

## **Association Of Anxiety Disorder With Hypertension And Coronary Heart disease:A Review**

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### **I. Introduction**

The link between anxiety with hypertension and cardiovascular disease has been of interest for many years. A number of studies indicate that symptoms of anxiety are among the psychological factors associated with the development of hypertension. Anxiety is also known to heighten the sympatho-adrenal activity a biological pathway which increases risk of cardiovascular disease.

The objective of this article is to summarise the recent evidence of association between anxiety with hypertension and cardiovascular disease.

### **Epidemiology**

Anxiety disorders can be viewed as a family of related but distinct mental disorders which include: (1)panic disorder(2)agoraphobia (3)specific phobia(4)social anxiety disorder/phobia (5)generalized anxiety disorder. The anxiety disorders make up one of the most common group of psychiatric disorders. The national comorbidity study reported that one of four persons met the diagnostic criteria for at least one anxiety disorder and that there is a 12 month prevalence rate of 17.7%. Women are more likely to have an anxiety disorder than men. The prevalence of anxiety disorder decreases with higher socio economic status.<sup>1</sup>

In 2013 CHD was the most common cause of death globally, resulting in 8.14 million deaths (16.8%) up from 5.74 million deaths (12%) in 1990. In the United States in 2010 about (20%) of those over 65 had CHD, while it was present in (7%) of 45-64 years and (1.3%) of 18-45 years. Rates are higher among men than women of a given age.<sup>2</sup>

### **II. Anxiety And Hypertension**

Symptoms of anxiety and depression have been included among psychological factors associated with development of hypertension. Anxiety produces symptoms and responses that can raise blood pressure. Numerous studies from around the world have investigated the links between anxiety disorders and hypertension with mixed results.

A strong association has been found between presence of hypertension and generalized anxiety disorder (GAD) and major depressive disorder (MDD) among U.S. veterans.<sup>3</sup> Another study extracted from The Danish Psychiatric Central Research Register revealed that patients with anxiety disorder had higher rates of hypertension compared to the general Danish population.<sup>4</sup> While a study among adults in Hong Kong showed that hypertension was associated with anxiety but not with depression.<sup>5</sup> A quantitative review of prospective evidence linking psychological factors with hypertension development from 2002 showed moderate support for psychological factors as predictors of hypertension development, with the strongest support for anger, anxiety, and depression variables.<sup>6</sup> Wei and Wang found that 12% of known hypertensive patients have anxiety symptoms. Female gender, the duration of hypertension, and the history of hospitalization were shown to be associated with the occurrence and severity of anxiety symptoms in patients with hypertension.<sup>7</sup>

Thombre and colleagues found that pre-pregnancy depression or anxiety symptoms (i.e., lifetime history and 1 year prior to pregnancy) were associated with hypertensive disorders during pregnancy.<sup>8</sup> Women with anxiety liability was associated with an increased risk of and a higher systolic blood pressure, co-morbid anxiety disorder had a significantly higher blood pressure after adjustment for other risk-factors.<sup>9</sup> Patients with high anxiety sensitivity have also been found to have higher relative risks of medication non-adherence than their low anxiety sensitivity counterparts.<sup>10</sup> In contrast, prospective studies of 17,410 men and women over 11 and 22 years indicated that symptoms of anxiety and depression are associated with decrease in blood pressure.<sup>11</sup> Further, a cross-sectional study found an inverse relationship between high anxiety and lower blood pressure.<sup>12,13</sup> Tikhonoff and colleagues showed that a cumulative effect of symptoms of anxiety and depression across adulthood results in lower SBP in late middle age that is not explained by lifestyle factors and antihypertensive treatment.<sup>14</sup> A population-based study in New York City showed no consistent difference between participants with mild hypertension and those with normal blood pressure on any of the psychological variables.<sup>15</sup> Yan et al. found that among young otherwise healthy adults, anxiety was not associated with an increased risk of developing hypertension. They did find dose dependent relationships

between risk of new onset hypertension and time urgency/impatience and achievement striving/competitiveness.<sup>16</sup>

