VILNIUS UNIVERSITY

INDRAJA VELIČKIENĖ

Is Anxiety Sensitivity Associated with Coronary Heart Disease, Anxiety Disorders and Inflammation Markers (IL-6, IL-8)

Summary of the Doctoral Dissertation

Biomedical Sciences, Medicine (06B)

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VILNIAUS UNIVERSITETAS

INDRAJA VELIČKIENĖ

JAUTRUMAS NERIMUI, JO RYŠYS SU KORONARINE ŠIRDIES LIGA, NERIMO SUTRIKIMAIS IR UŽDEGIMO RODIKLIAIS (IL-6 IR IL-8)

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LIST OF ABBREVIATIONS

ASI, Anxiety Sensitivity Index

ASI-R-36, Anxiety Sensitivity Index Revised–36

IL-6, interleukin 6

IL-8, interleukin 8

VMHC, Vilnius Mental Health Centre

VULSC, Vilnius University Hospital Santariskiu Clinics Cardiology ward

1. Introduction

Anxiety disorders are increasing in prevalence. According to a review of the literature from 1980 to 2004, lifetime prevalence rates for total anxiety disorders varied from 10.6% to 16.6%. Women generally had higher prevalence rates than men across all anxiety disorder categories, but the magnitude of this difference varied. Philosopher H. Rosa speaks about the change in the pace of life and that acceleration contributes to relationship, communication, and stress. Furthermore, there is growing evidence to suggest that stress and anxiety disorders play a role in general inflammation, causing slow changes in the circulatory system and vascular endothelium leading to the development of cardiac diseases. Acute and chronic stress hormones induce an imbalance in pro- and anti-atherosclerotic factors, and influence the initiation of stress-related endothelial dysfunction up to myocardial infarction.

Anxiety sensitivity predicts the subsequent development of anxiety symptoms and panic attacks as well as functional changes. The anxiety sensitivity explanation concerns the fear of arousal-related sensations arising from beliefs that these sensations have harmful consequences. Normal anxiety is useful and causes better performance, but increased anxiety levels cause decreased goal performance for anxious individuals. The Anxiety Sensitivity Index (ASI-R-36) has been used in studies to measure a link between anxiety disorders and coronary heart disease. One aim of the present study was to determine whether a link exists between anxiety disorders and coronary heart disease in a selected population. Data from previously published studies show that factors such as gender, physical activity, and family status are connected with the ASI-R-36 score for individuals. According to previous reports, there are sex differences in anxiety disorders, with women being more likely to suffer from anxiety. Furthermore, the age of onset for anxiety disorders is earlier for women, and relapse of panic disorder occurs more often in women than in men. Recurrence of panic symptoms during a 5-year follow-up has been shown by Yonkers and colleagues to be higher in women (82%) than in men (5%).

According to a recently published study by Endrighi and colleagues, IL-6 reactivity was significantly greater in postmenopausal females than in males at 45 min ($M = 0.37 \pm 0.04$ vs. 0.20 ± 0.03 pg/mL, $p = .01$) and at 75 min ($M = 0.57 \pm 0.05$ vs. 0.31 ± 0.05 pg/mL, $p = .004$) post-stress. Their results were independent of age, adiposity, socioeconomic position, depression, smoking and alcohol consumption, physical activity, statin use, testing time, task appraisals, hormone replacement, and baseline IL-6. Other significant predictors of IL-6 reactivity were lower household wealth, afternoon testing, and baseline IL-6.

1.1. The goal of the Research

To determine the importance of Anxiety Sensitivity, demographic/risk factors for individuals diagnosed with anxiety disorders and coronary heart disease and investigate an association with inflammatory markers (IL-6 and IL-8).

1.2. The objectives of the Research

1. To evaluate the Anxiety Sensitivity according to ASI-R-36 scale and it's link with the risk and socio-demographic factors in:
   a. participants diagnosed with coronary heart disease
   b. participants diagnosed with anxiety disorders,
   c. control group;
2. To compare participants diagnosed with anxiety disorders (F41.0; F41.1) and participants diagnosed with coronary heart disease (I20; I21):
   a. using the Anxiety Sensitivity Index,
   b. using its subscales and socio-demographic characteristics;
3. To investigate inflammatory markers IL-6 and IL-8 in men diagnosed either with coronary heart disease (I20; I21) or anxiety disorders (F41.0; F41.1).

4. To identify links between inflammatory markers (IL-6 and IL-8) and the Anxiety Sensitivity Scale and its subscales in male participants.

a. to compare the Anxiety Sensitivity level and inflammatory markers (IL-6 and IL-8);

b. to compare subscales means with inflammatory markers (IL-6 and IL-8).

1.3. The Novelty of the Research

Recent research examining anxiety has connected psychological and physical anxiety symptoms with functional changes in an individual's system, although it remains controversial whether these changes impact either functional or morphological signs. Recent achievements in understanding molecular and cellular changes have led to depression and anxiety being linked with inflammation and inflammatory markers. Interleukins 6 and 8 have been discussed in connection to stress and cardiovascular diseases mainly in the last two decades. Interleukin 6 (IL-6) has been investigated in studies analysing anxiety disorders, whereas interleukin 8 (IL-8) is more known to cause proliferation and adhesion, interacting and activating different cell types. Few studies have examined IL-8 in the context of psychiatric disorders. In one study, older patients diagnosed with coronary heart disease were more prone to have depression when their IL-8 concentration was increased. Interestingly, in another study conducted in the United States, the IL-6 concentration was decreased in participants who were more likely to display neurotic character trait.

