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Candidate Biomarkers to Evaluate the Association between Psychosocial Factors and Cardiovascular Diseases

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Abstract

The association between psychosocial factors and cardiovascular diseases had been suggested. This review was performed to assess, from literature data, the pertinence of using new biomarkers in the occurrence or prognosis of cardiovascular diseases in a psychosocial context. We choose to consider wide-ranging descriptions of stress from psychological factors (occupational stress, financial strain, marital stress, social isolation, etc.) that may influence a physical health outcome (cardiovascular diseases).We addressed literature data confirming the link between candidate biomarkers (such as cortisol, endothelial dysfunction, pro-inflammatory cytokines, and allostatic load) and cardiovascular diseases in a context of psychosocial factors. It was shown a link between cortisol, endothelial dysfunction, pro-inflammatory cytokines, and the incidence or prognosis of cardiovascular diseases in a psychosocial context. Allostatic load index was also identified as a pertinent tool in the assessment of the cumulative psychosocial factors burden exerted on the body.

Keywords: Psychosocial factors • Biomarkers • Cortisol • Endothelial dysfunction • Inflammation markers • Allostatic load • Cardiovascular diseases.

Abbreviations: AMI : Acute Myocardial Infarction • AL : Allostatic Load • CRP : C-Reactive Protein • DHEA-S: Dehydroepiandrosterone-Sulphate • ELISA : Enzyme-Linked Immunosorbent Assay • ET : Endothelin • FMD : Flow-Mediated Dilation • GR : Glucocorticoid Receptor • HDL-cholesterol : High Density Lipoprotein-Cholesterol • HPA axis : Hypothalamus-Pituitary-Adrenal axis • ICH : Intra-Cerebral Hemorrhage • IMT : Intima-Media Thickness • IL : Inter-Leukin • PSF : Psychosocial Factors • MCP-1 : Monocyte Chimoattractant Protein-1 • NIHSS : National Institutes of Health Stroke Scale • NO : Nitric Oxide • NOS : Nitric Oxide Synthase • SNS : Sympathetic Nervous System • TIA : Transient Ischemic Attack • TNF-α : Tumour Necrosis Factor-α

Introduction

Cardiovascular diseases included pathological processes raising along the brain-heart and blood vessel axes such as intracerebral hemorrhage (ICH), transient ischemic attack (TIA), acute myocardial infarction (AMI), and peripheral arterial disease. Cardiovascular diseases are considered as the major complications of atherosclerosis (Ross R and Glomset JA, 1976). Yet, acute thrombotic complications of atherosclerosis such as ischemic stroke and myocardial infarction remain global leading causes of disability and mortality [1]. An estimated 17.9 million people died from these diseases in 2019 worldwide representing 32% of deaths. These deaths are mainly due to heart attack and stroke (World Health Organization, 2021). The number of fatalities is estimated to increase to over 24 million a year by 2030 and this imposes a huge in terms of disability and healthcare costs [2].

In addition to classic cardiovascular diseases risk factors such as hypertension, dyslipidemia, visceral obesity, visceral obesity and diabetes [3], recent works have examined the role of Psychosocial Factors (PSF) as a potential cause of these diseases [4-9]. Major PSF included occupational stress, financial strain, low socioeconomic status, marital stress, social isolation, perceived loneliness, and anxiety. The different components of PSF may act alone or combine in group and may exert effects at different stages of the life course [10,11].

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Three decades of research based on cohort studies provided evidence for psychosocial pathways leading to cardiovascular morbidity and mortality [12]. For example, across multiple international cohorts, patients who are unmarried, including those who are divorced, separated, widowed, or never married, have an increased rate of adverse cardiovascular events when compared to their married counterparts [13].

Besides, high prevalence of cardiovascular disease in patients with posttraumatic stress disorder was reported [14].

