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The Role of Psychosocial Stress on Cardiovascular Disease in Women:

JACC State-of-the-Art Review

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Abstract

Psychosocial stress can affect cardiovascular health through multiple pathways. Certain stressors, such as socioeconomic disadvantage, childhood adversity, intimate partner violence, and caregiving stress, are especially common among women. The consequences of stress begin at a young age and persist throughout the life course. This is especially true for women, among whom the burden of negative psychosocial experiences tends to be larger in young age and midlife. Menarche, pregnancy, and menopause can further exacerbate stress in vulnerable women. Not only is psychosocial adversity prevalent in women, but it could have more pronounced consequences for cardiovascular risk among women than among men. These differential effects could reside in sex differences in responses to stress, combined with women's propensity toward vasomotor reactivity, microvascular dysfunction, and inflammation. The bulk of evidence suggests that targeting stress could be an important strategy for cardiovascular risk reduction in women.

Keywords

cardiovascular disease; coronary heart disease; mental stress; psychosocial stress; women

Despite advances in its treatment and prevention, cardiovascular disease (CVD) remains the leading cause of death in women.[1] Although the age-adjusted death rate for CVD in the United States decreased from 1980 to 2010, there has been an upward trend in recent years.[1–3] Young and midlife women have shown worse trends than other groups for both incidence and case-fatality of coronary heart disease (CHD).[4,5] Compared with men, younger women continue to have worse morbidity, mortality, and quality of life after an acute myocardial infarction (MI), a difference that is not explained by traditional risk factors, comorbidities, disease severity, or treatment.[6]

Broadly speaking, stress is conceptualized as the perception of environmental demands that exceed an individual's ability to adapt to a certain situation.[7] Stress is ubiquitous in our society, but its timing and duration, as well as individual susceptibility and physiologic responses, are implicated in its subsequent impact on health and disease.[8] Evidence has consistently linked stressful exposures, and mental health conditions that are consequent to traumatic stress, such as mood and anxiety disorders and posttraumatic stress disorders (PTSDs), to adverse CVD outcomes in both healthy individuals and those with preexisting CVD.[9–11]

Women face unique propensity toward the cardiovascular consequences of psychosocial stress. Women have a distinctive burden of psychosocial adversities, especially at young ages and in midlife,[12–14] as well as stress-related mood and anxiety disorders.[14] Not only do women have a higher prevalence of these conditions than do men, but they are also more susceptible to adverse cardiovascular sequelae from these exposures.[12,14] To highlight such vulnerability, myocardial ischemia provoked by acute mental stress is 2-fold more common in women, especially among young and middle-aged women, than in men.[15,16]

Other cardiovascular conditions linked to intense stress, such as spontaneous coronary artery dissection (SCAD) and stress-induced cardiomyopathy, are overwhelmingly more common in women than in men.[17,18]

Women's cardiovascular vulnerability to psychosocial stress could reside in sex differences in responses to stress, from its perception to its behavioral, cognitive, affective, and biological sequelae.[19] It could also result from women's propensity toward vasomotor reactivity, microvascular dysfunction, and inflammation, which are all areas affected by stress.[20] Targeting stress, therefore, could be an important strategy for CVD reduction among women. The goal of this review is to provide a focused overview of the role of psychosocial stress on CVD in women, from unique exposure characteristics to underlying mechanisms, and its impact on clinical disease and outcomes. We cover the impacts of race/ethnicity and reproductive milestones, such as menarche, pregnancy, and menopause. We also discuss the prevention, management, and screening strategies for psychosocial stress in women. In this review, we refer to "gender" when social roles are implied and use the term "sex" when referring to biology. We use "women" and "men" when referring to adult humans and "females" and "males" when discussing animal research. "Female" and "male" are also used as adjectives when appropriate.

