

# Ischemic Heart Disease and Psychiatric Comorbidities: A Preliminary Local Survey

Shafti SS\*

Department of Psychiatry, University of Social Welfare and Rehabilitation Sciences (USWR), Iran

Received: 27 Apr 2020

Accepted: 08 May 2020

Published: 13 May 2020

**\*Corresponding author:**

Saeed Shoja Shafti, Department of Psychiatry, University of Social Welfare and Rehabilitation Sciences (USWR), Razi Psychiatric Hospital, Tehran, Iran, Fax: 0098-21-33401604, Tel: 0098-21-33401220, E-mail: ssshafiti@gmail.com

## 1. Abstract

**1.1. Introduction:** Psychosocial stresses and psychiatric problems may make worse the prognosis of patients with ischemic heart disease. Therefore, assessing their incidence among this group of patients may perhaps enhance our perception concerning their dynamic significance in the ground of psychological medicine.

**1.2. Method and Materials:** 101 ischemic heart patients, in the coronary care Unit, had been interviewed by an associate psychiatrist to find that is there any meaningful association between psychological complications or psychosocial strains and ischemic cardiac events.

**1.3. Results:** Ischemic events were meaningfully more prevailing amongst patients with both biological risk factors and psychiatric problems. Moreover, the quantity of patients suffering from psychological difficulties was meaning fully more than patients with no psychiatric complications. Besides, there was a substantial alteration between male and female participants as regards the category of psychosocial pressures. Seventy- nine percent of psychosocial stresses had been experienced by persons with psychological complications. Besides, while more dysthymic illness was evident in the acute assembly of participants, more minor or major depressive disorder was noticeable in the long-lasting group of cardiac patients; a variance which looked significant.

**1.4. Conclusion:** The high incidence of psycho-social stresses and psychiatric problems among ischemic heart patients, which might act as co- factors in triggering the pathogenicity of organic risk factors, ask for enough care for recognition, checking, and controlling of them, by way of reasonable clinical and psycho-social interventions.

**2. Keywords:** Coronary artery disease; Ischemic heart disease; Psychiatric comorbidities; Depression; Anxiety disorders; Psychosis

## 3. Introduction

Psychological pain can be generally demarcated as a negative internal state of the person that is dependent on analysis or evaluation of risk, hurt, or plea [1]. It is a well-known assertion that Myocardial infarction and sudden cardiac death can be elicited by emotive sufferings [2]. The susceptibility for these acute disorders is mainly determined by the existence of Coronary Artery Disease (CAD) and/or mechanical myocardial injury [3]. Long-lasting psychiatric, psychological and social situations can influence the slow progression of cardiovascular disease and may further boost the probability or extent of emotion -related causes of acute coronary syndromes, principally in patients with underlying cardiovascular disease [4, 5]. Misery and other psychological risk factors may have straight biologic and physiologic influences relevant to development of CAD. Moreover, risk linked with psychological distress may be interceded by adversative health actions such as smoking [6] and customary cardiovascular disease risk factors (for example, hypertension, dyslipidemia, and metabolic disorder) [7, 8]. Severe and prolonged overwhelming distress can result in clinical and sub-clinical conditions categorized by adverse effect that usually occur in psychiatric problems [9] and conditions that generally fall outside the range of clinical psychiatry such as vital exhaustion and burn-out syndrome. The amplified risk related with depression develops at levels well beneath clinical diagnostic standards for major depressive disorder [10]. Psychological distress is an unceasing process and proof proposes an association between rigorousness of psychological distress and bio- behavioral risks [11]. Nearly one in five acute coronary syndromes is heralded by an acute trigger [12]. On the other hand, while

acute psychological distress may play a contributing role in clinical syndromes, the role of psychological distress in heart disease differs with the period of the illness [13]. Acute stressors are principally of importance as causes of acute cardiac disorders in the attendance of relatively progressive coronary artery ailment, though incidents of continued high distress are connected with augmented susceptibility for acute conditions, and enduring distress is related with the slow progression of coronary artery disease [13]. While there seems to be a dose-response association between the severity of psychological suffering and the hazard of cardiac disease, more study is desired to define whether psychological distress by itself or clinical disorders, such as major depressive and anxiety disorders, are better conjecturers of adverse cardiac events [11]. It is important, as well, to consider the surroundings in which these problems are addressed [9]. In the current local evaluation, the rate of recurrence of psychiatric complications and psychosocial strains, which were existent earlier than ischemic events, had been appraised, to study their possible triggering effect with respect to the said morbid processes.

