Original paper

Primary prevention strategy for cardiovascular disease in Lithuania

("A Funding Programme for the Screening and Preventive Management of the High Cardiovascular Risk Individuals" – main results: 2006–2017 years)

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Summary

Cardiovascular diseases are the main cause of premature death worldwide. More than half of deaths were caused by cardiovascular diseases in 2017 in Lithuania. Primary prevention programmes encourage both medical staff and general population to pay attention to potential health issues as well as attempt to eradicate risk factors causing cardiovascular diseases. "A Funding Programme for the Screening and Preventive Management of the High Cardiovascular Risk Individuals" published in Lithuania has been implemented as of 2006.

Analysis of the results of the programme shows that the prevalent cases of arterial hypertension are gradually declining. However, the prevalence of dyslipidaemia is still not decreasing. The prevalence of other modifiable cardiovascular disease risk factors has erratic trends with a slight overall decline. Consequently, mortality rate of cardiovascular diseases has decreased by more than one third among middle-age population over the past 10 years.

Having higher availability of the anti-hypertensive and anti-lipid medications already achieved, the future plans include the aim of further reducing elevated blood pressure and effectively treating dyslipidaemia. In order to implement a strategy that focuses on smoking prevention, promotion of healthy nutrition and physical activity, a significant contribution is required from the state authorities.

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Keywords: cardiovascular disease, risk factors, primary prevention strategy

Abbreviations

ACE: Angiotensin-converting enzyme
AH: Arterial hypertension
ARB: Angiotensin II receptor blockers
BB: Beta blockers
BMI: Body mass index
BP: Arterial blood pressure
CCB: Calcium channel blockers
CVD: Cardiovascular disease
CHD: Coronary heart disease
DDD: Defined daily dose
DM: Diabetes mellitus
ESC: European Society of Cardiology
EVA: Early vascular aging
FRS1: 1991 Framingham model
HDL: High-density lipoproteins

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Hs-CRP: High sensitivity C-reactive protein
H-L test: Hosmer-Lemeshow test
IAS-Agla: Arbeitsgruppe Lipide und Atherosklerose model
IHD: Ischaemic heart disease
LitHiR Programme: (Lithuanian High cardiovascular Risk) Programme – Lithuanian national primary prevention programme "A Funding Programme for the Screening and Preventive Management of the High Cardiovascular Risk Individuals"
LDL: Low-density lipoprotein
MS: Metabolic syndrome
NCEP ATP III: National Cholesterol Education Program Adult Treatment Panel III
PAD: Peripheral artery disease
PPU: Primary prevention units
PROCAM: Prospective Cardiovascular Münster model
PWV: Pulse wave velocity
SCORE: Systematic Coronary Risk Evaluation model
SPU: Specialized prevention units
TG: Triglycerides

Introduction

Cardiovascular disease (CVD) is the main cause of premature death not only in Lithuania but also throughout the world. According to the data of the Institute of Hygiene of the Lithuanian Health Information Centre, the causes of death of the population of Lithuania have not changed for many years [1]. It is important that more than half (56.1%) of deaths were caused by cardiovascular diseases in 2017 (Fig. 1) – it is also the most common cause of death among both men and women (48.1% for men and 63.4% of women).

In Lithuania, morbidity and mortality rates of CVD are higher than in other Western European or Scandinavian countries [2]. In many developed European countries, the death rate of CVD between 1970 and 1990 fell significantly with the introduction of preventive measures. The World Health Organization indicates that more than three quarters of the CVD deaths can be avoided by modifying risk factors [3]. All of this demonstrates that not only early diagnosis of overt CVD and proper treatment is important but also the prevention of CVD.

Primary prevention programmes encourage not only medical staff but also general population to pay attention to potential health issues, to eradicate or at least to reduce the number of risk factors that cause CVD and to monitor population health. The importance of the prevention of CVD is also evident in the guidelines prepared by the European Society of Cardiology (ESC) in 2016, which highlight the significance of the implementation of the primary CVD prevention programmes [4]. One of the main guidelines emphasizes the need to identify individuals with high cardiovascular risk and to offer a primary prevention action plan. In order to achieve this aim in Lithuania, the state has issued "A Funding Programme for the Screening and Preventive Management of the High Cardiovascular Risk Individuals" (hereinafter the "LitHiR Programme"), carried out since 2006.

Cardiovascular risk factors

The CVD is closely related to the lifestyle and modifiable risk factors. More than 200 CVD risk factors are known, but not all of them are equally important. All risk factors for CVD are divided into two groups: modifiable and non-modifiable.

- Risk factors that can be managed (modifiable):
  - arterial hypertension (AH);
  - dyslipidaemia-elevated lipid levels in the blood;
  - smoking;

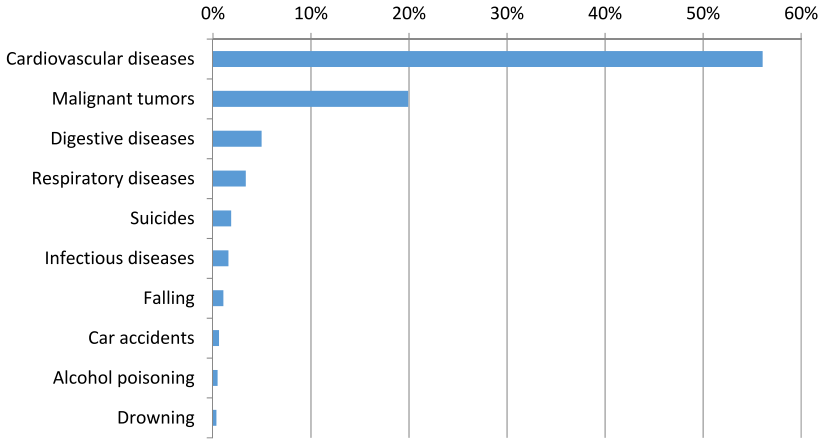


Figure 1. The structure of the causes of death in Lithuania 2017 [1].

  - diabetes mellitus or impaired glucose metabolism;
  - unbalanced diet;
  - obesity, especially abdominal;
  - low physical activity;
  - stress or depression;
  - hypercoagulation, serum hyperviscosity.
- Risk factors that cannot be managed (non-modifiable):
  - age (more than 45 years for men and more than 55 years for women);
  - male sex;
  - heredity: an early onset of CVD in relatives – parents, siblings, sisters (heart attack, stroke, sudden death in males up to 55 years old, female up to 65 years), familial dyslipidaemia;
  - diagnosed atherosclerotic vascular disease (cardiac, cerebral, peripheral arteries, etc.)

Scientific literature highlights that major CVD risks include AH, dyslipidaemia, in particular, low-density lipoprotein (LDL) cholesterol (also known as "bad" cholesterol), smoking and diabetes mellitus [5–8]. The ESC prevention guidelines underline the need to assess risk factors not in isolation but in combination with each other, since risk factors that cause CVD reinforce each other's effects [4]. These guidelines subdivide the risk of CVD into very high, high, intermediate and low risk. One of the most commonly found combinations of risk factors is a so-called metabolic syndrome, the presence of which implies an increased CVD risk due to diabetes mellitus and atherosclerosis. Such combination of risk factors is classified as posing an intermediate cardiovascular risk, however, the risk significantly increases when other risk factors (LDL-cholesterol increase, arterial and cardiac functional and structural changes, etc.) are present as well.

CVD prevention is particularly important in Lithuania, as there is still a high rate of CVD morbidity and mortality, with the high prevalence of young people suffering from CVD. It is no coincidence that according to ESC guidelines, Lithuania together with other countries in Eastern Europe, is not only included in the list of high-risk countries, but also distinguished as a country with very high risk.

Lithuania has been actively engaged in the LitHiR Programme. The aim of the LitHiR Programme is to reduce the prevalence of the CV risk factors and thereby to decrease the CVD-related mortality, and to facilitate the timely diagnosis of the vascular diseases caused by early atherosclerosis. The LitHiR Programme enrolled men aged 40 to 55 and women aged 50 to 65 years.

The LitHiR Programme consists of two steps:

- Initial risk assessment at the dedicated primary care centres (primary prevention units; PPU);
- Examination of patients with high and intermediate CVD risk at the specialized prevention units (SPU).

The results of the initial risk assessment by primary care specialists (general practitioners and nurses)

Over 200 thousand individuals are examined at primary care institutions every year (Fig. 2), and 5–10% of those identified with high CVD risk or metabolic syndrome are sent to SPU (see Fig. 23 further in the text).

According to the date of 1 January 2014, the target population for the initial risk assessment reached about 700 000 people.

Customized forms specifically designed for the Programme are in use since July 2009. The possibility to fill them out electronically is available since 2012.

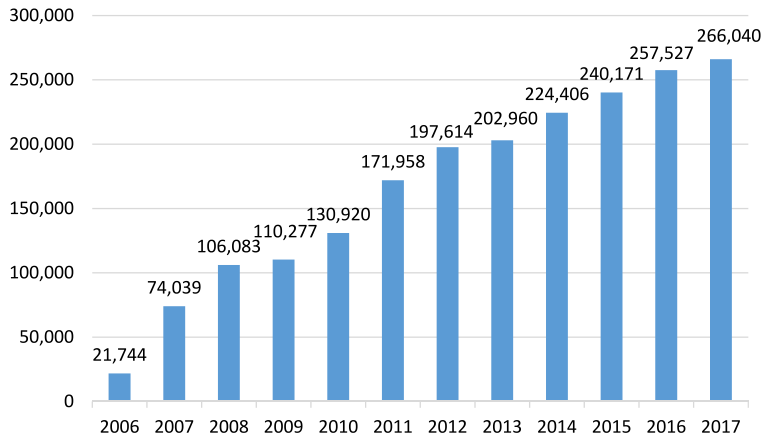


Figure 2. The inclusion of patients to the LitHiR Programme during the years 2006–2017 in the primary care institutions (source: National Health Insurance Fund).

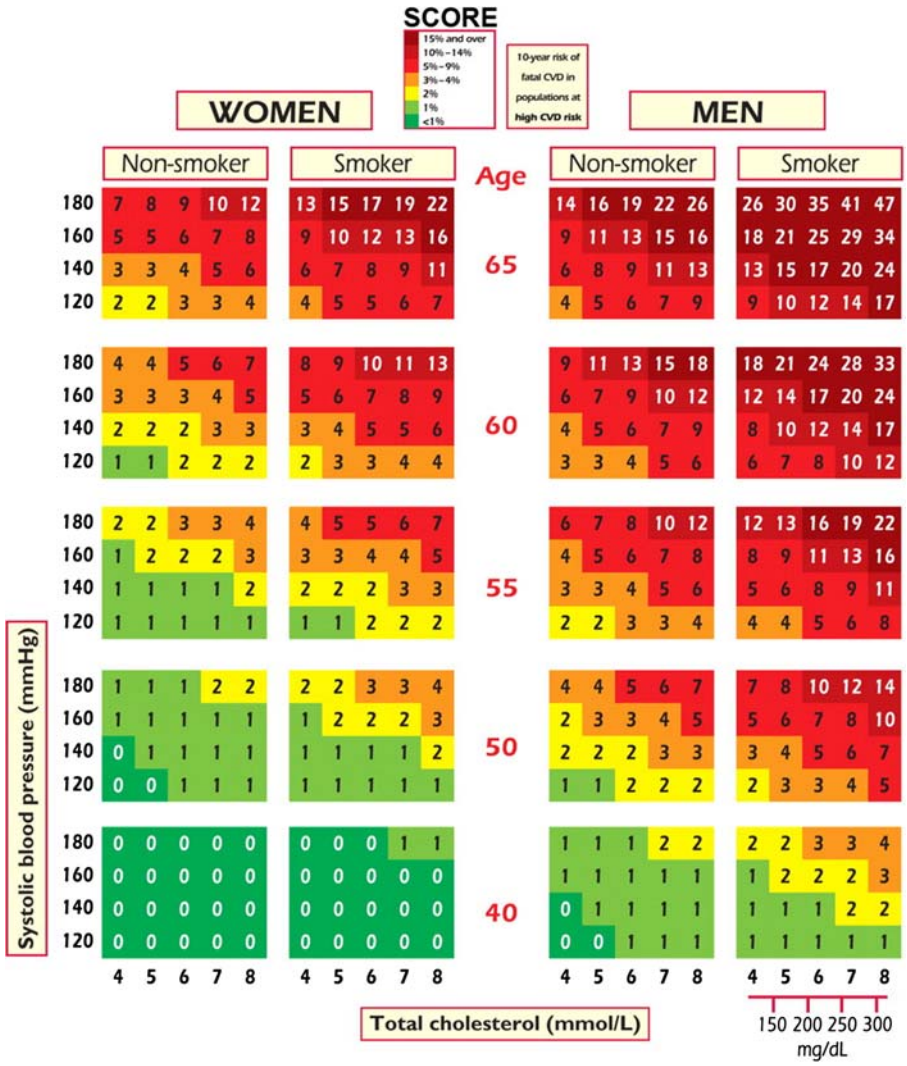


Figure 3. Determination of the first fatal cardiovascular event within 10 years (source: 2016, Guidelines for the prevention of the CVD [4]).

Initial assessment includes the following: the evaluation of the salient CVD risk factors, filling out electronic CVD risk assessment form, and calculating CVD risk according to SCORE (Systemic Coronary Risk Evaluation) model (Fig. 3) [9].

The presence of metabolic syndrome is assessed by the modified NCEP (National Cholesterol Education Program)-ATP III criteria [10].

Metabolic syndrome is confirmed when least three of the five criteria are present:

1. Waist circumference $\geq$ 102 cm (for men), $\geq$ 88 cm (for women);
2. Systolic blood pressure (BP) $\geq$ 130 mmHg and/or diastolic BP $\geq$ 85 mmHg or antihypertensive drugs being used;
3. Fasting glucose $\geq$ 5.6 mmol/L or patient being treated for hyperglycaemia;
4. Triglycerides (TG) $\geq$ 1.7 mmol/L or special treatment targeted to reducing the level of TG being applied;
5. High density lipoprotein (HDL) cholesterol < 1.03 mmol/L (for men), < 1.3 mmol/L (for women) or specific treatment being applied.

The individuals are divided into three groups according to the evaluation results:

1) low or intermediate risk;
2) intermediate risk with the suspicion of high risk–metabolic syndrome with additional risk factors (elevated cardiometabolic risk);
3) high risk.

General practitioners recommend preventive measures (diet, physical activity, smoking cessation, cholesterol levels and BP lowering medication, treatment for diabetes mellitus) for each patient (both low or intermediate and high-risk) in order to reduce CVD risk.

