Republic of Iraq

Ministry of Higher Education &Scientific Research

University of AL-Qadisiyah

College of Science

Department of Chemistry

Stress and Cardiovascular disease

Research submitted to

The Council of the Faculty of Science-University of Al-Qadisiyah

Partly to meet the requirements of

A bachelor's degree in Chemistry

By

Mustafa Kadom

Supervised by

Dr. Zainab N. Al-Abady

2019 A.D **1440 A.H**

بسم الله الرحمن الرحيم

(اقْرَأْ بِاسْمِ رَبِّكَ الَّذِي خَلَقَ (1) خَلَقَ الْإِنسَانَ مِنْ عَلَقٍ (2) اقْرَأْ وَرَبُّكَ الْأَكْرَمُ (3) الَّذِي عَلَّمَ بِالْقَلَمِ (4) عَلَّمَ الْإِنسَانَ مَا لَمْ يَعْلَمْ (5)

صدق الله العلي العظيم

سورة العلق

الاهداء

الى صاحبة القلب الكبير العظيمة العطاء سديدة النصح وعنوان الوفاء

تلك التي حملتني وهنا على وهن وفصالي في عامين

ملهمتي وقدوتي.....أمي

الى مساندي ومساعدي في الحياة الذي لولاه لما وصلت لما انا عليه الان

ذلك الذي تكبد عناء الأيام ليخرجني بأبهى صورة

مساعدي في الحياة.....أبي

الى كل من ساندني ووقف معي تشجيعا لي

اخوتي بالله واصدقائي

اهدي هذا العمل المتواضع عرفانا واحتراما لكل من ساندني ووقف معي

شكر وتقدير

اتقدم بالشكر الى رئاسة قسم الكيمياء وكذلك
اتقدم بالشكر والتقدير الى مشرفة البحث
الدكتورة زينب نجم كذلك الى كل من قدم يد
العون لمساعدتي في اكمال هذا البحث

متمنيا لهم الموفقية والنجاح الدائم

Contents:

