doi:10.25143/prom-rsu_2023-03_dt

Rīga Stradiņš University

Tarass Ivaščenko

Gpx and MDA Oxidative Stress Markers and Severity of Depression as Predictives of Recurrent Stable Coronary Heart Disease

Doctoral Thesis for obtaining a doctoral degree
"Doctor of Science (*PhD*)"

Sector group – Medical and Health Sciences
Sector – Clinical Medicine
Sub-Sector – Internal Diseases

Riga, 2023

Tarass Ivaščenko

ORCID 0000-0003-4971-6213

Gpx and MDA Oxidative Stress Markers and Severity of Depression as Predictives of Recurrent Stable Coronary Heart Disease

Doctoral Thesis for obtaining the scientific degree "Doctor of Science (*PhD*)"

Sector group – Medical and Health Sciences

Sector – Clinical Medicine

Sub-Sector – Internal Diseases

Supervisors of the Doctoral Thesis:

MD, PhD, Associate Professor **Vladimirs Voicehovskis**,
Rīga Stradiņš University, Department of Internal Diseases, Latvia

MD, PhD, Professor **Oskars Kalējs**,
Rīga Stradiņš University, Department of Internal Diseases, Latvia

Research project was supported by RSU *PhD* grant

Riga, 2023

Abstract

Background. Cardiovascular disease is a major cause of death globally, taking over one-third of all deaths worldwide. Multiple research results are confirming coronary heart disease and depression as highly comorbid, associating depression with an increased risk of incidents of coronary heart disease and vice versa, and depression is a strong predictor of coronary heart disease outcome. One of the mechanisms that may explain the interaction between depression and cardiovascular diseases is oxidative stress. Assessment of oxidative stress markers could modify risk stratification, diagnosis and prevention, and treatment of coronary heart disease and depression patients.

Aim. To investigate the relationships between oxidative stress biomarkers, the prevalence of depression, and the risk of recurrent stable coronary heart disease.

Methods. A retrospective case-control study, comparing patients with primary stable coronary heart disease with patients who have recurrent stable coronary heart disease by determining oxidative markers levels and depression signs and severity. Medical record analysis, structured interview, Geriatric Depression Scale, and blood samples to detect oxidative stress markers MDA and GPx were used as investigation methods.

Results and discussion. 174 patients were included in this study – 49.4% with primary coronary heart disease and 50.6% with recurrent. The majority of the sample (83.9%) had high levels of MDA and for the rest of them, the MDA level was considered normal. MDA level was slightly higher in primary stable coronary heart disease group without depression. For the majority of the patients (72.4%) the GPx level was normal, for 17.8% it was high, and for 9.8% – low. Slightly more than half of the patients were experiencing depression (44.3% – mild and 6.9% – severe). Oxidative stress is a risk factor for coronary heart recurrence, especially in depressed patients. The prevalence of depression was higher in patients with recurrent coronary heart disease. Patients with both high GPx and depression had 10.6 times higher chances of recurrent stable coronary heart disease compared to those with normal GPx and without depression.

Conclusions. Elevated GPx level was more common among patients with recurrent stable coronary heart disease. GPx levels were also higher in depressed patients with recurrent stable coronary heart disease. The majority of patients had high levels of MDA with higher rates in patients with primary stable coronary heart disease. More than a half of patients were experiencing mild or severe depression symptoms with higher rates among patients with recurrent stable coronary heart disease. Patients with high GPx and depression have higher chances of recurrent stable coronary heart disease. Increased MDA level is a risk factor for

stable coronary heart disease in general but it does not link to depression severity and recurrence of stable coronary heart disease. Hence antioxidant enzyme GPx is a more significant marker of the risk of depression and recurrence of stable coronary heart disease.

Keywords: stable coronary heart disease, depression, oxidative stress, MDA, GPx.

Anotācija

Oksidatīvā stresa marķieri GPx un MDA un depresijas smagums kā atkārtotu stabilas koronārās sirds slimības notikumu prognostiskie faktori

Ievads. Kardiovaskulārās slimības ir galvenais nāves cēlonis pasaulē – vairāk nekā trešdaļai visu nāvju. Vairāki pētījumu dati apstiprina, ka koronārajai sirds slimībai un depresijai ir augsta komorbiditāte, depresija ir saistīta ar paaugstinātu koronārās sirds slimības attīstības risku, un otrādi, kā arī depresija ir spēcīgs koronārās sirds slimības iznākuma prognostiskais faktors. Viens no galvenajiem mehānismiem, kas izskaidro mijiedarbību starp depresiju un koronāro sirds slimību, ir oksidatīvais stress. Oksidatīvā stresa marķieru novērtēšana var savlaicīgi mazināt atkārtotas hospitalizācijas risku sakarā ar koronāro sirds slimību, uzlabot diagnozes noteikšanu, ārstēšanu un profilaksi pacientiem ar koronāro sirds slimību un depresiju.

Mērķis. Izpētīt oksidatīvā stresa biomarķieru līmeņa izmaiņas un to iespējamo prevalējošo korelāciju ar depresiju un atkārtotu stabilas koronārās sirds slimības (SKSS) notikumu riskiem.

Metodes. Retrospektīvs gadījumu kontroles pētījums, kurā salīdzināti pacienti ar primāru un atkārtotu koronārās sirds slimības notikumu, nosakot oksidatīvā stresa marķieru līmeni un depresijas smagumu. Tika izmantotas šādas metodes: medicīnisko ierakstu analīze, strukturētas pacientu intervijas, geriatrijas depresijas skala, asins analīzes MDA un GPx līmeņa noteikšanai.

Rezultāti un diskusija. Pētījumā tika iekļauti 174 pacienti: 49,4 % ar primāru stabilu koronārās sirds slimības notikumu un 50,6 % ar atkārtotu notikumu. Lielākajai izlases daļai (83,9 %) bija augsti MDA rādītāji, bet pārējiem MDA bija normas robežās. MDA līmenis bija nedaudz augstāks pacientiem bez depresijas ar primāru stabilu koronāro sirds slimību. Lielākajai daļai pacientu (72,4 %) GPx līmenis bija normāls, 17,8 % tas bija augsts, bet 9,8 % – zems. Nedaudz vairāk nekā pusei pacientu konstatēja depresiju (44,3 % vidēji smagu un 6,9 % smagu). Oksidatīvais stress ir viens no riska faktoriem atkārtotai stabilai koronārajai sirds slimībai, it īpaši pacientiem ar depresiju. Depresijas izplatība bija augstāka pacientiem ar atkārtotu stabilas koronārās sirds slimības notikumu. Pacientiem ar augstu GPx līmeni un depresiju ir 10,6 reizes augstāks risks, ka koronārā sirds slimība attīstīsies atkārtoti salīdzinājumā ar pacientiem bez depresijas un ar normālu GPx līmeni.

Secinājumi. Paaugstināts GPx līmenis ir biežāk sastopams pacientiem ar atkārtotu stabilas koronārās sirds slimības notikumu. GPx līmenis bija augstāks depresīviem pacientiem ar atkārtotu stabilas koronārās sirds slimības notikumu. Lielākajai daļai pacientu bija augsts MDA ar augstākiem rādītājiem pacientiem ar primāru stabilu koronāro sirds slimību. Vairāk

nekā pusei pacientu tika konstatēti vidēji smagas vai smagas depresijas simptomi ar augstākiem rādītājiem pacientiem ar atkārtotu stabilu koronāro sirds slimību. Pacientiem ar augstu GPx līmeni un depresiju ir augstāki atkārtotu stabilas koronārās sirds slimības notikumu riski. Paaugstināts MDA līmenis ir riska faktors stabilai koronārajai sirds slimībai kopumā, bet nav saistīts ar depresijas smagumu un atkārtotu stabilas koronārās sirds slimības notikumu varbūtību. Līdz ar to GPx ir nozīmīgāks depresijas un atkārtotu stabilas koronārās sirds slimības notikumu riska faktors.

Atslēgvārdi: stabila koronārā sirds slimība, depresija, oksidatīvais stress, MDA, GPx.

Table of Contents

Abbreviations used in the Thesis

AD	Antidepressant
AI	Apoptosis index
AO	Antioxidant
BMI	Body mass index
CAD	Coronary artery disease
CHD	Coronary heart disease
CI	Confidence interval
CVD	Cardio-cerebrovascular diseases
D	Depression
GDS	Geriatric Depression Scale
GPx	Glutathione peroxidase
GR	Glutasereductase
GSH	Glutathione
GSSG	Glutathione disulphide
HPA	Hypothalamus–pituitary–adrenal axis
HRV	Heart rate variability
KYN	Kynurenine
LP	Lipopolysaccharide
MDA	Malondialdehyde
MDD	Major depressive disorder
MI	Myocardial infarction
NADP+	Nicotinamide adenine dinucleotide phosphate
NADPH	Reduced nicotinamide adenine dinucleotide
NSTEMI	Non-ST elevation
OR	Odds ratio
OS	Oxidative stress
PSCHD	Primary stable coronary heart disease
RAAS	Renin–angiotensin–aldosterone system
ROS	Reactive oxygen species
RSCHD	Recurrent coronary heart disease
SCHD	Stable coronary heart disease
STEMI	Subsequent ST elevation
SSRIs	Selective serotonin reuptake inhibitors
TAC	Total antioxidant capacity
TBA	Thiobarbituric acid

TRP	Tryptophan
WHO	World Health Organization
YLDs	Years lived with disability
YLLs	Years of life lost

Introduction

Epidemiological data indicate that cardiovascular diseases (CVD) and depression pose a huge global disease burden. The Global Burden of Disease 2016 (GBD, 2016) study showed that CVD was the number one reason for years of life lost (YLLs) globally (Moraga, 2016). Also, in 2017, GBD reported that major depressive disorder (MDD) was the third cause of years lived with disability (YLDs) after low back pain and headache disorders (James et al., 2017). Both, coronary heart disease (CHD) and depression (D) are leading causes of disability in high-income countries and are expected to become so globally by 2030 (Murray&Lopez, 2013).

Over the past 20 years, a multitude of research has found that not only is D more common in cardiac patients than in the general population, but D is also a risk factor for cardiac morbidity and mortality, associated with adverse cardiovascular outcomes, independent of traditional risk factors (Huffman et al., 2013). D in cardiac disease is common, persistent, underrecognized, and deadly. The prevalence of D is, compared with the general population, significantly higher in patients with coronary heart disease (CHD) (Whooley&Wong, 2013). Besides impairing patients' quality of life, D has profound negative effects on the long-term prognosis of individuals with any type of cardiovascular disorder. These facts further underscore the importance of the proper treatment of D in patients with CVD (Yekehtaz, 2013).

There is a lack of a definitive correlation between high-risk profiles, biological profiles, and the occurrence of CVD (Khawaja et al., 2009). The role of oxidative stress in cardiovascular disease processes, such as atherogenesis, ischemic-reperfusion injury, and cardiac remodelling, has been increasingly recognized in the past few decades. Oxidative stress is defined by the imbalance between the production of reactive oxygen species (ROS) and the endogenous antioxidant mechanisms to counteract the effects of ROS or to repair the resulting damages (Antoniades et al., 2009). Much of the recent research in these areas has focused on the role of the immune system and inflammation in both depression and CVD. Currently, an increasing number of studies suggest that levels of oxidative stress markers in body fluids correlate with atherosclerotic disease activity (Vichova&Motovska, 2013). The common risk factors increase the production of OS and reduce AO defences, thereby promoting the occurrence and development of interacted ischemic CVD and D. OS can also contribute to depressive disorder by acting on established etiopathological components of D, including lipid signalling, monoamine regulation, and inflammation (Moylan et al., 2014; Maes et al., 2011). Therefore, there is a need to understand the underlying mechanisms and find effective therapies to control CVD and D (Lin et al., 2019).

The role of OS in Stable CHD (SCHD) recurrence in patients with SCHD and D has not been studied previously. At the moment, there is insufficient evidence that routine screening of D in patients with SCHD will ultimately help improve the patient's condition (Hasnain et al., 2011; WHO, 2017), which is why the study of the relationship between SCHD, D and OS is very important.

Aim of the Thesis

The present study aimed to investigate changes in oxidative stress biomarker levels and its possible correlation with depression and recurrent stable coronary heart disease risks.

Objectives of the Thesis

1. To determine the prevalence and severity of depression among patients with primary and recurrent stable coronary heart disease.
2. To determine and compare oxidative stress marker MDA in patients with primary stable coronary heart disease and recurrent stable coronary heart disease.
3. To determine and compare oxidative stress marker GPx in patients with primary stable coronary heart disease and recurrent stable coronary heart disease.
4. To analyse correlations between oxidative stress marker MDA and severity of depression in patients with primary and recurrent stable coronary heart disease.
5. To analyse correlations between oxidative stress marker GPx and severity of depression in patients with primary and recurrent stable coronary heart disease.
6. To determine possible biomarkers as a risk factor for SCHD recurrence.

Hypothesis

Patients with recurrent stable coronary heart disease and depression would have a higher level of oxidative stress biomarkers than patients with primary stable coronary heart disease without depression, which can be used in diagnostic tools for the risk of recurrence of SCHD in patients with depression.

Novelty of the Thesis

For the first time in Latvia, the relationship between primary hospitalization, rehospitalization, and its possible connection with depression and oxidative stress markers was investigated. Also, before 2015 risk factor correlations between primary and recurrent stable coronary heart disease, depression, and oxidative stress (GPx and MDA) were not investigated. Those oxidative stress biomarkers were found more significant in D and RSCHD development.

Currently, there is no such institution in Latvia that collects and studies data about the interaction between somatic and mental diseases. On a national level, there are no systematically collected statistics about somatic patients with mental diseases and behavioural disorders and vice versa – patients with mental disorders who have somatic comorbidities, death causes, and drugs used in psychiatry that cause somatic side effects.

Practical significance of the work

The current study can contribute to creating a better understanding of the relationship between oxidative stress, depression, and coronary heart diseases. Also, it can help to improve risk assessment strategies for cardiovascular diseases and depression among patients with coronary heart disease, therefore reducing rehospitalization risks.

It is important to mention several revealed facts:

1. There is a link between depression and oxidative stress, and depression, oxidative stress, and stable coronary heart disease.
2. Depression screening in a hospital setting can significantly improve healthcare for patients with stable coronary heart disease.
3. Timely and adequate therapy (for example, antidepressants) reduces risks of rehospitalization, improves patients' quality of life, and reduces the average length of stay in hospitals and rehabilitation facilities, which is economically beneficial for the state.

Oxidative stress markers can be used as a diagnostic tool for depression and recurrent cardiac events. There is a wide variety of different oxidative stress markers, and in this study two of them were investigated (MDA and GPx). Unlike GPx, results show contradictory data of MDA assessment in patients with coronary heart disease. Therefore, GPx could be used as a diagnostic tool for ≥45 years old patients to evaluate recurrent coronary heart disease risk. It is fast, informative and reliable, could be used by cardiologists, general practitioners, gerontologists, psychiatrists and other specialists, who are involved in coronary heart disease treatment. Identifying patients with high risk of recurrent coronary heart disease early allows better patient follow-up assessment and evaluate the need for antidepressant and/or antioxidant therapy.

As mentioned above, barriers to recognition of depression include a lack of mental health expertise and training in cardiology practices, and many symptoms of D, such as fatigue, weight loss, poor appetite, or trouble sleeping, are easily confused with physical disease. Therefore, the measurement of oxidative stress marker GPx can be used as a diagnostic tool for D and the risk of recurrence in patients with CHD.

1. Literature

1.1. Cardiovascular Disease (CVD)

According to the World Health Organization data, cardiovascular disease (CVD) is the number 1 cause of death globally, taking an estimated 17.9 million lives each year, an estimated 31% of all deaths worldwide (WHO, 2017). European Heart Network report states CVD is the leading mortality cause in Europe, responsible for over 45% of all deaths – 3.9 million lives a year. Mortality rates of CVD are higher in males. It is important to mention strong geographical disparities with higher mortality rates in Eastern and Central Europe (EHIG, 2020; Wilkins et al., 2017).

In Latvia, CVD was the most common cause of death – 54.6% of all deaths, according to 2019 data (Ērglis et al., 2020). Moreover, CHD was the cause of 32.9% of total deaths (GBD, 2019).

The latest available statistics confirm that on average 15 000 people die from CVD in Latvia every year – in 2017 there were 815 people per 100 000 inhabitants and in 2019 the indicator slightly decreased to 784 people per 100 000 inhabitants (*SPKC*, 2020).

According to the World Health Organization, "CVD is a group of diseases that include both the heart and blood vessels, thereby including coronary heart disease (CHD), coronary artery disease (CAD), stroke, hypertensive heart disease, inflammatory heart disease, rheumatic heart disease, and other cardiovascular diseases" (WHO, 2011). CAD is usually used to refer to the pathologic process affecting the coronary arteries (usually atherosclerosis) whilst CHD includes the diagnoses of angina pectoris, MI, and silent myocardial ischemia. In turn, CHD mortality results from CAD (Sanchis-Gomar et al., 2016).

1. CVD incidence, prevalence, and healthcare burden

In a survey conducted in Latvia in 2018, it was found that people with CVD most often had: 28.5% hypertension, 16.8% high cholesterol, 8.7% arrhythmia, 4.4% heart failure, 4.2% CHD, 2.5% stroke, and 2.4% myocardial infarction. 23.4% of people noted that they tend to have pain or heaviness in the chest – with the highest proportion in the age groups of 55 years for men and 45 years for women (Ērglis et al., 2018).

As stated in the European Heart Network report, there were over 11.3 million new cases of CVD registered in Europe in 2015. The incidence of CVD increased over the last decades and the only countries to show a decrease in CVD cases in both sexes were Latvia and United Kingdom (Wilkins et al., 2017).

Prevalent cases of total CVD nearly doubled from 271 million in 1990 to 523 million in 2019, and the number of CVD deaths steadily increased from 12.1 in 1990, reaching 18.6 million in 2019 around the globe (Roth et al., 2020). As for prevalence in Europe, statistics claim there are 85 million people in Europe (49 million within European Union (EU)) living with CVD. Prevalence rates are higher in Eastern and Central Europe and over the past 25 years, the absolute number of CVD cases rose by 26% in females and by 32% in males which has corresponded with population aging. It is essential to specify the prevalence rates of CVD in the Baltic states. In 2015 CVD rates in males per 100 000 were: 7197 in Estonia, 7298 in Latvia, and 8226 in Lithuania with an average rate of 6308 in the EU. Prevalence rates of CVD per 100 000 females are lower: 5669 in Estonia, 5582 in Latvia, and 6346 in Lithuania with an average rate of 4921 in the EU (EHIG, 2020; Wilkins et al., 2017).

High CVD rates place a significant economic burden on the healthcare system. It should be noted that patient hospitalization rates in EU countries remain very high (Roth et al., 2020). However, the rates were lower in Cyprus (6.1 per 1000 patients hospitalized among men and 2.9 per 1000 among women), while the rates were higher in Lithuania (45.4 cases per 1000 men and 50.1 per 1000 women). It should be noted that even though men are hospitalized more often, it is women who spend longer time in hospitals – 12% longer with CVD in general, but the time spent in the hospital with acute myocardial infarction is 17% longer. Statistics on the Baltic States for 2012 are available: the average number of hospitalized patients per 1000 in Latvia was 31.2, and in Lithuania – 45.4, but the data on Estonia was not published. The average length of time spent in the hospital was 6.6 days in Latvia and 8.3 days in Lithuania. The average hospital discharge rate, or the number of patients discharged per 100 000 residents admitted due to CVD, is one of the indicators of the burden on the healthcare system. The average number in Europe in 2013 was 2,500 patients per 100 000 inhabitants. It should be noted that this number has increased over the last 30 years. The lowest rates are in Cyprus – 672 per 100 000, while the highest in the European Union is in Lithuania – 4765 per 100 000 inhabitants (Wilkins et al., 2017).

Data on drug treatment also indirectly indicates the prevalence, importance, and burden CVD places on healthcare. According to statistics, the use of antihypertensives and cholesterol-lowering drugs has changed: for example, in Estonia during the period since 2000. By 2013, the use of antihypertensive drugs had tripled, and in Luxembourg, it had quadrupled. The highest rates of the use of antihypertensive drugs are in Germany and Hungary, almost three times higher than in Austria and Turkey. The situation with cholesterol-lowering drugs is similar, as their use has increased, with the highest rates of use being in Slovakia and the United Kingdom, and the lowest – in Austria and Turkey. It is worth taking a separate look

at the medications prescribed to patients during inpatient hospitalization: statin use ranges from 73.5% in Lithuania to 96.1% in Greece, while the average use of b-blockers is lower, from 67.8% in the UK to 89.5% in Spain (Wilkins et al., 2017). The largest differences can be seen in prescribing Angiotensin-converting-enzyme inhibitors and Angiotensin receptor blockers – the lowest rate is in Belgium, which is 49%, and the highest is in the Czech Republic, which is 82.2% (Kotseva et al., 2015).

According to the data on the population of Latvia compiled in 2018, it was found that the most common reason for using medication was hypertension – 48.7% of respondents, the second most common reason was pain – 22.7%, and the third – was heart rhythm disorders – 16.6%. Other mentioned reasons included also anxiety (10.1% of people), hyperglycaemia (8.6%), and heart failure (7.5%) (Ērglis et al., 2020).

Separately the severity of CVD and the burden it places on healthcare and economics can be evaluated by the prevalence of surgical manipulations, however, it is difficult to analyse data on surgical procedures performed on patients hospitalized due to CVD, because some of this data is not available from private hospitals. But as an example, heart bypass anastomosis surgery was most commonly performed in Denmark (72.8 procedures per 100 000 residents) and least commonly in Spain (17.8 per 100 000 residents). In contrast, rates of transluminal coronary angioplasty procedures were the highest in Germany (385.9 procedures per 100 000 residents) and lowest in Romania (95.2 procedures per 100 000 residents). It is also important to look at fatality rates within a year from diagnosis. It should be mentioned that Latvia is one of the countries with the highest fatality rate – 15.4% of patients die within a year after being diagnosed with acute myocardial infarction, compared to 4.5% in Sweden (EHIG, 2020; Wilkins et al., 2017).

According to statistics, the average CVD-related costs in Europe are € 210 billion per year, of which 53% (111 billion) are direct healthcare costs, 26% (54 billion) are incapacity-related costs and 21% (45 billion) are informal care costs. In the meantime, coronary artery disease (CAD) related costs amount to € 59 billion a year. The amount of money spent varies greatly from country to country, depending on a variety of factors. For example, the cost per capita in Bulgaria is € 48 per CVD patient, while in Finland it is € 365. There is an opinion that the real costs are much higher due to indirect costs that are difficult to track, such as the impact CVD has on the family – the ability of relatives to continue working, pay for care and rehabilitation, and pay bills (Wilkins et al., 2017).

According to the collected data, in 2015, the CVD cost Latvia 130 thousand euros, with a 66 euro cost per capita, which makes up 10% of all health care funds. In Lithuania, the total cost was 226 thousand euros, with a 78 euro cost per capita (also 10% of all health care

expenses), while in Estonia 177 thousand euros were spent, with a 135 euro cost per capita (14% of all health care expenses) (Ērglis et al., 2020).

2. CVD risk factors

In line with previous publications, there are eight main risk factors for CVD, which can be divided into two groups:

- Medical risk factors: high blood pressure, high body mass index (BMI), high cholesterol, and high fasting plasma glucose.
- Behavioural risk factors: alcohol consumption, smoking, low levels of physical activity, and an unhealthy diet (Wilkins et al., 2017).

All risk factors can be divided into modifiable and non-modifiable:

- Nonmodifiable cardiovascular risk factors are age, gender, family history, and race.
- Modifiable risk factors are hypertension, weight, smoking, sedentary lifestyle, abnormal lipid profiles, inflammatory markers, diabetes, metabolic syndrome, and subclinical CAD (Khawaja et al., 2009; Kuller et al., 2006).

According to statistics, in 2015, out of all behavioural risk factors, in the European region, unhealthy diets had the greatest impact on mortality rates for both sexes. Taking into account the interaction of risk factors in calculating the average contribution to CVD-related death, it was found that diet-related factors had the highest impact on mortality rates – 47% of men and 38% of women in the European region and 67% of men and 61% of women in Central Asia (GBD, 2019; Wilkins et al., 2017).

According to published data, smoking not only promotes the formation of blood clots, increases blood pressure, and provokes inflammation of vascular walls and atherosclerosis, but also reduces exercise tolerance and increases the density of cholesterol in the blood plasma (Piepoli et al., 2016).

The latest data on Latvia show that smoking has decreased among men from 52% in 2014 to 38.3% in 2019. In total, 24.5% of people in Latvia are smokers (Ērglis et al., 2020).

The level of physical activity among the population of the European Union remains very low: only 8% state that they engage in physical activity five times a week or more, while 42% state that they never engage in physical activity. Lower rates are more common in southern and eastern European countries. Describing the situation in the Baltic States, it should be mentioned that 46% of people in Lithuania, 36% in Estonia, and 39% in Latvia never engage in physical activity (Wilkins et al., 2017). According to statistics from 2018, 36.3% of Latvians spend their free time sitting, while 46.2% do light physical activities and walk at least four times a week.

In addition, 15.2% of the population purposefully engages in regular physical activities (Ērglis et al., 2020).

Alcohol consumption is known to have negative effects because alcohol raises blood pressure and increases the number of triglycerides in the blood. And although in low doses it has a positive effect on the cardiovascular system, its negative effects usually outweigh all the benefits (Piepoli et al., 2016).

Alcohol consumption is highest in Eastern European countries and much lower in Southern and Northern Europe, and overall alcohol consumption in Europe has decreased over the past 30 years (Wilkins et al., 2017). In 2018, 79.2% of the population in Latvia consumed alcoholic beverages during the year (Ērglis et al., 2020).

In terms of medical risk factors, high blood pressure has the greatest negative impact – slightly stronger in Central Europe (62% of men and 60% of women) than in Western Europe (51% of men and 50% of women). The next most important factor was high cholesterol level, while BMI and high fasting plasma glucose made the smallest contributions to CVD-related deaths (Wilkins et al., 2017).

According to the data from 2018, 39.5% of the Latvian population had a normal BMI, which increased – 34.6%, and 24.1% of people were found obese. Compared to the data from 2009, the average BMI has increased (Ērglis et al., 2020).

According to statistics, high blood pressure is more common in Central and Eastern Europe, with the highest rates in Estonia, at 32% of the population. The lowest rate is in the UK – 15% of people living with hypertension. In contrast, the situation with blood cholesterol levels is the opposite – elevated cholesterol levels are more common in Western and Northern Europe, compared to Eastern European countries (Wilkins et al., 2017). Data on the population of Latvia show that slightly more than a quarter of the population lives with arterial hypertension. Its average duration is 16.2 years. 86.2% of people who have been diagnosed with hypertension take regular measurements of their blood pressure, and among them, 34.3% of arterial blood pressure measurements are usually optimal or not higher than 120/80 mmHg (Ērglis et al., 2020).

Data on cholesterol levels is available for 2009 when a study found that 75.2% of people had a total cholesterol level above 5 mmol/l. Compared to the data of 2018, this indicator has decreased to 63.2%. Also, according to the data from 2009, hyperglycaemia was detected in 28.7% of people, the highest prevalence being among men over the age of 45 (hyperglycaemia rates reached as high as 51%) (Ērglis et al., 2020).

According to compiled data, an average of 62% of men and 55% of women in Europe are overweight, of which 21% of men and 25% of women are obese (Wilkins et al., 2017).

According to the data from 2018, 39.5% of the Latvian population had a normal BMI, increased – 34.6%, and 24.1% of people were found obese. Compared to the data from 2009, the average BMI has increased. It is interesting to mention that 56.6% of people believe that their weight is normal (Ērglis et al., 2020).

1.2. Depression and Cardiovascular Disease

A person's psycho-emotional state plays an important role because stress, anxiety, and depression (D) become the cause of rapid heartbeat and high pressure. In addition, the European Society of Cardiology Guidelines for the Prevention and Treatment of Cardiovascular Disease mentions depression, anxiety, and stress as psycho-emotional risk factors for CVD. Several psychological states and traits, such as D, anxiety, anger, and stress, have also been implicated as potential risk factors for coronary artery disease (CAD) (Ērglis et al., 2020; Khawaja et al., 2009).

1.2.1. D prevalence among CVD

According to the literature, D has affected more than 264 million people worldwide. According to US data for 2017, 7.1% of adults (8.7% women and 5.3% men) experienced at least one episode of depression per year, most often between the ages of 17 and 25. Data on the European region show that 6.9% of the population suffers from depression (Wilkins et al., 2017).

According to Centre for Disease Prevention and Control of the Republic of Latvia (*SPKC*) data, during 2017 an average of 148.7 people per 100 000 residents with a diagnosis of F32 were registered, of which 30.6 cases per 100 000 residents had a mild depressive episode (F32.0), 107.9 people per 100 000 had a major depressive episode (F32 .1), 4 per 100 000 had a major depressive episode without psychotic features (F32.2), 3 per 100 000 had a major depressive episode with psychotic features (F32.3). It should be noted that in 2017, an average of 259.8 people per 100 000 residents with recurrent depressive disorders (F33) were registered (*SPKC*, 2020a).

In Latvia in 2018, according to self-reported data, 16.2% of the population mentioned that they suffer from anxiety and depression. However, examining the prevalence of depression, it was found that only 2.3% of respondents had depressive symptoms, with a higher proportion of respondents being in the age group from 65 to 74 (up to 5%). Out of all the detected cases,

5.4% were characterized by subclinical depression. It is an interesting fact that among the Latvian population, D was one of the causes of disability for 10% of women and 0% of men (Ērglis et al., 2020). Primary care numbers are significantly higher: 14.4% of primary care patients had D symptoms. 24.4% of those patients with D symptoms had a CVD. At the same time, there was almost half (13.1%) of many CVD patients without D (Vrublevska, 2018).

Published data suggest that D in cardiac disease is common, persistent, underrecognized, and deadly. Over the past 20 years, research has found that not only is D more common in cardiac patients than in the general population, but D is also a risk factor for cardiac morbidity and mortality, independent of traditional risk factors (Huffman et al., 2013). The authors concluded that D is an independent risk factor for CHD and is not related to other previously determined cardiac risk factors. This association persisted across all demographic groups in this well-designed, case-control study (Khawaja et al., 2009).

Based on the literature on patients with CVD, D is often chronic and recurrent. (Yekehtaz, 2013). Among patients with CVD hospitalized for acute cardiac events and found to meet criteria for depression during or shortly after admission, approximately 50–70% had ongoing depressive symptoms that preceded their cardiac event (Glassman et al., 2006; Lesperance et al., 2007). Furthermore, 15–20% of patients with CAD meet the criteria at any given time for the full syndrome of MDD (Kaptoge et al., 2014; Polanka et al., 2018); this rate of MDD is roughly threefold higher than in the general population (Cooper et al., 2011) and is similar to the rates of MDD in patients with chronic kidney disease and cancer (Huffman et al., 2013; Tomfohr et al., 2011).

The prevalence of D is, compared with the general population, significantly higher in patients with CHD (Whooley&Wong, 2013). More than one-fifth of all patients with CHD are depressed (with the risk of D highest in the most severe CHD cases), and up to one-third of them report elevated depressive symptoms. These are prevalence figures that are at least 4 times greater than in the general population (Hert&Detraux et al., 2018). Another 30–45% of patients with CHD suffer from clinically significant symptoms consistent with a minor D (Celano&Huffman, 2011).

If we look at figures from the community through to those who are hospitalized, we see rates of depression of 10% in general practice clinics (Cassano&Fava, 2002; Brown et al., 2009), which then increases to up to 30% in those with CHD in outpatient clinics (Dhar&Barton, 2016). In several studies, 17–44% of patients with CAD also have a diagnosis of major D (Yekehtaz et al., 2013).

The literature describes persistent D in patients with stable CAD. Furthermore, rather than being a transient reaction to a cardiac event, D for many patients exists for months or years before and persists long after the event (Huffman et al., 2013; Glassman et al., 2006; Lesperance et al., 2007; Huffman et al., 2011).

Statistics in Latvia show that in 20% of cases patients with CHD also have D, and this number increases to 30% among hospitalized patients. It should be noted that in the acute phase of MI depression is experienced by 65% of patients, but 25% of people experience depression between 18 and 24 months after MI (Ērglis et al., 2020).

1.2.2. Depression as an independent risk factor

There are three extensively replicated epidemiological observations regarding CHD and depression:

1. These conditions are highly comorbid.
2. D is associated with an increased risk of incident CHD and vice versa.
3. D is a strong predictor of poor prognosis in people with CHD (Khandaker et al., 2020)

Comorbidity. According to statistics, the prevalence of depression among CVD patients is significantly higher than in the general population (Glassman et al., 2006; Lesperance et al., 2007; Ērglis et al., 2020). Compared with non-depressed patients, the risk of cardiac arrest increased in less severely depressed patients. We can mention the fact that patients before MI experienced progressive worsening of depressive symptoms as an example (Khawaja et al., 2009). A meta-analysis has demonstrated that the overall risk of depressed but otherwise healthy individuals developing heart disease is 64% higher than for those without D (Van der Kooy et al., 2007). Five meta-analyses reported a 60–80% increased risk of CHD in participants with D (Lin et al., 2019).

The bidirectional link between CVD and depression. It should be noted that nowadays the public health sector faces a huge challenge as a result of the high prevalence and burden of disability caused by CVD and D. D, a frequently occurring disease, has a bidirectional relationship with ischemic CVD and partially shares common risk factors (such as obesity, hypertension, diabetes) and mechanisms (such as inflammation and oxidative stress (OS), immune response, cell death signalling pathway, and microbiome-gut-brain axis) with CVD, correlate with atherosclerotic disease activity (Khawaja et al., 2009; Lin et al., 2019).

D as a strong predictor of poor prognosis for CVD. Minor D symptoms are a risk factor for the future of a major depressive episode in patients with CHD, associated with an increased risk of secondary acute ischemic events, lower interventions, and increased mortality regardless

of traditional cardiac risk factors (Barth et al., 2004; Januzzi et al., 2000; Carney et al., 2004; Van Melle et al., 2004).

In addition, major D worsens the cardiovascular prognosis, particularly for CHD, by significantly increasing the risk of recurrent CHD. The relative risk of death in depressed patients during the 18 months following the cardiac event is twice that in non-depressed patients. Recent studies have also shown the harmful nature of D after myocardial infarction in terms of rehospitalization or getting access to cardiac rehabilitation, which is particularly beneficial in this context (Myers et al., 2012; Chauvet-Géliniera et al., 2013). D is a predictor of congestive heart failure after MI, and observation of patients 30 months after an MI episode revealed an increased risk of complications in patients with depression, an increased risk of arrhythmias and recurrent MI, and a risk of re-hospitalization for CVD (Khawaja et al., 2009).