Data of the prevalence of main risk factors (dyslipidaemia, AH, smoking, abdominal obesity,

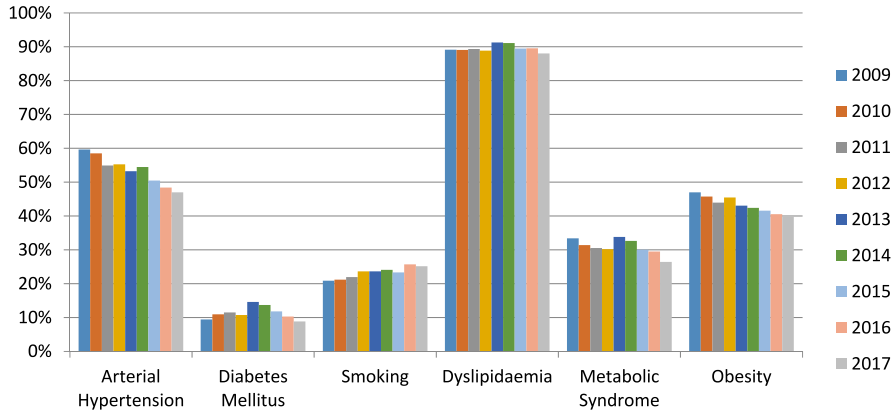


Figure 4. The prevalence of CV risk factors (%) among the participants of the LitHiR Programme during the years 2009–2017.

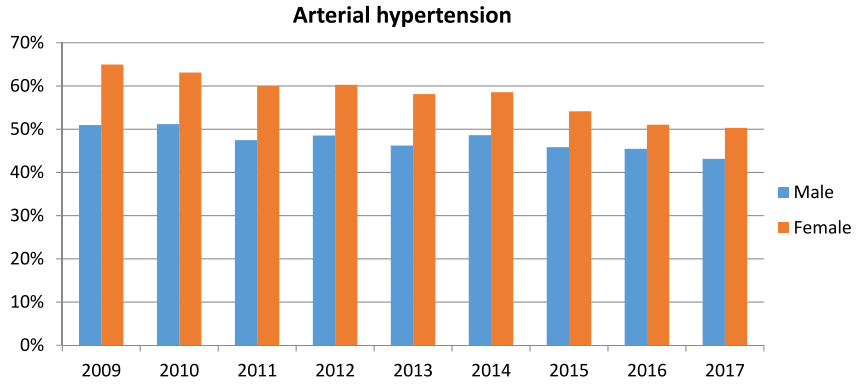


Figure 5. Trends of AH (%) among the persons included in the LitHiR Programme during the years 2009–2017.

diabetes mellitus and metabolic syndrome) and their trends from 2009 to 2017 is presented in Fig. 4.

Arterial hypertension

AH is the increased BP disease that leads to target organ damage [11]. AH is diagnosed when systolic office BP is $\geq$ 140 and/or diastolic office BP is $\geq$ 90 mmHg measured [11]. Systolic BP $\geq$ 130 mmHg and/or diastolic BP $\geq$ 85 mmHg were considered to be abnormal when examining subjects with metabolic syndrome.

Since the arteries supply blood to the vital organs, higher BP means higher chance of developing cardiovascular or cerebrovascular disease as well as renal function impairment. Changes in blood pressure are influenced by age, gender, blood lipid levels, smoking and other risk factors that lead to CVD progression [11]. It is important to mention that AH is not an isolated CVD risk factor. Since concomitant risk factors increase the overall CVD risk, a strict control of all risk factors is required [11].

The prevalence of AH in 2015 was found to be around 30–45% among adults [12]. The CV risk increase in patients with hypertension is partially attributed to the fact that many individuals do not even know that their BP is elevated and those who know do not have symptoms and therefore do not comply to treatment. The symptoms commonly are not present until the damage in the heart, blood vessels, and other organs is obvious. AH is the most important modifiable risk factor for CVD development. Therefore, AH treatment is of key importance for reducing the CVD risk.

Analysis of the results of the LitHiR Programme from 2009 to 2017 shows that the prevalent cases of AH in the primary prevention units are gradually declining (Fig. 5). However, even though the incidence of AH among middle-aged participants of the LitHiR Programme has decreased, the prevalence of AH across Lithuanian general population is still significantly higher than in the USA or western European countries.

In the past, the optimal AH control in Lithuania constituted a tiny portion of all AH cases. According to the data of CINDI (Countrywide Integrated Noncommunicable Diseases Intervention) study, in 2007, the target values for blood pressure were reached only in 2.6% men and 5.3% women [13] (Fig. 6, left block). Following the introduction of the LitHiR Programme, BP control among middle-aged subjects has significantly improved, reaching 24.2% in 2017 (Fig. 6, right block).

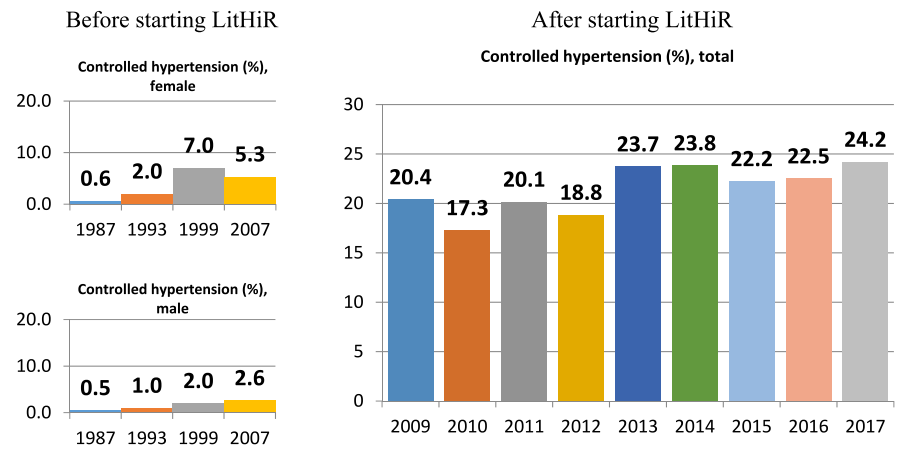


Figure 6. The improvement in AH control: optimal AH control in 1987 to 2007 (CINDI data [11]) and among the LitHiR Programme participants in 2009 to 2017.

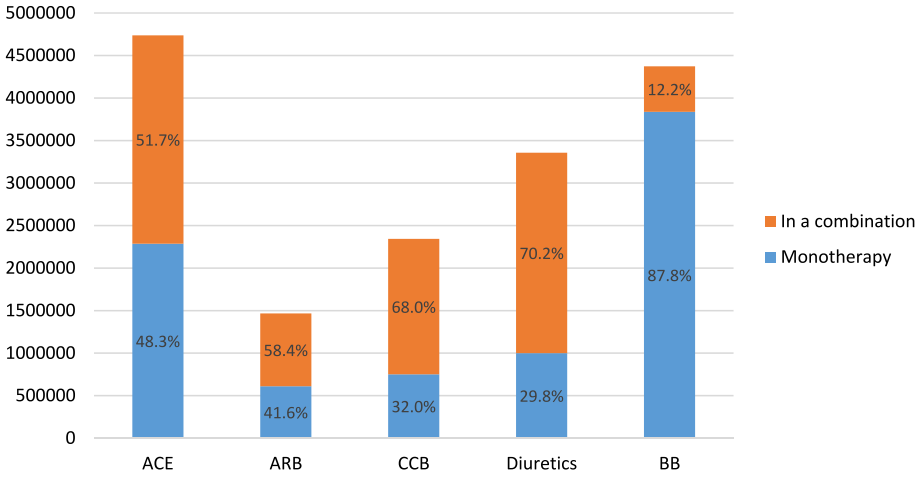


Figure 7. The use of antihypertensive drugs in Lithuania.

The prevalence of AH in Lithuania is higher than in the USA or economically developed European countries. In the years 1987, 1993, 1999 and 2007, the prevalence of AH among Lithuanian countrymen aged 25–64 years was, respectively, 62.2%, 57.9%, 59.3% and 60.3% among men and 51.2%, 52.4%, 42.1% and 44.6% among women [13]. According to the results of the LitHiR Programme, between the years 2009 and 2017, the prevalence of AH has decreased from 65.0% to 50.3% in women, and from 51.0% to 43.1% in men (Fig. 5).

The participants of the LitHiR Programme are informed about the benefit of reducing the salt intake, the hazards of smoking and excessive alcohol consumption, and about adopting other life-style modifications as needed. They are advised to lose weight with emphasis on the importance of increasing physical activity. The goal of reaching an optimal BP control would be greatly facilitated by introducing governmental policies that restrict the salt levels in the foods available on Lithuanian market.

Likewise, greater attention needs to be paid to the continuous use of the blood pressure lowering drugs. The choice of antihypertensive medicine in Lithuania is broad enough to allow for the treatment regimens that take into account patient's needs and concomitant diseases. Until recently, the availability of antihypertensive medicines (including polypill) in Lithuania was one of the best in Europe. At the present time, the following drug classes are used in the polypill combinations for treatment of AH in Lithuania: beta blockers (BB) in 12.2, angiotensin-converting enzyme (ACE) inhibitors in 51.7, angiotensin II receptor blockers (ARB) in 58.4, calcium channel blockers (CCB) in 68.0, diuretics – in 70.2 percent of cases (Fig. 7).

As the result of starting the LitHiR Programme, we observe trends toward younger men and women being first prescribed an antihypertensive drug (Fig. 8). This suggests that younger subjects are becoming more aware of AH treatment.

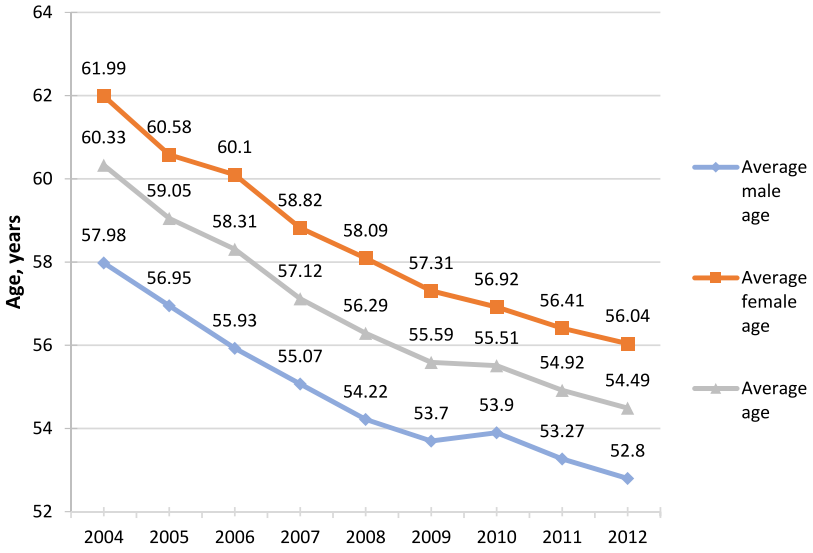


Figure 8. The average age for men and women first prescribed with antihypertensive treatment (source: I. Lisauskienė PhD thesis "Changes in cardiovascular medicines utilization and morbidity and mortality from cardiovascular disease in Lithuania", 2017).

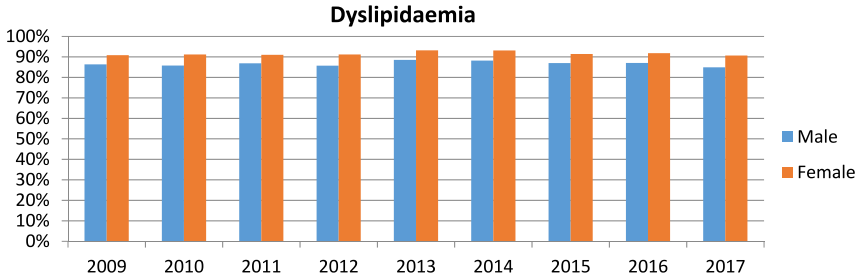


Figure 9. Trend of dyslipidaemia incidence (%) among the participants of the LitHiR Programme during the years 2009–2017.

The age of newly treated individuals declined each year, with the overall average age decrease from 60.3 years in 2004 to 54.5 years in 2012, the average age in women decreasing from 62 years to 56 years ($p < 0.001$) and the average age in men decreasing from 58 to 52.8 years, $p < 0.001$ (Fig. 8) [14].

Frequent changes in the physician's treatment plan, improper use of antihypertensive medicine by the patients, and low adherence to complex treatment schemes remain the main problems of AH treatment in Lithuania.

The data of Vilnius University Hospital Santaros Clinics shows that about 60% of patients in whom a drug-resistant AH is diagnosed and who therefore end up being prescribed more than three different antihypertensive drugs, are in fact not drug-resistant. The problem often lies in the prescription of inadequate drug combinations or low compliance due to the inconvenience of taking multiple pills. The use of the polypill (fixed drug combinations), which has been made available in the recent decade, has especially improved patients' adherence to treatment. Likewise, the effects of these fixed combinations are more potent and have milder side effects than multiple different pills.

Dyslipidaemia

Dyslipidaemia is a major risk factor for the development of CVD. The lowering of the LDL cholesterol by 2 mmol/L has been shown to reduce CVD risk by 45% [15]. According to the LitHiR Programme data, the extent of dyslipidaemia among middle-aged individuals is epidemic: about 90% of the middle-aged persons participating in the LitHiR Programme have dyslipidaemia (Fig. 9). Correspondingly, an increase in total cholesterol and LDL cholesterol was found in approximately 90% of middle-aged LitHiR Programme participants without overt CVD (Fig. 10) [16]. Average value of total cholesterol was 6.06 ± 1.18 mmol/L, LDL cholesterol 3.86 ± 1.03 mmol/L, TG 1.53 ± 0.98 mmol/L, HDL cholesterol 1.51 ± 0.42 mmol/L.

In the evaluation of the prevalence of dyslipidaemia among the LitHiR Programme participants during 2009–2017, the results are similar and there is no clear downward trend. Therefore, it can be concluded that the prevalence of dys-

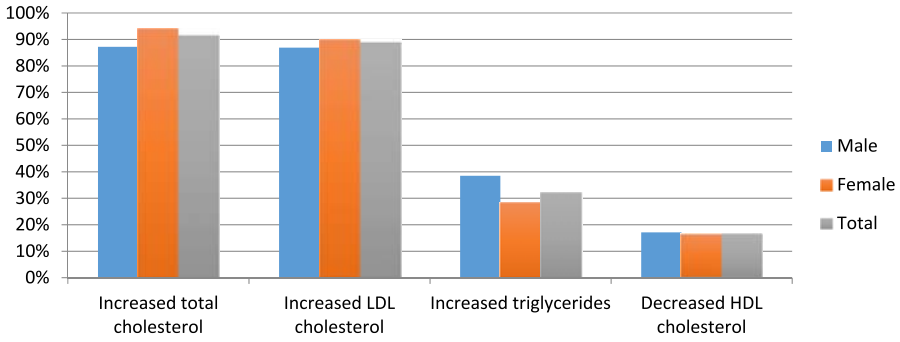


Figure 10. The prevalence of dyslipidaemia in the participants of the LitHiR Programme (%): (LDL – low density lipoprotein, HDL – high density lipoprotein) (source: E. Rinkuniene PhD thesis "The identification of patients at high-risk of cardiovascular disease and the optimization of methods of active primary prevention", 2014).

