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RESEARCH ARTICLE

The Association Between Psychosocial Stress and Cardiovascular Disease, a Systematic Review

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ABSTRACT

Chronic Stress is a prolonged and constant feeling of stress that can have important pathological consequences. Several recent studies demonstrated a bidirectional association between stress and cardiovascular diseases, moreover the implication of the locus coeruleus (LC)-norepinephrine (NE) system in stress-induced cardiovascular disease was investigated. Our review aims to delineate the link between psychosocial stress and the cardiovascular system and the neurobiological mechanisms that underlie that association. Furthermore, we will cover emerging approaches to manage stress-induced cardiovascular disease risk. The search strategy was performed based on the PRISMA 2020 guidelines. Electronic databases were searched for identifying studies regarding psychological stress and its impact on cardiovascular system. The importance of this review relies on the attempt to highlight the effect of stress in cardiovascular diseases. Moreover, it will bring attention to new directions for developing treatments and/or strategies for decreasing stress-induced cardiovascular vulnerability thus enhancing patient's quality of life.

Keywords: neurovascular diseases, cardiovascular diseases, psychological stress, coronary heart diseases, autonomic nervous system.

Introduction

Cardiovascular disease (CVD) is the leading major cause of death worldwide, 17.9 million deathsper year in 2015 were attributable to CVD and this number is expected to grow to more than 23.6million by 2030 (Chinnaiyan, 2019). Several epidemiological studies that investigates the triggersof CVD showed that psychological stress indicates a direct increase in this disease. As a definition, stress is often defined as a state of mental, physical, or emotional tension in response to various unexpected demanding factors or circumstances (Hering et al., 2015). Stressors can show intenselyor persistently and take various structures including major life changes (ex: job stress, marital discord, natural disaster), adverse socioeconomic factors (ex: income, crime, education), and psychiatric conditions (ex: anxiety, depression, post-traumatic stress disorder (Dar et al., 2019). The connection between stress and cardiovascular illness has been confirmed by several studies. For example, the INTERHEART study was the largest case-control study that evaluated the relationship between long-term stress and CHD. In this study, 15.152 patients with acute myocardial infarction and 14.820 control individuals free from CVD were enrolled from 52 countries worldwide. Long-term stress was included which comprised stress at work and home, financial strain, lack of control and depression. After adjusting for CVD risk factors, they found that the odds ratio for myocardial infarction (MI) was more than double among individuals who were exposed to psychosocial stress in addition to conventional risk factors compared to those freeof stress (Steptoe & Kivimäki, 2012). A cohort study in Sweden during up to 27 years of follow- up, also showed that stress-related disorders are strongly associated with cardiovascular disease by elevation of RR of cardiovascular diseases during the first year after diagnosis of stress-relateddisorder (Song et al., 2019). However, the brain is implicated in the control of cardiovascular function through several physiological mechanisms including the hypothalamo-pituitary-adrenal axis (HPA axis) and the autonomic nervous system. The result of these two systems is the releaseof glucocorticoids and noradrenaline respectively which increases arterial pressure and heart rate causing a high demand for oxygen in the myocardium (Dar et al., 2019). The mechanism by whichstress is linked to CVD begins in the brain by activation of HPA axis and the autonomic nervous system by its two branches: increasing the sympathetic nervous system (SNS) and decreasing parasympathetic nervous system (PSNS) activity (Rotenberg & McGrath, 2016) (fig1). Followinga stimulus, and after recognition of a potential threat by the body's receptors (tactile, temperature,pain receptors, as well the eyes and auditory organs), an action potential is transmitted through the afferent tract to the thalamus, and thus by subcortical afferent connections toward the amygdala, which is part of the limbic system. The amygdala, in turn will interpret images and sounds and generate stress reactions by stimulating the sympathetic nervous system via efferent subcortical projections to the hypothalamus and brain stem known as center for vital reactions, such as breathing, blood pressure, and heartbeat. The hypothalamus thus undergoes metabolic processes in collaboration with the autonomic nervous system in order to reduce stress (Jarczewski et al., 2019). For the activation of the HPA axis, under stress, the paraventricular nucleus of the hypothalamus synthesizes corticotrophin-releasing factor (CRF) and vasopressin. CRF stimulatesthe anterior pituitary gland to release adrenocorticotropic hormone (ACTH), which induces the adrenal cortex to produce glucocorticoids. Glucocorticoids play an important counter-regulatory role, increasing adiposity, hypertension, and insulin resistance leading to CVD (Osborne et al., 2020). Although, it decreases membrane adenylyl cyclase activity and cAMP levels, that is responsible to maintain endothelial function. It decreases the synthesis of nitric oxide that plays arole in adjusting vascular functions that promotes vasodilatation, decrease vascular resistance andinhibits platelet adhesion and aggregation (Golbidi et al., 2015). The autonomic nervous system isan integral component of stress physiology. Sympathetic hyperactivity and parasympatheticwithdrawal are core aspects of the acute stress response (Vaccarino et al., 2021). Accordingly, therelease of noradrenaline from the locus coerulus causes vasoconstriction, increases peripheral vascular resistance and promotes higher blood pressure and heart rate as well as lower heart rate variability (Osborne et al., 2020). The increase in sympathetic activation during stress leads to anincrease in renin production, which will convert the angiotensinogen into angiotensin 1, and the latter will give angiotensin 2 under the action of angiotensin-converting enzyme (ACE). The increase in circulating AngII thus increases the stimulation of physiologically active AT-1R (AngIItype 1 receptor) and consequently the anterior pituitary gland contributes to the formation and release of adrenocorticotropic hormone (ACTH), adrenal glucocorticoid, aldosterone and catecholamine. The pathophysiological effects of RAAS on the cardiovascular system are formedby AngII and aldosterone, and it is known that the production of AngII and aldosterone increasesthe expression of norepinephrine (NE) and inhibits the uptake of NE from the nerve endings. The cardiovascular effects of AngII are similar to those of sympathetic activation and excessive releaseof NE. Chronic exposure to the excessive amount of AngII causes exaggeratedly increased ventricular hypertrophy, vasoconstriction, and sodium retention. (Ayada et al., 2015). Angiotensin II is a potent stimulator of NADPH oxidase, the primary enzymatic origin of reactive oxygen species (ROS) in the cardiovascular system, whose activation triggers oxidative stress that inducesendothelial dysfunction (Inoue, 2014). In a recent study, compared

