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ASSOCIATION OF DEPRESSION AND ANXIETY WITH CARDIOVASCULAR CO-MORBIDITY AND 10-YEAR RISK OF CARDIOVASCULAR MORTALITY (SCORE) IN A PRIMARY CARE POPULATION OF LATVIA

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ABBREVIATIONS

CIDI	Composite International Diagnostic Interview
DALY's	Disability adjusted life years
DSM	Diagnostic and Statistical Manual of Mental Disorders, $4^{th}/5^{th}$ Edition
ES	European Union
GAD-7	Generalised Anxiety Disorder scale -7
GP	General practitioners
HADS	Hospital Anxiety and Depression Scale
HR	Hazard ratio
CHD	Coronary heart disease
CV	Cardiovascular
CVD	Cardiovascular disease
BMI	Body mass index
MDD	Major depressive disorder
MI	Myocardial infarction
MINI	Mini International Neuropsychiatric Interview
n	Number
OR	Odds ratio
p	Statistical significance
PAR	Population attributable risk
PHQ-9	The Patient Health Questionnaire -9
RF	Risk factors
RR	Relative risk
SCORE	Systematic Coronary Risk Evaluation
SD	Standard deviation
SPSS	Statistical Package for the Social Sciences

ICD-10	International Statistical Classification of Diseases and Related Health Problems, 10th revision
CI	Confidence interval
α	Cronach's α (alpha)
χ^2	Chi-squared test

1. INTRODUCTION

1.1. Topicality of the Problem

Anxiety and major depressive disorder (MDD) are the most common mental disorders in the European Union (EU) affecting 20.9 % of the population (99.4 million people every year). MDD has become already now the most important single contributor to the total disease burden not only in the EU but also worldwide, as measured by disability-adjusted life years (DALYs) (WHO, 2018; Wittchen, Jacobi, Rehm et al., 2011). Anxiety disorders are the most frequent mental disorders in the general population with a prevalence rate of 14 % (Wittchen, Jacobi, Rehm et al., 2011). Mental disorders, particularly anxiety and depression, are highly prevalent in patients with chronic somatic illnesses, affecting approximately 50 % of patients in primary care settings (Gili, Comas, García-García et al., 2010; Roca, Gili, Garcia-Garcia et al., 2009), and they are associated with poorer prognosis and increased treatment non-compliance, financial costs, other resource utilisation, lost productivity and disability (Egede, 2007; Scott, Bruffaerts, Tsang et al., 2007). Comorbidity of depression, anxiety and cardiovascular (CV) diseases (CVDs) is an especially important public health concern because CVDs are the leading cause of death globally, representing 31 % of all deaths (WHO, 2012). In Latvia, the mortality rate from CVDs is one of the highest in the EU, reaching 57 % of all death in 2015 (SKPC, 2015a, b), with the standard premature mortality from CVDs three times higher than on average than in the EU (Eurostat, 2013).

Depression and anxiety are highly prevalent in patients with CVDs (Rutledge, Linke, Krantz et al., 2009). Approximately one in five patients hospitalised for an acute coronary event meets the diagnostic criteria for MDD, and about half (40–65 %) demonstrate sub-syndromal depressive symptoms (Lichtman, Froelicher, Blumenthal et al., 2014), a prevalence rate that is at least three times higher than in the general population (Kessler, Berglund, Demler et

al., 2003). This proportion is even greater in stroke survivors, affecting nearly one in three patients (Hackett, Yapa, Parag et al., 2005; Hackett and Pickles, 2014). Clinically significant symptoms of anxiety have been reported in 20 % to 42 % of the CVD population (Campbell Burton, Murray, Holmes et al., 2013; Lane, Carroll, Ring et al., 2002; Todaro, Shen, Raffa et al., 2007).

Over the last 25 years, a large body of evidence has demonstrated that depression and anxiety are not only more common in CV patients, but that these two psychiatric conditions are also risk factors for increased cardiac morbidity and recurrent CV events and mortality, independent of traditional CV risk factors (Gan, Gong, Tong et al., 2014; Piepoli, Hoes, Agewall et al., 2016). The seminal INTERHEART study, involving 15,152 myocardial infarction (MI) cases from 52 countries, revealed that psychosocial factors such as depression and anxiety account for 32 % of the population attributable risk (PAR) for MI, a level of risk comparable to that of smoking (PAR, 35.7 %) and even greater than that of diabetes (PAR, 9.9 %) and hypertension (PAR, 17.9 %) (Yusuf, Hawken, Ounpuu et al., 2004). Depression predicts incident coronary heart disease (CHD) (relative risk (RR) = 1.9 (95 % confidence interval (CI): 1.49–2.42)) (Nicholson, Kuper and Hemingway, 2006) and stroke (hazard ratio (HR) = 1.45 (95 % CI: 1.29–1.63)) (Pan, Sun, Okereke et al., 2011). Previous meta-analyses evaluating the prognostic association of depression with mortality and new CV events in patients with already established CVDs demonstrated that depression is associated with a 1.6- to 2.6-fold increased risk of future major adverse cardiovascular events, cardiac mortality and all-cause mortality (Frasure-Smith and Lesperance, 2010; Meijer, Conradi, Bos et al., 2011), a level similar to traditional CV risk factors such as reduced left ventricular ejection fraction and diabetes (Rozanski, Blumenthal, Davidson et al., 2005). A meta-analysis by Roest et al. in 2010 summarising 20 prospective studies found that anxiety was associated with a 26 % increased risk of incident CHD (HR = 1.26; 95 % CI: 1.15–1.38) and a 48 % increased risk of cardiac mortality (HR = 1.48; 95 %

CI: 1.14–1.92), independent of demographic variables, biological risk factors, and health behaviors (Roest, Martens, de Jonge et al., 2010). A more recent meta-analysis that included 37 studies with 1,565,699 participants found an even stronger association and showed that anxiety was associated with a 52 % increased incidence of CVD (HR = 1.52, 95 % CI: 1.36–1.71) (Batelaan, Seldenrijk, Bot et al., 2016), despite some studies pointing at a possible protective role of anxiety in CVD prognosis (Meyer, Buss and Herrmann-Lingen, 2010; Meyer, Hussein, Lange et al., 2015). Another recent meta-analysis by Emdin et al. in 2016 concluded that the association of anxiety with stroke was stronger (RR = 1.71, 95 % CI: 1.18–2.50) than the association of anxiety with CHD (RR = 1.41, 95 % CI: 1.23–1.61) (Emdin, Odutayo, Wong et al., 2016).

The American Heart Association (AHA) has taken a lead role in highlighting the importance of depression in CV patients by recommending routine screening of all cardiac patients in 2008 (Huffman and Celano, 2015; Lichtman, Bigger, Blumenthal et al., 2008). However, a recent systematic review by Thombs and colleagues (2013) found no evidence that this strategy improves depression or cardiac outcomes (Thombs, Roseman, Coyne et al., 2013). Furthermore, in patients with already diagnosed CHD, mental health interventions for MDD showed moderate efficacy for reducing cardiac events, but remained controversial in the ability to reduce total mortality (Piepoli, Hoes, Agewall et al., 2016; Rutledge, Redwine, Linke et al., 2013). This finding underscores the importance of primary prevention of CVD and the need to identify the target population who would most benefit from depression and anxiety screening.

The Systematic Coronary Risk Evaluation (SCORE) function measures the 10-year risk of a fatal CVD. The SCORE charts have been elaborated to rapidly calculate CV mortality risk with sufficient accuracy in both high- and low-risk European population. Since 1994, the SCORE has been widely advocated by the joint recommendations from the European Association of

Preventive Cardiology, European Society of Cardiology, European Atherosclerosis Society and European Society of Hypertension (Conroy, Pyorala, Fitzgerald et al., 2003; Piepoli, Hoes, Agewall et al., 2016).

The largest cross-sectional surveys on CV risk factors in the EU called European Action on Secondary and Primary Prevention by Intervention to Reduce Events (EUROASPIRE) were conducted to determine whether the Joint European Societies guidelines on CVD prevention are being followed in clinical practice (Ian, Dan, Knut et al., 2007; Perk, De Backer, Gohlke et al., 2012). EUROASPIRE III and IV surveys concluded that large proportions of CV patients in the EU do not achieve lifestyle, risk factor and therapeutic targets and there are considerable variations between European countries in patients' CV risk factor prevalences and use of cardioprotective medications (Kotseva, De Bacquer, De Backer et al., 2016; Kotseva, Wood, De Backer et al., 2009). The Baltic States (Estonia, Latvia and Lithuania) appeared to be among the most profoundly CVD-affected countries within Europe with very high CV mortality rates compared to other countries in the EU (Eurostat, 2013; Kotseva, Wood, De Backer et al., 2009). It was explained by high prevalence of CV risk factors (dyslipidemia, obesity, diabetes and hypertension) that may relate to a larger proportion of poorer and older people, patients with lower education, as well as those outside social support networks, problems in doctor-patient relationship, inadequate dosing of drugs, unhealthy lifestyle (Erglis, Dzerve, Pahomova-Strautina et al., 2012; Viigimaa, Erglis, Latkovskis et al., 2014). Comorbidity of depression and/or anxiety with CVD as a possible explanation has not been sufficiently examined in the Baltic region. Search of the literature revealed only few studies from Lithuania and Estonia that provided conflicting results (Burokienė, Karčiauskaitė, Kasiulevičius et al., 2014a; Suija, Kalda and Maaroos, 2009). As the premature mortality rate from CVD in Latvia is alarmingly high (Eurostat, 2013), this topic is of particular importance for Latvia where there have been no studies to date.