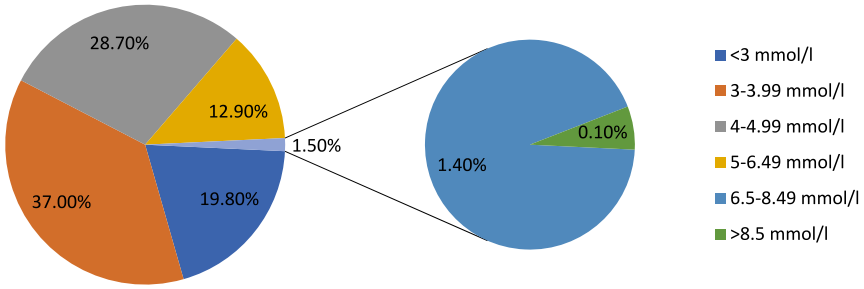


Figure 11. Distribution of LDL levels in middle-aged Lithuanian adults during the years 2009–2016.

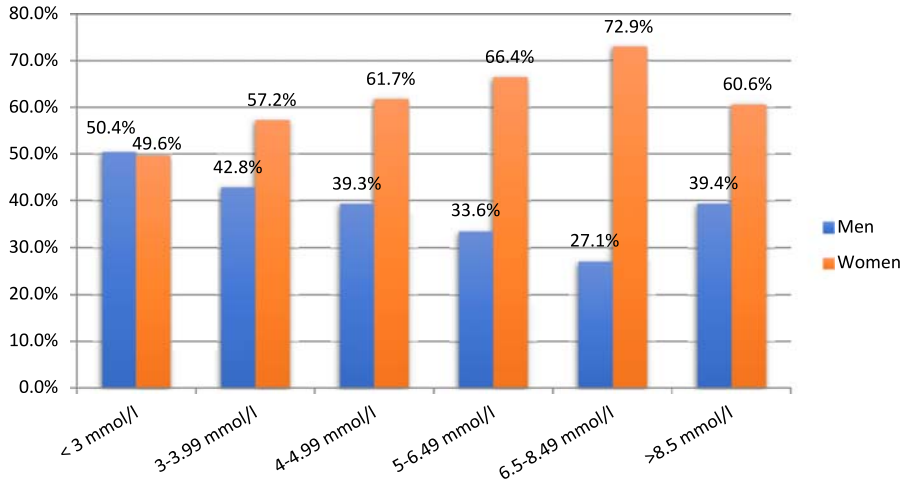


Figure 12. Differences in the LDL-C levels in the middle-aged Lithuanian men and women during the period 2009–2016.

lipidaemia is not decreasing and that its prevention and treatment is inadequate. Consequently, dyslipidaemia in Lithuania remains a poorly controlled risk factor. Given the prevalence of dyslipidaemia in Lithuania, and the benefits of its treatment for the primary prevention, no effort should be spared in timely diagnosing and adequately treating dyslipidaemia. This accords with the most recent 2016 European CVD prevention guidelines which underline the importance of dyslipidaemia correction [4].

According to the data of the LitHiR Programme, 19.8% of subjects without overt cardiovascular disease (n = 18 290, 49.6% women and 50.4% men, $p < 0.01$) had LDL less than 3 mmol/l. From 2009 to 2016, a significant decrease in number of subjects with normal LDL (< 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 levels in the middle-aged Lithuanian adults over the period of 2009–2016 is shown in Fig. 11. In the study population, LDL > 3 mmol/l was more frequently determined in women compared to men (Fig. 12).

Sixty-nine percent of participants (n = 63 644, 61.4% women and 38.6% men, $p < 0.01$) had

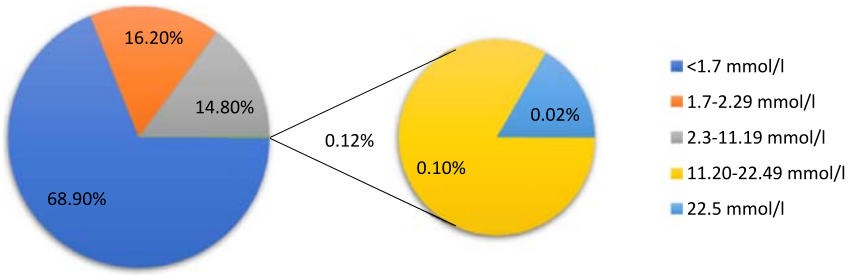


Figure 13. Distribution of TG levels in middle-aged Lithuanian adults during the period 2009–2016.

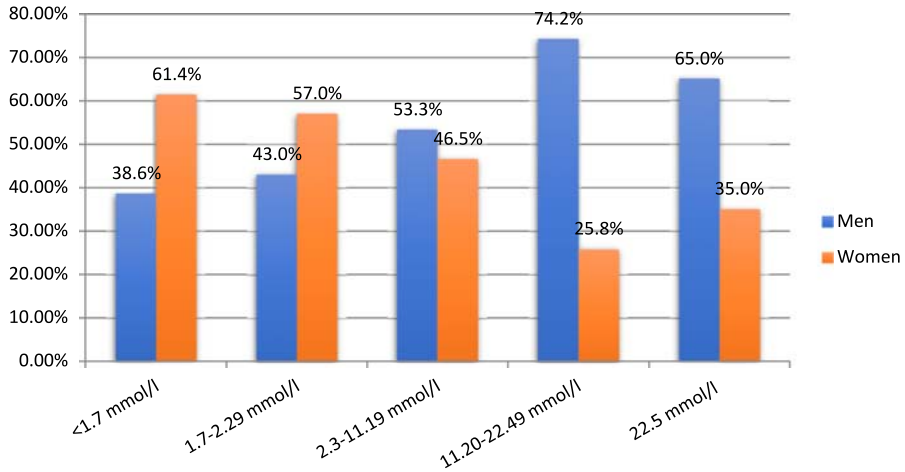


Figure 14. Differences in TG levels in the middle-aged Lithuanian men and women during the period 2009–2016.

the concentration of triglycerides less than 1.7 mmol/l. During the period 2009–2016, the prevalence of normal TG levels (< 1.7 mmol/l) decreased from 69.7 to 69.1% ($p < 0.001$) in all study participants. This pattern was confirmed in men (from 64.1% to 63.6%, $p = 0.002$), but mean TG values remained constant 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 Fig. 13. TG levels < 2.3 mmol/l were more commonly found in women, while TG > 11.2 mmol/l were more common among men (Fig. 14).

Severe dyslipidaemia was diagnosed in 13.4% of study subjects. Severe dyslipidaemia was more prevalent among women compared to men. When assessing the trends of prevalence of severe dyslipidaemia from 2009 to 2016, the prevalence decreased from 12.2% in 2009 to 11.6% in 2016 ($p < 0.013$).

Severe hypercholesterolemia (LDL ≥ 6 mmol/l) was detected in 3.2% (n = 2956) of subjects, while severe hypertriglyceridemia (TG ≥ 4.5 mmol/l) was observed in 2.0% (n = 1827) of subjects. The prevalence of severe hypercholesterolemia in the overall population decreased from 2.9% to 2.8% ($p = 0.003$) while the prevalence of severe hypertriglyceridemia increased from 2.2% to 2.3% ($p = 0.001$) in the period of 2009–2016 in Lithuania.

In the Programme population, 8.1% of the participants (54.5% women and 45.5% men) had atherogenic dyslipidaemia (TG > 1.7 mmol/l combined with HDL < 1.2 mmol/l in women and < 1.0 mmol/l in men). Normal levels of HDL were observed in 42.8% of subjects, whereas 43.6% had high concentrations of HDL, and 13.7% had low HDL.

Beside lifestyle and diet modification, the treatment of dyslipidaemia with statins is essential. It is largely due to the initiative of the LitHiR Programme that the Lithuanian Health Ministry and the Health Insurance Fund operators started to reimburse the lipid profile blood test in the primary care centres in 2005, and initiated a substantial reimbursement of statins not only for secondary but also for primary prevention in 2015. As a result, the use of statins has become widely available. It should be highlighted that until recently Lithuania was way behind the developed countries in respect to an adequate prescription of statins, the general population unreflectively accepting the myths of the alleged harms and neglecting the benefits of these thoroughly investigated medicines. The continued efforts of the medical professionals involved in the LitHiR Programme helped to overcome this backlog. The ef-

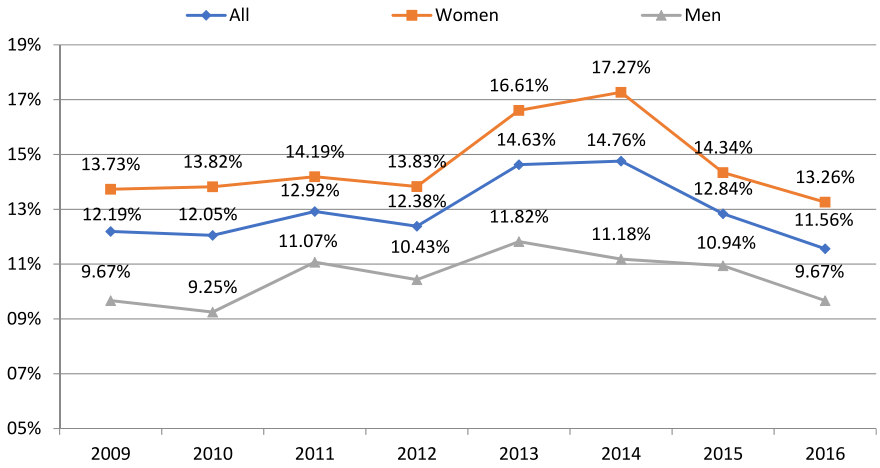


Figure 15. Trends in the prevalence of any type of severe dyslipidaemia among middle-aged Lithuanian adults from 2009 to 2016.

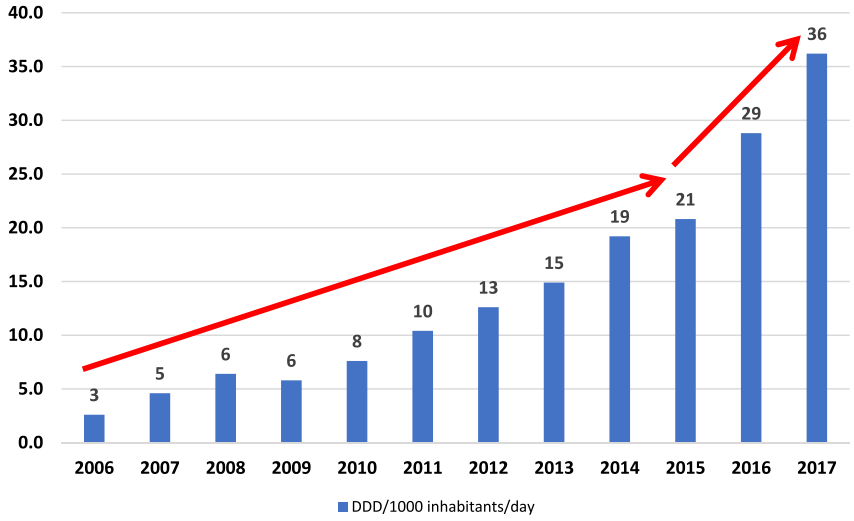


Figure 16. The usage of statins in Lithuania with new reimbursement arrangements (source: PharmaZOOM 2018 02). DDD – defined daily dose.

ficiency of preventive measures would be even more bolstered if medical professionals in the primary care institutions and specialized prevention units would work in teams including a physician, medical nurse and assisting public health professional. It can be expected that the development of healthy lifestyle skills and an adequate treatment with statins will help to halt the dyslipidaemia epidemic and further reduce the CVD risk among middle-aged subjects in the coming years.

The use of statins in Lithuania is lagging behind the neighbouring countries, Latvia and Estonia [17], but started to increase each year, especially in 2016 and 2017 (Fig. 16).

A significant improvement in statin reimbursement increased the prescription and use of these medications in Lithuania: in 2017 it reached 36 statin doses per thousand population daily. In other Eastern and Central European countries, such as the Czech Republic or Slovenia, this rate is over 100, while in Western Europe or the US the rate is around 120 statin doses per thousand population daily. Hence, we are still lagging behind the other countries by up to 4 times.

The reduction of deaths from the CVD worldwide is closely related to the use of statins (Fig. 17).

It is of key importance that these antiatherosclerotic medications have become widely available not only for secondary prevention but also for primary prevention (Fig. 18).

Smoking

Smoking is another important modifiable CVD risk factor. According to the World Health Organization, smoking annually causes over 1.6 million of premature deaths. In the EU, smoking kills over 650 000 people every year. Substances in tobacco smoke cause thrombosis and atherosclerosis, leading to the increased risk of myocardial infarction, sudden death, stroke, aor-

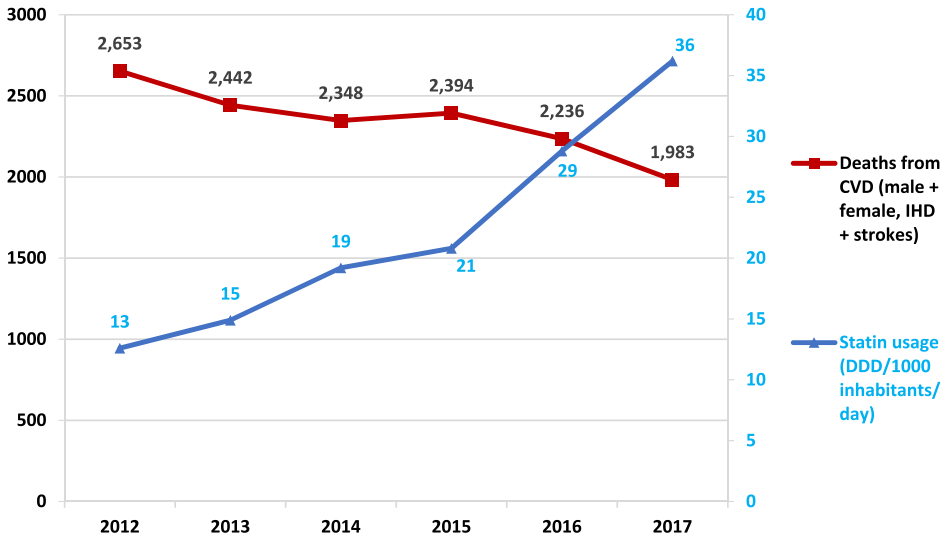


Figure 17. Statin usage and deaths from cardiovascular disease (CVD – cardiovascular disease, IHD – ischaemic heart disease) (source: 1. Health Information Centre, Institute of Hygiene, Ministry of Health of the Republic of Lithuania. Causes of death from 2012 to 2017 years. 2. PharmaZOOM 2018 02). DDD – defined daily dose.