### **III. Anxiety And CHD**

Anxiety is known to be associated with heightened sympatho-adrenal activity, suggesting a biological pathway through which anxiety could increase CVD risk.<sup>17</sup> Anxiety affects the cardiac function in more ways than just increasing the heart rate. Unmedicated, physically healthy MDD patients with and without comorbid anxiety had reduced heart rate variability (HRV) which is associated with an increased of CHD, while those with comorbid generalized anxiety disorder was found to have the greatest reductions in HRV.<sup>18</sup> Patients with phobic anxiety had lower HRV suggesting that phobic anxiety is associated with altered cardiac autonomic control, and hence increased risk of sudden cardiac death.<sup>19</sup> Compared with men reporting no symptoms of anxiety, men reporting two or more anxiety symptoms had elevated risks of fatal CHD.<sup>20</sup> A study of 735 older men (mean age 60 years) without a history of coronary disease or diabetes showed the presence of anxiety independently and significantly predicted the development of myocardial infarction during a mean follow-up of 12.4 years.<sup>21</sup>

Studies have also demonstrated a relationship between hostility or anger and measurements of subclinical atherosclerosis,<sup>22-25</sup> and have also linked hostility to progression of atherosclerosis during serial coronary angiography.<sup>26</sup> In a population-based sample of 726 men and women who were healthy at baseline, Paterniti and colleagues showed that high levels of sustained anxiety were independently associated with increased progression of atherosclerosis over a 4-year period, as measured by changes in common carotid artery intima media thickness.<sup>27</sup>

Haines and colleagues followed 1457 initially healthy men for about 10 years in the Northwick Park heart study. Those with the highest levels of phobic anxiety had a higher risk of fatal CHD than men reporting no anxiety, after controlling for a range of known coronary risk factors.<sup>28</sup> Furthermore, a recent study from a US population showed that anxiety was associated with 60% excess risk of CHD among men and women, an effect that was independent of traditional CHD risk factors.<sup>29</sup>

Meyer and colleagues followed up CHD patients undergoing elective percutaneous coronary interventions (PCI) over 5 years and found that higher anxiety levels were positively associated with fewer major adverse cardiovascular events (MACEs) as compared to non-anxious subjects. In contrast, anxious patients had a higher rate of repeat revascularization.<sup>30</sup> Further, studies by Kubzansky et. al showed that anxiety in healthy individuals contributes to the development of CHD.<sup>31-32</sup>

A meta-analysis of data from the United States, Asia and Europe from 20 different studies with an impressive 249,846 persons followed over a mean of 11.2 years examining the associations between anxiety and incident CHD in healthy individuals indicated that anxious persons were at risk of CHD (HR 1.26) and cardiac death (HR 1.48), independent of demographic variables, biological risk factors, and health behaviors.<sup>33</sup> In a nationwide survey of 49,321 young Swedish men examined for military service and followed over 37 years found that those with physician diagnosed anxiety were two times more at risk of developing CHD and acute MI.<sup>34</sup> The Nurses' Health Study of 72,359 women with no history of cardiovascular disease or cancer followed over 12 years showed that women with phobic anxiety had a higher risk of fatal CHD and sudden cardiac death.<sup>35</sup> The Framingham Offspring Study revealed that anxiety in men and in women were significantly related to total mortality and that tension also predicted AF in men.<sup>36</sup>

### **PTSD and CHD**

Evidence appears to link PTSD and CHD in several studies. A study by Boscarino<sup>37</sup> looked at a random sample of 4,328 male Vietnam veterans free of heart disease at baseline. Followed over 15 years, those with PTSD had higher risk of heart disease mortality (HR 2.25) than those without PTSD. Other studies have also shown links between PTSD and CHD.<sup>38,39</sup> In the Heart and Soul Study, which is a prospective cohort study of psychological factors in adults with cardiovascular disease, patients with PTSD reported more symptoms, more physical limitations, and lower quality of life than those without PTSD.<sup>40</sup>