1.2. Aim of the Study

The aim of this study was to examine the association of depression and anxiety with cardiovascular (CV) co-morbidity and the 10-year CV mortality risk (SCORE) in a primary care population of Latvia.

1.3. Tasks of the Study

1. To compare the prevalence of cardiovascular diseases (CVD) in patients with detected depression or anxiety and patients without clinically significant symptoms of depression or anxiety in primary care population of Latvia.
2. To compare the prevalence of a very high 10-year CV mortality risk (SCORE) in patients with detected depression or anxiety and patients without clinically significant symptoms of depression or anxiety in primary care population of Latvia.
3. To evaluate the link between depression, anxiety and CVD using multivariate analysis in primary care population of Latvia.
4. To assess the association of depression and anxiety with a very high 10-year CV mortality risk (SCORE) using multivariate analysis in primary care population of Latvia.

1.4. Hypotheses of the Study

1. The prevalence of CVD in patients with detected depression or anxiety is higher compared to patients without clinically significant symptoms of depression or anxiety in primary care population of Latvia.

2. The prevalence of a very high 10-year CV mortality risk in patients with detected depression or anxiety is higher compared to patients without clinically significant symptoms of depression or anxiety in primary care population of Latvia.

3. Depression and anxiety is associated with CVD and a very high 10-year CV mortality risk independant of socio-demographic, lifestyle CV and traditional CV risk factors.

1.5. Scientific Novelty of the Study

Although depression and anxiety have been recognised as independent risk factors for both development and prognosis of CVD, the role of these CV risk factors have been underrecognised in Latvia. The largest national epidemiological surveys which were previously carried out to assess the prevalence of cardiovascular risk factors in Latvian adults have not included depression and anxiety as risk factors (Erglis, Dzerve, Pahomova-Strautina et al., 2012; Ivanovs and Rancans, 2016; Kalvelis, Stukena, Bahs et al., 2011). This is the first study on the association of depression and anxiety with CVD and 10-year CV mortality risk in a primary care population in Latvia (Ivanovs, Kivite, Ziedonis et al., 2018a; Ivanovs, Kivite, Ziedonis et al., 2018b). This study addresses an important gap in the literature by focusing on Latvian, Baltic and East European populations.

1.6. Practical Implications of the Study

Recent evidence reported major cross-country differences in the determinants of disability among patients with CVD and supported implementation of country-specific programmes to reduce disability among CV patients (Assari, 2015). Therefore, local data are crucially important for the management of CV patients and for medical and nursing education, policy, and programme development in Latvia. Findings of this study could help to outline certain individuals for health providers to initiate screening for depression and anxiety to potentially improve their CV health.

1.7. Ethical Issues of the Study

All procedures complied with the ethical standards on human experimentation (World Medical Association Helsinki Declaration). Ethical permission was granted by the Rīga Stradiņš University Ethics Committee (No 8/ 18.06.2015.). Informed consent was obtained from all participants after they had received a full explanation of the purpose and nature of the study.

1.8. Outline of the Thesis

The Thesis consists of 114 pages in Latvian, in compliance with classical structure of a thesis. The work is structured in ten chapters: Introduction; Literature review, Subjects and Methods; Results; Discussion; Conclusions; Publications; Acknowledgements; References and Appendixes. Text of Thesis is supplemented by 6 Tables, 1 Figure and 7 Appendixes. Reference list consists of 303 cited references.

2. SUBJECTS AND METHODS

The cross-sectional study was carried out in 2015 within the framework of the National Research Programme BIOMEDICINE 2014–2017 to assess the prevalence of the most frequent mental disorders in primary care settings in Latvia. Patients were recruited from 24 primary care facilities all over the country (16 in urban and 8 in rural areas). The survey was conducted in Latvian and Russian (the two most commonly spoken languages in Latvia).

The inclusion criteria were as follows: all consecutive treatment-seeking patients attending primary care facility, persons who were 18 years of age or older, and subjects who had provided their informed consent. The exclusion criteria were as follows: persons who declined to be enrolled in this research project, persons who were younger than 18 years of age, and persons who presented with an urgent health complaints requiring immediate intervention.

During a one-week period at each primary care facility, all consecutive patients who corresponded to the inclusion criteria were invited to complete a nine-item Patient Health Questionnaire (PHQ-9) and a seven-item Generalised Anxiety Disorder scale (GAD-7) in Latvian or Russian (language as preferred by a participant) followed by an interview with a structured socio-demographic questionnaire and measurements of height, weight, waist circumference, blood pressure and total cholesterol on the same study visit. Assessment of CV risk factors was based on recommendations and criteria of the 2012 Joint European Societies' guidelines on cardiovascular disease prevention (Perk, De Backer, Gohlke et al., 2012) and questionnaires of the Finbalt Health Monitor System survey (Kasmel, Helasoja, Lipand et al., 2004). The Mini International Neuropsychiatric Interview (MINI) was conducted over the telephone by a specially trained psychiatrist within a period of two weeks after the first contact. The MINI interview was used to identify current and/or lifetime episodes of major depressive disorder and most common anxiety disorders (generalised

anxiety disorder, panic disorder, agoraphobia, social phobia, obsessive-compulsive disorder and post-traumatic stress disorder). Additionally, information about the diagnosis of depression and anxiety disorders, prescription of cardiovascular and psychotropic medications, and blood test results of lipids, glucose and glycated hemoglobin from the previous three months were obtained from medical documents.

2.1. Association of Depression and Anxiety with Cardiovascular Diseases

CVD was defined as an atherosclerotic vascular disease in the heart (CHD, angina, MI), brain (cerebrovascular disease, transient ischemic attack, stroke) and periphery (peripheral arterial disease), or a combination of these conditions (Piepoli, Hoes, Agewall et al., 2016). Diagnoses of CVD were confirmed using medical records.

2.1.1. Statistical Analysis

Statistical Package for the Social Sciences (SPSS) version 20.0 (IBM SPSS Corp.) was used for all statistical analyses. Statistical significance was evaluated at the level of $p < 0.05$. Crude and stratified percentages were used for descriptive statistics. To identify factors associated with the presence of CVDs, univariate and multivariate analyses were carried out. The multivariate model was developed by using binary logistic regression. To avoid multi-collinearity, separate regression models were elaborated for two indicators of depression as independent predictors of CVD- lifetime depressive episode (identified by the MINI interview) and current depressive symptoms (detected through the PHQ-9 instrument). For the final model of multivariate analysis, generalised anxiety disorder (according to the MINI) was chosen, as it gave the best-fitting regression model when compared to other anxiety disorders identified by the MINI or to clinically relevant anxiety symptoms detected by the GAD-7 questionnaire.

2.2. Association of Depression and Anxiety with 10-year Cardiovascular Mortality Risk

CV mortality risk was assessed using the Systematic Coronary Risk Evaluation (SCORE) system that measures the 10-year risk of a fatal CV event (e.g. stroke, myocardial infarction or aneurysm of the aorta). The SCORE risk assessment is derived using data from 12 European cohort studies with 205,178 participants covering a wide geographic spread of countries at different levels of CV risk. The SCORE charts have been elaborated to calculate risk in both high- and low-risk European population. The reported predictive values representing areas under receiver operating characteristic curves for SCORE have ranged from 0.71 to 0.84 (Conroy, Pyorala, Fitzgerald et al., 2003). Total CV risk estimation using SCORE is a crucial tool for supporting clinicians during the optimisation of individual CV risk reduction in apparently healthy individuals. This risk estimation is based on the following risk factors: gender, age, smoking, systolic blood pressure and total cholesterol. The threshold for very high risk is defined as a calculated SCORE $\geq$ 10 %, and it was used as a cut-off score in our study (Piepoli, Hoes, Agewall et al., 2016; The European Society of Cardiology, 2012). SCORE was calculated for each individual patient using the electronic version of the high risk chart developed and supported by the European Society of Cardiology (The European Society of Cardiology, 2012).

2.2.1. Statistical Analysis

Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) version 20.0 (IBM SPSS Corp.). Statistical significance was considered as $p < 0.05$. Differences of the study sample between comparative SCORE groups were detected using Chi-Square test or Fisher's exact test.

To examine associations of depression and anxiety with the SCORE function, an univariate and stepwise multivariate analysis (using binary logistic

regression) was conducted according to the conceptual hierarchical framework model (Victora, Huttly, Fuchs et al., 1997), in which possible confounding variables were distributed into three groups: proximal (positive family history, diabetes, use of antihypertensive, cholesterol lowering medications and antidepressants), intermediate (body mass index/waist circumference, depression and/or anxiety, sedentary lifestyle, consumption of fresh vegetables and fruits, consumption of fish, alcohol use) and distal factors (education, employment status, marital status, place of residence). Factors that were used in the calculation of the SCORE function (gender, age, blood pressure, total cholesterol, smoking status) were excluded from the list of independent variables in regression analysis.

As current depressive episode according to the MINI and anxiety symptoms detected by the GAD-7 did not show statistically significant results in the univariate analysis, these measures were not included in the final regression model. To gain more statistical power, we combined all anxiety disorders according to the MINI into one current anxiety variable for the final analysis, including generalised anxiety disorder, panic disorder, post-traumatic stress disorder, and agoraphobia. Previous research has demonstrated that these anxiety disorders contribute to the risk of developing CVD and a worse prognosis of CVD (Piepoli, Hoes, Agewall et al., 2016; Pogosova, Saner, Pedersen et al., 2015).