Therefore, in the present study, we examined anxiety sensitivity in healthy male and female participants and in those diagnosed with anxiety disorders or coronary heart disease, hypothesising that anxiety sensitivity is higher in participants with coronary heart disease than in controls. We also examined whether inflammation plays a role in anxiety sensitivity by determining IL-6 and IL-8 levels and ASI scores in men diagnosed with anxiety disorders or coronary heart disease.

2. Study Subjects and Methods

The research was carried out in 2010-2016 in Vilnius University Santariškės Clinics and Vilnius Town Mental Health Centre. In order to carry out the research, the approval No. 158200-04-301-78 of Committee of Ethics of Research in Biomedicine of Vilnius region was obtained.

2.1. Participants

The inclusion criteria for this retrospective study were adults aged 18 to 65 years who agreed to participate in the study. The exclusion criteria included any medical condition that might cause inflammation (e.g., cough, increased temperature, or cancer). Individuals were asked to participate in the study after they were admitted to the Vilnius Mental Health Centre (VMHC) or Vilnius University Hospital Santariskiu Clinics Cardiology (VULSC) ward. Interviews were conducted 2–10 days after their admission and consent to participate. No payment or any extra services were provided to participants, although they were informed about their plasma IL-6 and IL-8 levels as well as their score on the Anxiety Sensitivity Index–Revised 36 (ASI-R-36) assessment. Control group participants who agreed to be included in the study participated from various institutions. All participants gave their informed consent. The participants were divided into three groups: (1) control group (n = 137), healthy volunteers; anxiety group (n = 59), volunteer participants who were receiving treatment for anxiety disorders at the VMHC; (3) cardiology group (n = 44), volunteer participants who were receiving treatment for coronary heart disease at the VULSC.

2.2. Measures

Anxiety sensitivity indices were measured in all participants using the ASI-R-36. This assessment consists of 36 questions, each with a choice of answers graded from 0 (very little) to 4 (very much). The total maximum score was 144. The ASI-R-36 is divided into six subscales based on the fear of the following: (1) cardiac symptoms, (2) respiratory symptoms, (3) gastrointestinal symptoms, (4) neurological symptoms, (5) loss of cognitive control, and (6) publicly observable

reactions. The ASI-R-36 was translated into Lithuanian and validated by being translated back to English. The final version was approved by two psychiatrists.

All participants also answered a questionnaire that evaluated their social situation and factors such as living arrangements, marital status, and employment as well as a self-evaluation of their physical activity (low, moderate, or intense). Other factors evaluated were cholesterol level, blood pressure, cigarette and alcohol consumption, family status and diabetes.

The medical records and diagnoses were obtained for participants diagnosed with anxiety disorders or coronary heart disease who had agreed to participate in the study and had filled in the questionnaire and ASI-R-36 assessment. Anxiety disorder diagnoses were made according to the International Statistical Classification of Diseases and Related Health Problems (10th Revision; ICD-10) criteria.

The levels of IL-6 and IL-8 were obtained for 54 male participants. Male rather than female participants were selected for this portion of the study to obtain more consistent results because of the potential confounding influence of hormonal changes occurring during the female menstrual cycle and because less research has been conducted in men assessing ASI-R-36 scores and diagnoses as well as investigating inflammation. One day after the questionnaire was completed, fasting blood samples were obtained from the participants between 7:00 and 9:00 a.m. The blood was centrifuged and the obtained plasma was frozen. All plasma IL-6 and IL-8 levels were determined in the same laboratory at Vilnius University Santariskiu Clinics, using the Immulite 1000 Immunoassay System (Siemens Healthcare) according to the manufacturer's instructions to control for differences in interpretation.

The ASI- R-36 was originally constructed as a unitary scale. However, analytic research on the ASI-R-36 demonstrated that it is both a hierarchical and multidimensional scale, consisting of a higher-order factor (i.e., global AS) and lower-order dimensions pertaining to fears of physical, cognitive, and social anxiety symptoms. It is important to use subscales while considering general psychopathology and to understand illness symptoms, impact on everyday functioning, and specific aspects of the anxiety response (e.g., respiratory

symptoms). Pearson's correlation coefficient has been used to show connections between these subscales and indicates that all the subscales have statistically significant associations with one another and the ASI-R-36.

The strongest correlation is between dissociative neurological symptoms and the ASI; the most distant correlation is between the fear of gastrointestinal symptoms and the fear of loss of cognitive function.

