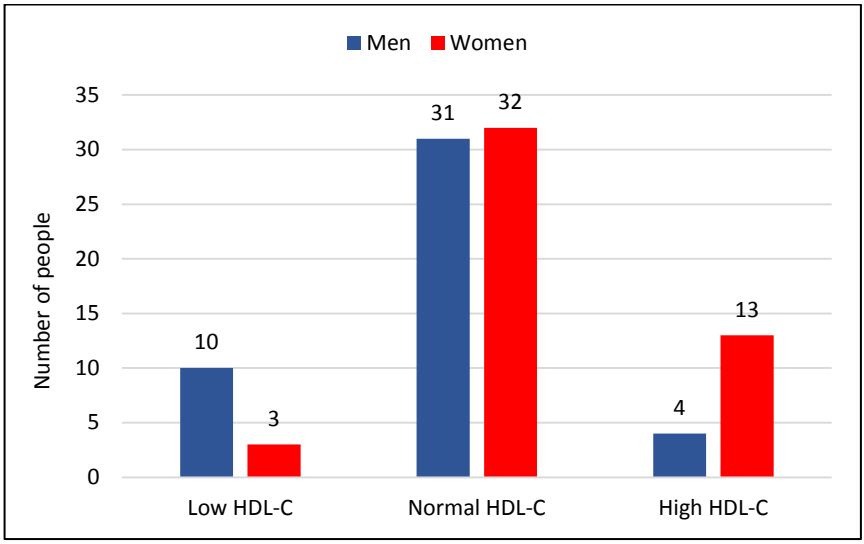


Figure 37. *The associations between HDL-C concentration and gender in the study population, p=0.015 (n=93).*

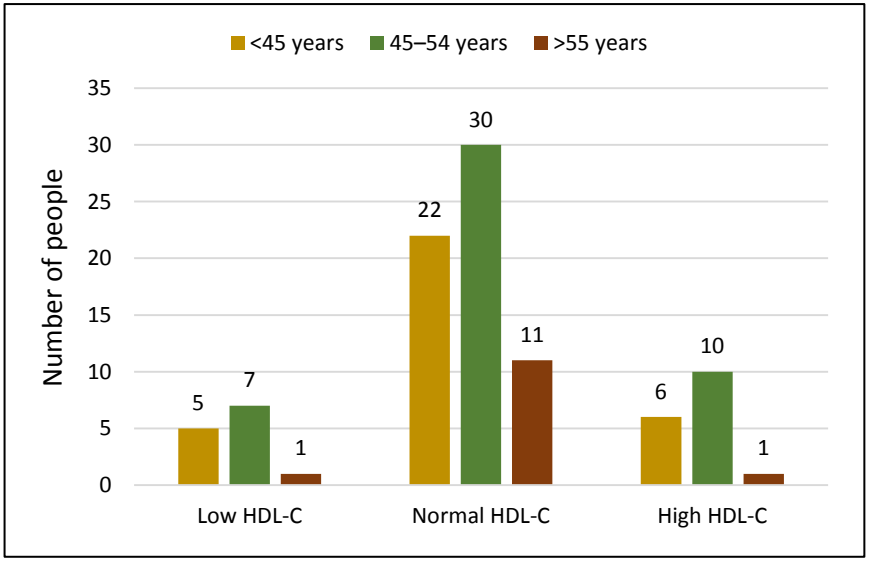


Figure 38. *The associations between HDL-C concentration and age in the study population p=0.715 (n=93).*

3.2.6.2 Relations of HDL-C Concentration with Other Cardiovascular Risk Factors

Normal levels of HDL-C were most frequently found among patients with I* obesity (Figure 39, p=0,02). Associations between HDL-C levels and other cardiovascular risk factors (abdominal obesity, AH, smoking, family history of CHD) were not found. Normal HDL-C concentrations were more prevalent among patients consuming alcohol in comparison with those who do not drink alcoholic beverages, p=0.004 (Figure 40). Although physically active subjects tended to have normal levels of HDL-C more frequently than people with insufficient physical activity, significant differences were not found (Figure 41).