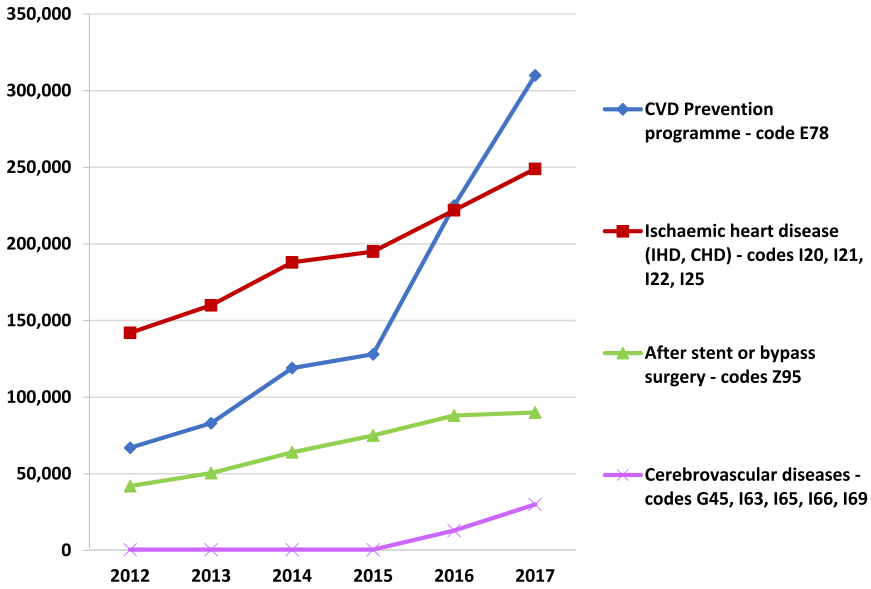


Figure 18. The use of reimbursed statins grew mainly in the subjects participating in the LitHiR Programme (men 40–55, women 50–65 years old). (source: SoftDent 2018). CVD – cardiovascular disease, IHD – ischaemic heart disease, CHD – coronary heart disease. The International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Australian Modification (ICD-10-AM) was used to assign codes to diseases.

tic aneurysm and peripheral artery disease (PAD). Current smokers have significantly increased risk of incident heart failure [18]. Also, tobacco smoking can lead to a greater risk of a dangerous heart rhythm problem such as atrial fibrillation [19].

Cigarette smoking has been shown to be associated with the development of acute thrombotic events [20]. This is confirmed by the statistical data which indicates that 50% of acute myocardial infarction cases in young and middle-aged individuals can be attributed to smoking-induced thrombosis [21]. Likewise, current smokers have been shown to have a 2.7-fold increased risk of myocardial infarction [22]. In addition, smokers have a higher probability of recurrent myocardial infarction [23]. The meta-analysis demonstrated an interesting fact that smoking only one cigarette a day increases a risk of developing CVD and there is no safe level of smoking with respect to the development of CVD [24].

Smoking cigarettes 4-fold increases the risk of PAD development, and PAD symptoms in smokers manifest about a decade earlier than in non-smokers [25]. Compared with non-smokers, smokers are more prone to limb amputation,

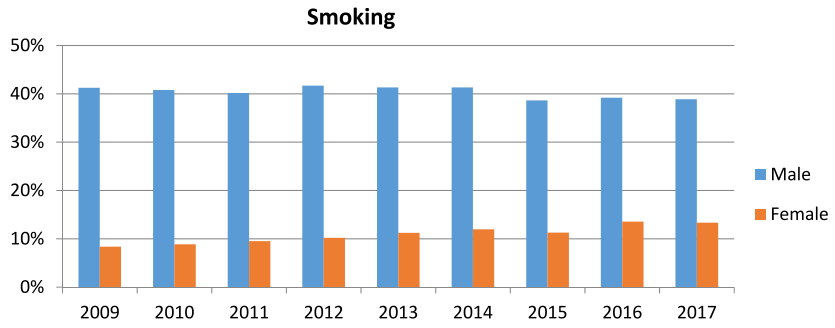


Figure 19. The prevalence of smokers (%) among the participants of the LitHiR Programme during the years 2009–2017.

have a decreased artery bypass graft efficacy and poorer survival rates [25].

In addition, cigarette smoking is a risk factor for ischaemic and haemorrhagic strokes and subarachnoid bruising. The risk of having a stroke in smokers is 2–4 times greater in comparison with non-smokers or subjects who had stopped smoking for more than 10 years [26].

It has been shown that even the passive smoking increases a risk of CVD morbidity and mortality by 25–30% [27].

In 2007 smoking in public places was banned in Lithuania, and the ban on smoking in vehicles near persons under 18 years and/or pregnant women came into force in 2015. These prohibitions allowed for decreasing the rates of smoking in Lithuania. In recent years, however, the number of smokers is increasing again, among both men and women, as shown by LitHiR Programme data analysis (Fig. 19).

The number of smokers in Lithuania has decreased significantly over the last 12 years. Over the period of 2000 to 2010, smoking prevalence among men has decreased from 52% to 34%. Smoking prevalence among women remained almost unchanged and 15% of women smoked in 2010. This situation was mainly determined by the public prevention measures, such as smoking ban which has been in force since 2007 and prohibits tobacco smoking in public places. However, according to our study, smoking prevalence has increased (19.3% in 2009, 21.2% in 2010, 22.9% in 2011, 22.7% in 2012; $p < 0.001$). This was mostly influenced by the growing number of smoking women (from 7.4% in 2009 to 9.4% in 2012). Despite the fact that the number of smoking men was higher than of women, the prevalence of smoking among men has not changed significantly from 2009 to 2012 (39.4 in 2009, 39.6 in 2012). This shows that a problem of tobacco smoking has not yet been resolved and there is a need for further aggressive efforts made by doctors, the state and society in order to limit the spread of this important risk factor.

Smoking cessation is the most economically advantageous strategy for preventing CVD. After 10 to 15 years after smoking cessation, atherosclerotic plaques are reduced, and CVD risk becomes similar (but not identical) to that of the non-smokers. In patients with the history of heart attack, smoking cessation decreases the risk of death from CVD by 36% over a two-year period. Thus, the maximum effect of smoking cessation occurs after a few years.

Nicotine addiction is a chronic disease which often requires a close follow-up by the health care professionals and, on the part of the subject, repeated attempts to stop smoking. The likelihood of the tobacco smoking cessation increases when conventional medical treatment (replacement nicotine therapy, varenicline) is combined with counselling, such as individual or group cognitive behavioural therapy. Family physicians and other medical professionals should inform smokers about the existence of effective treatment methods and refer them to a nicotine addiction treatment centre. In the light of foregoing, smoking cessation treatment demands uniting efforts on both sides, the patient treated and the health care team.

Obesity, metabolic syndrome and diabetes

In the last decades, we observe a worldwide overweight and obesity epidemic, which has been styled as "global obesity". According to the World Health Organization data released in 2008, 1.5 billion of adults, 20 years old and older, are overweight (BMI = 25.0–29.9 kg/m^2). Among them, there are 200 million men and almost 300 million women who are obese (BMI > 30 kg/m^2). This exceeds the number of people who are undernourished and have lower than normal body weight [28].

In Lithuania, high and very high-grade obesity affects about 62.6 thousand individuals [29]. This is one of the most important risk factors for CVD and various other diseases. The LitHiR Programme has shown that the incidence of obesity is gradually decreasing from 2009 to 2017.

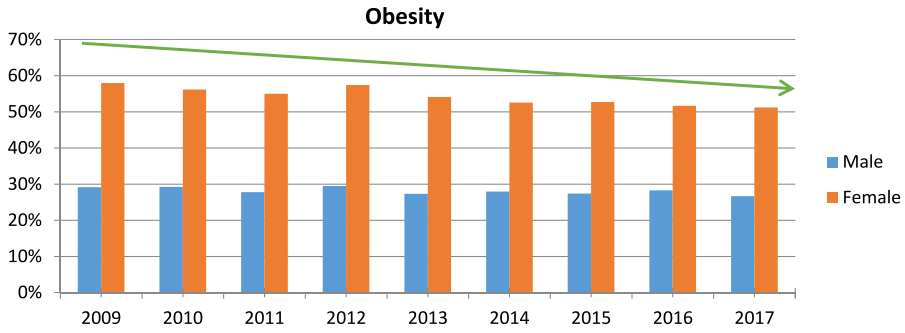


Figure 20. Prevalence of obesity (%) among the participants of the LitHiR Programme during the years 2009–2017.

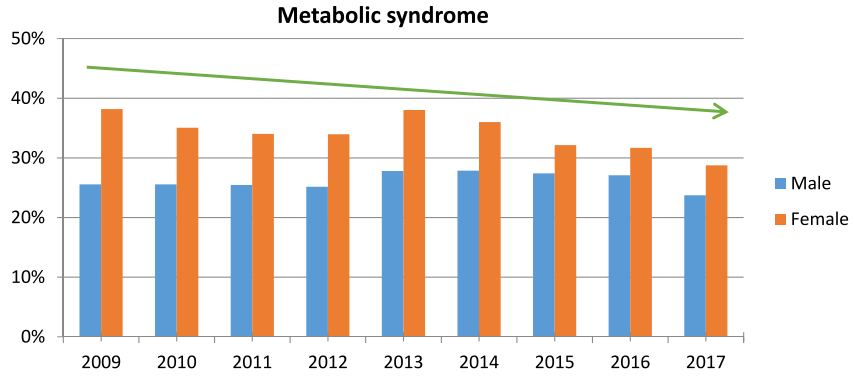


Figure 21. Prevalence of metabolic syndrome (%) among the participants of the LitHiR Programme during the years 2009–2017.

The number of obese women declined from 58.0% to 51.2% and the prevalence of obese men decreased from 29.2% to 26.7% (Fig. 20).

Cardiometabolic risk is especially high when body weight increase is more than 30% above normal, dominates abdominal obesity (the accumulation of fat on the waist), and these disadvantageous types of obesity are combined with dyslipidaemia (increased triglycerides and/or decreased HDL cholesterol), impaired glucose metabolism, and elevated blood pressure. These features comprise what is called metabolic syndrome (MS), sometimes nicknamed as a "deadly quartet". It has been established that MS in middle-aged men increases the odds of CV death from 2.6 to 3 times and the odds of general mortality from 1.9 to 2.1 times [30]. In addition, MS five times elevates the risk of diabetes [31]. According to the results of the LitHiR Programme, the relative downward trend of incidence of MS is observed from 2009 to 2017 in the population studied (Fig. 21).

If the individual components of MS are not assessed, the risk of MS subjects can be easily underestimated: commonly such subjects are automatically assigned to the intermediate risk group [4]. To prevent this oversight and to reduce the related long-term health care costs, LitHiR Programme dedicates special attention to MS subjects. All subjects, diagnosed with MS or diabetes mellitus at the primary care level, are referred to the specialized prevention unit for a thorough risk assessment.

Type 2 diabetes mellitus is another significant risk factor for CVD. Patients with DM have early microvascular and macrovascular complications: atherosclerotic vascular lesions, increased risk of acute cardiovascular events, renal, ocular and nerve damage. Notably, complication-related treatment expenses have the greatest share in the DM overall treatment costs. Furthermore, almost 3.2 million people in the world die due to diabetes complications annually.

Type 2 DM accounts for about 90% of all instances of diabetes mellitus. It has become one of the main causes of premature death, mainly due to CVD, in about 80% of these patients. The LitHiR Programme data from 2009 to 2017 demonstrates a steady presence of type 2 DM in Lithuania, with the prevalence of about 10% every year (Fig. 22). The combined efforts of family physicians, diabetologists, endocrinologists, and cardiologists should be directed at a more accurate evaluation, treatment, and complication management of this life-threatening cardiometabolic disease.

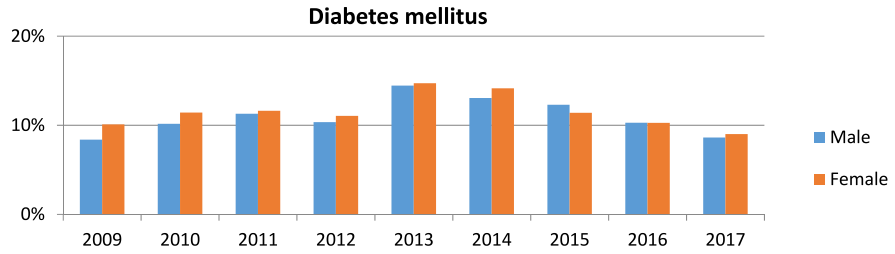


Figure 22. The prevalence of type 2 diabetes mellitus (%) among the participants of the LitHiR Programme during the years 2009–2017.

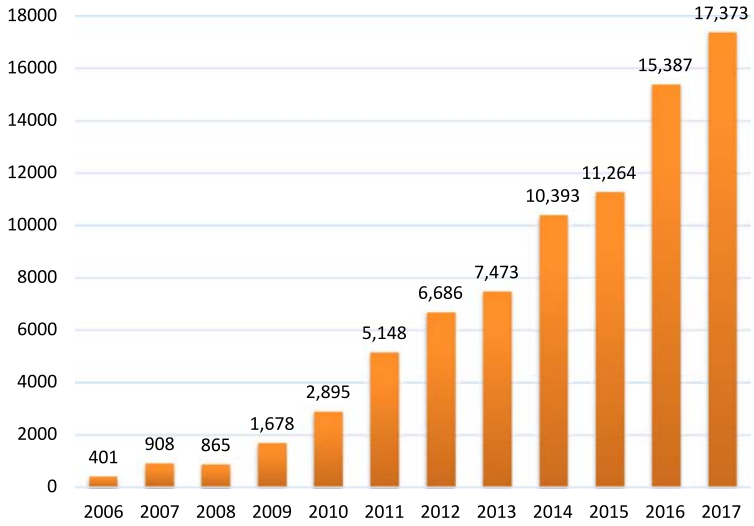


Figure 23. The number of comprehensive cardiovascular assessment visits in the specialized prevention units during the years 2006-2017 (source: National Health Insurance Fund).