#### 4. Method and Materials

101 ischemic heart patients, who were admitted in the Coronary Care Unit (CCU), were elected systematically during a 6-months period, from August 2011 up to December of the same year. After the primary work-up and management by a cardiologist and just before release from CCU, an inclusive clinical interview was accomplished by an associate colleague (psychiatrist) to explore the presence of any kind of psychiatric symptom or stress in patients. In this regard, supplementary data, too, was obtainable from patient's families, personnel, and medicinal doctors, who were meeting cases every day. Psychiatric disorders had been identified in line with the criteria of 'Diagnostic and Statistical Manual of Mental Disorders, 4th edition, text revision (DSM IV-TR)' [14], which was the basis of diagnosis during present evaluation. In addition, a self-made form, as a kind of assist for surveyor (the aforesaid psychiatrist), had been designed, which involved all psychiatric symptoms, substance abusing, physiognomies of type A behavior pattern, and psycho-social stresses. Precedence of signs and strains before admittance was a requisite for ultimate exploration.

#### 5. Statistical Analysis

Statistics were evaluated by  $Z$  and chi-square ( $\chi^2$ -test) formulary. The statistical significance was demarcated as  $P$  value equal or less than 0.05.

#### 6. Results

According to data, 40.6%, 36.6% and 22.8% of patients had been diagnosed as unstable angina, acute myocardial infarction, and congestive heart failure, respectively. 49.5% of cases were female and 50.5% of them were male patients. In the present sample, acute infarction was meaningfully more widespread amongst men and unstable angina amid women ( $P < 0.01$ ). Moreover, while 22.8% of cases were single or widowed, 77.2% were married ( $P < 0.05$ ). Patients were between 32 and 84 years old (mean =  $56.72 \pm 14.57$ ) with 43.6% above 60. Among them 33.7% had academic educations, 7.9% had

high school diploma, 15.8% were uneducated, and the remaining had some literacy. 51.48% of the patients were from families with an income no less than 500 US Dollars per family member per year. 38.6% had personal house and 61.4% were tenant or else. In the present assessment, no significant relationship was evident between the above-mentioned factors (as psychosocial strains) and ischemic events. While 44.5% of participants had concomitant mental difficulties and organic risk-factors (hypertension, hyperlipidemia, cigarette smoking or diabetes mellitus),

14.9% of them had neither psychiatric problem nor somatic risk factor. In this regard, 21.78% had organic risk-factor with no mental disorder and 18.81% had a psychiatric disorder without any organic risk-factor (Table 1). Amongst the aforementioned risk-factors, hypertension was noticeable in 55%, diabetes mellitus in 38%, hyperlipidemia in 37%, and cigarette smoking in 32% of patients. More than one medical risk-factor was evident in 62% of the patients, which was more prevalent among female cases. According to analysis, ischemic happenings were meaningfully more widespread amongst participants with both mental complications and organic risk-factors, in comparison with patients without both of them ( $P < 0.05$ ). As stated by the findings, co-morbidity of these two had augmented the danger of cardiac happenings around three times, and presence of psychiatric complications had amplified the disadvantageous influences of organic risk-factors around two times. Totally, 63.36% of cases had some kind of psychiatric problem. Amid them, 67% had some type of depressive ailment, like major depressive disorder, minor depressive disorder or dysthymic disorder, and 15% had an anxiety disorder, like generalized anxiety disorder, obsessive compulsive disorder, or phobia. 17% of cases did not have any particular disease and so could be categorized as Not Otherwise Specified (NOS) (Table 2) (Figure 1 and 2). As regards the psychiatric symptoms, 42.6% of cases had depressed attitude and exhaustion, 48.5% had petulance and hostility, 39.6% reported sleeplessness, 23.7% stated loss of interest, 17.9% indicated loss of appetite, and 25.7% had declared anxiety as a distressing sign in the previous months. Regarding substance abuse, 4% reported alcohol misuse and addiction, 3% had addiction on opium, and 20.8% were in need of on cigarette smoking. So, quantity of patients with mental complications was meaningfully more than patients without that ( $P < 0.05$ ). Also, depression was around two-timing and anxiety 1.5-times more common among female patients ( $P < 0.001$ ) (Table 3). Regarding psycho-social stresses, 52% of men and 47% of women had experienced some kind of strain thru the days in advance admission (Table 4) (figure 3). By the way, 58% of men and 17% of women were experiencing numerous pressures. Family tension for females and economic strain for males were the most prevailing stresses (49% and 44%, respectively), which revealed a significant difference ( $P < 0.01$ ). Concerning association between mental complications and strains and according to the findings, among patients without psychiatric difficulties ( $n = 37$ ), the ratio of patients without stress ( $n = 25$ ) to patients with that ( $n = 12$ ) was '2.08:1', and in the crowd with mental difficulties ( $n = 64$ ) the ratio for patients with strain ( $n = 41$ ) to patients without tension ( $n = 17$ ) was '2.76:1'. Therefore around 79% of total pressures were experienced by pa-