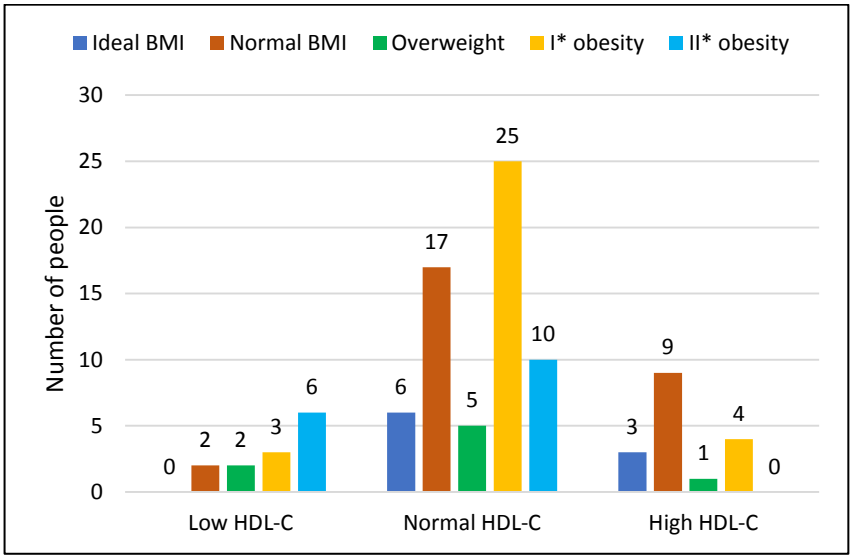


Figure 39. *The associations between HDL-C concentration and BMI in the study population, p=0.02 (n=93).*

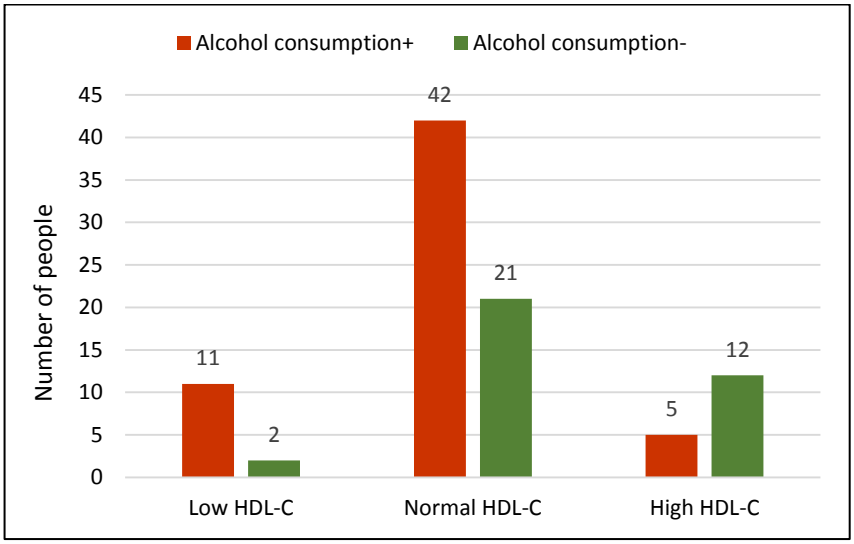


Figure 40. *The associations between HDL-C concentration and alcohol consumption in the study population, p=0.004 (n=93).*

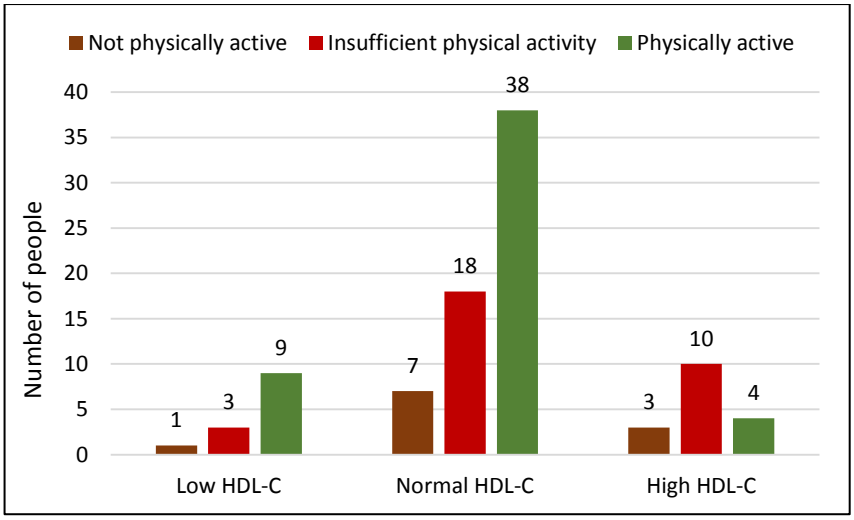


Figure 41. *The associations between HDL-C concentration and physical activity in the study population, p=0.068 (n=93).*