3. RESULTS

From 1756 approached subjects, 152 declined to participate in this study. The mean response rate was 91.3 %, it varied between 86.3–93.7 % across 24 primary care facilities all over the country. Those who declined did not significantly differ in the basic sociodemographic characteristics from the study sample. In total, 1604 patients were approached to complete the PHQ-9 and the GAD-7 questionnaires, which were completed by 1585 of participants.

3.1. Association of Depression and Anxiety with Cardiovascular Diseases

3.1.1. Description of the Study Sample

For those who completed both questionnaires, information about the presence of CVD diagnosis was available in 1565 subjects, 489 (31.2 %) men and 1076 (68.8 %) women, which were included in the final analysis. CVD (angina, myocardial infarction, stroke, transient ischemic attack, chronic cerebrovascular disorder and/or peripheral arterial disease) was detected in 17.1 % (n = 268) of the studied population. The prevalence of CVD was slightly higher among men than women, with values of 18.4 % and 16.5 %, respectively.

One third (31.2 %) of the study sample were males, and one third (28.8 %) had a university degree. Slightly more than a half (55.8 %) of the respondents had reached or exceeded the age of 55 years, and half (51.9 %) were employed. One fifth (19.9 %) of the study subjects were residing in the capital city, Riga (Table 3.1).

Table 3.1

Description of the study sample; prevalence of cardiovascular diseases in subgroups of the independent variables

Independent variables	CVD positive		CVD negative		Total	
	n	%	n	%	n	%
Gender						
Male	90	18.4	399	81.6	489	31.2
Female	178	16.5	898	83.5	1076	68.8
Age						
≤ 54 years	15	2.2	677	97.8	692	44.2
≥ 55 years	253	29.0	620	71.0	873	55.8
Education						
9-years basic and unfinished basic education	58	27.2	155	72.8	213	13.7
General or vocational secondary and unfinished secondary education	147	16.5	746	83.5	893	57.5
Higher and unfinished higher education	61	13.6	387	86.4	448	28.8
Employment status						
Economically inactive	208	31.5	452	68.5	660	42.4
Unemployed	5	5.7	83	94.3	88	5.7
Employed	54	6.7	754	93.3	808	51.9
Place of residence						
Riga	111	35.7	200	64.3	311	19.9
Other city	121	16.2	627	83.8	748	47.8
Rural	36	7.1	470	92.9	506	32.3
Positive family history of premature CVD (< 55 years in men and < 65 years in women)						
Unknown	16	24.2	50	75.8	66	4.2
Yes	96	16.2	497	83.8	593	38.1
No	155	17.3	743	82.7	898	57.7
Smoking status						
Ever smoked	79	14.5	465	85.5	544	35.0
Never smoked	188	18.6	824	81.4	1012	65.0
Alcohol use, episodes of heavy drinking in last 12 months (5 or more doses of alcohol at once)						
Yes	23	9.0	232	91.0	225	16.4
No	244	18.7	1058	81.3	1302	83.6

Table 3.1 continued

Independent variables	CVD positive		CVD negative		Total	
	n	%	n	%	n	%
Consumption of fresh vegetables and fruits ≥ 200 g per day (2–3 servings)						
Yes	187	16.2	968	83.8	1155	74.2
No	80	19.9	322	80.1	402	25.8
Consumption of fish ≥ 2 times per week, one of which to be oily fish						
Yes	108	17.6	505	82.4	613	39.4
No	159	16.8	785	83.2	944	60.6
Sedentary lifestyle (30 min. of moderate physical activity)						
Unable to perform	50	29.1	122	70.9	172	11.1
1 time a week or less	94	13.9	580	86.1	674	43.5
2–3 times a week	34	16.4	173	83.6	207	13.4
4–6 times a week	20	11.2	158	88.8	178	11.5
Every day	68	21.3	251	78.7	319	20.5
Body mass index, kg/m^2						
≤ 24.99 (normal + underweight)	62	13.0	415	87.0	477	30.8
≥ 25.00 (overweight + obese)	203	19.0	868	81.0	1071	69.2
Diabetes mellitus						
Yes	42	29.6	100	70.4	142	9.1
No	226	15.9	1197	84.1	1423	90.9
Total cholesterol, mmol/l						
< 5 (normal)	133	22.0	471	78.0	604	39.2
5+ (increased)	131	14.0	807	86.0	938	60.8
Systolic hypertension, mm Hg						
< 140 (below)	134	15.1	755	84.9	889	57.4
140+ (hypertension)	131	19.9	528	80.1	659	42.6
Diastolic hypertension, mm Hg						
< 90 (below)	196	18.4	870	81.6	1066	68.9
90+ (hypertension)	69	14.3	413	85.7	482	31.1
Anxiety (MINI, any anxiety disorder)						
Yes	37	15.9	196	84.1	233	16.1
No	209	17.2	1007	82.8	1216	83.9

End of Table 3.1

Independent variables	CVD positive		CVD negative		Total	
	n	%	n	%	n	%
Anxiety (GAD-7)						
Yes	30	19.2	126	80.8	156	10.1
No	234	16.8	1156	83.2	1390	89.9
Agoraphobia (MINI)						
Yes	19	16.2	98	83.8	117	8.1
No	227	17.0	1105	83.0	1332	91.9
Generalised anxiety disorder (MINI)						
Yes	16	18.0	73	82.0	89	6.1
No	230	16.9	1130	83.1	1360	93.9
Panic disorder (MINI)						
Yes	1	9.1	10	90.9	11	0.8
No	245	17.0	1193	83.0	1438	99.2
Depression (PHQ-9)						
Yes	58	25.4	170	74.6	228	14.7
No	206	15.6	1112	84.4	1318	85.3
Current depression (MINI)						
Yes	34	22.8	115	77.2	149	10.3
No	212	16.3	1088	83.7	1300	89.7
Lifetime depression (MINI)						
Yes	80	19.7	327	80.3	407	28.1
No	166	15.9	876	84.1	1042	71.9
Antihypertensive medications						
Yes	226	29.4	542	70.6	768	49.1
No	42	5.3	755	94.7	797	50.9
Cholesterol lowering medications						
Yes	117	49.2	121	50.8	238	15.2
No	151	11.4	1176	88.6	1327	84.8
Antidepressants						
Yes	10	21.3	37	78.7	47	3.0
No	258	17.0	1260	83.0	1518	97.0

A positive family history of premature CVD was reported in 38.1 % of respondents. At the time of the questionnaire, one third (35.0 %) of the study subjects were tobacco smokers, 16.4 % had five or more drinks of alcohol at least once during the preceding year, one quarter (25.8 %) did not include fresh fruits and vegetables in their meals daily, and 60.6 % reported that they did not eat fish regularly (i.e., at least twice per week). Daily moderate physical activity was reported by one fifth (20.5 %) of individuals. More than two thirds (69.2 %) of

the patients were overweight according to BMI, and more than half had increased levels of total cholesterol (60.8 %). The prevalence of diabetes among the respondents was 9.1 %. Systolic or diastolic hypertension were present in 42.6 % and 31.1 % of patients, respectively. Thus, at the time of the questionnaire, 49.1 % of the individuals were taking antihypertensive medications, and 15.2 % were taking cholesterol lowering medicines (Table 3.1).

As shown in Table 3.1, anxiety disorders (according to the MINI) were identified in 16.1 % of patients (8.1 % had agoraphobia, 6.1 % had generalised anxiety disorder and 0.8 % had panic disorder). Anxiety screening (by using the GAD-7 instrument) was positive for one tenth (10.1 %) of the study subjects. Current depressive symptoms (PHQ-9 $\geq$ 10) were present in 14.7 % (n = 228) of the individuals. According to the MINI questionnaire, 10.3 % (n = 149) had current and 28.1 % (n = 407) had lifetime depressive episode. Antidepressants were used by 3.0 % of individuals, which could have been for depression or anxiety disorders.

3.1.2. Factors Associated with CVD

In the univariate analyses, the factors statistically significantly associated with the presence of CVD (i.e., increasing the odds of CVD) were older age, lower education, economical inactivity, urban place of residence, smoking status, episodes of heavy drinking, being overweight, the presence of diabetes, systolic hypertension, depression and intake of antihypertensive or cholesterol lowering medications (Table 3.2).

Table 3.2

Factors associated with CVD in univariate analysis

Independent variable	OR	95 % CI	p
Gender Male vs. female	1.14	0.86–1.51	0.37
Age $\geq$ 55 years vs. $\leq$ 54 years	**18.42**	**10.82–31.36**	**< 0.001**

Table 3.2 continued

Independent variable	OR	95 % CI	p
Education			
9-years basic/unfinished basic vs. higher and unfinished higher	**2.37**	**1.58–3.56**	**< 0.001**
General/vocational secondary, unfinished secondary vs. higher/unfinished higher	1.25	0.91–1.73	0.18
Employment status			
Economically inactive vs. employed	**6.43**	**4.66–8.86**	**< 0.001**
Unemployed vs. employed	0.84	0.33–2.16	0.71
Place of residence			
Riga vs. rural	**7.25**	**4.81–10.93**	**< 0.001**
Other city vs. rural	**2.52**	**1.70–3.72**	**< 0.001**
Positive family history of premature cardiovascular disease (< 55 years in men and < 65 years in women)			
Unknown vs. no	1.53	0.85–2.76	0.16
Yes vs. no	0.93	0.70–1.22	0.59
Smoking status			
Ever vs. never	**0.75**	**0.56–0.99**	**0.04**
Alcohol use, episodes of heavy drinking in last 12 months (5 or more doses of alcohol at once)			
Yes vs. no	**0.43**	**0.27–0.68**	**<0.001**
Consumption of fresh vegetables and fruits ≥ 200 g per day (2–3 servings)			
Yes vs. no	1.29	0.96–1.72	0.09
Consumption of fish ≥ 2 times per week, one of which to be oily fish			
Yes vs. no	0.95	0.72–1.24	0.69
Sedentary lifestyle (30 min. of moderate physical activity)			
Unable to perform vs. every day	1.51	0.99–2.31	0.06
1 time a week or less vs. every day	**0.60**	**0.42–0.85**	**0.004**
2–3 times a week vs. every day	0.73	0.46–1.14	0.17
4–6 times a week vs. every day	**0.47**	**0.27–0.80**	**0.005**
Body mass index, kg/m^2			
≥ 25.00 (overweight and obese) vs. ≤ 24.99 (normal and underweight)	**1.57**	**1.15–2.13**	**0.004**
Diabetes mellitus			
Yes vs. no	**2.23**	**1.51–3.28**	**< 0.001**
Total cholesterol, mmol/l			
5+ (increased) vs. < 5 (normal)	**0.58**	**0.44–0.75**	**< 0.001**
Systolic hypertension, mm Hg			
140+ (hypertension) vs. < 140 (below)	**1.40**	**1.07–1.82**	**0.01**