### **Panic Disorder and CHD**

PD is another form of anxiety spectrum disorders that has some links to cardiac disease. PD is characterized by extreme feelings of fear and symptoms including sweating, palpitations, and shortness of breath, among others. Given the extreme arousal of panic episodes and the similarity of symptoms to an acute cardiac event, interest has developed in the potential connections between the two conditions. Two case-control studies have shown some evidence for a role for panic in CHD. A study in 2005 using data from over 30 U.S. health insurance plans looked at almost 40,000 patients with diagnosed panic disorder and an equal number without. Those with PD had close to double the risk of developing CHD (HR 1.87).<sup>41</sup> Further, the large General Practice Research Database in the UK looked at incidence of CHD, MI, and CHD-related deaths in 57,000

adults with PD compared to over 340,000 without. Those followed under 50 years of age with new onset panic disorder had a higher risk of MI (HR 1.38). There was also a higher incidence of CHD for all ages in those with PD, but more pronounced in those under 50 years.<sup>42</sup>

### **Anger And CHD**

Many features of anger are similar to anxiety and numerous studies have investigated links with CHD. The Veteran's Administration's Normative Aging Study used various scales from the Minnesota Multiphasic Personality Inventory to show that anger was associated with coronary events<sup>43</sup> and that type A behavior and depression were associated with incident CHD.<sup>44,45</sup> A high trait anger level has also been shown to be associated with increased risk of stroke in persons younger than 60 years.<sup>46</sup> Still further, anger and hostility have been shown to predict the development of atrial fibrillation in the Framingham Offspring Study.<sup>47</sup> Symptoms of anxiety and depression in the NHANES follow-up study<sup>48</sup> and hostility and depressive symptoms in the Coronary Artery Risk Development in Young Adults were shown to be associated with incident hypertension in previously normotensive persons.<sup>49,50</sup>

### **IV. Potential Mechanisms**

As stated previously, stress is commonly experienced through anxiety. Stress in the body is mediated via the Hypothalamic-Pituitary-Adrenal axis with catecholamines as the final common pathway. Through changes in circulating catecholamine levels, psychosocial stress can adversely affect autonomic and hormonal homeostasis which can further lead to inflammation, metabolic abnormalities, endothelial dysfunction, hypertension, and insulin resistance.<sup>51</sup> These factors, particularly inflammation and hypertension, then contribute to the development and progression of CHD. Other potential mechanisms include increase in adverse behaviors due to stress and anxiety that impact health such as increased eating, smoking, and alcohol use and decreased exercise.<sup>52</sup> Mainous et al. showed that association between stress and coronary artery calcification, a marker of atherosclerosis, follows through a path of unhealthy lifestyle habits.<sup>53</sup> In turn, development of hypertension and risk of CHD are increased in people who lack these "healthy habits." There is also a growing body of research in potential chromosomal and genetic markers related to stress and adverse cardiovascular outcomes. For example, an apo-lipoprotein E genetic variant was found to be associated with unfavorable metabolic markers like higher triglycerides and larger waist circumference among a higher stress group of caregivers of relatives with Alzheimer's.<sup>54</sup> Further, telomeres are repetitive DNA sequences that shortens with age and act as protective caps on the ends of chromosomes. Numerous studies have shown that shorter telomeres are related to atherosclerosis and risk of MI and stroke<sup>55,56</sup> and psychological stress is related to more rapidly shortening telomeres.<sup>57,58</sup>

**Limitations:** There are few limitations worth noting from this review study. First there were very few prospective studies, which can address causation and are heterogeneous in terms of clinical populations, methods, and measures. Second a majority of the studies are cross-sectional and do not allow us to determine causal relationship. Meta-analyses could clarify some of these questions for us, but we would need a more solid foundation of high quality studies that use similar measures of anxiety for this. Finally, we were unable to address whether treatment of anxiety reduces incident hypertension, CHD. No study has been published regarding reduction of hypertension or any cardiovascular disease following treatment of anxiety.