A strong positive connection was found between ApoA1 and HDL-C concentrations in both severe dyslipidemia (r=0.866) and control (r=0.63) groups (Table 21). In patients without SD, an increasing HDL-C is associated with a decreasing ApoB/ApoA1 ratio (r=-0.56). Increasing TG and BMI were associated with decreasing HDL-C concentrations. An increase in waist circumference was related to a decrease in HDL-C levels in women with SD (r=-0.309). In subjects with SD, a significant decrease of the HDL function was observed while the concentration of HDL-C had increased (Table 21).

Table 21. *Spearman's correlation coefficients between HDL-C concentration and other characteristics in groups with and without severe dyslipidemia.*

Characteristics	**HDL-C** (mmol/l)			
	SD–	**SD+**	**SD+**	
			Men	Women
HDL-C function (%)	-0.146	**-0.335***	-0.123	-0.198
Age (years)	0.130	0.061	0.059	-0.030
TC (mmol/l)	**0.342***	0.277	-0.008	**0.327***
TG (mmol/l)	**-0.380***	**-0.608***	**-0.582***	-0.217
LDL-C (mmol/l)	-0.057	**0.412***	0.083	0.232
Apo A1 (mmol/l)	**0.866***	**0.630***	**0.713***	**0.755***
Apo B (mmol/l)	-0.097	0.275	-0.065	0.126
Apo A2 (mmol/l)	**0.410***	**0.418***	**0.317***	**0.455***
Apo E (mmol/l)	0.140	**-0.314***	-0.160	0.050
Apo B/Apo A1	**-0.567***	-0.015	**-0.325***	-0.104
Lp(a) (g/l)	-0.263	0.232	-0.141	-0.015
BMI (kg/m2)	**-0.327***	**-0.531***	**-0.461***	**-0.441***
WC (cm)	0.183	**-0.583***	-0.189	**-0.309***

*** statistically significant as p<0.05;**

Abbreviations: HDL-C – high-density lipoprotein cholesterol; TC – total cholesterol; TG – triglycerides; LDL-C – low-density lipoprotein cholesterol; Apo – apolipoprotein; Lp(a) – lipoprotein(a); BMI – body mass index; WC – waist circumference.

Irrespective of age, a strong negative relation between HDL-C and TG was observed (r=-0.588; r=-0.326; r=-0.775) as well as a positive connection between HDL-C and Apo A1 concentrations (r=0.864; r=0.669; r=0.803) (Table 22). A negative association between the Apo B/Apo A1 ratio and HDL-C concentration decreased with age (Table 22). Age did not have any effect on the HDL function in this study.

Table 22. *Spearman's correlation coefficients between HDL-C concentration and other characteristics across different age groups.*

Characteristics	**HDL-C** (mmol/l)		
	<45y	45-54y	≥55y
HDL function (%)	-0.217	-0.267	0.006
Age (years)	-0.330	0.282	-0.365
TC (mmol/l)	0.110	0.226	-0.177
TG (mmol/l)	**-0.588***	**-0.326***	**-0.775***
LDL-C (mmol/l)	0.032	0.168	-0.083
Apo A1 (mmol/l)	**0.864***	**0.669***	**0.803***
Apo B (mmol/l)	0.127	0.065	-0.349
Apo A2 (mmol/l)	-0.014	**0.600***	0.511
Apo E (mg/l)	-0.108	0.040	-0.481
Apo B/Apo A1	**-0.374***	-0.143	-0.535
Lp(a) (g/l)	-0.295	0.138	0.194
BMI (kg/m2)	**-0.561***	**-0.400***	-0.398
WC (cm)	-0.272	-0.273	-0.209

*** statistically significant as p<0,05;**

Abbreviations: HDL-C – high-density lipoprotein cholesterol; TC – total cholesterol; TG – triglycerides; LDL-C – low-density lipoprotein cholesterol; Apo – apolipoprotein; Lp(a) – lipoprotein(a); BMI – body mass index; WC – waist circumference.