to a control group, the exposureof adult male rats to unpredictable stressors leads to HPA axis dysfunction, and activation of RAAS increasing circulating corticosterone, aldosterone, and plasma renin (Grippo & Johnson, 2009). Locus coerulus-norepinephrine activation is an important pathway in stress response that occurs in parallel with the HPA axis causing endocrine response. The same stressor that initiates the HPAresponse to stress also activates the LC-NE system, including shock, auditory stress and social stress (Wood et al., 2017). However, with the growing evidence of the association between stressand cardiovascular disease, several studies were done targeting new techniques to reduce stress inorder to prevent CVD, by intervening behaviorally with several techniques or by using pharmaceutical therapies. Behavioral interventions such as yoga, transcendental meditation, praying and exercise programs are shown to be useful in primary prevention by reducing hypertension and related CVD risks (Hering et al., 2015). For example, a study showed that transcendental meditation helps reducing stress, and exerts a beneficial effect on secondary prevention by diminishing the risk of overall mortality, MI, and strokes in addition to improvementin blood pressure (Hering et al., 2015). Besides, transcendental meditation has also been shown tobe associated with neuroplasticity, development of novel neural circuits, and the alteration in the default mode network, which are all thought to be responsible for the constant self- rumination, the hallmark of a stressful state (Chinnaiyan, 2019). In addition to the importance of these stress reduction strategies that play a distinguished role in physiological benefits, they modify structuresand connectivity of stress-associated neural centers including the amygdala and thus reducing systemic inflammation, blood pressure and other health behaviors. It also alters gene expression by amplifying genetic pathways targeting insulin production and attenuating pro-inflammatory pathways (Osborne et al., 2020). There are also several effective pharmacological therapies including selective serotonin reuptake inhibitors, beta-blockers and anti-inflammatory known to have several beneficial effects in reducing CVD. However, many recent studies showed that selective serotonin reuptake inhibitors (SSRI) decreased the risk of CVD and myocardial infractionand that beta-adrenergic blocking agents will reduce the effect of autonomic nervous system reaction by antagonizing stress induced catecholamine response centrally and peripherally. Anti- inflammatory therapies including statins and cholesterol lowering therapies have been showed toreduce arterial inflammation and prevention of future CVD risk (Dar et al., 2019). A lot of articleswere done to discuss the effect of psychological stress on CVD, and the therapies that reduce stressand help in managing cardiovascular diseases, however, the aforementioned articles were only reviews and here become the importance of doing a systematic review that combine these two topics. Moreover, it will bring attention to behavioral interventions for developing strategies for decreasing stress-induced cardiovascular vulnerability thus enhancing patient's quality of life.

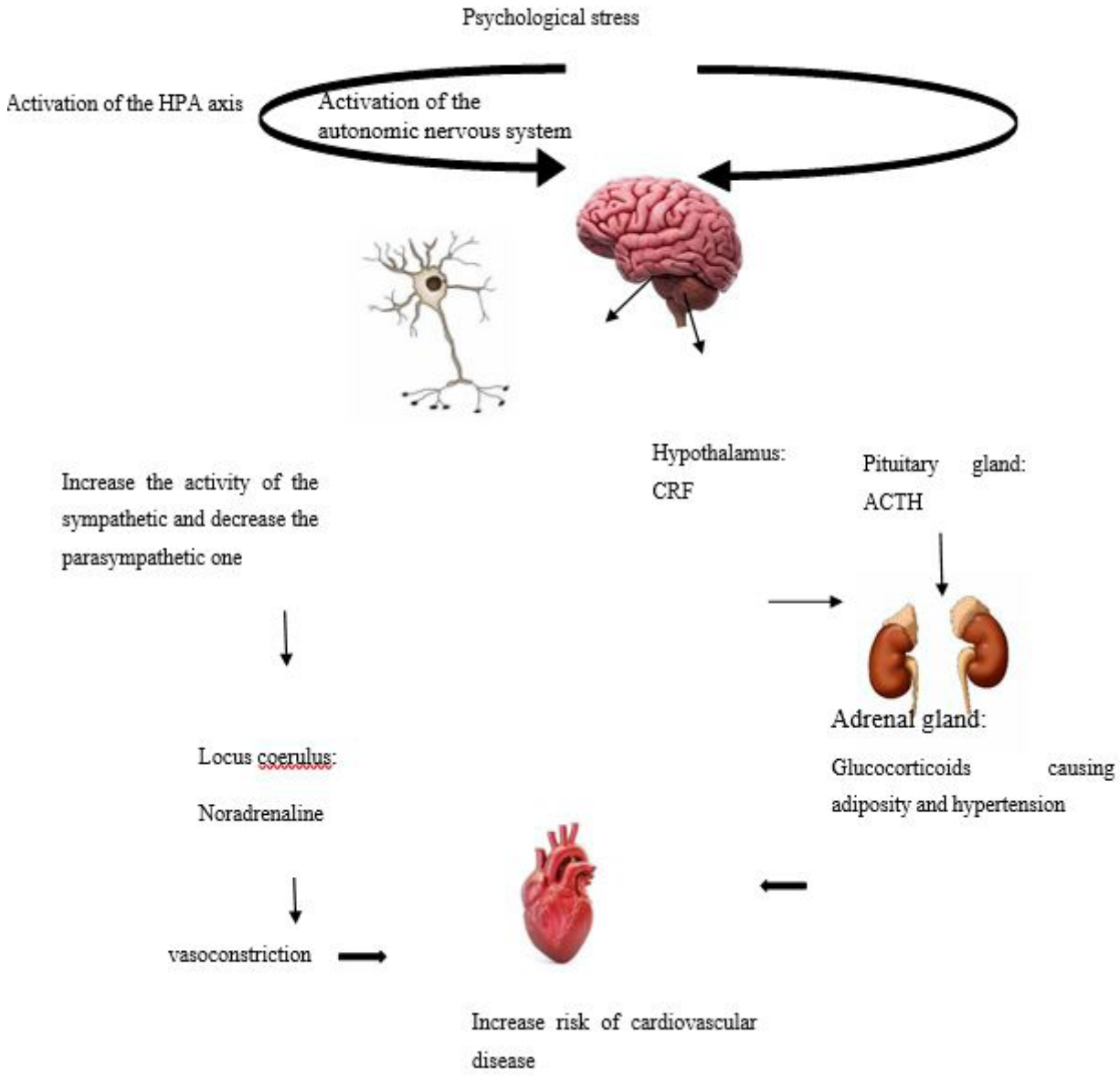

Figure1: Activation of the hypothalamo-pituitary-adrenal axis and the autonomic nervous system by stressors

Methods

This systematic review provides an overview of the association between psychosocial stress and cardiovascular disease, and the different ways to manage stress in order to prevent occurring diseases. It was conducted according to the Preferred Reporting Items for Systematic Review andMeta-analysis (PRISMA-2009) guidelines. Pubmed was the only database searched, and in order to develop an appropriate search strategy, first, a very clear research question was defined meetingthe PICO elements: to assess the effect of psychosocial factors on cardiovascular diseases. By using the appropriate Mesh terms, the search strategy on pubmed was: "stress, psychological"[MeSH Terms] AND "Cardiovascular Diseases"[MeSH Terms]). All the articles included in this systematic review met the inclusion and the exclusion criteria: studies that discussdiseases related to cardiovascular diseases were included, articles published from 2012 to 2022, articles published in English language and also clinical and preclinical studies were included. Allarticles from books, newspapers, meta-analyses, and reviews were excluded as articles that discussdiseases not related to cardiovascular system and the ones not published in English language wereexcluded as well. All resulting articles were checked manually by two authors and screening wasdone manually. First, by reading abstract and titles, all articles that are not related to the topic were eliminated. Second, all texts were read and screened depending on the chosen eligibility criteria. Data extraction included study characteristics, sample characteristics (age, gender…), and outcome data such as tools used to assess the intervention (psychological stress in individuals enrolled in the study) and for the cardiovascular events seen following this intervention.