PSYCHOSOCIAL STRESS IN WOMEN

Stress is inherently complex because it is experienced at multiple levels—social, psychologic, and biological—and at each level, there are many definitions and assessment methods.[21,22] Furthermore, stressful events can precede common psychiatric conditions, including depression, anxiety, and PTSD, with symptoms of these conditions occasionally serving as proxies for measuring stress.[21] A distinction is often made between acute and chronic stress. Acute stressors are short-term stress-inducing events (shorter than 1 week).[23] Because of their high intensity, they can trigger cardiovascular events in individuals at high risk, such as those with underlying coronary atherosclerosis.[21] Chronic stressors on the other hand, are negative experiences that can persist over an extended period, such as months or years, and can be continuous or recurring. Because of their persistent and cumulative nature, chronic stressors are thought to facilitate the development and progression of diseases, including CVD.[8]

The distinction between acute and chronic stressors is not absolute.[23] The repetition of acute stressors can lead to cumulative chronic effects, and stressful experiences, whether acute or chronic, but especially if traumatic and with onset in early life, can have enduring consequences and result in biological maladaptation affecting the risk of CVD or disease progression[14,24] (Figure 1). For women, the burden of negative psychosocial experiences tends to be greater in young age and midlife, as many stressful experiences occur during this time period, including childhood abuse and other early life adversities,[13] intimate partner violence,[25,26] caregiving burden,[27–29] and socioeconomic disadvantage.[30,31] Furthermore, menarche, pregnancy, and menopause can exacerbate stress.

Part of the link between stressful exposures, either acute or chronic, and CVD risk may involve psychiatric conditions associated with stress and trauma, such as PTSDs, depression,

and anxiety disorders. Not only do women face a higher prevalence of these conditions compared with men, unlike psychiatric conditions unrelated to trauma,[14] but they also may have heightened susceptibility toward the risk of cardiometabolic outcomes such as CHD and diabetes mellitus from these disorders.[14,32] For example, depression is a more powerful predictor of major adverse cardiovascular outcomes such as death, hospitalization for MI, or new coronary revascularization procedures in women than in men, especially at a younger age.[33] Specific sources of stress that are especially prevalent in women are summarized below.

SOCIOECONOMIC DISADVANTAGE.

Financial adversity and limited access to education and employment opportunities are associated with an adverse psychosocial status.[34] Substantial evidence has documented associations between socioeconomic disadvantage and poor cardiovascular health outcomes,[30] and women may be more affected because they are overrepresented among low-income earners and underrepresented among higher-income earners.[35] In addition, some studies have shown stronger associations of low socioeconomic status with CHD and CVD in women compared with men.[31] Among midlife women, financial strain, low education, and, to a lesser extent, low income over 12 years, were associated with subclinical CVD assessed according to carotid intima media thickness and carotid plaque.[36] The associations persisted after controlling for standard CVD risk factors.[36] Differences in access to quality care,[37] neighborhood environments,[38] and behavioral factors, such as poor diet quality and a sedentary lifestyle,[35] account for a large part of the association between low socioeconomic status and CVD.

CHILDHOOD ADVERSITY.

Also, referred to as early life stress or trauma, childhood adversity is defined as perceived threats to the safety or security of bodily integrity, family, or social structure of a child.[13] These exposures have long been linked to adverse cardiometabolic outcomes[13] and are more common in girls than in boys, especially sexual abuse.[39] Little is known, however, whether the association of early adversity with CVD differs by sex or gender. In a study of young and middle-aged individuals from the general population, early life stress was a more powerful predictor of incident CVD in women than in men.[40] Regardless of the presence or absence of sex or gender differences in the association with CVD, childhood adversity remains a robust risk factor among women. In the Nurses' Health Study II, women who had experienced severe physical or sexual abuse had approximately 50% higher risk of CVD events after adjusting for demographic and family factors.[41] The association was largely explained by CVD risk factors arising after childhood. Other studies have supported the mediating effect of health behaviors.[42] However, while health behaviors and CVD risk factors clearly play a role, these exposures are thought to cause enduring changes in the nervous, endocrine, and immune regulatory systems that may affect the risk of chronic conditions in adult life, through the process of "biological embedding."[13,43]

INTIMATE PARTNER VIOLENCE.