3.2.6.3 An Evaluation of the HDL Function in the Study Population (n=93)

A below average HDL function was found in 67.7% (n=63) of subjects (n=93) (Figure 42). An average function of HDL in the study population was 47.5%. The descriptive statistics of the HDL function are presented in Table 23. Significant differences in the HDL function between men and women were not detected (Figure 43). After an evaluation of men and women with SD, a below average HDL function was found to be more common among women, although the difference was not statistically significant (Figure 44).

Table 23. *The descriptive statistics of the HDL function in the study population (n=93).*

HDL function (%)		**Result**
Mean		44.75
Standard deviation		11.61
Smallest observation		13.06
Largest observation		69.15
Deciles	66.6 (2/3)	49.21
	75 (3/4)	51.83

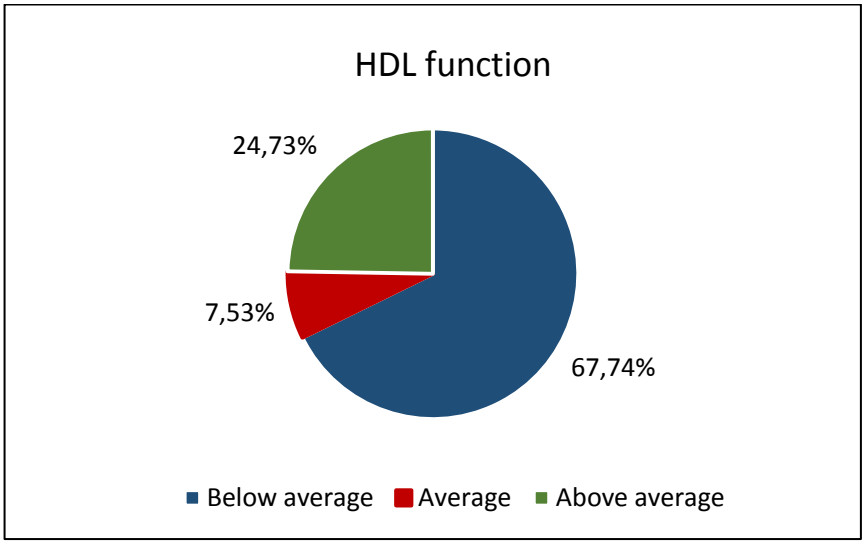


Figure 42. *An evaluation of the HDL function in the study population (n=93).*

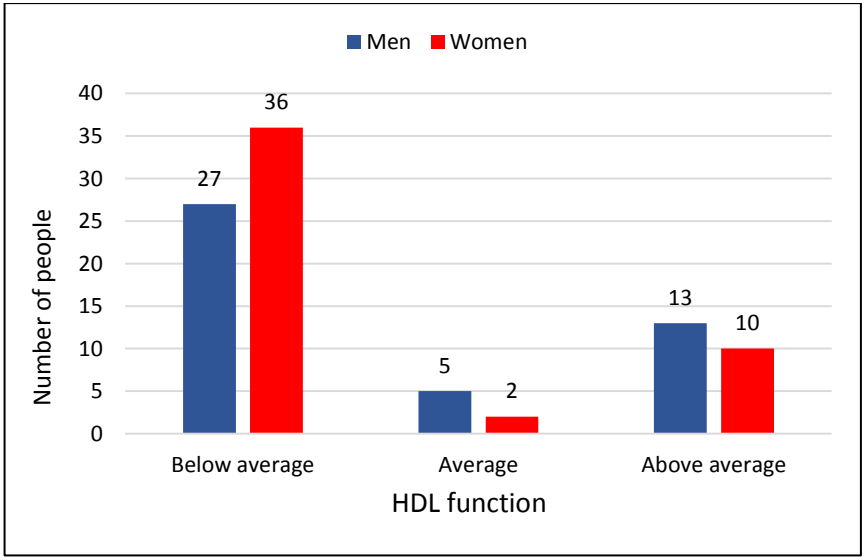


Figure 43. *The distribution of the HDL function among different genders, p=0.238 (n=93).*