Results

After reviewing articles from the last 10 years, the search done on Pubmed yielded 2644 articles of which 234 articles remained after removing meta-analysis, books and reviews. 17 articles wereincluded in this systematic review after excluding the other ones because of the irrelevant abstractsand titles. (fig2)

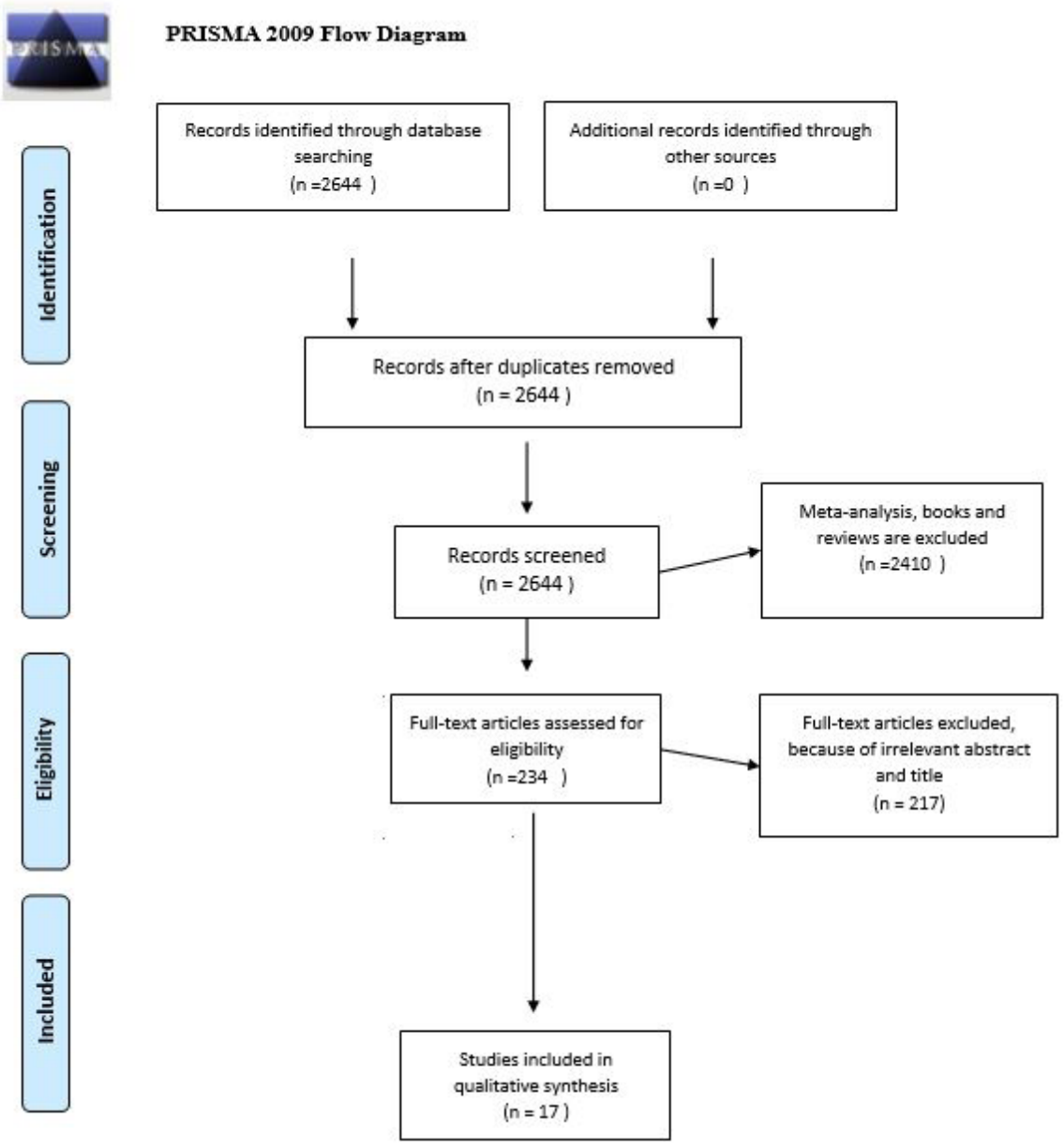

Figure 2: flow diagram of the different phases of a systematic review according to PRISMA guidelines

In the first study done by (Kershaw et al., 2014), coronary heart disease (CHD) and stroke incidence were the highest among individuals with high level of stressful life event, reaching 34.7(95% CI 32.3, 37.4) and 28.7(95% CI 26.5 31.2) respectively. Similar findings were obtainedfor social strain, the CHD and stroke incidence reach a value of 33.8(95% CI 31.7, 36.0) and 28.8(95% CI 26.9, 30.9). In further analysis and after adjusting for confounding factors, the highestlevel of stressful life events and social strain were associated with high incident coronary heart disease. Only waist circumference and diabetes status from the biological risk factors can have an impact on stressful life event, social strain-CHD association. Waist circumference attenuated the relationship between high stressful life event and CHD by 28.6% and the relationship between high strain and CHD by 29.2%. Diabetes attenuated the associations of high stressful life event and social strain with CHD by 20.1% and 19.6%, respectively. This attenuation was even strongerin models simultaneously adjusted for waist circumference and diabetes status (42.5% for stressfullife event and 43.1% for strain), suggesting that they were independent mediators. Besides, in models adjusted for sociodemographic characteristics and depressive symptoms, high social strainwas associated with higher incident ischemic stroke (HR, 1.15; 95% CI, 1.02, 1.28), but not incident hemorrhagic stroke

(HR, 0.89; 95% CI, 0.70, 1.14). Findings were similar for high versuslow stressful life event with hemorrhagic (HR, 1.21; 95% CI, 0.91, 1.61) and ischemic stroke (HR,1.13; 95% CI, 0.99, 1.30) (Kershaw et al., 2014).