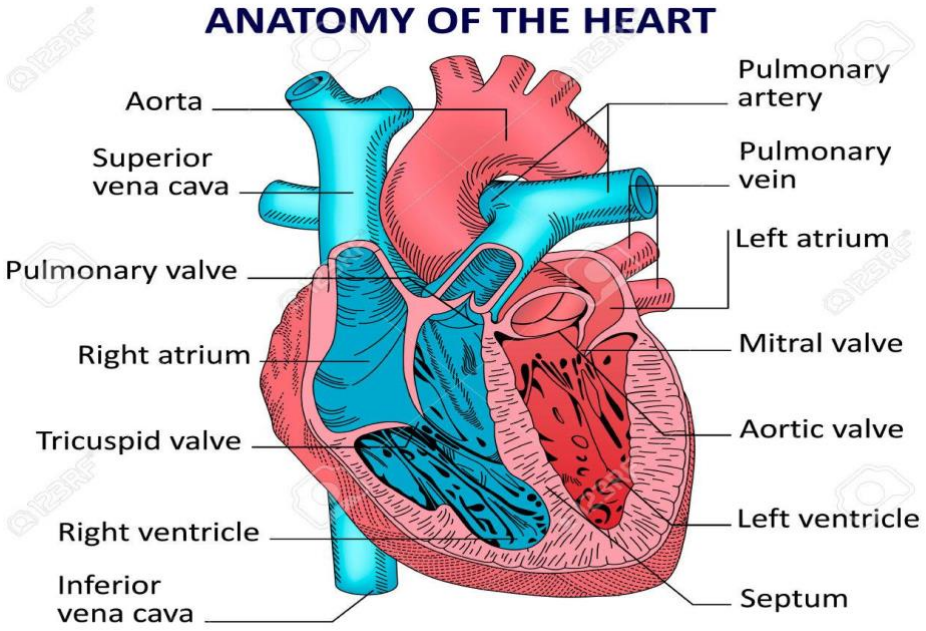
Summary

As the largest single cause of death on the planet cardiovascular disease (CVD), in all its forms is an important in life or death matter. CVD is not a single disease, but a cluster of diseases and injuries that affect the cardiovascular system (the heart and blood vessels). There are several types of CVD such as coronary heart disease (CHD), rheumatic heart disease, congenital heart disease and Other cardiovascular diseases. The major risk factors associated with CVD are smoking, obesity, diabetes, high blood pressure, and high LDL cholesterol. The concentration of cholesterol in serum seems to be affected by diet especially by dietary fat. Moreover, there is evidence that psychological stress also tends to increase serum cholesterol, even when the diet is held constant. Furthermore, there are many factors that are suggested to be related to CHD mainly; depression, social isolation or lack of social support, and some other factors.

1.1 Introduction

As the largest single cause of death on the planet cardiovascular disease (CVD) (1), in all its forms is an important in life or death matter. CVD is not a single disease, but a cluster of diseases and injuries that affect the cardiovascular system (the heart and blood vessels).These are most commonly diseases of the heart and of the blood vessels of the heart and brain. In general they affect people in later life (with incidence rising sharply after the 30-44 age range), although, according to a leading cardiologist, by around 35 years old, most who will get a form of CVD, already have the beginnings of the disease (2).

As mentioned, CVD is actually a collection of diseases affecting the cardiovascular system (1). These include;+ coronary heart disease; angina; stroke; rheumatic heart disease; congenital heart disease; peripheral arterial disease; aortic aneurysm and dissection; deep vein thrombosis; and other, less common, cardiovascular diseases (2).



1.2 Types Of CVD

1.2.1. Coronary heart disease (CHD)

Coronary heart disease (CHD), also called coronary artery disease (CAD) and atherosclerotic heart disease, is the end result of the accumulation of atheromatous plaques(3) within the walls of the arteries that supply the myocardium (the muscle of the heart).

While the symptoms and signs of coronary heart disease are noted in the advanced state of disease, most individuals with coronary heart disease show no evidence of disease for decades as the disease progresses before the first onset of symptoms, often a "sudden" heart attack, finally arise. After decades of progression, some of these atheromatous plaques may rupture and (along with the activation of the blood clotting system) start limiting blood flow to the heart muscle. The disease is the most common cause of sudden death.

1.2.2 Rheumatic heart disease

Rheumatic heart disease is a condition in which the heart valves are damaged by rheumatic fever caused by streptococcal infection. Rheumatic fever is an inflammatory disease that can affect many of the body's connective tissues — especially those of the heart, joints, brain or skin. Anyone can get acute rheumatic fever, but it usually occurs in children five to 15 years old.(4)

The rheumatic heart disease that results can last for life. Every year at least eight out of every 1,000 babies born in the UK have some sort of heart defect. About half of these babies have a minor defect and will not need any treatment but the rest will need either medical treatment or surgery (4,5).

1.2.3. Congenital heart disease

Congenital heart disease is a broad term that can describe a number of different abnormalities affecting the heart, all of which are abnormalities of the heart's structure and function caused by abnormal or disordered heart development before birth (4).

In some cases, such as coarctation of the aorta, it may not present itself for many years and a few lesions such as a small ventricular septal defect (VSD) may never cause any problems and are compatible with normal physical activity and a normal life span. Some congenital heart diseases can be treated with medication alone, while others require one or more surgeries (5).

The risk of death from congenital heart disease surgery in the USA has dropped from approximately 30% in the 1970s to less than 5% in most cases today. Box 1 shows some of the major congenital heart diseases, taken from the British Heart Foundation (BHF).

1.2.4 Other cardiovascular diseases

These could include the following:

1) Tumors of the heart

2) Vascular tumours of the brain

3) Disorders of the heart muscle (cardiomyopathy),

4) Heart valve diseases and disorders of the lining of the heart (6,7).