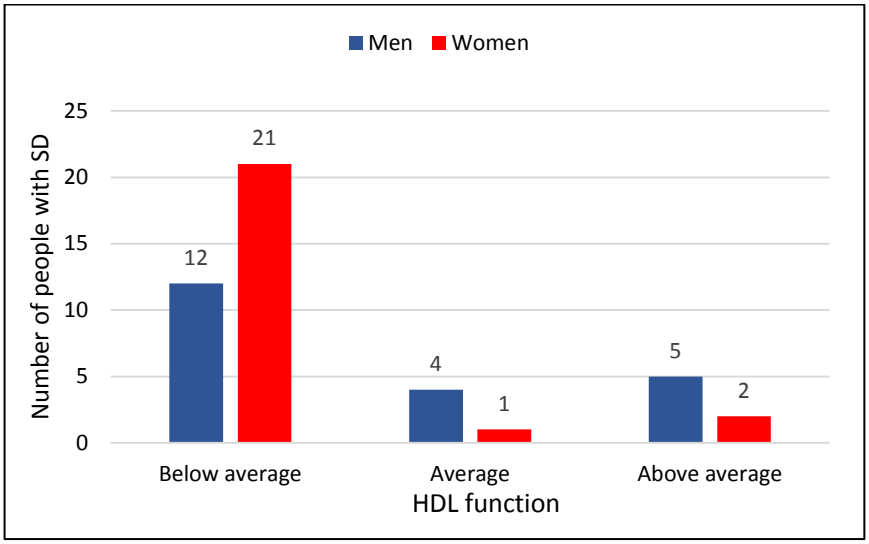


Figure 44. *The distribution of the HDL function among men and women with severe dyslipidemia, p=0.068 (n=45).*

In this study, we have found a significant negative connection between HDL-C concentration and the HDL function (r=-0.228) (Table 24). After evaluating men and women separately, no significant relation was established (Table 25).

Table 24. *The associations of the HDL function with HDL-C concentration in the study population.*

	Sample	**HDL-C**
HDL function (%)	Total	**-0.228 (0.028*)**
	Women	-0.198 (0.177)
	Men	-0.123 (0.421)

*** statistically significant as p<0.05;**
Abbreviations: HDL-C – high-density lipoprotein cholesterol.

Table 25. *The associations of the HDL function with severe dyslipidemia.*

	Gender	**SD+**	**SD –**
HDL function (%)	Men	-0.112 (0.601)	-0.146 (0.497)
	Women	-0.02 (0.933)	-0.146 (0.497)

*** statistically significant as p<0.05;**
Abbreviations: HDL-C – high-density lipoprotein cholesterol; SD+ – patients with severe dyslipidemia; SD – – patients without severe dyslipidemia.

3.2.6.4 The Associations of the HDL Function with Other Cardiovascular Risk Factors

Patients with normal BMI and I* obesity had a below average HDL function more frequently compared to people with overweight and II* obesity (Figure 45). Significant associations of the HDL function and other cardiovascular risk factors (abdominal obesity, AH, smoking, a family history of CHD, alcohol consumption) were not established. Although, among physically active subjects, a below average HDL function was more common compared to patients with insufficient physical activity, this difference was not statistically significant (Figure 46).