Table 1. Pearson correlations between the subscales of the Anxiety Sensitivity Index-R-36

Subscale	1	2	3	4	5	6	7
1	-						
2	0.84***	-					
3	0.84***	0.73***	-				
4	0.68***	0.59***	0.59***	-			
5	0.81***	0.52***	0.56***	0.45***	-		
6	0.91***	0.73***	0.70***	0.60***	0.72***	-	
7	0.80***	0.56***	0.55***	0.45***	0.68***	0.79***	-

1, Anxiety Sensitivity Index; 2, Fear of cardiovascular symptoms; 3, Fear of respiratory symptoms; 4, Fear of gastrointestinal symptoms; 5, Fear of publicly observable anxiety reactions; 6, Fear of dissociative and neurological symptoms; 7, Fear of loss of cognitive control. ***$p < 0.001$

2. RESULTS

As previously stated, three groups were used in this study: individuals diagnosed with anxiety disorders (met ICD-10 criteria for panic disorder, generalised anxiety disorder) at the VMHC, individuals diagnosed with coronary heart disease (diagnosed by cardiologist and met ICD-10 codes I20 and I21) at the VULSC, and healthy individuals who volunteered. The number of people who declined to participate was not documented because data were recorded only after participants signed the consent form and agreed to fill in the questionnaire. The data obtained for all three groups were normally distributed.Participants consisted of 240 individuals, 54.8% women and 45.2% men. The participants' characteristics based on their questionnaire answers are shown in Table 2.

Table 2. Association of patient characteristics with the three study groups

Factors	**Cardiac group %**	**Anxiety group %**	**Control group (%)**	χ^2	***p***
gender					
females	2.2	14.2	34.9	34.41	**0.000**
males	16.8	11.2	20.7		
Age					
18–29	0	10.4	29.0	74.99	**0.000**
30–39	0.5	6.8	9.0		
40–49	5.0	4.1	7.7		
50 >	14.5	4.5	7.7		
Family status					
lives alone	2.7	8	19.7	7.34	0.290
lives with family	15.2	17.5	36.8		

Factors	**Cardiac group %**	**Anxiety group %**	**Control group (%)**	χ^2	*p*
Occupation					
employed/studies	10.9	16.8	46.4	27.33	**0.000**
unemployed	4.1	9.5	12.3		
Physical activity					
low	2.8	8.9	7.0	12.79	**0.012**
moderate	9.9	15.5	39.4		
intensive	3.3	2.3	10.8		
Smoking					
Does not smoke	11.5	16.5	41.3	2.19	0.334
Smoke	3.2	9.6	17.9		
Alcohol consumption					
Does not consume	5.5	14.3	25.3	14.51	**0.006**
Consumes 1–3 units	6.9	8.8	31.8		
consumes more then 4 units	2.8	2.8	1.8		
Blood pressure					
Normal	24.2	30.5	39.1	1.42	0.491
Increased	0.8	1.6	3.9		

An association was found between ASI scores and both gender and physical activity. Women were significantly more likely than men to have high ASI-R-36 scores, and participants who were physically active had lower ASI-R-36 scores. This latter result is consistent with previous research showing physical activity to be a protective factor against stress, anxiety, coronary heart disease, and other illnesses such as diabetes and hypertension. A step-wise linear regression analysis showed that participants with moderate and intense physical activity had lower ASI-R-36 scores than those with low physical activity ($\beta = -0.26$, $p = 0.017$; one variable of physical activity $F = 6.87$, $p = 0.011$, $R^2 = 0.08$). Other factors (marriage, unemployment, and smoking and alcohol consumption) had no significant effect on the ASI score.

Characteristics, including gender, age, employment, and smoking and alcohol consumption, were examined based on ASI-R-36 scores. Anxiety showed a clear connection with gender and physical activity. Although living alone appeared to be associated with anxiety sensitivity, this result was not statistically significant. Previous studies have highlighted the significance of relationship quality for the female population because this had a great impact in their wellbeing and anxiety levels. However, the present study did not address relationship quality, and this may be assessed in future studies. Employment status was not significantly associated with the ASI-R-36 score, although previous studies have found that stressful work conditions lead to higher anxiety sensitivity.

Comparing the results in Tables 2 shows that there are differences in the groups based on various characteristics. There is a clear difference in the age groups. This is consistent with a hypothesis that long-term stress left untreated causes morphological changes and precipitates anxiety disorders later in life.

The results shown in Tables 3 indicate that statistically significant differences existed in the ASI-R-36 scores for the participants in the three groups. Both the ASI-R-36 and the subscale scores (fear of cardiovascular symptoms, respiratory symptoms, gastrointestinal symptoms, neurological symptoms, and loss of