The association between PSF and heart diseases had been suggested in a wide range of populations, including young, older, men, women, socioeconomic strata, lifestyle, and conventional risk factors [15-18]. PSF seem to be associated with increased risk of coronary heart disease [10].

Socioeconomic status is also inversely associated with coronary heart disease and it has been proposed that psychosocial pathways may play a mediating role [19-21]. In addition, there is also a clear social gradient in stroke mortality and morbidity, as lower socioeconomic groups worldwide have consistently higher rate of stroke than higher socioeconomic groups [22,17,23]. These bodies of evidence document the robust association of cardiovascular diseases with a context of PSF.

Two main mechanisms have been suggested to explain the link between stress exposure and cardiovascular diseases incidence or prognosis in established disease. The first hypothesis proposes that PSF affect cardiovascular health indirectly, through the modification of lifestyle behaviors such as smoking, poor dietary habits, physical inactivity, medication nonadherence, alcohol consumption, and weak sleep duration [24,25]. But this hypothesis does not explain entirely the link between adverse behavioral risk profile and stress-related disorders. The second hypothesis involves a direct pathway, through dysregulation of the Sympathetic Nervous System (SNS) and the hypothalamus-pituitary-adrenalaxis (HPA) that could induce inflammatory, metabolic, and haemostatic changes which have atherogenic effects and increase the risk of cardiovascular events [26-29].

The underling mechanisms linking PSF with cardiovascular diseases are complex. Biomarkers may identify new pathophysiological pathways, help the diagnosis and management of the disease. Moreover, biomarkers able to detect earlier phases of disease development would facilitate targeted strategies to prevent pathological complications. These strategies have prognostic significance so help to improve patient outcomes or are able to assess the risk stratification in asymptomatic individuals at higher risk [30-32].

Of note, alterations in neuro-hormonal stress response systems (catecholamines) happen quickly following exposure to stress and cannot be used as a biomarker to traduce underling chronic psychosocial stress exposure [33,34].

The aim of the current review is mainly focused on the identification of candidate biomarkers in cardiovascular diseases related to stress. We choose to consider wide-ranging descriptions of stress from psychological factors (occupational stress, financial strain, marital stress, social isolation). Regarding biomarkers, a special attention will be given to cortisol, endothelial function, inflammatory markers, and allostatic load.

Cortisol as a Biomarker of Cardiovascular Diseases Related to Psychosocial Stress

Cortisol is secreted by the adrenal cortex after activation of the HPA axis. This steroid hormone is involved in the regulation of a large panel of physiologic functions such as glucose and lipid metabolisms, body composition, and the immune system [35]. Cortisol is also called stress hormone. The prolonged activation of the HPA axis by chronic stress may result in cortisol distruption and metabolic dysfunction such as elevated fasting insulin and HOMA insulin-resistance index, dyslipidemia, visceral obesity, hypertension, and arterial stiffness [36-39].

Several literature data confirmed that cortisol is associated with metabolic disorders, main cause leading to cardiovascular diseases, in relation with psychosocial stress. For instance, a recent systematic review of 40 research articles demonstrated that cortisol was the biomarker used most frequently and was positively associated with PSF, including job strain, low socioeconomic status, and environmental factors. In this key paper, psychosocial stress was associated with metabolic risk factors such as vascular pathology (hypertension, blood pressure fluctuation, and carotid artery plaque) as well as high blood glucose, dyslipidemia, and elevated cardiac enzymes [40].

Low socioeconomic status was associated with both visceral obesity, perturbed cortisol secretion, as well as cortisol escape from dexamethasone suppression [36,41]. It also was identified a strong association between visceral obesity and blunted dexamethasone response in person with symptoms of anxiety and depression [42].