Usually defined as physical, sexual, and psychosocial abuse perpetrated by a spouse or partner, intimate partner violence affects 25% of ever-partnered or ever-married women aged

15 to 49 years in the United States at some point in their lifetime.[44] This exposure has been linked to greater prevalence of CVD risk factors and adverse lifestyle behaviors among women.[26] In a cohort of 18,547 women from a primary care registry in the United Kingdom, exposure to domestic violence was associated with 29% to 51% increased risk of CHD, stroke/transient ischemic attack, diabetes mellitus, and all-cause mortality.[45] Limited data suggest that the type of intimate partner violence may affect CVD risk. Emotional abuse by an intimate partner has shown stronger associations with the development of hypertension than has sexual or physical violence.[25] Sexual trauma during military service, which occurs in 38% of women compared with only 4% of men, is associated with a 20% greater risk of hypertension in women compared with only 6% greater risk in men.[46]

MARITAL STRESS.

Being married or living with a partner is an aspect of one's social support system that has been related to a lower risk of CVD and total mortality in population studies.[47,48] Conversely, divorce and marital stress have been related to excess CVD risk.[48,49] The link between marital stress or quality and cardiovascular risk appears stronger among women than men.[50] Among female patients with CHD, marital stress was associated with 2.9-fold increased risk of recurrent coronary events.[51] Among young and middle-aged survivors of an MI, severe marital stress was associated with more angina, poor quality of life and all-cause hospital readmissions in both sexes.[52] Although the literature is not entirely consistent and there is a potential for reverse causation, the marital relationship is an important dimension as a potential source of stress that may affect women's cardiovascular health.

CAREGIVING STRESS.

Women are estimated to represent >80% of caregivers worldwide, and caregiving burden has been linked to increased stress among female caregivers.[27] The burden of unpaid spousal caregiving service has been associated with an increased risk of CVD in both women and men,[28,53] but among women, caring for a disabled spouse may have enhanced risk compared with caring for people other than a spouse.[29] The relationship between prolonged spousal caregiving and CVD varies by race, demonstrating a harmful effect among Whites and a possible protective effect among non-Whites.[53] Furthermore, the adverse effects of caregiving may especially relate to those who report strain or have additional sources of stress.

IMPACT OF REPRODUCTIVE MILESTONES: MENARCHE, PREGNANCY, AND MENOPAUSE

Menarche, pregnancy, and menopause, within the context of psychosocial factors, are important considerations for future CVD among women.

MENARCHE.

Although the data are controversial, childhood adversity and family dysfunction have been linked with early menarche, and greater parent-child warmth and family cohesion with

later pubertal development.[54] Early life stressors associated with early menarche include family conflict, parental divorce, sexual abuse, paternal absence, and presence of a stepfather during or shortly before the menarche age.[55] Early menarche is associated with worse cardiovascular health among women.[56] However, the relationship between menarche age and CVD may be U-shaped as both early age (<12 years) and late age (>17 years) at menarche are associated with CVD risk.[57] The increase in CVD risk associated with early menarche is at least partly explained by excess adiposity, which could potentially be an important focus for primary prevention among women with early menarche.[56]

PREGNANCY.

Maternal psychosocial stress of many sources and pregnancy-specific stress predispose to poor cardiovascular health during pregnancy.[58] Stress has been associated with virtually all pregnancy complications, such as preterm labor, low-birth-weight babies, and pregnancy-induced hypertension, which in turn have been linked to maternal morbidity and mortality and CVD in later life.[59] Maternal stress can increase the risk of adverse pregnancy outcomes by disrupting adaptations in the immune, endocrine, and nervous systems that support healthy pregnancy, and has long-term consequences on behavioral, physiologic, and immunologic functioning of the offspring throughout his or her life.[60] Consequently, the American College of Gynecology recommends screening for psychosocial risk factors at least once during each trimester for women seeking pregnancy assessments, regardless of social status, educational level, or race/ethnicity, and appropriately managing psychosocial stressors as part of routine pregnancy care.[61] Management of psychosocial stress during pregnancy involves stress management education (which includes providing information on available resources and making suggestions for useful changes) and providing referrals to specialized services when needed.[61]

MENOPAUSE.