**Implications:** Anxiety and hypertension are common and often co-morbid conditions treated in primary care practices.<sup>59</sup> Psychiatrist and cardiologist need to be aware of the links between anxiety disorders and CHD to prevent mortality and unfavorable outcomes in terms of both mental and physical health. A growing evidence base suggests that more integrated ways of working, with collaboration between mental health and other professionals, offers the best chance of improving outcomes for individuals with both mental health and physical conditions.<sup>60</sup>

### **V. Conclusions**

From this review it appears that there is an association between anxiety with hypertension and CHD. The relationship between anxiety and hypertension can be bidirectional. The strongest evidence comes from prospective studies looking at anxiety disorders and development of CHD, with the recent meta-analysis providing the strongest evidence yet for links between anxiety and CHD/CHD mortality<sup>33</sup>. Future research will likely need to be twofold, including studies on treatment of anxiety in the setting of CHD and the subsequent cardiovascular outcomes. Lastly researchers will need to answer how physician should screen CHD patient for anxiety disorder and which strata of patients should receive appropriate referral to a psychiatrist for appropriate management. Similarly psychiatrist should not take for granted the physical status of anxiety patients, so basic screening should be done and referral to a cardiologist should be done as soon as any cardiac problem is detected.

## References

- [1]. Sadock BJ, Sadock VA, Ruiz P, Kaplan and Sadock's Synopsis of Psychiatry, 11<sup>th</sup> ed. Philadelphia: Wolters Kluwers; 2015: 418
- [2]. (<http://www.wikipedia.org>) coronary heart disease. accessed on 13.4.2015
- [3]. Carroll D, Phillips AC, Gale CR, Batty GD. Generalized anxiety and major depressive disorders, their comorbidity and hypertension in middle-aged men. *Psychosomatic Medicine* 2010;72(1): 16-19.
- [4]. Johannessen L, Strudsholm U, Foldager L, Munk-Jørgensen P. Increased risk of hypertension in patients with bipolar disorder and patients with anxiety compared to background population and patients with schizophrenia. *Journal of Affective Disorders* 2006;95(1-3):13-17.
- [5]. Cheung BM, Au T, Chan S, Lam C, Lau SH, Lee S. et al. The relationship between hypertension and anxiety or depression in Hong Kong Chinese. *Experimental & Clinical Cardiology* 2005;10(1):21-24.
- [6]. Rutledge T, Hogan BE. A quantitative review of prospective evidence linking psychological factors with hypertension development. *Psychosomatic Medicine* 2002;64(5):758-766.
- [7]. Wei TM, Wang L. Anxiety symptoms in patients with hypertension: A community based study. *International Journal of Psychiatry in Medicine* 2006;36(3):315-322.
- [8]. Thombre MK, Talge NM, Holzman CI. Association between pre-pregnancy depression/anxiety symptoms and hypertensive disorders of pregnancy. *Journal of Women's Health* 2015;24(3):228-236.
- [9]. Winkel S, Einsle F, Pieper L, Höfler M, Wittchen HU, Martini J. Associations of anxiety disorders, depressive disorders and body weight with hypertension during pregnancy. *Archives of Women's Mental Health* Nov 2014.
- [10]. Alcántara C, Edmondson D, Moise N, Oyola D, Hiti D, Kronish IM. Anxiety sensitivity and medication nonadherence in patients with uncontrolled hypertension. *Journal of Psychosomatic Research* 2014;77(4):283-86.
- [11]. Hildrum B, Romild U, Holmen J. Anxiety and depression lowers blood pressure: 22-year follow-up of the population based HUNT study, Norway. *BMC Public Health*. 2011 28;11:601.
- [12]. Hildrum B, Mykletun A, Stordal E, Bjelland I, Dahl AA, Holmen J. Association of low blood pressure with anxiety and depression: The Nord-Trøndelag Health Study. *Journal of Epidemiology and Community Health* 2007;61(1):53-58.
- [13]. Hildrum B, Mykletun A, Holmen J, Dahl AA. Effect of anxiety and depression on blood pressure: 11-year longitudinal population study. *British Journal of Psychiatry* 2008;193(2):108-113.
- [14]. Tikhonoff V, Hardy R, Deanfield J, Friberg P, Kuh D, Muniz G, Pariente CM, Hotopf M, Richards M. Symptoms of anxiety and depression across adulthood and blood pressure in late middle age: the 1946 British birth cohort. *Journal of Hypertension* 2014, 32:1590-99.
- [15]. Friedman R, Schwartz JE, Schnall PL, Landsbergis PA, Pieper C, Gerin W, Pickering TG. Psychological variables in hypertension: Relationship to casual or ambulatory blood pressure in men. *Psychosomatic Medicine* 2001;63(1):19-31.