The LitHiR Programme data on the comprehensive cardiovascular assessment measurements and results in the specialized prevention units

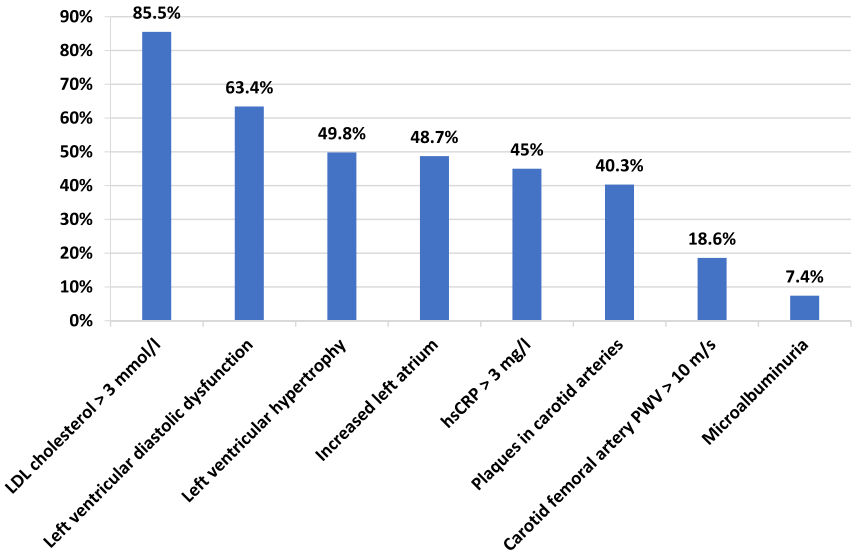
According to LitHiR Programme, subjects in whom high or very high cardiovascular risk, type 2 DM, or MS are identified at the primary care level are referred to specialized prevention units (SPU) for a comprehensive cardiovascular assessment: an electrocardiogram stress test, cardiac and vascular ultrasound, arterial wall studies (measurements of arterial stiffness and endothelium-dependent vasodilatation), and additional laboratory testing, including high-sensitivity C-reactive protein (hs-CRP). In total, 80 471 such assessments were carried out in SPU for 5.9% of the whole LitHiR Programme population from the year 2006 to 2017 (Fig. 23). The aim of this programme is to increase availability of such a specialized assessment by providing it to no less than 10% of the subjects screened according to the LitHiR inclusion criteria at the primary prevention units and to patients with suspected familial dyslipidaemia and resistant arterial hypertension in all age groups.

The comprehensive specialized assessment described above leads to identifying early atherosclerotic arterial lesions and/or previously undiagnosed CVD as well as subjects with high and very high CVD risk and elevated cardiometabolic risk (MS plus additional risk factors) and applying the necessary measures of educating patients and prescribing an intensive CVD prevention and treatment. Primary prevention units are also informed about the assessment results and prevention and treatment recommendations for each patient. In 1–2 years, re-examining of these subjects in SPU is recommended in order to evaluate the effectiveness of prescribed CVD prevention and treatment measures.

In the SPU, the cardiometabolic risk of subjects with MS is reassessed. In order to stratify the risk, rule out CVD and identify optimal preventive strategy, additional instrumental studies evaluating early vascular aging (carotid intima-media thickness measurement, peripheral and aortic stiffness tests) as well as additional laboratory tests were performed.

In a large proportion of MS subjects, besides the presence of 3, 4 or 5 components of MS, additional risk factors have been found (Fig. 24).

At least one additional CVD risk factor was found in 98.8% of patients with established MS. Therefore, the assessment of patients at the SPU



*** Defining increased aortic stiffness as PWV > 8.6 m/s would result in 46.9%.**

Figure 24. Additional risk factors co-existing with metabolic syndrome components (LDL cholesterol – low density lipoprotein cholesterol, hs-CRP – high sensitivity C-reactive protein, PWV – pulse wave velocity).

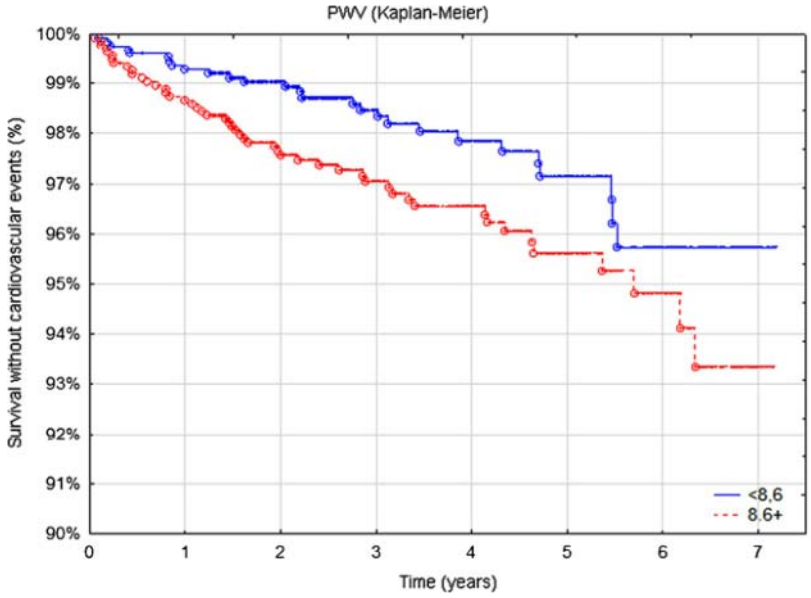


Figure 25. Comparison of the event-free survival rates in subjects with PWV < 8.6 m/s and ≥ 8.6 m/s.

allows for reclassifying a large portion of individuals with established MS from intermediate to high CVD risk group.

High-sensitivity C-reactive protein is a key prognostic marker for an increased risk of CVD. We have found that it was elevated in 46% of the cases investigated.

Left ventricular hypertrophy and/or an enlargement of the left atrium is another finding associated with a significant increase in cardiovascular risk. According to LitHiR data, in subjects with MS, left ventricular hypertrophy was present in 49.8% and left atrium enlargement was found in 48.7% of cases.

Scientific literature demonstrates that the presence of early vascular aging (EVA) significantly deteriorates cardiovascular prognosis. The main measure for the assessment of EVA is aortic pulse wave velocity (PWV). A meta-analysis of seventeen long-term observation studies, which evaluated 15 877 individuals with observation time of 7.7 years, revealed that the increase in PWV by 1 m/s is related to the increase of cardiovascular risk by about 10% [32].

The follow-up study of 3.9 ± 1.7 years, carried out in 2728 LitHiR participants repeatedly examined at the SPU, has demonstrated that the CVD risk significantly increases when aortic PWV exceeds 8.6 m/s (Fig. 25).

The results of the LitHiR Programme demonstrated that there were 46.9% subjects with elevated aortic stiffness (PWV > 8.6 m/s). The results suggest that the evaluation of early atherosclerosis, assessed as aortic PWV and carotid intima-media thickness, enables to reclassify MS patients from medium to high CVD risk and, correspondingly, to apply a more adequate preventive treatment. The presence of additional risk factors (such as vascular markers of early atherosclerosis) alongside with MS components indicates that subject has elevated cardiometabolic risk, which is equivalent to high CVD risk category.

Several studies in patients with elevated CV risk demonstrate that there is a significant correlation between the various indices of arterial stiffness (PWV, cardio-ankle vascular index, augmentation index) and the left ventricular diastolic dysfunction. Since left ventricular diastolic dysfunction is considered to be an early preclinical marker of cardiovascular disorders which cause heart failure over time, the determination of the pathogenetic factors for left ventricular diastolic dysfunction is of key importance for choosing an optimal medical treatment.

According to the analysis performed in 1208 LitHiR subjects with MetS, left ventricular diastolic dysfunction in these subjects is highly prevalent (75.7%, n = 915 of study subjects). Furthermore, the carotid-femoral PWV was found to be a significant independent prognostic marker of the left ventricular diastolic dysfunction. The risk was for diastolic dysfunction and early heart failure with preserved ejection fraction was also increased by age and obesity. There were 95% overweight subjects (BMI > 25 kg/m^2) and 60% had BMI > 30 kg/m^2. Subjects with left ventricular diastolic dysfunction displayed higher BMI and waist circumference.

According to the results of longitudinal observation (follow-up duration 3.8 $\pm$ 0.6 years), the increase in carotid-femoral PWV and aortic augmentation index was strongly associated with negative trend of left ventricular diastolic function. It should be noted that carotid-femoral PWV was more closely correlated with the left ventricular diastolic function parameters than other indices of arterial stiffness, namely, augmentation index, cardio-ankle vascular index, and aortic pulse pressure. The results of longitudinal observation allowed better understanding of the relation between arterial stiffness and left ventricular diastolic dysfunction.

The lifestyle changing strategy, in particular, diet modification and adequate physical activity, play a key role in fighting MS and its consequences. The study carried out in LitHiR patients at Vilnius University Hospital Santaros Klinikos, has demonstrated that 8-week heart rate controlled aerobic physical training significantly improved cardiometabolic risk [33]. It is appropriate, therefore, to consider the reimbursement of 8-week supervised aerobic physical training programme on outpatient basis one time per year. The subsequent step in improving the cardiometabolic status of the MS subjects would be an implementation of the self-monitored physical training program, which uses tracking from home. Such a policy of aerobic physical training carried out under medical supervision would enable a "break" in changing a lifestyle and would motivate MS subjects to continue physical workouts throughout the year. Now we are creating the environment for home-based physical training for MS subjects and the possibility of remote monitoring of their training results.

The tools of cardiovascular risk assessment in metabolic syndrome subjects

Cardiovascular risk assessment, which is personalized and repeatedly performed, serves the clinician in assessing the patient's risk and defining the treatment goals, monitoring the effort and effect, as well as motivating and engaging patients in the process. While initial risk assessment plays an important role in initiating the prevention strategy, a regular risk reassessment allows for further strategy adjustments and drives patients' motivation to engage in the process. Patient engagement and empowerment are means to increase population involvement and adherence to recommendations, better lifestyle choices, pursuing clinical goals which potentially translate to reduction in mortality and morbidity.

Studies of a number of chronic conditions, such as DM, report high CVD risk despite the value of existing validated and widely used risk assessment tools [34]. There is an increasing number of evidences that this exponentially growing population with MS, has a risk assessment measured incorrectly using the usual common risk assessment algorithms developed and improved mostly in isolated 1970–1980 populations, despite the subsequent adaptation of risk scales. Recent studies report that unhealthy lifestyle, low physical activity, poor diet and stress are leading to higher chronic condition prevalence globally, including MS [35]. Data from clinical observations confirm that widespread, verified risk assessment measures are not tailored to the risk assessment in the growing population of people with MS or DM, potentially wrongly classifying these patients to high or low risk groups [35–37].

Published data confirm that most of the US risk assessment models of external validation, and the

risk scores in the European cohorts, overestimate the risk in our group of patients.

A quarter of our planet's population is estimated to have MS [35,38]. Although MS is not an absolute risk indicator for CVD, in people with this syndrome, data report a CVD risk increase up to 100% comparing MS to non-MS [31].

According to the LitHiR data analysis, in subjects with MS, the actual cardiovascular risk significantly differs from that calculated by the Reynolds risk assessment tool in nearly all the decimal places. The Hosmer-Lemeshow (H-L) test confirmed that this model is not suitable for accurate risk assessment. Furthermore, the well-established risk calculator from the 1998 Framingham's risk assessment score has been shown to have some deviations, not consistent throughout the risk groups. Same findings were observed with respect to other score risks, namely, IAS-Agla ("Arbeitsgruppe Lipide und Atherosclerosis"), PROCAM, and FRS1. The Framingham Adult Treatment Panel III, a risk calculation model in different decimal places showed different fluctuations, but the test result showed a rather good fit for the models. The H-L test for the risk calculator in the widely used SCORE has shown to have an intermediate suitability of the risk assessment ($p = 0.301$). Based on the results obtained, it has been found that the risk of cardiovascular events, measured by these algorithms, does not accurately identify the future number of cardiovascular events for patients with MS (study submitted for publication). Thus, some cardiovascular risk assessment models selected for analysis are better than others, but no results were sufficiently accurate. Therefore, we proposed that, in MS subjects, the criteria for the risk assessment, along with the MS components, should include additional risk factors, thus making possible the estimation of cardiometabolic risk.

Program evaluation in terms of prevalence and mortality trends

Since CVD is the leading cause of morbidity and mortality in Lithuania and Europe, a proactive CVD prevention, that is, an identification of high cardiovascular risk subjects and the subsequent choice of the optimal preventive treatment strategy are of high importance in modern medicine. According to the World Health Organization, CVD on the European continent is the leading cause of death. In the European Union the high incidence of CVD and associated work incapacity result in a cost of 169 billion Euros per year [39].

The LitHiR Programme made a positive effect on CVD mortality in middle-aged subjects in Lithuania. The overall decline in CVD mortality among 45–65-year-old subjects (Fig. 26) is seen throughout the LitHiR Programme. Mortality rate decreased by more than one third (36.9%) in the last 10 years.

The statistics of the past decade reveal that despite the decreasing mortality rate, the prevalence of CVD tended to increase until 2014 (24.4%), and during the last three years the prevalence of CVD declined slightly, decreasing by 3.6% (Fig. 27). This decrease can be linked to a significant improvement in arterial hypertension control, decreasing frequency of MS, and to the gradual increase in statin consumption. The early manifestation of atherosclerosis and poor dyslipidaemia control remain the major problems in clinically oriented primary prevention in Lithuania. It is important to note that CVD still affects nearly every third person 45–65 years of age (30.9%).

The highest prevalence and mortality rates of cardiovascular diseases are caused by ischemic heart disease and stroke. In Lithuania, the mortality rate of ischemic heart disease has been one of the largest in Europe and it surpasses the European Union average 4.4 times. The mortality rate of strokes in Lithuania exceeds the European

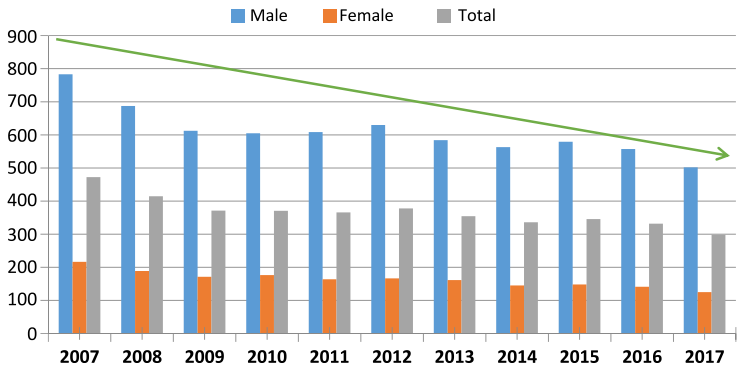


Figure 26. Mortality rates from cardiovascular diseases per 100 000-population aged 45–64 years during 2007–2017 (source: Health Information Centre, Institute of Hygiene, Ministry of Health of The Republic of Lithuania).