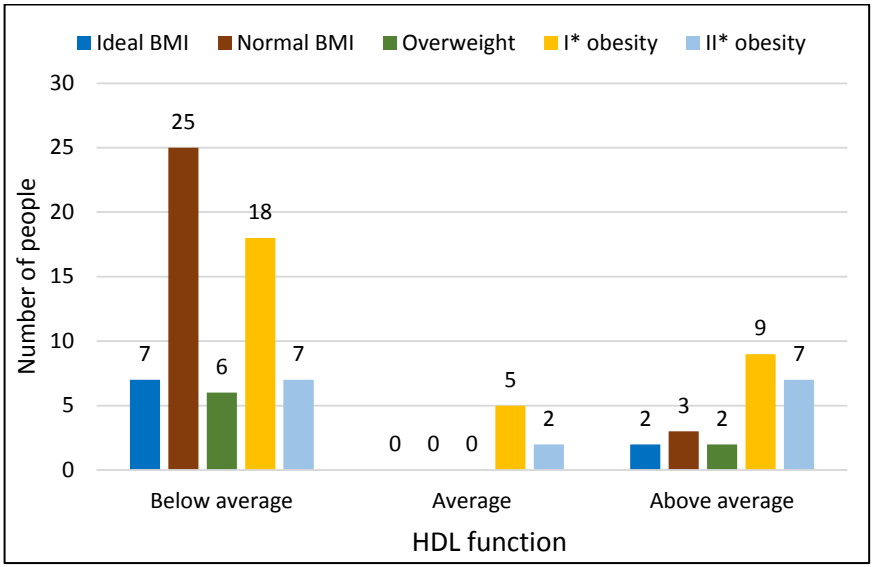


Figure 45. *The associations of BMI with the HDL function in the study population, p=0.05 (n=93).*

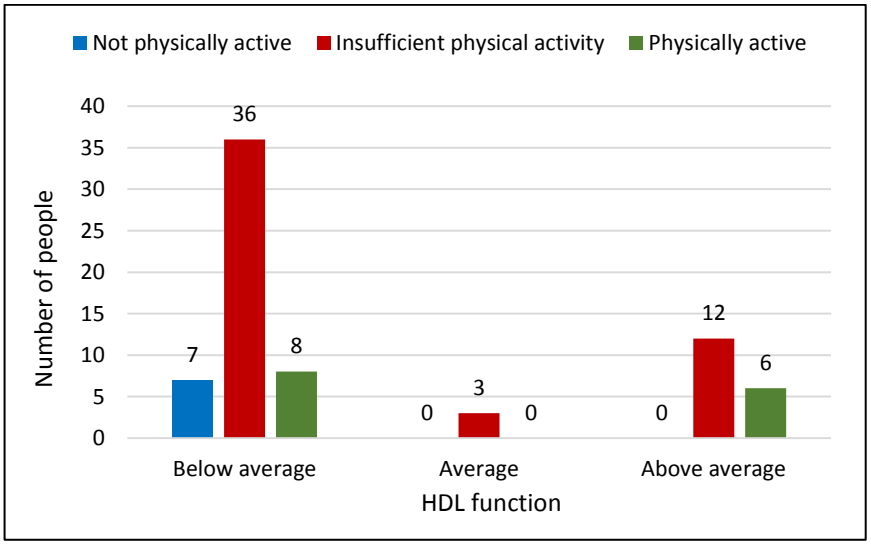


Figure 46. *The associations of physical activity with the HDL function in the study population, p=0.197 (n=93).*

After assessing the HDL function among all men and women and in relation to other cardiovascular risk factors, significant differences were not found. But while analyzing the group of men with SD, we found that that men with SD and a normal BMI more frequently had a below average HDL function (Figure 47).

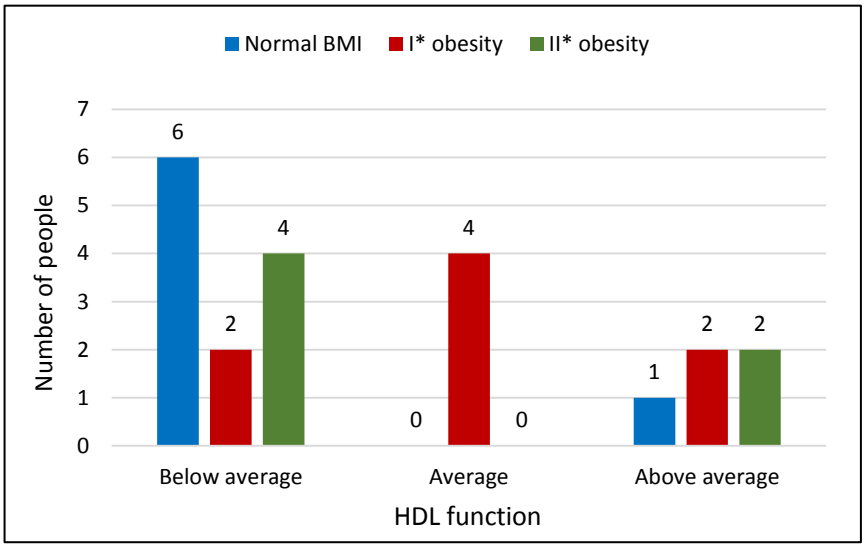


Figure 47. *The HDL function in different groups of men with severe dyslipidemia according to BMI, p=0.049 (n=21).*