It is important to note that D increases all causes of cardiac mortality. For example, according to published data, patients with CVD and D are 2.8 times more likely to die within a year after MI than people without CVD (Khawaja et al., 2009).

One of the factors influencing poor prognosis is the fact that patients with D have poor medication adherence, which directly affects the CVD treatment process. In addition, patients with D are more likely to have an unhealthy and sedentary lifestyle (Khawaja et al., 2009).

1.2.3. D diagnostic features of patients with CVD

By collected data, depressive symptoms are diagnosed in less than 15% of cases (Guck et al., 2001) and only 25% of patients with CHD and severe D are diagnosed with the psycho-emotional disorder and approximately only half of them receive adequate antidepressants (AD) therapy (Moryś et al., 2016). Barriers to the recognition of depression include a lack of mental health expertise and training in cardiology practices and the perception that this is not part of the treatment mission. Additionally, many symptoms of psychological distress are easily confused with physical disease, for example, fatigue, weight loss, poor appetite, or trouble sleeping. It is believed that all patients with CAD should also be screened for D, as this not only affects CVD outcomes but also affects secondary prevention outcomes (Glassman et al., 2006).

According to US data, only half of the patients with CAD are asked about D symptoms. Standardized D-detection tools are not used by cardiovascular physicians who nevertheless try to determine the presence of D. One of the reasons why patients with CVD are not adequately screened for D is the fact that 49% of cardiovascular physicians are unaware that D is an independent risk factor for CAD (Khawaja et al., 2009). But it is important to mention, that these data were published a decade ago, therefore the situation might have changed over the years.

It is also important to mention, D in Latvia is not only underdiagnosed but also most likely confused with neurotic disorders, thus supporting the need to implement depression screening tools in primary care in Latvia (Vrublevska, 2018).

According to the literature, the recommended test time is one month after revascularisation as two months and six months post-revascularization are stronger predictors of D (Khawaja et al., 2009).

The diagnosis of D can be difficult in people with CVD, as D symptoms such as fatigue and low energy are common in people with CVD and may also be a side effect of some drugs used to treat CVD such as beta blockers. The diagnosis may be further complicated in such patients by their responses to their disease, which may include denial, avoidance, withdrawal, and anxiety (Goodman et al., 2008; Carney&Freedland, 2008).

Given the sometimes-sudden onset of a cardiovascular event, the normal psychological reaction to disease requires the patient to adapt, which leads to a certain physiological D in mood, the time to come to terms with the possible loss related to the disease, and the sometimes very much changed prospects for life (Chauvet-Géliniera et al., 2013).

In a study of hospitalized patients with a variety of cardiac conditions, those who met the criteria for clinical D during admission had improvement in adherence (to diet, exercise, and medication) if their D improved following hospitalization. This suggests that reduced adherence to key secondary prevention behaviours in D cardiac patients may be modifiable with the treatment of the D symptoms (Bauer et al., 2012). Non-completion rates in cardiac rehabilitation are in the order of 44% compared to 29% in the non-depressed group (Swardfager et al., 2011).

1.3. Inflammation as a pathophysiological link between D and CVD

Literature data suggest that inflammation is very often an initial step in the disease process followed by an immunological response. But the immunological response may be initiated practically at the same time as the onset of inflammation. During the inflammatory process, dysfunctions develop over time in various molecules, which can contribute to the development of a form of chronic disease. Such a process has been confirmed in the development of diabetes, cancer, and CVD (Armstrong&Stratton, 2016).

Although CVD and D are very different pathologies, they share some common pathophysiological characteristics and risk factors, such as the increased production of pro-inflammatory cytokines, endothelial dysfunction, blood flow abnormalities, decreased glucose metabolism, elevated plasma homocysteine levels and disorder in vitamin D metabolism

(Trebatická et al., 2017). Possible mechanisms of how D and CHD are related via pathophysiological changes are shown in Figure 1.1.

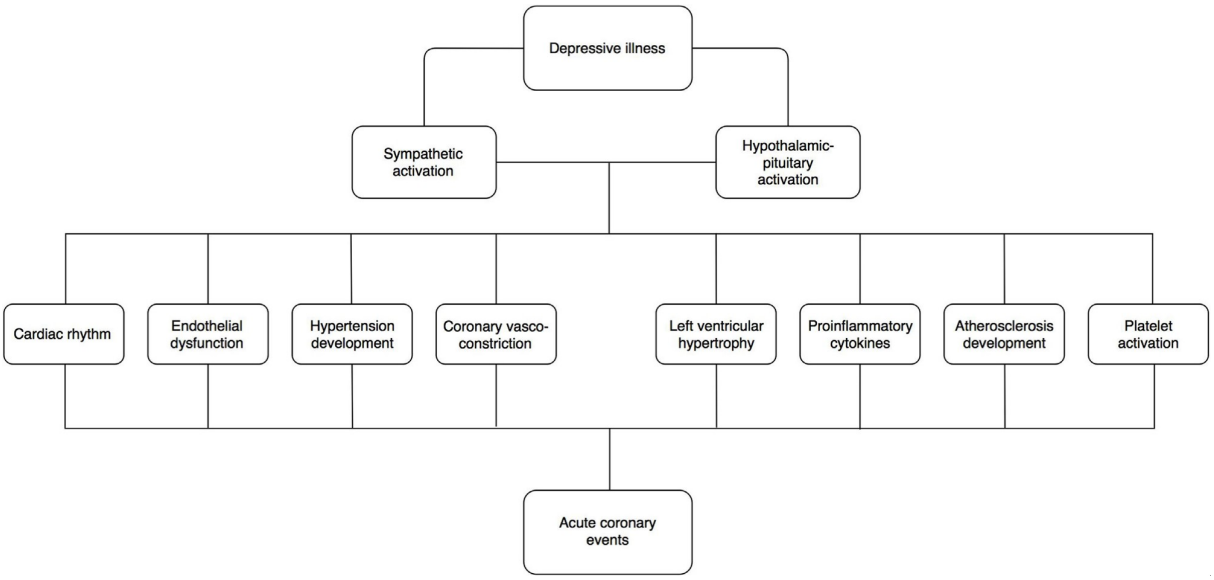

Figure 1.1 **Possible mechanisms whereby depression confers elevated cardiac risk** (by Dhar&Barton, 2016)

As pathophysiological mechanisms, we may also count inflammatory processes and abnormal platelet functioning, microbiome-gut-brain pathway, the hyperactivity of noradrenergic and hypothalamic pituitary adrenal cortisol system, effects of brain-derived neurotrophic factor (BDNF) and related factors, changes in serotonin / kynurenine pathways and D-induced altered autonomic tone (Khawaja et al., 2009).

1.3.1. Chronic inflammatory hypothesis

The inflammatory hypothesis as a common physiopathological pathway in mood disorders and CVD is being put forward more and more frequently (Frasure-Smith&Lespérance, 2010). C-reactive protein (CRP) is a non-specific marker of systemic inflammation that can be found practically in all patients with D and is often elevated. CRP can activate coronary endothelium and accumulates in the plaques. Elevated levels are one of the predictors of the incident and recurrent MI and cardiac death (Khawaja et al., 2009).

Also, C-reactive protein correlates with peripheral arterial disease. Similar observations have been reported in patients with inflammatory markers such as IL-6 and serum amyloid A. This is one of the reasons why the US Heart Association recommends C-reactive protein analysis as a screening tool to detect asymptomatic patients and those who are at high risk for CVD. It is important to note that in CVD cases, the immunological response in the infarcted area is very important, as it initiates repair processes in cardiac tissue – leukocytes ensure the

removal of dead cells and molecular fragments, while cytokine and growth factor release facilitates the formation of highly vascularized granulation tissue to maintain myocardial wall integrity (Khawaja et al., 2009).

However, prolonged inflammation or inflammatory mediator feedback dysregulation may reduce collagen deposition and provoke ventricular dilatation. In addition, poor control of the inflammatory response may also increase immune infiltrate in the unaffected part of the myocardium, increasing matrix protein deposition, provoking increased fibrosis, and impairing diastolic function (Fioranelli et al., 2018).

According to the literature, D is associated with abnormal platelet functioning, which manifests as platelet activation and increased adhesiveness in response to physiological stress, thus possibly triggering an adverse coronary event. It should be noted that patients with major D are hypersensitive to thrombin stimulation, which may affect the course of D and promote the development of CVD (Khawaja et al., 2009).

Researchers suggest a hybrid model like the hybrid dependence of D and CHD, in which there is a bi-directional relationship between D and inflammation (Matthews, 2010). It is worth noting that chronic inflammation of a low degree is an inalienable component of D (Adifbair et al., 2016).

D is associated not only with inflammatory reactions taking place in the body but also with an increased amount of pro-inflammatory cytokines and increased lipid peroxidation (Vaváková et al., 2015). D is connected with current inflammatory reactions in the body and an increased level of lipid peroxidation, leading to oxidative stress (OS) (Lin et al., 2019). Moreover, the hypothesis that inflammation and OS are factors in both mood disorders and CHD seems to be growing stronger (Chauvet-Géliniera et al., 2013). It should be noted that postmortem analysis of depressed patients who committed suicide showed robust microglial activation (which promotes neuroinflammation) in the brain, as well as elevated serum levels of IL-1β, IL-6, and TNF-α (Armstrong&Stratton, 2016).

1.3.2. Endothelial dysfunction

Prolonged mental stress, which is commonly experienced in those suffering from major depression, has been shown to induce prolonged endothelial dysfunction. This endothelial dysfunction is one of the early signs of future cardiovascular deterioration (Dhar&Barton, 2016). Endothelial dysfunction has been linked to the development of ischemic CAD in patients with atherosclerosis. For example, while a normal endothelium typically releases nitric oxide in response to serotonin to ensure adequate blood flow through the coronary arteries, in atherosclerotic arteries it fails to do so. This results in vasoconstriction in areas of

atherosclerosis and may provide a mechanism for myocardial ischemia and coronary thrombosis. (Huffman et al., 2013) The relationship between depression and endothelial dysfunction is likely due to reduced endothelium-derived nitric oxide (NO). The reduced NO-dependent response is likely due to lower expression of endothelial NO synthase (eNOS). Higher levels of cortisol and increased inflammation in depression can down-regulate eNOS. Endothelin is a powerful vasoconstrictor, and its levels are higher in patients with D (Vaccarino et al., 2019).

D also has been associated with impaired endothelial function in healthy patients (Cooper et al., 2010; Tomfohr et al., 2011), in those at risk for CVD (Pizzi et al., 2008), and those with established CVD (Huffman et al., 2013).

1.3.3. Increased platelet activity and thrombosis

Increased platelet activation and thrombosis, increased susceptibility to blood coagulation due to changes in several stages of the coagulation cascade, including activation and aggregation of platelets; decrease in the number of circulating endothelial progenitor cells and associated processes of arterial reconstruction represent another pathological mechanism for the association between depression and CHD (Nemeroff 2012). D has been implicated with increased platelet reactivity, which will increase the relative risk of thrombus formation and arterial occlusion (Dhar&Barton, 2016). The platelet hyper-reactivity could at least partially explain the increased vulnerability of depressed patients to acute thrombotic events and ischemic heart disease (Amadio et al., 2020). Platelet adhesion, activation, and aggregation are important components of cardiac disease, and increased platelet activity may lead to coronary events on this basis. Serotonin plays a key role in platelet biology through its binding with 5-hydroxytryptamine (5-HT) receptors on platelets. In atherosclerotic arteries, serotonin leads to platelet aggregation. (Huffman et al., 2013). Further evidence of platelet activation can be shown by elevated levels of beta-thromboglobulin, which are raised in depressed CHD patients (Dhar&Barton, 2016). High white blood cell counts, fibrinogen, and raised platelet activation contribute to a prothrombotic state, thrombus formation, and myocardial ischemia (Barth et al., 2004).

1.3.4. Microbiome-gut-brain pathway

CHD and D share some common pathophysiological characteristics and risk factors, such as cell death signalling pathway, and microbiome-gut-brain axis (Lin et al., 2019), increased susceptibility to blood coagulation due to changes in several stages of the coagulation

cascade, including activation and aggregation of platelets; oxidative stress; subclinical hypothyroidism; decrease in the number of circulating endothelial progenitor cells and associated processes of arterial reconstruction; increased variability of heart rate; and the presence of genetic factors (Nemeroff, 2012).

1.3.5. Homeostatic regulation changes in CVD and D

Individuals with comorbid depression and CVD may also have imbalances in the homeostatic regulation of different biological systems, with alterations observed in the hypothalamus–pituitary–adrenal (HPA) axis, renin–angiotensin–aldosterone system (RAAS), and serotonin / kynurenine pathways that are accompanied by inflammation and endothelial dysfunction (Mattina et al., 2019; Halaris, 2017).

Another system that plays a significant role in the inflammatory response is the renin-angiotensin-aldosterone-system (RAAS), whose main function is blood pressure regulation. When dysfunctional, the RAAS appears to contribute to the comorbidity of CVD and depression (Mattina et al., 2019). According to the literature, the hyperactivity of the noradrenergic system is observed in patients with CVD and D. Sympathetic outflow is increased in depressed patients as compared to non-depressed patients through negative stress effects of catecholamines on the heart, blood vessels, and platelets. Further support of the catecholamine association with D is that increased urinary catecholamine levels are associated with negative emotions and decreased social support, and high norepinephrine and low platelets serotonin are associated with MI and D (Khawaja et al., 2009). Following the chronic activity, the RAAS becomes maladaptive, resulting in endothelial dysfunction and a pro-inflammatory milieu that advances the progression of atherosclerosis and leads to CVD development. (Mattina et al., 2019). Though much of the research examining RAAS activity has focused on its relation to CVD risk and outcomes, recent research has implicated RAAS dysfunction in depression, as well (Murck et al., 2014). Findings from both human and nonhuman animal studies have linked aldosterone to depression. A depressed individual has greater aldosterone levels when coupled with a social stressor (Häfner et al.,2012). In a cross-sectional study was found that individuals suffering both, depressed symptomatology and hypertension, exhibited highly significantly increased aldosterone levels ($p < 0.001$) and slightly, not significantly increased renin levels ($p = 0.08$) compared to individuals with no depressed symptomatology and no hypertension. Notably that no significant activation of the RAAS was seen in only depressed or only hypertensive individuals (Häfner et al., 2013).

Depression is associated with autonomic imbalance and activation of the Hypothalamic-Pituitary-Adrenal axis. Studies over the last 40 years have identified stress-responsive HPA axis dysregulation to be the most consistent biological mechanism, with the toxicity arising from excessive glucocorticoid (GC) and corticotropin-releasing hormone (CRH) release (Athira et al., 2020). Endocrine changes associated with depression include alterations in corticotropin-releasing factor (CRF), dysregulated adrenocorticotropic hormone (ACTH) responses to CRF,83 enhanced adrenal responses to ACTH, and elevated circulating cortisol levels. Several of these changes may affect the immune system leading to excessive secretion of cytokines such as interleukin (IL)-1, IL-6, and tumour necrosis factor (TNF)-a. (Vaccarino et al., 2019).

Hypercortisolaemia causes an increased risk of a metabolic syndrome-type state, which includes glucose intolerance, hyperlipidaemia, and increased visceral fat mass. This metabolic syndrome not only confers a higher risk of cardiovascular disease but has also been shown to drive sympathetic activation (Dhar&Barton, 2016). The stimulation of the HPA axis could thus correlate with the development of atherosclerosis and show another biological similarity between mood disorders and CHD (Chauvet-Gélinier a et al., 2013). Depressive disorders have been also associated with alterations in adrenergic and dopaminergic receptors availability, the consequent modification in the downstream pathways in the brain (Pecina et al., 2017; Grace et al., 2016), and changes in peripheral levels of catecholamines. The catecholamines are adaptive and maladaptive stress hormones; they activate behavioural and physiological processes facilitating the overcoming of stress (Motiejunaite et al., 2020). In agreement with previous data, more recent studies showed that patients suffering from depression and other major affective disorders have increased urinary levels of adrenaline (epinephrine / EPI), noradrenaline (norepinephrine / NE), and dopamine (DA). Catecholamines are essential constituents of physiologic cardiovascular regulation, since human platelets express both adrenergic and dopaminergic receptors, the high catecholamine levels may easier explain the association between depression and CVD (Amelirad et al., 2019; Amadio, 2020).

Post-mortem studies show that patients with D have many more neurons that produce corticotropin-releasing factor compared to people without D. Thus, D leads to CVD causing the hypothalamus to release corticotropin-releasing factor, which in turn raises corticosteroid levels and may trigger atherosclerosis, hypertension, hypertriglyceridemia, and hypercholesterolemia (Khawaja et al., 2009). Studies show that changes in the HPA axis also led to the formation of atherosclerotic plaques, promoting insulin resistance and dyslipidaemia (Fioranelli et al., 2018).

1.3.6. Changes in serotonin / kynurenine pathways

This type of inflammatory-mediated change to the kynurenine pathway appears to be involved in both CVD and MDD diseases. Seventeen studies examined levels of kynurenic acid (KYNA), quinolinic acid (QUIN), and KYN, respectively. This meta-analysis revealed that patients with depression had decreased levels of KYNA and KYN, in comparison to controls. (Ogyu et al., 2018). Thus, people with CVD often have increased serum kynurenine to tryptophan ratios (KYN / TRP), a result of an increased tryptophan (TRP) breakdown. Furthermore, the KYN / TRP ratio, as well as other kynurenine metabolites, are strongly associated with an increased risk of poor outcomes following stroke (Brouns et al., 2010), and cardiovascular-related mortality in the general population (Zuo et al., 2016). TRP is an important source for protein production, but also the generation of one of the most important neurotransmitters, 5-hydroxytryptamine (serotonin). Tryptophan breakdown leads to reduced serotonin availability. Additionally, the accumulation of neurotoxic KYN metabolites such as quinolinic acid produced by microglia can contribute to the development of depression via NMDA glutamatergic stimulation. Thus, increased TRP catabolism was proposed as a pathway leading to mood dysregulation (Schrocksnadel et al., 2006). Furthermore, syndromal depression and adjustment disorder with depressed mood were proposed as contributors to CVD and myocardial infarction ("broken heart syndrome") (Lewis, 2005). Moreover, increased cardiovascular comorbidity and adverse cardiovascular event endpoints have been reported in subjects with depressive mood disorders (Kuehl et al., 2012; Goldstein, 2006; Patel, 2013; Mangge et al., 2014). Depressed coronary heart disease patients show greater serum KYN / TRP ratio compared with those without depression (Nikkheslat et al., 2015), suggesting that depression coupled with CVD leads to increased activation of the kynurenine pathway (Mattina et al., 2019).

1.3.7. Effects of brain-derived neurotrophic factor (BDNF) and related factors.

In addition to the previous mechanisms, BDNF may also play an important role in the connection between depression and cardiac outcomes. BDNF has an important role in several physiologic processes important to cardiovascular health BDNF influences endothelial function (Alhusban et al., 2017), monocyte activation (Amadio et al., 2016)], and thrombus dimension and stability (Amadio et al., 2019]. It takes part in cardiovascular development (Emanueli et al., 2014) but also in the onset of cardiovascular alterations and disease (Pius-Sadowska et al., 2017), including hypertension (Becker et al., 2015, Becker et al., 2017), atherosclerosis (Lee et al., 2012; Chaldakov et al., 2004) and thrombosis (Amadio, 2020).

Endothelial cells are vital to vascular health and, as noted, endothelial function is independently associated with cardiac outcomes (Huffman, 2013)

Depression has been strongly and consistently linked to low levels of BDNF (Hashimoto et al., 2010), and it is thought that BDNF signalling mediates the hippocampal neurogenesis that has been linked to depression recovery (Castren&Rantamaki, 2010, Huffman, 2013). Reductions in serum and plasma BDNF have been found in patients affected by depression (Yoshida et al., 2012, Shimizu et al., 2003), and in those who committed suicide (Birkenhäger et al., 2012, Kim et al., 2007).

Furthermore, BDNF may be an important mediator of the previously noted HPA axis effects on depression and cardiovascular disease. The glucocorticoid receptor interacts with the specific receptor of BDNF, TrkB, and excessive glucocorticoid interferes with BDNF signalling; therefore, excess glucocorticoids may be associated with adverse outcomes via BDNF-mediated effects on endothelial cells and cardiomyocytes. (Kunugi et al., 2010, Huffman et al., 2013).

1.3.8. D-induced altered autonomic tone

The autonomic nervous system maintains homeostatic balance in the body in response to environmental changes and physiological stimuli. Autonomous dysregulation acts as an intermediary in the pathological processes of CVD and during stress. This is due to central and peripheral neurophysiological mechanisms involved in the development of arrhythmias, acute coronary events, and worsening heart failure. The neuro-cardiac axis is a series of complex reflex control networks that include afferent, efferent, electrical, and mechanical components of the heart that participate in the formation of autonomic response to stress stimuli (Vaccarino et al., 2019, Penninx et al., 2017).

Chronic dysregulation of autonomic function, characterized by an imbalance between the sympathetic and parasympathetic systems, is thought to be a key mechanism linking depression to CHD risk and adverse cardiovascular outcomes (Penninx et al., 2017). Sympathetic hyperactivity and parasympathetic withdrawal may lower the threshold for myocardial ischemia and ventricular arrhythmias and potentially predispose to sudden cardiac death. (Vaccarino et al., 2019, Penninx et al., 2017). The sympathetic outflow is increased in depressed patients as compared to non-depressed patients through the negative stress effects of catecholamines on the heart, blood vessels, and platelets. Further support of the catecholamine association with D is that increased urinary catecholamines levels are associated with negative emotions and decreased social support, and high norepinephrine and low platelets serotonin are associated with myocardial infarction (MI) and D. (Khawaja et al., 2009).

Heart rate variability (HRV) is one of the non-invasive markers of life-threatening arrhythmias and endothelial damage. It is also an indirect marker of chronic stress. Heart rate variability is a dynamic variation of heart rate and if it is reduced, it indicates excessive sympathetic activity and reduced vagal tone (Fioranelli et al., 2018). HRV is considered a measure of neurocardiac function that reflects heart-brain interactions and autonomic nervous system dynamics. An optimal level of HRV within an organism was found to reflect healthy function and an inherent self-regulatory capacity (Reynard et al., 2011), adaptability (Thayer et al., 2009), or emotional and stress resilience (Appelhans et al., 2006; An et al., 2016). By contrast, reduced HRV has been linked to stress vulnerability (Penninx et al., 2017). Shifted sympathovagal balance toward the sympathetic branch leads to electric instability of the heart. Reduced HRV was shown to be an independent risk factor for sudden cardiac death, while increased HRV was associated with reduced cardiac mortality (Vaccarino et al., 2019).

HRV is modulated by the cardiac vagus and has been described in MDD patients. Where were analysed 21 studies in total, were published between 2002 and 2017. In total, 967 patients with MD, were enrolled in these studies. Their results were compared to 1,050 healthy controls. Eighteen studies investigated autonomic nervous system function measured by HRV in depression, and 14 (78%) studies have reported reduced variability of the heart rate, compared to healthy controls (Pinter et al., 2019).

It should be noted that patients with D may have reduced parasympathetic nervous system responses, which leads to a disturbed balance between the sympathetic and parasympathetic nervous systems. As a result, heart rate variability decreases rapidly. D-induced altered autonomic tone associated with low heart rate variability leads to dysrhythmias. Such changes are most expressed in depressed patients with CAD and CHD and negatively affect survival after MI (Khawaja et al., 2009).

1.4. Cardiovascular Disease, Depression, and Oxidative Stress

Oxidative stress as a concept appeared in 1985 and its definition was supplemented in 2007 and reads as follows: “oxidative stress is an imbalance between oxidants and antioxidants in favour of the oxidants, leading to a disruption of redox signalling and control and / or molecular damage” (Sies&Jones, 2007). Oxidative stress activates the immune-inflammatory pathways (Liu et al., 2015; Moylan et al., 2014). According to the literature, OS provokes a whole cascade of reactions: the initiation of the disease began at the molecular level – with the development of OS, free radicals are formed and lipid peroxidation begins, which initiates an inflammatory response. In turn, inflammation initiates a neovascular response and begins to form proinflammatory cytokines. At this stage, patients usually have no symptoms, but the next

level is already clinical, when the person is in a pre-disease state and, as OS reactions continue, the acute phase of the disease begins, which then progresses to the chronic phase (Armstrong&Stratton, 2016).

According to Lin (2019), many studies have shown that D is an independent factor in the pathogenesis of CVD, but it is still unclear whether D can cause CVD and how it affects the course of CVD. One of the mechanisms that may explain the interaction between D and CVD is oxidative stress (Lin et al., 2019). Because it was studied that OS is an emergency mechanism that relates to both CVD and D pathophysiology (Adifbair et al., 2017; Kander et al., 2017). In addition, the role of OS is related to common risk factors for CVD and D: obesity, diabetes, and hypertension. These three factors intensify the OS response in the body and reduce the anti-OS response (Lin et al., 2019).

Despite the potentially important role of the OS in the pathogenesis of CVD and D, according to available research results, by 2015, the role of OS in the development of D in patients with CHD has not been studied (Vaváková et al., 2015).

1.4.1. Oxidative stress pathophysiology

Under normal conditions, oxidation and antioxidative systems work in balance and are beneficial to physiological processes. On the other hand, when this balance is disturbed, excessive reactive oxygen species (ROS) are formed, which the antioxidant system cannot hold. As a result, OS and a number of pathological reactions, including mitochondrial dysfunction and destruction of homeostasis, develop (Lin et al., 2019).

ROS is a collective term to include superoxide (O_2▪−), hydrogen peroxide (H_2O_2), hydroxyl radical (OH▪), singlet oxygen ($1O_2$), peroxyl radical (LOO▪), alkoxyl radical (LO▪), lipid hydroperoxide (LOOH), peroxynitrite ($ONOO^-$), hypochlorous acid (HOCl), and ozone (O_3). Some of these substances have unpaired electrons, so they belong to free radicals – superoxide, hydroxyl, peroxyl, and alkoxyl radical. There are several ways in which free radicals can be formed in the organism because a chain reaction can occur when the formation of one free radical promotes the formation of other free radicals and is therefore divided into primary, secondary, and tertiary (Vichova&Motovska, 2013; Bartekova et al., 2016).

It is also important to mention the redox or oxidation-reduction described in the literature, which is a type of chemical reaction that involves a transfer of electrons between two species. According to the data collected, redox includes four principles, also called “redox code”:

1. The first redox principle is the use of the reversible electron accepting and donating properties of nicotinamide in NAD and NADP, which ensures the organization of metabolism and acts almost in equilibrium. Substrate oxidations are linked to the reduction of NAD+ and NADP+, which in turn are linked to ATP production, catabolism, and anabolism, respectively.
2. The second principle is that metabolism is linked to structure through kinetically controlled redox switches in the proteome, which determine macromolecular interactions, activity, and function.
3. The third principle is that activation / deactivation cycles of redox metabolism support spatio-temporal sequencing in the differentiation and life cycles of cells.
4. The fourth principle states that redox forms an adaptive system that responds to environmental changes through subcellular systems to the levels of cell and tissue organization. The redox network must be adaptive to be able to maintain the health of the organism even in changing environmental conditions and, in cases where this system is functionally impaired, it contributes to the development of diseases. (Jones&Sies, 2015; Bartekova et al., 2016).

Any oxidative imbalance resulting in the accumulation of oxidants will inflict oxidative damage on cells, such as alteration of cellular macromolecules, lethal changes in genetic materials, such as DNA and RNA, an increase in the rate of cell death by programmed- and non-programmed-cell death (apoptosis / pyroptosis / necroptosis / ferroptosis or necrosis), and structural damage to tissues and organs (Dhama et al., 2019). The highest levels of OS are in the plasma membrane, mitochondria, nucleus, Golgi, and lysosomes (Armstrong&Stratton, 2016).

Accumulation of oxidants induces lipid peroxidation and disturbances in physiological adaptation and cellular signalling pathways; which, together, inflict oxidative stress (Puppel et al., 2015). Lipid peroxidation products, such as malondialdehyde (MDA), cause changes in the metabolism of dopamine, induce the synthesis of protein-reactive dopaminergic toxins (Rees, 2007), and have an inhibitory effect on the reduction of nucleotide excision by direct interaction with cellular repair proteins (Feng, 2006).

1.4.2. Oxidative Stress and Cardiovascular Disease

OS is considered an important mechanism for the development of CVD (Kander et al., 2017). In the past two decades, numerous studies have demonstrated the importance of oxidative stress in the development of atherosclerosis and ischemia-reperfusion injury (Vichova&Motovska, 2013). OS may be an early causative factor in CVD pathology rather than a late consequence (Vaváková et al., 2017).

As described in the literature, patients with CHD develop coronary artery obstruction, which can significantly reduce myocardial perfusion. Obstruction is usually caused by atherosclerosis, which provokes a decrease in the lumen of the blood vessel. This results in reduced blood flow, resulting in insufficient oxygen and metabolic substrates in the area (Kander et al., 2017).

This phenomenon is commonly called low-flow ischemia. However, in cases where vascular spasms occur or if a blood clot forms in the coronary artery, there is a possibility that the vascular lumen will be completely closed and this is called no-flow ischemia (Armstrong&Stratton, 2016).

The most effective way to restore blood flow to the myocardial area is through reperfusion. As the body responds to ischemia, collateral blood vessels open, but very often this does not solve the problem, and intervention is required when reperfusion is provided by coronary bypass or thrombolytic therapy (Lee et al., 2012).

However, if reperfusion is initiated too late, an ischemia-reperfusion injury develops, which can be explained by the development of irreversible pathological changes in the heart, and reperfusion ischemic damage can only exacerbate and promote greater cardiac dysfunction (Bartekova et al., 2016; Armstrong&Stratton, 2016).

One of the main causes of ischemia-reperfusion injury is oxidative stress and intracellular Ca^{2+}-overload. The OS can be characterized by reduced functional performance, metabolic changes, and ultrastructural changes. Excessive oxyradical formation provokes a number of changes in the organelles of the heart cells – in sarcolemmas, mitochondrias, myofibrils, and sarcoplasmic reticulum (Nakamura et al., 2011).

It should be noted that ROS causes changes in proteins that lead to enzyme malfunctions and changes in activity. Lipid peroxidation not only reduces membrane fluidity and increases its permeability, but also alters gene expression, which ultimately leads to impaired cardiac function recovery due to ischemia-reperfusion injury (Bartekova et al., 2016; Armstrong&Stratton, 2016).

The primary sources of ROS in heart tissue are mitochondrial cytochromes, as well as xanthine oxidoreductase, nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, and nitric oxide synthase (NOS) (Lee et al., 2012).

In cardiomyocytes, ROS production is stimulated by norepinephrine via the α1-adrenergic receptor, but in smooth muscle and endothelial cells, ROS is mainly formed by NADPH oxidation, where vasoconstrictive agents such as angiotensin II (through angiotensin-1 receptor) receptors ETA and ETB) (Lee et al., 2012).

In turn, NOS catalyses the formation of nitric oxide (NO) from the substrate L-arginine in the presence of tetrahydrobiopterin (BH4) as a co-factor. When this co-factor level decreases, so do the chemical reactions that result in the formation of O_2▪ instead of NO, which acts protectively, which, in turn, further increases the amount of ROS in the cell. Another substance that affects the formation of ROS is xanthine oxidoreductase, which can promote the formation of superoxide as a result of chemical reactions and its role in the pathophysiology of ischemia-reperfusion injury has been studied in recent years (Vichova&Motovska, 2013; Bartekova et al., 2016).

As described in the literature, mitochondria play a critical role in cellular energy metabolism when ATP is formed in the cell by oxidative phosphorylation (Armstrong&Stratton, 2016).

The process takes place in the inner mitochondrial membrane to form ATP through electron transport from NADH and FADH2 to oxygen and during this process, ROS is formed as by-products (Vichova&Motovska, 2013).

Thus, oxidative phosphorylation also contributes to oxidative damage to the cell. There are grounds to believe that the pathophysiology of ischemia-reperfusion injury is also closely related to the cell's incapability of adequate energy production due to ischemia. In addition, reduced oxygen levels contribute not only to the overproduction of ROS but also to mitochondrial Ca^{2+}-overload and activation of apoptosis, which ultimately causes cardiomyocyte death. Moreover, the heart has a much higher number of mitochondria than other organs, and it is mitochondria that are the largest source of intracellular ROS in cardiomyocytes. It should be emphasized that OS provokes disturbances in the flow of Ca^{2+} ions through sarcolemmas and the sarcoplasmic reticulum, resulting in excessive accumulation of Ca^{2+} in the cells. It is important to note that it is not entirely clear whether mitochondria promote OS formation by producing large amounts of ROS, or vice versa – ROS alters mitochondrial function and depresses cardiac function. Both mechanisms may work simultaneously (Bartekova et al., 2016; Nakamura et al., 2011).

According to the authors of the research, one of the main manifestations of OS in cardiomyocytes is phospholipid membrane oxidation. ROS and reactive nitrogen species are electrophilic substances that are most commonly involved in lipid peroxidation, and these reactions result in the formation of lipid peroxidation products. The most immediate targets of lipid peroxidation are those lipids that form the phospholipid bilayer of mitochondrial membranes (Vichova&Motovska, 2013; Armstrong&Stratton, 2016).

It should be noted that there are huge numbers of unsaturated phospholipids in mitochondria, and among those is cardiolipin – a phospholipid that is found exclusively in mitochondria and is prone to peroxidation. Cardiolipin levels decrease rapidly when peroxidation takes place, and this phenomenon is observed in various kinds of CVD as one of the pathological processes. As a result, mitochondria are not only the largest source of endogenous LPPs but also the peroxidation target of LPPs in the heart (Vichova&Motovska, 2013; Armstrong&Stratton, 2016).

Studies looking at the role of lipid peroxidation have shown that the peroxidation process reduces membrane fluidity (lipid structure becomes more rigid) and increases membrane permeability – substances that normally cannot pass through entering through membrane pores. Another process is the formation of lipid radicals as a result of a peroxidative chain reaction. This means that phospholipid changes in the membrane resulting from OS play an important role in the impairment of cardiac mitochondria and promote depressed cardiac function (Bartekova et al., 2016; Armstrong&Stratton, 2016).

OS also causes protein alternations, which become the cause of myofilament protein degradation and changes in sarcomeric proteins, which are very important for heart contractions. It should be noted that OS can alter DNA transcription, translation, and integrity of the DNA repair systems. Changes also affect intracellular signalling (Vichova&Motovska, 2013; Bartekova et al., 2016).