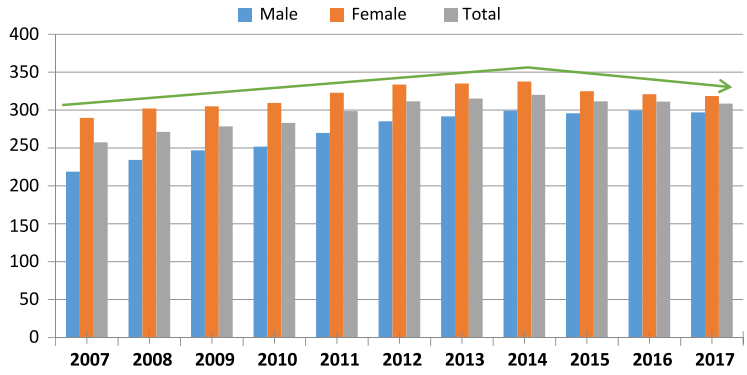


Figure 27. Prevalence of cardiovascular diseases per 100 000 population aged 45–64 years during 2007–2017 (source: Health Information Centre, Institute of Hygiene, Ministry of Health of The Republic of Lithuania).

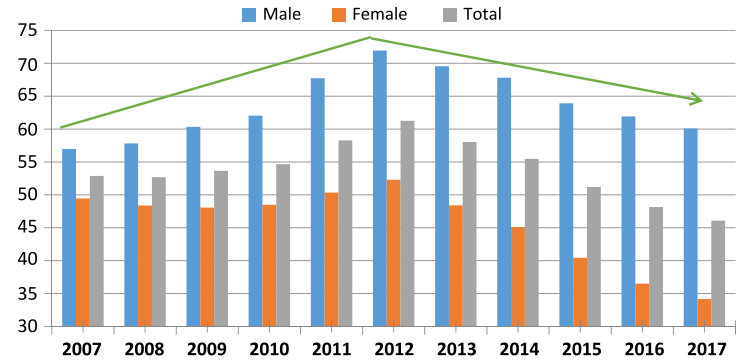


Figure 28. Prevalence of ischemic heart disease per 1000 population aged 45–64 years during 2007–2017 (source: Health Information Centre, Institute of Hygiene, Ministry of Health of The Republic of Lithuania).

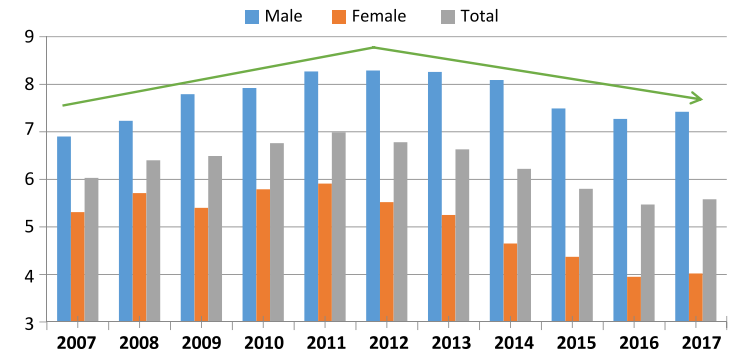


Figure 29. Prevalence of stroke per 1000 population aged 45–64 years during 2007–2017 (source: Health Information Centre, Institute of Hygiene, Ministry of Health of The Republic of Lithuania).

Union average about 2.7 times. When specifying cardiovascular morbidity, it was observed that the prevalence of ischemic heart disease (Fig. 28) and stroke (Fig. 29) was decreasing, starting from 2012 and onwards. The prevalence of ischemic heart disease decreased by a quarter (24.8%) and the prevalence of stroke by almost a fifth (17.7%).

The highest prevalence and mortality rates of cardiovascular diseases are determined in the working age groups (from 45 to 65 years). These findings represent an important economic burden in the state of Lithuania. Therefore, the effective CVD prevention and proper treatment of early CVD manifestations should be prioritized in the health care system.

Conclusions

As a result of the ongoing LitHiR Programme, and on the account of the ongoing educational activities in preventive medicine, which encourage people to focus on CVD risk, more people are now committed to modification of CVD risk factors and CVD treatment.

The future plans for the LitHiR Programme entail the development of the team-based approach, where physicians, nurses, and public health care professionals would work together with the di-

etitians and the physical therapy and rehabilitation specialists. With the higher availability of the anti-hypertensive and anti-lipid medications already achieved, it is possible to reach a significant reduction in high blood pressure and effectively treat dyslipidaemia. Focusing on smoking prevention, promotion of healthy nutrition and physical activity are the key points of the strategy that cannot be implemented without the significant contribution of the state authorities.

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References

[1] Health Information Centre, Institute of Hygiene, Ministry of Health of The Republic of Lithuania, Causes of death 2017, Vilnius 2018. http://www.hi.lt/uploads/pdf/leidiniai/Statistikos/Mirties_priezastys/MPR_2017_isankstiniai.pdf.
[2] WHO HFA Mortality database, 2009.
[3] Perk J, De Backer G, Gohlke H, Graham I, Reiner Z, Verschuren M, et al. European Guidelines on cardiovascular disease prevention in clinical practice (version 2012). The Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of nine societies and by invited experts). Eur Heart J 2012;33:1635–701.
[4] Piepoli MF, Hoes AW, Agewall S, Albus C, Brotons C, Catapano AL, et al. European Guidelines on cardiovascular disease prevention in clinical practice (version 2016). The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts). Eur Heart J 2016;37:2315–81.
[5] Stamler J, Vaccaro O, Neaton JD, Wentworth D. Diabetes, other risk factors, and 12-yr cardiovascular mortality for menscreened in the Multiple Risk Factor Intervention Trial. Diabetes Care 1993;16:434–4.
[6] Verschuren WM, Jacobs DR, Bloemberg BP, Kromhout D, Menotti A, Aravanis C, et al. Serum total cholesterol and longtermcoronary heart disease mortality in different cultures:twenty-five-year follow-up of the Seven Countries Study. JAMA 1995;274:131–6.
[7] MacMahon S, Peto R, Cutler J, Collins R, Sorlie P, Neaton J, et al. Blood pressure, stroke, and coronary heart disease, I: prolonged differences in blood pressure: prospective observational studies corrected for the regression dilution bias. Lancet 1990;335:765–74.
[8] Collins R, Peto R, MacMahon S, Hebert P, Fiebach NH, Eberlein KA, et al. Blood pressure, stroke, and coronary heart disease, II: short-term reductions in blood pressure: overview of randomised drug trials in their epidemiological context. Lancet 1990;335:827–38.
[9] Conroy RM., Pyorala K, Fitzgerald AP, Sans S, Menotti A, De Backer G, et al. on behalf of the SCORE project group. Estimation of ten-year risk of fatal cardiovascular disease in Europe: the SCORE project. Eur Heart J 2003;24:987–1003.
[10] Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). JAMA 2001;285:2486–97.
[11] Williams B, Mancia G, Spiering W, Rosei EA, Azizi M, Burnier M, et al. 2018 ESH/ESC Guidelines for the management of arterial hypertension The Task Force for the management of arterial hypertension of the European Society of Cardiology (ESC) and the European Society of Hypertension (ESH). Eur Hear J 2018(39):3021–104.
[12] Chow CK, Teo KK, Rangarajan S, Islam S, Gupta R, Avezum A. PURE Study Investigators. Prevalence, awareness, treatment, and control of hypertension in rural and urban communities in high-, middle-, and low-income countries. JAMA 2013;310:959–68.
[13] Grabauskas V, Klumbienė J, Petkevičienė J, Petrauskienė A, Tamošiūnas A, Kriaučionienė V, et al. Lėtinių neinfekcinių ligų rizikos veiksnių paplitimas tarp Lietuvos kaimiškųjų rajonų gyventojų: CINDI programos tyrimas, 2007 m. Medicina (Kaunas) 2008;44(8):633–9.
[14] Lisauskienė I. Širdies ir kraujagyslių sistemą veikiančių vaistų vartojimo ir sergamumo bei mirštamumo nuo šios sistemos ligų kitimai Lietuvoje. Daktaro disertacija. Moksl. vadovė prof. J. Gulbinovič. – Vilnius, 2017, 213 p.
[15] MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. Lancet 2002;360:7–22.
[16] Rinkūnienė E. Didelės kardiovaskulinės rizikos asmenų nustatymo ir aktyvios pirminės prevencijos metodu optimizavimas. Daktaro disertacija. Mokslinė vadovė prof. Ž. Petrulionienė, moksl. konsultantas prof. A. Laucevičius. – Vilnius, 2014, 153 p.
[17] Baltic Statistics on Medicines 2013–2015. http://www.vvkt.lt/eng/Statistics-on-consumption-of-medicinal-products-in-three-Baltic-States/956.
[18] Gopal DM, Kalogeropoulos AP, Georgiopoulou VV, Smith AL, Bauer DC, Newman AB, et al. Cigarette Smoking Exposure and Heart Failure Risk in Older Adults: The Health, Aging, and Body Composition Study. Am Heart J 2012;164(2):236–42.
[19] Aune D, Schlesinger S, Norat T, Riboli E. Tobacco smoking and the risk of atrial fibrillation: A systematic review and meta-analysis of prospective studies. Eur J Prev Cardiol 2018;25(13):1437–51.
[20] Barua RS, Ambrose JA. Mechanisms of Coronary Thrombosis in Cigarette Smoke Exposure. Arterioscler Thromb Vasc Biol 2013;33:1460–7.
[21] Benowitz NL. Cigarette smoking and cardiovascular disease: pathophysiology and implications for treatment. Prog Cardiovasc Dis 2003;46:91–111.
[22] Attard R, Dingli P, Doggen CJM, Cassar K, Farrugia R, Wettinger SB. The impact of passive and active smoking on inflammation, lipid profile and the risk of myocardial infarction. Open Heart 2017;4(2):e000620.
[23] Rea TD, Heckbert SR, Kaplan RC, Smith NL, Lemaitre RN, Psaty BM. Smoking status and risk for recurrent coro-

nary events after myocardial infarction. Ann Intern Med 2002;137(6):494–500.
[24] Hackshaw A., Morris JK, Boniface S, Tang JL, Milenković D. Low cigarette consumption and risk of coronary heart disease and stroke: meta-analysis of 141 cohort studies in 55 study reports. BMJ 2018;360:j5855.
[25] Olin JW, Sealove BA. Peripheral Artery Disease: Current Insight Into the Disease and Its Diagnosis and Management. Mayo Clin Proc 2010;85(7):678–92.
[26] Shah RS., Cole JW. Smoking and stroke: the more you smoke the more you stroke. Expert Rev Cardiovasc Ther 2010;8(7):917–32.
[27] He J, Vupputuri S, Allen K, Prerost MR, Hughes J, Whelton PK. Passive smoking and the risk of coronary heart disease–a meta-analysis of epidemiologic studies. N Engl J Med 1999; 340(12):920–6.
[28] Gardner G, Halweil B. Underfed and overfed: the global epidemic of malnutrition. Washington, DC: Worldwatch Institute, 2000.
[29] Brimas G. Chirurginis nutukimo gydymas. Vilnius: Ciklonas, 2005, 352 p.
[30] Lakka HM, Laaksonen DE, Lakka TA, Niskanen LK, Kumpusalo E, Tuomilehto J, et al. The metabolic syndrome and total and cardiovascular disease mortality in middle-aged men. JAMA 2002;288(21):2709–16.
[31] Alberti KG, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA, et al. Harmonizing the metabolic syndrome: a joint interim statement of the international diabetes federation task force on epidemiology and prevention; National heart, lung, and blood institute; American heart association; World heart federation; International atherosclerosis society; And international association for the study of obesity. Circulation 2009;120(16):1640–5.
[32] Vlachopoulos C, Aznaouridis K, Stefanadis C. Prediction of cardiovascular events and all-cause mortality with arterial stiffness: a systematic review and meta-analysis. J Am Coll Cardiol 2010;55(13):1318–27.
[33] Slivovskaja I. Individualios aerobinės fizinės treniruotės veiksmingumas asmenims, kuriems nustatytas metabolinis sindromas. [The effectiveness of individual aerobic training in subjects with metabolic syndrome]. Daktaro disertacija. Moksl. vadovas prof. A. Juocevičius, moksl. konsultantė dr. L. Ryliškytė. – Vlnius, 2018, 200 p.
[34] Matheny M, McPheeters ML, Glasser A, Mercaldo N, Weaver RB, Jerome RN, et al. Systematic Review of Cardiovascular Disease Risk Assessment Tools. Evidence Syntheses/Technology Assessments, No. 85. 2011, 394 p.
[35] Grundy SM. Metabolic Syndrome Pandemic. Arterioscler Thromb Vasc Biol 2008; 28(4):629–36.
[36] Koller MT, Steyerberg EW, Wolbers M, Stijnen T, Bucher HC, Hunink MG, et al. Validity of the Framingham point scores in the elderly: results from the Rotterdam study. Am Heart J 2007;154(1):87–93.
[37] Reissigova J, Zvarova J. The Framingham risk function underestimated absolute coronary heart disease risk in Czech men. Methods Inf Med 2007;46(1):43–9.
[38] Mottillo S, Filion KB, Genest J, Joseph L, Pilote L, Poirier P, et al. The Metabolic Syndrome and Cardiovascular Risk. A Systematic Review and Meta-Analysis. Am Coll Cardiol 2010;56(14):1113–32.
[39] Leal J, Luengo-Fernández R, Gray A, Petersen S, Rayner M. Economic burden of cardiovascular diseases in the enlarged European Union. Eur Heart J 2006l;27(13):1610–9.