End of Table 3.2

Independent variable	OR	95 % CI	p
Diastolic hypertension, mm Hg 90+ (hypertension) vs. < 90 (below)	0.74	0.55–1.00	0.05
Generalised anxiety disorder (MINI) Yes vs. no	1.08	0.62–1.88	0.80
Anxiety symptoms (GAD-7) Yes vs. no	1.18	0.77–1.79	0.45
Lifetime depression (MINI) Yes vs. no	1.29	0.96–1.74	0.09
Depressive symptoms (PHQ-9) Yes vs. no	**1.84**	**1.32–2.57**	**< 0.001**
Antihypertensive medications Yes vs. no	**7.50**	**5.30–10.61**	**< 0.001**
Cholesterol lowering medications Yes vs. no	**7.53**	**5.55–10.22**	**< 0.001**
Antidepressants Yes vs. no	1.32	0.65–2.69	0.44

After adjustment, only six out of the mentioned 11 factors remained significant predictors of CVD. Older age had one of the strongest associations with the CVD, and it increased the odds approximately five times ($p < 0.001$). Economic inactivity doubled the odds of having a CVD ($p < 0.001$). Residence in the capital city increased the risk of CVD approximately nine times ($p < 0.001$), and living in another urban area increased the odds more than three times ($p < 0.001$) when compared to living in a rural area (Table 3.3).

Table 3.3

Factors associated with CVD in multivariate analyses, logistic regression models

Independent variable	Model 1			Model 2		
	aOR1[a]	95 % CI	p	aOR2[b]	95 % CI	p
Gender Male vs. female	1.37	0.87–2.15	0.17	1.35	0.87–2.11	0.18
Age ≥ 55 years vs. ≤ 54 years	**5.29**	**2.80–9.99**	**< 0.001**	**5.46**	**2.87–10.38**	**< 0.001**

Table 3.3 continued

Independent variable	Model 1			Model 2		
	aOR1[a]	95 % CI	p	aOR1[a]	95 % CI	p
Education						
9-years basic/unfinished basic vs. higher and unfinished higher	1.65	0.94–2.91	0.08	1.55	0.87–2.74	0.13
General/vocational secondary, unfinished secondary vs. higher/unfinished higher	1.11	0.73–1.70	0.63	1.03	0.67–1.58	0.89
Employment status						
Economically inactive vs. employed	**2.39**	**1.55–3.69**	**< 0.001**	**2.28**	**1.47–3.52**	**< 0.001**
Unemployed vs. employed	1.18	0.38–3.62	0.78	1.25	0.40–3.88	0.70
Place of residence						
Riga vs. rural	**9.22**	**5.31–16.04**	**< 0.001**	**8.98**	**5.16–15.63**	**< 0.001**
Other city vs. rural	**3.26**	**1.98–5.36**	**< 0.001**	**3.08**	**1.87–5.07**	**< 0.001**
Positive family history of premature cardiovascular disease (< 55 years in men and < 65 years in women)						
Unknown vs. no	1.09	0.47–2.53	0.85	0.97	0.42–2.26	0.95
Yes vs. no	1.16	0.79–1.69	0.45	1.12	0.77–1.63	0.57
Smoking status						
Ever vs. never	1.15	0.73–1.82	0.53	1.17	0.75–1.85	0.49
Alcohol use, episodes of heavy drinking in last 12 months (5 or more doses of alcohol at once)						
Yes vs. no	0.72	0.38–1.37	0.32	0.71	0.37–1.35	0.29

Table 3.3 continued

Independent variable	Model 1			Model 2		
	aOR1[a]	**95 % CI**	**p**	**aOR1[a]**	**95 % CI**	**p**
Consumption of fresh vegetables and fruits ≥ 200 g per day (2–3 servings)						
Yes vs. no	0.90	0.60–1.35	0.61	0.87	0.58–1.31	0.51
Consumption of fish ≥ 2 times per week, one of which to be oily fish						
Yes vs. no	1.01	0.71–1.45	0.94	1.00	0.70–1.44	1.00
Sedentary lifestyle (30 min. of moderate physical activity)						
Unable to perform vs. every day	0.69	0.38–1.23	0.21	0.67	0.37–1.21	0.19
1 time a week or less vs. every day	**0.62**	**0.39–0.99**	**0.04**	**0.60**	**0.38–0.96**	**0.03**
2–3 times a week vs. every day	0.87	0.48–1.59	0.65	0.88	0.48–1.62	0.69
4–6 times a week vs. every day	0.63	0.30–1.30	0.21	0.62	0.30–1.29	0.20
Body mass index, kg/m^2						
≥ 25.00 (overweight and obese) vs. ≤ 24.99 (normal and underweight)	0.86	0.56–1.32	0.49	0.86	0.56–1.33	0.51
Diabetes mellitus						
Yes vs. no	0.96	0.57–1.63	0.89	0.94	0.56–1.60	0.83
Total cholesterol, mmol/l						
5+ (increased) vs. < 5 (normal)	0.76	0.52–1.10	0.14	0.77	0.53–1.12	0.17
Systolic hypertension, mm Hg						
140+ (hypertension) vs. < 140 (below)	1.03	0.69–1.54	0.87	0.98	0.65–1.46	0.91

End of Table 3.3

Independent variable	Model 1			Model 2		
	aOR1[a]	**95 % CI**	**p**	**aOR1[a]**	**95 % CI**	**p**
Diastolic hypertension, mm Hg 90+ (hypertension) vs. < 90 (below)	0.96	0.61–1.45	0.77	0.94	0.60–1.46	0.77
Generalized anxiety disorder (MINI) Yes vs. no	0.75	0.36–1.56	0.44	0.64	0.30–1.38	0.25
Anxiety symptoms (GAD-7) Yes vs. no	1.19[c]	0.67–2.12	0.55	0.89[c]	0.49–1.63	0.71
Lifetime depression (MINI) Yes vs. no	**1.52**	**1.02–2.25**	**0.04**	-	-	-
Depressive symptoms (PHQ-9) Yes vs. no	-	-	-	**2.08**	**1.30–3.32**	**0.002**
Antihypertensive medications Yes vs. no	**3.45**	**2.16–5.49**	**< 0.001**	**3.37**	**2.11–5.36**	**< 0.001**
Cholesterol lowering medications Yes vs. no	**2.99**	**1.99–4.50**	**< 0.001**	**3.01**	**2.00–4.54**	**< 0.001**
Antidepressants Yes vs. no	1.51	0.60–3.80	0.38	1.63	0.66–4.07	0.9

aOR1[a]: adjusted odds ratio, Model 1 (lifetime depression according to MINI included)
aOR[b]: adjusted odds ratio, Model 2 (current depression according to PHQ-9 included)
[c] Adjusted for all variables except generalized anxiety disorder (MINI) to avoid multi-collinearity

Individuals who performed moderate physical activity for 30 minutes once a week or less had decreased odds of having CVD compared to individuals who reported physical activity every day ($p = 0.03$). Patients who were using antihypertensive or cholesterol lowering medications had three times higher odds of having a CVD ($p < 0.001$). Patients who were using antihypertensive or cholesterol lowering medications had three times higher odds of having a CVD ($p < 0.001$).

OR for current depressive symptoms (according to the PHQ-9) was 1.52 ($p = 0.04$) and for lifetime depressive episode (detected by the MINI) the OR was 2.08 ($p = 0.002$) (Table 2). The current depressive episode according to the MINI did not show statistically significant results in the univariate analysis or any multivariate model. None of the anxiety measures (MINI and GAD-7) showed statistically significant associations with CVD in either the univariate or the multivariate analyses.

Gender stratified analysis of study population showed that current depressive symptoms (according to the PHQ-9) were associated with 2.04 ($p = 0.004$) higher odds of having CVD in women, but not in men (data not shown).

3.2. Association of Depression and Anxiety with 10-year Cardiovascular Mortality Risk (SCORE)

3.2.1. Description of the Study Sample

Among those who completed both screening questionnaires, the SCORE measure was calculated for 1569 subjects (69.0 % women), who were included in the final analysis. Of the eligible study subjects, 23.4 % ($n = 367$) showed a very high 10-year CV mortality risk according to the SCORE (≥ 10 %). Clinical symptoms of depression (PHQ-9≥10) were present in 15.0 % ($n = 233$) of individuals. According to the MINI, 10.2 % ($n = 148$) had current and 28.1 %

(n = 410) had a lifetime depressive episode. Clinically relevant anxiety symptoms (GAD-7≥10) were detected in 10.1 % (n = 156) individuals. According to the MINI, 15.9 % (n = 232) had a current anxiety disorder. A complete description of the sample is shown in Table 3.4.