On one hand, literature data showed that stress alters many brain areas, including the hippocampus, medial prefrontal cortex, and amygdala. The medial prefrontal cortex is highly sensitive to stress and plays an important role in the regulation of emotions and coping with environmental challenges [43]. On the other hand, similar damage such as hippocampal damage, loss of dendritic plasticity, and memory impairments are present in patients with hypercortisolism syndrome. Impairments of executive functions, language skills, motor functions, and information processing speed were also reported [44]. Interestingly, metyrapone, corticosterone-synthesis inhibitor, was able to prevent ischemia-induced loss of synaptic function in the hippocampus of rat [45]. These data provide further clarification that the brain functioning can be impacted by stress and cortisol.

Incidence and prognosis impact of cortisol on cardiovascular diseases related to stress were widely studied and there is convincing evidence linking cortisol with stroke [46]. In fact, the level of cortisol reflects stroke severity and acts as an early risk assessment of the severity of disease and prognosis. The prospective observational study of Zi WJ and Shuai J showed that Chinese patients with a poor outcome and nonsurvivors had significantly increased serum cortisol levels on admission. There was a positive correlation between levels of cortisol and the National Institutes of Health Stroke Scale (NIHSS), glucose levels, and infarct volume. According to this study, cortisol can be seen as an independent short-term prognostic marker of functional outcome and death patients with acute ischemic stroke, even after adjustment for confounding factors. This study suggested that combined model with cortisol can add significant predictive information to the clinical score of the NIHSS [47].

Similarly, other studies have found that elevated plasma or urinary cortisol concentrations in acute ischemic stroke are related to greater stroke severity, larger infarct volume and/or unfavorable outcome, including death [48,49]. Moreover, these patients had a worse prognosis after stroke characterized by the development of infectious disease related to an immune dysregulation resulting from neuroendocrine disturbance and immunosuppressive properties of cortisol [50]. More precisely, Yang X et al sowed that 8am serum cortisol level was considered an additional prognostic factor for patients with ICH [51].

In community-dwelling elderly patients [52] demonstrated that higher hair cortisol levels were associated with a history of cardiovascular diseases, including coronary heart disease, stroke, and peripheral arterial disease. Importantly, this risk was similar to the effect of traditional cardiovascular risk factors such as hypertension, abdominal obesity, and dyslipidemia, suggesting that long-term elevated cortisol may also be a relevant risk factor. Curiously, no associations were found between long-term cortisol levels and chronic non-cardiovascular diseases [52].

A recent report has demonstrated that hair cortisol was increased in patients admitted with AMI as compared to levels in control subjects, indicating that systemic cortisol exposure within the three months before admission to the emergency department was higher in patients who developed an AMI than who were admitted for other reasons such as non-myocardial chest pain, infections, and syncope [53]. The study of Manenschijn L is cross-sectional and can therefore only suggest an association between hair cortisol levels and a history of cardiovascular diseases. However, Pereg's study showed that high cortisol levels are present before the onset of a cardiovascular event and consider that hair cortisol level is interesting with regard to its accuracy to predict AMI onset. Taken together, these findings suggest that this association may reflect a causative link.

Hamer M et al provide support for the hypothesis that hyper-reactivity of the HPA axis is one of the mechanisms through which psychosocial stress may influence the risk of coronary heart disease. The authors included healthy men and women participants without history or objective signs of coronary heart disease, and they showed a prospective association between cortisol stress reactivity and progression of sub-clinical atherosclerosis state, coronary artery calcification, which leads to clinical endpoint (coronary heart disease). This association was largely independent of conventional risk factors and was most evident in participants without detectable coronary artery calcification at baseline, which further supports the notion that heightened cortisol reactivity might be important in the etiology of atherosclerosis and is not a simple marker of disease progression [54].

Another emerging strand of evidence links cortisol with heart diseases is provided by the study of Lazzarino AI, et al. The authors found that heightened cortisol response to mental stress was associated with detectable plasma levels of high-sensitivity cardiac troponin T. This robust association between cortisol response and cardiac troponin were found even after adjustment for demographic and clinical variables associated with cardiovascular diseases as well as for inflammatory factors. This trong association remained even when healthy participants without coronary calcification were included or when data were adjusted for coronary calcification in participants with positive Agatston score [55].

