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State-of-the-Art Review

Psychosocial stress and cardiovascular disease

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ABSTRACT

Mahatma Gandhi once famously said: "poverty is the worst type of violence". He was referring to the state of political and social unrest that was pervading his nation, and the impact that humiliating defeat had on those who suffered in dire straits. Today, there is mounting evidence that social disparities cause intense psychosocial stress on those on whom they are imposed and can result in adverse cardiovascular outcomes. In modern society we still witness large disparities in living conditions between races, regions, continents and nations. Even in more privileged nations, we often witness the existence of "food and social deserts" in the middle of large urban centers. Sizable segments of the population are deprived of the comforts and privileges enjoyed by others; food quality and choices are limited, opportunities to exercise and play are scarce or unsafe, physical and verbal violence are prevalent, and racially driven conflicts are frequent. It has become apparent that these conditions predispose to the development of cardiovascular disease and affect its outcome negatively. Besides the increase in incidence of traditional risk factors, such as smoking, hypertension, insulin resistance and obesity, several other pathophysiological mechanisms involving the neuro-endocrine, inflammatory and immune pathways may be responsible for the noted negative outcomes. In this manuscript we review some of the evidence linking social distress with adverse cardiovascular outcomes and the potential subtending mechanisms and therapeutic interventions.

1. Introduction

The World Health Organization defines social determinants of health as "the circumstances in which people are born, grow, live, work, and age, and the systems put in place to deal with illness" [1]. Therefore, a combination of strictly interconnected conditions influences the health outcome of an individual, most of which are outside the control of an individual. More privileged segments of the population have greater access to financial and instrumental resources, and greater political influence. One of the most relevant social determinants of health is childhood development and care, that heavily influence long-term health outcomes of underprivileged individuals [2]. Education, employment and income are closely related and affect the health outcome of individuals through increased awareness of health issues and access to prevention and care. The Department of Housing and Urban Development in the United States of America conducted an experiment to investigate the impact of income and residential conditions on health [3] and offered 3 options to 4498 women from 5 US cities: a voucher to move to a low-poverty neighborhood, a voucher to move to any neighborhood or no change of residential status. At the end of 10 and 15 years of follow-up, there was a significantly lower prevalence of obesity and diabetes among the women who moved to a higher income neighborhood compared to those who stayed in their original neighborhoods. At the same time, moving to better neighborhoods improved the mental health of those who relocated [4]. The individual support provided by a partner in a married or de-facto couple, or by a network of people in a larger societal group, appears to also influence cardiovascular outcomes [5–8].

Therefore, it is apparent that the socioeconomic status and living conditions of an individual or an ethnic, cultural, racial group influence the health outcomes of that segment of the population. Whether this is solely due to the prevention and control of traditional risk factors, or to the additional impact of socio-economic-developmental factors on stress and long-term cardiovascular complications, is the focus of this review.

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2. Psychosocial stress as a result of social factors affecting living conditions

Stress can be defined as an individual's feeling of inability to cope with overwhelming environmental demands [9]. Socio-economic factors can contribute to promote stress, and health behaviors are often influenced by the socio-economic circumstances in which an individual lives. Some of the most important determinants of health are the education level attained by an individual, employment, income and health literacy. In a large study of several Western European countries and the United States, the education level of the population was uniformly inversely proportional to the probability of cardiovascular disease (CVD), [10] and the gap seems to be widening [11]. In the classic Whitehall study of British civil servants, the coronary artery disease mortality was higher as the job grade decreased, [12] and the trend persisted after a very long follow-up [13]. Similarly, unemployment and employment uncertainty have been linked with worse cardiovascular outcomes [14].

The effect of a stressful situation and the response to it, vary between individuals carrying different short- and long-term consequences. Stressful situations can be acute and short-lived, or accumulate over time and become chronic. Humans are naturally prepared to face stress and our coordinated stress response physiology enables the organism to counteract the stressor. However, chronic adverse exposures can induce maladaptive responses to stress and turn a natural defense mechanism into harmful responses for the cardiovascular system and the general health of the individual (see pathophysiology section below) [15]. Several factors may influence how stress is dealt with by an individual, such as timing, duration, intensity of the stressful event and the individual's susceptibility to its effects. Acute stress is sometimes defined as a stressful condition lasting up to one week in duration, while chronic stress is defined as an exposure lasting longer than 6 months [15].