Table 3.4

Description of the study sample; prevalence of a very high cardiovascular mortality risk in subgroups of independent variables

Independent variable	SCORE ≥ 10 %		SCORE ≤ 9 %		Total	
	n	%	n	%	n	%
Proximal factors						
Positive family history of early onset CVD						
Don't know	24	37.5	40	62.5	64	4.1
Yes	124	21.0	467	79.0	591	37.9
No	218	24.1	688	75.9	906	58.0
Diabetes mellitus						
Yes	75	53.6	65	46.4	140	9.1
No	292	20.9	1102	79.1	1394	90.9
Antihypertensives						
Yes	290	38.4	466	61.6	756	48.2
No	77	9.5	736	90.5	813	51.8
Cholesterol lowering medicines						
Yes	124	52.8	111	47.2	235	15.0
No	243	18.2	1091	81.8	1334	85.0
Antidepressants						
Yes	12	25.5	35	74.5	47	3.0
No	355	23.3	1167	76.7	1522	97.0
Intermediate factors						
Body mass index, kg/m^2						
< 18.50 (underweight)	2	7.4	25	92.6	27	1.7
18.50–24.99 (normal)	143	26.8	391	73.2	534	34.1
25.00–29.99 (overweight)	132	24.0	419	76.0	551	35.2
30.00+ (obese)	88	19.4	366	80.6	454	29.0
Waist circumference, cm						
Increased (88+ females; 102+ males)	209	27.3	557	72.7	766	49.1

Table 3.4 continued

Independent variable	SCORE ≥ 10 %		SCORE ≤ 9 %		Total	
	n	%	n	%	n	%
Waist circumference, cm						
Normal (≤ 88 females; ≤ 102 males)	156	19.6	639	80.4	795	50.9
Sedentary lifestyle (30 min. of moderate physical activity)						
Unable to perform	62	36.7	107	63.3	169	10.9
1 time a week or less	141	20.7	540	79.3	681	43.8
2–3 times a week	44	21.2	164	78.8	208	13.4
4–6 times a week	35	20.1	139	79.9	174	11.2
Every day	82	25.5	240	74.5	322	20.7
Depression (PHQ-9)						
Yes	73	31.3	160	68.7	233	15.0
No	289	21.9	1030	78.1	1319	85.0
Current depression (MINI)						
Yes	42	28.4	106	71.6	148	10.2
No	292	22.3	1017	77.7	1309	89.8
Lifetime depression (MINI)						
Yes	97	23.7	313	76.3	410	28.1
No	237	22.6	810	77.4	1047	71.9
Anxiety (MINI, any anxiety disorder)						
Yes	43	18.5	189	81.5	232	15.9
No	291	23.8	934	76.2	1225	84.1
Anxiety (GAD-7)						
Yes	37	23.7	119	76.3	156	10.1
No	325	23.3	1071	76.7	1396	89.9
Generalised anxiety disorder (MINI)						
Yes	18	19.8	73	80.2	91	6.2
No	317	23.2	1051	76.8	1368	93.8
Panic disorder (MINI)						
Yes	1	9.1	10	90.9	11	0.8
No	334	23.1	1114	76.9	1459	99.2
Alcohol use, episodes of heavy drinking in the last year (5 or more doses of alcohol at once)						
Every day or almost every day	4	28.6	10	71.4	14	0.9
3–4 times a week	5	16.7	25	83.3	30	1.9
1–2 times a week	22	16.4	112	83.6	134	8.6
More rare	78	16.7	389	83.3	467	29.9
Never during the past year	257	28.1	659	71.9	916	58.7
Consumption of fresh vegetables and fruits						
Yes	258	22.4	896	77.6	1154	73.9
No	108	26.5	299	73.5	407	26.1

End of Table 3.4

Independent variable	SCORE ≥ 10 %		SCORE ≤ 9 %		Total	
	n	%	n	%	n	%
Consumption of fish ≥ 2 times per week						
Yes	151	24.9	455	75.1	606	38.8
No	215	22.5	740	77.5	955	61.2
Distal factors						
Education						
9-years basic and unfinished basic education	83	38.8	131	61.2	214	13.7
General or vocational secondary and unfinished secondary education	207	23.2	685	76.8	892	57.3
Higher and unfinished higher education	75	16.6	377	83.4	452	29.0
Employment status						
Economically inactive	260	39.4	400	60.6	660	4.3
Unemployed	16	18.2	72	81.8	88	5.6
Employed	90	11.1	722	88.9	812	52.1
Marital status						
Single	19	12.4	134	87.6	153	9.8
Live separately, divorced, widowed	144	31.7	310	68.3	454	29.1
Married, cohabiting	203	21.3	750	78.7	953	61.1
Place of residence						
Riga	123	39.4	189	60.6	312	19.9
Other city	160	21.4	588	78.6	748	47.7
Rural	84	16.5	425	83.5	509	32.4

3.2.2. Factors Associated with very High Cardiovascular Mortality Risk

In the final multivariate analysis model, a very high risk of CV mortality was significantly associated with three proximal factors: presence of diabetes, use of antihypertensive and cholesterol lowering medicines. Among distal factors, three variables increased the risk of CV mortality: lower education level, inactive economic status or unemployment, and urban place of residence.

The only intermediate factors that remained significantly associated with a SCORE ≥ 10 % after adjustment for socio-economic and traditional CV risk factors were depression (according to the PHQ-9) and anxiety (according to the MINI). Subjects with clinical symptoms of depression had a 1.57 (p = 0.03) times higher odds of very high CV risk. Interestingly, current anxiety disorder showed a preventive effect on CV mortality. Subjects with diagnosed anxiety disorder had a 0.58 lower odds (p = 0.02) of having a SCORE ≥ 10 %.

Results from logistic regression models are shown in Table 3.5 and Table 3.6.

Table 3.5.

Factors associated with a very high CV mortality risk (SCORE ≥ 10 %) in univariate and the first model (proximal factors) of stepwise multivariate analysis [a,b]

Independent variable	OR[c]	95 % CI	p	OR1[d]	95 % CI	p
Proximal factors						
Positive family history of early onset CVD						
Don't know vs. no	1.89	1.12–3.21	0.02	1.81	1.01–3.24	**0.045**
Yes vs. no	0.84	0.65–1.08	0.17	0.66	0.50–0.87	**0.003**
Diabetes mellitus						
Yes vs. no	4.36	3.05–6.22	< 0.001	2.45	1.66–3.62	< **0.001**
Antihypertensive medications						
Yes vs. no	5.95	4.51–7.85	< 0.001	4.26	3.17–5.74	< **0.001**
Cholesterol lowering medications						
Yes vs. no	5.02	3.75–6.71	< 0.001	2.55	1.86–3.51	< **0.001**
Antidepressants						
Yes vs. no	1.13	0.58–2.20	0.73	1.05	0.50–2.21	0.90
Intermediate factors						
Body mass index, kg/m^2						
< 18.50 (underweight) vs. 18.50–24.99 (normal)	0.33	0.08–1.43	0.14	-	-	-

Table 3.5 continued

Independent variable	OR[c]	95 % CI	p	OR1[d]	95 % CI	p
Body mass index, kg/m^2						
25.00–29.99 (overweight) vs. 18.50–24.99 (normal)	1.29	0.97–1.78	0.08	-	-	-
30,00+ (obese) vs. 18.50–24.99 (normal)	1.52	1.13–2.06	0.006	-	-	-
Waist circumference, cm						
Increased (88+ females; 102+ males) vs. normal (≤ 88 females; ≤ 102 males)	1.54	1.21–1.98	< 0.001	-	-	-
Sedentary lifestyle (30 minutes of moderate physical activity)						
4–6 times a week vs. every day	0.74	0.47–1.15	0.18	-	-	-
2–3 times a week vs. every day	0.79	0.52–1.19	0.26	-	-	-
1 time a week or less vs. every day	0.76	0.56–1.04	0.09	-	-	-
Unable to perform vs. every day	1.70	1.14–2.53	0.01	-	-	-
Depression (PHQ-9)						
Yes vs. no	1.63	1.18–2.21	0.002	-	-	-
Anxiety disorder (MINI, any anxiety disorder)						
Yes vs. no	0.73	0.51–1.04	0.08	-	-	-
Alcohol consumption, episodes of heavy drinking in the last year (5 or more doses of alcohol at once)						
Every day or almost every day vs. never during the past year	1.03	0.32–3.30	0.97	-	-	-
3–4 times a week vs. never during the past year	0.51	0.19–1.35	0.18	-	-	-
1–2 times a week vs. never during the past year	0.50	0.31–0.81	0.005	-	-	-
More rare vs. never during the past year	0.51	0.39–0.68	< 0.001	-	-	-
Consumption of fresh vegetables and fruits (≥ 200 g every day)						
No vs. yes	1.25	0.97–1.63	0.09	-	-	-

End of Table 3.5

Independent variable	OR[c]	95 % CI	p	OR1[d]	95 % CI	p
Consumption of fish (≥ 2 times a week)						
No vs. yes	0.88	0.69–1.11	0.28	-	-	-
Distal factors						
Education						
9-years basic and unfinished basic education vs. higher and unfinished higher education	3.19	2.20–4.61	< 0.001	-	-	-
General or vocational secondary and unfinished secondary education vs. higher and unfinished higher education	1.52	1.13–2.04	0.005	-	-	-
Employment status						
Economically inactive vs. employed	5.21	3.98–6.82	< 0.001	-	-	-
Unemployed vs. employed	1.78	0.99–3.20	0.052	-	-	-
Marital status						
Single vs. married, cohabiting	0.52	0.32–0.87	0.01	-	-	-
Live separately, divorced, widowed vs. married, cohabiting	1.72	1.34–2.21	< 0.001	-	-	-
Place of residence						
Riga vs. rural	3.29	2.38–4.56	< 0.001	-	-	-
Other city vs. rural	1.38	1.03–1.84	0.03	-	-	-