1.3 The major risk factors associated with CVD

1.3.1.Smoking

Smoking increases the risk of developing coronary heart disease is by 2–4 times. Smoking is a powerful independent risk factor for sudden cardiac death in patients with coronary heart disease; where smokers have about twice the risk of non-smokers.(8) Exposure to other people's smoke increases the risk of heart disease even for non-smokers; the British Heart Foundation estimates that regular exposure to second hand smoke can increase the risk of CHD by up to 25%.(9). Cigarette smoking interacting with other risk factors greatly increases CHD risk. The mechanisms by which smoking increases the risk of CVD are relatively well understood.

The main risk is in the increased tendency towards thrombosis seen in smokers, which can lead to myocardial infarction.(10) Other mechanisms include increased atherosclerosis, blood pressure, heart rate, cardiac output and coronary blood flow. Smoking also increases the levels of carbon monoxide in the body, which binds to haemoglobin, reducing the amount of oxygen reaching body tissues.(11) The number of cigarettes smoked in 2000 was estimated at 5,500 billion, a number that has been rising with increasing world population. The number of daily smokers worldwide is thought to be around 1 billion men and 250 million women.(12)

1.3.2 Obesity

Obesity, particularly in those with excess fat around the waist, increases the chance of developing CHD even if no other risk factors are present. Excess weight increases strain on the heart, raises blood pressure and blood cholesterol and triglyceride levels, and lowers HDL cholesterol levels. All of these factors can increase the risk of atherosclerosis and thrombolytic embolism. It also increases the risk of developing type II diabetes, another risk factor for CVD. The WHO estimated that in 2005, around 1.6 billion people were overweight, with 400 million people obese (13).

1.3.3 Diabetes

Diabetes is a disease that affects an individual's ability to maintain an appropriate blood glucose level. The disease has two forms, Type I and Type II diabetes. Type I diabetes is also known as insulin dependent diabetes and is caused by the body not producing any insulin. Type II diabetes is the more common form of the disease, and occurs when the body either does not produce enough insulin or cells do not process the insulin properly.(14)

Both of these forms can lead to an increased risk of CVD via increased cholesterol levels, hypertension and atherosclerosis.(15) Insulin resistance is also related to CHD (16). WHO estimates suggest that more than 180 million people worldwide have diabetes; with this number likely to more than double by 2030. In 2005, an estimated 1.1 million people died from diabetes worldwide (17). In the USA, a survey of deaths in 1986 suggested that 60−75% of people with diabetes die from cardiovascular disease (18).

1.3.4 High blood pressure

High blood pressure (hypertension) is strongly linked to both cardiac diseases and those of the vascular system. High blood pressure affects the heart by causing it to thicken and stiffen as it has to work harder to pump blood; this can lead to heart attacks. The effect on the vascular system is one of pressure on vasculature walls, leading to aneurisms and stroke.

High blood pressure is a very common problem in developed countries, with one in four adults in the USA diagnosed with hypertension, although this represents a drop in the numbers since the 1980s when prevalence was around one in two (19). It is expected that global hypertension rates will rise in the next 20 years, reaching 1.5 billion adults globally, up to 1/3 from ¼ of the world population.(20)

1.3.5 High LDL cholesterol

The basic method by which LDL cholesterol (low density lipoprotein cholesterol) increases the risk of CVD is by increasing the fatty deposits in blood vessels, leading to atherosclerosis. Recently, research has suggested that this is more of an active process than previously thought, with LDL cholesterol actually activates endothelial cells to express adhesion molecules that speed the process of atherosclerosis (21).

A WHO analysis in 2004 looked at the prevalence of high cholesterol levels in a number of countries and estimated that a total of 4.4 million deaths worldwide were due to “non-optimal cholesterol” (22).

Cholesterol levels have on the whole been rising globally (23), and are expected to continue rising in predictions up to 2030 (although interestingly, North America and Western Europe are expected to have a drop in cholesterol levels (24).