It should be noted that OS also has a negative effect on endogenous antioxidants. Antioxidants are substances that are formed in the body and inhibit or prevent oxidative damage to subcellular molecules. Typically, antioxidants act through several mechanisms, such as inhibiting ROS formation, scavenging ROS and their precursors, facilitating endogenous antioxidant formation, and reducing apoptotic cell death by upregulating the anti-apoptotic Bcl-2 gene (Steven et al., 2019).

Superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx) act as endogenous antioxidants. Under the influence of SOD, superoxide becomes oxygen and H2O2. CAT, in turn, converts H2O2 into oxygen and water. GPx catalyzes H2O2 peroxidation, forming water and oxidized glutathione. Its activity is much higher compared to CAT, so GPx

plays a very important role as an H2O2 scavenger (Bartekova et al., 2016; Cheraghi et al., 2019).

Redox status in cardiomyocytes largely depends on the balance between ROS production and the availability of endogenous antioxidants, so great efforts are required to maintain redox balance in cases of CHD when normal blood flow in the coronary arteries is impaired. On the one hand, cardioprotection can also be ensured with exogenous antioxidants, which accordingly increase the availability of endogenous antioxidants and therefore can reduce and impede further oxidative damage to the organelles (Steven et al., 2019).

Thus, antioxidant therapy is one of the promising treatment strategies for reducing cardiac dysfunction caused by ischemia-reperfusion injury. On the other hand, the results of research on exogenous antioxidants are ambiguous. The question of whether exogenous antioxidants are effective in combating OS and its consequences has been addressed in studies repeatedly. Decreased CVD morbidity and mortality were observed in people on a polyphenol-rich diet, as they had a positive effect on SOD and GPx function while reducing MDA levels. Selenium, which is an active component of the GPx centre, had a positive effect on the reduced / oxidized glutathione ratio, and vitamin E reduced mortality caused by CVD. It should be noted that N-Acetyl Cysteine (NAC) demonstrated significant exogenous antioxidant properties, reducing OS and improving glutathione redox status. It is important to note that part of the studies was experimental and performed on animals, the real results of the use of exogenous antioxidants by patients with CVD are controversial (Lee et al., 2012; Bartekova et al., 2016).

1.4.3. Oxidative Stress and Depression

The literature suggests that OS is the leading cause of D (Bhatt et al., 2020). D pathogenesis is influenced by genetic factors, psychosocial, environmental, and biological factors. A study of the pathophysiology of MDD concludes that it is associated with genetic predisposition, deranged monoamine synthesis, and function, as well as changes in brain function and structure – changes in neuroplasticity, decreased volume of hippocampal and frontal cortex. But one of the main causes of structural change during D is OS. Increased lipid peroxidation has been associated with the presence and severity of depressive symptoms (Mazereeuw et al., 2017). D is associated not only with inflammatory reactions taking place in the body but also with an increased amount of pro-inflammatory cytokines and increased lipid peroxidation leading to oxidative stress (Vaváková et al., 2015).

Studies have suggested that depression was accompanied by oxidative stress dysregulation, including abnormal total antioxidant capacity (TAC), antioxidants, free radicals, oxidative damage, and autoimmune response products (Adifbair et al., 2016; Liu et al., 2015). Preclinical and clinical studies suggest that increased ROS formation and exhaustion of the antioxidant system are responsible for changes in brain structure. The oxidative products include products of oxidative damage of LP, protein, and DNA in depression. Abnormal malondialdehyde (MDA) levels in depression have been reported (Liu et al., 2015; Bal et al., 2012).

As a consequence of OS, pro-inflammatory signalling pathways are activated, and they are associated with D pathogenesis, because, for example, MDD is associated with various inflammatory processes and increased pro-inflammatory cytokine levels, and reduced nerve growth (Chauvet-Géliniera et al., 2013).

It should be noted that the negative effects of OS become more expressed with age. OS in the brain not only damages neuronal DNA but also causes molecular abnormalities that lead to psychological conditions. ROS is closely associated with a number of pathophysiological processes, including inflammation, mitochondrial dysfunction, hypoactive NMDA receptor, and the impairment of fast-spiking GABA interneurons (Kaya et al., 2012).

These facts suggest that OS is associated with neurodegeneration. Elevated ROS modulate the HPA axis and this in turn alters GABA and serotonergic transmission. Activation of the HPA axis increases the levels of OS and glucocorticoids released during stress. The literature suggests that treatment of patients with D with antidepressants leads to suppression of the HPA axis (Bhatt et al., 2020; Chauvet-Géliniera et al., 2013).

Increased ROS and amplified expression of the genes correlate with MDD pathogenesis and its progress. The brain is much more susceptible to the negative effects of OS and ROS than all other organs because the brain is a major oxygen consumer and is rich with oxidizable lipids. Increased oxygen consumption leads to increased ROS. Changes in the balance between ROS and the antioxidant system cause changes in brain function and changes in neuronal signalling. It should be noted that physiological ROS levels are important in the maintenance and regulation of vital physiological functions (Bhatt et al., 2020).

Elevated lipid peroxidation in the brain is a contributing factor for MDD. The amount of MDA in the brain that is formed as a result of lipid peroxidation indicates OS processes during the depression. Similarly, the activity of antioxidant enzymes such as catalase and superoxide dismutase suggests an important role of OS in D development. One of the indicators is also reduced GSH. When ROS production exceeded the ability of the antioxidant system to deal with them, massive protein oxidation and lipid peroxidation began. This is important for

the brain, as it has not only a high lipid content but also increased energy requirements. As a result of the chain reaction, apoptosis is activated in the neurons, leading to neuronal death (Pinchuk et al., 2019; Bhatt et al., 2020).

Patients with D have markedly lower plasma levels of antioxidants, such as zinc, Q10, vitamin E and GSH (especially important as they regulate and regenerate immune cells), compared to healthy individuals, and have reduced antioxidant capacity. The activity of antioxidant enzymes in patients with D is also reduced – GPx activity is significantly lower, which allows ROS to accumulate. This reduced activity correlates with the severity of depression and neuroprogression. It should be noted that some studies did not reveal any differences between GPx levels in patients with D and controls. Therefore, it can be assumed that GPx activity in patients with D is not completely clear (Kaya et al., 2012; Bhatt et al., 2020). But it is possible that higher GPx activity could have been a compensatory mechanism for the excess production of free radicals in depressed patients (Liu et al., 2015).

Also, when comparing serum MDA levels, the study authors conclude that it is higher in patients with MDD compared to controls. Also, when testing in groups of patients with other conditions, if the patient also has D, MDA levels are higher (Bhatt et al., 2020).

According to data, D symptoms due to OS are more expressed in obese women. Increased activity of OS biomarkers is observed in both overweight and depressive conditions. Reduced n3-PUFA, OS, and chronic proinflammatory signalling mechanisms are thought to play an important role in D development. It also supports the hypothesis that D pathophysiological processes are based on a combination of OS and inflammation (Bhatt et al., 2020; Trebatická et al., 2017).

Thus, many clinical studies have accordingly associated D with an increase in the level of OS markers and lower overall antioxidant (AO) activity (Adifbair et al., 2016; Cumurcu et al., 2009; Black et al., 2015; Sarandol et al., 2007).

1.4.4. Oxidative stress biomarkers – MDA and GPx

According to the literature, OS biomarkers can be analysed in cells and tissues, blood, urine, saliva, tears, and synovial fluid samples (Armstrong&Stratton, 2016). Heart failure under both acute and chronic conditions is associated with increased levels of OS markers (e.g., MDA, glutathione peroxidase GPx). These findings suggest that CHD status may be determined by OS activity rather than the degree of coronary stenosis. Elevated concentrations of a variety of oxidative stress markers were linked with a more frequent occurrence of cardiac events (Vichova&Motovska, 2013).

One of the most important and extensively studied oxidants is MDA. In the field of modern biology to assess oxidative stress, MDA is an extensively utilized biomarker. MDA is one of the most commonly used indicators of lipid peroxidation (Del Rio et al., 2005), it can also be more resistant than other markers of the late stage (4-HNE, 8-ISO) of lipid peroxidation (Mazereeuw et al., 2017). The MDA molecule is stable and relatively inactive, compared with free radicals, however, it can not only significantly affect the stability and function of cells, but can also be indirectly involved in the OS reaction (Voicehovskis, 2013). And being a marker of lipid peroxidation, the MDA level increases significantly with D (Frey et al., 2006). Results of the studies (Pezeshkian et al., 2001) showed that MDA levels increased significantly in heart diseases.

An important moment is that most potent antioxidant actions are mediated by enzymes, especially superoxide glutathione peroxidase (GPx) (Dhama et al., 2019). The main biological role of GPx in the body is protection against damage caused by free radicals and active forms of oxygen (Vaváková et al., 2015). The level of serum glutathione peroxidase is an excellent measure of the oxidative status of an individual and is most often employed in diagnostics (Dhama et al., 2019). The higher GPx activity could have been a compensatory mechanism for the excess production of free radicals in depressed patients (Liu et al., 2015).

Researchers also reported an increase in MDA and GPx levels in patients with coronary artery disease. GPx activation was significantly higher in patients with coronary artery disease than in healthy controls (Kaya et al., 2012). It was found that serum GPx and MDA were significantly greater in CHD patients than in healthy controls (Cheraghi et al., 2019). Some other investigations have also reported an increase in MDA and GPx levels in patients with CAD (Pezeshkian et al., 2001).

It has been demonstrated that AO enzyme activities are reduced in CHD, and this is linked to increased disease risk. Many studies have indicated that free radical generation increases and AO defences decrease in response to increased OS in CHD patients. Activity levels of the AO enzymes GPx, and non-enzymatic AOs, are considered predictors of CHD (Vichova&Motovska, 2013; Cheraghi et al., 2019).

1.4.5. Oxidative Stress as Mediating Factor Between Depression and Coronary Heart Disease

The hypothesis that inflammation and OS are factors in both mood disorders and CHD seems to be growing stronger (Chauvet-Géliniera et al., 2013). Increased lipid peroxidation may be particularly relevant to depressive symptoms among patients with coronary artery disease (CAD) given the involvement of oxidative stress in that condition (Mazereeuw et al., 2017).

Moreover, other researches confirm that the OS directly increases the risk of D in patients with CVD whereas it increases the risk of CVD in depressed people. In summary, the common risk factors increase the production of OS and reduce AO defences, thereby promoting the occurrence and development of interacted ischemic CVD and D (Lin et al., 2019). It has been shown that depressed patients have elevated levels of platelet adhesion and aggregation leading to increased risk for cardiovascular events (Nezafati et al., 2015). OS can independently and directly affect stroke, CHD, and D (Lin et al., 2019).

Several pieces of evidence have pointed to the involvement of altered tryptophan metabolism in inflammation and the development of mood disorders (Mattina et al., 2019). Higher levels of serum kynurenine compared with tryptophan (KYN / TRP ratio), have been demonstrated in CVD patients and provide evidence for altered kynurenine synthesis (Wirleitner et al., 2003). The KYN / TRPratio, as well as other kynurenine metabolites, are strongly associated with an increased risk of poor outcomes following stroke (Brouns et al., 2010) and cardiovascular-related mortality in the general population (Zuo et al., 2016). Furthermore, depressed coronary heart disease patients show greater serum (KYN / TRP) ratio compared with those without depression (Nikkheslat et al., 2015), suggesting that depression coupled with CVD leads to increased activation of the kynurenine pathway (Mattina et al., 2019). Activation of the kynurenine pathway following chronic inflammation is modified to increase the production of neurotoxic metabolites and release reactive oxygen species, resulting in lipid peroxidation and neurodegenerative brain changes (Wang et al., 2015; Jeon&Kim, 2017).

1.4.6. Oxidative Stress and Antidepressant Therapy

Considering the negative cardiac and cognitive effects of persistent D in patients with CHD, adequate treatment with antidepressants is a clinically important need in the case of CHD Patients who respond to antidepressant therapy within the first year of treatment have shown to experience significantly lower rates of morbidity and mortality (Jiang, 2011). Several studies have shown that the new generation of antidepressants, in particular selective serotonin reuptake inhibitors, are well tolerated, have a satisfactory efficacy-tolerance profile, and are easy to use in patients with cardiovascular disease (Chauvet-Géliniera et al., 2013). In addition, these molecules show clinical efficacy, acting on physio-pathological elements by improving endothelial function while reducing the concentration of inflammation markers (C-reactive protein, interleukin-6) (Pizzi et al., 2009). In the same way, a meta-analysis showed that selective serotonin reuptake inhibitors used in the wake of acute coronary syndrome led to fewer rehospitalizations (Chauvet-Géliniera et al., 2013; Mazza et al., 2009).

There is an increasing body of evidence supporting that D may be associated with changes in OS markers and that AD agents (especially long-term treatment) may increase AO defences. Augmentation of AO defences may be one of the mechanisms underlying the neuroprotective effects of ADs observed in the treatment of D (Celano&Huffman, 2011). The meta-analysis supports the fact that the serum total antioxidant capacity (TAC), paraoxonase, and antioxidant levels are lower, and the serum-free radical and oxidative damage product levels are higher than controls in depressed patients. Meanwhile, the antioxidant levels are increased and the oxidative damage product levels are decreased after antidepressant medication (Liu et al., 2015).

The use of SSRIs may prevent the development of atherosclerotic plaques and also arterial thrombosis (Nezafati et al., 2015). Normalization of the levels of Reactive Oxygen species and AO activity after successful AD therapy (Cumurcu et al., 2009) suggests that OS mechanisms can be especially important in the study of the pathophysiology and prognosis of D (Adifbair et al., 2016). Patients with heart failure, who respond to AD therapy within the first year of treatment have been shown to experience significantly lower rates of morbidity and mortality (Jiang et al., 2011). Several lines of evidence indicate that different cardiovascular considerations should be inspected in patients who need to take AD medications (Yekehtaz et al., 2013).

Normalization of the levels of reactive oxygen species and antioxidant (AO) activity after successful antidepressant (AD) therapy (Cumurcu et al., 2009) suggests that OS mechanisms can be especially important in the study of pathophysiology and prognosis of D (Adifbair et al., 2017).

1.5. Summary of the literature

In this part were reviewed epidemiological and pathophysiological aspects underline the frequent co-occurrence of D and CVD. OS is considered an emergency mechanism that relates to both CVD and D pathophysiology (Adifbair et al., 2016). OS directly increases the risk of D in patients with CVD, whereas it increases the risk of CVD in depressed people. Furthermore, OS acts as a link between ischemic CVD and D (Lin et al., 2019). Despite the potentially important role of the OS in the pathogenesis of CHD and D, only a few researchers studied the role of OS in the development of D in patients with CHD. Furthermore, the role of OS in stable CHD (SCHD) recurrence in patients with SCHD and D has not been studied previously.

Clinicians should investigate the presence of D in patients with heart disease. When D screening is paired with a management protocol or system of care (e.g., a care management program) to treat D in persons with CVD, there has been consistent evidence for improved

patient outcomes (including, in some studies, improved adherence, reduced cardiac symptoms, reduced cardiac events, and improved blood pressure and lipids). Patients who meet the full criteria for D should be treated, whether cardiac events are recent or remote (Celano&Huffman, 2011).

Assessment of oxidative stress markers could modify risk stratification, diagnosis and prevention, and treatment of patients with both coronary artery disease and depression, in patients with and without previous cardiac history (Vichova&Motovska, 2013). Appropriate, individualized antidepressant therapy by reducing the level of oxidative stress may help reduce the risk of SVD (both primary event and recurrence) in patients with depression. This requires further longitudinal, large-sample-size, cohort studies to provide more conclusive outcomes.

2. Methods

It is a retrospective case-control study that was conducted to compare patients with PSCHD with patients who have RSCHD by determining oxidative markers levels and D signs and severity. No intervention was attempted to alter the course of the SCHD.

2.1. Study participants and research locale

To test the hypothesis that patients with RSCHD have higher OS and D scores than patients with PSCHD, it was decided to create two groups of patients and compare them by OS marker levels and D symptoms and their severity. Re-evaluation of the same patients (who were diagnosed with PSCHD and subsequently hospitalized with RSCHD) was not performed due to geographical barriers, difficulties in communicating with the patient electronically or by telephone, the fact that the actual place of residence of some patients does not match their registered address, the possibility that they will receive further care in another health care facility, as well as taking into account the age of the patients and the relatively high mortality rates. Therefore, it was decided to create two patient groups – with PSCHD and with RSCHD, and to compare one to the other.

2.2. Criteria for inclusion and exclusion of research participants

The inclusion and exclusion criteria for both groups were the same, with the only difference: for PSCHD patients – primary hospitalization due to first event of CHD, while for RSCHD –hospitalization due to recurrent event of CHD.

Inclusion criteria:

a) patients with SCHD – by classification ICD-10: I20 Angina pectoris; I25 Chronic ischemic heart disease;
b) patients are stable, with stable vital signs;
c) age ≥ 45 years;
d) non-smokers;
e) not vegetarian;
f) do not drink alcohol at least during the last 1 year;
g) use prescribed drugs regularly.

Exclusion criteria:

a) patients with diagnoses I21 Acute myocardial infarction; I22 Subsequent ST elevation (STEMI) and non-ST elevation (NSTEMI) myocardial infarction; I23 Certain current complications following ST elevation (STEMI) and non-ST

elevation (NSTEMI) myocardial infarction (within 28 days); I24 Other acute ischemic heart diseases;

b) unstable patients, patients in intensive care unit;
c) age < 45 years;
d) approved diabetes mellitus type 1 and 2;
e) glucose tolerance disturbances;
f) any acute illnesses;
g) irregular usage of prescribed drugs;
h) any F diagnosis;
i) obesity (BMI ≥ 30).

Data on the regularity of medication use and adherence were obtained in the form of a self-report. People who drink alcohol, smoke, or have excluded meat from their diet, as well as patients with low medication adherence, were excluded from the study because these are confounding factors that potentially affect OS levels.

Patients were selected based on convenience, including all patients with PSCHD or RSCHD who met the study inclusion criteria over a certain period. Time period: from November 1, 2015, to July 15, 2017, until the required number of study participants was collected.

The sample size was calculated based on several factors. First of all, it should be taken into account that the calculation requires data on the difference in the prevalence of D between PSCHD and RSCHD patients, but currently, there is no such data on the situation in Latvia. Also, the hospital database does not specifically indicate for which patient the hospitalization is primary and for which it is repeated, at least roughly determine the flow of patients according to these criteria.

According to the Centre for Disease Prevention and Control of the Republic of Latvia, processing statistics by these criteria violates the terms of confidentiality and therefore cannot be provided. For the reasons mentioned above, the sample size was calculated using foreign data, which indicate that 15–18% of patients with medically stable CHD have major depression, and the 1-year prevalence of clinically significant depression is about 30% in these patients (SPKC, 2020a; Carney&Freedland, 2008). Obtaining partial statistical data from the Latvian centr of cardiology, it is known that in 2014, 2264 patients were discharged with the diagnosis I20.8, 909 patients were discharged with the diagnosis I25.1 and 35 patients were discharged with the diagnosis I25.0. As a result, the sample size with 80% statistical power was calculated – 86 study participants in each group.

It should be noted that the selection process in both groups was identical according to the set criteria. A total of 191 people were invited to participate in the study, and 17 patients refused to participate in the study. A total of 174 participants were enrolled in this study:

1) 86 in-patients with a RSCHD;
2) 88 in-patients with a PSCHD.

There were no statistically significant differences between the two groups by gender and age (Chi-square test, $p = 0.1$ and $p = 0.2$, OR $p < 0.05$).

2.3. Research site

The study site was the Latvian Centre of Cardiology in Pauls Stradiņš University Hospital – the leading hospital in cardiology, invasive cardiology, transplantology, vascular diseases, neurology and neurosurgery, and internal medicine in Latvia. It is important to mention, that patients were diagnosed by cardiologists of Latvian Centre of Cardiology.

The Latvian Centre of Cardiology provides a set of highly qualified third-level healthcare services in the field of cardiology (including CHD cases) to patients from all regions of Latvia.

2.4. Ethical aspects

Information about the nature and course of the study was provided to all study participants. Patients filled out an informed consent form and a questionnaire. To ensure the anonymity of personal data, all patient personal data (name, surname) were coded.

All procedures complied with the ethical standards on human experimentation (World Medical Association Helsinki Declaration). The approval for this study was obtained from the Ethics Committee of Riga Stradins University. RSU Ethics Committee's decision to “agree to a study” was received on October 29, 2015 (No. 22/29.10.2015).

2.5. The course of the research

The primary selection of patients was done with the assistance of the Latvian Centre of Cardiology medical staff, including all those who were admitted to the Latvian Centre of Cardiology due to CHD. To understand whether each patient met the study criteria, their medical records were further examined, determining their diagnosis and comorbidities. In cases where the patient met the criteria, he / she was invited to participate in the study. If the prospective study participant agreed, he / she was then interviewed.

Compliance with the study criteria was examined in depth during the interview. If the patient complied, he / she was asked to complete the Latvian version of the Geriatric Depression Scale questionnaire, and the study participant was asked to submit to a blood test in the morning. Patients' blood samples were delivered to the RSU Scientific Laboratory of Biochemistry, where their OS parameters – MDA and GPx – were further analysed.

The RSU Scientific Laboratory of Biochemistry is a certified laboratory involved in the national comparative interlaboratory quality system and is part of the international (Labquality OY, Finland) external quality control system.

2.6. Investigation methods

2.6.1 Analysis of medical records

With the permission of the Latvian Centre of Cardiology, when a potential study participant joined, data from his / her history after the primary doctor's examination were analysed – primary diagnosis, co-morbidity, and examination results, as well as BMI.

2.6.2 Structured interview

The interview was conducted to make sure that the potential study participant met all the criteria of the study, as patients' histories usually do not include data on bad habits, eating habits, and medication adherence.

After getting the necessary information, if the patient met the criteria, he / she was asked to complete the GDS questionnaire.

2.6.3 Geriatric Depression Scale

The severity of depressive symptoms was assessed using the long 30-item form of the Geriatric Depression Scale (GDS), (Yesavage, 1982–1983), a valid Latvian version of GDS-LAT (Voicehovskis, 2013). It is a 30 "yes or no" self-report questionnaire. One point is assigned to each answer and the cumulative score is rated on a scoring grid. The grid sets a range of 0–9 as "normal", 10–19 as "mildly depressed", and 20–30 as "severely depressed".

2.6.4 Blood sample analysis

From each patient the blood samples were taken to measure OS parameters: MDA and GPx.

MDA levels are determined using thiobarbituric acid reactive substance:

a) Test object: plasma (anticoagulant – Li heparin; EDTA).
b) Method: manual, spectrophotometric, according to the manufacturer's instructions.
c) Device: Sunrise Basic absorption microplate reader (*TECAN*, Austria).
d) Reagent kits: *OxiSelect™ TBARS Assay* (MDA *Quantitation*), Cat. STA-330.
e) Manufacturer: *CellBiolabs*, *Inc*. (USA).

The principle of the method: MDA determines the color intensity of the reaction with thiobarbituric acid (TBA) in an acid medium at 95 °C, after optical density in butanol extract at 532 nm. MDA is calculated from the standard curve using the MDA reference substance 1,1,3,3-tetraethoxypropane (Armstrong&Browne, 1994; Armstrong, 1998; Boyum, 1966).

Reference interval: 3,45–7,45 μmol/L. The results are interpreted for scientific purposes because the number of people in the control group is too small to develop reference values.

GPx determination method:

a) Test object: blood (anticoagulant – Li-heparin).
b) Sample preparation: dilute 0.05 ml of heparinized blood with 1 ml of dilution solution and incubate for five minutes at 37 °C; add one ml of Drabkin's reagent, mix well and use for analysis.
c) Method: automatic spectrophotometric, according to the manufacturer's instructions for the RX Daytona RX Daytona Analyser (Randox laboratories, Ltd., Crumlin, UK).
d) Technology code: La / Kim 184.
e) Device: RX Daytona Analyser (Randox laboratories, Ltd., Crumlin, UK).
f) Reagent kit: RANSEL, Cat. No. RS504.
g) Quality control: Calibrator and control – lyophilized bovine serum – RANSEL Control Cat. No. SC 692.
h) Manufacturer: Randox Laboratories, Ltd., Crumlin, UK.

The principle of the method: glutamate peroxidase catalyses the oxidation of glutathione (GSH) in the presence of opaque hydroperoxide. Oxidative glutathione (GSSG) under the influence of glutasereductase (GR) and NADPH transforms into reduced form – GSH, simultaneously oxidizing NADPH to NADP+. Glutathione peroxidase activity corresponds to an absorption drop at 340 nm due to the oxidation of NADPH. One unit corresponds to the

amount of enzyme produced by 1.0 μM NADPH oxidation at NADP+1 minute at 340 nm at 37 °C (Paglia, 1967).

Reference interval:

a) RSU Biochemistry Lab.: 8530 ± 2352 U / L (average ± standard deviation (SD)).

b) RANDOX: 7526 ± 3355 U / L (average ± SD).

2.7. Statistical analysis

Data were analysed using SPSS 23.0 officially licensed software**.** Statistical significance of the prevalence of dependent variables between the strata of independent variables was tested by using the Chi-square test. The normal distribution of parametric variables was checked using the Kolmogorov-Smirnov test. In case of normal distribution, the means of dependent variables were compared between strata of independent variables using the T-test of ANOVA. If the criteria of normal distribution were not met the alternative tests (Mann-Whitney U test and Kruskal-Wallis test) were used. For the detection of correlations between parametric variables Spearman correlation analysis was used (correlation considered as weak if $r < 0.3$, mean, if r is ranged from 0.3–0.8 and as strong if $r > 0.8$). For multivariate analysis linear, binary, and multinomial logistic regressions were applied. Results are considered statistically significant if $p < 0.05$.

3. Results

3.1. Patient demographics

In the study, there were 174 responders participating – 49.4% (n = 86) of them had experienced recurrent SCHD and 50.6% (n = 88) of them formed a control group (patients of primary SCHD).

There were no differences between the distribution of patients in the primary and the recurrent groups by gender and mean age (Figure 3.1).

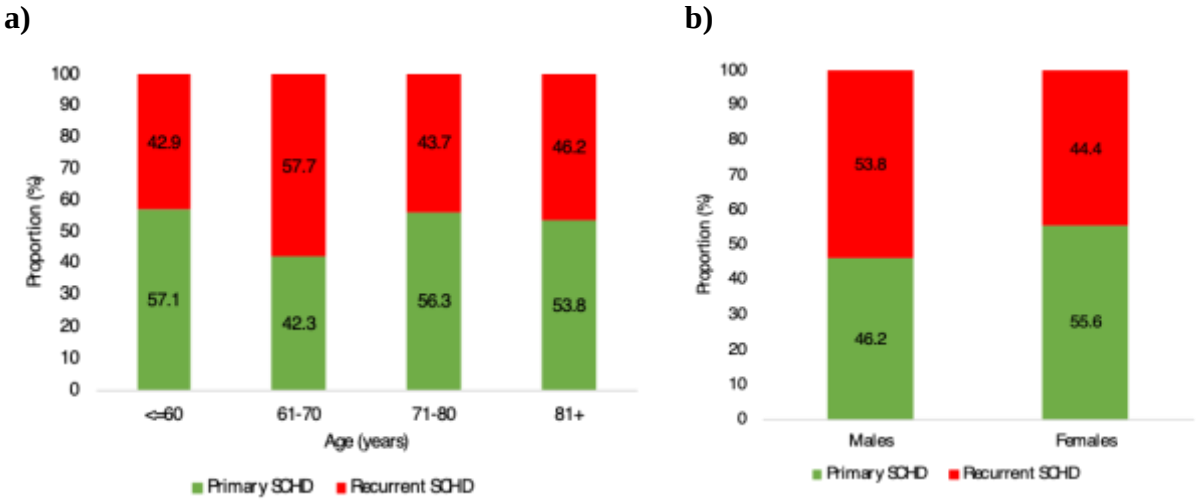

Figure 3.1 **The proportion by age a) and gender b) in patients with PSCHD and RSCHD**

Half of the total sample (53.4%) were males. The majority of the sample (83.9%) had a high level of MDA and for the rest of them, the MDA level was considered normal (i.e., a low level of MDA was not detected for any of the patients). For the majority of the patients (72.4%) the GPx level was normal, for 17.8% it was high, and for 9.8% – low. Slightly more than half of the patients were experiencing a D (44.3% – mild D and 6.9% – severe D) (Table 3.1).

Table 3.1

Description of the sample (total and stratified by SCHD status)

Independent variable	Total		Primary SCHD		Recurrent SCHD		p*
	n	%	n	%	n	%	
Sex							
Male	93	53.4	43	48.9	50	58.1	0.22
Female	81	46.6	45	51.1	36	41.9	

Table 3.1 continued

Independent variable	Total		Primary SCHD		Recurrent SCHD		p*
	n	%	n	%	n	%	
Age							
81+	13	7.5	7	8.0	6	7.0	0.34
71–80	48	27.6	27	30.7	21	24.4	
61–70	71	40.8	30	34.1	41	47.7	
≤ 60	42	24.1	24	27.3	18	20.9	
MDA							
Low	–	–	–	–	–	–	
High	146	83.9	76	86.4	70	81.4	0.37
Normal	28	16.1	12	13.6	16	18.6	
GPx							
Low	31	17.8	17	19.3	14	16.3	**0.003**
High	17	9.8	2	2.3	15	17.4	
Normal	126	72.4	69	78.4	57	66.3	
GDS							
Severe	12	6.9	6	6.8	6	7	0.65
Mild	77	44.3	36	40.9	41	47.7	
No	85	48.9	46	52.3	39	45.3	

* Statistically significant if $p < 0.05$

As Table 3.1 shows, groups of recurrent and primary SCHD did not differ according to any of the aforementioned variables except the GPx level – among patients of recurrent SCHD there was a lower proportion of individuals with a normal level of GPx when compared to primary SCHD patients (66.3% and 78.4%, respectively) ($p = 0.003$).

3.2. MDA level

There was a high MDA level found in 146 patients and a normal MDA level – in 28 patients in both groups together. In the primary SCHD group a high MDA level was in 76 (86,4%) patients, in the recurrent SCHD group a high MDA level was in 70 (81,4%) patients. The mean score was slightly higher in the primary SCHD group, but, based on the binary logistic regression test, there was no statistically significant difference between the subgroups ($p = 0.23$). MDA indicators distribution depending on the deviation from the norm is shown in

Table 3.1. The mean score, minimum, maximum indicators, and standard deviation are illustrated in Table 3.2.

Table 3.2

Factors associated with recurrent SCHD in univariate and multivariate analysis (if independent variables are nonparametric measures)

Independent variable	Primary SCHD		Recurrent SCHD		OR*	95% CI	p**	Adjusted OR*	95% CI	p**
	n	%	n	%						
Sex										
Male	43	46.2	50	53.8	1.45	0.80–2.65	0.22	1.63	0.85–3.12	0.14
Female	45	55.6	36	44.4	1	–	–	1	–	–
Age										
81+	7	53.8	6	46.2	1.14	0.33–3.99	0.83	1.48	0.35–6.28	0.60
71–80	27	56.3	21	43.8	1.04	0.45–2.39	0.93	1.34	0.52–3.43	0.55
61–70	30	42.3	41	57.7	1.82	0.84–3.94	0.13	2.25	0.96–5.31	0.06
< = 60	24	57.1	18	42.9	1	–	–	1	–	–
MDA										
Low	–	–	–	–	–	–	–	–	–	–
High	76	52.1	70	47.9	0.69	0.31–1.56	0.37	0.53	0.22–1.27	0.15
Normal	12	42.9	16	57.1	1	–	–	1	–	–
GPx										
Low	17	54.8	14	45.2	1.00	0.45–2.20	0.99	0.96	0.42–2.19	0.92
High	2	11.8	15	88.2	**9.10**	**1.99–41.37**	**0.004**	**11.29**	**2.31–55.06**	**0.003**
Normal	69	54.8	57	45.2	1	–	–	1	–	–
GDS										
Severe	6	50.0	6	50.0	1.18	0.35–3.95	0.79	0.82	0.18–3.67	0.80
Mild	36	46.8	41	53.2	1.34	0.72–2.49	0.35	1.31	0.66–2.60	0.44
No	46	54.1	39	45.9	1	–	–	1	–	–

*OR – odds ratio; **Statistically significant if $p < 0.05$

In the next part, GPx levels are analysed.

3.3. GPx level

There was found a high GPx level in 17 patients, a low level – in 31, and a normal level in 126 patients in both groups together. In primary SCHD group high GPx level was in 2 (2,3%), patients, low – in 17 (19,35) and normal – in 69 (78,4%) patients. In recurrent SCHD group high GPx level was found in 15 (17, 4%), patients, low – in 14 (16,3 %) and normal – in 57 (66,3%) patients. The mean score was slightly higher in the recurrent SCHD group. Based on the binary logistic regression test, there was no statistically significant difference between the subgroups ($p = 0.06$). GPx indicators distribution depending on the deviation from the norm is shown in Table 3.1. The mean score, minimum, maximum, and standard deviation are illustrated in Table 3.2.

3.4. Depression prevalence and severity

Mild depression was detected in 77 patients (44,3%), and severe depression – in 12 (6,9%) in both groups together. In the primary SCHD group, severe depression was detected in 6 (6,8 %) patients and mild depression – in 36 (40.9%) patients. In the recurrent SCHD group, severe depression was detected in 6 (7%) patients and mild depression – in 41 (47,7%) patients. No depression was found in 46 (52,3 %) in the primary SCHD group and 39 (45,3%) in the recurrent SCHD group. Based on the binary logistic regression test, there was no statistically significant difference between the subgroups ($p = 0.42$) by depression prevalence and severity. GDS distribution depending are shown in Table 3.1. The mean score, minimum, maximum, and standard deviation of the GDS scale are illustrated in Table 3.2.

3.5. Correlation between OS markers

The correlation of OS factors (MDA and GPx indicators) was found to be positive and statistically significant but yet weak ($r = 0.18$, $p = 0.017$) (Figure 3.2).