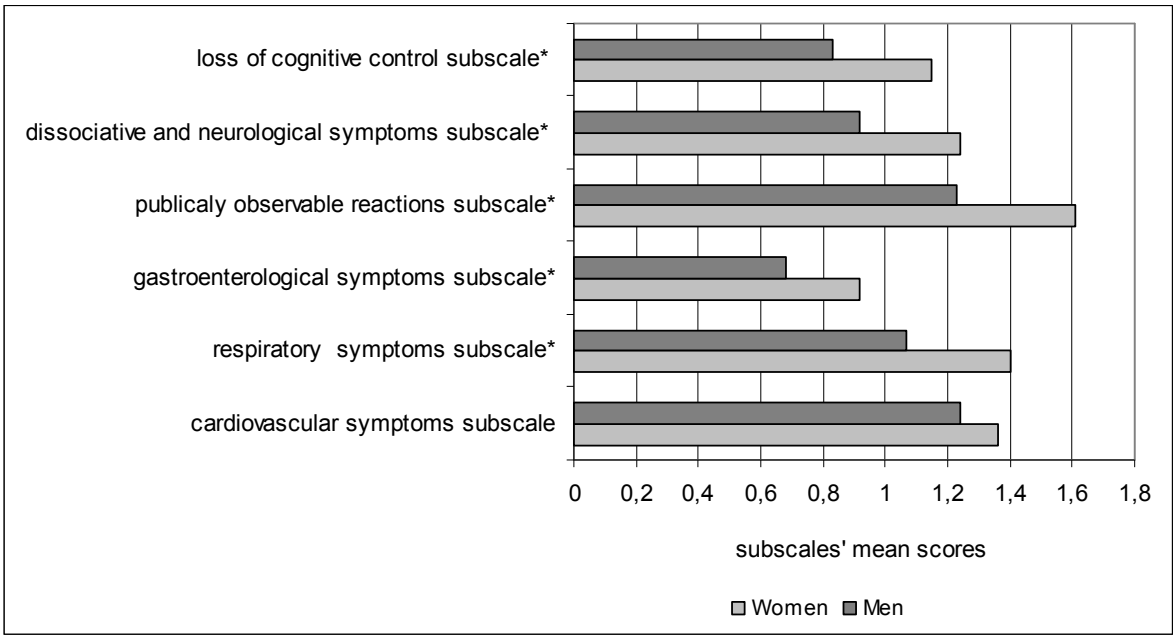
cognitive control) were higher in the group treated for anxiety disorders at the VMHC than in those treated for coronary heart disease at the VULSC or in the healthy control group. The results of the *a posteriori* Bonferroni test showed that there was a significant difference between the three groups based on their ASI scores (fear of respiratory, gastrointestinal, dissociative, and neurological symptoms, fear of publicly observable anxiety reactions, and fear of cognitive control loss). The individuals in the group diagnosed with anxiety disorders were more anxious than those in the other two groups. The results of the *a posteriori* test also provided evidence that individuals with coronary heart disease scored higher than those in the other two groups for fear of cardiovascular symptoms, which is consistent with the clinical picture of the illness and traumatic experience.

Table 3. Comparison of the ASI-R-36 and subscale scores in the three study groups

Index (Scale/Subscale)	Cardiac group		Anxiety group		Control Group		F	p
	Mean	SN	M	SN	M	SN		
Anxiety Sensitivity Index	34.16	23.44	62.7	29.93	36.53	22.58	24.36	**0.000**
Fear of cardiac symptoms	1.55	1.11	1.84	1.18	1.04	0.92	12.83	**0.000**
Fear of respiratory symptoms	1.16	0.78	1.76	1.06	1.05	0.87	11.52	**0.000**
Fear of gastrointestinal symptoms	0.61	0.78	1.04	0.92	0.73	0.79	3.45	**0.034**
Fear of publicly observable anxiety reactions	1.02	0.68	1.96	0.95	1.29	0.76	16.49	**0.000**
Fear of dissociative and neurological symptoms	0.97	0.60	1.70	0.91	0.91	0.66	26.70	**0.000**
Fear of loss of cognitive control	0.59	0.56	1.64	1.00	0.80	0.69	26.63	**0.000**

To examine anxiety levels based on gender, differences in the ASI-R-36 and subscale scores between men and women were compared using Student's *t* tests (graph 1). Women scored significantly higher than men for all measures except for fear of cardiac symptoms, which scored the same in both genders.

These results are consistent with those in previous studies that found that women were more likely than men to experience anxiety disorders and were able to express their emotions and feelings more accurately.



Graph 1. Comparison of the subscale scores based on gender, * - marks statistically significant results.

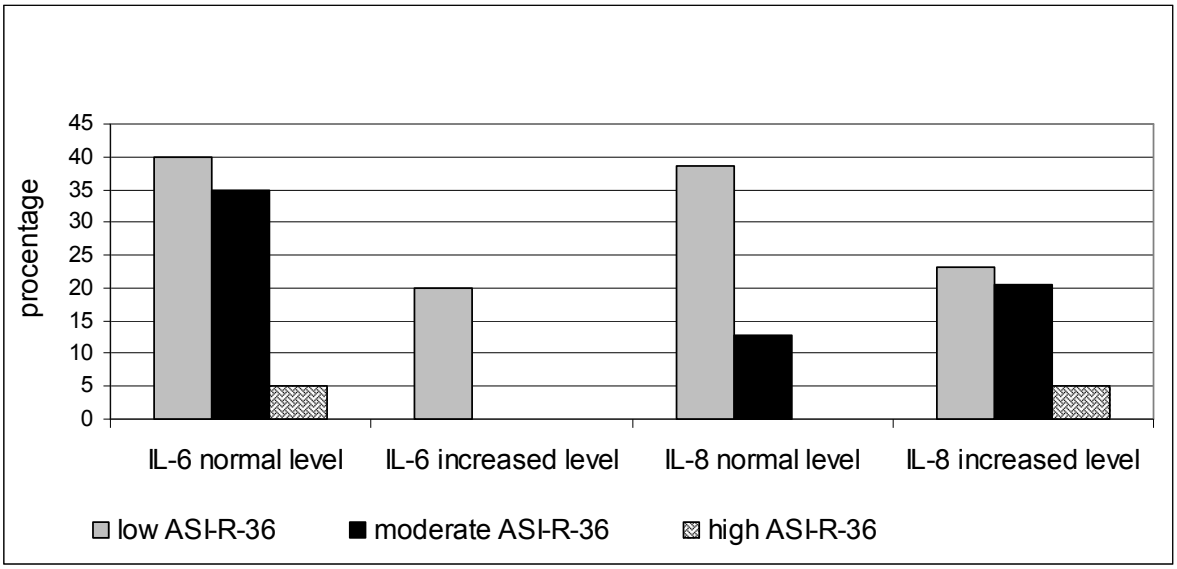
A similar analysis was conducted to examine the differences between scores in the group composed of individuals diagnosed at the VULSC with coronary heart disease and the healthy control group, and the results are shown in Table 6. Only two statistically significant differences were detected between these two groups. Individuals diagnosed with coronary heart disease displayed higher scores than those in the control group on fear of cardiovascular and respiratory symptoms. The fear of publically observable anxiety reactions score was also increased in the group with coronary heart disease, but this was not statistically significant.