1.3.6 Other risk factors

Several other risk factors are important in the onset of CVD. For example, physical inactivity is seen as a large risk factor. Physical activity can reduce cholesterol levels, decrease obesity and cause the heart and muscles to work harder in pumping blood around the body. Alcohol intake is also a risk factor, and one that is complex since low levels of alcohol can reduce the risk of heart disease (through antioxidant polyphenols inhibiting the oxidation of LDL cholesterol) but high levels of alcohol intake actually increase the risk of CHD and stroke (by increasing blood pressure) (25).

Another key risk factor often cited is nutrition, with poor diet having a direct effect on fat concentrations in the body (increasing the risk of high cholesterol and obesity), sugar levels in the blood (increasing the risk of developing type II diabetes) and salt levels in the blood (increasing blood pressure and the risk of stroke) (26, 27).

1.4 Effect of stress on other risk in CHD

The concentration of cholesterol in serum seems to be affected by diet especially by dietary fat. However, there is evidence that psychological stress also tends to increase serum cholesterol, even when the diet is held constant (28). In longitudinal study of

naval underwater demolition trainees **(Raha et al, 1971),** found a positive correlation between each subject's serum cholesterol and his reported mood and feelings of depression, anger, fear and lethargy, over a period of 2 months.

Thus, it seems that any form of emotional distress is associated with increase serum cholesterol over prolonged periods. Many of the problems in studying the relationship between stress and CHD have been encountered also in the study of hypertension. The prevalence of hypertension does not always follow that of CHD, for example, in Japan, hypertension is common but CHD is not.

Nevertheless, both epidemiological and experimental studies have shown that elevated arterial blood pressure is related to environmental conditions, which are perceived as threatening, or requiring some adaptation (29). This is reflected in a different incidence of hypertension in urban as compared with rural population (30) and in groups with different socioeconomic status in the same community (31).

Continual recordings of blood pressure during the day and night in people going about their usual daily lives have shown how variable blood pressure is, particularly in response to situation involving social interaction with other people (32). The mechanisms producing these variations are uncertain, but probably involve increased secretion of the catechol amines, adrenaline and noradrenaline (33), the secretion of which is known to be increased by emotional arousal of any kind.

1.5.Stress and coronary heart disease

1.5.1.Deffination of stress

Although the term “stress” is in general use, it is so imprecise that, in agreement with other review groups (34), the expert working group examined separately those variables that are commonly regarded as components of stress, these include:

- depression, anxiety, panic disorder;
- social isolation and lack of quality social support;
- acute and chronic life events;
- psychosocial work characteristics; and
- Type A behaviour, hostility.

1.6.Work stress and cardiovascular disease: a life course perspective

1.6.1 Step 1: Work Stress Increases the Risk of Incident CVD in Healthy Workers.

Numerous studies have been conducted related to step1. In general, the excess CVD risk for workers exposed to work stress is 10%-40% compared with those without work stress (35), as measured by the well-established work stress model, mainly **Karasek’s Job-Demand-Control (JDC) model (36) and Siegrist’s effort-reward imbalance (ERI) model (37).** Notably, in most prior prospective studies, work stress had been measured on only one single occasion, i.e., at baseline.

1.6.2.Step 2: Work Stress Determines the Process of Return to Work after CVD Onset.

Generally, people would be absent from work for a while after CVD onset, and the traditional research and practical applications related to return to work focus on several determinants, such as medical factors (severity of disease and comorbidity), demographic distributions (age, gender, education), and psychiatric conditions (depression) (38,39).

The routine cardiac rehabilitation (CR) programs do not include any educational and training activities concerning psychosocial stress in the workplace(40). A few studies in later years indicated that a high level of work stress and a low level of job satisfaction were also the major risk factors for nonreturn to work following CVD (41, 42).

Accordingly, recent recommendations from the Cardiac Rehabilitation Section of the European Association of Cardiovascular Prevention and Rehabilitation of the European Society of Cardiology are, however, highlighting the importance of psychosocial risk factors including work stress as “a component of every CR program”(43).