Addendum. Published papers on the subject

1. Articles

1.1. Scholarly articles in Clarivate Analytics Web of Science databases:

1. Laucevičius A, Rinkūnienė E, Skorniakov V, Petrulionienė Ž, Kasiulevičius V, Jatužis D, et al. High-risk profile in a region with extremely elevated cardiovascular mortality. Hellenic Journal of Cardiology 2013;54(6): 441–447.
2. Ozery-Flato M, Parush N, El-Hay T, Visockienė Ž, Ryliškytė L, Badarienė J, et al. Predictive models for type 2 diabetes onset in middle-aged subjects with the metabolic syndrome. Diabetology & Metabolic Syndrome 2013,5:36.
3. Scuteri A, Cunha PG, Rosei EA, Badarienė J, Bekaert S, Cockcroft JR, et al. Arterial stiffness and influences of the metabolic syndrome: A cross-countries study. Atherosclerosis 2014;233(2):654–660.
4. Laucevičius A, Rinkūnienė E, Petrulionienė Ž, Puronaitė R, Kasiulevičius V, Jatužis D, et al. Prevalence of high-risk profile in middle-aged subjects with arterial hypertension: A nationwide survey. Blood Pressure 2014;23(5):281–287.
5. Rinkūnienė E, Laucevičius A, Petrulionienė Ž, Dženkevičiūtė V, Kutkienė S, Skujaitė A, et al. The prevalence of dislipidemia and its relation to other risk factors: a nationwide survey of Lithuania. Clinical Lipidology 2015;10(3):219–225.
6. Laucevičius A, Ryliškytė L, Balsytė J, Badarienė J, Puronaitė R, Navickas R, et al. Association of cardio-ankle vascular index with cardiovascular risk factors and cardiovascular events in metabolic syndrome patients. Medicina (Kaunas) 2015;51:152–58.
7. Laucevičius A, Rinkūnienė E, Skujaitė A, Petrulionienė Ž, Puronaitė R, Dženkevičiūtė V, et al. Prevalence of cardiovascular risk factors in Lithuanian middle-aged subjects participating in the primary prevention program, analysis of the period 2009–2012. Blood Pressure, 2015; 24(1):41–47.
8. Scuteri A, Franco OH, Majiid A, Badarienė J, Boytsov S, Cheng HM, et al. For the MARE Consortium. The relationship between the metabolic syndrome and arterial wall thickness: A mosaic still to be interpreted. Atherosclerosis 2016;255:11–16.
9. Solovjova S, Ryliškytė L, Čelutkienė J, Badarienė J, Navickas R, Puronaitė R, et al. Aortic stiffness is an independent determinant of left ventricular diastolic dysfunction in metabolic syndrome patients. Blood Pressure 2016;25(1):11–20.
10. Rinkūnienė E, Butkutė E, Puronaitė R, Petrulionienė Ž, Dženkevičiūtė V, Kasiulevičius V, et al. Arterial function parameters in patients with metabolic syndrome and severe hypertriglyceridemia. Journal of Clinical Lipidology 2017;11(4):901–907.
11. Slivovskaja I, Ryliškytė L, Šerpytis P, Navickas R, Badarienė J, Čelutkienė J, et al. Aerobic Training Effect on Arterial Stiffness in Metabolic Syndrome. The American Journal of Medicine 2018;131(2):148–155.
12. Kutkienė S, Petrulionienė Ž, Laucevičius A, Petrylaitė M, Maskeliūnaitė D, Puronaitė R, et al. 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.
13. De Smedt D, Annemans L, De Backer G, Kotseva K, Rydčn L, Wood D, et al. Cost-effectiveness of optimized adherence to prevention guidelines in European patients with coronary heart disease: Results from the EUROASPIRE IV survey. International Journal of Cardiology 2018;272:20–25.
14. Dadoniene J, Čypienė A, Rinkūnienė E, Badarienė J, Laucevičius A. Vitamin D, cardiovascular and bone health in postmenopausal women with metabolic syndrome. Advances in Clinical and Experimental Medicine 2018; 27(11):1555–1560.
15. Kutkienė S, Petrulionienė Ž, Laucevičius A, Matuzevičienė G, Kasiulevičius V, Petrulionytė E, et al. Cardiovascular risk profile of patients with atherogenic dyslipidemia in middle age Lithuanian population. Lipids in Health and Disease 2018;17:208.
16. Kutkienė S, Petrulionienė Ž, Laucevičius A, Čerkauskienė R, Staigytė J, Šaulytė A, et al. Lipid profile evaluation and severe hypercholesterolaemia screening in the middle-aged population according to nationwide primary prevention programme in Lithuania. Atherosclerosis 2018;277:267–272.
17. Petrulionienė Ž, Gargalskaitė U, Kutkienė S, Staigytė J, Čerkauskienė R, Laucevičius A. Establishing a national screening programme for familial hypercholesterolaemia in Lithuania. Atherosclerosis 2018;277:407–412.
18. Kutkienė S, Petrulionienė Ž, Laucevičius A, Šerpytis P, Kasiulevičius V, Staigytė J, et al. 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(1):233.

19. Nilsson PM, Laurent S, Cunha PG, Olsen MH, Rietzschel E, Franco OH, et al. Metabolic syndrome, Arteries REsearch (MARE) Consortium. Characteristics of healthy vascular ageing in pooled population-based cohort studies: the global Metabolic syndrome and Artery REsearch Consortium. Journal of Hypertension 2018;36(12):2340–2349.
20. Laučytė-Cibulskienė A, Boreikaitė E, Aučina G, Gudynaitė M, Rudminienė I, Anisko S, et al. Usefulness of pretransplant aortic arch calcification evaluation for kidney transplant outcome prediction in one year follow-up. Renal Failure 2018;40(1):201–208.
21. Laučytė-Cibulskienė A, Petravičiūtė M, Gudynaitė M, Gumbys L, Valančienė D, Galiauskienė K, et al. Mismatch between stiffness in elastic and muscular arteries as a predictor of vascular calcification in dialysis patients. Aging Clinical and Experimental Research 2018;30(4):375–382. IF 2.121 (*VUL SK*)
22. Topouchian J, Labat C, Gautier S, Bäck M, Achimastos A, Blacher J, et al. Effects of metabolic syndrome on arterial function in different age groups: the Advanced Approach to Arterial Stiffness study. Journal of Hypertension 2018;36(4):824–833.
23. De Bacquer D, De Smedt D, Kotseva K, Jennings C, Wood D, Rydén L, et al. EUROASPIRE Investigators. Incidence of cardiovascular events in patients with stabilized coronary heart disease: the EUROASPIRE IV follow-up study. Eur J Epidemiol 2019;34: 247–58.
24. Valaikienė J, Ryliškytė L, Valaika A, Puronaitė R, Dementavičienė J, Vaitkevičius A, et al. A High Prevalence of Intracranial Stenosis in Patients with Coronary Artery Disease and the Diagnostic Value of Transcranial Duplex Sonography. Journal of Stroke & Cerebrovascular Diseases 2019 Jan 7. pii: S1052-3057(18)30722-5.
25. Ryliškytė L, Navickas R, Šerpytis P, Puronaitė R, Zupkauskienė J, Jucevičienė A, et al. Association of aortic stiffness, carotid intima-media thickness and endothelial function with cardiovascular events in metabolic syndrome subjects. Blood Press 2019;28:131–8.
26. Kutkienė S, Petrulionienė Ž, Laucevičius A, Čerkauskienė R, Samuilis A, Augaitienė V, et al. Achilles tendon ultrasonography – a useful screening tool for cardiovascular risk estimation in patients with severe hypercholesterolemia. Atheroscler Suppl. 2019 Mar;36:6–11.
27. Berūkštis A, Jarašūnas J, Daškevičiūtė A, Ryliškytė L, Baranauskas A, Steponenienė R, et al. How to interpret 24-h arterial stiffness markers: comparison of 24-h ambulatory Mobil-O-Graph with SphygmoCor office values. Blood Press Monit 2019;24:93–8.
28. Berukštis A, Navickas R, Neverauskaitė-Piliponienė G, Ryliškytė L, Misiūra J, Vajauskas D, et al. Arterial destiffening starts early after renal artery denervation (Research Article). Int J Hypertens 2019 Mar 3;2019: 3845690.

1.2. Articles in peer-reviewed scientific journals of Lithuania:

1. Laucevičius A, Kasiulevičius V, Jatužis D, Petrulionienė Ž, Ryliškytė L, Rinkūnienė E, et al. Lithuanian High Cardiovascular Risk (LitHiR) primary prevention programme – rationale and design. Seminars in Cardiovascular Medicine 2012;18:3.
2. [Rimševičius L, Tracevičiūtė J, Ryliškytė L, Badarienė J, Čypienė A. Petrulionienė, Ž, et al. Galutinių glikozilinimo produktų kaupimosi sąsajos su ankstyvu inkstų pažeidimu organizme ligonių, sergančių metaboliniu sindromu]. Medicinos teorija ir praktika 2012; 18(4.2):588–91 (in Lithuanian).
3. [Rinkūnienė E, Laucevičius A, Petrulionienė Ž, Badarienė J. Lietuvos didelės kardiovaskulinės rizikos pacientų atrankos ir prevencinių priemonių (LitHiR) programos rezultatai: dislipidemijos paplitimas tarp vidutinio amžiaus suaugusių Lietuvos gyventojų]. Medicinos teorija ir praktika, 2012;18(4.2):636–642. (in Lithuanian).
4. Rimševičius L, Aksionova D, Miglinas M, Badarienė J, Ryliškytė L, Čypienė A, et al. Rationale of screening for early kidney damage in patients with high cardiovascular risk: nephrologist's point of view. Seminars in Cardiovascular Medicine, 2013;19:1–8.
5. Rinkūnienė E, Petrulionienė Ž, Dženkevičiūtė V, Kutkienė S, Puronaitė R, Kizlaitis R, et al. Tradicinių rizikos veiksnių paplitimas tarp pacientų, sergančių arterine hipertenzija. Medicinos teorija ir praktika 2013;19(2):124–129.
6. Rimševičius L, Kaklauskaitė G, Rekašius T, Badarienė J, Laucevičius A, Miglinas M. Inkstų pažeidimo paplitimas nacionalinėje patikros programoje tarp suaugusių vidutinio amžiaus asmenų, turinčių didelę kardiovaskulinę riziką. Medicinos teorija ir praktika 2014; 20(3):231–238
7. Badarienė J, Čelutkienė J, Petrikonytė D, Balsytė J, Rinkūnienė E, Ryliškytė L, et al. Diagnostic value of electrocardiogram stress testing in patients with metabolic syndrome. Seminars in Cardiovascular Medicine 2015; 21:9–15.

8. Slivovskaja I, Bužinskaitė J, Ryliškytė L, Balsytė J, Navickas R, Puronaitė R, et al. Positive impact of a 4-week duration supervised aerobic training on anthropometric, metabolic, hemodynamic and arterial wall parameters in metabolic syndrome subjects. Seminars in Cardiovascular Medicine 2017;23:11–16.
9. Jakutis G, Juknevičius V, Barysienė J, Matačiūnienė D, Petrauskienė B, Petrulionienė Ž, et al. A rare case of REM sleep-related bradyarrhythmia syndrome with concomitant severe hypertension: a case report and a review of literature. Acta Medica Lituanica 2018;25(1):1–6.

2. Books:

1. [Laucevičius A, Rinkūnienė E, Kasiulevičius V, Jatužis D, Petrulionienė Ž, Ryliškytė L, et al. Didelės kardiovaskulinės rizikos pirminės prevencijos strategija Lietuvoje: "Asmenų, priskirtinų širdies ir kraujagyslių ligų didelės rizikos grupei, atrankos ir prevencijos priemonių finanasavimo programa" – pagrindiniai 2006-2017 metų rezultatai: metodinė priemonė] / Recenzentai: prof. J. Čelutkienė, prof. B. Petrauskienė. (VU MF, Higienos institutas, VMTI Inovatyvios medicinos centras). – Vilnius: UAB "Vaistų žinios", 2018, 36 p. ISBN 9786098215069 (in Lithuanian).
2. [Aidietienė S, Jatužis D, Kovaitė M, Lapinskas V, Laucevičius A, Marinskis G, et al. Širdies ir kraujagyslių sistemos chronobiologijos ir chronoterapijos pagrindai: mokymo priemonė] / Atsakingas redaktorius – LMA tikrasis narys, prof. A. Laucevičius; Recenzentai: prof. J. Čelutkienė, prof. V. Kasiulevičius. (Vilniaus universiteto Medicinos fakultetas) – Vilnius: UAB "Vaistų žinios", 2018 m. – 104 p. ISBN 9786098215076 (in Lithuanian).

3. Conference abstracts:

1. Ryliškytė L, Visockienė Z, Ryliškienė K, Navickas R, Badarienė J, Jakaitienė A, et al. Predictors of arterial markers in metabolic syndrome patients: arterial hypertension and gender outbid dyslipidemia (abstract). Artery 12: The 12th International conference in a series of meetings to provide a forum for discussion on arterial structure and function, 18-20 October, 2012, Tech Gate, Vienna, Austria. Artery Research 2012;6(4):160.
2. Navickas R, Ryliškytė L, Jakaitienė A, Visockienė Z, Badarienė J, Laucevičius A. In high CVD risk group arterial function markers correlate weakly with PWV and AIXHR75 as exceptions (abstract). Artery 12: The 12th International conference in a series of meetings to provide a forum for discussion on arterial structure and function, 18–20 October, 2012, Tech Gate, Vienna, Austria. Artery Research 2012;6(4):159.
3. Ryliškytė L, Laucevičius A, Badarienė J, Navickas R, Solovjova S. C-Reactive protein but not advanced glycation end-products are related to altered glucose metabolism and arterial stiffening in the middle aged metabolic syndrome subjects: Data from a cross sectional study. Artery Research 2013;7(3–4): 128–129.
4. Navickas R, Ryliškytė L, Puronaitė R, Solovjova S, Badarienė J, Laucevičius A. Aortic pulse wave velocity is an independent cardiovascular event predictor in high cardiometabolic risk group (poster presentation). Artery 14, The MECC, 9–11 October 2014, Maastricht, The Netherlands. Artery Research 2014;8(4):160.
5. Ryliškytė L, Čelutkienė J, Solovjova S, Puronaitė R, Badarienė J, Navickas R, et al. Aortic stiffness is an independent determinant of left ventricular diastolic dysfunction in metabolic syndrome patients (poster presentation). Artery 14, The MECC, 9–11 October 2014, Maastricht, The Netherlands. Artery Research 2014;8(4):160.
6. Rimševičius L, Miglinas M, Laucevičius A. Renal profile in a cohort of patients with high cardiovascular risk. Journal of Hypertension 2014;32(e-Supplement 1):e262–e263.
7. Rimševičius L, Kaklauskaitė G, Rekašius T, Miglinas M, Badarienė J, Čypienė A, et al. Body mass index as the key obesity-related predictor of changes in echocardiogram parameter sindicative of left ventricular hypertrophy. 25th European Meeting on Hypertension and Cardiovascular Protection, June 12–15, 2015, Milan, Italy. Journal of Hypertension 2015;33(e-Supplement 1):e167.
8. Miglinas M, Kaklauskaitė G, Rimševičius L, Rekašius T, Badarienė J, Ryliškytė L, et al. Body mass index as an obesity indicator of the best predictive value for cardiovascular disease risk factors in a cohort of middle aged high risk patients. Hospitalis 2015;85 (Suppl.1):7S.
9. Rinkūnienė E, Jucevičienė A, Dženkevičiūtė V, Petrulionienė Ž, Puronaitė R, Bieliauskaitė G, et al. Hypertriglyceridemia Effect On Arterial Function Parameters In Middle Aged Patients With Metabolic Syndrome (PS073, abstract). World Congress of Cardiology and