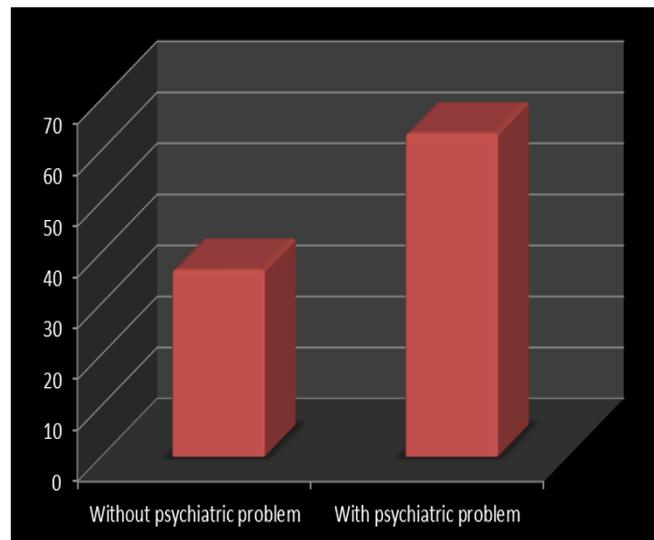
tients who had mental complications and this occurrence was affiliated with four times escalation in the risk of cardiac events, against patients with no similar complications ( $P < 0.0001$ ) (Table 5). While in this regard no significant difference was evident between males and females, with exclusion of psychiatric complications, no significant difference was evident, too, between patients with or without stress ( $P > 0.05$ ). Nevertheless, while among patients with myocardial infarction the ratio of male patients with stress to female patients was '2:1', in the cluster of patients with unstable angina it was '1:1.4', and in all the said crowds the patients with tension were numerically more than cases without that. Characteristics of type A behavior, as well, were noticeable in 32%, 13%, and 14% of patients with myocardial infarction, unstable angina, and congestive heart failure, in turn (Table 6). While in the infarcted group the ratio of man to woman with type A behavior was '2.6:1', this variance was not important ( $DF = 2, \chi^2 = 6.04, P < 0.25$ ). Likewise, in the infarcted group, around 60% had some kind of the depressive illnesses; 18% as minor or major depressive disorder, and 42% as dysthymic disorder. In the long-lasting group of patients (unstable angina and congestive heart failure), as well, 51% were identified as minor or major depressive disorder and 18% as dysthymic disorder, and in general 69% of cases in the later group had some sort of depression (Table 7). Consequently, the ratio of depression in the acute infarcted patients to prolonged ischemic cases was approximately '1:2.7', and for dysthymic disorder it was almost '2.6:1'. Accordingly, a substantial variance ( $P < 0.001$ ) was evident as regards the severity of depression between acute and prolonged patients; a pattern which was not observable concerning anxiety disorders.