Of note, it is possible that the single serum cortisol measurement may be influenced by the physical stress due to the actuate illness or the emotional stress associated with the hospital admission. Measurements of only one time point may yield inconclusive results. Especially when we know that some other studies, using serum or saliva specimen collection, have not shown associations between cortisol and cardiovascular risk factors [56,57] or reported that low cortisol levels were associated with cardiovascular risk factors [58]. Cortisol is a HPA axis-related hormone with a robust circadian rhythm where levels typically peak in the morning hours and decline across

the day [59]. So, it is possible that the single serum cortisol measurement may be biased by confounding factors. Scalp hair is a novel matrix that allows for measurement of hormones over a period of several months and it is easy to assess using an Enzyme-Linked Immunosorbent Assay (ELISA) method [60].

Obviously, we cannot rule out the role of unmeasured confounding risk factors or genetic influences that might account for cortisol response patterns and cardiovascular diseases risks such as Glucocorticoid Receptor (GR) polymorphism which may be related to higher pro-inflammatory activity and greater risk [61].

Endothelial dysfunction as a biomarker of cardiovascular diseases related to psychosocial stress.

Endothelial dysfunction is a well-established response to cardiovascular risk factors and precedes the development of atherosclerosis and is associated with increased risk of plaque rupture and many adverse outcomes manifestation. It is characterized by reduction of the bioavailability of vasodilators particularly Nitric Oxide (NO) and/or an increase in endothelium-derived contracting factors. The resulting imbalance leads to an impairment of endothelium-dependent vasodilation, which is the functional characteristic of endothelial dysfunction [62].

There is evidence for robust link between cardiovascular diseases and endothelial dysfunction in a context of PSF. In fact, in animal models particularly non-human primates, it was shown that experimentally induced psychosocial stress, by changing the social status of female monkeys from dominant to subordinate, causes endothelial damage and accelerates atherosclerosis which in turn might impact development and progression of cardiovascular diseases [63].

Of note, Flow-Mediated Dilation (FMD) of the brachial artery is the reference technique to measure arterial tonometry and decreased FMD reflects decreased/impaired endothelial function. This concept has emmerged as an essential indicator to predict recurrent cardiovascular events. In this context, using a community-based sample of employed individuals, Charles LE et al demonstrated that female blue-collar workers had the lowest mean FMD value and those in the management/professional and services categories (white coller) had the highest mean values. Moreover, these findings suggest that alterations of endothelial function may be one of the pathways linking occupational categories to FMD [64]. It was proposed that there are several mechanisms through which occupational category may be associated with endothelial function and they include psychological stress and unhealthy lifestyle behaviors [65].Similarly, a previous study demonstrated that participants perceiving themselves to be of lower social status in their communities exhibited reduced endothelial function (lower FMD) [66]. Furthermore, Chen H et al showed that stress score, as measured by the Depression Anxiety Stress Scales, was an independent powerful predictor for decreased brachial FMD [28]. More recently, depression, which is considered as a risk factor for poor prognosis after an acute coronary syndrome [67], was characterized by an endothelial dysfunction, and may contribute to the development of coronary artery disease [68].

Social isolation and perceived loneliness are also major PSF [69,70]. In this regard, the best illustration of the deleterious effect of this psychosocial stress in animal research is provided by the report of Peuler JD, et al. The authors showed, using a model system of social stressors that prairie vole, Microtus ochrogaster, a highly social rodent species, developed an impairment of vascular endothelial function after experimental isolation. This impaired endothelium-dependent vasodilation was not observed in wild animals. These findings confirm clearly that PSF-related stress may play a role in endothelial dysfunction [71].

Carotid Intima-Media Thickness (IMT) and ankle-brachial index are used to estimate the burden of atherosclerosis when patients are still asymptomatic. Overall increases in vascular wall thickness could indicate general vascular dysfunction. Local increases in vascular wall thickness are likely indicative of vascular remodeling and plaque formation, which precede vessel occlusion and ischemic events.