A chronic exposure does not have to be continuous, but can be intermittent, without a defined starting and ending point. It can be actual (such as verbal, physical or sexual violence), or perceived and conducive to reactive states of anxiety, anger, depression or post-traumatic stress disorder (PTSD). Acute stress is not linked to the development of atherosclerotic CVD, but it can lead to deterioration of pre-existing conditions and precipitation of acute CVD events. An example is represented by stress cardiomyopathy (Takotsubo syndrome) that is the result of acute stressful events inducing a powerful sympathetic stimulation and coronary microvascular constriction, or acute spontaneous coronary artery dissection [16]. Both syndromes interestingly occur more frequently in women.

On the contrary, chronic stress has the potential to initiate a cascade of events that promote the development and progression of the atherosclerotic process [15,17]. The cumulative effect of stress on the physical and mental health of an individual is known as allostatic load. The load can be particularly damaging when it starts to accumulate in childhood, as the consequences of maladaptive responses to stress occur through their life-course. Indeed, socio-economic disadvantage in-utero is linked with the highest probability of long-term cardiovascular complications [18]. Children of malnourished, smoking or abused mothers tend to be born "small for gestational age" (low birth weight), and have been reported to suffer a higher rate of diabetes mellitus, hypertension and cardiovascular events [19]. In general, childhood adversity is associated with a high burden of risk factors for CVD, [20] and as a result, it has been linked with development of CVD later in life [21–24]. This is likely due to a combination of stress hormones release leading to dysmetabolism, enhanced inflammatory responses, endothelial dysfunction and vascular hyper-reactivity, all contributing to the increase in atherosclerotic vascular risk [25–27]. It should be noted that adverse childhood conditions (physical, mental and sexual abuse, poverty, poor living conditions, nutrition and health care), often result in negative behaviors later in life, with greater incidence of smoking, substance abuse, less physical activity and development of obesity among individuals exposed to childhood hardship [28–30]. As a result, the CVD morbidity of adults who grew in unfavorable circumstances during their childhood is expected to be higher than that of individuals with no stress during their early years of life [20]. While targeting unhealthy behaviors is important, it is not sufficient to reduce CVD risk, and addressing the socio-economic circumstances in which an individual lives may be very impactful. A place of residence that offers difficult access to medical care, limited recreational activities or poor food options, predisposes those who live within it to develop risk factors for CVD, [31] and suffer from cardiovascular events. Low neighborhood income was found by Kelli et al [32] to be a determinant of cardiovascular outcome in urban food deserts, defined as zones where food choices are scarce and food quality is low. Low-cost foods are often rich in carbohydrates and saturated fats that render them flavorful but high in calories, leading to obesity, insulin resistance and diabetes mellitus, while fruits and vegetables are more expensive and consumed at a lower rate in low income areas [33]. Additionally, low income area residents tend to be less psychically active, smoke more, seek healthcare less often and be less compliant with medical advice [34–36]. Topel et al [37] described a higher incidence of non-fatal myocardial infarction, and cardiovascular death both among patients with prior events and CVD naïve individuals living in these circumstances.

Ultimately, a neighborhood can influence the behavior of an individual through social support; if an individual feels part of a social network that gives her/him a sense of reciprocal care, and esteem, [38] that individual may be more prone to adhere to a set of rules that will improve the personal as well the network's health behavior. The contrary can be expected of individuals living in isolation, as often seen in the setting of lower-income communities. Among 32,624 health professionals the long-term incidence of stroke and cardiovascular death was double in individuals without the support of a social network compared to those with such a support [6]. Elderly patients post-myocardial infarction showed a 3-fold increased risk of mortality 6 months post-event in the absence of emotional support [8]. Adherence to medical advice and compliance with drug treatment are lower in neighborhoods with lower health literacy, [39] or those with low family and social support [40,41]. The racial mix of the neighborhood also influences the patient-provider relationship and trust, with a higher trust afforded to physicians of the same race than a different race [42].