**Table 1:** Prevalence of psychiatric problems and biological risk factors among cardiac patients.

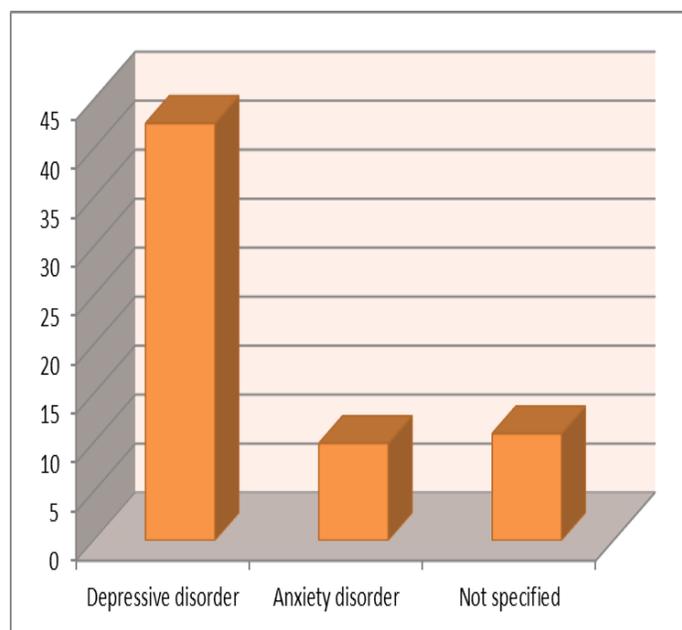
Cardiac patients	Male	%	Female	%	Total
Without psychiatric problem Without biological risk factor	11	21.6	4	8	15
Without psychiatric problem With biological risk factor	13	25.5	9	18	22
With psychiatric problem Without biological risk factor	7	13.7	12	24	19
With psychiatric problem With biological risk factor	20	39.2	25	50	45
<b>Total</b>	<b>51</b>	<b>100</b>	<b>50</b>	<b>100</b>	<b>101</b>

**Table 2:** Prevalence of psychiatric problems among patients.

Psychiatric problems	Male	%	Female	%	Total	%
Depressive disorder	14	13.9	29	28.7	43	42.57
Anxiety disorder	4	3.9	6	5.9	10	9.90
Not specified	9	8.9	2	1.9	11	10.89
Without psychiatric problem	24	23.8	13	12.9	37	36.67
<b>Total</b>	<b>51</b>	<b>50.5</b>	<b>50</b>	<b>49.5</b>	<b>101</b>	<b>100</b>



**Figure 1:** Dominance of psychiatric problems among cardiac patients.



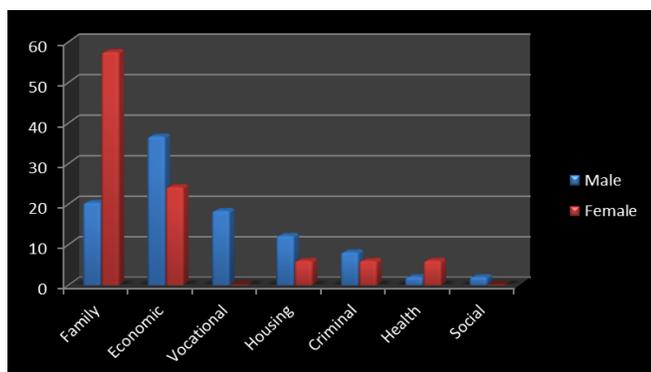
**Figure 2:** Frequency of psychiatric problems among cardiac patients.

**Table 3:** Prevalence of psychiatric problems among male and female cardiac patients.

Psychiatric problems	Male	%	Female	%	Total	%
Depressive disorder	14	13.9	29	28.7	43	42.57
Anxiety disorder	4	3.9	6	5.9	10	9.90
Not specified	9	8.9	2	1.9	11	10.89
Without psychiatric problem	24	23.8	13	12.9	37	36.67
<b>Total</b>	<b>51</b>	<b>50.5</b>	<b>50</b>	<b>49.5</b>	<b>101</b>	<b>100</b>

**Table 4:** prevalence of psychosocial stresses among male and female cardiac patients.

Psychosocial stresses	Male	%	Female	%	Total
Family	10	20.40	19	57.57	29
Economic	18	36.73	8	24.24	26
Vocational	9	18.36	0	0	9
Housing	6	12.24	2	6.06	8
Criminal	4	8.16	2	6.06	6
Health	1	2.04	2	6.06	3
Social	1	2.04	0	0	1
<b>Total</b>	<b>49</b>	<b>100</b>	<b>33</b>	<b>100</b>	<b>82</b>

**Figure 3:** Frequency of psychosocial stresses among male and female cardiac patients.**Table 5:** Prevalence of psychosocial stresses among patients with or without psychiatric problems.