Westcott and his colleagues showed that 3.84% of women that participated in this study developedarterial fibrillation, and tended to have higher levels of financial, traumatic life event, neighborhood stress and lower everyday discrimination stress scores than women without arterialfibrillation. Only traumatic life event was significantly associated with arterial fibrillation (OR 1.32, CI (1.12-1.52), p<0.0007), after adjusting for age, race, cardiovascular disease risk factors, socioeconomic status, and psychosocial status (depression and anxiety) (Westcott et al., 2018). These findings are similar to the one done by (Santosa et al., 2021) they found that after adjustingfor age and sex, the rate of all causes of death increase with an increased level of stress (from 7.8[95% CI, 7.5-8.1] events per 1000 person-years up to 9.7 [95% CI 8.7-10.7]) as for CHD (from 4.7 [95% CI, 4.5-5.0] events per 1000 person-years up to 5.5 [95% CI, 4.7-6.3] events per 1000- person years and from. However, the rate of stroke decreased from 4.3 (95% CI, 4.0-4.5) events per 1000 person-years in those with no stress to 3.2 (95% CI, 2.6-3.8) events per 1000 person- years in those with high stress. After adjusting for socioeconomic and demographic factors the association between stress and CVD is attenuated but still significant. The risks increased with increasing the level of stress for death (low stress: HR, 1.09 [95% CI, 1.03-1.16]; high stress: HR,1.17 [95% CI, 1.06-1.29]) and for CHD (low stress: HR, 1.09 [95% CI, 1.01-1.18]; high stress: HR, 1.24 [95% CI, 1.08-1.42]). High stress, but not low or moderate levels of stress, was significantly associated with CVD (HR, 1.22 [95% CI, 1.08-1.37]) and stroke (HR, 1.30 [95% CI,1.09-1.56]) after adjustment. Moreover, the study done by (Wang et al., 2021) that assesses the impact of job strain on cardiovascular diseases found that all associations were attenuated after adjustment for race/ethnicity, education, family income, and job tenure. Job control and job strainwere no longer significantly related to coronary heart disease (CHD) risk (job control HR, 0.98 [95% CI, 0.92–1.05]; high job strain HR, 1.00 [95% CI, 0.91–1.11]). However, the associations between high stressful life event scores and high social strain with greater CHD risk remained statistically significant (high stressful life event HR, 1.12 [95% CI, 1.02–1.23]; high social strain HR, 1.09 [95% CI, 1.01–1.18]). In the absence of social strain, job strain was not associated withCHD risk in women. Among women with high social strain, CHD risk was 25% higher for womenwith high job strain and 50% higher for passive jobs compared with women with low job strain after adjustment for age and stressful life event scores (HR, 1.25 [95% CI, 1.07–1.46]; HR, 1.50 [95% CI, 1.30–1.74], respectively). Same for the study done by (Cabeza de Baca et al., 2019) they found that in the fully adjusted model of all confounding factors, financial strain was associated with decreased likelihood of having ideal cardiovascular health status (1 stressor: OR = 0.77, 95%CI = 0.68, 0.87; 2 stressors: OR = 0.62, 95% CI = 0.52, 0.75;3+ stressors: OR = 0.41, 95% CI = 0.35, 0.49). Inability to pay bills and perceived family financial situation displayed the largest (inverse) associations with ideal cardiovascular health (B = −0.35, 95% CI = −0.41, −0.30; B =−0.37, 95% CI = −0.41, −0.32, respectively, in fully adjusted model. However, the studies done by (Tawakol et al., 2019) and (Goyal et al., 2020) showed the implication of the amygdala in the pathway leading to cardiovascular diseases. In the first one it shows that lower AmygA (standardized β [95% CI]: −0.18 [−0.26, −0.06], p=0.002) and lower arterial inflammation (−0.11 [−0.17, −0.02], p=0.012) in subjects with higher income. Moreover, higher AmygA (0.15 [0.01, 0.21], p=0.034), and non-significantly higher arterial inflammation (0.05 [−0.05, 0.14], p=0.308),in subjects living in neighborhoods with higher crime rates. After adjusting for risk factors associated with lower SES (i.e., smoking and obesity), we observed a ~6-fold higher MACE risk in individuals in the lowest (vs. highest) quartile of neighborhood median income (6.31 [1.41, 28.18], p=0.016). AmygA is a predictive of MACE in low income and high crime rate respectively (1.63 [1.28, 2.07], p<0.001); and (1.59 [1.20, 2.11], p=0.001). After adjusting for CVD risk factorsand neighborhood median income, AmygA is associated with both hematopoietic tissue activity (β [95% CI]: 0.190 [0.077, 0.306], p=0.001) and arterial inflammation (0.202 [0.100, 0.346], p<0.001) that predicts MACE. In the second study that assess the impact of stress on CVD in patients with psoriasis, a disease caused by stress and leads to cardiovascular diseases showed thatindividuals with psoriasis had high cardiovascular risk with a Framingham risk of 3.5(1.0-6.0) > 1.3(0.4-3.9), high risk of insulin resistance by a high homeostasis model assessment of insulin resistance (HOMA-IR) [3.5 (1.6 – 5.3) vs 2.3 (1.6 – 3.4), p=0.03] and higher C-reactive protein levels [3.0 (1.6 – 8.7) vs 1.1 (0.7 – 2.6), p=0.001]. Moreover, AmygA was higher in severe psoriasis patients (1.12 ± 0.11 vs 1.06 ± 0.12, p=0.02), as was hematopoietic system activity as measured by SUVs in bone marrow (4.05 ± 1.15 vs 3.52 ± 0.96, p=0.03). Furthermore, there wasevidence of subclinical cardiovascular disease assessed by 18FDG-PET/CT derived aortic vascularinflammation (1.78 ± 0.32 vs 1.62 ± 0.20, p=0.02) and CCTA derived coronary artery characteristics [total coronary plaque burden (1.37 ± 0.73 vs 1.05 ± 0.33, p<0.001) and non- calcified coronary plaque burden (1.29 ± 0.69 vs 1.04 ± 0.34, p<0.001)]. Baseline resting AmygAassociated with atherosclerotic disease: aortic vascular inflammation [β=0.31, p<0.001] and non- calcified coronary plaque burden [β=0.27, p<0.001]. AmygA was associated with aortic vascular inflammation accounting for 20.9% and with non-calcified coronary plaque burden accounting or36.7% by the mediation of the bone marrow. Otherwise, the study done by (Dar et al., 2019) showed that

among individuals exposed to at least one chronic socioeconomic or environmental stressor (n=166), 12 (7.2%) developed major adverse cardiovascular events (MACE) over a median follow-up of 3.75 years. Within stress exposed group AmygA is associated with MACE risk in univariable (standardized HR [95% CI]: 1.624 [1.205, 2.188], P=0.001) and multivariable models (1.927 [1.370, 2.711], P<0.001; adjusted for age, sex, and CVD risk factors) and regardlessof the number or types of chronic external stressors. In other words, lower AmygA (ie, higher neuro-biological (NB)Resilience) associated with an 86% reduction in MACE risk (log-rank P=0.004). Also, among stress-exposed individuals (n=166), lower AmygA associated with lower bone marrow (ie, leukopoietic) activity (standardized β [95% CI]: 0.192 [0.030–0.353], P=0.020.(table 1)