[a] Statistically significant associations bolded, [b] Cells in the table are left empty intentionally due to the stepwise multivariate analysis according to conceptual hierarchical framework model (see Methods part for more detailed information)
[c] OR: crude odds ratio
[d] aOR1: adjusted odds ratio in first model, proximal factors adjusted

Table 3.6

Factors associated with a very high CV mortality risk (SCORE ≥ 10 %) in the second and third model of stepwise multivariate analysis [a,b]

Independent variable	aOR2[e]	95 % CI	p	aOR3[f]	95 % CI	p
Proximal factors						
Positive family history of early onset CVD						
Don't know vs. no	2.09	1.08–4.06	0.03	1.23	0.62–2.46	0.55
Yes vs. no	0.69	0.51–0.93	0.01	0.88	0.64–1.20	0.42
Diabetes mellitus						
Yes vs. no	2.88	1.84–4.52	< 0.001	2.52	1.63–3.89	**< 0.001**
Antihypertensive medications						
Yes vs. no	5.13	3.59–7.32	< 0.001	3.22	2.29–4.53	**< 0.001**
Cholesterol lowering medications						
Yes vs. no	2.50	1.77–3.52	< 0.001	2.07	1.44–2.95	**< 0.001**
Antidepressants						
Yes vs. no	-	-	-	-	-	-
Intermediate factors						
Body mass index, kg/m^2						
< 18.50 (underweight) vs. 18.50–24.99 (normal)	0.31	0.04–2.48	0.27	-	-	-
25.00–29.99 (overweight) vs. 18.50–24.99 (normal)	0.95	0.65–1.40	0.80	-	-	-
30,00+ (obese) vs. 18.50–24.99 (normal)	0.76	0.46–1.25	0.28	-	-	-
Waist circumference, cm						
Increased (88+ females; 102+ males) vs. normal (≤ 88 females; ≤ 102 males)	0.71	0.48–1.07	0.10	-	-	-
Sedentary lifestyle (30 minutes of moderate physical activity)						
4–6 times a week vs. every day	0.93	0.55–1.56	0.78	-	-	-
2–3 times a week vs. every day	0.88	0.54–1.44	0.61	-	-	-
1 time a week or less vs. every day	0.70	0.48–1.02	0.06	-	-	-

Table 3.6 continued

Independent variable	aOR2[e]	95 % CI	p	aOR3[f]	95 % CI	p
Sedentary lifestyle (30 minutes of moderate physical activity)						
Unable to perform vs. every day	1.04	0.64–1.70	0.87	-	-	-
Depression (PHQ-9)						
Yes vs. no	1.65	1.12–2.42	0.01	1.57	1.06–2.33	**0.03**
Anxiety disorder (MINI, any anxiety disorder)						
Yes vs. no	0.58	0.38–0.89	0.01	0.58	0.38–0.90	**0.02**
Alcohol consumption, episodes of heavy drinking in the last year (5 or more doses of alcohol at once)						
Every day or almost every day vs. never during the past year	1.24	0.30–5.14	0.76	-	-	-
3–4 times a week vs. never during the past year	0.68	0.21–2.18	0.51	-	-	-
1–2 times a week vs. never during the past year	0.94	0.51–1.73	0.84	-	-	-
More rare vs. never during the past year	0.78	0.55–1.10	0.15	-	-	-
Consumption of fresh vegetables and fruits (≥ 200 g every day)						
No vs. yes	1.12	0.81–1.54	0.50	-	-	-
Consumption of fish (≥ 2 times a week)						
No vs. yes	0.96	0.71–1.28	0.77	-	-	-
Distal factors						
Education						
9-years basic and unfinished basic education vs. higher and unfinished higher education	-	-	-	2.25	1.39–3.65	**0.001**

Independent variable	aOR2[e]	95 % CI	p	aOR3[f]	95 % CI	p
Education						
General or vocational secondary and unfinished secondary education vs. higher and unfinished higher education	-	-	-	1.29	0.90–1.84	0.17
Employment status						
Economically inactive vs. employed	-	-	-	2.87	2.07–3.98	< **0.001**
Unemployed vs. employed	-	-	-	2.05	1.05–4.01	**0.04**
Marital status						
Single vs. married, cohabiting	-	-	-	0.65	0.35–1.23	0.19
Live separately, divorced, widowed vs. married, cohabiting	-	-	-	0.94	0.69–1.29	0.71
Place of residence						
Riga vs. rural	-	-	-	4.00	2.62–6.10	< **0.001**
Other city vs. rural	-	-	-	1.55	1.08–2.22	**0.02**

[a] Statistically significant associations bolded, [b] Cells in the table are left empty intentionally due to the stepwise multivariate analysis according to conceptual hierarchical framework model (see Methods part for more detailed information)
[e] aOR2: adjusted odds ratio in the second model, proximal and intermediate factors adjusted
[f] aOR3: adjusted odds ratio in the third model, proximal, intermediate and distal factors adjusted

4. DISCUSSION

4.1. Association of Depression and Anxiety with Cardiovascular Diseases

This is the first study in Latvia that explores association between CVD and depression and anxiety in the primary care population. The main findings of this cross-sectional study were that individuals with current depressive symptoms (PHQ-9 ≥ 10) demonstrated 2.08 (95 % CI: 1.30–3.32, p = 0.002) times higher odds of having a CVD, and a lifetime depressive episode according to the MINI was associated with an adjusted OR for CVD of 1.52 (95 % CI: 1.02–2.25, p = 0.04).

4.1.1. Association of Depression and CVD

An overview of 59 prognostic studies from three meta-analyses demonstrated that depression was associated with a 1.5- to 2.7-fold increased risk of incident CVD (Frasure-Smith and Lesperance, 2010; Rugulies, 2002). A more recent and updated meta-analysis by *Gan et al.* reviewed 30 prospective studies (n = 893,850) published up to April 2014 with a follow-up duration ranging from 2 to 37 years. They found a more modest association of depression, with CHD and MI reporting pooled RRs of 1.30 (95 % CI: 1.22–1.40) and 1.30 (95 % CI: 1.18–1.44), respectively (Gan, Gong, Tong et al., 2014). Due to the cross-sectional nature of this study, it is impossible to draw conclusions about causality of the established link between depression and CVDs. But our findings in the context of previous research suggest that depression might be a risk factor for increased CV morbidity in Latvian population that has to be investigated in future prospective studies. Although we found a cross-sectional relationship between the current depressive symptoms (PHQ-9 ≥ 10) and lifetime depressive episode according to the MINI, unexpectedly there was no statistically significant association with a diagnosis of current depressive episode detected with the

structured psychiatric interview (MINI). The finding could be explained in two ways. First, 97 individuals of the study population who completed the PHQ-9 questionnaire were not interviewed with the MINI, so this omission could have attenuated the statistical power of the MINI results. Second, the MINI is a categorically based depression assessment tool that could have excluded individuals with sub-syndromal depressive symptoms from case status. On the other hand, the PHQ-9 is a dimensional assessment tool, which could have allowed the inclusion of people with clinically significant depressive symptoms who failed to meet the formal criteria for DSM-IV and ICD-10 diagnosis. However, the existing evidence showed that sub-threshold depressive symptoms were significantly associated with increased disability, morbidity and mortality (Meeks, Vahia, Lavretsky et al., 2011). Therefore, the statistically significant association of the PHQ-9 score ≥ 10 with CVD in the Latvian primary care population is considered as a clinically relevant finding and an easily assessed marker for primary care providers to target.

Evidence about the comorbidity of depression and CVD in other Baltic countries is contradictory. A cross-sectional study in Lithuania involving 317 individuals from primary care centers in 20 cities investigated the association between psychosocial stress, manifested as anxiety and depression, and CVD using the HADS (Burokienė, Karčiauskaitė, Kasiulevičius et al., 2014a). *Burokiene et al.* demonstrated a modest but significant correlation between CVD and current depressive symptoms (OR = 1.18; 95 % CI: 1.07–1.31, p = 0.001) but found no statistically important correlation between current anxiety symptoms and CVD. On the other hand, a cross-sectional study involving 1,094 patients from 23 primary care practices across Estonia that explored which co-morbid diseases are associated with depression (using the Depression Section of the Composite International Diagnostic Interview) did not confirm higher co-morbidity of CVD in depressed patients when compared to non-depressed individuals (Suija, Kalda and Maaroos, 2009).

Specific genetic, behavioral and pathophysiological factors have been established as contributing to the initiation, progression, and clinical manifestation of athero-thrombotic CVD in those suffering from depression and anxiety disorders. Behavioral factors are related to unhealthy lifestyle (smoking, excessive alcohol consumption, unhealthy diet, sedentary behavior) and poor treatment adherence (medical treatment regimen, maintaining smoking cessation, participation in cardiac rehabilitation) (DiMatteo, Lepper and Croghan, 2000; Doyle, Rohde, Rutkowska et al., 2014; Gehi, Haas, Pipkin et al., 2005; Goldstein, Gathright and Garcia, 2017; Swardfager, Herrmann, Marzolini et al., 2011). Pathophysiological factors worsening CVD include dysregulation in the autonomic nervous system and hypothalamic-pituitary-adrenal axis as well as metabolic and immuno-inflammatory dysregulations. These pathophysiological factors can lead to coronary vasoconstriction, hypertension, left ventricular hypertrophy, reduced heart rate variability, endothelial dysfunction, platelet activation, hypercoagulability, and the production of pro-inflammatory cytokines (C-reactive protein, interleukin-6, intercellular adhesion molecule-1). These changes elevate the risk of ventricular arrhythmias, MI and stroke (Dhar and Barton, 2016; Penninx, 2017; Pogosova, Saner, Pedersen et al., 2015).