Table 4. Comparison of ASI-R-36 and subscale scores between coronary heart disease and healthy control groups

Scale/subscale	Control group		Cardiac group		t	p
	Mean	SN	Mean	SN		
Anxiety Sensitivity Index ASI - R -36	42.85	27.09	43.99	29.34	-0.26	0.797
Fear of cardiac symptoms	1.18	1.02	1.80	1.17	-3.38	**0.001**
Fear of respiratory symptoms	1.18	0.95	1.51	1.00	-1.99	**0.048**
Fear of gastrointestinal symptoms	0.81	0.84	0.84	0.87	-0.23	0.817
Fear of publicly observable anxiety reactions	1.15	0.86	1.40	0.94	0.30	0.768
Fear of dissociative and neurological symptoms	1.11	0.81	1.05	0.87	0.40	0.693
Fear of loss of cognitive control	1.02	0.86	0.96	0.93	0.41	0.682

We next examined plasma IL-6 and IL-8 levels to test the hypothesis that they are higher in the group diagnosed with anxiety disorders than in either the group diagnosed with coronary heart disease or the control group. However, according to the data provided by the manufacturer of the kits used to determine IL-6 and IL-8 (Siemens Healthcare), IL-6 and IL-8 levels are less than 5,0 pg/ml for IL-8 and less than 5.9 ng/l for IL-6 in a healthy population (the control samples included in the kits were used). Thus, interleukin levels were examined only in men and only in two groups: individuals diagnosed with anxiety disorders and individuals with coronary heart disease. To compare IL-6 and IL-8 levels between these two groups, we used categorical data, that is, the results were considered either increased or normal; thus, the chi-square test was used to determine the statistical significance of the results. The results showed that a significant

difference existed. Contrary to our original expectations, we found that normal levels of IL-6 were associated with intermediate or high levels of anxiety in men. However, levels of IL-8 were normal and increased.



Graph 2. Percentage of men with normal and increased IL-6 and IL-8 levels based on ASI-R-36 scores

Student's *t* tests were also used to compare individuals who had an increased level of IL-8 with those who did not, and the results are shown in Table 5. Several statistically significant differences between these two groups were observed. There was normal Il 6 concentration for those with low, intermediate and high ASI-R-36 scores. Men who had normal and increased IL-8 levels had normal and higher ASI-R-36 scores and pronounced scores for fear of losing cognitive control. There may also be an association for men who fear respiratory symptoms and dissociative neurological symptoms to have an increased level of IL-8. The other ASI-R-36 subscales did not show any significant differences among individuals with increased IL-8 levels.

Table 5. ASI-R-36 and subscale scores stratified by normal and increased plasma Il-8 levels in men

Scale/subscale	Normal Interleukin 8 level		Increased Interleukin 8 level		t	p
	Mean	SN	Mean	SN		
Anxiety Sensitivity Index	35.20	23.61	48.84	33.21	-1.49	0.146
Fear of cardiovascular symptoms	1.41	1.21	1.54	1.16	-0.35	0.725
Fear of respiratory symptoms	1.12	0.86	1.39	1.07	-0.89	0.377
Fear of gastro-intestinal symptoms	0.60	0.92	0.92	0.96	-1.09	0.282
Fear of publicly observable anxiety reactions	1.09	0.73	1.49	0.94	-1.48	0.147
Fear of dissociative and neurological symptoms	0.83	0.63	1.22	1.00	-1.46	0.152
Fear of loss of cognitive control	0.66	0.49	1.26	1.06	-2.29	**0.027**

When we compared individuals with increased and normal IL-6 levels based on their ASI-R-36 and subscale scores we found that nearly all the ASI-R-36 subscales scores differed between these two groups (Table 6). Except for a fear of cardiovascular symptoms, which showed no significant difference, individuals with an increased IL-6 level had significantly lower subscale scores.