Cardiovascular / Health World Heart Federation, 4–7 June, 2016, Mexico City, Mexico. Global Heart 2016;11(Suppl 2):E28.
10. Laurent S, Parati G, Chazova IE, Sirenko Y, Erglis A, Laucevičius A, et al. One Month Blood Pressure Lowering Efficacy Results of a Novel First-Line Treatment in Hypertension. 26th European Meeting on Hypertension and Cardiovascular Protection, 10–13 June 2016, Paris, France. Journal of Hypertension 2016;34(e-Supplement 2):e194.
11. Kutkienė S, Petrulionienė Ž, Laucevičius A, Gargalskaitė U, Staigytė J, Šaulytė A, et al. Trends of cardiovascular risk factors among groups with different high density lipoprotein cholesterol and triglycerides serum concentrations (Meeting Abstract: SAG141). 85th Congress of the European-Atherosclerosis-Society (EAS), APR 23-26, 2017, Prague, Czech Republic. Atherosclerosis 2017;263:e80–e81. (ISI)
12. Kutkienė S, Petrulionienė Ž, Laucevičius A, Gargalskaitė U, Staigytė J, Šaulytė A, et al. Trends in cardiovascular risk profile among middle-aged Lithuanian adults with atherogenic dyslipidemia from 2009 to 2015 (Meeting Abstract: PO226). 85th Congress of the European-Atherosclerosis-Society (EAS), APR 23–26, 2017, Prague, Czech Republic. Atherosclerosis 2017;263:e180–e180.(ISI)
13. Kutkienė S, Petrulionienė Ž, Laucevičius A, Gargalskaitė U, Staigytė J, Šaulytė A, et al. Comparison of laboratory features between low highdensity Lipoprotein cholesterol group and both low highdensity lipoprotein cholesterol and high triglycerides group (Meeting Abstract: PO227). 85th Congress of the European-Atherosclerosis-Society (EAS), APR 23-26, 2017, Prague, Czech Republic. Atherosclerosis 2017;263:e180–e180.(ISI)
14. Rinkūnienė E, Butkutė E, Puronaitė R, Petrulionienė Ž, Dženkevičiūtė V, Kasiulevičius V, et al. Impact of hypertriglyceridemia on arterial function parameters (poster). // 26th Nordic-Baltic Congress of Cardiology 2017, 1-3 June 2017, Vilnius, Lithuania. (Lithuanian Society of Cardiology, Nordic-Baltic Cardiology Alliance, Lithuanian University of Health Science, Vilnius University, Faculty of Medicine). Medicina 2017;53 (Suppl 1):50.
15. Laučytė-Cibulskienė A, Petravičiūtė M, Gudynaitė M, Rimševičius L, Ryliškytė L, Laucevičius A, et al. Influence of beta2-microglobulin on arterial stiffness in end stage renal disease (poster) // 26th Nordic-Baltic Congress of Cardiology 2017, 1-3 June 2017, Vilnius, Lithuania. (Lithuanian Society of Cardiology, Nordic-Baltic Cardiology Alliance, Lithuanian University of Health Science, Vilnius University, Faculty of Medicine). Medicina-Lithuania 2017;53 (Suppl 1):84.
16. Ginčaitė A, Rimševičius L, Ryliškytė L, Badarienė J, Laucevičius A, Miglinas M. Risk factors of arterial stiffness measured by cardio-ankle vascular index in patients with mildly decreased glomerular filtration rate (abstract PP.01.33). 27th European Meeting on Hypertension and cardiovascular protection, June 16–19, 2017, Milan, Italy. Journal of Hypertension 2017;35(e-Supplement 2):e100.
17. Miglinas M, Ginčaitė A, Rimševičius L, Ryliškytė L, Badarienė J, Laucevičius A. Differences in arterial stiffness measured by cardio-ankle vascular index in patients with normal and decreased renal function (abstract). Artery 17: Congress, 12–14 October 2017, Pisa, Italy. Artery Research 2017;20:92.
18. Solovjova S, Puronaitė R, Jakštaitė A, Ryliskytė L, Čelutkienė J, Laucevičius A. The association between metabolic syndrome components, arterial markers of early atherosclerosis and left ventricular diastolic dysfunction (abstract). Artery 17: Congress, 12–14 October 2017, Pisa, Italy. Artery Research 2017;20:98.
19. Laucevičius A, Ryliškytė L, Solovjova S, Badarienė J, Čelutkienė J, Puronaitė R, et al. Is metabolic syndrome high or moderate cardiovascular (cardiometabolic) risk entity: results of Lithuanian High Cardiovascular Risk (LitHiR) programme // 7th Baltic Atherosclerosis Congress, April 6-7, 2018, Tallinn, Estonia. Scientific Committee Members: prof. A. Laucevičius (Baltic Atherosclerosis Society, Estonian society of Cardiology, Estonian Endocrine Society). Programme:14–15
20. Laučytė-Cibulskienė A, Ginčaitė A, Rimševičius L, Ryliškytė L, Laucevičius A, Miglinas M. Should We Calculate Aortic-Brachial Gradient In Women? Results Of A Large Cohort Study. Journal of Hypertension 2018;36
(Suppl 1):e141–e141.
21. Kutkienė S, Petrulionienė Ž, Laucevičius A, Gargalskaitė U, Skiauterytė E, Petrylaitė M, et al. The importance of LDL-cholesterol and triglycerides levels assessment for familial hypercholesterolemia screening in the middle-aged Lithuanian adults // 86th EAS Congress, May 5–8, 2018, Lisbon, Portugal. Atherosclerosis 2018;275:e213–e214.
22. Kutkienė S, Petrulionienė Ž, Laucevičius A, Gargalskaitė U, Staigytė J, Česnavičiūtė I, et

al. Association of serum lipid profile and cigarette smoking among middle-aged Lithuanian adults // 86th EAS Congress, May 5–8, 2018, Lisbon, Portugal. Atherosclerosis 2018;275:e214–e214.
23. Kutkienė S, Petrulionienė Ž, Laucevičius A, Gargalskaitė U, Šaulytė A, Navickaitė A, et al. Association of serum lipid profile and physical activity among middle-aged Lithuanian adults // 86th EAS Congress, Lisbon, Portugal, May 5–8, 2018. Atherosclerosis 2018;275: e214–e214.
24. Kutkienė S, Petrulionienė Ž, Laucevičius A, Gargalskaitė U, Staigytė J, Petrulionytė E, et al. The analysis of non-HDL cholesterol quantity among middle-aged Lithuanian adults with different lipid profiles // 86th EAS Congress, May 5–8, 2018, Lisbon, Portugal. Atherosclerosis 2018;275:e214–e215.
25. Kutkienė S, Petrulionienė Ž, Laucevičius A, Gargalskaitė U, Šaulytė A, Petrulionytė E, et al. Association of serum lipid profile and family history of coronary heart disease among middle-aged Lithuanian adults // 86th EAS Congress, May 5–8, 2018, Lisbon, Portugal. Atherosclerosis 2018;275:e215–e215.
26. Kutkienė S, Petrulionienė Ž, Laucevičius A, Gargalskaitė U, Navickienė G, Kovaitė M, et al. Association of serum lipid profile and dietary habits among middle-aged Lithuanian adults // 86th EAS Congress, May 5–8, 2018, Lisbon, Portugal. Atherosclerosis 2018;275:e215–e215.
27. Kutkienė S, Petrulionienė Ž, Laucevičius A, Gargalskaitė U, Šaulytė A, Kovaitė M, et al. Association of serum lipid profile and arterial hypertension and among middle-aged Lithuanian adults // 86th EAS Congress, May 5–8, 2018, Lisbon, Portugal. Atherosclerosis 2018;275:e215–e215.
28. Kutkienė S, Petrulionienė Ž, Laucevičius A, Gargalskaitė U, Šaulytė A, Kovaitė M, et al. Association of serum lipid profile and diabetes mellitus among middlie aged Lithuanian adults // 86th EAS Congress, May 5–8, 2018, Lisbon, Portugal. Atherosclerosis 2018;275:e215–e216.
29. Kutkienė S, Petrulionienė Ž, Laucevičius A, Gargalskaitė U, Skiauterytė E, Petrulionytė E, et al. The distribution of LDL-cholesterol levels in the middle-aged Lithuanian adults during the period of 2009–2016 // 86th EAS Congress, May 5–8, 2018, Lisbon, Portugal. Atherosclerosis 2018;275:e225–e226.
30. Kutkienė S, Petrulionienė Ž, Laucevičius A, Gargalskaitė U, Skiauterytė E, Petrulionytė E, et al. The distribution of triglycerides levels in the middle-aged Lithuanian men and women during the period of 2009–2016 // 86th EAS Congress, May 5–8, 2018, Lisbon, Portugal. Atherosclerosis 2018;275:e226–e226.
31. Berūkštis A, Laucevičius A. Modification of the sympathetic nervous system in treatment of hypertension, one of the biggest evolutionary diseases // "Evoliucinė medicina: sveikata ir ligos besikeičiančioje aplinkoje/ Evolutionary medicine: Health and diseases in changing environment": 4-oji tarptautinė konferencija Nepriklausomybės atkurimo 100-mečiui, Vilnius, 2018 m. birželio 5–10 d. Rengėjas – VU Medicinos fakultetas. Acta Medica Lituanica 2018;25(Supplement):27.
32. Berūkštis A, Neverauskaitė-Piliponienė G, Misonis N, Juknevičius V, Balsytė J, Laucevičius A. Modification of sympathetic tone by renal artery denervation causes early, significant and sustained arterial de-stiffening. Abstracts from ARTERY 18, 18-20 October, 2018, Guimarães, Portugal // Artery research 2018;24:97.
33. Ryliškytė L, Navickas R, Puronaitė R, Jucevičienė A, Laucevičius A. Relationship between carotid intima-media thickness, endothelial function, aortic stiffness and cardiovascular events among metabolic syndrome subjects. Abstracts from ARTERY 18, 18-20 October, 2018, Guimarães, Portugal // Artery research 2018;24:98.
34. Slivovskaja I, Balsytė J, Ryliškytė L, Badarienė J, Navickas R, Laucevičius A. Aortic but not peripheral pulse wave velocity is improved after Heart Rate targeted aerobic physical training in metabolic syndrome subjects. Abstracts from ARTERY 18, 18-20 October, 2018, Guimarães, Portugal // Artery research 2018;24:100.
35. Solovjova S, Ryliškytė L, Puronaitė R, Čelutkienė J, Laucevičius A, Badarienė J, et al. Arterial stiffness and Left Ventricular Diastolic Function in patients with metabolic syndrome: Longitudinal study. Abstracts from ARTERY 18, 18-20 October, 2018, Guimarães, Portugal // Artery research 2018; 24:121–122.
36. Valaikienė J, Ryliškytė L, Valaika A, Puronaitė R. The influence of gender on visualization of intracranial segments by TCCS in patients with severe coronary artery disease // 23rd Meeting of the European Society of Neurosonology and Cerebral-Hemodynamics (ESNCH), Apr 13-16, 2018, Prague, Czech Republic. European Journal of Neurology 2018;25(Suppl 1):55–56. IF 4.621
37. Solovjova S, Puronaitė R, Stuopelytė M, Ryliškytė L. Coherence between arterial stiffness and left ventricular diastolic function in

patients with metabolic syndrome: longitudinal study // "Evoliucinė medicina:sveikata ir ligos besikeičiančioje aplinkoje / Evolutionary medicine: Health and diseases in changing environment": 4-oji tarptautinė konferencija Nepriklausomybės atkurimo 100-mečiui, Vilnius, 2018 m. birželio 5-10 d. Rengėjas – VU Medicinos fakultetas. Acta Medica Lituanica 2018;25(Supplement):76–77.

4. PhD theses:

1. Rinkūnienė E. Didelės kardiovaskulinės rizikos asmenų nustatymo ir aktyvios pirminės prevencijos metodu optimizavimas. Daktaro disertacija. Mokslinė vadovė prof. Ž. Petrulionienė, moksl. konsultantas prof. A. Laucevičius. – Vilnius, 2014, 153 p. (2014.12.19)
2. Rimševičius L. Ankstyvas inkstų pažeidimas ir jo sąsajos su širdies ir kraujagyslių rizikos veiksniais tarp asmenų, kuriems nustatyta padidinta kardiovaskulinė rizika. Daktaro disertacija. Moksl. vadovas prof. M. Miglinas, moksl. konsultantas prof. habil. dr. A. Laucevičius – Vilnius, 2015, 200 p. (2015.01.06)
3. Andrejevaitė V. Rūkančių vyrų nerimo sutrikimų sąsajos su aterosklerozės, hemostazės bei arterijų sienelės struktūros ir funkcijos rodikliais. Daktaro disertacija. Moksl. vadovas prof. V. Šapoka. – Vilnius, 2016, 209 p. (2016.10.26)
4. Navickas R. Arterial and Molecular Biomarkers for Improved Cardiovascular Disese and Diabetes Risk Assessment Comparative Study. [Arterinių ir molekulinių širdies ir kraujagyslių ligų bei cukrinio diabeto rizikos biožymenų palyginamasis tyrimas]. Daktaro disertacija. Moksl. vadovas prof. habil. dr. A. Laucevičius. – Vilnius, 2016, 104 p. (2016.12.08)
5. Lisauskienė I. Širdies ir kraujagyslių sistemą veikiančių vaistų vartojimo ir sergamumo bei mirštamumo nuo šios sistemos ligų kitimai Lietuvoje. Daktaro disertacija. Moksl. vadovė prof. J. Gulbinovič. – Vilnius, 2017, 213 p. (2017.10.18)
6. Slivovskaja I. Individualios aerobinės fizinės treniruotės veiksmingumas asmenims, kuriems nustatytas metabolinis sindromas. Daktaro disertacija. Moksl. vadovas prof. A. Juocevičius, moksl. konsultantė dr. L. Ryliškytė. – Vilnius, 2018, 200 p. (2017.12.12)
7. Kutkienė S. Dislipidemijų įvertinimo ir modifikavimo įtaka širdies ir kraujagyslių ligų etiopatogenezei bei prevencijai ir sąsajos su kitais aterosklerozę skatinančiais rizikos veiksniais. Daktaro disertacija. Moksl. vadovė prof. Ž. Petrulionienė. – Vilnius, 2018, 118 p. (2018.12.06)
8. Laučytė-Cibulskienė A. Arterial stiffness and other biomarkers as vascular remodeling and cardiovascular risk predictors in patients on renal replacement therapy. Daktaro disertacija. Moksl. vadovai: prof. M. Miglinas, prof. habil. dr. K. Strupas. – Vilnius, 2018, 118 p. (2018.09.06)
9. Solovjova S. Arterijų funkcijos ir struktūros rodiklių pokyčio ir kairiojos skilvelio diastolinės disfunkcijos sąsajų tyrimas asmenų grupėje, esant metaboliniam sindromui. Daktaro disertacija. Moksl. vadovai: prof. habil. dr. A. Laucevičius ir dr. L. Ryliškytė. – Vilnius, 2018, 169 p. (2019.01.10)