Reference	Population characteristics	Methodology	Main result
(Kershaw et al., 2014)	Data used from the women's health initiative (WHI). It is an observational study (cohort) of 93676 women ages 50-79years and enrolledfrom 1993-1998	-participants completed a questionnaireabout life changes to assess stressful life events. Social strain was assessed by a questionnaire that targets social relationships -assessing confounders that may influence the association of stress andCVD -outcome data were obtained each yearby updated medical history questionnaire or direct contact byclinical follow up visits	-in further analysis and after adjusting for confounding factors, the highest level of stressfullife events and social strain were associated with high incident coronary heart disease. -in models adjusted for sociodemographic characteristics and depressive symptoms. High social strain was associated with higher incident ischemic stroke, but not incident hemorrhagic stroke. Findings were similar for high versus lowSLE with hemorrhagic and ischemic stroke.
(Westcott et al., 2018)	Data used from the women's health cohort study (WHS). The WHS stress study is a continued observational follow up in which 24809 women without knownCVD or arterial fibrillation participated.	-participants competed a questionnairethat evaluate 8 stress domains (work, work-family spillover, financial, traumatic life event, everyday discrimination, intimate partner stress,neighborhood stress, negative life event within past 5 years) -detection of arterial fibrillation was done through an annual questionnaire completed by the participants and also by reviewing medical history likeelectrocardiographic review	-Women with AF tended to have higher levels of financial, traumatic life events than women withoutAF -Only traumatic life events was significantly associated with AF, after adjusting for age, race, cardiovascular disease risk factors, socioeconomicstatus, and psychosocial status (depression and anxiety)

(Santosa et al. 2021)	This is a prospective cohort study of 118706individuals aged 35 to 70 years without prior CVD from 27 dif-ferentcountries that differ in economic and social circumstances from 2008 till march 2021	-psychosocial stress was assessed by 2single-item questions relating to stressat work and home -Life events stress was defined as whether respon-dents had experienced any of a number of specified major adverse life events in the past year (eg,loss of job, retirement, loss of crop or business failure, mari-tal separation or divorce, death of spouse, death or major illness of close family member) -Level of financial stress was categorized as wheth-er respondents had felt financial stress in the last 12 months -total stress was calculated by summing the score of psychological stress, major life events, and financial stress	- after adjusting for age and sex, the rate of all causes death and CHD increase with increased levelof stress. However, the rate of stroke decreased in those with high stress. -After adjusting for socioeconomic and demographic factors the association between stressand CVD is atten-uated but still significant.

		- assessing covariates (sociodemographic characteristics) -CVD information was obtained from participants or family members, medical records and physician reports	
(Wang et al., 2021)	This is a cohort study. Data was taken from WHI-OS, 80825 women were included in the study With a mean age of 63 years.	-job strain was assessed by Karasek Job Demand–Control Model, it has been applied to the relationship between job strain and health outcomes, including cardiovascular problem. It describes job demand and job control by which jobs are categorized into: active work (high demand and high control), high strain (high demand and low control), low strain (low demand and high control), and passive work (low demand and low control). -information about stressful life events was collected by using a questionnaire that ask participants about their experience in the past year in 11 major life events -social strain was assessed by questions about negative social relationships -finding all covariates that may affect the relation between stress and CVD - CHD is diagnosed based on n cardiac pain, cardiac enzyme and troponin levels, and ECG findings by a local physician adjudicator and by reviewing medical records	- After adjusting for confounding factors, the associations between high stressful life event scores and high social strain with greater CHD risk remained statistically significant. - there is an interaction between job strain and social strain, Among women with high social strain, CHD risk was 25% higher for women with high job strain and 50% higher for passive jobs compared with women with low job strain

(Tawakol et al., 2019)	The study's finding are derived from a retrospective, longitudinal, observational imaging study. In this study 509 individuals participated without prior CVD, cancer, chronic inflammation or autoimmune disease and with an age above 30 years	-MACE adjudication was performed by two cardiologists blinded to clinical and imaging data. -SES measures were derived from the U.S. Census Bureau's 2015 American Community Survey 5-Year Estimates and Massachusetts Uniform Crime Reporting database by the Federal Bureau of Investigation -Image analyses was conducted by an investigator who was blinded to all clinical and SES data. -AmygA associates with anxious temperament, clinical manifestations of stress related disorders , risk of subsequent incident diabetes, non- calcified coronary artery plaques and risk of MACE.	-lower AmygA and lower arterial inflammation was observed in subjects with higher income. However, higher AmygA and higher arterial inflammation was observed in subjects living in neighborhoods with higher crime rates. -After adjusting for risk factors associated with lower SES (i.e., smoking and obesity), we observed a ~6-fold higher MACE risk in individuals in the lowest (vs. highest) quartile of neighborhood median income. -after adjusting for CVD risk factors and neighborhood median income, AmygA associated with both hematopoietic tissue activity and arterial inflammation that predicts MACE - ↓SES → ↑AmygA → ↑hematopoietic tissue activity → ↓arterial inflammation → ↑MACE

(Cabeza de Baca et al., 2019)	It is an observational cohort follow up of the WHS study. A total of 22048 women with a mean age of 72.1 years without cancer or CVD history participated in this study.	-financial strain was assessed by a questionnaire that ask about acute negative life events inventory, difficulty paying bills and perception of family perception situation. The financial stress score is reported into 4 categories: No financial strain, one financial stressor, two financial stressors, and three or more financial stressors, with individuals who reported no financial strain as the reference group -ideal cardiovascular was assessed using self-reported data from the stress study questionnaire and coded as ideal, intermediate, or poor. Diet and physical activities were assessed each in a separate questionnaire. -assessing for covariates	-in the fully adjusted model of all confounding factors, financial strain was associated with decreased likelihood of having ideal cardiovascular health status. -Inability to pay bills and perceived family financial situation displayed the largest (inverse) associations with ideal cardiovascular health
(Goyal et al., 2020)	This is a case-cohort study done between 2013-2017 at the national institute of health. A total of 164 psoriasis patients as well as 47 volunteers with mean age 50 years participated in this study.	-aortic vascular inflammation and hematopoietic system activity was determined by FDG PET/CT. - a single reader placed right and left 3D-volume regions of interest with a fixed volume in the desired area and measured 18FDG uptake as standardized uptake value (SUV) using a dedicated software (OsiriX MD, Geneva, Switzerland). Amygdalar activity (AmygA) was calculated by dividing the maximum SUVs in each amygdala by the mean SUVs in ipsilateral temporal lobes for correction of amygdala SUV values.	Moreover, AmygA was higher in severe psoriasis patients, as was hematopoietic system activity as measured by SUVs in bone marrow. Furthermore, there was evidence of subclinical cardiovascular disease assessed by 18FDG- PET/CT. -Baseline resting AmygA associated with atherosclerotic disease: aortic vascular inflammation and non-calcified coronary plaque burden. -AmygA was associated with aortic vascular inflammation accounting for 20.9% and with non-calcified coronary plaque burden accounting or 36.7% by the mediation of the bone marrow.