Cardiac patients	With stress	%	Without stress	%	Total
Without psychiatric problem	12	20.33	25	59.52	37
With psychiatric problem	47	79.66	17	40.47	64
<b>Total</b>	<b>59</b>	<b>100</b>	<b>42</b>	<b>100</b>	<b>101</b>

**Table 6:** Prevalence of type A behavior among patients.

Cardiac patients	Males with type A behavior	Females with type A behavior	Male and females without type A behavior	Total
Myocardial infarction	8	3	23	34
Unstable angina	3	4	46	53
Congestive heart failure	1	1	12	14
<b>Total</b>	<b>12</b>	<b>8</b>	<b>81</b>	<b>101</b>

**Table 7:** Prevalence of psychiatric problems among acute and chronic ischemic patients.

Duration of cardiac disorders	Depression (major + minor)	Dysthymic disorder	Anxiety disorders	NOS	Total
Acute	6	14	5	6	33
Chronic	17	6	5	5	33
<b>Total</b>	<b>23</b>	<b>20</b>	<b>10</b>	<b>11</b>	<b>64</b>

## 7. Discussion

Cardiovascular psychological risk factors can be grouped based on the period and chronological immediacy to the occurrence of ischemic disorders:

- 1) acute psychological risk-factors that may act as causes of coronary happenings within one hour;
- 2) occasional psychological risk-factors with a duration lasting from a number of weeks to two years;
- 3) chronic psychological risk factors that stimulate the gradual progression of cardiac illness [15].

These psychological risk-factors often should be realized in the context of genetic background dynamics and customary organic risk-factors such as diabetes mellitus, dyslipidemia and hypertension. On the other hand, since numerous patients will not meet traditional classification standards for psychiatric diagnosis, innovative psychiatric and psychological strategies should be settled to address distress-related psychological risk-factors. So, it is essential to appraise psychological suffering in terms of its environmental precipitants and causes that may intensify susceptibility to these happenings (i.e. discrimination, low socio-economic position, and adversative early life experiences) along with psychological and social dynamics that can act as safeguards (coping style, social care and positivity) [15]. Moreover, innovative physiologic and biologic cardiovascular disease markers are constantly developed to enhance risk grouping for adversative cardiovascular wellbeing consequences. Such unique biomarkers may not only increase identification of cases who are “at risk”, but may likewise rise our knowledge regarding bio-behavioral processes by which psychological distresses are related to adverse cardiac illness. For instance, psychological pain and sadness are connected with amplified oxidative tension markers, which may have significant consequences for the distress- cardiovascular disease passageways [15]. Anyhow, more study is required on the interaction between behavioral and biologic links of psychological distress [12]. This would possibly lead to multidimensional checking of high-risk cases that are treated with psychological and behavioral mediations [16]. For example, even in the lack of clinical cardiac ailment, the effectiveness of antidepressants is a smaller amount if patients have biological risk-factors or psychological stresses [16]. Maybe an organized health-care tactic, rather than person-based depression management policies, may be better in decreasing secondary cardiac happenings in clinically depressed individuals with cardiovascular disease [17]. Contrary to the various conclusions for antidepressant managements, declining psychological strains seems to have more reliable effects in declining adversative cardiac events [18]. Back to our discussion, objectives of the present assessment could be identified as:

- 1) prevalence of psychiatric difficulties among ischemic heart patients;
- 2) probing any meaningful relationship between psycho-social stresses and ischemic events; and
- 3) searching any noticeable harmful influence thanks to TABP.