Charles LE et al have shown that job strain, represented by longer hours of work, is associated with higher IMT. Significant positive associations were observed between work hours and common carotid IMT among women, even after adjustment for age, race/ethnicity, education, annual household income, and cardiovascular diseases-related risk factors. In addition, longer hours of work were significantly associated with lower levels of ankle-brachial index, which is an indicator of atherosclerosis and can serve as a prognostic marker for cardiovascular events among men [72].

Blocking cortisol production with metyrapone in healthy participants prevented adverse clinical effects such as mental stress-induced endothelial dysfunction (FMD) [61]. Based on the aforementioned case, it is reasonable to speculate that a strong link between cortisol and endothelial dysfunction/FMD exists. On the other hand, it is khown that glucocorticoids stimulate strongly the production and release of endothelin (ET), a potent vasoconstrictor, by vascular smooth muscle cells [73]. Conversely, glucocorticoids are known to inhibit the NO Synthase (NOS), which is an enzyme catalyzing the production of NO, a powerful vasodilator and the key factor involved in the phenomenon of FMD. Taken together, this information provide arguments in favour of the role of glucocorticoids in the impairement endothelial function in cell and tissue models [74-77]. Consequently, it is no wonder that cortisol mediates mental stress-induced impairment of endothelial function in humans.

Inflammation as a Biomarker of Cardiovascular Diseases Related to Psychosocial Stress

According to the inflammatory theory of atherosclerosis, inflammation may be the starting point of the atherosclerotic process that results ultimately in a host of clinical complications, including ischemia, acute coronary syndrome, and stroke [3,78,79]. On the other hand, accumulating data provided argument in favor of positive association between stressful events and distress, specially workplace stressors, and increased production of pro-inflammatory cytokines, such as C-Reactive Protein (CRP) and Tumor Necrosis Factor-α (TNF-α), which are associated with a spectrum of age-related diseases such as heart diseases and stroke [80,81].

Meta-analytic associations have shown that work-related psychosocial factors could affect the flexibility and balance of the immune system [82]. Similarly, it was demonstrated that psychological stress is an independent coronary heart disease risk factor associated with increased inflammation [83].

The study of Asberg M, et al showed that prolonged psychosocial stress leads to a significant increase in the level of Monocyte Chemoattractant Protein-1 (MCP-1). The authors included participants, mainly white-collar workers, on long-term sick-leave for a work stress-related disorder (burnout) and healthy controls. MCP-1 levels were more than twice as high in the sick leave group compared to the healthy controls [84].

It is well documented that high levels of CRP predict coronary heart disease [85]. The analyses performed by Emeny R, et al provide new evidence for CRP association with stress. A strong association between job strain and CRP was observed in age and sex adjusted models, as well as in models adjusted for classic coronary heart disease risk factors [86,87].In accordance with this context, another study showed that CRP levels were increased in high stressed group of Taiwanese young drivers [88].

Negative emotions, such as depression and anxiety, increase the production of Inter-Leukin-6 (IL-6). The study of Kiecolt-Glaser JK, et al highlighted the deleterious longer-term immunological consequences of chronic stress. In fact, they showed that the average annual rate of increase in serum IL-6 was about fourfold higher in men and women who were chronically stressed by caring for a spouse with dementia than in similar individuals who did not have caring responsibilities [89].Of interest, the IL-6, is an important inducer of CRP, and the combination of the two molecules is important in the process that leads to the development of cardiovascular diseases [90].

The study of Epel ES, et al provided a better understanding of the underlying mechanism. According to this study chronic stress might be associated with premature ageing of immune cells. Telomerase activity and telomere length, which are two cellular markers indicating cell ageing, were measured in peripheral-blood mononuclear cells obtained from mothers

caring for a chronically ill child, as well as from mothers of healthy children. Of note, careers reported greater stress than controls. The clinical investigations demonstrated that higher level of stress was associated with lower telomerase activity and shorter telomere length [91].