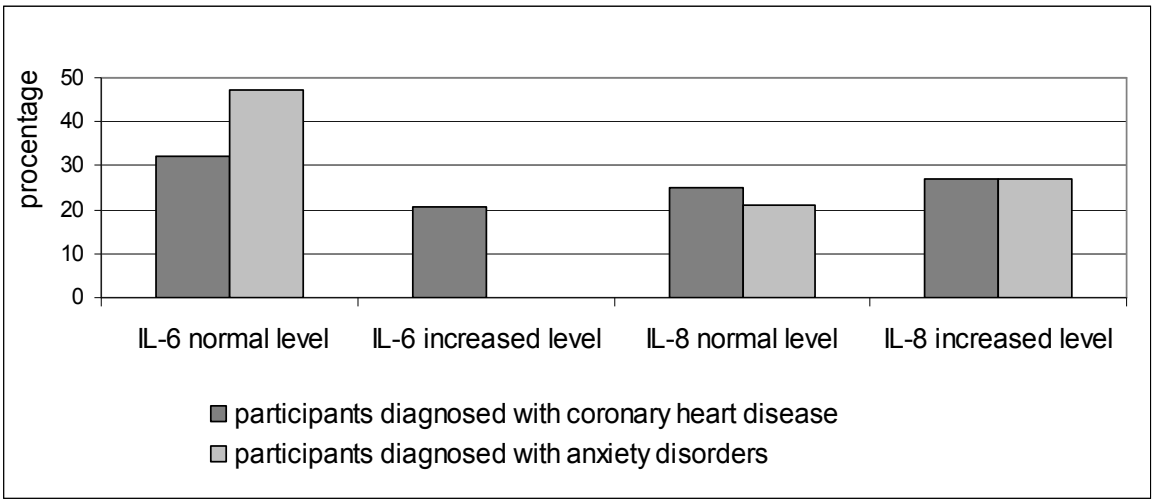
Table 6. ASI-R-36 and subscale scores stratified by normal and increased plasma IL-6 levels in men

Scale/subscale	Normal Interleukin 6		Increased Interleukin 6		t	p
	Mean	SN	Mean	SN		
Anxiety Sensitivity Index	48.13	28.68	18.00	12.19	2.88	**0.006**
Fear of cardiovascular symptoms	1.71	1.27	0.94	0.82	1.71	0.094
Fear of respiratory symptoms	1.42	1.00	0.76	0.65	1.86	0.071
Fear of gastro-intestinal symptoms	0.92	0.99	0.26	0.46	1.94	0.060
Fear of publicly observable anxiety reactions	1.43	0.87	0.77	0.56	2.18	**0.035**
Fear of dissociative and neurological symptoms	1.17	0.89	0.43	0.30	2.44	**0.019**
Fear of loss of cognitive control	1.08	0.92	0.42	0.41	2.08	**0.044**

We used binary logistic regression analysis to determine whether a relationship existed between plasma IL-6 levels and the ASI-R-36 subscales. We found that the ASI-R36 (main) score predicted IL-6 levels. As the ASI-R-36 score increased, the probability that individuals would have a normal IL-6 level increased. However, none of the subscales predicted IL-6 levels when all other subscales scores were controlled.

Individuals treated at the two different hospitals were evaluated according to the ASI-R-36 subscale scores by using Student's *t* test (graph 3). We found that individuals treated for coronary heart disease at the VULSC were less likely to worry and be anxious than those treated for anxiety disorders at the VMHC. There was also a significant difference in the ASI-R-36 subscale score for fear of gastrointestinal symptoms between the two groups ($t = -1.99$, $p = 0.05$).

However, no significant difference was detected between these two groups in their ASI subscale score for fear of cardiovascular symptoms (t = −1.03, p = 0.306).



Graph 3. Comparison of IL-6 and IL-8 levels for individuals diagnosed with coronary heart disease and anxiety disorders

4. DISCUSSION

The overall goal of this study was to determine whether any association existed between anxiety disorders (panic disorder, general anxiety disorder) or coronary heart disease and scores on the ASI-R-36. The ASI-R-36, a measure used to evaluate anxiety sensitivity, would be expected to be increased in individuals diagnosed with anxiety disorders, and we found this to be the case in the present study. Previous studies have reported an increase in ASI-R-36 scores for patients diagnosed with anxiety disorders as well as for those diagnosed with coronary heart disease, suggesting that anxiety and stress are two major factors in the pathogenesis of cardiac disease. However, we found no increase in ASI-R-36 scores among patients diagnosed with coronary heart disease, except the fear of cardiovascular symptoms subscales scores were similar in both groups.

However, we found an obvious difference in gender: more women than men scored higher on the ASI-R-36, consistent with the findings of Younker et al. and other studies. According to some researchers, women may be more likely to express their worries and describe emotional states than men, who may not be willing to accept that they might be susceptible to stress or to make any connection with mental illnesses. This would yield more false negative results. However, there is no evidence to support any of these opinions at present.
Recent research has shown a role of inflammation in anxiety disorders. We found some associations with plasma IL-6 and IL-8 levels and ASI-R-36 and subscale scores. Contrary to our hypothesis, plasma IL-6 levels were normal, rather than increased, in individuals with higher ASI-R-36 scores. Previous studies examining IL-6 levels have provided evidence for both increases and normal levels in various disorders or physiological states. In other studies, baseline cortisol levels first appeared to be associated with either an increase or decrease but were later found to be linked with previous trauma, traits, and other factors. Many factors are associated with interleukin fluctuations. Some interleukins are pro- or anti-inflammatory, enhancing one another and taking part in an inflammatory chain response. This is still being intensively investigated because there are many close connections between inflammation and various disorders, not only in anxiety and depression but also in cardiac disease and even cancer. Anxiety and anger responses to psychological stress have also been associated with a significant IL-6 concentration increase. It could be that coping mechanisms, learned responses, and previous experiences and exposure have some impact on the change in IL-6 levels.