- [16]. Yan LL, Liu K, Matthews KA, Daviglus ML, Ferguson TF, Kiefe CI. Psychosocial factors and risk of hypertension: The Coronary Artery Risk Development in Young Adults (CARDIA) study. *Journal of the American Medical Association* 2003;290(16):2138-48.
- [17]. Paine, Nicola J, Watkins, Lana L, Blumenthal, James A, Kuhn, Cynthia M, Sherwood, Andrew. Association of depressive and anxiety symptoms with 24-hour urinary catecholamines in individuals with untreated high blood pressure. *Psychosomatic Medicine* 2015;77(2):136-44.
- [18]. Kemp AH, Quintana DS, Felmingham KL, Matthews S, Jelinek HF. Depression, comorbid anxiety disorders, and heart rate variability in physically healthy, unmedicated patients: implications for cardiovascular risk. *PLoS ONE* 7(2): e30777.
- [19]. Kawachi I, Sparrow D, Vokonas PS, Weiss ST. Decreased heart rate variability in men with phobic anxiety (data from the Normative Aging Study). *American Journal of Cardiology* 1995;75(14): 882-85.
- [20]. Kawachi I, Sparrow D, Vokonas PS, Weiss ST. Symptoms of anxiety and risk of coronary heart disease. The Normative Aging Study. *Circulation* 1994;90(5):2225-29.
- [21]. Shen BJ, Avivi YE, Todaro JF, Spiro A 3rd, Laurenceau JP, Ward KD, Niaura R. Anxiety characteristics independently and prospectively predict myocardial infarction in men: the unique contribution of anxiety among psychological factors. *Journal of the American College of Cardiology* 2008;51(2): 113-19.
- [22]. Matsumoto Y, Uyama O, Shimizu S, et al. Do anger and aggression affect carotid atherosclerosis? *Stroke*. 1993; 24:983-86.
- [23]. Julkunen J, Salonen R, Kaplan GA, Chesney MA, Salonen JT. Hostility and the progression of carotid atherosclerosis. *Psychosomatic Med*. 1994; 56:519-25.
- [24]. Matthews KA, Owens JF, Kuller LH, Sutton-Tyrrell K, Jansen-McWilliams L. Are hostility and anxiety associated with carotid atherosclerosis in healthy postmenopausal women? *Psychosomatic Med*. 1998; 60:633-38.
- [25]. Knox SS, Adelman A, Ellison RC. Hostility, social support, and carotid artery atherosclerosis in the National Heart, Lung, and Blood Institute Family Heart Study. *Am J Cardiol*. 2000; 86:1086-89.
- [26]. Angerer P, Siebert U, Kothny W, Muhlbauer D, Mudra H, von Schacky C. Impact of social support, cynical hostility and anger expression on progression of coronary atherosclerosis. *J Am Coll Cardiol*. 2000; 36:1781-88.
- [27]. Paterniti S, Zureik M, Ducimetiere PJT, Feve JM, Alperovitch A. Sustained anxiety and 4-year progression of carotid atherosclerosis. *Arterioscler Thromb Vasc Biol*. 2001;21:136-41.
- [28]. Haines AP, Imeson JD, Meade TW. Phobic anxiety and ischaemic heart disease. *BMJ (Clin Res Ed)*. 1987; 295(6593):297-99.
- [29]. Thurston R, Kubzansky LD, Kawachi I, Berkman L. Do depression and anxiety mediate the link between educational attainment and coronary heart disease? *Psychosomatic Med*. 2006; 68:25-32.
- [30]. Meyer T, Hussein S, Lange HW, Herrmann-Lingen C. Anxiety is associated with a reduction in both mortality and major adverse cardiovascular events five years after coronary stenting. *European Journal of Preventive Cardiology* 2015, Vol. 22(1) 75-82
- [31]. Kubzansky LD, Cole SR, Kawachi I, Vokonas P, Sparrow D. Shared and unique contributions of anger, anxiety, and depression to coronary heart disease: a prospective study in the normative aging study. *Annals of Behavioral Medicine* 2006;31(1):21-29.
- [32]. Kubzansky LD, Kawachi I, Weiss ST, Sparrow D. Anxiety and coronary heart disease: A synthesis of epidemiological, psychological, and experimental evidence. *Annals of Behavioral Medicine* 1998;20(2):47-58.
- [33]. Roest AM, Martens EJ, de Jonge P, Denollet J. Anxiety and risk of incident coronary heart disease: A meta-analysis. *American College of Cardiology* 2010;56(1):38-46.
- [34]. Janszky I, Ahnve S, Lundberg I, Ahnve S, Lundberg I, Hemmingsson T. Early-onset depression, anxiety and risk of subsequent coronary heart disease. 37-year follow-up of 49,321 young Swedish men. *American College of Cardiology* 2010;56: 31-37.
- [35]. Albert CM, Chae CU, Rexrode KM, Manson JE, Kawachi I. Phobic anxiety and risk of coronary heart disease and sudden cardiac death among women. *Circulation* 2005 Feb 1;111(4):480-487.
- [36]. Eaker ED, Sullivan LM, Kelly-Hayes M, D'Agostino RB Sr, Benjamin EJ. Tension and anxiety and the prediction of the 10-year incidence of coronary heart disease, atrial fibrillation, and total mortality: The Framingham Offspring Study. *Psychosomatic Medicine* 2005 Sep-Oct;67(5):692-696.