2.1. *Race and social distress*

Racial disparities continue to persist across the world; according to the 2023 statistics of the American Heart Association, non-Hispanic Blacks continue to have the lowest health scores and continue to suffer the highest cardiovascular mortality in the United States compared to Hispanics and non-Hispanic Whites [43]. In spite of the decline in cardiovascular morbidity and mortality of the past 2 decades, the difference in outcome between people of Black race and other races remained essentially unchanged, and this is true even when comparing people of the same education level [44]. According to a recent analysis of the Atherosclerosis Risk in Communities (ARIC) study, people of Black race with low income, or with low education had higher odds of worsening cardiovascular health over time, compared to other races [45]. In a study of people living in the United States, Asian Americans (longest living) lived on average 14 years longer than people of Black race (shortest life span) [46]. Discrimination and bias, either open or implicit, are present not only in North America but in every nation across the world. Discrimination based on race, sex, faith, ethnicity, socio-economic status, political ideology or any other form of it, is psychologically profoundly harmful to those exposed to it, and has severe long-term health consequences. Gestational diabetes developed more frequently among 595 US pregnant women who perceived discrimination (based on race, sex, income level or social status, age, and physical appearance) than among those who did not [43]. Markers of subclinical atherosclerosis such as aortic calcification and increased

carotid intima-media thickness, were significantly more pronounced in black women than white women who experienced or perceived discrimination [47,48]. Heart rate and blood pressure increased significantly more during a laboratory mental stress among people who had experienced racist offenses than among those who did not [49]. Mental stress-induced myocardial ischemia (MSIMI), in a laboratory setting, is more frequently observed in patients with established CAD who perceived discrimination in daily life, than among non-discriminated individuals [50]. The association was stronger among black women. Black patients with known CVD have worse endothelial function and suffer more adverse outcomes associated with it than white patients [51]. Health professionals may unconsciously contribute to the problem. Older evidence suggested that health care professionals may be less inclined to resort to invasive procedures or prescribe medications for black women compared to white men [52,53]. The physician-patient interaction may be less cordial or be biased by stereotypes if it occurs between people of different races, especially if patients are of Black race [54,55]. The reliance on medical advice and compliance with therapies are greater if provided by a professional of the same race or ethnicity, especially in social networks with low education, health literacy and ambient support [42]. The epidemiological evidence is clear that individuals of Black race on average have a lower socio-economic status, suffer more social injustices and have a lower overall health status than non-Hispanic whites in North America [56]. Despite the improvements of the last few decades, we are still far from reaching a level of racial equality and fairness that will allow the attainment of better cardiovascular and health outcomes for all [57,58].

3. Pathophysiology of stress and cardiovascular disease

An international analysis of 11,119 patients with recent myocardial infarction revealed that as many as one third of the participants had been exposed to 2 or more life stressors in the months leading to the event [59]. A recent publication highlighted that a composite score taking into account various types of psychosocial stressors in patients with coronary heart disease, was predictive of cardiovascular death, non-fatal myocardial infarction or hospital admission for congestive heart failure during follow-up [60]. Despite the consistent association between psychosocial distress and adverse outcomes, the pathophysiology of this association remains somewhat elusive [15]. The prevailing hypothesis is that undue stress ignites a complex cascade of events involving the neuro-endocrine, immune and inflammatory systems leading to dysmetabolism and endothelial damage and eventually atherosclerosis inception and destabilization, as well as microvascular dysfunction (**Central illustration**).