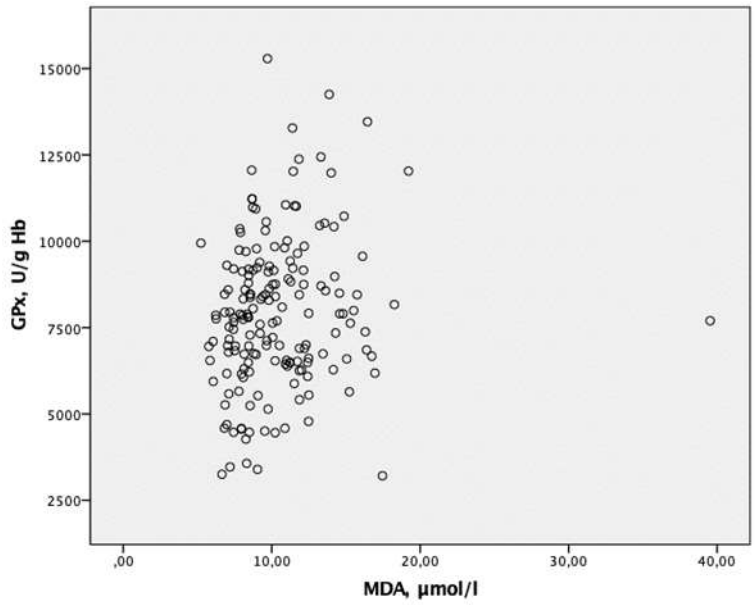

Figure 3.2 **The correlation between GPx and MDA indicators**

The correlation of OS indicators in women with PSCHD was not statistically significant (r = 0.12, p = 0.414) and in men (r = –0.11, p = 0.946) (Figure 3.3).

a) **b)**

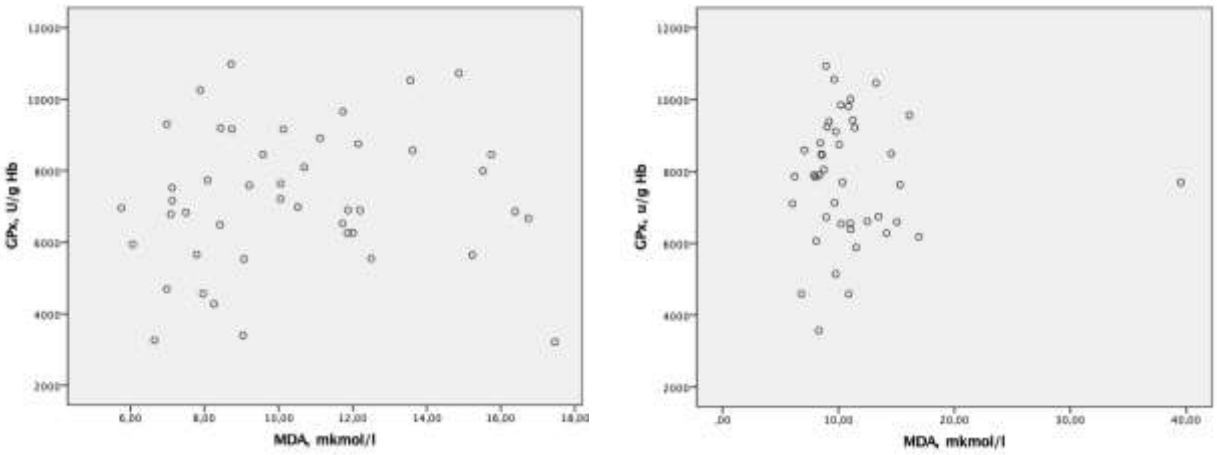

Figure 3.3 **The correlation of OS markers in women (a) and men (b) with PSCHD**

On the contrary, the correlation of OS indicators in women with RSCHD was statistically significant, but low positive (r = 0.39, p = 0.017). The correlation of OS markers in men with RSCHD was not statistically significant (r = 0.26, p = 0.06) (Figure 3.4).

a) **b)**

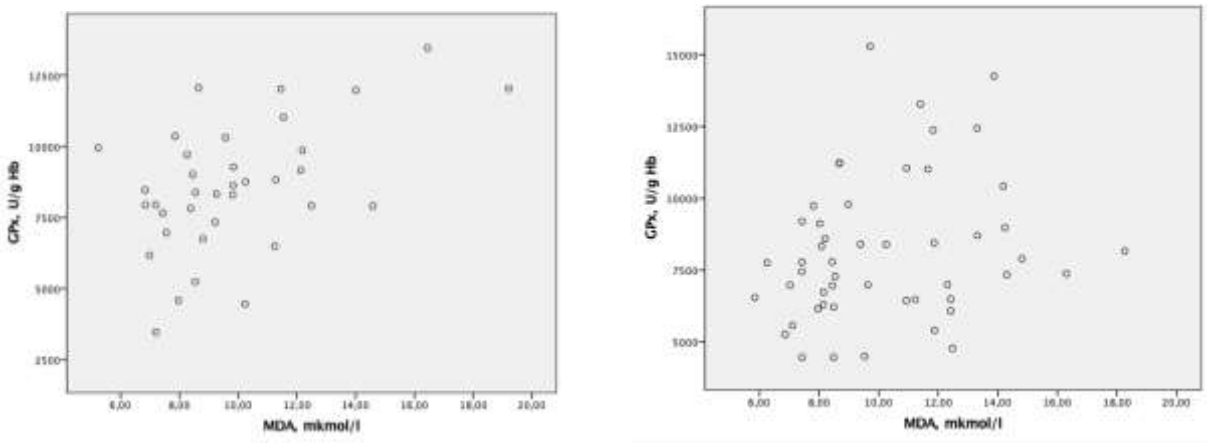

Figure 3.4 **Correlation of OS markers in women (a) and men (b) with RSCHD**

3.6. Factors associated with the recurrent SCHD

When the independent variables are analysed as parametric values, it was found that the only factor statistically different between primary and recurrent SCHD patients, was GPx, i.e., among patients of recurrent SCHD mean GPx value is significantly higher than among patients of primary SCHD (8329.8 and 7474.5 U/g Hb, respectively) (p = 0.01) (see Table 3.2, Figure 3.5).

a) **b)**

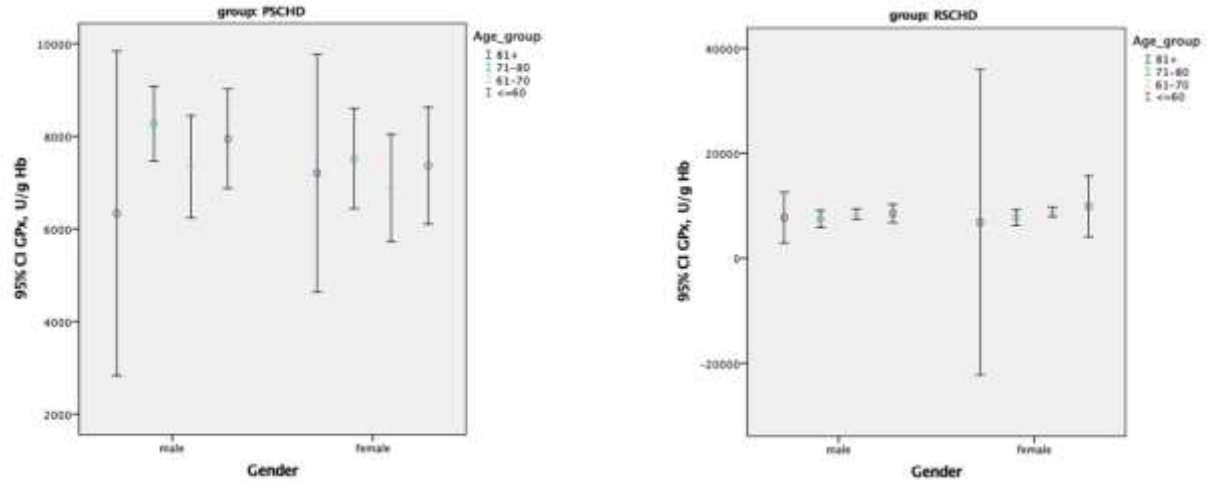

Figure 3.5 **GPx value among patients with PSCHD (a) and RSCHD (b)**

The mean age was slightly higher among patients of primary SCHD as well as the median MDA, whereas the median GDS value was higher among patients with recurrent SCHD. But, as has been mentioned already before, these tendencies cannot be considered statistically significant. The multivariate analysis hasn't changed the conclusion. After the adjustment, the only factor significantly associated with the recurrent status of SCHD was

GPx (p = 0.008). But as regards the measure of OR – the increase in GPx per unit is making so small changes in OR that it was not detectable within two decimal figures. This was the reason why in the further data analysis the parametric measures were categorized and analysed as nonparametric variables.

As it's seen in Table 3.2, there is a tendency for the odds of recurrent SCHD to be higher among males, older patients, and persons with mild D. Interestingly that the odds of recurrent SCHD are lower among patients with high levels of MDA. But these observations are not statistically significant in univariate, or multivariate analyses. The only factor showing stable and statistically significant association with recurrent SCHD is GPx level, i.e., in multivariate analysis independently from other factors high levels of GPx are associated with 11.29 times higher odds of having recurrent SCHD status (p = 0.003).

3.7. Factors associated with the D

Patients with present D were experiencing both – high levels of MDA and GPx – more often than responders with no D (11.2% and 8.2%, respectively). But this trend cannot be considered statistically significant (p = 0.51). And vice versa – among patients with simultaneously high levels of MDA and GPx the prevalence of D is higher than among patients with normal levels of MDA and GPx or with high or low levels of just one of the indicators (58.8% and 50.3%, respectively). And the level of statistical significance of the mentioned observation is surely the same, i.e., not reaching the level of significance (p = 0.51) (Table 3.3).

Table 3.3

Prevalence of high levels of MDA and GPx simultaneously in relation to the presence of D

Status of depression	High both – MDA and GPx		Normal MDA and GPx or high one of them		Total	
	n	%	n	%	n	%
Present	10	11.2	79	88.8	89	100.0
Absent	7	8.2	78	91.8	85	100.0

And vice versa – among patients with simultaneously high levels of MDA and GPx the prevalence of depression is higher than among patients with normal levels of MDA and GPx or with high or low levels of just one of the indicators (58.8% and 50.3%, respectively). And the level of statistical significance of the mentioned observation is surely the same, i.e., not reaching the level of significance (p = 0.51) (see Table 3.4).

Table 3.4

Prevalence of depression according to the status of simultaneously high levels of MDA and GPx

Status of depression	High both – MDA and GPx		Normal MDA and GPx or high one of them	
	n	%	n	%
Present	10	58.8	79	50.3
Absent	7	41.2	78	49.7
Total	17	100.0	157	100.0

If the measures of the severity of depression (GDS) and levels of OS are analysed as parametric variables, there a slightly negative correlation can be observed between GDS and MDA (ρ=–0.035) and a slightly positive correlation between GDS and GPx (ρ=0.087). So, both of the correlations have to be considered as weak. And both of them are lacking statistical significance (p = 0.65 and p = 0.25, respectively) (see Figure 3.6).

a) **b**)

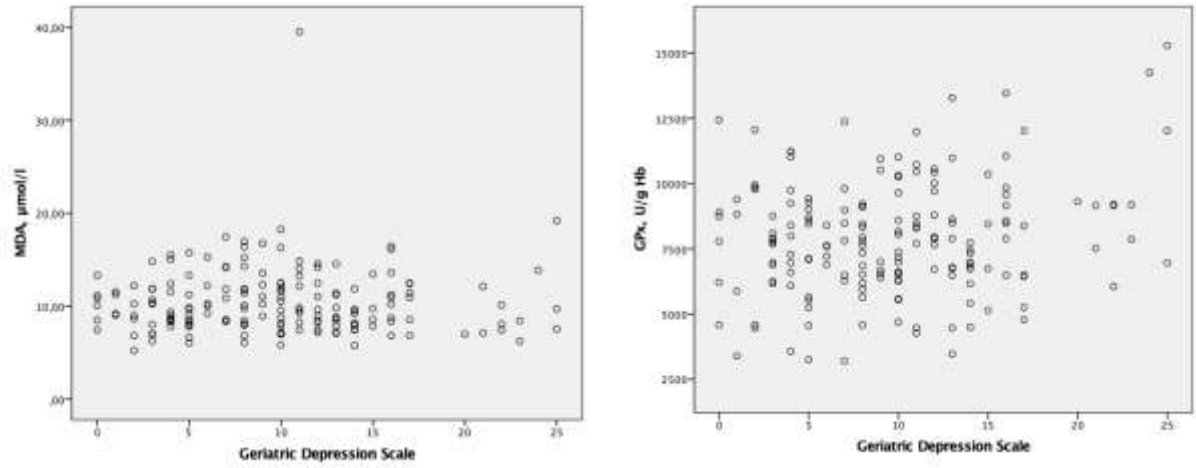

Figure 3.6 **Correlation between GDS and MDA indicator (a) and GDS and GPx indicator (b)**

When the dependent and independent variables are analysed as nonparametric ones, it can be seen from the univariate analysis that there is a tendency that higher odds of severe or mild depression there are for people of older age, for those having high levels of GPx and for people with the recurrent status of SCHD. Whereas odds are lower among males, people with high levels of MDA, and low levels of GPx. But it must be underlined that all the mentioned associations are not statistically significant. The only significant association was found between severe depression and age over 81 years (vs 60 or fewer years OR 18.67; p = 0.006) and mild depression and age group "71–80 years" (vs 60 or fewer years OR 4.51; p = 0.001) (Table 3.5).

Table 3.5

Factors associated with severity of D in univariate analysis

Inde-pendent variable	Severe D		Mild D		No D		OR (severe vs no D)	95% CI	p	OR (mild vs no D)	95% CI	p
	n	%	n	%	n	%						
	12	**6.9**	**77**	**44.3**	**85**	**48.8**						
Sex												
Male	5	5.4	40	43.0	48	51.6	0.55	0.16–1.88	0.34	0.83	0.45–1.55	0.56
Female	7	8.6	37	45.7	37	45.7	1	–	–	1	–	–
Age												
81+	4	30.8	6	46.2	3	23.1	**18.67**	**2.35–148.43**	**0.006**	4.67	1.00–21.81	0.05
71–80	4	8.3	29	60.4	15	31.3	3.73	0.61–22.80	0.15	**4.51**	**1.80–11.32**	**0.001**
61–70	2	2.8	30	42.3	39	54.9	0.72	0.10–5.41	0.75	1.80	0.79–4.10	0.17
< = 60	2	4.8	12	28.6	28	66.7	1	–	–	1	–	–
MDA												
Low	–	–	–	–	–	–	–	–	–	–	–	–
High	8	5.5	63	43.2	75	51.4	0.27	0.07–1.05	0.06	0.60	0.25–1.44	0.25
Normal	4	14.3	14	50.0	10	35.7	1	–	–	1	–	–
GPx												
Low	1	3.2	13	41.9	17	54.8	0.45	0.05–3.84	0.46	0.82	0.37–1.84	0.63
High	3	17.6	7	41.2	7	41.2	3.27	0.70–15.25	0.13	1.07	0.35–3.24	0.91
Normal	8	6.3	57	45.2	61	48.4	1	–	–	1	–	–
SCHD												
Recurrent	6	7.0	41	47.7	39	45.3	1.18	0.35–3.95	0.79	1.34	0.72–2.49	0.35
Primary	6	6.8	36	40.9	46	52.3	1	–	–	1	–	–

After the adjustment (see Table 3.6) the association between older age and severe or mild depression became stronger.

Table 3.6

Factors associated with severity of D in multivariate analysis

Independent variable	aOR (severe vs no D)	95% CI	p	aOR (mild vs no D)	95% CI	p
Sex						
Male	0.48	0.12–1.93	0.30	0.91	0.47–1.76	0.79
Female	1	–	–	1	–	–
Age						
81+	**38.01**	**3.35–431.96**	**0.003**	**5.43**	**1.10–26.77**	**0.04**
71–80	5.89	0.72–48.40	0.10	**4.63**	**1.80–11.92**	**0.002**
61–70	0.69	0.08–5.82	0.73	1.75	0.75–4.09	0.19
< = 60	1	–	–	1	–	–
MDA						
Low	**–**	**–**	**–**	**–**	**–**	**–**
High	**0.16**	**0.03–0.82**	**0.03**	0.60	0.23–1.53	0.28
Normal	1	–	–	1	–	–
GPx						
Low	0.19	0.02–1.95	0.16	0.67	0.28–1.63	0.38
High	**11.69**	**1.60–85.46**	**0.02**	1.66	0.52–5.27	0.39
Normal	1	–	–	1	–	–
SCHD						
Recurrent	0.93	0.15–5.95	0.94	1.39	0.58–3.34	0.46
Primary	1	–	–	1	–	–

Thus, it can be concluded that the age of 81 years or older increases the odds of severe depression 38.01 times (p = 0.003) (when compared to people of the age 60 years or less) and increases the odds of mild depression 5.54 times (p = 0.04). And the age of 71–80 years increases the odds of mild depression 4.63 times when compared to younger patients.

Also, both indicators of oxidative stress are showing statistically significant associations with severe depression. High GPx levels are increasing the odds of severe depression 11.69 times (p = 0.02) independently from other factors (including SCHD status). Whereas high

levels of MDA are decreasing the odds of severe depression more than six times (OR 0.16; p = 0.03).

The rest of the factors (sex and the status of SCHD) are not showing significant associations with D.

3.8. Factors associated with the recurrent SCHD in relation to the presence of D

If only people with D were analysed (n=89), the findings remained the same as for the total sample – the only factor significantly increasing the odds of experiencing recurrent SCHD was the high level of GPx (OR 12.76; p = 0.03). As regards the other factors – there was a tendency that higher odds of experiencing recurrent SCHD for males and people aged 61–71 (compared to the younger ones). People with high levels of MDA are having almost 40% lower odds of experiencing recurrent SCHD. But the mentioned tendencies cannot be considered statistically significant (see Table 3.7).

Table 3.7

Factors associated with recurrent SCHD in univariate and multivariate analysis among patients with D

Independent variable	Primary SCHD		Recurrent SCHD		OR*	95% CI	p**	Adjusted OR*	95% CI	p**
	n	%	n	%						
Sex										
Male	20	44.4	25	55.6	1.25	0.54–2.88	0.60	1.16	0.46–2.91	0.76
Female	22	50.0	22	50.0	1	–	–	1	–	–
Age										
81+	7	70.0	3	30.0	0.32	0.06–1.79	0.20	0.56	0.09–3.71	0.55
71–80	17	51.5	16	48.5	0.71	0.20–2.49	0.59	1.43	0.33–6.15	0.63
61–70	12	37.5	20	62.5	1.25	0.34–4.49	0.73	2.60	0.58–11.78	0.22
< = 60	6	42.9	8	57.1	1	–	–	1	–	–
MDA										
Low	–	–	–	–	–	–	–	–	–	–
High	34	47.9	37	52.1	0.87	0.31–2.46	0.79	0.64	0.21–1.97	0.44
Normal	8	44.4	10	55.6	1	–	–	1	–	–
GPx										
Low	5	35.7	9	64.3	2.23	0.68–7.40	0.19	3.04	0.80–11.60	0.10
High	1	10.0	9	90.0	**11.18**	**1.34–93.37**	**0.03**	**12.76**	**1.34–121.84**	**0.03**
Normal	36	55.4	29	44.6	1	–	–	1	–	–

* OR – odds ratio; **Statistically significant if p < 0.05

Further – by switching the D and SCHD from being the dependent variables to being independent ones (and making markers of oxidative stress the dependent variables), it can be concluded that high levels of GPx are more frequent among patients of recurrent SCHD regardless of the status of depression whereas the low levels of GPx are more prevalent among primary SCHD patients with no depression. These tendencies seem to be statistically significant ($p = 0.02$). When the four strata of depression and SCHD status are further compared pairwise, it is concluded that the high levels of GPx are significantly more frequent within the group "depression and recurrent SCHD" (19.1%) than within the groups "no depression and primary SCHD" (2.2%; $p = 0.03$) or within the group "depression and primary SCHD" (2.4%; $p = 0.03$). The rest of the pairwise combinations are not statistically significant (see Table 3.8).

Table 3.8

Prevalence of high levels of GPx in relation to the presence of D and recurrent SCHD

Status of depression in relation to SCHD	Low GPx		High GPx		Normal GPx	
	n	%	n	%	n	%
Depression + recurrent SCHD	9	19.1	9	19.1*^	29	61.7
Depression + primary SCHD	5	11.9	1	2.4^	36	85.7
No depression + recurrent SCHD	5	12.8	6	15.4	28	71.8
No depression + primary SCHD	12	26.1	1	2.2*	33	71.7

* $p = 0.03$, ^$p = 0.03$

The same observations are present for high levels of both – MDA and GPx. They are more frequent among patients of recurrent SCHD regardless of the status of depression. And the observation can be considered statistically significant ($p = 0.006$). But when the four strata are further compared pairwise, it is concluded that the high levels of MDA and GPX are significantly more frequent within the group "depression and recurrent SCHD" (19.1%) than within the groups "no depression and primary SCHD" (2.2%; $p = 0.03$) or within the group "depression and primary SCHD" (2.4%; $p = 0.04$) (see Table 3.9).

Table 3.9

Prevalence of simultaneously high levels of MDA and GPx in relation to the presence of D and recurrent SCHD

Status of D in relation to SCHD	High both – MDA and GPx		Normal MDA and GPx or high one of them	
	n	%	n	%
D + recurrent SCHD*^	9	19.1	38	80.9
D + primary SCHD^	1	2.4	41	97.6
No D + recurrent SCHD	6	15.4	33	84.6
No D + primary SCHD*	1	2.2	45	97.8

* p = 0.03, ^p = 0.04, statistically significant if p < 0.05

Tables 3.10 and 3.11 show that the frequency of recurrent SCHD is the highest within the groups with high levels of GPx regardless of the presence of depression when compared to the strata with normal or low levels of GPx. And this tendency is statistically significant (p = 0.006). Analyzing the strata pairwise it is concluded that the prevalence of recurrent SCHD is significantly higher among patients with depression and high levels of GPx (90.0%) when compared to people with no depression and normal or low levels of GPx (42.3%; p = 0.02) or patients with depression but normal or low levels of GPx (48.1%; p = 0.04) (Table 3.10, Figure 3.7).

Table 3.10

Prevalence of simultaneously high levels of MDA and GPx in relation to the presence of D and recurrent SCHD

Status of depression and GPx	Recurrent SCHD		Primary SCHD	
	n	%	n	%
Depression + high GPx*^	9	90.0	1	10.0
No depression + high GPx	6	85.7	1	14.3
Depression + normal or low GPx^	38	48.1	41	51.9
No depression + normal or low GPx*	33	42.3	45	57.7

* p = 0.02, ^p = 0.04

Figure 3.7 shows the prevalence of high levels of GPx in relation to the presence of D.

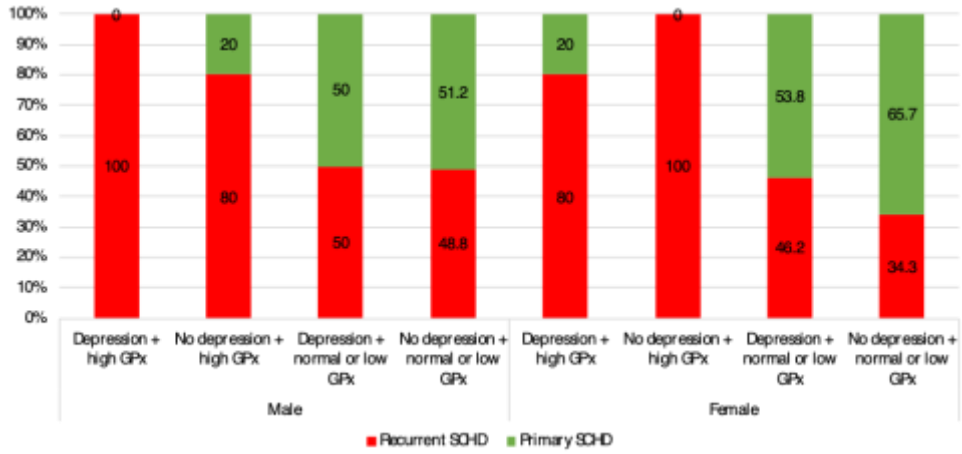

Figure 3.7 **Prevalence of high levels of GPx in relation to the presence of D and recurrent SCHD in men and women**

The levels of MDA are not giving any additional impact on the relationship between the status of depression in combination with levels of GPx and the status of SCHD. The conclusions are identical to the ones described above for the combination of the depression and GPx alone (see Table 3.11, Figure 3.8).

Table 3.11

Prevalence of high levels of MDA in relation to the presence of D and recurrent SCHD

Status of depression, MDA and GPx	**Recurrent SCHD**		**Primary SCHD**	
	n	**%**	**n**	**%**
Depression + high MDA + high GPx	9	90.0	1	10.0
No depression + high MDA + high GPx	6	85.7	1	14.3
Depression + normal MDA + normal or low GPx	38	48.1	41	51.9
No depression + normal MDA + normal or low GPx	33	42.3	45	57.7

* p = 0.02, ^p = 0.04

Figure 3.8 shows the prevalence of high MDA levels in relation to the presence of depression.

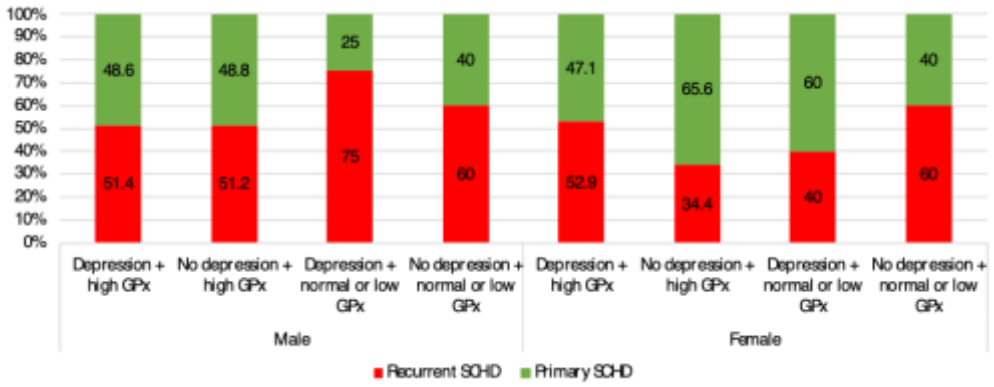

Figure 3.8 **Prevalence of high levels of MDA in relation to the presence of D and recurrent SCHD in men and women**

When the levels of MDA and GPx are analysed as parametric variables, it can be seen that the mean value of MDA is the highest among patients with no depression and primary SCHD (11.04, SD 3.05) and the lowest among people with no depression and recurrent SCHD (9.68, SD 2.40). But the differences in mean MDA among the four strata of depression and SCHD status are not statistically significant ($p = 0.40$) (Figure 3.9).

Whereas for the mean values of GPx the conclusion is the opposite – the mean level is the highest among people with no depression but recurrent SCHD (8458.36, SD 1949.61) and the lowest among patients with no depression and primary SCHD (7011.76, SD 1882.16). I.e., both groups of recurrent SCHD have the highest mean values of GPx regardless of the status of depression. And these observations are statistically significant ($p = 0.008$). Further comparing the mean GPx between strata of the status of D and SCHD it has been found that the mean level of GPx is significantly lower among patients with no depression and primary SCHD when compared to the people with no depression but recurrent SCHD ($p = 0.001$), among patients with depression and primary SCHD ($p = 0.009$) and people with depression and recurrent SCHD ($p = 0.01$) (Figure 3.9).

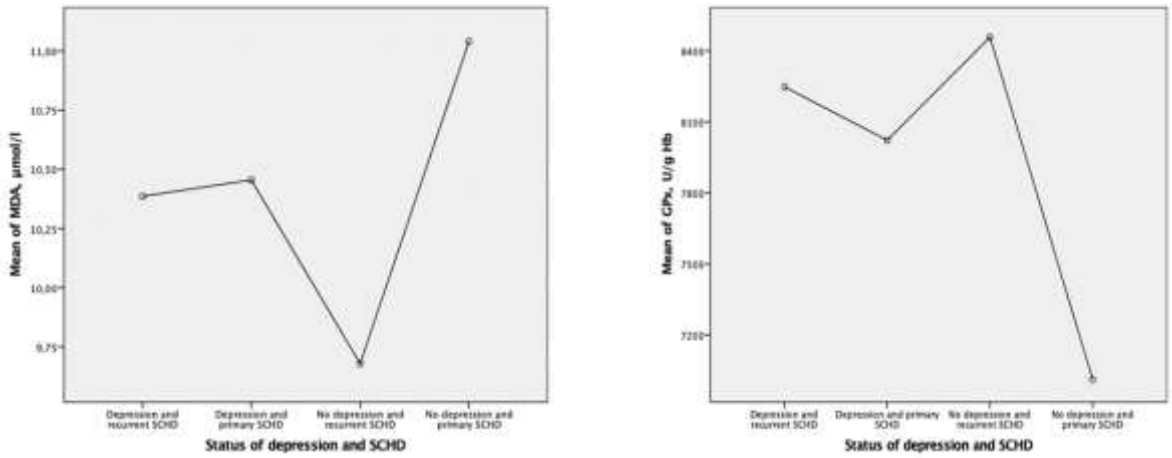

Figure 3.9 **Mean levels of MDA (a) and GPx (b) according to the presence of D and recurrent SCHD**

Further, the cross-tabulation analysis revealed that the group "D + high GPx" had 10.6 times higher chances of recurrent SHCD compared to the "no D + normal GPx" group (Table 3.12).

Table 3.12

Prevalence and odds of recurrent SCHD stratified by the presence of D and the level of GPx

Dependent variables	OR (95% CI)	p
D, low GPx	2.12	0.22
D, high GPx	**10.61**	**0.03**
D, normal GPx	0.95	0.89
No D, low GPx	0.49	0.23
No D, high GPx	7.07	0.08
No D, normal GPx	1	–

Statistically significant if $p < 0.05$.

4. Discussion

As mentioned above, the present study aimed to investigate the relationships between OS level, the prevalence of D, and the risk of recurrent SCHD. The hypothesis was that in recurrent SCHD patients and D would be a higher level of OS than in patients with primary SCHD without D.

4.1. Prevalence of D

The result of the research revealed that the prevalence of D was in 51.2% of all patients, which is in accordance with previous research. Basing on the literature, between 31–45% of patients with coronary heart disease (CHD), including those with stable coronary artery disease, unstable angina, or myocardial infarction (MI), suffer from clinically significant depressive symptoms (Celano&Huffman, 2011).

By our expectations in the recurrent SCHD patients' the prevalence of D was higher (47.7 % in the primary group and 54.7 % in the recurrent group), though the difference between primary and recurrent patients wasn't statistically significant ($p = 0.44$). Multivariate logistic regression results indicated that as the D indicators increase by 1 unit, the chances of recurrent SCHD increase 1.04 times or 4%, but it wasn't statistically significant.

The small difference between groups could be explained by 1) the presence of D a long time before primary hospitalization, not only after the cardiac event; 2) all the patients were enrolled in the research before hospital discharge, which means sometimes after 7–10 days of treatment and adherence to sleep and nutrition. In a study of hospitalized patients with a variety of cardiac conditions, those who met the criteria for clinical depression during admission had improvement in adherence (to diet, exercise, and medication) if their D improved following hospitalization. This suggests that reduced adherence to key secondary prevention behaviours in depressed cardiac patients may be modifiable with the treatment of the depressive symptoms (Bauer et al., 2012).

4.2. OS level

There were analysed two markers of OS: were MDA – lipid peroxidation product, which shows OS level, and antioxidant(AO) enzyme GPx – a marker of the body's defence against OS.

In most of all patients was found high MDA level (in 146 patients, or 83.9 %) from 174, which is similar to the literature. Results of the studies of Pezeshkian et al. (2001). showed that MDA levels increased significantly in heart diseases. Some other investigations have also

reported an increase in MDA and GPx levels in patients with CAD (Armstrong, 1998). Despite our expectations, in the primary SCHD group, the MDA level was slightly higher, though there was no statistically significant difference between the subgroups. Moreover, cross-tabulation analysis indicates that a higher MDA level was in a patient with primary SCHD without depression (in 91.3% of patients). Though there weren't statistically significant differences between subgroups ($p = 0.38$), this tendency could be taken into account.

In turn, the GPx level was significantly higher in the recurrent SCHD subgroup ($p = 0.01$). Multivariate analysis showed that a higher GPx level 11.29-fold increased the risk of SCHD. Kaya et al. (2012), also reported an increase in MDA and GPx levels in patients with coronary artery disease. GPx enzyme activation was significantly higher in patients with coronary artery disease than in healthy controls (Kaya et al., 2012). As well the result of the present research revealed that in patients with recurrent SCHD is a slightly lower GPx level than in patients with primary SCHD. It has been demonstrated that AO enzyme activities are reduced in CHD, and this is linked to increased disease risk. Many studies have indicated that free radical generation increases and AO defences decrease in response to increased OS in CHD patients. Activity levels of the AO enzymes GPx, and non-enzymatic AO, are considered predictors of CHD (Cheraghi et al., 2019).

The discrepancies – higher MDA levels in patients with primary SCHD – can be explained by several factors. First, OS may be an early causative factor in CVD pathology rather than a late consequence (Vaváková et al., 2017) and OS and inflammation develop long before the onset of the first symptoms. We could suppose that OS in recurrent SCHD patients was longer than in the primary, but activation of AO enzymes partially compensated for high OS level. The fact that GPx level was higher in patients with recurrent SHCD, which means antioxidative system defence activation, could confirm this assumption. Second, the use of beta-blockers. All of both groups' patients took beta-blocker therapy during hospitalization. Previous research found that treatment with beta-blockers such as metoprolol, carvedilol, and bisoprolol reduces the levels of OS (Nakamura et al., 2011; Kukin et al., 2011). Unfortunately, in the present study we didn't have information on the use of beta-blockers before hospitalization. We could assume that patients with recurrent SCHD used beta blockers longer than patients with primary SCHD – a long time before hospitalization. The longer beta-blocker use could explain lower MDA levels in the recurrent SCHD group. Third, we did not have data on psychoactive drug use or psychological support of the patients before they were enrolled in the study or other factors that could affect the MDA level.

An interesting finding in the present research was the cross-tabulation analysis indicated that both OS markers (MDA and GPx) together were significantly higher in the recurrent SCHD subgroup, and compared pairwise, it was found that the high levels of MDA and GPx are significantly more frequent within the group “D and recurrent SCHD” than within the groups “no D and primary SCHD” ($p = 0.03$) or within the group “depression and primary SCHD” ($p = 0.04$). Analyzing the strata pairwise it was found that the prevalence of recurrent SCHD is significantly higher among patients with depression and high levels of GPx (90.0%) when compared to people without depression and normal or low levels of GPx ($p = 0.02$) or patients with depression but normal or low levels of GPx ($p = 0.04$). Moreover, as it’s the group “D + high GPx” had 10.6 times higher chances of recurrent SHCD compared to the “no D + normal GPx” group. Hence, we can suppose that OS indeed is a risk factor for SCHD recurrence, especially in patients with D. Although the division into groups of combinations entailed a small number of people in each subgroup, we suggest taking these findings into account in further studies. As mentioned above, these only in-patients before discharge were included in the study, who already observed a certain sleep regimen and diet, and received appropriate treatment and care, which could reduce the symptoms of both depression and OS. That could explain the small number of patients with both depression and OS in each primary and recurrent SCHD subgroup.