1.5.3.Step 3: Patients with CVD Experience Higher Work Stress after Return to Work

To date, rehabilitation programs have mainly focused on return to work among those with chronic diseases, while less attention has been paid to helping them to remain in employment (44). Because of their reduced health related work performance (45), work environments (such as task and worktime arrangements) may be re-designed for chronically ill workers.

However, a recent review suggests that workers with chronic diseases experience a poor quality of working life after return to work (46). It has been hypothesized that functional impairments may conceivably limit the ability of employees with chronic diseases to cope with their workload; meanwhile, they seem to have limited resources to influence their work arrangements that cause a sense of reduced autonomy; in addition, chronically ill workers often experience less promotion opportunities and financial improvement after return to work (46) .

1.7.Factors that are related to CHD

1.7.1.Depression a risk factor for CHD

There was strong and consistent evidence across all the reviews that depression is an independent risk factor for clinical CHD and its prognosis . The association exists for men and women, subjects living in different countries, and various age groups.

Furthermore, the CHD risk is directly related to the severity of depression: a 1–2-fold increase in CHD for minor depression and 3–5- fold increase for major depression (34,47, 50) The strength of the association is of similar magnitude to that of standard risk factors such as smoking or hypercholesterolaemia.

1.7.2 Social isolation or lack of social support risk factorsfor CHD

There is strong and consistent evidence across all the reviews that social isolation and lack of quality social support are independent risk factors for CHD onset and prognosis: the risks are increased 2–3-fold and 3–5-fold, respectively. The association exists for both men and women, subjects living in different countries, and various age groups. An association was found in studies that examined some aspect of the size and nature of a person's social network and in studies that examined the type of support received (34, 48, 51, 52).

1.7.3.Acute life-event "stressors" trigger CHD events

Acute life event "stressors" can trigger CHD events, although it is very difficult to study and quantify the magnitude of effects. Acute "stressors" include significant common events such as bereavement as well as catastrophic events such as earthquakes or terrorist attacks (48,52,53). Although the deleterious physiological effects of acute "stressors" as CHD triggers are well documented, the role of chronic "stressors" in CHD onset and prognosis remains unclear.

1.7.4.Work-related "stressors" risk factors for CHD

This topic refers specifically to the characteristics of the work environment as distinct from the life-event "stressors" referred to above. The studies included in one review (34) under psychosocial work characteristics were heterogeneous, with a wide variety of factors being examined individually.

1.7.5.Anxiety disorders risk factors for CHD

A review of primary studies where anxiety was the specific exposure (4), rather than anxiety associated with depression, found an equal number of positive and null findings among both the aetiological and the prognostic studies and concluded there was no association with CHD. Other reviews came to the opposite conclusion or were equivocal (48, 49).

When the reasons for the discordance between the reviews of aetiological studies were explored, it was found that the reviews which had concluded that there was (49) or may be (48) an association between anxiety and CHD had included fewer of the "negative" primary studies than the review which concluded that there was no clear association (34).

This latter review also summarised the primary studies more fully. For those reasons the Expert Working Group gave more credence to that review (34). In addition, when the reasons for the discordance between the two reviews of prognostic studies were explored, it was found that the review which had concluded that there was no clear association between anxiety and the prognosis of CHD had included 18 large primary studies (34), whereas the review which concluded that there was an association (48) included only four primary studies, two of which were small and one which included patients with cardiopulmonary disease. The Expert Working Group therefore gave greater.

References

1- WHO (2004) "Atlas of Heart Disease and Stroke", available at http://www.who.int/cardiovascular_diseases/resources/atlas/en/index.html

2- From interview with a BHF professor of cardiovascular sciences, on 15th May 2006

3- Abnormal inflammatory accumulations of macrophage white blood cells.