(Dar et al., 2020)	This is a retrospective, longitudinal, observational study. 254 participated in this study without pervious history of CVD, cancer or autoimmune disease, of these 166 were chronically exposed to at least one socioeconomic or environmental stressor with an age of ≤30 years	-Patient records were retrieved using hospital electronic medical records -Included subjects were also required to have: **(1)** at least 3 follow-up visit notes over a period of ≥1 year after imaging to ensure adequate follow-up **(2)** data available for socioeconomic and environmental stressors at their addresses **(3)** 18F-FDG-PET/CT brain images allowing the measurement of amygdalar activity (AmygA).	- among individuals exposed to at least one chronic socioeconomic or environmental stressor (n=166), 12 (7.2%) developed MACE over a median follow-up of 3.75 years -within stress exposed group AmygA is associated with MACE risk k in univariable and multivariable models (adjusted for age, sex, and CVD risk factors) and regardless of the number or types of chronic external stressors -among stress-exposed individuals, higher AmygA associated with increased MACE risk. In other words, lower AmygA (ie, higher NBResilience) associated with an 86% reduction in MACE risk.
		-CT images that measures arterial leukopoietic activity were analyzed by an investigator blinded to all clinical and stressor data. -Socioeconomic measures were derived from the US Census Bureau's 2015 American Community Survey 5- Year Estimates	-Among stress-exposed individuals (n=166), lower AmygA associated with lower bone marrow (ie, leukopoietic) activity).

Table1: results of the studies that investigates the association between psychological stress andCVD

CVD: cardiovascular diseases, SLE: stressful life event, AF: arterial fibrillation, CHD: coronary heart disease, AmygA: amygdalar activity, NBR resilience: neurobiological resilience, MACE: major cardiovascular events

Moreover, in the study done by (Schneider et al., 2019), they found that patients randomized to transcendental meditation group presents significantly lower left ventricular mass index (-7.55 gm/m2) compared to the health education group after 6 months following the intervention. Similarly, in the study done by (Schneider et al., 2012), over an average follow-up of 5.4 years, there was a 48% risk reduction in the primary end point in the transcendental meditation (TM) group (hazard ratio [HR], 0.52; 95% confidence interval[CI], 0.29-0.92)(P =.025). The TM groupalso showed a 24% risk reduction in the secondary end point (HR, 0.76; 95% CI, 0.51-0.1.13) (P=.17). There was also a significant net difference of −4.9 mm Hg in systolic BP in the TM group compared with HE group (95% CI, −8.3 to −1.5 mm Hg) (P = .01). For diastolic BP, there was a net difference of −1.6 mm Hg (95% CI, −3.4 to 0.3 mm Hg) (P = .27). In the study done by (PonteMárquez et al., 2019), after 8 weeks post-intervention visit, they found a reduction of 3 mmHg inclinically measured SBP in the group receiving stress reduction therapy based on mindfulness skills compared to the control group (130.54 mmHg vs 133.21 mmHg; p = 0.02). As for the studydone by (Katsarou et al., 2014), they notice that, in the group receiving stress management techniques as well as on Mediterranean diet principles, BMI did not change significantly from baseline, but stress score significantly decreased and MedDiet score significantly increased, without any changes at the level of physical activity. Although, the intervention group showed significantly lower systolic BP after the completion of the intervention (P = 0.009), and lower diastolic BP (P =0.016). Another study done by (Nijjar et al., 2019), and after 3-months post- randomization, they observed improvement in SBP in the mindfulness based stress reduction (MBRS) group compared to controls: 3-month SBP Δ was −2.02 (SD, 9.11) mmHg for the MBSRgroup and +1.89 (SD, 7.79) mmHg for the control group (difference (95% CI) = −3.84 (−9.57,+1.90)

(p=0.18)). The MBSR group showed also either greater improvement or less worsening of other CV risk factors (with the exception of HDL). These findings are similar to results of the study done by (Sherwood et al., 2017), they observe that patients randomized to stress managementprogram or aerobic exercise indicates an improvement in SBP(3 .2 (SE = 1.5) % for SM, 1.7 (SE = 1.5) % for EX, and −0.7 (SE = 1.4) % for UC) dipping and DBP(1.2 (SE = 1.9) % for SM, 2.5 (SE = 1.9) % for EX, and −3.0 (SE = 1.8) % for UC)dipping compared to usual care condition. Inthe study done by (Hughes et al., 2013) also they found that there is a 4.9 mmHg reduction in clinical systolic blood pressure observed in the MBSR group which exceeded the reduction in theprogressive muscle relaxation (PMR) group 0.7 mm Hg and that the 1.9 mm Hg reduction in clinicDBP observed in the MBSR treatment condition was a larger reduction in DBP than the 1.2 mm Hg increase observed in the PMR group. Finally, in the study done by (Hewett et al., 2017), examining the effect of 16 week Bikram yoga program on cardiovascular disease, they found thatthe analyses of covariance revealed no significant change in the high-frequency component of HRV ($p = 0.912$, partial $\eta2 = 0.000$) or in any secondary outcome measure between groups over time. However, regression analyses revealed that higher attendance in the experimental group wasassociated with significant reductions in diastolic blood pressure ($p = 0.039$; partial $\eta2 = 0.154$), body fat percentage ($p = 0.001$, partial $\eta2 = 0.379$), fat mass ($p = 0.003$, partial $\eta2 = 0.294$) and body mass index ($p = 0.05$, partial $\eta2 = 0.139$). Moreover, in the study done by (Rafanelli et al., 2020) they noticed that patients who were randomized to cognitive behavioral therapy and well- being therapy showed improvement in depressive symptoms compared to clinical management (p=0.040). Treatment was also related to a significant amelioration of biomarkers in particular, they found a significant decrease in cases with a high platelet count (from 52 to 36%; $p < 0.05$; median = 226 × 103 /mm3), lower HDL cholesterol (from 52 to 34%; $p < 0.05$; median = 47 mg/dL), and a higher D-dimer level (from 56 to 40%; $p < 0.05$; median = 0.31 m./L FEU) (table 2)

Reference	Population characteristics	Methodology	Main result
(Schneideret al., 2019)	This is a randomized, controlled, single blindedclinical study and was	-patients included with a systolic blood pressure of 120-179 mm Hg and/or diastolic blood pressure of 80-	-After 6months of intervention, the TM grouphad significantly lower LVMI than the HE group.
	conducted between 1994- 1999. The study included men and women aged 20-75 years old.	109 mm Hg with or without antihypertensive medications -patient with history of CVD abnormalities and behavioral disorders were excluded. -patients were tested for the outcomes at the beginning and after 6 months following the intervention - echocardiography was used to measure left ventricular mass Blood pressure was measured by a trained research technician -psychological functions were assessed by specific scales	