3.1. Neurocardiac Axis

After the sensory cortex perceives a stressful stimulus, the limbic system, of which the hippocampus, pre-frontal cortex and the amygdala are a part, activates the hypothalamus, the pituitary gland and the sympathetic nervous system. The result is the release of large quantities of cortisol and catecholamines by the adrenal glands, an increase in heart rate and peripheral vascular constriction. Acutely, these changes may be sufficient to provoke angina based on powerful vasoconstriction and increased myocardial oxygen demand, [61] or destabilize a pre-existing atherosclerotic plaque precipitating an acute coronary syndrome. In the chronic setting, sympathetic stimuli induce the release of large amounts of inflammatory mediators and pro-inflammatory cells from the bone marrow, the spleen, ganglia and lymph nodes. The result is the promotion of a generalized state of inflammation, metabolic and vascular alterations, and pro-thrombotic conditions that collectively may lead to the development of insulin resistance, obesity, endothelial dysfunction and ultimately atherosclerotic CVD. It has been proposed that both excessive and blunted cardiovascular reactivity to mental stress are linked to adverse cardiovascular health, although it is not clear how blunted reactivity may be predisposing patients to worse health conditions [62,63]. A blunted response can be defined as an inability to raise heart rate and blood pressure sufficiently during an acute stress, and it could be the result of an exhaustion of the natural neural pathways in response to prolonged stress [64]. Blunted reactivity has also been linked with some cardiovascular risk factors such as diabetes mellitus, although the mechanism in this case may be bidirectional, since diabetes is known to be associated with deterioration of autonomic nervous system functions [65]. Finally, some evidence suggests that the intracardiac neural system may have a role in the development of long-term damage resulting from prolonged stress exposure [66].

3.2. Immune-inflammatory pathways

The presence of adrenergic receptors in the bone marrow, spleen, other lymphoid organs as well as immune cells themselves, [67] facilitates the release of chemokines, inflammatory cells and progenitor cells in response to sympathetic stimulation. Inflammatory chemokines are increased in patients exposed to stress, [68,69] and the importance of chronic inflammation cannot be overemphasized [70,71]. Children exposed to adverse social circumstances exhibit markers of enhanced inflammation decades after having been exposed to trauma [72]. However, there may be important differences between sexes in the inflammatory response to stress. Women with prior cardiovascular events tend to have a higher baseline level of interleukin-6 (IL6), and demonstrate a greater increase in IL-6 levels in response to a standardized mental stress in the laboratory [73]. Additionally, the propensity to respond with a heightened inflammatory response to stress appears to be linked with MACE in women but not in men [74]. These observations highlight the substantial differences between sexes in the neuro-endocrine-inflammatory-immune axes, [75,76] and the importance of considering such differences in the therapeutic planning stages [77]. Oxidative pathways along with lipid peroxidation are also increased in patients with stress and depression, [78] and drive the development of endothelial dysfunction [79].

Progenitors cells are released to repair the vascular endothelial lining in subjects with risk factors, [80] and appear to be released in large numbers in response to mental stress [81]. Their release is associated with high activity of the limbic brain areas responsible for emotional response to stress and fear, and these changes were associated with adverse cardiovascular events during follow-up [81]. Lower progenitor cell counts have been associated with increased probability of events in patients with established coronary artery disease [82–84].

These data highlight the importance of the involvement of the immune and inflammatory systems in the development of CVD in states of chronic stress. Ultimately, a combination of mechanisms similar to those leading to atherosclerosis in the general population with traditional risk factors, seems to be implicated in the development of atherosclerotic CVD and its complications in patients exposed to chronic stress. Maladaptive responses to persistent or intermittent long-term stressors will affect the inflammasome, metabolome, immune and vascular functions sufficiently to ignite a precipitation of noxious events.

4. Investigating stress as a source of cardiovascular risk

Despite the clear epidemiological evidence linking stress with CVD, objective and reproducible methods to assess the presence of stress in a person's life, and its impact on their cardiac health are currently not available. Quantifying perceived stress is particularly arduous, although its consequences can be severe. The stress inherent with perceived financial instability, for instance, has been linked with worse cardiovascular health indices in the Women's Health Study [85] and a higher risk of cardiovascular events in the general population [86]. Therefore, a full investigation of stress should involve the social setting of patients, their perception of stressful events, and the cognitive or emotional effect that stress had on them, such as the generation of anxiety, depression,

anger, or post-traumatic stress disorder (PTSD) [87]. Importantly, psychiatric disorders that can ensue from severe stress, such as depression and PTSD, have also been linked with adverse CV outcomes [88,89]. A fairly established measure of the effects of stress on the CV system is the assessment of heart rate variability (HRV), that provides an appraisal of the autonomic activity of an individual. Numerous studies have also employed ambulatory blood pressure monitoring trying to establish a link between change in blood pressure and heart rate and stressful events in a person's daily life [90,91]. A more objective, but time delimited assessment of the effects of stress on the cardiovascular system, can be obtained during controlled laboratory mental stress testing [92]. With this method, an individual patient is exposed to standardized mental stressors, such arithmetic tasks or recall of traumatic experiences, [93] and it appears to be most effective when it exposes an individual to a loss of control and a negative social evaluation [94].