4- http://www.urmc.rochester.edu/smd/Rad/stroke.htm

5- http://www.bhf.org.uk/hearthealth/printout.asp?secID=1&secondlevel=77&thirdlevel=362&artID=500

6- Thom et al. (2006) "Heart Disease and Stroke Statistics - 2006 Update: A Report From the American Heart Association Statistics Committee and Stroke Statistics Subcommittee", *Circulation*, 113, e85-e151

7- WHO (2004) "Atlas of Heart Disease and Stroke", available at http://www.who.int/cardiovascular_diseases/resources/atlas/en/index.html

8- http://www.americanheart.org/presenter.jhtml?identifier=4726

9- BHF Health promotion research group (2006), Op Cit

10- Smith, Fischer and Sears (2000) "Environmental Tobacco Smoke, Cardiovascular Disease, and the Nonlinear Dose-Response Hypothesis", *Toxicological Sciences*, 54, 462-472

11- http://mens-health.health-cares.net/smoking-cardiovascular-disease.php

12- WHO (2002) “The tobacco atlas”, available at http://whqlibdoc.who.int/publications/2002/9241562099.pdf

13- http://www.who.int/mediacentre/factsheets/fs311/en/index.html

14- See the website of the American Diabetes Association, http://www.diabetes.org/about-diabetes.jsp

15- http://diabetes.niddk.nih.gov/dm/pubs/stroke/#connection

16- Press release from NIH, http://www.nhlbi.nih.gov/new/press/sep01-99.htm

17- http://www.who.int/mediacentre/factsheets/fs312/en/index.html

18- http://www.clinicalevidence.com/ceweb/conditions/dia/0601/0601_background.jsp

19- http://www.fauxpress.com/kimball/med/heart/h2/bloodpres.htm

20- Kearney, Whelton, Reynolds, Muntner, Whelton and He (2005) Global burden of hypertension: analysis of worldwide data, *The Lancet*, 365:9455, 217-223

21- Ganjia, Kamannaa and Kashyap (2003) Niacin and cholesterol: role in cardiovascular disease (review), *The Journal of Nutritional Biochemistry*, 14:6 , 298-305

22- Ezzati, Lopez, Rodgers and Murray (2004) Comparative Quantification of Health Risks: Global and Regional Burden of Disease Attribution to Selected Major Risk Factors, World Health Organisation, Chapter 7. Available at: http://www.who.int/publications/cra/chapters/volume1/0391-0496.pdf

23- Ezzati, Lopez, Rodgers and Murray (2004) p444

24- Ibid, p446, Table 7.18

25- http://www.bhf.org.uk/news/index.asp?secID=16&secondlevel=241&thirdlevel=1875&artID=8138

26- WHO (2004) “Atlas of Heart Disease and Stroke”, chapter 2

27- World population estimates taken from Population division, Department of Economic and Social Affairs, (1999) “World at 6 billion”, United Nations Secretariat, USA, Part 1, page 5 (available at) http://www.un.org/esa/population/publications/sixbillion/sixbilpart1.pdf

28- FRIEDMAN, M., ROSENMAN, R. H., and CARROL, V., 1958, Changes in the serum cholesterol and blood-clotting time in men subjected to cyclio variation of occupational stress. Circulation,

17, 852-861.

29- HENRY, J. P., and CASSEL, J. C., 1969, Psychosocial factors in essential hypertension. Recent epidemiologic and animal experimental evidence. American of Journal Epidemiology., 90,

171-200.

30- GAMPEL, M. B., SLOME, C., SCOTCH, N., and ABRAMSON, J. H., 1962, Urbanization and hyper tension among Zulu adults. Journal of Chronic Diseases., 15, 67-70.

31- LANGFORD, H. G., WATSON, R. L., and DOUGLAS, B. H., 1968, Factors affecting blood pressure in population groups. Transactions of the Association of American Physicians, 81, 135-145. LEVI, L., 1965, The urinary output of adrenalin and noradrenalin during pleasant and unpleasant emotional states. Psychosomatic Medicine, 27, 30.-85

32- BEVAN, A. T., HONOUR, A. J., and STOTT, F. H., 1969, Direct arterial pressure recording in unrestrained man. Clinical Science., 36, 329-334.