There is a need to add that it’s the first research comparing OS and depression in primary and recurrent patients with SCHD. Previous studies compared OS levels in CHD patients and healthy controls. Cheraghi et al (2019), found that serum GPx and MDA were significantly greater in CHD patients than in healthy controls (Cheraghi et al., 2019). Moreover, other researches confirm that the OS directly increases the risk of depression in patients with cardiovascular diseases, whereas it increases the risk of cardiovascular diseases in depressed people. In summary, the common risk factors increase the production of OS and reduce antioxidant defences, thereby promoting the occurrence and development of interacted ischemic CVD and depression (Lin et al., 2019).

Depression, a frequently occurring disease, has a bidirectional relationship with ischemic CVD and partially shares common risk factors (such as obesity and diabetes) and mechanisms (such as inflammation and OS) with CVD, providing a new direction for future research. Based on the literature on patients with CVD, D is often chronic and recurrent. Among patients with CVD hospitalized for acute cardiac events and found to meet criteria for D during or shortly after admission, approximately 50–70% had ongoing depressive symptoms that preceded their cardiac event. This finding is consistent with literature that describes persistent D in patients with stable CAD. Depressed patients with unstable CAD appear to be at even

greater risk for poor cardiac outcomes. OS can independently and directly affect stroke, CHD, and D. Furthermore, OS acts as a link between ischemic CVD and D. (Lin et al., 2019) Several lines of evidence indicate that different cardiovascular considerations should be inspected in patients who need to take AD medications (Yekehtaz et al., 2013). There is an increasing body of evidence supporting that D may be associated with changes in OS markers and that AD agents (especially long-term treatment) may increase AO defences. Augmentation of AO defences may be one of the mechanisms underlying the neuroprotective effects of ADs observed in the treatment of D (Celano&Huffman, 2011). It has been shown that depressed patients have elevated levels of platelet adhesion and aggregation leading to increased risk for cardiovascular events. The use of SSRIs may prevent the development of atherosclerotic plaques and also arterial thrombosis (Nezafati et al., 2015). Patients, who respond to AD therapy within the first year of treatment have been shown to experience significantly lower rates of morbidity and mortality (Yekehtaz et al., 2013).

Further research is necessary to fully understand underlying processes in terms of OS and D, that provoke recurrence of CHD events. In summary, there is a need to find effective therapies to control CVD and D. When D screening is paired with a management protocol or system of care (e.g., a care management program) to treat D in persons with CVD, there has been consistent evidence for improved patient outcomes (including, in some studies, improved adherence, reduced cardiac symptoms, reduced cardiac events and improved blood pressure and lipids). Patients who meet the full criteria for D should be treated, whether cardiac events are recent or remote (Celano&Huffman, 2011). OS directly increases the risk of D in patients with CVD, whereas it increases the risk of CVD in depressed people. The common risk factors increase the production of OS and reduce AO defences, thereby promoting the occurrence and development of interacted ischemic CVD and D (Lin et al., 2019).

4.3. Limitations of the study:

1. There were rather heterogenous groups by age and gender in both groups, which could influence the results. MDA appears to be sensitive to both gender and age. It is significantly lower and shows a greater age dependence in women than in men. The age-dependent slope of the steady state concentration is maximal at the age between 50 and 55 years, indicating that it may be attributed to the change of metabolism in the postmenopausal period. Interestingly, total glutathione decreased with age simultaneously with the increase in MDA (Pinchuk et al., 2019).

2. In the current study there weren’t take into account patients’ anthropometric dates, only persons with BMI > 30 were excluded, based on the literature, there was no clear association between obesity and systemic OS in subjects with BMI add less than 30 kg/m2 (Ito et al., 2019).
3. In the present research authors couldn’t exclude other factors that affect D and / or OS in patients in relation to SCHD recurrence (dietary intake, substance use disorder, chronic somatic disorder, difficult life events no relationships, no family, poor social life, lower socioeconomic status, etc.)

Conclusions

1. More than a half of patients were experiencing mild or severe depression symptoms with higher rates among patients with recurrent stable coronary heart disease.
2. Majority of patients had high levels of MDA with higher rates in patients with primary stable coronary heart disease.
3. GPx level was normal in the majority of patients, but the elevated level was more common among patients with recurrent stable coronary heart disease.
4. MDA level was slightly higher in the primary stable coronary heart disease group without depression. Therefore, increased MDA level is a risk factor for stable coronary heart disease in general but it does not link to depression severity and recurrence of stable coronary heart disease.
5. GPx level was significantly higher in depressed patients with recurrent stable coronary heart disease compared to patients without depression and to patients with primary stable coronary heart disease. Patients with both high GPx and depression had 10.6 times higher chances of recurrent stable coronary heart disease compared to those with normal GPx and without depression.
6. According to the findings of the study we suppose that a high level of GPx is a risk factor for SCHD recurrence, especially in patients with D.

Practical recommendations

1. It is extremely important to measure depression levels in all patients with SCHD.
2. It is important to develop a multidisciplinary approach in SCHD patient treatment, combined with liaison psychiatry.
3. According to available literature data and research results patients with primary and recurrent events of SCHD differ biochemically by OS markers, therefore it is important to analyse the necessity to revise treatment options and combinations, for example, antidepressant and / or AO use in each case individually. We might suggest timely use antidepressants can reduce the risk of rehospitalization and increase expenses connected with treatment.
4. As GPx is a more significant marker of the risk of depression and recurrence of stable coronary heart disease, it is important to implement GPx in diagnostics at an early stage of SCHD.

Bibliography

1. Adifbair, A., Saleem, M., Lanctôt, K. and Herrmann, N. 2016. Potential biomarkers for depression associated with coronary artery disease: a critical review. *Curr Mol Med.* 16, 137–164. DOI: 10.2174/1566524016666160126144143
2. Amadio, P., Zara, M., Sandrini, L., Ieraci, A. and Barbieri, S. S. 2020. Depression and Cardiovascular Disease: The Viewpoint of Platelets. *International Journal of Molecular Sciences*. 21(20), 7560. https://doi.org/10.3390/ijms21207560
3. Amelirad, A., Shamsasenjan, K., Akbarzadehlaleh, P. and Sarvar, D. P. 2019. Signalling Pathways of Receptors Involved in Platelet Activation and Shedding of These Receptors in Stored Platelets. *Adv. Pharm. Bull*. 9, 38–47.
4. An, E., Nolty, A., Rensberger, J., Hennig, N., Amano, S. and Buckwalter, J. 2016. B-65 Heart rate variability as an index of stress resilience. *Arch Clin Neuropsychol*. 31(6), 637.3–637. doi:10.1093/arclin/acw043.140
5. Antoniades, C., Antonopoulos, A. S., Bendall, J. K. and Channon, K. M. 2009. Targeting redox signalling in the vascular wall: from basic science to clinical practice. *Curr Pharm Des.* 15(3), 329–342. DOI: 10.2174/138161209787354230
6. Appelhans, B. M. and Luecken, L. J. 2006. Heart rate variability as an index of regulated emotional responding. *Rev Gen Psychol.*10 (3), 229–240. doi:10.1037/1089-2680.10.3.229
7. Armstrong, D. and Browne, R. 1994. The analysis of free radicals, lipid peroxides, antioxidant enzymes and compounds related to oxidative stress as applied to the clinical chemistry laboratory. *Free Radicals in Diagnostic Medicine*. 366, 43–58.
8. Armstrong, D. 1998. Free Radicals and Antioxidant Protocols. *Methods Mol Biol*. 108, 315–324.
9. Armstrong, D. and Stratton, D. 2016. *Oxidative Stress and Antioxidant Protection*. John Wiley&Sons, New Jersey. 281–307
10. Athira, K. V., Bandopadhyay, S., Samudrala P. K., Naidu, V. G. M., Lahkar, M. and Chakravarty, S. 2020. An Overview of the Heterogeneity of Major Depressive Disorder: Current Knowledge and Future Prospective. *Curr Neuropharmacol.* 18(3), 168–187. doi: 10.2174/1570159X17666191001142934. PMID: 31573890; PMCID: PMC7327947.
11. Bal, N., Acar, S. T., Yazici, A., Yazici, K. and Tamer, L. 2012. Altered levels of malondialdehyde and vitamin E in major depressive disorder and generalized anxiety disorder. *Journal of Psychiatry&Neurological Sciences.* 25(3), 206–211. DOI: 10.5350/DAJPN2012250302
12. Bartekova, M., Barancik, M. and Dhalla, N. S. 2016. Role of Oxidative Stress in Subcellular Defects in Ischemic Heart Disease. Biochemistry of Oxidative Stress. Physiopathology and Clinical Aspects. Springer International Publishing Switzerland. 129–141.
13. Barth, J., Schumacher, M. and Herrmann-Lingen, C. 2004. Depression as a risk factor for mortality in patients with coronary heart disease: a meta-analysis. *Psychosom Med.* 66(6), 802–813. doi: 10.1097/01.psy.0000146332.53619.b2
14. Bauer, L. K., Caro, M. A., Beach, S. R., Mastromauro, C. A., Lenihan, E., Januzzi, J. L. and Huffman, J. C. 2012. Effects of depression and anxiety improvement on adherence to medication and health behaviours in recently hospitalized cardiac patients. *Am J Cardiol.* 109(9), 1266–1271. https://doi.org/10.1016/j.amjcard.2011.12.017
15. Bhatt, S., Nagappa, A. N. and Patil, C. R. 2020. Role of oxidative stress in depression. *Drug Discovery Today*. doi:10.1016/j.drudis.2020.05.001
16. Birkenhäger, T. K., Geldermans, S., Broek, W. W. V. D., Van Beveren, N. and Fekkes, D. 2012. Serum brain-derived neurotrophic factor level in relation to illness severity and episode duration in patients with major depression. *J. Psychiatr. Res.* 46, 285–289.

17. Black, C. N., Bot, M., Scheffer, P. G., Cuijpers, P. and Penninx, B. W. 2015. Is depression associated with increased oxidative stress? A systematic review and meta-analysis. *Psychoneuroendocrinology*. 51, 164–175. https://doi.org/10.1016/j.psyneuen.2014.09.025

18. Boyum, A. 1966. *J. of Clinical Investigation.* 21: Supplement 97.

19. Brouns, R., Verkerk, R., Aerts, T., Surgeloose D., Wauters, A., Scharpé, S. and De Deyn, P. P. 2010. The role of tryptophan catabolism along the kynurenine pathway in acute ischemic stroke. *Neurochem Res.* 35(9), 1315–1322. https://doi.org/10.1007/s11064-010-0187-2

20. Brown, A. D., Barton, D. A. and Lambert, G. W. 2009. Cardiovascular abnormalities in patients with major depressive disorder: autonomic mechanisms and implications for treatment. *CNS Drugs*. 23(7), 583–602. https://doi.org/10.2165/00023210-200923070-00004

21. Carney, R. M. and Freedland, K. E. 2008. Depression in patients with coronary heart disease. *Am J Med.* 121(11 Suppl 2), S20-S27. https://doi.org/10.1016/j.amjmed.2008.09.010

22. Carney, R. M., Blumenthal, J. A., Freedland, K. E., Youngblood M. et al. 2004. Depression and late mortality after myocardial infarction in the Enhancing Recovery in Coronary Heart Disease (ENRICHD) study 2004. *Psychosom Med.* 66, 466–474.

23. Cassano, P. and Fava, M. 2002. Depression and public health: an overview. *J Psychosom Res.* 53(4), 849–57. https://doi.org/10.1016/S0022-3999(02)00304-5

24. Celano, C. M. and Huffman, J. C. 2011. Depression and cardiac disease: a review. *Cardiol Rev.* 19(3), 130–142. doi: 10.1097/CRD.0b013e31820e8106

25. Chauvet-Géliniera, J. C., Trojak B., Vergès-Patois B., Cottin Y. and Bonin B. 2013. Review on depression and coronary heart disease. *Arch Cardiovasc Dis.* 106(2), 103–110. https://doi.org/10.1016/j.acvd.2012.12.004

26. Cheraghi, M., Ahmadvand, H., Maleki, A., Babaeenezhad, E., Shakiba, S. and Hassanzadeh, F. 2019. Oxidative stress status and liver markers in coronary heart disease. *Rep Biochem Mol Biol.* 8(1), 49–55.

27. Cooper, D. C, Milic, M. S., Tafur, J. R. et al. 2010. Adverse impact of mood on flow-mediated dilation. *Psychosomatic Medicine*. 72(2), 122–127.

28. Cumurcu, B. E., Ozyurt, H., Etikan I., Demir S. and Karlidag R. 2009. Total antioxidant capacity and total oxidant status in patients with major depression: impact of antidepressant treatment. *Psychiatry Clin Neurosci.* 63(5), 639–645. https://doi.org/10.1111/j.1440-1819.2009.02004.x

29. Del Rio, D., Stewart, A. J. and Pellegrini, N. 2005. A review of recent studies on malonaldehyde as toxic molecule and biological marker of oxidative stress. Nutr Metab Cardiovasc Dis. 15(4), 316–328. https://doi.org/10.1016/j.numecd.2005.05.003

30. Dhama, K., Latheef, S. K., Dadar, M., Samad, H. A., Munjal, A., Khandia, R., Karthik, K., Tiwari, R., Yatoo, M. I., Bhatt, P., Chakraborty, S., Singh, K. P., Iqbal, H., Chaicumpa, W. and Joshi, S. K. 2019. Biomarkers in stress related diseases/disorders: diagnostic, prognostic, and therapeutic values. *Front Mol Biosci.* 6, 91. https://doi.org/10.3389/fmolb.2019.00091

31. Dhar, A. K. and Barton, D. A. 2016. Depression and the Link with Cardiovascular Disease. *Front Psychiatry.* 7, 33. https://doi.org/10.3389/fpsyt.2016.00033

32. European Health Information Gateway. Mortality rates, 2017. WHO https://gateway.euro.who.int/en/hfa-explorer/

33. Ērglis, A., Dzērve-Tāluts, V. un Bajāre, I. 2020. *Latvijas iedzīvotāju kardiovaskulāro un citu neinfekcijas slimību riska faktoru šķērsgriezuma pētījums* [Cross-sectional study of cardiovascular and noninfectious diseases risk factors among Latvia's inhabitants]. Latvijas Universitātes Kardioloģijas un reģeneratīvās medicīnas zinātniskais institūts, Rīga. 13. (in Latvian).

34. Feng, Z., Hu, W., Marnett, L. J. and Tang, M. S. 2006. Malondialdehyde, a major endogenous lipid peroxidation product, sensitizes human cells to UV and BPDE-induced killing and mutagenesis through inhibition of nucleotide excision repair. *Mutat Res.* 601(1–2), 125–136. https://doi.org/10.1016/j.mrfmmm.2006.06.003

35. Fioranelli, M., Bottaccioli, A. G., Bottaccioli, F., Bianchi, M., Rovesti, M. and Roccia, M. G. 2018. Stress and Inflammation in Coronary Artery Disease: A Review. *Psychoneuro-endocrineimmunology Based. Front. Immunol.* 9, 2031. doi: 10.3389/fimmu.2018.02031

36. Frasure-Smith, N. and Lespérance, F. 2010. Depression and cardiac risk: present status and future directions. *Heart.* 96(3), 173–176. http://dx.doi.org/10.1136/hrt.2009.186957

37. Frey, B. V., Valvassori, S. S., Réus, G. Z., Martins, M. R., Petronilho, F. C., Bardini, K., Dal-Pizzol, F., Kapczinski, F. and Quevedo, J. 2006. Changes in antioxidant defence enzymes after d-amphetamine exposure: implications as an animal model of mania. *Neurochem Res.* 31(5), 699–703.

38. Glassman, A. H., Bigger, J. T., Gaffney, M., Shapiro, A. P. and Swenson, J. R. 2006. Onset of major depression associated with acute coronary syndromes: relationship of onset, major depressive disorder history, and episode severity to sertraline benefit. *Arch Gen Psychiatry.* 63(3), 283–288. doi:10.1001/archpsyc.63.3.283

39. World Health Organization, Mendis, S., Puska, P. and Norrving, B. 2011. Global Atlas on cardiovascular disease prevention and control. *World Health Organization*. 155.

40. GBD 2017 Disease and Injury Incidence and Prevalence Collaborators. 2018. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet.* 392(10159), 1789–1858. https://doi.org/10.1016/S2468-1253(19)30333-4

41. GBD 2016 Causes of Death Collaborators. 2017. Global, regional, and national age-sex specific mortality for 264 causes of death, 1980–2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet.* 390(10100), 1151–1210. https://doi.org/10.1016/S0140-6736(17)32152-9

42. Goldstein, M. M. 006. Depression–An independent risk factor for cardiovascular disease. *JAAPA.* 19(9), 40–42.; 44; 46.

43. Goodman, J., Shimbo D., Haas D. C., Davidson K. W. and Rieckmann N. 2008. Incident and recurrent major depressive disorder and coronary artery disease severity in acute coronary syndrome patients. *J Psychiatr Res.* 42(8), 670–675. https://doi.org/10.1016/j.jpsychires.2007.07.004

44. Grace, A. A. 2016. Dysregulation of the dopamine system in the pathophysiology of schizophrenia and depression. *Nat. Rev. Neurosci.* 17, 524–532.

45. Guck, T. P., Kavan, M. G., Elsasser, G. N. and Barone, E. J. 2011. Assessment and treatment of depression following myocardial infarction. *Am Fam Physician.* 64(4), 641–648.

46. Halaris, A. 2017. Inflammation-associated co-morbidity between depression and cardiovascular disease. *Curr Top Behav Neurosci.* 31, 45–70. DOI: 10.1007/7854_2016_28

47. Hasnain, M., Vieweg, W. V., Lesnefsky, E. J. and Pandurangi, A. K. 2011. Depression screening in patients with coronary heart disease: a critical evaluation of the AHA guidelines. *J Psychosom Re.* 71(1), 6–12. https://doi.org/10.1016/j.jpsychores.2010.10.009

48. Häfner, S., Baumert, J., Emeny, R. T. et al. 2012. To live alone and to be depressed, an alarming combination for the renin– angiotensin–aldosterone-system (RAAS). *Psychoneuroendocrinology*. 37, 230–237.

49. De Hert, M., Detraux, J. and Vancampfort, D. 2018. The intriguing relationship between coronary heart disease and mental disorders. *Dialogues Clin Neurosci.* 20(1), 31–40. doi: 10.31887/DCNS.2018.20.1/mdehert

50. Huffman, J. C., Celano, C. M., Beach, S. R., Motiwala, S. R. and Januzzi, J. L. 2013. Depression and cardiac disease: epidemiology, mechanisms, and diagnosis. *Cardiovasc Psychiatry Neurol.* 2013, 695925. https://doi.org/10.1155/2013/695925

51. Huffman, J. C., Mastromauro, C. A., Sowden, G. L., Wittmann, C., Rodman, R. and Januzzi, J. L. 2011. A collaborative care depression management program for cardiac inpatients: depression characteristics and in-hospital outcomes. *Psychosomatics*. 52(1), 26–33. https://doi.org/10.1016/j.psym.2010.11.021

52. Ito, F., Yoko Sono Y. and Ito, T. 2019. Measurement and Clinical Significance of Lipid Peroxidation as a Biomarker of Oxidative Stress: Oxidative Stress in Diabetes, Atherosclerosis, and Chronic Inflammation. *Antioxidants*. 8, 72.

53. James, S. L., Abate, D., Abate, K. H. et al. 2018. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet*. 392(10159), 1789– 1858.

54. Januzzi, J. L., Jr, Stern, T. A., Pasternak, R. C. and DeSanctis, R. W. 2000. The influence of anxiety and depression on outcomes of patients with coronary artery disease. *Arch Intern Med.* 160(13), 1913–1921. doi:10.1001/archinte.160.13.1913

55. Jeon, S. W. and Kim, Y. K. 2017. Inflammation-induced depression: its pathophysiology and therapeutic implications. *J Neuroimmunol.* 313, 92–98. https://doi.org/10.1016/j.jneuroim.2017.10.016

56. Jiang, W., Krishnan, R., Kuchibhatla, M., Cuffe, M. S., Martsberger, C., Arias, R. M., O'Connor, C. M. and SADHART-CHF Investigators. 2011. Characteristics of depression remission and its relation with cardiovascular outcome among patients with chronic heart failure (from the SADHART-CHF Study). *Am J Cardiol.* 107(4), 545–551. https://doi.org/10.1016/j.amjcard.2010.10.013

57. Jones, D. P. and Sies, H. 2015. The redox code. *Antioxid Redox Signal.* 23, 734–746.

58. Kander, M. C., Cui, Y. and Liu, Z. 2017. Gender difference in oxidative stress: a new look at the mechanisms for cardiovascular diseases. *J Cell Mol Med.* 21(5), 1024–1032. https://doi.org/10.1111/jcmm.13038

59. Kaptoge, S., Seshasai, S. R. K., Gao, P. et al. 2014. Inflammatory cytokines and risk of coronary heart disease: new prospective study and updated meta-analysis. *Eur Heart J*. 35, 578–589.

60. Kaya, Y., Çebı, A., Söylemez, N., Demır, H., Alp, H. H. and Bakan, E. 2012. Correlations between Oxidative DNA Damage, Oxidative Stress and Coen-zyme Q10 in Patients with Coronary Artery Disease. *Int J Med Sci.* 9(8), 621–626. doi: 10.7150/ijms.4768

61. Khandaker, G. M., Zuber, V., Rees, J., Carvalho, L., Mason, A. M., Foley, C. N., Gkatzionis, A., Jones, P. B. and Burgess, S. 2020. Shared mechanisms between coronary heart disease and depression: findings from a large UK general population-based cohort. *Mol Psychiatry.* 25(7), 1477–1486. https://doi.org/10.1038/s41380-019-0395-3

62. Khawaja, I. S., Westermeyer, J. J., Gajwani, P. and Feinstein, R. E. 2009. Depression and coronary artery disease: the association, mechanisms, and therapeutic implications. *Psychiatry (Edgmont)*. 6(1), 38–51.

63. Kim, Y.-K., Lee, H.-P., Won, S.-D., Park, E.-Y. et al. 2007. Low plasma BDNF is associated with suicidal behaviour in major depression. *Prog. Neuro-Psychopharmacol. Biol. Psychiatry*. 31, 78–85.

64. Kotseva et al. 2015. EUROASPIRE IV: A European Society of Cardiology survey on the lifestyle, risk factors and therapeutic management of coronary patients from 24 European countries. *European Journal of Preventive Cardiology*.

65. Kuehl, L. K., Penninx, B. W. and Otte, C. 2012. Depression: risk factor for cardiovascular disease. *Nervenarzt*. 83(11), 1379–1384.

66. Kukin, M. L., Kalman, J., Charney, R. H., Levy, D. K., Buchholz-Varley, C., Ocampo, O. N. and Eng, C. 2011. Prospective, randomized comparison of effect of long-term treatment with metoprolol or carvedilol on symptoms, exercise, ejection fraction, and oxidative stress in heart failure. *Pharmaceuticals*. 4, 1099.

67. Kuller, L. H., Arnold, A. M., Psaty, B. M., Robbins, J. A., O'Leary, D. H., Tracy, R. P., Burke, G. L., Manolio, T. A. and Chaves, P. H. M. 2006. 10-year follow-up of subclinical cardiovascular disease and risk of coronary heart disease in the Cardiovascular Health Study. *Arch Intern Med.* 166(1), 71–78. doi:10.1001/archinte.166.1.71

68. Kunugi, H., Hori, N. Adachi and Numakawa, T. 2010. Interface between hypothalamic-pituitary-adrenal axis and brainderived neurotrophic factor in depression. *Psychiatry and Clinical Neurosciences*. 64(5), 447–459.

69. Lewis, S. 2005. Broken heart syndrome: perspectives from East and West. *Adv Mind Body Med.* 21(2), 3–5.

70. Lespérance, F., Frasure-Smith, N., Koszycki, D., Laliberté, M. A., van Zyl, L. T., Baker, B., Swenson, J. R., Ghatavi, K., Abramson, B. L., Dorian, P., Guertin, M. C. and CREATE Investigators. 2007. Effects of citalopram and interpersonal psychotherapy on depression in patients with coronary artery disease: the Canadian cardiac randomized evaluation of antidepressant and psychotherapy efficacy (CREATE) trial. *JAMA.* 297(4), 367–379. doi:10.1001/jama.297.4.367

71. Lin, D., Wang, L., Yan, S., Zhang, Q., Zhang, J. H. and Shao, A. 2019. The Role of Oxidative Stress in Common Risk Factors and Mechanisms of Cardio-Cerebrovascular Ischemia and Depression. *Oxid Med Cell Longev.* 2019, 2491927. https://doi.org/10.1155/2019/2491927

72. Liu, T., Zhong S., Liao, X., Chen J., He, T., Lai, S. and Jia Y. 2015. A Meta-Analysis of Oxidative Stress Markers in Depression. *PLoS One.* 10(10), e0138904. https://doi.org/10.1371/journal.pone.0138904

73. Maes, M., Galecki, P., Chang, Y. S. and Berk, M. 2011. A review on the oxidative and nitrosative stress (O&NS) pathways in major depression and their possible contribution to the (neuro)degenerative processes in that illness. *Prog Neuropsychopharmacol Biol Psychiatry.* 35(3), 676–692. https://doi.org/10.1016/j.pnpbp.2010.05.004

74. Mangge, H., Stelzer, I., Reininghaus, E. Z., Weghuber, D., Postolache, T. Ta and Fuchs, D. 2014. Disturbed tryptophan metabolism in cardiovascular disease. *Curr Med Chem.* 21(17), 1931–7. doi: 10.2174/09298673216661403041055 26.

75. Matthews, K. A., Schott, L. L., Bromberger, J. T., Cyranowski, J. M., Everson-Rose, S. A. and Sowers, M. 2010. Are there bidirectional associations between depressive symptoms and C-reactive protein in mid-life women? *Brain Behav Immu.* 24(1), 96–101. https://doi.org/10.1016/j.bbi.2009.08.005

76. Mattina, G. F., Van Lieshout, R. J. and Steiner, M. 2019. Inflammation, depression and cardiovascular disease in women: the role of the immune system across critical reproductive events. *Ther Adv Cardiovasc Dis.* 13. https://doi.org/10.1177/1753944719851950

77. Mazereeuw, G., Herrmann, N., Andreazza, A. C., Scola, G., Ma, D., Oh, P. I. and Lanctôt, K. L. 2017. Oxidative stress predicts depressive symptom changes with omega-3 fatty acid treatment in coronary artery disease patients. *Brain behav immune.* 60, 136–141. https://doi.org/10.1016/j.bbi.2016.10.005

78. Mazza, M., Lotrionete, M., Biondi-Zoccai, G., Abbate, A., Sheiban, I. and Romagnoli, E. 2010. Selective serotonin reuptake inhibitors provide significant lower re-hospitalization rates in patients recovering from acute coronary syndromes: evidence from a meta-analysis. *J Psychopharmacol*. 24(12), 1785–1792.

79. Moryś, J. M., Bellwon, J., Adamczyk, K. and Gruchała, M. 2016. Depression and anxiety in patients with coronary artery disease, measured by means of self-report measures and clinician-rated instrument. *Kardiol Pol.* 74(1), 53–60. DOI: 10.5603/KP.a2015.0116

80. Motiejunaite, J., Amar, L. and Vidal-Petiot, E. 2020. Adrenergic receptors and cardiovascular e ects of catecholamines. *Ann. d'Endocrinol.*

81. Moylan, S., Berk, M., Dean O. M., Samuni Y., Williams, L. J., O'Neil, A., Hayley, A.C., Pasco, J. A., Anderson, G., Jacka, F. N. and Maes, M. 2014. Oxidative&nitrosative stress in depression: why so much stress? *Neurosci Biobehav Rev.* 45, 46–62. https://doi.org/10.1016/j.neubiorev.2014.05.007

82. Murray, C.J. and Lopez, A.D. 2013. Measuring the global burden of disease. *N Engl J Med.* 369(5), 448–57. DOI: 10.1056/NEJMra1201534

83. Murck, H., Büttner, M., Kircher, T. et al. 2014. Genetic, molecular and clinical determinants for the involvement of aldosterone and its receptors in major depression. *Nephron Physiol*. 128, 17–25.

84. Myers, V., Gerber, Y., Benyamini, Y., Goldbourt, U. and Drory, Y. 2012. Post-myocardial infarction depression: increased hospital admissions and reduced adoption of secondary prevention measures – a longitudinal study. *J Psychosom Res.* 72(1), 5–10. https://doi.org/10.1016/j.jpsychores.2011.09.009

85. Nakamura, K., Murakami, M., Miura, D., Yunoki, K., Enko, K., Tanaka, M., Saito, Y., Nishii, N., Miyoshi, T., Yoshida, M., Oe, H., Toh, N., Nagase, S., Kohno, K., Morita, H., Matsubara, H., Kusano, K. F., Ohe, T. and Hiroshi Ito, H. 2011. Beta-Blockers and Oxidative Stress in Patients with Heart Failure. *Pharmaceuticals*. 4, 1088–1100.

86. Nemeroff, C. B. and Goldschmidt-Clermont, P. J. 2012. Heartache and heartbreak – the link between depression and cardiovascular disease. *Nat Rev Cardiol.* 9(9), 526–539. https://doi.org/10.1038/nrcardio.2012.91

87. Nezafati, M. H, Vojdanparast, M. and Nezafati, P. 2015. Antidepressants and cardiovascular adverse events: A narrative review. *ARYA Atheroscl.* 11(5), 295–304.

88. Nikkheslat, N., Zunszain, P. A, Horowitz, M. A, Barbosa, I. G., Parker, J. A., Myint, A. M., Schwarz, M. J., Tylee, A. T., Carvalho, L. A. and Pariante, C. M. 2015. Insufficient glucocorticoid signalling and elevated inflammation in coronary heart disease patients with comorbid depression. *Brain Behav Immun.* 48, 8–18. https://doi.org/10.1016/j.bbi.2015.02.002

89. Ogyu, K., Kubo, K., Noda, Y., Iwata, Y., Tsugawa, S., Omura, Y., Wada, M., Tarumi, R., Plitman, E., Moriguchi, S., Miyazaki, T., Uchida, H., Graff-Guerrero, A., Mimura, M. and Nakajima, S. 2018. Kynurenine pathway in depression: A systematic review and meta-analysis. *Neurosci Biobehav Rev*. 90, 16–25. doi: 10.1016/j.neubiorev.2018.03.023

90. Paglia, D. V. 1967. Studies on the quantitative and qualitative characterization of erythrocyte glutathione peroxidase. *J. Lab. Clin. Med.* 70, 158–169.

91. Patel, A. 2013. Review: the role of inflammation in depression. *Psychiatr Danub*. 25(Suppl 2), 216–223.

92. Pecina, M., Sikora, M., Avery, E. T., Heernan, J., Peciña, S., Mickey, B. J. and Zubieta, J.-K. 2017. Striatal dopamine D2/3 receptor-mediated neurotransmission in major depression: Implications for anhedonia, anxiety and treatment response. *Eur. Neuropsychopharmacol*. 27, 977–986.

93. Penninx, B. W. 2017. Depression and cardiovascular disease: epidemiological evidence on their linking mechanisms. *Neurosci Biobehav Rev.* 74, 277–286.

94. Pezeshkian, M., Nouri, M., Zahraei, M., Afrasiabi, A. and Abadi, N. A. 2001. Study of MDA, antioxidant vitamins, lipoproteins serum levels and anthropometry parameters in coronary artery disease patients. *Med J Islam Acad Sci.* 14, 5–8.

95. Piepoli, M. F., Hoes, A. W., Agewall, S., Albus, C. et al. 2016. European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice Developed with the special contribution of the European Association for Cardiovascular Prevention&Rehabilitation (EACPR). *European Heart Journal*. 37(29), 2315–2381. https://doi.org/10.1093/eurheartj/ehw106

96. Pinchuk, I., Weberb, D., Kochlikb, B., Stuetzd, W., Toussainte, O., Debacq-Chainiauxe, F., Dollef, M. E., Jansenf, E. H., Gonosg, E. S., Sikorah, E., Breusingd, N., Gradinarui, D., Sindlingerj, T., Moreno-Villanuevaj, M., Burklej, A., Tilman, T. and Gruneb, Lichtenberga, D. 2019. Gender- and age-dependencies of oxidative stress, as detected based on the steady state concentrations of different biomarkers in the MARK-AGE study. *Redox Biology.* 24.

97. Pinter, A., Szabolcs Szatmari, Jr., Horvath,T., Penzlin, A. I., Barlinn,K., Siepmann, M. and Siepmann, T. 2019. Cardiac dysautonomia in depression – heart rate variability biofeedback as a potential add-on therapy. *Neuropsychiatric Disease and Treatment.* 15, 1287–1310.

98. Pizzi, C., Mancini, S., Angeloni, L., Fontana, F., Manzoli, L. and Costa, G. M. 2009. Effects of selective serotonin reuptake inhibitor therapy on endothelial function and inflammatory markers in patients with coronary heart disease. *Clin Pharmacol Ther.* 86(5), 527–532. https://doi.org/10.1038/clpt.2009.121

99. Pizzi, C., Manzoli, L., Mancini, S. and Costa, G. M. 2008. Analysis of potential predictors of depression among coronary heart disease risk factors including heart rate variability, markers of inflammation, and endothelial function. *European Heart Journal*. 29(9), 1110–1117.

100. Polanka, B. M., Berntson, J., Vrany, E. A. and Stewart, J. C. 2018. Are Cardiovascular Risk Factors Stronger Predictors of Incident Cardiovascular Disease in U.S. Adults With Versus Without a History of Clinical Depression? *Annals of behav. med*. 52(12), 1036–1045. DOI: 10.1093/abm/kay007

101. Puppel, K., Kapusta, A. and Kuczyńska, B. 2015. The etiology of oxidative stress in the various species of animals, a review. *J Sci Food Agric.* 95(11), 2179–2184. https://doi.org/10.1002/jsfa.7015

102. Rees, J.N., Florang, V. R., Anderson, D. G. and Doorn, J. A. 2007. Lipid peroxidation products inhibit dopamine catabolism yielding aberrant levels of a reactive intermediate. *Chem Res Toxicol.* 20(10), 1536–1542. https://doi.org/10.1021/tx700248y

103. Reynard, A., Gevirtz, R., Berlow, R., Brown, M. and Boutelle, K. 2011. Heart rate variability as a marker of self-regulation. *Appl Psychophysiol Biofeedback.* 36(3), 209–215. doi:10.1007/s10484-011- 9162-1

104. Roth, G. A., Mensah, G. A., Johnson, C. O., Addolorato, G. et al. 2020. Global Burden of Cardiovascular Diseases and Risk Factors, 1990–2019: Update From the GBD 2019 Study. J Am Coll Cardiol. 76 (25), 2982–3021.