- [37]. Boscarino JA. A prospective study of PTSD and early-age heart disease mortality among Vietnam veterans: Implications for surveillance and prevention. *Psychosomatic Medicine* 2008 Jul;70(6):668-676.
- [38]. Kang HK, Bullman TA, Taylor JW. Risk of selected cardiovascular diseases and posttraumatic stress disorder among former World War II prisoners of war. *Annals of Epidemiology* 2006;16(5):381-386.
- [39]. Kubzansky LD, Koenen KC, Spiro A, III, Vokonas PS, Sparrow D. Prospective study of posttraumatic stress disorder symptoms and coronary heart disease in the Normative Aging Study. *Archives of General Psychiatry* 2007;64(1):109-116.
- [40]. Cohen BE, Marmar CR, Neylan TC, Schiller NB, Ali S, Whooley MA. Post-traumatic stress disorder and health-related quality of life in patients with coronary heart disease: Findings from the Heart and Soul Study. *Archives of General Psychiatry* 2009 Nov;66(11):1214-1220.
- [41]. Gomez-Camirero A, Blumentals WA, Russo LJ, Brown RR, Castilla-Puentes R. Does panic disorder increase the risk of coronary heart disease? A cohort study of a National Managed Care Database. *Psychosomatic Medicine* 2005;67:688-691
- [42]. Walters K, Rait G, Petersen I, Williams R, Nazareth I. Panic disorder and risk of new onset coronary heart disease, acute myocardial infarction, and cardiac mortality: Cohort study using the general practice research database. *European Heart Journal* 2008;29(24): 2981-2988.
- [43]. Kawachi I, Sparrow D, Spiro A, 3rd, Vokonas P, Weiss ST. A prospective study of anger and coronary heart disease. The Normative Aging Study. *Circulation* 1996; 94(9):2090-2095.
- [44]. Kawachi I, Sparrow D, Kubzansky LD, Spiro A 3rd, Vokonas PS, Weiss ST. Prospective study of a self-report type A scale and risk of coronary heart disease: Test of the MMPI-2 type A scale. *Circulation*. 1998;98(5):405-412.
- [45]. Sesso HD, Kawachi I, Vokonas PS, Sparrow D. Depression and the risk of coronary heart disease in the Normative Aging Study. *American Journal of Cardiology* 1998; 82(7):851-856.
- [46]. Williams JE, Nieto FJ, Sanford CP, Couper DJ, Tyroler HA. The association between trait anger and incident stroke risk: The Atherosclerosis Risk in Communities (ARIC) Study. *Stroke* 2002;33(1):13-19.
- [47]. Eaker ED, Sullivan LM, Kelly-Hayes M, D'Agostino RB Sr., Benjamin EJ. Anger and hostility predict the development of atrial fibrillation in men in the Framingham Offspring Study. *Circulation* 2004;109(10):1267-1271.
- [48]. Jonas BS, Franks P, Ingram DD. Are symptoms of anxiety and depression risk factors for hypertension? Longitudinal evidence from the National Health and Nutrition Examination Survey I Epidemiologic Follow-up Study. *Archives of Family Medicine* 1997;6(1):43-49.