33-NESTEL, P. J., 1969, Blood pressure and catecholamine excretion after mental stress in labile hypertension. Lancet, 1, 692-694.

34-Kuper H, Marmot M, Hemingway H. Systematic review of prospective cohort studies of psychosocial factors in the aetiology and prognosis of coronary heart disease. *Semin Vasc Med* 2002; 2: 267-314.

35-Kivimki M, Kawachi I. Work Stress as a Risk Factor for Cardiovascular Disease. Curr Cardiol Rep 2015; 17: 630.

36- Karasek RA. Job demands, job decision latitude, and mental strain: implications for job redesign. Admin Sci Q 1979; 24: 285-308.

37- Siegrist J. Adverse health effects of high-effort / low-reward conditions. J Occup Health Psychol 1996; 1: 27-41.

38- Mital A, Desai A, Mital A. Return to work after a coronary event. J Cardiopulm Rehabil 2004; 24: 365-373.

39- Vooijs M, Leensen MC, Hoving JL, et al. Disease-generic factors of work participation of workers with a chronic disease: a systematic review. Int Arch Occup Environ Health 2015; 88: 1015-1029.

40- Jelinek MV, Thompson DR, Ski C, et al. 40 years of cardiac rehabilitation and secondary prevention in post-cardiac ischaemic patients. Are we still in the wilderness ? Int J Cardiol 2015; 179: 153-159.

41- Fukuoka Y, Dracup K, Takeshima M, et al. Effect of job strain and depressive symptoms upon returning to work after acute coronary syndrome. Soc Sci Med 2009; 68: 1875-1881.

42- Worcester MU, Elliott PC, Turner A, et al. Resumption of work after acute coronary syndrome or coronary artery bypass graft surgery. Heart Lung Circ 2014; 23: 444-453.

43-Pogosova N, Saner H, Pedersen SS, et al. Psychosocial aspects in cardiac rehabilitation: From theory to practice. A position paper from the Cardiac Rehabilitation Section of the European Association of Cardiovascular Prevention and Rehabilitation of the European Society of Cardiology. Eur J Prev Cardiol 2015; 22: 1290-1306.

44-Varekamp I, Verbeek JH, van Dijk FJ. How can we help employees with chronic diseases to stay at work? A review of interventions aimed at job retention and based on an empowerment perspective. Int Arch Occup Environ Health 2006; 80: 87-97.

45- Detaille SI, Heerkens YF, Engels JA, et al. Common prognostic factors of work disability among employees with a chronic somatic disease: a systematic review of cohort studies. Scand J Work Environ Health 2009; 35: 261-281.

46- de Jong M, de Boer AG, Tamminga SJ, et al. Quality of working life issues of employees with a chronic physical disease: a systematic review. J Occup Rehabil 2015; 25: 182-196.

47- Musselman DL, Evans DL, Nemeroff CB. The relationship of depression to cardiovascular disease: epidemiology, biology and treatment. *Arch Gen Psychiatry* 1998; 55: 580-592.

48- Rozanski A, Blumenthal JA, Kaplan J. Impact of psychological factors on the pathogenesis of cardiovascular disease and implications for therapy. *Circulation* 1999; 99: 2192-2217.

49- Kubzansky LD, Kawachi I. Going to the heart of the matter. Do negative emotions cause coronary heart disease *J Psychosom Res* 2000; 48: 323-337.

50- Scheier MF, Bridges MW. Person variables and health: personality predispositions and acute psychological states as shared determinants for disease. *Psychosom Med* 1995; 57: 255-268.

51- Eriksen W. The role of social support in the pathogenesis of coronary heart disease: a literature review. *Fam Pract* 1994; 11: 201-209.

52-Tennant C. Life stress, social support and coronary heart disease. *Aust N Z J Psychiatry* 1999; 33: 636-641.

53- Hemingway H, Malik M, Marmot M. Social and psychosocial influences on sudden cardiac death, ventricular arrhythmia and cardiac autonomic function. *Eur Heart J* 2001; 22: 1082-1101.