In contrast to IL-6, we found that part of the participants diagnosed with either anxiety or cardiac disorders had increased IL-8 levels, suggesting that both groups of disorders might be associated with inflammatory responses. Consistent with our hypothesis, that the inflammatory response may play a role in anxiety disorders, IL-8 levels were increased in individuals with high ASI-R-36 scores, but not statistically significantly. Although few previous studies have compared

ASI-R-36 scores and IL-8 levels, some researchers have found links between anxiety and IL-8 level changes in blood plasma.

Inflammation and oxidative stress in central and peripheral systems are involved in many diseases, including cancer, cardiovascular diseases, neurodegenerative diseases, and psychiatric disorders such as anxiety disorders. Inflammation and oxidative stress link with the same pathogenesis pathways and induce inflammatory responses. High anxiety levels significantly increase the generation of reactive oxygen species in peripheral blood lymphocytes, granulocytes and monocytes. A wide range of studies has revealed the role of inflammation and subsequent changes in the markers. For example, one study showed that oxidative stress alters the defence mechanisms of myocytes. Confirming these findings, the present study showed there is no identified statistically significant link with anxiety and inflammation and that there is a need for continued research examining how anxiety and psychological perception initiate numerous reactions in the body, leading ultimately to inflammatory responses.

LIMITATIONS

This study had a few limitations that should be considered. The selected population was narrow, owing to the inclusion only of participants at two hospitals, and the inclusion criteria may have prevented greater participation. In addition, stigmatisation had a negative impact on the included participants as some individuals refused to participant in the study because mental health terminology and expressions were used. This was especially evident among patients diagnosed with coronary heart disease.

There was a difference between the groups of individuals diagnosed with anxiety disorders and those with cardiac disorders regarding their understanding of emotions and feelings. This was evident while interviewing participants. For example, those in the anxiety disorders group were better able to identify significant life events compared with participants with cardiac disorders, who found it more difficult. One patient said that no significant life events had

occurred, but when explaining his admission circumstances, he revealed that he had been brought to hospital from his mother's funeral. An emotion recognition questionnaire would have been useful for evaluating such differences. However, this was compensated for in part by asking more open-ended questions and by spending more time interviewing the participants. This helped to clarify patients' stories so that the collected data were more accurate. Finally, interleukin levels were measured between the first and tenth day of admission to the cardiology ward because we felt it was too intrusive to approach patients in intensive care who had just experienced myocardial infarction.

5. CONCLUSIONS

1. The study results suggest that socio-demographic characteristics influence:

a. An association between anxiety and gender. Women were significantly more likely than men to have high ASI-R-36 scores;

b. The difference between the subscales describing the fear of respiratory, gastroenterological, observable anxiety symptoms, dissociative and neurological symptoms. Women scored significantly higher then men. However there was no significant difference in the comparison of fear of cardiovascular symptoms subscale according to gender;

c. ASI-R-36 scores related to physical activity. Participants with moderate and intense physical activity had lower ASI-R-36 scores than those with low physical activity. No other factors (marital status, employment status, smoking, alcohol consumption) significantly affected ASI-R-36 scores.

2. The comparison between participants diagnosed with anxiety disorders, participants diagnosed with coronary heart disease and the control group showed:

a. Participants diagnosed with anxiety disorders scored significantly higher on ASI-R-36, but those diagnosed with coronary heart disease and the control group both displayed lower ASI-R-36 scores.

b. Participants diagnosed with anxiety disorders scored significantly higher on most of the ASI-R-36 subscales except the subscale representing the

fear of cardiovascular symptoms. The fear of developing cardiovascular symptoms in both groups (anxiety disorder and coronary heart disease groups) was similar; no significant difference was observed;

c. Participants diagnosed with coronary heart disease and the control group had similar ASI-R-36 scores and similar scores of most of the subscales, except for the fear of respiratory and cardiovascular symptoms. The scores were significantly higher in participants diagnosed with coronary heart disease compared to the control group;

d. Participants diagnosed with anxiety disorders had significantly higher ASI-R-36 scores and subscales scores compared to the control group.

3. Inflammatory markers investigated for male participants showed:

a. Participants diagnosed with anxiety disorders had a normal concentration of IL-6, but those diagnosed with coronary heart disease had an increased concentration of IL-6. The difference was significant;

b. Participants diagnosed with anxiety disorders and participants diagnosed with coronary heart disease had increased levels of IL-8, that suggests that both disorders may be associated with inflammation.

4. Higher Anxiety Sensitivity and subscales scores were associated with Interleukins concentration:

a. Male participants with moderate and higher ASI-R-36 scores had an increased level of IL-8. That supports the hypothesis that IL-8 is associated with ASI-R-36 scores, but results were not statistically significant;

b. Male participants with an increased IL-8 level scored significantly higher on the fear of loss of cognitive control subscale;

c. However, IL-6 levels were not associated with Anxiety Sensitivity scores;

d. Fear of publically observable anxiety symptoms, fear of loss of cognitive control and dissociative symptoms subscales were higher compared to normal IL-6 levels and that supports the conclusion that IL-6 does not have effect on ASI-R-36 scores.

DECLARATIONS

Ethics approval and consent to participate

This study was approved by Lithuania's Bioethics Committee. All participants gave their informed consent.

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PUBLICATIONS

Indraja Veličkienė, Vita Danilevičiūtė, Valmantas Budrys "Panikos sutrikimo ryšys su širdies kraujagyslių ligomis", Sveikatos mokslai, 2010; 2 (20): 3092-3096.