With respect to the first query and along with the outcomes, frequency of psychiatric illnesses, specifically depression amongst patients with ischemic heart disease was significantly high. On the other hand, by with respect to chronicity or acuteness of cardiac events, it was obvious that there was a straight affiliation between chronicity of cardiac ailments and severity of sadness. In a comparatively analogous study in India on patients with IHD, anxiety and depressive disorders were found in a noticeable percentage of patients and around 95.4% of patients recounted some kind of psychological problem [15], which was quantitatively far more than the outcomes of the current assessment. On the other hand, while anxiety and depression were more prevailing among women, in comparison with men, male cases with no definable psychological complications were two-folds more than female cases. This finding showed that unfavorable effects of mental difficulties might have some gender-based physiognomies. Otherwise, such a variance is similar, too, to the frequency of anxiety and depression in general public. Regarding the interaction of organic risk factors and psychological difficulties, we found a two-times escalation in the pathogenicity of organic risk-factors in attendance of mental complications, and three-times upsurge in cardiac harms when both of organic risk-factors and mental difficulties co-exist. Most of the patients in the present evaluation had both of them. Concerning psycho-social stress and its interaction with ischemic happenings, findings revealed that the chance of cases with mental problems in comparison with cases without psychological difficulties, for personal experience of psychosocial strain, were around '4:1'. Thus, around 80% of psychosocial pressures had been concentrated in cases with psychiatric problems. Therefore, maybe psychosocial strains and mental complications have a reciprocal aggravating influence on each other. Likewise, it is a renowned fact

that psychological stress-induced ischemia is much more common than exercise-induced ischemia in cases with clinically established coronary heart illness. Females and bachelor males are at higher risk for psychological stress-induced ischemia [16]. While psychological strain induces transitory myocardial ischemia in 1/3 to 1/2 of patients with CAD, it is usually with no pain and happens at lesser levels of oxygen demand than ischemia induced by muscular exercise and, also, not connected to the severity of coronary blockade. Though stress-induced hemodynamic fluctuations, principally upsurges in systemic vascular resistance, coronary artery vasoconstriction, and micro-vascular variations, may all contribute to the process of ischemia, there is huge changeability in responses to mental stress [17]. So, this gloomy course together with the harmful effects of organic risk-factors can be claimed as the most risky combination. Moreover, in the present study, there was a substantial dissimilarity between men and women, with regard to explanation of psychosocial strains, who had declared domestic struggles and financial difficulties, separately, as their most essential stresses. So, maybe more incidents of ischemic happenings amongst wedded people, in comparison with the singles, could be ascribed to the joint unfavorable effect of numerous strains. In view of more acute infarctions in men in comparison with women and, besides, more feeling of tension among infarcted men, might disclose, over again, gender-based adversative effect of strain

on severity of cardiac happenings, an occurrence which was obvious, once again, regarding the link between type A behavior and intensity of cardiac happenings among men. Furthermore, management of psychiatric syndromes in ischemic heart patients can be perplexing due to cardiovascular side effects of many of the psychotropic drugs, besides potentiality of drug interactions. Additionally, many of the hypertensive or cardiac drugs have psychiatric side effects. Anyhow, acute psychological distress is an important cause of severe coronary diseases [18]. In general, psychological distress is related with adversative cardiovascular consequences via probable biologic pathways, including neuro-hormonal issues, autonomic nervous system dysregulation, raised inflammation and coagulation factors and decreased response to harm, in addition to adversative health activities such as smoking, physical indolence, unfortunate nutritional behaviors and treatment non-adherence [20]. Absence of cohort group, limitation of outcomes to a solitary hospital, and also small sample sizes were among the weaknesses of the current estimation. Certainly, supplementary methodical investigations in future will increase our understanding regarding these dynamic interactions in the realm of psychological medicine.

## 8. Conclusion

The high incidence of psycho-social stresses and psychiatric problems among ischemic heart patients, which might act as co-factors in triggering the pathogenicity of organic risk factors, ask for enough care for recognition, checking, and controlling of them, by way of reasonable clinical and psycho-social interventions.