(Ponte Márquez et al., 2019)	This prospective randomized open-label blinded-endpoint (PROBE) study included a total of 42 patients, aged between 18 and 70 years; they were recruited between July 2014 and March 2015	-patients with history of CVD abnormalities, previous experience of meditation, yoga and similar techniques were excluded -In weekly 2-h sessions over 8 weeks, the intervention group received group- based stress-reduction therapy based on mindfulness skills -Four visits were made as follows (W = week): W0, baseline (pre- intervention) visit; W4, mid-point visit; W8, post-intervention visits; and W20, follow-up visit.	-After 8 weeks post-intervention there is a reduction in clinically measured SBP in the intervention group compared to the control group
(Katsarou et al., 2014)	This is a randomized controlled pilot study conducted from November 2009 till February 2010, it included 36 participants.	-inclusion criteria: age: 18 years old; diagnosed hypertension according to the international guidelines, under steady medical treatment -Exclusion criteria included inability to participate because of mental or physical causes. -patients were randomly assigned into intervention and control group -the intervention consists of practicing on stress management techniques as well as on Mediterranean diet principles	-In the intervention group, BMI did not change significantly from baseline, but stress score significantly decreased and MedDiet score significantly increased, without any changes at the level of physical activity. Although, the intervention group showed significantly lower systolic BP and lower diastolic BP, whereas no significant changes regarding diastolic BP between the two groups were observed.
(Schneider et al., 2012)	This is a randomized controlled trial conducted between March 1998 and July 2007 of 201 participants.	-Exclusion criteria were acute myocardial infarction (MI), stroke, or coronary revascularization within the previous 3 months; chronic heart failure, cognitive impairment; and non-cardiac life threatening illness	- Over an average follow-up of 5.4 years, there was a 48% risk reduction in the primary end point in the TM group, and also showed a 24% risk reduction in the secondary end point - There was a significant net difference in systolic and diastolic BP in the TM group compared with HE group

		-Subjects were randomly assigned to either the TM or health education (HE) group -Subjects were assessed at baseline, month 3 and every 6 months thereafter for clinical events, blood pressure (BP), body mass index (BMI). Lifestyle behaviors and psychosocial distress factors were assessed annually. -The primary end point was the composite of all-cause mortality, myocardial infarction, or stroke. Secondary endpoints included the composite of cardiovascular mortality, revascularizations, and cardiovascular hospitalizations; blood pressure (BP); psychosocial stress factors; and lifestyle behaviors.	
(Nijjar et al., 2019)	This is a pilot randomized trial study of 47 patients with a mean age of 58.6 years.	-patients were allocated to either mindfulness-based stress reduction or control group for a duration of 8 weeks - patients were followed up at 3,6 and 9 months following the intervention	-At 3-months post-randomization, we observed improvement in SBP in the MBSR group compared to controls -The MBSR group showed either greater improvement or less worsening of other CV risk factors (with the exception of HDL), although none of the differences was statistically significant.

(Hewett et al., 2017)	This is a randomized controlled trial of 63 participants, recruited between august 2014 and September 2015	-participants were randomized to an experimental group (16 weeks of bikram yoga classes three to five times per week with a duration of 90 min), or a control group -Heart rate variability, systolic and diastolic blood pressure, hematological outcomes as well as anthropometrics and body composition outcomes, health status covariates, attendance and adverse events.	-Analyses of covariance revealed no significant change in the high-frequency component of HRV or in any secondary outcome measure between groups over time. However, regression analyses revealed that higher attendance in the experimental group was associated with significant reductions in diastolic blood pressure, body fat percentage, fat mass and body mass index.
(Rafanelli et al., 2020)	This is a randomized controlled trial of 100 patients with mean age of 58.8 years followed for 30 months	-patients were randomized to either a combination of 8 sessions of cognitive behavioral therapy and 4 sessions of well-being therapy or to a clinical management group -the cardiologists evaluated the patients every 6 months to monitor changes in cardiac events -Psychological assessment included both observer-rated and self-reported measures before the beginning of the	-CBT/WBT sequential combination was associated with a significant improvement in depressive symptoms compared to CM. Treatment was also related to a significant amelioration of biomarkers In particular, they found a significant decrease in cases with a high platelet count, lower HDL cholesterol, and a higher D-dimer
		interventions (baseline, pretreatment), at the end (post-treatment), and 3, 6, 12, and 30 months after the end of treatment	

(Hughes et al., 2013)	This is a randomized controlled trial of 56 men and women aged between 30-60 years.	-participants were equally randomized to either mindfulness based stress reduction program for 8 weeks or to progressive muscle relaxation program for the same duration -clinic blood pressure was the first outcome measured pre and post intervention -ambulatory blood pressure was the second outcome measured using a device that takes BP measurements during a continuous 24h period.	-there is a 4.9 mmHg reduction in clinical systolic blood pressure observed in the MB SR group which exceeded the reduction in the PMR group 0.7 mm Hg - the 1.9 mm Hg reduction in clinic DBP observed in the MBSR treatment condition was a larger reduction in DBP than the 1.2 mm Hg increase observed in the PMR group
(Sherwood et al., 2017)	This is a secondary analysis of a randomized controlled trial of 134 patients with CHD aged 40-84 years. The study was conducted from January 1999 through February 2003.	-44 patients were randomized to either stress management program, 48 to the aerobic exercise program and 42 to usual care program - nocturnal blood pressure dipping changes, daytime blood pressure and nighttime blood pressure changes were assessed at baseline and following the intervention	-EX and SM groups indicates an improvement in SBP dipping and DBP dipping compared to UC condition

Table 2: results of the studies that shows the impact of behavioral interventions in managingstress and CVD

LVMI: left ventricular mass index, SBP: systolic blood pressure, TM: transcendental meditation, MBSR: mindfulness-based stress reduction, CBT: cognitive behavioral therapy, WBT: well-being therapy, EX: aerobic exercise, SM: stress management

Discussion

In this systematic review, we screened 2644 articles and selected 17 articles that are included in the study. In the first 8 studies that examines the relationship between psychological stress and CVD showed in the most of the studies that social strain, traumatic life events, stressful life eventsand financial strain were associated with increased risk of cardiovascular diseases like atrial fibrillation and stroke. These findings were similar to the results mentioned in many reviews. A cohort study of more than 6 million adults has shown that the relative risk of cardiovascular diseaseafter stress induced by receiving diagnosis of cancer was 5.6(95% CI 5.2-5.9) during the first weekand 3.3(95% CI 3.1-3.4) during the first 4 weeks (Kivimäki & Steptoe, 2018). In the JACC studya total of 73.424 Japanese subjects without any history of CVD and stroke completed a questionnaire about their perceived stress. The results shoes that women with high level of stress have a twofold higher risk of mortality due to stroke (Inoue, 2014). Similarly, this relationship is also studied after the 2004 Northridge earthquake, the risk of death from cardiac attack increasedby 2.5-fold on the day it occurred (Dar et al., 2019). In a German study, and during the 2006 FIFAworld cup, the incidence of cardiac events was 2 times higher (95% CI 1.7-2.4) on match days including the German national group than in the control period (Kivimäki & Steptoe, 2018). In theWhitehall 2 study, longer duration of work-related stress was associated with a greater morning rise in cortisol level and reduced heart-rate variability, suggesting a direct effect of stress on the autonomic nervous system and neuroendocrine function. Also, social isolation has been associatedwith an increase level of molecular stress markers such as cortisol and epinephrine (Steptoe & Kivimäki, 2012). Analysis of data on more than 500000 men and women showed that individualsworking long hours (>55h per week) had 1.3 times (95% CI 1.1-1.6) higher risk of incident strokethan individuals working the standard hours per week (35-40h) (Kivimäki & Steptoe, 2018). Moreover, two studies showed that stressors such as lower socioeconomic status will stimulates the activation of the amygdala leading to an increase in arterial inflammation, and causing CVD. These findings are similar to the study done by (Tawakol et al., 2017),