3.2.7. Genetic Testing in Patients with Severe Dyslipidemia

The group with severe dyslipidemia consisted of 110 (51.6%) patients, but genetic testing was decided to be performed in 13 subjects – this was done after clinical evaluations of the probability of familial hypercholesterolemia (FH) in accordance with the Dutch Lipid Clinic Network criteria. LDL receptor (LDLR) mutations were found in four patients, confirming the diagnosis of FH. Five patients tested negative for any evaluated mutations associated with FH. The remaining four people did not agree to analysis due to personal reasons. Mutations in Proprotein convertase subtilisin/kexin type 9 (PCSK9) gene and ApoB gene were not detected.

CONCLUSIONS

1. Dyslipidemia is very common (89.7%) and one of the most important cardiovascular risk factors with an increasing prevalence being observed during the period of 2009–2016 in Lithuania (from 89.1% to 89.5%). The diagnosis and treatment of dyslipidemia is delayed and inadequate.
2. Dyslipidemia is associated with a greater probability of possessing all major CVD risk factors (diabetes mellitus, arterial hypertension, abdominal obesity, metabolic syndrome and obesity), except smoking, compared to adults without dyslipidemia. An unbalanced diet, an insufficient level of physical activity and a family history of CHD were also more common among subjects with dyslipidemia.
3. Atherogenic dyslipidemia is associated with an unfavorable cardiovascular risk profile. Subjects with atherogenic dyslipidemia more frequently possess other cardiovascular risk factors compared to people with isolated hypertriglyceridemia or low HDL-C.
4. The prevalence of severe hypertriglyceridemia increased from 2.2% to 2.3%, while a decreased prevalence was found for severe dyslipidemia (from 12.1% to 11.6%) as well as severe hypercholesterolemia (from 2.9% to 2.8%) for the period of 2009–2016 in Lithuania. Severe hypertriglyceridemia was associated with having other major CVD risk factors more often (except for family history of CHD) compared to severe hypercholesterolemia.
5. In the prospective part of the study, patients with severe dyslipidemia more frequently happened to be obese and have arterial hypertension, histories of CHD in their families, menopause and insufficient levels of physical activity compared to a control group. For the evaluation and long-term monitoring of patients with severe dyslipidemia, useful investigations include a body composition analysis, an Achilles tendon

ultrasonography, a carotid artery ultrasound as well as genetic testing (if available).

6. An insufficient function of HDL was observed in 67.7% of study subjects. An inverse relationship was determined between the HDL function and the plasma concentration of HDL-C (r=-0.228).

PRACTICAL RECOMMENDATIONS

- The diagnosis and treatment of dyslipidemia, as well as the patient-physician relationship, should be improved, as these are one of the most important health problems of middle-aged Lithuanians.
- Dyslipidemia is often detected alongside other cardiovascular risk factors and requires special attention while assessing the cardiovascular risk of a particular patient.
- It is necessary to pay more attention to diagnosis, treatment and long-term monitoring as well as the evaluation of cardiovascular risks and the management of patients with severe dyslipidemia.
- Body composition analysis is necessary and useful for evaluating patients with severe dyslipidemia as well as for monitoring their body composition changes while making lifestyle interventions or other preventative measures required to manage cardiovascular risks.
- The ultrasound imaging of the Achilles tendon and carotid arteries is useful for evaluating and monitoring patients with severe dyslipidemia.
- The CAC score is not an appropriate diagnostic tool in the algorithm of severe dyslipidemia examination.
- While suspecting familial hypercholesterolemia, genetic testing is helpful for establishing a definite diagnosis, finding the best treatment options, maintaining a better patient-physician relationship and screening family members for the index case.

- Further extensive studies are needed to analyze the function of HDL in Lithuania and support the findings of this study.