In the laboratory setting it is possible to simultaneously administer a stress and measure the physiological responses to it, such as heart rate and blood pressure responses, peripheral vasoconstriction,[95] altered endothelial function, [96] increased arterial stiffness, [97] as well as a number of inflammatory, neuro-endocrine and immune-response biomarkers [98]. Additionally, myocardial ischemia can be induced by mental stress testing and can be measured with a functional stress test such a nuclear perfusion imaging, radionuclide angiography or stress echocardiography [99].

4.1. Vasomotor response to laboratory mental stress

The normal hemodynamic response to exercise includes an increase in heart rate and systolic blood pressure with a decrease in diastolic pressure and peripheral resistance. In contrast, the response to mental stress is an increase in peripheral resistance and diastolic blood pressure along with an increase in heart rate and systolic blood pressure. These responses can be measured after a mental stress test performed in a controlled laboratory setting, as described above. The occurrence of peripheral vasoconstriction can be evaluated by means of peripheral arterial tonometry (PAT) as the ratio of stress over rest blood volume, measured with a fingertip sensor. Men tend to have a more intense peripheral arterial vasoconstriction with mental stress testing than women, [100,101] although women tend to have more intense microvascular constriction [102].

There appears to be a correlation between coronary artery and peripheral vasomotor response to mental stress test, such that mental stress induces constriction in both territories [95]. A more intense peripheral vasoconstrictor response to mental stress is associated with adverse long-term CV events [103]. Similarly, a temporary decline in endothelial function, measured as a decline in flow-mediated vasodilation with mental stress compared to a test performed in non-stressful conditions, has also been associated with adverse cardiovascular events [104]. However, while peripheral microvascular vasoconstriction is an independent predictor of events for women but not men, endothelial dysfunction is a predictor for both sexes [105].

Of interest and relevant to the topic of this review, patients with prior CVD who develop peripheral vasoconstriction during stress, activate areas of the brain involved in emotional regulation, [106] and activation of the pre-frontal cortex during stress is associated with an adverse cardiovascular prognosis [107].

4.2. Mental stress induced myocardial ischemia (MSIMI)

Myocardial ischemia during mental stress occurs in about 15-20% of patients with established coronary artery disease. It occurs more often in women than men, typically at lower workloads (heart rate-blood pressure product) than during exercise and it is often asymptomatic, it can occur in patients with no ischemic changes during an exercise stress test and even in patients previously revascularized [108,109]. Peripheral vasoconstriction seems to be a predisposing factor to developing MSIMI, [98] and younger women are twice as likely as men to develop MSIMI [110,111].

There appear to be sex differences in the mechanisms subtending the development of MSIMI; for women stress-induced peripheral vasoconstriction seems to be the main driver, while for men an increase in heart rate and blood pressure seem to be more important [101]. Enhanced platelet aggregation has been reported in patients with MSIMI [112]. Along with the inflammatory, immune and oxidative responses highlighted below, this may justify the enhanced risk of atherosclerotic CVD events linked with MSIMI. In a recent publication, Vaccarino et al [113] showed that MSIMI is associated with a 2.5-fold increase in the composite endpoint of cardiovascular death and first or recurrent nonfatal myocardial infarction. Despite its utility to assess the response of an individual patient to acute stress, laboratory testing is inherently limited by its short duration and disassociation with the events of daily life, where stress can be intermittent or continuous, at times mild and others intense, and can be modified by social and environmental parameters.