Indraja Veličkienė, Vita Danilevičiūtė, Žaneta Petrulionienė "Nerimo jautrumo indeksas socialiniame kontekste", Medicinos teorija ir praktika, 2014 – T.20(Nr.1) 43-47p.

Eglė Palevičiūtė, Žaneta Petrulionienė, Indraja Veličkienė "Psichosocialinių ir elgsenos rizikos veiksnių įtaka ūminio miokardo infarkto išsivystymui", Medicinos teorija ir praktika, 2011; 17(Nr. 3): 293–297.

Ingrida Kazlauskaitė, Indraja Veličkienė, Vita Danilevičiūtė "Įveikos būdų ryšys su antipsichotikų vartojimo režimo laikymusi", 2014 – T.20(Nr.1) 6-13 p.

Presentations/Poster Presentations:

1. Presentation “Panikos sutrikimų tyrimo organizavimas ir preliminarūs duomenys”, in the IV International Forensic Psychiatry conference “Adaptacijos norma ir patologija”, 2009 m.

2. Presentation “Panikos sutrikimo ryšys su širdies kraujagyslių ligomis” VULSK Cardiologist meeting, 2009 m.

3. Poster “Anxiety Sensitivity Index in the Social Context” Presentation ISAD International Conference, 2014 m., Berlin.

4. Presentation “Anxiety in a Social Insecurity Context” in the conference ‘Evolutionary medicine: new solutions for the old problems’, 2012, Vilniuje.

5. Presentation „Biologinis nerimo sutrikimų pagrindas“,in the conference “Trečioji universitetinė LSMU MA Psichiatrijos klinikos ir VU MF Psichiatrijos klinikos mokslinė konferencija” „Organiniai ir simptominiai psichikos sutrikimai“, Kaunas, 2010.

6. Presentation “Anxiety Sensitivity Index in Social Diversity". In the 16th conference of Bridging Eastern and Western Psychiatry, Vilnius, 2013.

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EDUCATION

UNIVERSITY:	Vilnius University
	Vilnius, Lithuania
DATES ATTENDED:	1998 – 2005
DEGREE:	MD
DEGREE:	2010 October – present

for preparation of doctoral dissertation in medicine (PhD) in Vilnius University

OTHER QUALIFICATIONS

Medical doctor‘s license Vilnius University, Lithuania, July 2006

Specialty General Psychiatry, Vilnius University, Lithuania, July 2010

Courses

1. M.de Wolf (Amsterdam Psichoanalysis institute director) „Attachment“, “Transference Focused Psychotherapy”, “The Psychotherapeutic Relation” seminars in 2008 – 2009;
2. Psychological Therapies in Psychiatry, 1 month course, Oxforshire and Buckinghamshire MHP NHS Trust, 2010;

3. „Psichoterapijos pagrindai gydytojams“, 96 hours, EVS group, 2011, supervision 16 hours;

4. Cognitive Behavioral Therapy for Anxiety Disorders and Deppression, attended 150 hours training course held by Lithuania Health Science University, 2011;

5. Child Protection (Level 2), Caldicott, Complaint, COSHH, HEALTH and SAFETY, Infection control, Loneworker, Riddor/Risk Incident Reporting & violence and aggression, 2011;

6. Section 12 and Approved Clinician Introductory courses, Springfield hospital, London June 2015.

7. Mentalization Based Treatment for Adolescents, Anna Freud Center, led by Peter Fonagy and Trudy Rossouw, 18-19 April 2016, continued monthly supervisions(10 hours).

REGISTRATION

Registered with GMC with the full license to practise, Training recognise by Royal College of Psychiatrist as equivalent. Specialist register entered on the 19/04/2011, specialty General psychiatry. GMC number 7065373
Royal College of Psychiatry membership number 926119.
Section 12 approved and Approved Clinician Status since 03/09/2015.

Employment History Summary:

Date (start and finish)	Job title	Location
24 October 2016 – present	Consultant Psychiatrist	Eating Disorders Services, Addenbrooke's hospital/ Community Eating Disorder Services, Cambridgeshire and Peterborough NHS Foundation trust, Cambridge, UK

16 December 2015 – 18 November 2016	Acting Consultant Psychiatrist	Psychiatry Intensive Care Unit, The Huntercombe Hospital Norwich, UK
22 January 2015 - 12 December 2015	Locum Specialist doctor, Psychiatry	Psychiatry Intensive Care Unit, Hellesdon Hospital, Drayton Road, Norwich, NR5 2BE, UK
14 April 2014 – 16 May 2014	Staff grade doctor, Psychiatry	Ward S3, Eating disorders, Addenbrooke's hospital, Cambridgeshire and Peterborough NHS Foundation trust, Cambridge, UK
1 August 2010 – 20/01/2015	Psychiatrist	Vilnius Mental Health Centre Vilnius, Lithuania
7 April 2010 – 6 June 2010	SHO	Oxfordshire and Buckinghamshire Mental health team, Community service and inpatient ward Tindal centre, Aylesbury, UK
15 February 2010 – 19 February 2010	Staff grade(middle grade) as locum	Cygnet Hospital Ealing, London, UK
1 September 2009 – 12 February 2010	Senior Psychiatry Resident	Vilnius Mental Health Centre Vilnius, Lithuania
5 May 2008 – 27 November 2009	Assistant Doctor	Trakai Hospital Trakai, Lithuania