LIST OF PUBLICATIONS

1. Rinkuniene E., Laucevicius A., Petrulioniene Z., Dzenkeviciute V., **Kutkiene S.**, Skujaite A., Kasiulevicius V. The prevalence of dislipidemia and its relation to others risk factors: the nationwide survey of Lithuania. *Clinical Lipidology* 2015; 10(3):2019-225. (IF 0.54).

2. **Kutkiene S.**, Petrulioniene Z., Laucevicius A., Petrylaite M., Maskeliunaite D., Puronaite R., Kovaite M., Kalibataite I., Rinkuniene E., Dzenkeviciute V., Kasiulevičius V. Severe dyslipidemia and concomitant risk factors in the middle-aged Lithuanian adults: a cross-sectional cohort study. *Lipids in Health and Disease* 2018; 17:88. doi: 10.1186/s12944-018-0731-7 (IF 2.073)

3. **Kutkiene S.**, Petrulioniene Z., Laucevicius A., Cerkauskienė R., Staigyte J., Saulyte A., Petrulionyte E., Gargalskaite U., Skiauteryte E., Matuzeviciene G., Kovaite M., Rinkuniene E. Cardiovascular risk profile of patients with Atherogenic Dyslipidemia in middle aged Lithuanian population. *Lipids in Health and Disease* 2018; 17:208. doi: 10.1186/s12944-018-0851-0 IF (2.073)

4. **Kutkiene S.**, Petrulioniene Z., Laucevicius A., Cerkauskienė R., Staigyte J., Saulyte A., Petrulionyte E., Gargalskaite U., Skiauteryte E., Matuzeviciene G., Kovaite M., Rinkuniene E. Lipid profile evaluation and familial hypercholesterolemia screening in middle-aged population according to nationwide primary prevention programme in Lithuania. *Atherosclerosis* 2018, 277:267-272. (IF 4.467)

5. Petrulioniene Z., Gargalskaite U., **Kutkiene S.**, Staigyte J., Cerkauskienė R., Laucevicius A. Establishing a national screening programme for familial hypercholesterolemia in Lithuania. *Atherosclerosis* 2018, 277:407-412. (IF 4.467)

6. **Kutkiene S.**, Petrulioniene Z., Laucevicius A., Serpytis P., Kasiulevicius V., Staigyte J., Saulyte A., Petrulionyte E., Gargalskaite U., Skiauteryte E., Matuzevičiene G., Kovaite M., Rinkuniene E.

Cardiovascular risk assessment of dyslipidemic middle-aged adults without overt cardiovascular disease over the period of 2009-2016 in Lithuania. *Lipids in Health and Disease* 2018; 17:233. doi: 10.1186/s12944-018-0883-5 (IF 2.073)

7. **Kutkienė S.**, Petrulionienė Ž., Sausdravas R., Šarapnickienė I., Petrylaitė M., Rutkauskienė I., Gargalskaitė U., Kovaitė M., Rinkūnienė E., Dženkevičiūtė V., Kasiulevičius V. Šeiminė hipercholesterolemija. *Medicinos teorija ir praktika* 2016; 22(5):441-451.

8. **Kutkienė S.**, Petrulionienė Ž., Sausdravas R., Šarapnickienė I., Petrylaitė M., Rutkauskienė I., Gargalskaitė U., Kovaitė M., Rinkūnienė E., Dženkevičiūtė V., Kasiulevičius V. Antrinės dislipidemijų priežastys. *Medicinos teorija ir praktika* 2016; 22(5):452-458.

9. Janavičiūtė G., Petrulionienė Ž., **Kutkienė S.** Dislipoproteinemijų klasifikacija ir laboratorinė diagnostika. *Laboratorinė medicina* 2016, 18,(2):93-101.

PRESENTATIONS GIVEN AT CONFERENCES ON THE SUBJECT OF THIS DISSERTATION

1. **Kutkiene S**. Severe dyslipidemia and cardiovascular risk in the middle aged Lithuanian adults. Symposium of the International Atherosclerosis Society ISA Conference "Anitschkow Days," June 2–4, 2016, St. Petersburg, Russia (poster presentation).

2. **Kutkiene S.** Prevalence of cardiovascular risk factors in middle-aged subjects of high risk Lithuanian population. The 84th EAS Congress, May 29–June 1, 2016, Innsbruck, Austria (oral presentation).

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