We examined whether our finding of the association of depression and CVD could be explained by other common traditional and non-traditional CV risk factors, including smoking, exercise, body mass index, and alcohol consumption (Nicholson, Kuper and Hemingway, 2006). In their meta-analysis, *Nicholson et al.* reported that only half (10 out of 21) of the studies evaluated this range of CV risk factors (Nicholson, Kuper and Hemingway, 2006). In the logistic regression analysis of our study, the association between depressive measures and CVD morbidity remained significant even after adjustment for the traditional CV risk factors.

4.1.2. Association of Anxiety and CVD

In contrast to depression, which in numerous studies has been linked to the increased morbidity and mortality of CVDs, it is less known about the influence of anxiety symptoms and anxiety disorders. The most recent meta-analysis, summarising a total of 37 studies including 1,565,699 participants, demonstrated a 52 % increased risk of CVD onset (HR = 1.52, 95 % CI: 1.36–1.71) for patients with anxiety symptoms and disorders. This finding seemed to be independent of traditional CV risk factors and depression (Batelaan, Seldenrijk, Bot et al., 2016). The most extensively studied anxiety disorders associated with the onset and progression of CVDs, adverse cardiovascular outcomes, including mortality, are generalised anxiety disorder, panic disorder and post-traumatic stress disorder (Celano, Daunis, Lokko et al., 2016). However, in contrast, some studies reported beneficial effects of anxiety on CV morbidity and mortality (Meyer, Buss and Herrmann-Lingen, 2010; Meyer, Hussein, Lange et al., 2015). These studies proposed left ventricular function as an important factor that may modulate the prognostic significance of anxiety and may improve risk stratification in CV patients.

We have not found a statistically significant association of GAD (detected by the MINI) with CVD ($p = 0.25$). This could be explained by the insufficient sample size of our study population. Only 89 individuals corresponded to the MINI diagnostic criteria of GAD. Similarly, a previously mentioned cross-sectional study in the primary care population of Lithuania (n = 317) by Burokiene et al. also reported no significant correlation between anxiety and CVD (Burokienė, Karčiauskaitė, Kasiulevičius et al., 2014a). There is a need for larger studies with increased numbers of patients conducted in Latvia and the Baltic region to explore the association of anxiety and CVD morbidity with sufficient statistical power.

4.1.3. Association of other CV Risk Factors and CVD

Several reports have shown that some well-established CV risk factors, such as tobacco smoking, heavy drinking and sedentary lifestyle (Piepoli, Hoes, Agewall et al., 2016), may be associated with major depression and anxiety disorders (Figueiredo, Silva, Pereira et al., 2017; Khalid, Kunwar, Rajbhandari et al., 2000; Pacek, Storr, Mojtabai et al., 2013; Ziedonis, Hitsman, Beckham et al., 2008). Although the univariate analysis of our study demonstrated relationships between these risk factors and CVD, after adjustment, only sedentary lifestyle maintained a statistically significant association with CVD. It was found in our study that moderate physical activity once a week or less decreased the odds of CVD when compared to everyday activity. This might be explained by the fact that individuals who are performing physical activity more frequently are more likely to have been detected as having a higher risk for CVD and thus have received a strong recommendation from the primary care physician to practice a health-promoting lifestyle. Our data analysis shows a tendency for some binge drinking episodes within the last 12 months to be preventive in relation to CVD when compared with absence of alcohol abuse. This might be because the population of non-abusers partially consists of people who have stopped their heavy drinking habit due to some cardiovascular health threats. In future studies, it might be prudent to use more sensitive instrument for alcohol consumption that takes into account not only recent but also lifetime habits.

Another new finding was the highest adjusted odds ratio of 8.98 (95 % CI: 5.16–15.63, $p < 0.001$) for individuals living in the urban area of Riga (capital of Latvia) compared to those living in rural areas. This result seems to be consistent with the data obtained in the Prospective Urban Rural Epidemiologic cohort study involving more than 150,000 adults in 17 high-, middle-, and low-income countries (Yusuf, Rangarajan, Teo et al., 2014). *Yusuf et al.* (2014) reported that urban communities had a higher CV risk-factor burden than rural

communities but had lower rates of CV events and lower case fatality rates. Our study adds to this finding by *Yusuf et al.* and other similar studies that reported the significance and relevance of considering the place of residence (urban versus rural) as an important moderator and/or confounding factor to include in future studies on CV risks and outcomes (Nicholson, Kuper and Hemingway, 2006; Roest, Martens, de Jonge et al., 2010).

4.2. Association of Depression and Anxiety with 10-year Cardiovascular Mortality Risk (SCORE)

This is the first study in Latvia to explore the relationship between depression, anxiety and the 10-year risk of a first fatal atherosclerotic event in primary care population based on the SCORE system. The most relevant findings were that patients with clinical symptoms of depression (PHQ-9 $\geq$ 10) demonstrated a 1.57 times higher odds of a very high 10-year CV risk as measured by the SCORE function, but current anxiety disorder (MINI) reduced the risk of CV mortality with an OR of 0.58. These findings remained statistically significant even after adjusting for multiple socio-demographic and traditional CV risk factors.

4.2.1. Association of Depression and 10-year CV Mortality Risk

A global overview of the literature from approximately 50 prognostic studies on the link between depression and CVD from the last 25 years concluded that clinically relevant depressive symptoms are associated with a 1.6 to 2.2-fold higher risk of adverse outcomes (Frasure-Smith and Lesperance, 2010; Pogosova, Saner, Pedersen et al., 2015); however, prior studies in the Baltic nations have been contradictory. A prospective cohort study of primary care population (n = 1,115) in Lithuania examined the association of the metabolic syndrome, current major depressive episode, lifetime major depressive episode, and GAD with ten-year CV mortality (Butnoriene, Bunevicius, Saudargiene et

al., 2015). *Butnoriene et al.* (2015) found that lifetime major depressive episode was associated with an elevated risk of CV mortality in women (HR = 1.86; p = 0.019) adjusted for conventional CV risk factors. In men, neither current MDE nor lifetime MDE were associated with mortality. Another study from Lithuania by *Burokiene and colleagues* (Burokienė, Karčiauskaitė, Kasiulevičius et al., 2014b) showed a more modest but statistically significant association of CV morbidity and clinically relevant depressive symptoms (OR = 1.18; p = 0.001). Surprisingly, a cross-sectional study involving 1,094 patients from 23 family practices across Estonia did not indicate higher co-morbidity of CVD in depressed patients when compared to non-depressed patients (Suija, Kalda and Maaroos, 2009). The current findings about the association of depression with CV mortality are in line with prior studies identifying depression as an independent risk factor for CV morbidity and mortality.

Although many studies have examined the association of depression with separate traditional CV risk factors, including arterial hypertension, hypercholesterolemia, diabetes and obesity, only one publication was found that used the SCORE system (Koponen, Jokelainen, Keinanen-Kiukaanniemi et al., 2010). *Koponen et al.* reported that clinically relevant depressive symptoms were associated with a 2.9-fold higher (95 % CI 1.4–5.7) 10-year CV mortality risk in men and a 1.4-fold higher (95 % CI 1.1–4.2) risk in women using the SCORE function (Koponen, Jokelainen, Keinanen-Kiukaanniemi et al., 2010). Despite similar objectives, there were several significant differences in methodology of this study. In the study by *Koponen et al.* a "high/very high" risk for CV mortality was defined as a SCORE ≥ 3 % (Koponen, Jokelainen, Keinanen-Kiukaanniemi et al., 2010). In this study, SCORE ≥ 10 % was chosen as a threshold for a very high risk of CV mortality in accordance with the European Guidelines on cardiovascular disease prevention in clinical practice (2016) (Piepoli, Hoes, Agewall et al., 2016).

We also used additional confounding factors such as place of residence and anxiety, which appeared to have a significant impact on the SCORE results.

4.2.2. Association of Anxiety and 10-year CV Mortality Risk

In contrast to depression, the relationship between anxiety and CVD is less clear. Meta-analysis by *Roest and colleagues* (2010) summarising 20 studies with 249,846 participants found that anxious persons were at an increased risk for incident CAD (HR = 1.26; $p < 0.0001$) and CV mortality (HR = 1.48; $p = 0.003$), independent of sociodemographic characteristics, traditional and lifestyle CV risk factors (Roest, Martens, de Jonge et al., 2010). However, the meta-analytic assessment on the link between anxiety and CAD was not controlled for depression, which is a very frequent comorbid condition with anxiety. Since the publication of that review in 2010, more recent studies have suggested that anxiety may act as a protective factor in certain instances (Meyer, Buss and Herrmann-Lingen, 2010; Meyer, Hussein, Lange et al., 2015). The most recent meta-analysis (2016) also included studies focusing on stroke and peripheral vascular disease, summarising 37 studies with 1,565,699 participants (Batelaan, Seldenrijk, Bot et al., 2016). *Batelaan et al.* found that clinically relevant anxiety symptoms were associated with a 1.52 times higher risk of incident CV morbidity (95 % CI 1.36–1.71). Although the data on the prognostic influence of anxiety are complex and even controversial, most publications support the association of anxiety with CV mortality, but they do so to a lesser extent compared with depression. In addition, a few studies have been performed in the Baltic region, but none have examined the association of anxiety with the SCORE function. *Butnoriene et al.* (Butnoriene, Bunevicius, Saudargiene et al., 2015) showed that current GAD predicted greater CV mortality in women (HR = 1.86–1.99; $p \leq 0.025$), but not in men. A small study (n = 64) from Estonia also reported differences between young male and female post-MI patients,

indicating that females suffered a higher level of cognitive worry and were less able to relax in the prodromal period of MI (Uuskula, 1996).