105. Sanchis-Gomar, F., Perez-Quilis, C., Leischik, R. and Lucia, A. 2016. Epidemiology of coronary heart disease and acute coronary syndrome. *Ann Transl Med.* 4(13), 256. doi: 10.21037/atm.2016.06.33

106. Sarandol, A., Sarandol, E., Eker, S. S., Erdinc, S., Vatansever, E. and Kirli, S. 2007. Major depressive disorder is accompanied with oxidative stress: short-term antidepressant treatment does not alter oxidative antioxidative systems. *Hum Psychopharmacol.* 22(2), 67–73. https://doi.org/10.1002/hup.829

107. Schrocksnadel, K., Wirleitner, B., Winkler, C. and Fuchs, D. 2006. Monitoring tryptophan metabolism in chronic immune activation. *Clin Chim Acta.* 364(1–2), 82–90.

108. Sherwood, A. L., Hinderliter, L. L., Watkins, R., Waugh, A. and Blumenthal, J. A. 2005. Impaired endothelial function in coronary heart disease patients with depressive symptomatology. *Journal of theAmerican College of Cardiology.* 46(4), 656–659.

109. Shimizu, E., Hashimoto, K., Okamura, N., Koike, K. et al. 2003. Alterations of serum levels of brain-derived neurotrophic factor (BDNF) in depressed patients with or without antidepressants. *Biol. Psychiatry.* 54, 70–75.

110. Sies, H. and Jones, D. P. 2007. Oxidative stress. In: Fink, G. *Encyclopedia of Stress.* Vol 3, 2nd ed. Elsevier, Amsterdam. 45–48.

111. *SPKC*. 2020. *Mirstība sadalījumā pa galvenajiem nāves cēloņiem, reģioniem, pilsētām un novadiem*. Veselības statistikas datubāze. Pieejams no: https://statistika.spkc.gov.lv/pxweb/lv/Health/Health__Mirstiba/MOR30_Iedzivotaju_mirst_terit_sadalijuma.px/table/tableViewLayout2/

112. *SPKC*. 2020a. *Pacientu ar psihiskiem un uzvedības traucējumiem sadalījums pa diagnozēm.* Veselības statistikas datubāze. Pieejams no: https://statistika.spkc.gov.lv/pxweb/lv/Health/Health__Saslimstiba_Slimibu_Izplatiba__Psihiski_un_uzvedibas_traucejumi/PUT011_dg_abs_relat.px/table/tableViewLayout2/

113. Swardfager, W., Herrmann, N., Marzolini, S., Saleem, M., Farber, S. B., Kiss, A., Oh, P. I. and Lanctôt, K. L. 2011. Major depressive disorder predicts completion, adherence, and outcomes in cardiac rehabilitation: a prospective cohort study of 195 patients with coronary artery disease. *J Clin Psychiatry.* 72(9), 1181–1188. DOI: 10.4088/JCP.09m05810blu

114. Thayer, J. F., Hansen, A. L., Saus-Rose, E. and Johnsen, B. H. 2009. Heart rate variability, prefrontal neural function, and cognitive performance: the neurovisceral integration perspective on self-regulation, adaptation, and health. *Ann Behav Med*. 37(2), 141–153. doi:10.1007/s12160-009-9101-z

115. Tomfohr, M. L., Murphy, M., Miller, G. E. and Puterman, E. 2011. Multiwave associations between depressive symptoms and endothelial function in adolescent and young adult females. *Psychosomatic Medicine*. 73(6), 456–461.

116. Trebatická, J., Dukát, A., Ďuračková, Z. and Muchová, J. 2017. Cardiovascular Diseases, Depression Disorders and Potential Effects of Omega-3 Fatty Acids. *Physiol Res.* 66(3), 363–382. DOI: 10.33549/physiolres.933430

117. Vaccarino, V., Badimon, L., Bremner, J. D., Cenko, E. et all. 2020. Depression and coronary heart disease: 2018 position paper of the ESC working group on coronary pathophysiology and microcirculation. *European heart journal*. *41*(17), 1687–1696.

118. van der Kooy, K., van Hout, H., Marwijk, H., Marten, H., Stehouwer, C. and Beekman, A. 2007. Depression and the risk for cardiovascular diseases: systematic review and meta analysis. Int J Geriatr Psychiatry. 22(7), 613–26. https://doi.org/10.1002/gps.1723

119. van Melle, J.P., de Jonge, P., Spijkerman, T. A., Tijssen, J. G., Ormel, J., van Veldhuisen, D. J., van den Brink, R. H. and van den Berg, M. P. 2004. Prognostic association of depression following myocardial infarction with mortality and cardiovascular events: a meta-analysis. *Psychosom med.* 66(6), 814–822. doi: 10.1097/01.psy.0000146294.82810.9c

120. Vaváková, M., Ďuračková, Z. and Trebatická, J. 2015. Markers of Oxidative Stress and Neuroprogression in Depression Disorder. *Oxid Med Cell Longev*. 2015, 898393. https://doi.org/10.1155/2015/898393

121. Vavakova, M., Trebaticka, J., Dukat, A., Durackova, Z. and Muchova, J. 2017. Cardiovascular Diseases, Depression Disorders and Potential Effects of Omega-3 Fatty Acids. *Physiol. Res.* 66, 363–382.

122. Vichova, T. and Motovska, Z. 2013. Oxidative stress: Predictive marker for coronary artery disease. *Exp clin cardiol.* 18(2), e88–e91.

123. Voicehovskis, V. V., Margolina, J., Voicehovska, J. G. and Miksons, A. 2013. Validation of the Latvian version of the Geriatric depression scale (GDS). *Psychother Psychosom.* 82(S1), 122–123.

124. Vrublevska, J. 2018. *Depresijas izplatība Latvijas vispārējā populācijā un primārajā aprūpē Rīgā un Rīgas rajonā.* Promocijas darbs. Rīga.

125. Wang, Q., Liu, D., Song, P. and Zou, M. H. 2015. Tryptophan- kynurenine pathway is dysregulated in inflammation, and immune activation. *Front Biosci (Landmark Ed).* 20, 1116–1143. doi: 10.2741/4363

126. Whooley, M. A. and Wong, J. M. 2013. Depression and cardiovascular disorders. *Annu Rev Clin Psychol.* 9, 327–354. https://doi.org/10.1146/annurev-clinpsy-050212-185526

127. Wilkins, E., Wilson, L., Wickramasinghe, K., Bhatnagar, P., Leal, J., Luengo-Fernandez, R., Burns, R., Rayner, M.. and Townsend, N. 2017. *European Cardiovascular Disease Statistics 2017.* European Heart Network, Brussels.

128. Wirleitner, B., Rudzite, V., Neurauter, G., Murr, C., Kalnins, U., Erglis, A., Trusinskis, K. and Fuchs, D. 2003. Immune activation and degradation of tryptophan in coronary heart disease. *Eur J Clin Invest.* 33(7), 550–554. https://doi.org/10.1046/j.1365-2362.2003.01186.x

129. Who.int. 2020. Cardiovascular diseases (CVDs). [online] Available at: https://www.who.int/news-room/fact-sheets/detail/cardiovascular-diseases-(cvds). Accessed 10.05.2020

130. Yekehtaz, H., Farokhnia, M. and Akhondzadeh, S. 2013. Cardiovascular considerations in antidepressant therapy: an evidence-based review. *J Tehran Heart Cent.* 8(4), 169–176.

131. Yesavage, A. B. 1982–1983. Development and validation of a geriatric depression screening scale: a preliminary report. *J. Psychiatr. Res.* 17(1), 37–49.

132. Yoshida, T., Ishikawa, M., Niitsu, T., Nakazato, M. et al. 2012. Decreased Serum Levels of Mature Brain-Derived Neurotrophic Factor (BDNF), but Not Its Precursor proBDNF. in Patients with Major Depressive Disorder. *PLoS ONE*. 7(8), e42676. https://doi.org/10.1371/journal.pone.0042676

133. Zuo, H., Ueland, P. M., Ulvik, A., Eussen, S. J., Vollset, S. E., Nygård, O., Midttun, Ø., Theofylaktopoulou, D., Meyer, K. and Tell, G. S. 2016. Plasma biomarkers of inflammation, the kynurenine pathway, and risks of all-cause, cancer, and cardiovascular disease mortality. *Am J Epidemiol.* 183(4), 249–258. https://doi.org/10.1093/aje/kwv242

Annexes

Annex 1

Ethics Committee Permission

Veidlapa Nr. E-9 (2)

RSU ĒTIKAS KOMITEJAS LĒMUMS NR. 22 / 29.10.2015.

Rīga, Dzirciema iela 16, LV-1007
Tel. 67061596

	Komitejas sastāvs	Kvalifikācija	Nodarbošanās
1.	Profesors Olafs Brūvers	Dr.theo.	teologs
2.	Profesore Vija Sīle	Dr.phil.	filozofs
3.	Asoc.prof. Santa Purviņa	Dr.med.	farmakologs
4.	Asoc.prof. Voldemārs Arnis	Dr.biol.	rehabilitologs
5.	Profesore Regīna Kleina	Dr.med.	patalogs
6.	Profesors Guntars Pupelis	Dr.med.	ķirurgs
7.	Asoc.prof. Viesturs Liguts	Dr.med.	toksikologs
8.	Docente Iveta Jankovska	Dr.med.	
9.	Docents Kristaps Circenis	Dr.med.	

Pieteikuma iesniedzējs: **Doktorants Tarass Ivaščenko**
Medicīnas fakultāte

Pētījuma nosaukums: „ Depresijas simptomātika un oksidatīva stresa radītāji saistība ar stabilu Koronāro Sirds Slimību (KSS) gaitu"

Iesniegšanas datums: 28.10.2015.

Pētījuma protokols: Izskatot augstāk minētā pētījuma pieteikuma materiālus (protokolu) ir redzams, ka pētījuma mērķis tiek sasniegts veicot ar pacientiem/dalībniekiem, bez kāda apdraudējuma veselībai un dzīvībai, klīniski-analītisku darbu (asins paraugu ņemšanu un analīzes...), un pacientu/dalībnieku aptauju-anketēšanu, iegūto datu apstrādi un analīzi, kā arī izsakot priekšlikumus. Personu (pacientu, dalībnieku) datu aizsardzība, brīvprātīga informēta piekrišana piedalīties pētījumā un konfidencialitāte tiek nodrošināta. Līdz ar to pieteikums atbilst pētījuma ētikas prasībām.

Izskaidrošanas formulārs: ir

Piekrišana piedalīties pētījumā: ir

Komitejas lēmums: **piekrist** pētījumam

Komitejas priekšsēdētājs Olafs Brūvers Tituls: Dr. miss., prof.

Paraksts

ĒTIKAS KOMITEJA

Ētikas komitejas sēdes datums: 29.10.2015.

Annex 2

Research Permission

P.Stradiņa Klīniskas Universitātes Slimnīcas
Klīnisko pētījumu daļas vadītājam
Prof. *Dr.med.* Dainim Krieviņam

Ārsta-psihoterapeita Tarasa Ivaščenko

iesniegums.

Lūdzu atļaut veikt pētījumu promocijas darbam "Depresijas simptomātika un oksidatīva stresa radītāji saistība ar stabilu Koronāro Sirds Slimību (KSS) gaitu" Paula Stradiņa Klīniskās Universitātes Slimnīcas 27. un 32. nodaļās.
Pētījuma laikā paredzēts veikt 50 pacientu ar stabilu pirmreizējo KSS un 50 pacientu ar recidivējošo KSS anketēšanu, kā arī tiks ņemts asins bioķīmijas analīzem.

Pētījuma izpildīšanas vieta:
RSU Iekšķīgo slimību katedras Propedeitikas kursa bāze,
vadītāja Asoc.prof. *Dr.med.* Jūlija Voicehovska.

Promocijas darba vadītāji:
RSU Iekšķīgo slimību katedras docents *Dr.med.* Vladimirs Voicehovskis,
RSU Iekšķīgo slimību katedras prof. *Dr.med.* Oskars Kalējs

Rīgā, 2015.gada 11.augustā

Ar cieņu,

Tarass Ivaščenko.

Profesors Oskars Kalējs

VSIA "Paula Stradiņa klīniskā universitātes slimnīca"
Zinātniskā institūta direktors
Prof. Dainis Krieviņš
15.09.2015

Annex 3

Informed Consent Form

Izskaidrošanas formulārs pētījuma„ Depresijas simptomātika un oksidatīva stresa radītāji saistība ar stabilu Koronāro Sirds Slimību (KSS) gaitu" dalībniekiem un piekrišanas veidlapa

Labdien!

Aicinām Jūs piedalīties pētījumā „ **Depresijas simptomātika un oksidatīva stresa radītāji saistība ar stabilu Koronāro Sirds Slimību (KSS) gaitu.**". Lūdzam Jūs nodot asinis un aizpildīt anonīmu pētījuma anketu. Jums ir tiesības attiekties no anketas aizpildīšanas. Pētījuma anketas dati ir konfediciāli un iegūtie dati tiks izmantoti tikai pētījuma izstrādei, Jūsu vārda un uzvārda iniciāļi netiks minēti pētījumā.

Ārsts-psihoterapeits, speciālists psihosomatiskajā medicīnā
Tarass Ivaščenko
RSU Iekšķīgo slimību katedras un Psihosomatikas katedras docents
Vladimirs V.Voicehovskis
RSU Iekšķīgo slimību katedras un Psihosomatikas katedras prof
Oskars Kalējs

Piekrītu piedalīties pētījumā _____.

Paraksta atšifrējums _____ _____

Datums _____

Annex 4

Geriatric Depression Scale in Latvian

Vārds: _____ Datums: _____

Izvēlieties un apvelciet ar aplīti atbildi, kas atbilst Jūsu emocijām pēdējās nedēļas laikā:

	Vai Jūs esat apmierināts ar savu dzīvi?	Jā	Nē
	Vai Jūs esat atmetis daudz savu nodarbošanos un interešu?	Jā	Nē
	Vai Jums šķiet, ka Jūsu dzīvei nav jēgas?	Jā	Nē
	Vai Jums bieži ir garlaicīgi?	Jā	Nē
	Vai Jums ir pozitīvs skats uz nākotni?	Jā	Nē
	Vai Jums traucē domas, no kurām nevarat atbrīvoties?	Jā	Nē
	Vai Jums lielākoties ir labs noskaņojums?	Jā	Nē
	Vai Jūs baidāties no tā, ka ar Jums varētu notikt kas slikts?	Jā	Nē
	Vai Jūs lielākoties jūtaties laimīgs?	Jā	Nē
	Vai Jūs bieži jūtaties bezpalīdzīgs?	Jā	Nē
	Vai Jūs bieži jūtaties nemierīgs?	Jā	Nē
	Vai Jūs labāk paliekat mājās, nekā dodaties izmēģināt jaunas lietas?	Jā	Nē
	Vai Jūs bieži uztraucaties par nākotni?	Jā	Nē
	Vai Jums šķiet, ka Jums ir lielākas atmiņas problēmas nekā citiem?	Jā	Nē
	Vai Jums šķiet brīnišķīgi tas, ka tagad esat dzīvs?	Jā	Nē
	Vai Jūs bieži jūtaties nomākts un melanholisks?	Jā	Nē
	Vai Jūs jūtaties nevērtīgs tāds, kāds esat šobrīd?	Jā	Nē
	Vai Jūs daudz uztraucaties par pagātni?	Jā	Nē
	Vai Jūs dzīvi uztverat kā ļoti aizraujošu?	Jā	Nē
	Vai Jums ir grūti uzsākt jaunus darbus?	Jā	Nē
	Vai Jūs jūtaties enerģijas pilns?	Jā	Nē
	Vai Jums šķiet, ka Jūsu stāvoklis ir bezcerīgs?	Jā	Nē
	Vai Jums šķiet, ka liela daļa cilvēku ir labāki par Jums?	Jā	Nē
	Vai Jūs bieži uztraucaties par sīkumiem?	Jā	Nē
	Vai Jums bieži ir vēlme raudāt?	Jā	Nē
	Vai Jums ir grūtības koncentrēties?	Jā	Nē
	Vai Jūs no rīta mostaties ar prieku?	Jā	Nē
	Vai Jūs labprāt izvairāties no sabiedriskiem pasākumiem?	Jā	Nē

	Vai Jums ir viegli pieņemt lēmumus?	Jā	Nē
	Vai Jūsu prāts ir tikpat skaidrs kā agrāk?	Jā	Nē

Annex 5

First publication

Původní sdělení | Original research article

Oxidative stress, depression, and risk of recurrence of stable coronary heart disease

Tarass Ivascenko[a], Vladimirs V. Voicehovskis[a], Julija G. Voicehovska[a], Andrejs Skesters[a], Ketija Apsite[a], Julija Grigorjeva[a], Anda Kivite-Urtane[a], Natalija Pahomova[b], Oskars Kalejs[a]

[a] *Rigas Stradins university, Dzirciema str. 16, Riga LV-1007, Latvia*
[b] *"Medsport", Liela str. 19-2a, Riga LV-1016, Latvia*

ARTICLE INFO

Article history:
Submitted: 18. 3. 2021
Accepted: 3. 4. 2021
Available online: 1. 10. 2021

Klíčová slova:
Deprese
Geriatrická škála deprese
GPx
MDA
Oxidační stres
Stabilní ischemická choroba srdeční

SOUHRN

Souvislosti a cíle: Záměrem této studie je objasnit vztah mezi úrovní oxidačního stresu (OS), depresí (D) a rizikem opakovaného výskytu stabilní ischemické choroby srdeční (sICHS).
Metody: Retrospektivní studie se zúčastnilo 174 osob ve věku 45+: 86 hospitalizovaných pacientů kardiologického oddělení s rekurentní sICHS a 88 hospitalizovaných pacientů kardiologického oddělení s primární sICHS. Vážnost symptomů deprese byla hodnocena za použití 30bodového dotazníku Geriatrické škály deprese (GDS), platné lotyšské verze GDS-LAT. Každému pacientovi byly odebrány vzorky krve za účelem změření parametrů oxidačního stresu malondialdehydu (MDA) a glutathionu peroxidázy (GPx).
Výsledky: 83,9 % vzorků mělo vysokou koncentraci MDA. V 72,4 % byl vzorek hodnoty GPx normální, v 17,8 % byla hodnota vysoká a v 9,8 % nízká. O něco více než polovina pacientů má depresi (44,3 % mírnou D a 6,9 % těžkou D). GPx se statisticky lišila u primární a rekurentní sICHS (p = 0,003). Pacienti s D a vysokým GPx měli 10,6krát vyšší pravděpodobnost opakované sICHS ve srovnání s pacienty bez D a s normální GPx (p = pacienti s D měli obě hodnoty MDA a GPx vysoké častěji než účastníci bez D, ale nebylo to statisticky významné [p = 0,51]).
Závěr: V uvedené studii bylo zjištěno, že koncentrace antioxidačního (AO) enzymu GPx byla podstatně vyšší u depresivních pacientů s opakovanou sICHS ve srovnání s pacienty bez D a s pacienty s primární ICHS a pacienti s D i s vysokým GPx měli vyšší pravděpodobnost opakované sICHS ve srovnání s těmi bez D a s normálním GPx. Dá se předpokládat, že GPx je významnější marker rizika D a opakované sICHS. Koncentrace MDA ve většině z obou skupin (primární a opakovaná sICHS) pacientů by mohla dokazovat, že zvýšená koncentrace OS je všeobecně rizikový faktor ischemické choroby srdeční. Monitorování biomarkerů OS se zdá být významné ve zvládání komorbidity sICHS s D. Bylo by vhodné provést další studie, které by potvrdily tyto nálezy.

ABSTRACT

Aim: The aim of the study was to investigate the relationships between a level of oxidative stress (OS), depression (D) and risk of recurrence of stable coronary heart disease (SCHD).
Methods: A retrospective study was conducted on 174 participants, at the age 45+ years: 86 in-patients of the cardiology department with a recurrent SCHD and 88 in-patients of the cardiology department with primary SCHD. The severity of depressive symptoms was assessed using the long 30-item form of Geriatric Depression Scale (GDS), valid Latvian version of GDS-LAT. The blood samples were taken from each patient to measure oxidative stress parameters malondialdehyde (MDA) and glutathione peroxidase (GPx).
Results: 83.9% of the sample had high level of MDA. In 72.4% of the sample the GPx level was normal, in 17.8% it was high and in 9.8% low. Slightly more than a half of the patients were experiencing depression (44.3% – mild D and 6.9% – severe D). GPx was found statistically differing between primary and recurrent SCHD (p = 0,003). Patients with both D and high GPx had 10.6 times higher chances of recurrent SHCD compared to those without D and normal GPx (p = patients with present D were experiencing both – high levels

Address: Dr. Tarass Ivascenko, Martas str. 1a-30, LV-1011 Riga, Latvia, e-mail: tarass.ivascenko@gmail.com
DOI: 10.33678/cor.2021.046

Please cite this article as: Ivascenko T, Voicehovskis VV, Voicehovska JG, et al. Oxidative stress, depression, and risk of recurrence of stable coronary heart disease. Cor Vasa 2021;63:555–563.

Keywords:
Depression
GPx
Geriatric depression scale
MDA
Oxidative stress
Stable coronary heart disease

of MDA and GPx – more often than responders with no D, but this wasn't statistically significant [p = 0.51]). **Conclusion**: In the present study it was found that level of antioxidant (AO) enzyme GPx was significantly higher in depressed patients with recurrent SCHD compared to patients without D and to patients with primary SCHD and patients with both D and high GPx had higher chances of recurrent SCHD compared to those without D and normal GPx. It could be supposed that GPx is a more significant marker of risk of D and recurrence of SCHD. The high level of MDA in most of both (primary and recurrent SCHD) groups patients could evidence that increased OS is a risk factor for CHD in general. Monitoring OS biomarkers seems to be important in the management of SCHD comorbidity with D. Further studies are warranted to confirm these findings.

Introduction

The public health sector faces a huge challenge as a result of the high prevalence and burden of disability caused by ischemic cardiovascular disease (CVD) and depression (D). Accumulating evidence reveals that CVD and D are correlated and share common risk factors, particularly obesity, diabetes, and hypertension. They also share common mechanisms, including oxidative stress (OS), inflammation, and immune response, cell death signaling pathway, and microbiome-gut-brain axis.[1] According to the World Health Organization data CVDs are the number 1 cause of death globally, taking an estimated 17.9 million lives each year, an estimated 31% of all deaths worldwide.[2] Cardiovascular disease is a group of diseases that include both heart and blood vessels, thereby including coronary heart disease (CHD) and coronary artery disease (CAD), and several other conditions.[3] CAD is usually used to refer to the pathologic process affecting the coronary arteries (usually atherosclerosis) whilst CHD includes the diagnoses of angina pectoris, MI and silent myocardial ischemia. In turn, CHD mortality results from CAD.[4]

D in cardiac disease is common, persistent, underrecognized, and deadly. Over the past 20 years, research has found that not only is D more common in cardiac patients than in the general population, but D is also a risk factor for cardiac morbidity and mortality, independent of traditional risk factors.[5] The prevalence of D is, compared with the general population, significantly higher in patients with CHD.[6] More than one fifth of all patients with CHD are depressed (with the risk of D highest in the most severe CHD cases), and up to one third of them report elevated depressive symptoms. These are prevalence figures that are at least 4 times greater than in the general population.[7] A meta-analysis has demonstrated that the overall risk of depressed but otherwise healthy individuals developing heart disease is 64% higher than for those without D.[8] Five meta-analyses reported a 60–80% increased risk of CHD in participants with D.[1]

Depressive symptoms are diagnosed in less than 15% of cases and only 25% of patients with CHD and severe D are diagnosed with psycho-emotional disorder and approximately only half of them receive adequate antidepressant (AD) therapy.[9,10] Another 30–45% of patients with CHD suffer from clinically significant symptoms consistent with a minor D, and this is a risk factor for the future of a major depressive episode in patients with CHD, associated with an increased risk of secondary acute ischemic events, lower interventions and increased mortality regardless of traditional cardiac risk factors.[11–15]

In addition, major D worsens the cardiovascular prognosis, particularly for CHD, by significantly increasing the risk of recurrent CHD. The relative risk of death in depressed patients during the 18 months following the cardiac event is twice that in non-depressed patients. Recent studies have also shown the harmful nature of D after myocardial infarction in terms of rehospitalization or getting access to cardiac rehabilitation, which is particularly beneficial in this context.[16] Although CVD and D are very different pathologies, they share some common pathophysiological characteristics and risk factors, such as the increased production of pro-inflammatory cytokines, endothelial dysfunction, blood flow abnormalities, decreased glucose metabolism, elevated plasma homocysteine levels and disorder in vitamin D metabolism.[17]

D is associated not only with inflammatory reactions taking place in the body, but also with an increased amount of pro-inflammatory cytokines and increased lipid peroxidation.[18] D is connected with current inflammatory reactions in the body and an increased level of lipid peroxidation, leading to OS. Moreover, OS is considered an important mechanism for the development of CVD.[19] OS is an emergency mechanism that relates to both CVD and D pathophysiology.[20] Inflammation, OS, and activation of the hypothalamic-pituitary-adrenal (HPA) axis is D and cardiac co-morbidities. The inflammatory hypothesis as a common physiopathological pathway in mood disorders and CVD is being put forward more and more frequently. The hypothesis that inflammatory and OS are factors in both mood disorders and CHD seems to be growing stronger.[16]

Malondialdehyde (MDA) is one of the most commonly used indicators of lipid peroxidation, it can also be more resistant than other markers of the late stage (4-HNE, 8-ISO) of lipid peroxidation.[21,22] Heart failure under both acute and chronic conditions is associated with increased levels of OS markers (e.g. MDA, GPx). These findings suggest that CHD status may be determined by OS activity rather than the degree of coronary stenosis.[23] And being a marker of lipid peroxidation, the MDA level increases significantly with D.[24] The main biological role of GPx in the body is a protection against damage caused by free radicals and active forms of oxygen.[18] The higher GPx activity could have been a compensatory mechanism for the excess production of free radicals in depressed patients.[25]

Despite the potentially important role of the OS in pathogenesis of CHD and D, according to available research results, by 2015, the role of OS in the development of D in patients with CHD has not been studied.[18] Normalization of the levels of reactive oxygen species and antioxidant (AO) activity after successful AD therapy sug-

gests that OS mechanisms can be especially important in the study of pathophysiology and prognosis of D. [20,26] Therefore, there is a need to understand the underlying mechanisms and find effective therapies to control CVD and D.[1] The role of OS in stable CHD (SCHD) recurrence in patients with SCHD and D has not been studied previously. At the moment, there is insufficient evidence that routine screening of D in patients with SCHD will ultimately help improve the patient's condition, that is why the study of the relationship between SCHD, D, and OS is very important.[27]

Based on the foregoing, the aim of the present study was to investigate the relationships between OS level, prevalence of D, and risk of recurrent SCHD. The hypothesis was that in recurrent SCHD patients with D would be higher level or OS than in patients with primary SCHD without D.

Materials and methods

A retrospective case-control study was conducted on 174 participants, at the aged 45+ years old:

1) 86 in-patients of the cardiology department of the Paul Stradins Clinical University Hospital (Riga, Latvia) at the age of 45+ years, with a recurrence of SCHD and
2) 88 in-patients of the cardiology department of the same hospital at the age of 45+ years, with a primary SCHD. Each participant was a patient and was examined before discharge from the hospital. There were no statistically significant differences between two groups by gender and age (Chi-square test, $p = 0.1$ and $p = 0.2$, OR $p< 0.05$).

Inclusion criteria in research group were: Patients with SCHD (I20–I25) – by classification ICD-10: I20 angina pectoris; I21 acute myocardial infarction; I22 subsequent ST elevation (STEMI) and non-ST elevation (NSTEMI) myocardial infarction; I23 certain current complications following STEMI and NSTEMI myocardial infarction (within the 28 day period); I24 other acute ischemic heart diseases; I25 chronic ischemic heart disease; primary hospitalization related to CHD; re-hospitalization related to CHD; patients are stable; age ≥45 years; non-smokers; not vegetarian; do not drink alcohol at least during the last 1 year; use prescribed drugs on regular base.

Exclusion criteria in research group were: Age >45 years; approved diabetes mellitus type 1 and 2; glucose tolerance disturbances; any acute illnesses; irregular usage of prescribed drugs; any F diagnosis; obesity (BMI ≥30).

Ethical aspects

Information about the nature and course of the study was provided to all study participants. The patients filled an informed consent form and a questionnaire. To ensure anonymity of personal data, all patient personal data (name, surname) were coded. All procedures complied with the ethical standards on human experimentation (World Medical Association Helsinki Declaration). The approval for this study was obtained from the Ethics Committee of Riga Stradins University. RSU Ethics Committee's decision to "agree for a study" was received on October 29, 2015 (No. 22).

Investigation methods

Diagnoses of SCHD were confirmed using medical records and by a psychotherapist using a structured interview. The severity of depressive symptoms was assessed using the long 30-item form of Geriatric Depression Scale (GDS), valid Latvian version of GDS-LAT.[28,29]

The blood samples were taken from each patient to measure OS parameters: MDA and GPx.

MDA determination method: manual, spectrophotometric. MDA determines the color intensity of the reaction with thiobarbituric acid (TBA) in an acid medium at 95 °C, after optical density in butanol extract at 532 nm. MDA is calculated from the standard curve using the MDA reference substance 1,1,3,3-tetraethoxypropane.[30–32]

GPx – determination method: automatic spectrophotometric. Glutamate peroxidase catalyzes the oxidation of glutathione (GSH) in the presence of opaque hydroperoxide. Oxidative glutathione (GSSG) under the influence of glutasereductase (GR) and NADPH transforms into a reduced form – GSH, simultaneously oxidising NADPH to NADP+. GPx activity corresponds to an absorption drop at 340 nm due to oxidation of NAPH. One unit corresponds to the amount of enzyme produced by 1.0 μMNADPH oxidation atNADP+1 minute at 340 nm at 37 °C.33

Statistical analysis

Data were analyzed using SPSS 23.0 software. Statistical significance of the prevalence of dependent variables between the strata of independent variables was tested using Chi square test. Normal distribution of parametric variables was checked using Kolmogorov–Smirnov test. In case of normal distribution, the means of dependent variables were compared between strata of independent variables using T-test of ANOVA. If the criteria of normal distribution were not met, the alternative tests (Mann–Whitney U test and Kruskal–Wallis test) were used. For detection of correlations between parametric variables Spearman correlation analysis was used (correlation considered as week if $r< 0.3$, mean, if r is ranged from 0.3–0.8 and as strong if $r >0.8$). For multivariate analysis linear, binary and multinomial logistic regressions were applied. Results are considered as statistically significant if $p< 0.05$.

Results

Descriptive statistics

174 responders participated in the study – 49.4% (n = 86) of them have experienced recurrent SCHD and 50.6% (n = 88) of them formed a control group (patients of primary SCHD). There were no differences between distribution of patients in the primary and the recurrent groups by gender and mean age. A half of the total sample (53.4%) were males. Majority of the sample (83.9%) has high level of MDA and for the rest of them the MDA level was considered as normal (i.e. low level of MDA was detected for none of the patients). For majority of the patients (72.4%) the GPx level was normal, for 17.8% it was high

Table 1 – Description of the sample (total and stratified by SCHD status)

Independent variable	Total		Primary SCHD		Recurrent SCHD		p*
	n	%	n	%	n	%	
Sex							
Male	93	53.4	43	48.9	50	58.1	0.22
Female	81	46.6	45	51.1	36	41.9	
Age							
81+	13	7.5	7	8.0	6	7.0	0.34
71–80	48	27.6	27	30.7	21	24.4	
61–70	71	40.8	30	34.1	41	47.7	
≤ 60	42	24.1	24	27.3	18	20.9	
MDA							
Low	–	–	–	–	–	–	
High	146	83.9	76	86.4	70	81.4	0.37
Normal	28	16.1	12	13.6	16	18.6	
GPx							
Low	31	17.8	17	19.3	14	16.3	**0.003**
High	17	9.8	2	2.3	15	17.4	
Normal	126	72.4	69	78.4	57	66.3	
GDS							
Severe	12	6.9	6	6.8	6	7	0.65
Mild	77	44.3	36	40.9	41	47.7	
No	85	48.9	46	52.3	39	45.3	

* Statistically significant if $p < 0.05$

and for 9.8% low. Slightly more than a half of the patients are experiencing D (44.3% mild D and 6.9% severe D) (see Table 1).

As it can be seen in Table 1, groups of recurrent and primary SCHD did not differ according to none of the afore mentioned variables except the GPx level – among patients of recurrent SCHD there was lower proportion of individuals with normal level of GPx when compared to primary SCHD patients (66.3% and 78.4%, respectively) ($p = 0.003$).

Correlation between OS markers

Correlation of OS factors (MDA and GPx indicators) was found to be positive and statistically significant but yet weak ($r = 0.18$, $p = 0.017$).

Factors associated with the recurrent SCHD

When the independent variables are analyzed as parametric values, it was found that the only factor statistically differing between primary and recurrent SCHD patients, was GPx, i.e. among patients of recurrent SCHD mean GPx value is significantly higher than among patients of primary SCHD (8329.8 and 7474.5 U/g Hb respectively) ($p = 0.01$) (see Table 2). Mean age was slightly higher among patients of primary SCHD as well as the median MDA, whereas the median GDS value was higher among patients of recurrent SCHD. But, as it has been mentioned already before, these tendencies cannot be considered as statistically significant. The multivariate analysis hasn't changed the conclusion. After the adjustment the only factor significantly associated with recurrent status of SCHD was GPx ($p = 0.008$). But as regards the measure of OR, the increase in GPx per one unit is making so small changes in OR that it was not detectable within two decimal figures. This was the reason why in the further data analysis the parametric measures were categorized and analyzed as nonparametric variables.

As it's seen in Table 2, there is a tendency for odds of recurrent SCHD to be higher among males, older patients and persons with mild D. Interestingly that the odds of recurrent SCHD are lower among patients with high levels of MDA. But these observations are not statistically significant in univariate, or multivariate analyses. The only factor showing stable and statistically significant association with recurrent SCHD is GPx level, i.e. in multivariate analysis independently from other factors high levels of GPx is associated with 11.29 times higher odds of having recurrent SCHD status ($p = 0.003$).