- [49]. Davidson K, Jonas BS, Dixon KE, Markovitz JH. Do depression symptoms predict early hypertension incidence in young adults in the CARDIA study? *Coronary Artery Risk Development in Young Adults*. *Archives of Internal Medicine* 2000;160(10): 1495-1500.
- [50]. Yan LL, Liu K, Matthews KA, Daviglius ML, Ferguson TF, Kiefe CI. Psychosocial factors and risk of hypertension: the Coronary Artery Risk Development in Young Adults (CARDIA) study. *Journal of American Medical Association* 2003;290(16): 2138-2148.
- [51]. Curtis B, O'Keefe JH. Autonomic tone as a cardiovascular risk factor: The dangers of chronic fight or flight. *Mayo Clinic Proceedings* 2002;77:45-54.
- [52]. Bonnet F, Irving K, Terra JL, Nony P, Berthezne F, Moulin P. Anxiety and depression are associated with unhealthy lifestyle in patients at risk of cardiovascular disease. *Atherosclerosis* 2005;178(2):339-344.
- [53]. Mainous AG 3rd, Everett CJ, Diaz VA, Player MS, Gebregziabher M, Smith DW. Life stress and atherosclerosis: a pathway through unhealthy lifestyle. *International Journal of Psychiatry in Medicine* 2010;40(2):147-161.
- [54]. Kring SI, Brummett BH, Barefoot J, Garrett ME, Ashley-Koch AE, Boyle SH, Siegler IC, Sørensen TI, Williams RB. Impact of psychological stress on the associations between apolipoprotein E variants and metabolic traits: Findings in an American sample of caregivers and controls. *Psychosomatic Medicine* 2010 Jun; 72(5):427-433.
- [55]. Mainous AG 3rd, Codd V, Diaz VA, Schoepf UJ, Everett CJ, Player MS, Samani NJ. Leukocyte telomere length and coronary artery calcification. *Atherosclerosis* 2010 May;210(1):262-267.
- [56]. Fitzpatrick AL, Kronmal RA, Gardner JP, Psaty BM, Jenny NS, Tracy RP, et al. Leukocyte telomere length and cardiovascular disease in the Cardiovascular Health Study. *American Journal of Epidemiology* 2007;165:14-21.
- [57]. Epel ES, Blackburn EH, Lin J, Dhabhar FS, Adler NE, Morrow JD, Cawthon RM. Accelerated telomere shortening in response to life stress. *Proceedings of the National Academy of Sciences of the United States*. 2004 Dec 7;101(49):17312-17315.
- [58]. Simon NM, Smoller JW, McNamara KL, Maser RS, Zalta AK, Pollack MH, Nierenberg AA, Fava M, Wong KK. Telomere shortening and mood disorders: Pre-liminary support for a chronic stress model of accelerated aging. *Biological Psychiatry* 2006 Sep 1;60(5):432-435.
- [59]. McLaughlin T, Geissler EC, Wan GJ. Comorbidities and associated treatment charges in patients with anxiety disorders. *Pharmacotherapy* 2003;23(10):1251-1256.
- [60]. Yohannes AM, Doherty P, Bundy C, Yalfani A. The long-term benefits of cardiac rehabilitation of cardiac rehabilitation on depression, anxiety, physical activity and quality of life. *J Clin Nurs* 2010; 19: 2806-13.