One of the most unexpected findings of the study was that current anxiety disorder (MINI) was associated with a reduced CV mortality risk, suggesting a possible protective influence. This result is in agreement with the findings of *Meyer et al.* (2010), which showed that elevated symptoms of anxiety were associated with beneficial effects on survival in individuals with stable CV conditions (HR = 0.70; p = 0.031) comparing to individuals after acute MI with reduced systolic left ventricular function (HR = 1.32; p = 0.011) (Meyer, Buss and Herrmann-Lingen, 2010). Therefore, it has been hypothesised that prognostic influence of anxiety might be modulated through CVD severity (degree of left ventricular dysfunction).

4.3. Strengths and Limitations

The use of a structured diagnostic interview for detection of depressive episodes and anxiety disorders, a nationally representative primary care convenience sample including persons with a wide range of ages, and a hierarchical multivariate analysis including control for conventional CV, socio-economic risk factors, anxiety and place of residence are important strengths of this study.

There are several limitations to the results of the current study. First, because of the cross-sectional setting of this study, we could not draw definite conclusions about the causality of the identified relationships between clinically relevant depressive symptoms or anxiety disorders and CVD or CV mortality risk. Second, the PHQ-9 with a cut-off score of 10 points and higher has been accepted as a reliable instrument for detection of MDD in chronic physical diseases (Meader, Mitchell, Chew-Graham et al., 2011). However, the PHQ-9 is a screening tool and not a diagnostic criterion for MDD, which can result in false

positive cases. Moreover, there is an ongoing discussion about the optimal PHQ-9 thresholds specific for patients with CVD, with some studies indicating that the PHQ-9 cut-off score of ≥ 8 or even ≥ 6 would improve sensitivity and specificity of this instrument (Haddad, Walters, Phillips et al., 2013; Thombs, Ziegelstein and Whooley, 2008). Further studies are needed to clarify the optimal PHQ-9 threshold for the Latvian CVD population. Third, we combined all anxiety disorders according to the MINI, including generalised anxiety disorder, panic disorder, agoraphobia and post-traumatic stress disorder, in the current anxiety variable of the final analysis to gain more statistical power. Although these diagnoses share common basic symptoms of anxiety and neurobiological mechanisms (Bandelow, Baldwin, Abelli et al., 2016; Bandelow, Baldwin, Abelli et al., 2017), it was not possible to clarify whether the current findings were attributable to all included anxiety disorders.

5. CONCLUSIONS

1. Prevalence of CVD is higher in patients with depression (PHQ-9, MINI) when compared to individuals without depression; prevalence of CVD is not associated with anxiety.
2. Very high 10-year CV mortality risk is more prevalent in patients with clinically relevant depressive symptoms (PHQ-9) when compared to individuals without depression; SCORE ≥ 10 % prevalence is lower in patients with anxiety disorders (MINI) when compared to individuals without anxiety; however, this association is statistically significant only in multivariate analysis.
3. Depression (PHQ-9, MINI) is statistically significantly associated with CVD:
   3.1. The odds of having CVD were higher in patients with clinically relevant depressive symptoms according to the PHQ-9 ≥ 10 points (OR = 2.08, p = 0.002);
   3.2. The odds of having CVD were higher in patients with lifetime depressive episode according to the MINI interview (OR = 1.52, p = 0.04);
   3.3. CV patients have been identified as a target population for depression screening.
4. Depression (PHQ-9) and anxiety (MINI) are statistically significantly associated with a very high 10-year CV mortality risk (SCORE ≥ 10 %):
   4.1. The odds of having SCORE ≥ 10 % were higher in patients with clinically relevant depressive symptoms (PHQ-9) (OR = 1.57, p = 0.03);
   4.2. The odds of having SCORE ≥ 10 % were lower in patients with anxiety disorders (MINI) (OR = 0.58, p = 0.02);
   4.3. Individuals with SCORE ≥ 10 % have been identified as a target population for depression screening.

5.1. Practical Implications

The EUROASPIRE studies have shown that effectiveness of CV risk factors management in the EU is still far from optimal and that major cross-country differences exist (Kotseva, De Bacquer, De Backer et al., 2016; Kotseva, Wood, De Backer et al., 2009). The Baltic countries are among the most profoundly CVD-affected countries with higher CV mortality rates compared to other countries in the EU (Eurostat, 2013). Local data are very important to develop country-specific management programmes for CV patients (Assari, 2015). However, previous largest studies on CV risk factors prevalence in Latvian population have not assessed depression and anxiety as possible risk factors (Erglis, Dzerve, Pahomova-Strautina et al., 2012; Erglis, Mintale, Latkovskis et al., 2015; Kalvelis, Stukena, Bahs et al., 2011). Results of this study support the initial hypothesis that depression is associated with increased odds of having CVD and a very high 10-year CV mortality risk and is more prevalent in CV patients of primary care population in Latvia. These findings suggest that detection and treatment of depression should be included in CV patients` and management programmes and future research on CV risk factors in Latvia.

The American Heart Association has highlighted the importance of depression in CV patients by recommending routine screening with Patient Health Questionaire-2 (PHQ-2) and PHQ-9 of all cardiac patients already in 2008 (Huffman and Celano, 2015; Lichtman, Bigger, Blumenthal et al., 2008). Recently the PHQ-9 has been adopted and validated for Latvian population both in Latvian and Russian versions and appeared to be a reliable and effective instrument to evaluate depression among patients visiting their GP in Latvia (Rancans, Trapencieris, Ivanovs et al., 2018). Within the framework of the National Research Programme BIOMEDICINE an algorithm of depression diagnostics and treatment applicable to GPs was determined; it defined a target population of depression screening and included PHQ-9 scale, its interpretation

and necessary tactic, including treatment strategies were explained. After establishment of the algorithm of depression diagnostics and treatment for GPs a specific training course was introduced, and 10 “Depression School” training seminaries took place in Latvia from October to December 2016; 210 doctors were educated about prevalence of depression in Latvia, screening population, they were introduced to PHQ-9 scale, its use and interpretation as well as were trained in treating depression. It is necessary to organise education events on diagnostics and treatment of depression for GPs and cardiologists also in future.

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PUBLICATIONS

Scientific publications related to the topic of the Doctoral Thesis

1. Ivanovs, R., Kivite, A., Ziedonis, D., Mintale, I., Vrublevska, J., Rancans, E., 2018. Association of depression and anxiety with cardiovascular co-morbidity in a primary care population in Latvia: a cross-sectional study. *BMC Public Health,* 18**,** 328. (IF 2.420) https://doi.org/10.1186/s12889-018-5238-7
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1. Ivanovs, R., Trapencieris, M., Vrublevska, J., Logins, R., Bērze, L., Rancāns, E., 2016. Depresijas korelācija ar kardiovaskulāro risku (SCORE) primārajā aprūpē Latvijā (Eng. Correlation of depression with cardiovascular risk (SCORE) in primary care in Latvia). *RSU 2016. gada zinātniskā konference. Tēzes,* 1.lpp.
2. Ivanovs, R., Rancāns, E., Ķīvīte, A., Mintāle, I., Vrubļevska, J., Logins, R., Bērze, L., 2017. Depresijas un trauksmes saistība ar kardiovaskulārām slimībām primārajā aprūpē Latvijā (Eng. Relationship between depression and anxiety and cardiovascular disease in primary care in Latvia). *RSU 2017. gada zinātniskā konference. Tēzes,* 272.lpp.

Posters and oral presentations

1. Ivanovs, R., Trapencieris, M., Vrublevska, J., Logins, R., Bērze, L., Rancāns, E., 2016. Depression and its correlation with the risk of cardiovascular mortality in primary care population in Latvia. 24th European Congress of Psychiatry, Madride, Spānija. Poster presentation.
2. Ivanovs, R., Trapencieris, M., Vrublevska, J., Logins, R., Bērze, L., Rancāns, E., 2016. Women with depression have a higher risk of cardiovascular mortality in primary care population in Latvia. 29th ECNP Congress, Vīne, Austrija. Poster presentation.
3. Ivanovs, R., Rancāns, E., Ķīvīte, A., Mintāle, I., Vrubļevska, J., Logins, R., Bērze, L., 2016. Anxiety and its association with cardiovascular diseases in primary care population in Latvia. 29th ECNP Congress, Vīne, Austrija. Poster presentation.
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7. Ivanovs, R., Rancāns, E., Ķīvīte, A., Mintāle, I., Vrubļevska, J., Logins, R., Bērze, L., 2017. Anxiety associated with a reduction of cardiovascular mortality risk in primary care population in Latvia. 30th ECNP Congress, Parīze, Francija. Poster presentation.
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15. Vrubļevska, J., Ivanovs, R., Ķīvīte, A., Rancāns, E., 2017. Association of Depression and Anxiety with Cardiovascular diseases. World Psychiatric Organisation INTER ZONAL Congress, Viļņa, Lietuva. Oral presentation.

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