4.3. Electrocardiographic response to mental stress

HRV, or the beat-to-beat variation in the R-R interval, can be measured in the low and high-frequency domain, as well as other less frequently employed domains. A low high-frequency HRV is an indication of vagal tone withdrawal. Since HRV can be measured with wearable devices, such as short and long-term Holter monitors, it can provide an indirect assessment of the autonomic reactivity to daily life stressors as reported by individual patients. Importantly, abnormal HRV has been linked with adverse outcomes [114]. The significance of the low-frequency HRV is less clear but could reflect changes induced by both branches of the autonomic nervous system. In a recent publication, Osei et al [115] showed that a low HRV in the high-frequency domain was associated with a higher probability of inducing MSIMI. This confirmed the close association between autonomic nervous system deregulation and coronary artery reactivity in patients exposed to stress. An abnormal HRV has been associated with untoward events both in the general population and patients with CAD, underlying the prognostic importance of abnormal HRV responses induced by stress [116,117].

However, several factors can affect its measurement other than psychological disturbances, and other electrocardiographic techniques have been introduced that may provide a more specific assessment of autonomic reactivity. These include deceleration capacity (or time to heart rate recovery), [118] T-wave amplitude, [119] and distribution entropy [120].

4.4. Brain imaging

The involvement and importance of the activation of the central nervous system during stress can be inferred from studies of brain metabolism and blood flow. In a seminal publication utilizing imaging with ^{18}fluoro-deoxy-glucose (FDG), Tawakol et al [121] demonstrated that activation of the amygdala is associated with avid tracer uptake in the bone marrow and vasculature and is predictive of future adverse cardiovascular events in individuals with no prior cardiovascular history. Moazzami et al[107] extended this observation by measuring brain blood flow with ^{15}oxygen water during a laboratory controlled mental stress test in patients with prior CVD. The authors found that activation of the rostro-medial prefrontal cortex during mental stress was associated with major adverse cardiovascular events in the ensuing 3 years, an effect that was partially explained by an increase in IL-6 expression and a decrease in high-frequency HRV.

5. Conclusions

A recent epidemiological analysis of people living in the United States between 2015-2019 showed that female sex, married status, race and college education ranked among the top four factors influencing the

chance of a longer lifespan [122]. This highlighted the importance of social factors in influencing health outcomes throughout life. Persisting and deepening gaps in social status, new and expanding wars, racial and religious conflicts, famine, air and noise pollution in the environment, dissemination of inflammatory news through social networks, continue to produce a heavy burden of stress for the entire world population. The American Heart Association affirmed that the most significant opportunities for reducing death and disability from CVD in the United States lie with addressing the social determinants of this highly prevalent and incident ailment [123]. The European guidelines on prevention of CVD consider psycho-social distress as a modifiable risk factor, and suggest that a detailed assessment of the psycho-social status of the individual is required for every patient with a prior event [124]. Since stress can be the root cause of the development of more traditional risk factors, such as hypertension, obesity, diabetes mellitus, and smoking it should be investigated as a promoter in patients with these risk factors. Despite the strong epidemiological and laboratory evidence of a link between brain, heart, and vessels little is known of the effect of psychological, pharmacological and behavioral interventions to mitigate stress on cardiovascular health. Meditation, yoga, and biofeedback have been proposed as possible approaches to lowering the risk associated with psycho-social stress [125,126]. Exercise seems to improve cardiovascular outcomes in part through modulation of the neural-cardiac pathways described above [127]. There is an opportunity to improve patients' outcomes in secondary prevention through cardiac rehabilitation and the promotion of healthy behaviors beyond physical exercise [128–130]. Much remains to be done in terms of screening, diagnosis and therapy of the effects of stress on the cardiovascular system, but without a more equitable and stable psycho-social status all efforts may be futile. Without impactful policy changes at the societal level, the goal of a more equitable environment will not be reached [131,132]. Universal education, gainful employment and health care are the life essential needs that will potentially afford everyone a place at the table. Ignorance, poverty and emotional defeat can only promote stress and downstream untoward health effects.