## References:

- Schulman JK, Muskin PR, Shapiro PA. Psychiatry and cardiovascular disease. *FOCUS*. 2005; 3: 208-24.
- John S. Prevalence and pattern of psychiatric morbidity and health related quality of life in patients with ischemic heart disease in a tertiary care hospital. *Indian Journal of Psychiatry*. 2013; 55: 353-9.
- Aben I, Verhey F, Strik FJ, Lousberg R, Lodder RJ, Honig A. A comparative study into the one-year cumulative incidence of depression after stroke and myocardial infarction. *J Neurology Neurosurgery and Psychiatry*. 2003; 74: 581-5.
- Dimsdale JE. Psychological stress and cardiovascular disease. *J Am Coll Cardiol*. 2008; 51: 1237-46.
- Farisa R, Purcell H, Henein MY, Coats AJS. Clinical depression is common and significantly associated with reduced survival in patients with non-ischaemic heart failure. *Eur J Heart Fail*. 2002; 4: 541-51.
- Williams RB, Surwit RS, Siegler IC, Ashley-Koch AE, Collins AL, Helms MJ, et al. Central nervous system serotonin and clustering of hostility, psychosocial, metabolic, and cardiovascular endophenotypes in men. *Psychosom Med*. 2010; 72: 601-7.
- Vaccarino V, McClure C, Johnson BD, Sheps DS, Bittner V, Rutledge T, et al. Depression, the metabolic syndrome and cardiovascular risk. *Psychosom Med*. 2008; 70: 40-8.

8. Rudisch B, Nemeroff CB. Epidemiology of comorbid coronary artery disease and depression. *Biological Psychiatry*. 2003; 54: 227-40.
9. Frasure-Smith N, Lesperance F, Talajic M. The impact of negative emotions on prognosis following myocardial infarction: is it more than depression? *Health Psychol*. 1995; 14: 388-98.
10. Gustad T, Laugsand E, Janszky I, Dalen H, Bjerkeset O. Symptoms of anxiety and depression and risk of acute myocardial infarction: the HUNT 2 study. *Eur Heart J*. 2014; 35: 1394-403.
11. Rosengren A, Hawken S, Ounpuu S, Sliwa K, Zubaid M, Almahmeed WA, et al. Association of psychosocial risk factors with risk of acute myocardial infarction in 11,119 cases and 13,648 controls from 52 countries (the INTERHEART Study): case control study. *Lancet*. 2004; 364: 953-62.
12. Samuels MA. The brain-heart connection. *Circulation*. 2003; 116: 77-84.
13. Smolderen KG, Spertus JA, Reid KJ, Buchanan DM, Krumholz HM, Denollet J, et al. The association of cognitive and somatic depressive symptoms with depression recognition and outcomes after myocardial infarction. *Circ Cardiovasc Qual Outcomes*. 2009; 2: 328-37.
14. American Psychiatric Association (APA). *Diagnostic and Statistical Manual of Mental Disorders*. 4th ed. Text rev. Washington, DC: American Psychiatric Association. 2000.
15. Whooley MA, deJonge J, Vittinghoff E, Otte C, Moos R, Carney RM, et al. Depressive symptoms, health behaviours, and risk of cardiovascular events in patients with coronary heart disease. *JAMA*. 2008; 300: 2379-88.
16. Berkman LF, Blumenthal J, Burg M, Carney RM, Catellier D, Cowan MJ, et al. Effects of treating depression and low perceived social support on clinical events after myocardial infarction: The Enhancing Recovery in Coronary Heart Disease Patients (ENRICHD) Randomized Trial. *JAMA*. 2003; 289: 3106-16.
17. Rollman BL, Belnap BH, Lemenager MS, Mazumdar S, Houck PR, Counihan PJ, et al. Telephone-Delivered Collaborative Care for Treating Post-CABG Depression: A Randomized Controlled Trial. *JAMA*. 2009; 312: 3211-18.
18. Linden W, Phillips M J, Leclerc J. Psychological treatment of cardiac patients: a meta-analysis. *Eur Heart J*. 2007; 28: 2972-84.
19. Riba M, Wulsin L, Rubenfire M, *Psychiatry and Heart Disease: The Mind, Brain, and Heart*. John Wiley & Sons, Ltd. West Sussex, UK. 2012; 1-17.
20. Rugulies R. Depression as a predictor for coronary heart disease: a review and meta-analysis. *The American Journal of Preventive Medicine*. 2020; 23: 51-61.