Another noteworthy finding of the stronger effect of stress workplace on inflammatory markers is provided by the cross-sectional study of Fukuda H et al. The results showed that at a fixed point in time, the urinary IL-8 levels of nurses working in acute care department, who reported a higher level of professional stress, were almost twice higher than the levels of unstressed employed nurses working in another department. Curiously, mean urinary IL-8 and cortisol levels were positively correlated in women who lived stressful work experience, confirming thus the link between HPA axis dysregulation and inflammatory biomarkers [92]. More recently, a study of DeSantis AS et al, found that HPA axis activity may mediate the associations between psychosocial stressors and inflammatory processes (IL-6, IL-10, TNF-α). This study is in line with Fukuda's study and together provide argument in favor with associations of cortisol activity and inflammatory markers [93].

On the other hand, a link between stress-induced immune dysregulation and endothelial dysfunction is plausible. In fact, a study has found a positive relation between stress at work and increased perivascular inflammation (using CRP dosage) and endothelial dysfunction (as measured by IMT) [94].

Examining inter-relationship among cortisol, inflammatory markers, and endothelial function in a PSF context would be of a great interest to identify new biomarkers. In fact, based on the theoretical background, glucocorticoids may have proinflammatory effect in the endothelium, so it is hardly surprising that cortisol is linked to the inflammatory mechanisms and endothelial dysfunction [79,95-97].

Allostatic Load as a Biomarker of Cardiovascular Diseases Related to Psychosocial Stress

As we show above, stress is known to lead to adverse changes in multiple biological systems, including endocrine, metabolic, and immune systems, which may eventually cause cardiovascular diseases [98]. A large body of literature on stress and physiological functioning has focused on single biological markers such as cortisol and interleukin levels. However, emerging research on stress argue for the importance of simultaneously considering multiple processes rather than a single underling mechanism [99].

Allostatic Load (AL), is a multisystem indicator of physiological changes resulting from stress, which is computed using biological markers of multiple biological systems simultaneously [98]. The aim of AL is to summarize levels of physiological activity across range of regulatory systems related to stress response. The original formulation focused on different markers, including cardiovascular risk factors, HPA-axis activity, SNS activity, and biomarkers obtained from fasting blood [100]. Due to this multidimensionality, AL is thought to be a more comprehensive and sensitive measure of the effects of chronic stress on the body than any single biomarker [98,101]. In fact, even when the changes in each one of these systems are modest and not predictive of health outcomes, the cluster of changes across different multiple physiological systems present a health risk [102]. There is growing evidence that stress-related wear and tear of the body can be measured by the AL [103,104].

The traditional way of calculating an AL index has focused on the distribution of biomarkers within a given sample and then counting the number of dysregulated biomarkers for each individual [100]. AL index is constructed based on predefined cut-off values of many clinical biomarkers. Juster RP et al, used cortisol, Dehydroepiandrosterone-Sulphate (DHEA-S), CRP, fibrinogen, insulin, glycosylated haemoglobin, albumin, creatinine, pancreatic amylase, total cholesterol, high density lipoprotein cholesterol (HDL-cholesterol), and triglycerides. Systolic and diastolic blood pressure values based on three resting oscillometric recordings were included, in addition visceral obesity was assessed by waist-hip ratio. AL indices ranged from 0 to 15 [105].

Increased AL is associated with higher job demands in industrial workers in Germany, lower decision latitude and job strain in healthy Montreal workers, burnout, career instability, effort-reward imbalance and exhaustion [103-108]. It is worth noting that the study of Mauss D et al, published in 2016 replicates the former results published in 2015 in a large sample of German industrial employees using a short form AL. The revised form of AL included diastolic blood pressure, waist circumference, glycosylated hemoglobin, low-density lipoprotein, and heart rate variability. This short form of AL corroborated data obtained from the original one, which comprised 15 parameters. Based on these finding, AL index is a pertinent tool in the assessment of the cumulative burden exerted on the body through variation to adapt to life's strain [103,104,109,110].