Factors associated with the D

Patients with present D were experiencing both – high levels of MDA and GPx – more often than responders with no D (11.2% and 8.2%, respectively). But this trend cannot be considered as statistically significant ($p = 0.51$). And vice versa – among patients with simultaneously high levels of MDA and GPx the prevalence of D is higher

Table 2 – Factors associated with recurrent SCHD in univariate and multivariate analysis (if independent variables are nonparametric measures)

Independent variable	Primary SCHD		Recurrent SCHD		OR*	95% CI	p**	Adjusted OR*	95% CI	p**
	n	%	n	%						
Sex										
Male	43	46.2	50	53.8	1.45	0.80–2.65	0.22	1.63	0.85–3.12	0.14
Female	45	55.6	36	44.4	1			1		
Age										
81+	7	53.8	6	46.2	1.14	0.33–3.99	0.83	1.48	0.35–6.28	0.60
71–80	27	56.3	21	43.8	1.04	0.45–2.39	0.93	1.34	0.52–3.43	0.55
61–70	30	42.3	41	57.7	1.82	0.84–3.94	0.13	2.25	0.96–5.31	0.06
≤ 60	24	57.1	18	42.9	1			1		
MDA										
Low	–	–	–	–	–	–	–	–	–	–
High	76	52.1	70	47.9	0.69	0.31–1.56	0.37	0.53	0.22–1.27	0.15
Normal	12	42.9	16	57.1	1			1		
GPx										
Low	17	54.8	14	45.2	1.00	0.45–2.20	0.99	0.96	0.42–2.19	0.92
High	2	11.8	15	88.2	**9.10**	**1.99–41.37**	**0.004**	**11.29**	**2.31–55.06**	**0.003**
Normal	69	54.8	57	45.2	1			1		
GDS										
Severe	6	50.0	6	50.0	1.18	0.35–3.95	0.79	0.82	0.18–3.67	0.80
Mild	36	46.8	41	53.2	1.34	0.72–2.49	0.35	1.31	0.66–2.60	0.44
No	46	54.1	39	45.9	1			1		

* OR – odds ratio; ** statistically significant if $p < 0.05$.

Table 3 – Factors associated with recurrent SCHD in univariate and multivariate analysis among patients with D

Independent variable	Primary SCHD		Recurrent SCHD		OR*	95% CI	p**	Adjusted OR*	95% CI	p**
	n	%	n	%						
Sex										
Male	20	44.4	25	55.6	1.25	0.54–2.88	0.60	1.16	0.46–2.91	0.76
Female	22	50.0	22	50.0	1			1		
Age										
81+	7	70.0	3	30.0	0.32	0.06–1.79	0.20	0.56	0.09–3.71	0.55
71–80	17	51.5	16	48.5	0.71	0.20–2.49	0.59	1.43	0.33–6.15	0.63
61–70	12	37.5	20	62.5	1.25	0.34–4.49	0.73	2.60	0.58–11.78	0.22
≤ 60	6	42.9	8	57.1	1			1		
MDA										
Low	–	–	–	–	–	–	–	–	–	–
High	34	47.9	37	52.1	0.87	0.31–2.46	0.79	0.64	0.21–1.97	0.44
Normal	8	44.4	10	55.6	1			1		
GPx										
Low	5	35.7	9	64.3	2.23	0.68–7.40	0.19	3.04	0.80–11.60	0.10
High	1	10.0	9	90.0	**11.18**	**1.34–93.37**	**0.03**	**12.76**	**1.34–121.84**	**0.03**
Normal	36	55.4	29	44.6	1			1		

* OR – odds ratio; ** statistically significant if $p < 0.05$.

than among patients with normal levels of MDA and GPx or with high or low levels of just one of the indicators (58.8% and 50.3%, respectively). And the level of statistical significance of the mentioned observation is surely the same, i.e. not reaching the level of significance (p = 0.51).

Factors associated with the recurrent SCHD in relation to the presence of D

If only people with D were analyzed (n = 89), the findings remained the same as for the total sample – the only factor significantly increasing the odds of experiencing recurrent SCHD was the high level of GPx (OR 12.76; p = 0.03). As regards the other factors there was a tendency that higher odds of experiencing recurrent SCHD are for males and people aged 61–71 (compared to the younger ones). People with high levels of MDA have almost 40% lower odds of experiencing recurrent SCHD. But the mentioned tendencies cannot be considered as statistically significant (see Table 3).

Further – switching D and SCHD from being the dependent variables to be independent ones (and making markers of OS as the dependent variables), it was found that MDA and GPx are more frequent among patients of recurrent SCHD regardless of the status of D. And the observation can be considered as statistically significant (p = 0.006). But when the four strata are further compared pairwise, it is concluded that the high levels of MDA and GPX were significantly more frequent within the group "D and recurrent SCHD" (19.1%) than within the groups "no D and primary SCHD" (2.2%; p = 0.03) or within the group "D and primary SCHD" (2.4%; p = 0.04) (see Table 4).

Analyzing the for strata pairwise it was found that the prevalence of recurrent SCHD was significantly higher among patients with D and high levels of GPx (90.0%) when compared to people with no D and normal or low levels of GPx (42.3%; p = 0.02) or patients with D but normal or low levels of GPx (48.1%; p = 0.04).

The levels of MDA were not giving any additional impact on the relation between status of D in combination with levels of GPx and the status of SCHD. The conclusions were identical to the ones described above for the combination of the D and GPx alone (see Table 5).

Further, cross tabulation analysis revealed that the group "D + high GPx" had 10.6 times higher chances of recurrent SHCD compared to "no D + normal GPx" group (see Table 6).

Table 4 – Prevalence of simultaneously high levels of MDA and GPx in relation to the presence of D and recurrent SCHD

Status of D in relation to SCHD	High both – MDA and GPx		Normal MDA and GPx or high one of them	
	n	%	n	%
D + recurrent SCHD*^	9	19.1	38	80.9
D + primary SCHD^	1	2.4	41	97.6
No D + recurrent SCHD	6	15.4	33	84.6
No D + primary SCHD*	1	2.2	45	97.8

* p = 0.03, ^ p = 0.04. Statistically significant if p< 0.05.

Table 5 – Prevalence of simultaneously high levels of MDA and GPx in relation to the presence of D and recurrent SCHD

Independent variable Status of D, MDA and GPx	Recurrent SCHD		Primary SCHD	
	n	%	n	%
D + high MDA + high GPx*	9	90.0	1	10.0
No D + high MDA + high GPx^	6	85.7	1	14.3
D + normal MDA + normal or low GPx^	38	48.1	41	51.9
No D + normal MDA + normal or low GPx*	33	42.3	45	57.7

* p = 0.02, ^ p = 0.04. Statistically significant if p< 0.05.

Table 6 – Prevalence and odds of recurrent SCHD stratified by the presence of depression and the level of GPx

Dependent variables	OR (95% CI)	p
D, low GPx	2.12	0.22
D, high GPx	**10.61**	**0.03**
D, normal GPx	0.95	0.89
No D, low GPx	0.49	0.23
No D, high GPx	7.07	0.08
No D, normal GPx	1	

Statistically significant if $p < 0.05$

Discussion

As mentioned above, the aim of the present study was to investigate the relationships between OS level, prevalence of D, and risk of recurrent SCHD. The hypothesis was that in recurrent SCHD patients with D would be higher level or OS than in patients with primary SCHD without D.

Prevalence of D

The result of the research revealed that prevalence of D was in 51.2% of all patients what is in accordance with previous research. Based on the literature, between 31–45% of patients with CHD, including those with stable CAD, unstable angina, or myocardial infarction, suffer from clinically significant depressive symptoms.[11]

In accordance with our expectations in the recurrent SCHD patients prevalence of D was higher (47.7% in primary group and 54.7% in recurrent group), though the difference between primary and recurrent patients wasn't statistically significant (p = 0.44). Multivariate logistic regression results indicated that as the D indicators increase by 1 unit, the chances of recurrent SCHD increase 1.04 times or 4%, but it wasn't statistically significant.

A small difference between groups could be explained with :1) presence of D long time before primary hospitalization, not only after cardiac event; 2) all the patients were enrolled in the research before hospital discharge, that means sometimes after 7–10 days of treatment and adherence to sleep and nutrition. In a study of hospital-

ized patients with a variety of cardiac conditions, those who met criteria for clinical D during admission had improvement of adherence (to diet, exercise, and medication) if their D improved following hospitalization. This suggests that reduced adherence to key secondary prevention behaviors in depressed cardiac patients may be modifiable with treatment of the depressive symptoms.[34]

OS level

There were analyzed two markers of OS: MDA – lipid peroxidation product that shows OS level and AO enzyme GPx – marker of the body defense against OS.

In the most of all patients high MDA level was found (in 146 patients or in 83.9 %) from 174, what is similar with the literature. Results of the studies of Pezeshkian et al. (2001) showed that MDA levels increased significantly in heart diseases.[35] Some other investigates have also reported increase of MDA and GPx levels in patients with CAD.[31] In spite of our expectations, in primary SCHD group MDA level was slightly higher, though there was no statistically significant difference between the subgroups. Moreover, cross tabulation analysis indicates that higher MDA level was in patient with primary SCHD without D (in 91.3% of patients). Though there weren't statistically significant differences between subgroups (p = 0.38), this tendency could be taken into account.

In turn, GPx level was significantly higher in recurrent SCHD subgroup (p = 0.01). Multivariate analysis showed that higher GPx level 11.29 fold increased risk of SCHD. Kaya et al. (2012) also reported an increase of MDA and GPx levels in patients with CAD. GPx enzyme activation was significantly higher in patients with CAD than healthy controls.[36] The result of present research revealed also that GPx level in patients with recurrent SCHD is slightly lower than in patients with primary SCHD. It has been demonstrated that AO enzyme activities are reduced in CHD, and this is linked to the increased disease risk. Many studies have indicated that free radical generation increases and AO defenses decrease in response to increased OS in CHD patients. Activity levels of the AO enzymes GPx, and non-enzymatic AO, are considered as predictors of CHD.[37]

The discrepancies – higher MDA level in patients with primary SCHD – can be explained by several factors. First, OS may be an early causative factor in CVD pathology rather than a late consequence and OS and inflammation develops long before the onset of the first symptoms.[38] We could suppose that OS in recurrent SCHD patients was longer than in primary, but activation of AO enzymes partially compensated high OS level. The fact that GPx level was higher in the patients with recurrent SHCD, that means antioxidative system defense activation, could confirm this assumption. Second, use of beta-blockers. All of both groups' patients took a beta-blocker therapy during hospitalization. In previous researches was found that treatment with beta-blockers such as metoprolol, carvedilol and bisoprolol reduces the levels of OS.[39,40] Unfortunately, in the present study we didn't have information of use of beta-blockers before hospitalization. We could assume that patients with recurrent SCHD used beta-blockers longer than patients with primary SCHD – long time before hospitalization. The longer duration of beta-blocker therapy could explain lower MDA level in recurrent SCHD group. Third, we did not have data on psychoactive drug use or psychological support of the patients before they were enrolled in the study or other factors that could affect the MDA level.

Interesting finding in the present research was the cross tabulation analysis indicating that both OS markers (MDA and GPx) together was significantly higher in recurrent SCHD subgroup, and, moreover, compared pairwise, it was found that the high levels of MDA and GPx are significantly more frequent within the group "D and recurrent SCHD" than within the groups "no D and primary SCHD" (p = 0.03) or within the group "D and primary SCHD" (p = 0.04). Analyzing for strata pairwise it was found that the prevalence of recurrent SCHD is significantly higher among patients with D and high levels of GPx (90.0%) when compared to people without D and normal or low levels of GPx (p = 0.02) or patients with D but normal or low levels of GPx (p = 0.04). Moreover, as it's the group "D + high GPx" had 10.6 times higher chances of recurrent SHCD compared to "no D + normal GPx" group. Hence, we can suppose that OS indeed is a risk factor of SCHD recurrence, especially in patients with D. Although the division into groups of combinations entailed a small number of people in each subgroup, we suggest taking into account these finding in further studies. As mentioned above, there only in-patients before discharge were included in the study who already observed a certain sleep regimen and diets, and received appropriate treatment and care, which could reduce the symptoms of both D and OS. That could explain small number of patients with both D and OS in each primary and recurrent SCHD subgroups.

There is need to add that it's the first research comparing OS and D in primary and recurrent patients with SCHD. Previous studies compared OS level in CHD patients and in healthy controls. Cheraghi et al. (2019) found that serum GPx and MDA were significantly greater in CHD patients than in healthy controls.[37] Moreover, other researches confirm that the OS directly increases the risk of D in patients with CVDs, whereas it increases the risk of CVDs in depressed people. In summary, the common risk factors increase the production of OS and reduce antioxidant defenses, thereby promoting the occurrence and development of interacted ischemic CVD and D.[1]

D, a frequently occurring disease, has a bidirectional relationship with ischemic CVD and partially shares common risk factors (such as obesity and diabetes) and mechanisms (such as inflammation and OS) with CVD, providing a new direction for future research. Based on the literature in patients with CVD, D is often chronic and recurrent. Among patients with CVD hospitalized for acute cardiac events and found to meet criteria for D during or shortly after admission, approximately 50–70% had ongoing depressive symptoms that preceded their cardiac event. This finding is consistent with literature that describes persistent D in patients with stable CAD. Depressed patients with unstable CAD appear to be at even greater risk for poor cardiac outcomes. OS can independently and directly affect stroke, CHD and D. Furthermore, OS acts as a link between ischemic CVD and D.[1] Several lines of evidence indicate that different cardiovascular consider-

ations should be inspected in patients who need to take AD medications.[41] There is an increasing body of evidence supporting that D may be associated with changes in OS markers and that AD agents (especially long-term treatment) may increase AO defenses. It is possible that augmentation of AO defenses may be one of the mechanisms underlying the neuroprotective effects of ADs observed in the treatment of D.[11] It has been shown that the depressed patients have elevated level of platelet adhesion and aggregation leading increased risk for cardiovascular events. In fact, the use of SSRIs may prevent developing atherosclerotic plaques and also arterial thrombosis.[42] Patients who respond to AD therapy within the first year of treatment have shown to experience significantly lower rates of morbidity and mortality.[41]

In summary, there is a need to find effective therapies to control CVD and D. When D screening is paired with a management protocol or system of care (e.g., a care management program) to treat D in patients with CVD, there has been consistent evidence for improved patient outcomes (including, in some studies, improved adherence, reduced cardiac symptoms, reduced cardiac events and improved blood pressure and lipids). Patients who meet full criteria for D should be treated, whether cardiac events are recent or remote.[11] OS directly increases the risk of D in patients with CVD, whereas it increases the risk of CVD in depressed people. The common risk factors increase the production of OS and reduce AO defenses, thereby promoting the occurrence and development of interacted ischemic CVD and D.[1]

Limitations of the study

1) There were rather heterogenous groups as concerns age and gender in both groups, that could influence the results. MDA appears to be sensitive to both gender and age. It is significantly lower and shows a greater age-dependence in women than in men. The age-dependent slope of the steady state concentration is maximal at the age between 50 and 55 years, indicating that it may be attributed to the change of metabolism in the postmenopausal period. Interestingly, total glutathione decreased with age simultaneously with the increase in MDA.[43]
2) In the current study patients' anthropometric dates weren't take into account there, only people with BMI >30 were excluded, based on literature, that there was no clear association between obesity and systemic OS in subjects with BMI less than 30 kg/m^2.[44]
3) In the present research authors couldn't exclude other factors that affect D and/or OS in patients in relations to SCHD recurrence (dietary intake, substance use disorder, chronic somatic disorder, difficult life events no relationships, no family, poor social life, lower socioeconomic status etc.)

Conclusions

In the present study was found that AO enzyme GPx significantly higher in depressed patients with recurrent SCHD compared to patients without D and to patients with primary SCHD. Patients with both D and high GPx had 10.6 times higher chances of recurrent SHCD compared to those without D and normal GPx. It could be supposed that GPx is more significant marker of risk of D and recurrence of SCHD. Though MDA level was slightly higher in primary SCHD group without D, the high level of MDA in most of both (primary and recurrent SCHD) groups patients evidences that increased OS is a risk factor for SCHD in general, but not for recurrence of SCHD. Monitoring OS biomarkers seems to be important in the management of SCHD comorbidity with D. Further studies are warranted to confirm these findings.

Conflict of interest
None.

Funding
Research project was supported by RSU PhD grant.

Ethical statement
The article was written in accordance with ethical standards.

Informed consent
All the patients filled an informed consent form.

References

1. Lin D, Wang L, Yan S, et al. The Role of Oxidative Stress in Common Risk Factors and Mechanisms of Cardio-Cerebrovascular Ischemia and Depression. Oxid Med Cell Longev 2019;2019:2491927.
2. Cardiovascular diseases. World Health Organization 2017 May [cited 2020 May 5]. Available from: https://www.who.int/en/news-room/fact-sheets/detail/cardiovascular-diseases-(cvds)
3. World Health Organization. Global Atlas on Cardiovascular Disease Prevention and Control. Geneva: World Health Organization, 2011.
4. Sanchis-Gomar F, Perez-Quilis C, Leischik R, Lucia A. Epidemiology of coronary heart disease and acute coronary syndrome. Ann Transl Med 2016;4:256.
5. Huffman JC, Celano CM, Beach SR, et al. Depression and Cardiac Disease: Epidemiology, Mechanisms, and Diagnosis. Cardiovasc Psychiatry Neurol 2013;2013:1–14.
6. Whooley MA, Wong JM. Depression and cardiovascular disorders. Annu Rev Clin Psychol 2013;9:327–354.
7. Hert MD, Detraux J, Vancampfort D. The intriguing relationship between coronary heart disease and mental disorders. Dialogues Clin Neurosci 2018;20:31–39.
8. Van der Kooy K, van Hout H, Marwijk H, et al. Depression and the risk for cardiovascular diseases: Systematic review and meta analysis. Int J of Geriatr Psychiatry 2007;22:613–626.
9. Guck TP, Kavan MG, Elsasser GN, Barone EJ. Assessment and treatment of depression following myocardial infarction. Am Fam Physician 2001;64:641–647.
10. Moryś M, Bellwon J, Adamczyk K, Gruchała M. Depression and anxiety in patients with coronary artery disease, measured by means of self-report measures and clinician-rated instrument. Kardiol Pol 2016;74:53–60.
11. Celano CM, Huffman JC. Depression and cardiac disease: a review. Cardiol Rev 2011;19:130–142.
12. Barth J, Schumacher M, Herrmann-Lingen C. Depression as a risk factor for mortality in patients with coronary heart disease: a meta-analysis. Psychosom Med 2004;66:802–813.
13. Januzzi JL, Stern TA, Pasternak RC, DeSanctis RW. The influence of anxiety and depression on outcomes of patients with coronary artery disease. Arch Intern Med 2000;160:1913–1921.
14. Carney RM, Blumenthal JA, Freedland KE, et al. Depression and late mortality after myocardial infarction in the Enhancing

Recovery in Coronary Heart Disease (ENRICHD) study 2004. Psychosom Med 2004;66:466–474.
15. Van Melle JP, de Jonge P, Spijkerman TA, et al. Prognostic association of depression following myocardial infarction with mortality and cardiovascular events: a meta-analysis. Psychosom Med 2004;66:814–822.
16. Chauvet-Géliniera JC, Trojaka B, Vergès-Patois B, et al. Review on depression and coronary heart disease. Arch Cardiovasc Dis 2013;106:103–110.
17. Trebatická J, Dukát A, Ďuračková Z. Cardiovascular Diseases, Depression Disorders and Potential Effects of Omega-3 Fatty Acids. Physiol Res 2017;66:363–382.
18. Vaváková M, Ďuračková Z, Trebatická J. Markers of Oxidative Stress and Neuroprogression in Depression Disorder. Oxid Med Cell Longev 2015;2015:898393.
19. Kander MC, Cui Y, Liu Z. Gender difference in oxidative stress: a new look at the mechanisms for cardiovascular diseases. J Cell Mol Med 2017;21:1024–1032.
20. Adifbair A, Saleem M, Lanctôt KL, Herrmann N. Potential Biomarkers for Depression Associated with Coronary Artery Disease: A Critical Review. Curr Mol Med 2016;16:137–164.
21. Del Rio D, Stewart AJ, Pellegrini N. A review of recent studies on malonaldehyde as toxic molecule and biological marker of oxidative stress. Nutr Metab Cardiovasc Dis 2005;15:316–328.
22. Mazereeuw G, Herrmann N, Andreazza AC, et al. Oxidative stress predicts depressive symptom changes with omega-3 fatty acid treatment in coronary artery disease patients. Brain Behav Immun 2017;60:136–141.
23. Vichova T, Motovska Z. Oxidative stress: Predictive marker for coronary artery disease. Exp Clin Cardiol 2013;18:e88–e91.
24. Frey BV, Valvassori SS, Réus GZ, et al. Changes in antioxidant defense enzymes after d-amphetamine exposure: implications as an animal model of mania. Neurochem Res 2006;31:699–703.
25. Liu T, Zhong Z, Liao X, et al. A Meta-Analysis of Oxidative Stress Markers in Depression. PLoS ONE 2015;10:e0138904.
26. Cumurcu BE, Ozyurt H, Etikan I, et al. Total antioxidant capacity and total oxidant status in patients with major depression: impact of antidepressant treatment. Psychiatry Clin Neurosci 2009;63:639–645.
27. Hasnain M, Vieweg WVR, Lesnefsky EJ, Pandurangi AK. Depression screening in patients with coronary heart disease: a critical evaluation of the AHA guidelines. J Psychosom Res 2011;71:6–12.
28. Yesavage AB. Development and validation of a geriatric depression screening scale: a preliminary report. J Psychiatr Res 1982–1983;17:37–49.
29. Voicehovskis VM. Validation of the Latvian version of the Geriartric Depression Scale (GDS). Psychother Psychosom 2013;82:122–123.
30. Armstrong D, Browne R. The analysis of free radicals, lipid peroxides, antioxidant enzymes and compounds related to oxidative stress as applied to the clinical chemistry laboratory. Adv Exp Med Biol 1994;366:43–58.
31. Armstrong D. Free Radicals and Antioxidant Protocols. Methods Mol Biol 1998;108:315–324.
32. Boyum A. OxiSelect TBARS Assay Kit (MDA Quantitation). J Clin Invest 1966;21:597.
33. Paglia DV. Studies on the quantitative and qualitative characterization of erythrocyte glutathione peroxidase. J Lab Clin Med 1967;70:158–169.
34. Bauer LK, Caro MA, Beach SR, et al. Effects of depression and anxiety improvement on adherence to medication and health behaviors in recently hospitalized cardiac patients. Am J Cardiol 2012;109:1266–1271.
35. Pezeshkian M, Nouri M, Zahraei M, et al. Study of MDA, antioxidant vitamins, lipoproteins serum levels and anthropome-try parameters in coronary artery disease patients. Med J Islamic World Acad Sci 2001;14:5–8.
36. Kaya Y, Çebi A, Söylemez N, Demir H, et al. Correlations between Oxidative DNA Damage, Oxidative Stress and Coen-zyme Q10 in Patients with Coronary Artery Disease. Int J Med Sci 2012;9:621–626.
37. Cheraghi M, Ahmadvand H, Ali Maleki A, et al. Oxidative Stress Status and Liver Markers in Coronary Heart Disease. Rep Biochem Mol Biol 2019;8:49–55.
38. Vaváková M, Trebatická J, Dukát A, et al. Cardiovascular Diseases, Depression Disorders and Potential Effects of Omega-3 Fatty Acids. Physiol Res 2017;66:363–382.
39. Nakamura K, Murakami M, Miura D, et al. Beta-Blockers and Oxidative Stress in Patients with Heart Failure. Pharmaceuticals 2011;4:1088–1100.
40. Kukin ML, Kalman J, Charney RH, et al. Prospective, randomized comparison of effect of long-term treatment with metoprolol or carvedilol on symptoms, exercise, ejection fraction, and oxidative stress in heart failure. Pharmaceuticals 2011;4:1099.
41. Yekehtaz H, Farokhnia M, Akhondzadeh S. Cardiovascular Considerations in Antidepressant Therapy: An Evidence-Based Review. J Tehran Heart Cent 2013;8:169–176.
42. Nezafati MH, Vojdanparast M, Nezafati P. Antidepressants and cardiovascular adverse events: A narrative review. Atherosc 2015;11:295.
43. Pinchuk I, Weberb D, Kochlikb B, et al. Gender- and age-dependencies of oxidative stress, as detected based on the steady state concentrations of different biomarkers in the MARK-AGE study. Redox Biology 2019;24:1–7.
44. Ito F, Yoko Sono Y, Ito T. Measurement and Clinical Significance of Lipid Peroxidation as a Biomarker of Oxidative Stress: Oxidative Stress in Diabetes, Atherosclerosis, and Chronic Inflammation. Antioxidants 2019;8:72.

Second publication

sciendo

PROCEEDINGS OF THE LATVIAN ACADEMY OF SCIENCES. Section B.
Vol. 76 (2022), No. 2 (737), pp. 181–187.

DOI: 10.2478/prolas-2022-0028

Review

DEPRESSION AND OXIDATIVE STRESS INTERACTION IN STABLE CORONARY HEART DISEASE

Tarass Ivaščenko[1], Vladimirs V. Voicehovskis[1,#], Oskars Kalējs[1,2], Jūlija G. Voicehovska[1,5], Andrejs Šķesters[3], Natālija Pahomova[4], and Aivars Lejnieks[1,5]

[1] Internal Diseases Department, Rīga Stradiņš University, 16 Dzirciema Str., Rīga, LV-1007, LATVIA

[2] Pauls Stradiņš Clinical University Hospital, 13 Pilsoņu Str., Rīga, LV-1002, LATVIA

[3] Biochemical Scientific Lab., Rīga Stradiņš University, 5 Rātsupītes Str., Rīga, LV-1067, LATVIA

[4] "Medsport", 19-2a Lielā Str., Rīga, LV-1016, LATVIA

[5] Rīga East University Hospital, 2 Hipokrāta Str., Rīga, LV-1038, LATVIA

[#] Corresponding author, voiceh@me.com

Contributed by Aivars Lejnieks

It was concluded that depression (D) is an independent risk factor for cardiovascular diseases (CVD), and is not related to other previously determined cardiac risk factors. Compared with non-depressed patients, the risk of cardiac arrest increased in less severely depressed patients. D worsens the CVD prognosis by significantly increasing the risk of recurrent coronary heart disease (CHD). Some studies suggest that OS directly increases the risk of D in patients with CVD. Oxidative stress (OS) is considered an emergency mechanism that relates to both CVD and D pathophysiology. The common risk factors increase the production of OS and reduce antioxidant defences, thereby promoting the occurrence and development of interacted ischaemic CVD and D. At present, there is insufficient evidence that routine screening of D in patients with CHD will ultimately help improve the patient's condition. This review reiterates the need for a multidisciplinary approach, which is necessary to understand, diagnose and then treat this frequent co-morbid condition of CHD and D. Assessment of OS markers could modify risk stratification, diagnosis and prevention and treatment of patients with both CHD and D, in patients with and without previous cardiac history.

Key words: *stable coronary heart disease, mental health disorders, reactive oxygen species, malondialdehyde, glutatione peroxidase.*

INTRODUCTION

Epidemiological data indicate that cardiovascular disease (CVD) and depression (D) pose a huge global disease burden. The Global Burden of Disease 2016 study showed that CVD was the number one reason of years of life lost globally (Moraga, 2017). Also, it was reported that major depressive disorder was the third cause of years lived with disability after low back pain and headache disorders (GBD, 2017; 2018). Both coronary heart disease (CHD) and D are the leading causes of disability in high-income countries, and are expected to become so globally by 2030 (Murray and Lopez, 2013). Over the past 20 years, research has found that not only is D more common in cardiac patients than in the general population, but D is also a risk factor for cardiac morbidity and mortality, independent of traditional risk factors (Huffman *et al*., 2013). Besides impairing patients' quality of life, D has profound negative effects on the long-term prognosis of individuals with any type of cardiovascular disorder. These facts further underscore the importance for proper treatment of D in patients with CVD (Yekehtaz *et al*., 2013). The role of oxidative stress (OS) in CVD processes, such as atherogenesis, ischaemic-reperfusion injury and cardiac remodelling, has been increasingly

recognised in the past few decades. Much of the recent research in these areas has focused on the role of the immune system and inflammation in both depression and CVD. Currently, an increasing number of studies suggest that levels of OS markers in body fluids are raised (Vichova and Motovska, 2013). The common risk factors increase the production of reactive oxygen species (ROS) and reduce antioxidant (AO) defences, thereby promoting the occurrence and development of interacted ischaemic CVD and D (Lin *et al*., 2019).

The aim of this paper was to provide a narrative review of OS states associated with the risk of CVD in depressed patients. There is a need to find effective screening tools and therapies to control CVD and D. At present, there is insufficient evidence showing that routine screening of D in patients with CHD will ultimately help improve the patient's condition (Hasnain *et al*., 2011), which is why the study of the relationship between CHD, D, and OS is very important.

CARDIOVASCULAR DISEASE

According to the World Health Organization data, CVD is the leading cause of death globally, taking an estimated 17.9 million lives each year, an estimated 31% of all deaths worldwide (World Health Organization, 2017). Prevalent cases of total CVD nearly doubled from 271 million in 1990 to 523 million in 2019, and the number of CVD deaths steadily increased from 12.1 million in 1990, reaching 18.6 million in 2019 around the globe (Roth *et al*., 2020). In Latvia, CVD was the most common cause of death — 54.6% of all deaths, according to 2019 data (Ērglis *et al*., 2020). CVD is a group of diseases that include both the heart and blood vessels (World Health Organization, 2011), thereby including CHD and coronary artery disease (CAD), and several other conditions. CAD usually use to refer to the pathologic process affecting the coronary arteries (usually atherosclerosis), whilst CHD includes the diagnoses of angina pectoris, myocardial infarction, and silent myocardial ischaemia. CHD mortality results from CAD (Sanchis-Gomar *et al*., 2016). CAD continues to be a major focus of clinical and epidemiological research. Non-modifiable cardiovascular risk factors, such as age, gender, family history, and race, as well as modifiable risk factors, such as hypertension, weight, smoking, sedentary lifestyle, abnormal lipid profiles, inflammatory markers, diabetes, metabolic syndrome, and subclinical CAD, are associated with increased cardiovascular risk (Kuller *et al*., 2006; Khawaja *et al*., 2009). There is a lack of a definitive correlation between high-risk profiles, biological profiles, and the occurrence of CAD. A number of psychological states and traits, such as D, anxiety, anger, and stress, have also been implicated as potential risk factors for CAD (Khawaja *et al*., 2009).

DEPRESSION AND CARDIOVASCULAR DISEASE

A multitude of studies over the past 15 years have confirmed that depression is associated with adverse cardiovascular outcomes, independent of traditional risk factors. D in cardiac disease is common, persistent, under-recognised, and deadly. The prevalence of D is, compared with the general population, significantly higher in patients with CHD (Whooley and Wong, 2013).