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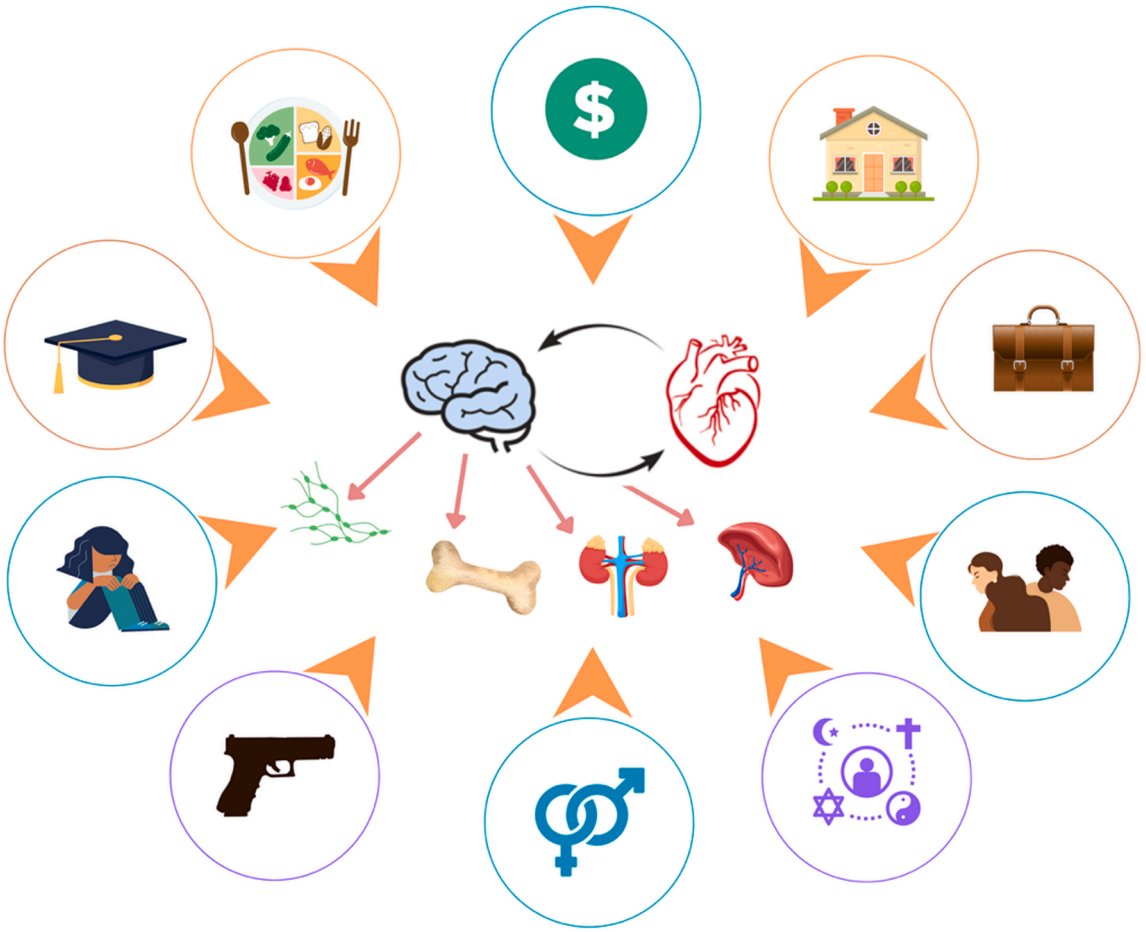

CENTRAL ILLUSTRATION LEGEND

Several social factors induce stress and stimulate a response from the central nervous system via the prefrontal cortex and limbic system. Signals through the autonomic nervous system are sent to the heart, with a bidirectional communication between heart and central nervous system, and to the adrenal glands, the bone marrow, spleen, lymph nodes and ganglia. In the acute phase these mechanisms result into increase heart rate and blood pressure, and vasoconstriction, along with a state of generalized inflammation, enhanced platelets adhesion, immune activation, and metabolic derangements. In the chronic phase these changes are responsible for the development of atherosclerotic cardiovascular disease. From the top and moving clockwise are some of the most relevant social determinants of health: income, housing and neighborhood, employment, racial, religious and gender discrimination, violence (physical, verbal, sexual etc), childhood adversity, education and food insecurity.

CRediT authorship contribution statement

Paolo Raggi: Writing – review & editing, Writing – original draft, Supervision, Software, Data curation, Conceptualization. **Arshed A. Quyyumi:** Writing – review & editing, Writing – original draft, Conceptualization. **Michael Y. Henein:** Writing – review & editing, Writing – original draft. **Viola Vaccarino:** Writing – review & editing, Writing – original draft, Methodology, Funding acquisition, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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