Other studies found no effect of job strain on AL [111,112]. Number and type of biomarkers vary by study, and this may explain this difference.

Strengthen and Weaknesses of these Biomarkers

From the key papers of this review, the data about the psychosocial stress impact on cardiovascular diseases are reliable. The evaluations of these papers used rigorous methodology and then lead us to draw firm conclusions. This review highlights the potential of new biomarkers to reveal cardiovascular diseases occurrence and prognosis in a psychosocial context.

Although there has been much recent progress in identifying cardiovascular diseases risk biomarkers related to psychosocial stress context, the emergence of each new biomarker or group of biomarker raises questions of mechanistic relevance. In other words: (1) How much do these new markers worth? (2) Are the target molecules a biomarker, or are they related in a causal way to the disease pathogenesis? (3) Will the biomarkers help clinicians to improve patient outcomes? (4) How should clinicians incorporate these new biomarkers into clinical practice/standard care? (5) What is the overall improvement of diagnostic offered by these new biomarkers? (6) Several differences exist between women and men in the incidence, clinical course, outcome, and comorbidities, so more attention should be given to these differences in order to counteract these confounding factors [113,114]. (7) The potential role of genetics in these complex relationships is unknown. It is possible that individuals who have special variants of the polymorphisms associated with increased production of cortisol for example show worse immunological dysregulation when confronted to stressful events. (8) We should keep in mind that overall the most powerful indexes are based on a combination of data, including clinical, electrocardiographic, and biological measurements [115-120]. Finally, data replication in larger studies is necessary to reveal the concrete significance of these biomarkers in the development or prognosis of cardiovascular diseases [121-128].

Conclusion

Our study is mainly focused on the identification of new candidate biomarkers for cardiovascular diseases related to psychosocial stress. In this review we addressed literature data approving the link between cortisol, endothelial dysfunction, inflammation, and AL in the development and progression of these diseases. Here we choose to collect data from a wide range of cardiovascular diseases to have more information on the effect of psychosocial stress. We considered wide-ranging descriptions of stress from PSF that may influence a physical health outcome through a psychological mechanism.

Psychosocial stress is theoretically modifiable. It is currently the subject of increased attention through interventions based on stress reduction. There are many studies addressing the role of stress prevention in the cardiovascular disease development and progression in comparison with lifestyle risk factors and standard risk factors. Most behavioral interventions designed to attenuate the stress based on health educational program or music therapy and pharmacological tests, based on randomized controlled trials of anti-depressant treatment to reduce psychosocial stress in primary and secondary prevention of cardiovascular disease have not shown a real benefit. However, mind-body interventions such as Regular yoga practice and tai chi seem very promising in this field. Curiously, compelling evidence suggest that these practices have generally produced positive immune and endocrine changes and might be the main strategies to avoid negative effects of occupational stress.

Recent technological advances, including the signature emerging from multiple omics approaches (transcriptomics for example) could potentially capture the inherent biological state during psycoloical stress. The approach using data-driven from computational modeling, have raised the prospect of identifying the potential of new candidate biomarkers. Further assessment of these signatures regarding for example oxidative stress, inflammation, vascular smooth muscle cells proliferation, and thrombosis in diverse populations will be essential to make the underlying pathological process of cardiovascular diseases related to psychological factors context more comprehensively. We posit that this strategy may contribute to determining and deciphering the complex underlying process and merits further attention particularly when considering the impact of such cardiovascular disorders on public health.

Conflicts of Interest

None.

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Authors' Contributions

HA analyzed the literature and wrote the manuscript. MZ and HA read and approved the final manuscript.

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Competing Interests

The authors declare that they have no competing interests.

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