There are three extensively replicated epidemiological observations regarding CHD and depression: 1) these conditions are highly comorbid, 2) depression is associated with increased risk of incident CHD and vice versa, and 3) depression is a strong predictor of poor prognosis in people with CHD (Khandaker *et al*., 2020). Depression, a frequently occurring disease, has a bidirectional relationship with ischaemic CVD and partially shares common risk factors (such as obesity and diabetes) and mechanisms (such as inflammation and OS) with CVD, which are correlated with atherosclerotic disease activity (Lin *et al*., 2019). More than one-fifth of all patients with CHD are depressed (with the risk of D highest in the most severe CHD cases), and up to one-third of them report elevated depressive symptoms. These are prevalence figures that are at least four times greater than in the general population (De Hert *et al*., 2018). A meta-analysis demonstrated that the overall risk of depressed but otherwise healthy individuals developing heart disease is 64% higher than for those without D (Van der Kooy *et al*., 2007). Five meta analyses reported a 60–80% increased risk of CHD in patients with D (Lin *et al*., 2019). If we look at figures from the community through to those who are hospitalised, we see rates of depression of 10% in general practice clinics (Cassano and Fava, 2002; Brown *et al*., 2009), which then increases to up to 30% in those with CHD in outpatient clinics (Dhar and Barton, 2016). In several studies, 17 to 44 per cent of patients with CAD also have a diagnosis of major D (Yekehtaz *et al*., 2013). Depressive symptoms are diagnosed in less than 15% of cases (Guck *et al*., 2011) and only 25% of patients with CHD and severe D are diagnosed with psycho-emotional disorder and approximately only half of them receive adequate antidepressant (AD) therapy (Moryś *et al*., 2016). Another 30–45% of patients with CHD suffer from clinically significant symptoms consistent with a minor D (Celano and Huffman, 2011), and this is a risk factor for the future of a major D episode in patients with CHD, associated with an increased risk of secondary acute ischaemic events, lower interventions and increased mortality, regardless of traditional cardiac risk factors (Januzzi *et al*., 2000; Barth *et al*., 2004; van Melle *et al*., 2004). Among patients with CVD hospitalised for acute cardiac events and found to meet criteria for depression during or shortly after admission, approximately 50–70% had ongoing depressive symptoms that preceded their cardiac event (Glassman *et al*., 2006; Lesperance *et al*., 2007) this finding is consistent with literature that describes persistent depression in patients with stable CAD. Furthermore, rather than being a transient reaction to a cardiac event, depression for many patients exists for months or years before and persists long after the event (Glassman *et al*., 2006; Lesperance *et al*., 2007; Huffman *et al*., 2011; 2013). Basing on the literature in patients with CVD, D is often chronic and recurrent. Among patients with CVD hospitalised for acute cardiac events and found to meet criteria for D during or shortly after admission, ap-

proximately 50–70% had ongoing depressive symptoms that preceded their cardiac event. This finding is consistent with literature that describes persistent D in patients with stable CAD. Depressed patients with unstable CAD appear to be at even greater risk for poor cardiac outcomes (Yekehtaz *et al*., 2013). D also has a significant effect on the outcome of cardiovascular diseases in patients with stable CHD (Frasure-Smith and Lespérance, 2010). Several previous papers suggest that depression can influence cardiovascular function, and vice versa cardiovascular diseases also influence affective states (Trebatická *et al*., 2017). Compared with non-D patients, the risk of cardiac arrest increased in less severely depressed patients. The authors concluded that D is an independent risk factor for CHD and is not related to other previously determined cardiac risk factors. This association persisted across all demographic groups in this well designed, case-control study (Khawaja *et al*., 2009). In addition, major D worsens the cardiovascular prognosis, particularly for CHD, by significantly increasing the risk of recurrent CHD. The relative risk of death in depressed patients during the 18 months following the cardiac event is twice that in non-depressed patients (Chauvet-Géliniera *et al*., 2013). Recent studies have also shown the harmful nature of D after myocardial infarction in terms of rehospitalisation or getting access to cardiac rehabilitation, which is particularly beneficial in this context (Myers *et al*., 2012). In fact, non-completion rates in cardiac rehabilitation have been shown to be in the order of 44% compared to 29% in the non-depressed group (Swardfager *et al*., 2011). Although CVD and D are very different pathologies, accumulating evidence reveals that CVD and D both are correlated and share common risk factors, particularly obesity, diabetes, and hypertension (Khawaja *et al*., 2009). Researchers suggest a hybrid model like the hybrid dependence of D and CHD, in which there is a bi-directional relationship between D and inflammation (Matthews, 2010). It is worth noting that chronic inflammation of low degree is an inalienable component of D (Adifbair *et al*., 2016). The inflammatory hypothesis as a common physio-pathological pathway in mood disorders and CVD is being put forward more and more frequently. CHD and D share some common patho-physiological characteristics and risk factors, such as increased production of pro-inflammatory cytokines, endothelial dysfunction, blood flow abnormalities, decreased glucose metabolism, elevated plasma homocysteine levels and disorder in vitamin D metabolism (Frasure-Smith and Lespérance, 2010), cell death signalling pathway, microbiome-gut-brain axis (Lin *et al*., 2019), increased susceptibility to blood coagulation due to changes in several stages of the coagulation cascade, including activation and aggregation of platelets, OS, subclinical hypothyroidism, decrease in the number of circulating endothelial progenitor cells and associated processes of arterial reconstruction, increased variability of heart rate, and the presence of genetic factors (Nemeroff and Goldschmidt-Clermont, 2012). Individuals with comorbid depression and CVD may also have imbalances in homeostatic regulation of different biological systems, with alterations observed in the hypothalamus–pituitary–adrenal axis, renin–angiotensin–aldosterone system, and serotonin/kynurenine pathways that are accompanied by inflammation and endothelial dysfunction (Halaris, 2017; Mattina *et al*., 2019). Sympathetic outflow is increased in depressed patients as compared to non-depressed patients through negative stress effects of catecholamines on the heart, blood vessels, and platelets. Further support of the catecholamine association with D is that increased urinary catecholamine levels are associated with negative emotions and decreased social support, and high norepinephrine and low platelet serotonin levels are associated with MI and D. D-induced altered autonomic tone associated with low heart rate variability leading to dysrhythmias (Khawaja *et al*., 2009). The diagnosis of D can be difficult in people with CVD, as D symptoms such as fatigue and low energy are common in people with CVD and may also be a side effect of some drugs such as beta blockers used to treat CVD. The diagnosis may be further complicated in such patients by their responses to their disease, which may include denial, avoidance, withdrawal, and anxiety (Carney and Freedland, 2008; Goodman *et al*., 2008). Given the sometimes sudden onset of a cardiovascular event, the normal psychological reaction to disease requires the patient to adapt, which leads to a certain physiological D in mood, the time to come to terms with the possible loss related to the disease and the sometimes very much changed future prospects for life (Chauvet-Géliniera *et al*., 2013). In a study of hospitalised patients with a variety of cardiac conditions, those who met criteria for clinical D during admission had improvement of adherence (to diet, exercise, and medication) if their D improved following hospitalisation. This suggests that reduced adherence to key secondary prevention behaviours in D cardiac patients may be modifiable with treatment of the D symptoms (Bauer *et al*., 2012). Considering the negative cardiac and cognitive effects of persistent D in patients with CHD, adequate treatment with AD is a clinically important need in the case of CHD. Patients who respond to AD therapy within the first year of treatment have been shown to experience significantly lower rates of morbidity and mortality (Jiang *et al*., 2011). Several studies have shown that the new generation of AD, in particular selective serotonin reuptake inhibitors, are well tolerated, have a satisfactory efficacy-tolerance profile and are easy to use in patients with cardiovascular disease (Chauvet-Géliniera *et al*., 2013). In addition, these molecules show clinical efficacy, acting on physio-pathological elements by improving endothelial function while reducing the concentration of inflammation markers (C-reactive protein, interleukin-6) (Pizzi *et al*., 2009). In the same way, a meta-analysis showed that selective serotonin re-uptake inhibitors used in the wake of an acute coronary syndrome led to fewer re-hospitalisations (Mazza et al., 2010; Chauvet-Géliniera *et al*., 2013).

CARDIOVASCULAR DISEASE, DEPRESSION AND OXIDATIVE STRESS

Oxidative stress. OS is defined by the imbalance between the production of reactive oxygen species (ROS) and the endogenous AO mechanisms to counteract the effects of ROS or to repair the resulting damages (Antoniades *et al*., 2009). Any oxidative imbalance resulting in the accumulation of oxidants will inflict oxidative damage on cells, such as al-

teration of cellular macromolecules, lethal changes in genetic materials, such as DNA and RNA, an increase in the rate of cell death by programmed- and non-programmed-cell death (apoptosis / pyroptosis / necroptosis / ferroptosis or necrosis), and structural damage to tissues and organs (Dhama *et al*., 2019). Accumulation of oxidants induces lipid peroxidation and disturbances in physiological adaptation and cellular signalling pathways, which together inflict OS (Puppel *et al*., 2015). Lipid peroxidation products, such as malondialdehyde (MDA), cause changes in the metabolism of dopamine, induce the synthesis of protein reactive dopaminergic toxins (Rees, 2007) and have an inhibitory effect on the reduction of nucleotide excision by direct interaction with cellular repair proteins (Feng, 2006). One of the most important and extensively studied oxidants is MDA. In the field of modern biology to assess OS, MDA is an extensively utilised biomarker. MDA is one of the most commonly used indicators of lipid peroxidation (Rio *et al*., 2005) and can be more resistant than other markers of the late stage (4-Hydroxynonenal, 8-isoprotane) of lipid peroxidation (Mazereeuw *et al*., 2017). The MDA molecule is stable and relatively inactive, compared with free radicals; however, it can not only significantly affect the stability and function of cells, but can also be indirectly involved in the OS reaction (Voicehovskis, 2013). The most potent AO actions are mediated by enzymes, especially superoxide glutathione peroxidase (GPx) (Dhama *et al*., 2019). The main biological role of GPx in the body is protection against damage caused by free radicals and active forms of oxygen (Vaváková *et al*., 2015). The level of serum GPx is an excellent measure of the oxidative status of an individual and is most often employed in diagnostics (Dhama *et al*., 2019). OS is an emerging mechanism relevant to both CVD and D pathophysiology (Adifbair *et al*., 2016).

Oxidative stress and depression. Studies have suggested that depression was accompanied by OS dysregulation, including abnormal total AO capacity, AO, free radicals, oxidative damage and autoimmune response products (Liu et al., 2015; Adifbair *et al*., 2016). The oxidative products include products of oxidative damage of lipoproteins, proteins and DNA in D. Abnormal MDA levels in D have been reported (Bal *et al*., 2012; Liu *et al*., 2015). Increased lipid peroxidation has been associated with the presence and severity of D symptoms (Mazereeuw *et al*., 2017). D is associated not only with inflammatory reactions taking place in the body, but also with an increased amount of pro-inflammatory cytokines and increased lipid peroxidation leading to OS (Vaváková *et al*., 2015). Thus, many clinical studies have accordingly associated D with an increase in the level of OS markers and lower overall AO activity (Sarandol *et al*., 2007; Cumurcu *et al*., 2009; Adifbair *et al*., 2016; Black *et al*., 2015). OS can also contribute to depressive disorder by acting on established aetiopathological components of D, including lipid signalling, monoamine regulation and inflammation (Maes *et al*., 2011; Moylan *et al*., 2014). The higher GPx activity might be a compensatory mechanism for the excess production of free radicals in D patients (Liu *et al*., 2015).

Oxidative stress and cardiovascular disease. OS activates the immune inflammatory pathways (Moylan *et al*., 2014; Liu *et al*., 2015). It was found that serum GPx and MDA were significantly greater in CHD patients than in healthy controls (Cheraghi *et al*., 2019). Moreover, OS is considered an important mechanism for the development of CVD (Kander *et al*., 2017). In the past two decades, numerous studies have demonstrated the importance of OS in the development of atherosclerosis and ischaemia-reperfusion injury (Vichova and Motovska, 2013). Inflammation, OS and activation of the hypothalamus–pituitary–adrenal axis are D and cardiac co-morbidities (Chauvet-Gélinier *et al*., 2013). OS may be an early causative factor in CVD pathology rather than a late consequence (Trebatická *et al*., 2017). Results of studies (Pezeshkian *et al*., 2001) showed that MDA levels increased significantly in heart diseases. Some other studies also reported increase of MDA and GPx levels in patients with CAD (Pezeshkian *et al*., 2001).

Studies have also reported increase of MDA and GPx levels in patients with coronary artery disease. GPx activation was significantly higher in patients with coronary artery disease than in healthy controls (Kaya *et al*., 2012). It has been demonstrated that AO enzyme activities are reduced in CHD, and this is linked to the increased disease risk. Many studies have indicated that free radical generation increases and AO defences decrease in response to increased OS in CHD patients. Activity levels of the AO enzymes GPx, and non-enzymatic AOs, are considered as predictors of CHD (Vichova and Motovska, 2013; Cheraghi *et al.*, 2019). Heart failure under both acute and chronic conditions is associated with increased levels of OS markers (eg, MDA, GPx). These findings suggest that CHD status may be determined by OS activity rather than the degree of coronary stenosis. Elevated concentrations of a variety of OS markers were linked with a more frequent occurrence of cardiac events (Vichova and Motovska, 2013).

Oxidative stress as a mediating factor between depression and coronary heart disease. The hypothesis that inflammation and OS are factors in both mood disorders and CHD seems to be growing stronger (Chauvet-Gélinier *et al*., 2013). Increased lipid peroxidation may be particularly relevant to D symptoms among patients with CAD, given the involvement of OS in that condition (Mazereeuw *et al*., 2017). Moreover, other research confirmed that the OS directly increases the risk of D in patients with CVD, whereas it increases the risk of CVD in depressed people. In summary, the common risk factors increase the production of OS and reduce AO defences, thereby promoting the occurrence and development of interacted ischaemic CVD and D (Lin *et al*., 2019). It has been shown that depressed patients have elevated levels of platelet adhesion and aggregation leading increased risk for cardiovascular events (Nezafati *et al*., 2015). OS can independently and directly affect stroke, CHD and D (Lin *et al*., 2019). Several pieces of evidence have pointed to the involvement of altered tryptophan metabolism in inflammation and the development of mood disorders (Mattina *et al*., 2019). Higher levels of serum kyn-

urenine compared with tryptophan, have been demonstrated in CVD patients and provide evidence for altered kynurenine synthesis (Wirleitner *et al*., 2003). The kynurenine/tryptophan ratio, as well as other kynurenine metabolites, are strongly associated with increased risk of poor outcomes following stroke (Brouns *et al*., 2010) and cardiovascular related mortality in the general population (Zuo *et al*., 2016). Furthermore, CHD patients with D show greater serum kynurenine/tryptophan ratio compared with those without D (Nikkheslat *et al*., 2015), suggesting that D coupled with CHD leads to increased activation of the kynurenine pathway (Mattina *et al*., 2019). Activation of the kynurenine pathway following chronic inflammation is modified to increase the production of neurotoxic metabolites and release ROS, resulting in lipid peroxidation and neurodegenerative brain changes (Wang *et al*., 2015; Jeon and Kim, 2017).

Oxidative stress and antidepressant therapy. There is an increasing body of evidence supporting that D may be associated with changes in OS markers and that AD agents (especially long-term treatment) may increase AO defences. It is possible that augmentation of AO defences may be one of the mechanisms underlying the neuroprotective effects of ADs observed in the treatment of D (Celano and Huffman, 2011). Meta-analysis supports the facts that the serum total AO capacity, paraoxonase and AO levels are lower, and the serum free radical and oxidative damage product levels are higher, in D patients than in controls. Also, the AO levels are increased and the oxidative damage product levels are decreased after AD medication (Liu *et al*., 2015). In fact, the use of selective serotonin reuptake inhibitors may prevent developing atherosclerotic plaques and also arterial thrombosis (Nezafati *et al*., 2015). Normalisation of the levels of ROS and AO activity after successful AD therapy (Cumurcu *et al*., 2009) suggests that OS mechanisms can be especially important in the study of pathophysiology and prognosis of D (Adifbair *et al*., 2016). Among patients with heart failure, those who respond to AD therapy within the first year of treatment have been shown to experience significantly lower rates of morbidity and mortality (Jiang *et al*., 2011). Several lines of evidence indicate that different cardiovascular considerations should be evaluated in patients who need to take AD medication (Yekehtaz *et al*., 2013).

CONCLUSION

Despite the potentially important role of the OS in pathogenesis of CHD and D, there are only a few studies on the role of OS in the development of D in patients with CHD. Furthermore, the role of OS in stable CHD recurrence in patients with stable CHD and D has not been studied previously. Assessment of OS markers could modify risk stratification, diagnosis and prevention and treatment of patients with both CVD and D, in patients with and without previous cardiac history. Appropriate, individualised AD therapy by reducing the level of OS may help reduce the risk of CVD (both primary event and recurrence) in patients with D. This requires further longitudinal, large-sample size, cohort studies to provide more conclusive outcomes. Summarising all of the above, a retrospective case-control study is necessary to identify and examine the relationship between the severity of D symptoms and indicators of OS in primary stable CDH patients and in patients with recurrent stable CHD.

REFERENCES

Adifbair, A., Saleem, M., Lanctôt, K., Herrmann, N. (2016). Potential biomarkers for depression associated with coronary artery disease: A critical review. *Curr. Mol. Med.,* **16**, 137–164.

Antoniades, C., Antonopoulos, A. S., Bendall, J. K., Channon, K. M. (2009). Targeting redox signaling in the vascular wall: from basic science to clinical practice. *Curr. Pharm. Des.,* **15** (3), 329–342.

Bal, N., Acar, S. T., Yazıcı, A., Yazıcı, K., Tamer, L. (2012). Altered levels of malondialdehyde and vitamin E in major depressive disorder and generalized anxiety disorder. *J. Psychiatry Neurol. Sci.,* **25** (3), 206–211.

Barth, J., Schumacher, M., Herrmann-Lingen, C. (2004). Depression as a risk factor for mortality in patients with coronary heart disease: A meta-analysis. *Psychosom. Med.,* **66** (6), 802–813.

Bauer, L. K., Caro, M. A., Beach, S. R., Mastromauro, C. A., Lenihan, E., Januzzi, J. L., Huffman, J. C. (2012). Effects of depression and anxiety improvement on adherence to medication and health behaviors in recently hospitalized cardiac patients. *Amer. J. Cardiol.,* **109** (9), 1266–1271.

Black, C. N., Bot, M., Scheffer, P. G., Cuijpers, P., Penninx, B. W. (2015). Is depression associated with increased oxidative stress? A systematic review and meta-analysis. *Psychoneuroendocrinology,* **51**, 164–175.

Brouns, R., Verkerk, R., Aerts, T., Surgeloose D., Wauters, A., Scharpé, S., De Deyn, P. P. (2010). The role of tryptophan catabolism along the kynurenine pathway in acute ischemic stroke. *Neurochem. Res.,* **35** (9), 1315–1322.

Brown, A. D., Barton, D. A., Lambert, G. W. (2009). Cardiovascular abnormalities in patients with major depressive disorder: autonomic mechanisms and implications for treatment. *CNS Drugs*, **23** (7), 583–602.

Huffman, J. C., Mastromauro, C. A., Sowden, G. L., Wittmann, C., Rodman, R., Januzzi, J. L. (2011). A collaborative care depression management program for cardiac inpatients: Depression characteristics and in-hospital outcomes. *Psychosomatics,* **52** (1), 26–33.

Carney, R. M., Freedland, K. E. (2008). Depression in patients with coronary heart disease. *Amer. J. Med.,* **121** (11, Suppl 2), S20–S27.

Cassano, P., Fava, M. (2002). Depression and public health: An overview. *J. Psychosom. Res.,* **53** (4), 849–857.

Celano, C. M., Huffman, J. C. (2011). Depression and cardiac disease: A review. *Cardiol. Rev.,* **19** (3), 130–142.

Chauvet-Gélinier, J. C., Trojak B., Vergès-Patois B., Cottin Y., Bonin B. (2013). Review on depression and coronary heart disease. *Arch. Cardiovasc. Dis.,* **106** (2), 103–110.

Cheraghi, M., Ahmadvand, H., Maleki, A., Babaeenezhad, E., Shakiba, S., Hassanzadeh, F., (2019). Oxidative stress status and liver markers in coronary heart disease. *Rep. Biochem. Mol. Biol.,* **8** (1), 49–55.

Cumurcu, B. E., Ozyurt, H., Etikan I., Demir S., Karlidag R. (2009). Total antioxidant capacity and total oxidant status in patients with major depression: Impact of antidepressant treatment. *Psychiatry Clin. Neurosci.,* **63** (5), 639–645.

De Hert, M., Detraux, J., Vancampfort, D. (2018). The intriguing relationship between coronary heart disease and mental disorders. *Dialogues Clin. Neurosci.,* **20** (1), 31–40.

Dhama, K., Latheef, S. K., Dadar, M., Samad, H. A., Munjal, A., Khandia, R., Karthik, K., Tiwari, R., Yatoo, M. I., Bhatt, P., Chakraborty, S., Singh, K. P., Iqbal, H., Chaicumpa, W., Joshi, S. K. (2019). Biomarkers in stress

related diseases/disorders: Diagnostic, prognostic, and therapeutic values. *Front Mol. Biosci.,* **6**, p. 91.

Dhar, A. K., Barton, D. A. (2016). Depression and the link with cardiovascular disease. *Front Psychiatry,* **7**, 33.

Ērglis, A., Dzērve-Tāluts, V., Bajāre, I. (2020). *Latvijas iedzīvotāju kardiovaskulāro un citu neinfekcijas slimību riska faktoru šķērsgriezuma pētījums* [Cross-sectional study of cardiovascular and noninfectious diseases risk factors among Latvia's inhabitants]. Latvijas Universitātes Kardioloģijas un reģeneratīvās medicīnas zinātniskais institūts, Rīga. 13 pp. (in Latvian). https://esparveselibu.lv/sites/default/files/2020-10/LATVIJAS%20IEDZĪVOTĀJU%20KARDIOVASKULĀRO%20%20UN%20CITU%20NEINFEKCIJAS%20SLIMĪBU%20RISKA%20FAKTORU%20ŠĶĒRSGRIEZUMA%20PĒTĪJUMS%20.pdf (accessed 12.03.2022).

Feng, Z., Hu, W., Marnett, L. J., Tang, M. S. (2006). Malondialdehyde, a major endogenous lipid peroxidation product, sensitizes human cells to UV and BPDE-induced killing and mutagenesis through inhibition of nucleotide excision repair. *Mutat. Res.,* **601** (1–2), 125–136.

Frasure-Smith, N., Lespérance, F. (2010). Depression and cardiac risk: Present status and future directions. *Heart,* **96** (3), 173–176.

GBD 2017 Disease and Injury Incidence and Prevalence Collaborators (2018). Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990–2017: A systematic analysis for the Global Burden of Disease Study 2017. *Lancet,* **392** (10159), 1789–1858.

Glassman, A. H., Bigger, J. T., Gaffney, M., Shapiro, A. P., Swenson, J. R. (2006). Onset of major depression associated with acute coronary syndromes: Relationship of onset, major depressive disorder history, and episode severity to sertraline benefit. *Arch. Gen. Psychiatry,* **63** (3), 283–288.

Goodman, J., Shimbo D., Haas, D. C., Davidson, K. W., Rieckmann, N. (2008). Incident and recurrent major depressive disorder and coronary artery disease severity in acute coronary syndrome patients. *J. Psychiatr. Res.,* **42** (8), 670–675.

Guck, T. P., Kavan, M. G., Elsasser, G. N., Barone, E. J. (2011). Assessment and treatment of depression following myocardial infarction. *Amer. Fam. Physician,* **64** (4), 641–648.

Halaris, A. (2017). Inflammation-associated co-morbidity between depression and cardiovascular disease. *Curr. Top Behav. Neurosci.,* **31**, 45–70.

Hasnain, M., Vieweg, W. V., Lesnefsky, E. J., Pandurangi, A. K. (2011). Depression screening in patients with coronary heart disease: A critical evaluation of the AHA guidelines. *J. Psychosom. Res.,* **71** (1), 6–12.

Huffman, J. C., Celano, C. M., Beach, S. R., Motiwala, S. R., Januzzi, J. L. (2013). Depression and cardiac disease: Epidemiology, mechanisms, and diagnosis. *Cardiovasc. Psychiatry Neurol.,* **2013**, 695925.

Januzzi, J. L., Jr, Stern, T. A., Pasternak, R. C., DeSanctis, R. W. (2000). The influence of anxiety and depression on outcomes of patients with coronary artery disease. *Arch. Intern. Med.,* **160** (13), 1913–1921.

Jeon, S. W., Kim, Y. K. (2017). Inflammation-induced depression: Its pathophysiology and therapeutic implications. *J. Neuroimmunol.,* **313**, 92–98.

Jiang, W., Krishnan, R., Kuchibhatla, M., Cuffe, M. S., Martsberger, C., Arias, R. M., O'Connor, C. M., SADHART-CHF Investigators (2011). Characteristics of depression remission and its relation with cardiovascular outcome among patients with chronic heart failure (from the SADHART-CHF Study). *Amer. J. Cardiol.,* **107** (4), 545–551.

Kander, M. C., Cui, Y., Liu, Z. (2017). Gender difference in oxidative stress: A new look at the mechanisms for cardiovascular diseases. *J. Cell Mol. Med.,* **21** (5), 1024–1032.

Kaya, Y., Çebı, A., Söylemez, N., Demır, H., Alp, H. H., Bakan, E. (2012). Correlations between oxidative DNA damage, oxidative stress and coen-zyme Q10 in patients with coronary artery disease. *Int. J. Med. Sci.,* **9** (8), 621–626.

Khandaker, G. M., Zuber, V., Rees, J., Carvalho, L., Mason, A. M., Foley, C. N., Gkatzionis, A., Jones, P. B., Burgess, S. (2020). Shared mechanisms between coronary heart disease and depression: Findings from a large UK general population-based cohort. *Mol. Psychiatry,* **25** (7), 1477–1486.

Khawaja, I. S., Westermeyer, J. J.., Gajwani, P., Feinstein, R. E. (2009). Depression and coronary artery disease: The association, mechanisms, and therapeutic implications. *Psychiatry (Edgmont),* **6** (1), 38–51.

Kuller, L. H., Arnold, A. M., Psaty, B. M., Robbins, J. A., O'Leary, D. H., Tracy, R. P., Burke, G. L., Manolio, T. A., Chaves, P. H. M. (2006). 10-year follow-up of subclinical cardiovascular disease and risk of coronary heart disease in the Cardiovascular Health Study. *Arch. Intern. Med.,* **166** (1), 71–78.

Lespérance, F., Frasure-Smith, N., Koszycki, D., Laliberté, M. A., van Zyl, L. T., Baker, B., Swenson, J. R., Ghatavi, K., Abramson, B. L., Dorian, P., Guertin, M. C., CREATE Investigators (2007). Effects of citalopram and interpersonal psychotherapy on depression in patients with coronary artery disease: The Canadian cardiac randomized evaluation of antidepressant and psychotherapy efficacy (CREATE) trial. *JAMA,* **297** (4), 367–379.

Lin, D., Wang, L., Yan, S., Zhang, Q., Zhang, J. H., Shao, A. (2019). The role of oxidative stress in common risk factors and mechanisms of cardiocerebrovascular ischemia and depression. *Oxid. Med. Cell Longev.,* **2019**, 2491927.

Liu, T., Zhong S., Liao, X., Chen J., He, T., Lai, S., Jia Y. (2015). A meta-analysis of oxidative stress markers in depression. *PLoS One,* **10** (10), e0138904.

Maes, M., Galecki, P., Chang, Y. S., Berk, M. (2011). A review on the oxidative and nitrosative stress (O&NS) pathways in major depression and their possible contribution to the (neuro)degenerative processes in that illness. *Prog. Neuropsychopharmacol. Biol. Psychiatry,* **35** (3), 676–692.

Matthews, K. A., Schott, L. L., Bromberger, J. T., Cyranowski, J. M., Everson-Rose, S. A., Sowers, M. (2010). Are there bidirectional associations between depressive symptoms and C-reactive protein in mid-life women? *Brain Behav. Immun.,* **24** (1), 96–101.

Mattina, G. F., Van Lieshout, R. J., Steiner, M. (2019). Inflammation, depression and cardiovascular disease in women: The role of the immune system across critical reproductive events. *Ther. Adv. Cardiovasc. Dis.,* **13**, doi: 10.1177/1753944719851950.

Mazereeuw, G., Herrmann, N., Andreazza, A. C., Scola, G., Ma, D., Oh, P. I., Lanctôt, K. L. (2017). Oxidative stress predicts depressive symptom changes with omega-3 fatty acid treatment in coronary artery disease patients. *Brain Behav. Immun.,* **60**, 136–141.

Mazza, M., Lotrionte, M., Biondi-Zoccai, G., Abbate, A., Sheiban, I., Romagnoli, E. (2010). Selective serotonin reuptake inhibitors provide significant lower re-hospitalization rates in patients recovering from acute coronary syndromes: Evidence from a meta-analysis. *J. Psychopharmacol.,* **24** (12), 1785–1792.

Moryś, J. M., Bellwon, J., Adamczyk, K., Gruchała, M. (2016). Depression and anxiety in patients with coronary artery disease, measured by means of self-report measures and clinician-rated instrument. *Kardiol. Pol.,* **74** (1), 53–60.

Moylan, S., Berk, M., Dean O. M., Samuni Y., Williams, L. J., O'Neil, A., Hayley, A. C., Pasco, J. A., Anderson, G., Jacka, F. N., Maes, M. (2014). Oxidative & nitrosative stress in depression: why so much stress? *Neurosci. Biobehav. Rev.,* **45**, 46–62.

Murray, C. J., Lopez, A. D. (2013). Measuring the global burden of disease. *New Engl. J. Med.,* **369** (5), 448–57.

Myers, V., Gerber, Y., Benyamini, Y., Goldbourt, U., Drory, Y. (2012). Post-myocardial infarction depression: Increased hospital admissions and reduced adoption of secondary prevention measures — a longitudinal study. *J. Psychosom. Res.,* **72** (1), 5–10.

Nemeroff, C. B., Goldschmidt-Clermont, P. J. (2012). Heartache and heartbreak — the link between depression and cardiovascular disease. *Nat. Rev. Cardiol.,* **9** (9), 526–539.

Nezafati, M. H, Vojdanparast, M., Nezafati, P. (2015). Antidepressants and cardiovascular adverse events: A narrative review. *ARYA Atheroscl,* **11** (5), 295–304.

Nikkheslat, N., Zunszain, P. A, Horowitz, M. A, Barbosa, I. G., Parker, J. A., Myint, A. M., Schwarz, M. J., Tylee, A. T., Carvalho, L. A., Pariante, C. M. (2015). Insufficient glucocorticoid signaling and elevated inflammation in coronary heart disease patients with comorbid depression. *Brain Behav. Immun.*, **48**, 8–18.

GBD 2016 Causes of Death Collaborators (2017). Global, regional, and national age-sex specific mortality for 264 causes of death, 1980–2016: A systematic analysis for the Global Burden of Disease Study 2016. *Lancet*, **390** (10100), 1151–1210.

Pezeshkian, M., Nouri, M., Zahraei, M., Afrasiabi, A., Abadi, N. A. (2001). Study of MDA, antioxidant vitamins, lipoproteins serum levels and anthropometry parameters in coronary artery disease patients. *Med. J. Islam. Acad. Sci.*, **14**, 5–8.

Pizzi, C., Mancini, S., Angeloni, L., Fontana, F., Manzoli, L., Costa, G. M. (2009). Effects of selective serotonin reuptake inhibitor therapy on endothelial function and inflammatory markers in patients with coronary heart disease. *Clin. Pharmacol. Ther.*, **86** (5), 527–532.

Puppel, K., Kapusta, A., Kuczyńska, B. (2015). The etiology of oxidative stress in the various species of animals, a review. *J. Sci. Food Agric.*, **95** (11), 2179–2184.

Rees, J. N., Florang, V. R., Anderson, D. G., Doorn, J. A. (2007). Lipid peroxidation products inhibit dopamine catabolism yielding aberrant levels of a reactive intermediate. *Chem. Res. Toxicol.*, **20** (10), 1536–1542.

Del Rio, D., Stewart, A. J., Pellegrini, N. (2005). A review of recent studies on malonaldehyde as toxic molecule and biological marker of oxidative stress. *Nutr. Metab. Cardiovasc. Dis.*, **15** (4), 316–328.

Roth, G. A., Mensah, G. A., Johnson, C. O., Addolorato, G., Ammirati, E., Baddour, L. M., Barengo, N. C., Beaton, A. Z., Benjamin, E. J., Benziger, C. P., *et al.* (2020). Global Burden of Cardiovascular Diseases and Risk Factors, 1990-2019: Update From the GBD 2019 Study. *J. Amer. Coll. Cardiol.*, **76** (25), 2982–3021.

Sanchis-Gomar, F., Perez-Quilis, C., Leischik, R., Lucia, A. (2016). Epidemiology of coronary heart disease and acute coronary syndrome. *Ann. Transl. Med.*, **4** (13), 256.

Sarandol, A., Sarandol, E., Eker, S. S., Erdinc, S., Vatansever, E., Kirli, S. (2007). Major depressive disorder is accompanied with oxidative stress: Short-term antidepressant treatment does not alter oxidative antioxidative systems. *Hum. Psychopharmacol.*, **22** (2), 67–73.

Swardfager, W., Herrmann, N., Marzolini, S., Saleem, M., Farber, S. B., Kiss, A., Oh, P. I., Lanctôt, K. L. (2011). Major depressive disorder predicts completion, adherence, and outcomes in cardiac rehabilitation: a prospective cohort study of 195 patients with coronary artery disease. *J. Clin. Psychiatry*, **72** (9), 1181–1188.

Trebatická, J., Dukát, A., Ďuračková, Z., Muchová, J. (2017). Cardiovascular diseases, depression disorders and potential effects of Omega-3 fatty acids. *Physiol. Res.*, **66** (3), 363–382.

Van der Kooy, K., van Hout, H., Marwijk, H., Marten, H., Stehouwer, C., Beekman, A. (2007). Depression and the risk for cardiovascular diseases: Systematic review and meta analysis. *Int. J. Geriatr. Psychiatry*, **22** (7), 613–626.

van Melle, J. P., de Jonge, P., Spijkerman, T. A., Tijssen, J. G., Ormel, J., van Veldhuisen, D. J., van den Brink, R. H., van den Berg, M. P. (2004). Prognostic association of depression following myocardial infarction with mortality and cardiovascular events: A meta-analysis. *Psychosom. Med.*, **66** (6), 814–822.

Vaváková, M., Ďuračková, Z., Trebatická, J. (2015). Markers of oxidative stress and neuroprogression in depression disorder. *Oxid. Med. Cell. Longev.*, **2015**, 898393.

Vichova, T., Motovska, Z. (2013). Oxidative stress: Predictive marker for coronary artery disease. *Exp. Clin. Cardiol.*, **18** (2), e88–e91.

Voicehovskis, V. V., Margolina, J., Voicehovska, J. G, Miksons, A. (2013). Validation of the Latvian version of the Geriatric depression scale (GDS). *Psychother. Psychosom.*, **82** (S1), 122–123.

Wang, Q., Liu, D., Song, P., Zou, M. H. (2015). Tryptophan- kynurenine pathway is dysregulated in inflammation, and immune activation. *Front Biosci. (Landmark Ed)*, **20**, 1116–1143.

Whooley, M. A., Wong, J. M. (2013). Depression and cardiovascular disorders. *Annu. Rev. Clin. Psychol.*, **9**, 327–354.

Wirleitner, B., Rudzite, V., Neurauter, G., Murr, C., Kalnins, U., Erglis, A., Trusinskis, K., Fuchs, D. (2003). Immune activation and degradation of tryptophan in coronary heart disease. *Eur. J. Clin. Invest.*, **33** (7), 550–554.

World Health Organization, Mendis, S., Puska, P., Norrving, B. (eds.) (2011). *Global Atlas on Cardiovascular Disease Prevention and Control.* World Health Organization. 155 pp.

Yekehtaz, H., Farokhnia, M., Akhondzadeh, S. (2013). Cardiovascular considerations in antidepressant therapy: An evidence-based review. *J. Tehran Heart Cent.*, **8** (4), 169–176.

Zuo, H., Ueland, P. M., Ulvik, A., Eussen, S. J., Vollset, S. E., Nygård, O., Midttun, Ø., Theofylaktopoulou, D., Meyer, K., Tell, G. S. (2016). Plasma biomarkers of inflammation, the kynurenine pathway, and risks of all-cause, cancer, and cardiovascular disease mortality. *Amer. J. Epidemiol.*, **183** (4), 249–258.

Received 28 April 2021
Accepted in the final form 5 December 2021

DEPRESIJAS UN OKSIDATĪVĀ STRESA MIJIEDARBĪBA STABILĀ KORONĀRĀ SIRDS SLIMĪBĀ

Depresija (D) ir neatkarīgs kardiovaskulāro slimību (KVS) riska faktors, nesaistīts ar citiem iepriekš noteiktiem sirds slimību riska faktoriem. Pacientiem ar mazāk smagu depresiju tika konstatēts lielāks sirdsdarbības apstāšanās risks nekā pacientiem, kuriem depresijas nebija. D pasliktina KVS prognozi, ievērojami palielinot atkārtotas koronārās sirds slimības (KSS) risku. Daži pētījumi liecina, ka oksidatīvais stress (OS) tieši palielina D risku pacientiem ar KVS. OS tiek uzskatīts par mehānismu, kas saistīts gan ar KVS, gan ar D patofizioloģiju. Kopējie riska faktori palielina OS izstrādi un samazina antioksidantu aizsargspējas, tādējādi veicinot mijiedarbotu išēmisku KVS un D rašanos un attīstību. Pašlaik nav pietiekamu pierādījumu tam, ka profilaktisks D skrīnings pacientiem ar KSS palīdzēs uzlabot pacientu stāvokli. Šajā apskatā atkārtoti uzsvērta nepieciešamība pēc daudzdisciplināras pieejas, lai izprastu, diagnosticētu un pēc tam ārstētu šos bieži vien vienlaicīgi sastopamos saslimšanas gadījumus ar KSS un D. OS marķieru novērtējums varētu mainīt riska stratifikāciju, diagnostiku, profilaksi un ārstēšanu pacientiem, kuriem ir KSS un D, gadījumos ar un bez iepriekšējām sirds slimībām anamnēzē.