during median follow-up of 3.7 years of 293 people, 22 individuals experienced cardiovascular diseases. Amygdalar activityrobustly predicted the risk of developing a subsequent cardiovascular event, yielding adjusted standardized HRs of approximately 1.6 (i.e., a 16-times increased risk of a cardiovascular event for each increase of one SD in amygdalar signal). Amygdalar activity was associated with increased bone-marrow activity (r=0·47; p<0·0001), arterial inflammation (r=0·49; p<0·0001), and risk of cardiovascular disease events (standardized hazard ratio 1.59, 95% CI 1·27–1·98; p<0·0001). However, psychological resilience is known to play an important role in disease development and prognosis, slow the progression of the disease, and decrease the inflammatory response of stress to the cardiac structures. Resilience is defined as the ability to withstand or recover quickly from difficult conditions, or resistance to stress. And this is influenced by severalfactors like social and cultural ones (Chinnaiyan, 2019). Likewise, this was verified by (Dar et al.,2020), they found that lower amygdalar activity (higher neurobiological resilience) was associatedwith greater reduction in cardiovascular disease. In the review done by (Golbidi et al., 2015), someanimals were exposed to psychological stress by forcing them to swim in a container filled with water, or by exposing the animals to social defeat stress. In both cases animals shows atherosclerotic effects including increase in cholesterol, triglycerides blood levels and decrease inHDL levels. Besides, in the other 9 studies, several behavioral interventions like transcendental meditation, stress reduction based on mindfulness skills, healthy diet, yoga, cognitive behavioral therapy shown to have impact generally in reducing systolic and diastolic blood pressure and thusreducing CVD risk. These findings were similar to the studies mentioned in the review. For example, approach using cognitive behavioral therapy (CBT) and the use of internet based interventions (a free accessible CBT program E-touch) for stress management showed to be beneficial in reducing cardiac events (Tan & Morgan, 2015). In a series of studies with moderatelysized samples of 100 to 150 patients with CAD, Blumenthal et al have repeatedly shown that augmentation of a standard cardiac rehabilitation-based exercise program with cognitive behavioral stress management training conferred impressive relative risk reduction of events compared with standard cardiac rehabilitation (9.1%×20.6% at 3 years, relative risk, 0.26 [95% CI, 0.07–0.90]; P=0.03) and stress management training compared with standard cardiac rehabilitation (18% versus 33% at 5 years; hazard ratio=0.49 [95% CI, 0.25–0.95]; P=0.035)(Meadows et al., 2020). The stress-management program was carried out on a group basisover 20 sessions, based on cardiovascular health education, self-monitoring, relaxation, and cognitive restructuring. After 7 years of follow-up, 20% and 7% of the usual care and stress management groups died, respectively (HR 0.3, 95% CI 0.1-0.7) (Steptoe & Kivimäki, 2012). However, several studies were done on animal models to help in better understanding the human health and diseases under study. For example, adult male rats were exposed to 4 weeks of chronicmild stress or isolation from a same-sex sibling, produces behavioral changes consistent with depressive symptoms. These animals also produced several clinical cardiac alterations including elevated resting heart rate and reduced heart rate variability. After few weeks, only cardiac eventspersists with recovery from depression (Grippo, 2009). Same for studies concerning monkeys, Subordinate monkeys have higher basal cortisol levels, secrete more cortisol in response to an adrenocorticotropin challenge compared to dominants. Also, they had an increase in heart rate thatexacerbate coronary artery atherosclerosis(Shively et al., 2009). Moreover, subordinate mice had shorter lifespan (12.4% decrease in median lifespan compared to dominants), hyperglycemia, increase in cellular senescence markers (p53, p16ink4a), earlier onset of tumors and atherosclerotidesions (Razzoli et al., 2018). Studies showed that psychological stress is associated with several diseases including upper respiratory diseases, cancer and neurodegenerative diseases. First, in a more controlled study, people were exposed to a rhinovirus and then quarantined to control for exposure to other viruses. Those individuals with the most stressful life events and highest levels of perceived stress and negative affect had the greatest probability of developing cold symptoms.In a subsequent study of volunteers inoculated with a cold virus, it was found that people enduring chronic, stressful life events (i.e., events lasting a month or longer including unemployment, chronic underemployment, or continued interpersonal difficulties) had a high likelihood of catching cold, whereas people subjected to stressful events lasting less than a month did not (Schneiderman et al., 2005). Second, Stress can generate amyloid precursor protein (APP),increase beta-amyloid (Aβ) peptide, APs, and NFTs formation that are relevant to the pathogenesisof AD. Excessive immune cell activation due to stress will cause neuro-inflammation, that is characterized by an elevated cytokines, chemokines and other neurotoxic mediators in the centralnervous system that may cause neurodegenerative diseases such as Alzheimer disease(Kempuraj et al., 2020). Finally, chronic stress induces suppression of protective immune response that eliminates infection, cancer and pathogens. Catecholamine and glucocorticoid hormones have been identified as the major physiological mediators of chronic stress induced suppression of protective immunity which in turn could contributes to increased tumor progression and metastasis. Also, chronic stress may induce chronic inflammation by an increase in circulating pro-inflammatory factors, though to be critical factor for tumor initiation, progression and metastasis(Antoni & Dhabhar, 2019).

Conclusion and future perspectives

There is a growing evidence showing the implication of psychosocial stress in triggering CVD. Inthis review, psychological stress and specifically job stress and the low economic status has beenshown to be implicated in several cardiovascular events including strokes, arterial fibrillation andcoronary heart diseases. Besides, behavioral interventions implicated in reducing stress showed their effect on the cardiovascular system by reducing systolic and diastolic blood pressure, cholesterol levels and body fat percentages. Clarifying the pathways linking these two componentsincluding the HPA axis and the autonomic nervous system and several complex structures in the brain at a molecular level remains a leading cause in finding several treatments in order to preventCVD. Despite this evidence, there is a need to do further studies to find more brain structures involved in this mechanism in order to find more reliable treatments targeting prevention CVD risks.

Conflict of interests

The authors declare no conflict of interests

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