The menopause transition is characterized by biological, hormonal, social, and psychologic changes that make women vulnerable to psychologic distress.[62,63] Perceived stress, anxiety, and depression are all related to worse menopause symptoms as assessed with the Menopause Rating Scale and worse physical health after menopause as assessed with the Short-Form Health Survey.[62,64] Early life adversities, such as socioeconomic difficulties, early parental divorce (before 5 years of age), paternal absence (from 6 to 11 years of age), and sexual abuse, as well as lower literacy and occupational status in adulthood, are associated with an earlier age of natural menopause.[65] Early onset of menopause (before 40 years of age), either natural or surgical, has been linked with an increased risk of CVD,[66] which may be partly mediated by vasomotor symptoms and autonomic dysfunction, processes that are influenced by stress.[64] However, a recent mendelian randomization study cast doubt that the association of early menopausal age and CVD is causal.[56] Nonetheless, the bulk of evidence suggests that attention to both mental and cardiovascular health should be a priority for postmenopausal women.

IMPACT OF RACE AND ETHNICITY: BLACK WOMEN AND HISPANIC WOMEN

For underrepresented ethnic communities and other groups from disadvantaged backgrounds, such as some immigrant populations, the social context in daily life (residential segregation, discrimination, unhealthy environments, financial strain, and poor access to resources) is tightly interconnected with psychosocial stress and may explain why marginalized groups have higher levels of stress and mental health symptoms than nonmarginalized White individuals.[67]

BLACK WOMEN.

Black women in the United States continue to face startling health disparities compared with White women, including higher rates of CVD, hypertension, and obesity and lower life expectancy.[68,69] For Black women, psychosocial stress is embodied in the concept of gendered racism, a hybrid phenomenon that includes discrimination, harassment, prejudice, and blended race and gender stereotyping.[68] The socioeconomic disadvantage that Black women may face limits their access to empowering resources to counter their dually marginalized social identity,[70] thereby promoting maladaptive coping. The superwoman schema, or strong Black woman identity, is an example of maladaptive coping that represents a tendency to be resilient despite social adversity.[68] Among young and middle-aged Black women, discrimination and negative life events have been associated with cardiometabolic risk factors and subclinical and clinical CVD.[71–73] These increased risks extend to Black women with CHD. In the post-MI population, those who report discrimination are more likely to develop myocardial ischemia with mental stress, an association that is more prominent among Black women.[74] Stress and maladaptive coping may affect the Black woman's perception of risk, engagement in preventive behaviors, and adoption of self-care activities.

HISPANIC WOMEN.

Hispanics/Latinos in the United States represent a heterogeneous group regarding CVD prevalence, culture, and genetic composition, differing based on the country of origin.[75] Generally, psychosocial stress is associated with greater prevalence of CVD risk factors (hypertension, diabetes, and smoking) in Hispanic populations.[76] Hispanic women report more psychosocial difficulties than Hispanic men, and among Hispanic women but not men, greater psychosocial distress is related to obesity.[77] Perceived psychosocial stress is also greater among midlife Hispanic women than among non-Hispanic White women, but there are variations according to the country of origin and degree of acculturation.[78] The psychosocial burden is greatest among Puerto Rican women, who report higher levels of depression and anxiety than other Hispanic women.[78] Among Hispanic immigrant women, acculturating to the more individualistic U.S. culture has adverse psychologic sequelae, often referred to as "acculturation stress.[79] Discrimination is another important source of psychosocial stress in Hispanic individuals. However, Hispanic/Latino immigrants, both men and women, have lower self-reported CVD prevalence than U.S.-born Hispanics.[75] Psychosocial factors such as strong social/familial ties are hypothesized to play a role,

but more research is needed.[75] Paradoxically, Hispanic immigrants, regardless of their country of origin, have higher CVD mortality than U.S.-born Hispanics, possibly owing to suboptimal management of risk factors and delays in seeking cardiovascular care.[75]

PATHOPHYSIOLOGICAL MECHANISMS THAT LINK PSYCHOSOCIAL STRESS WITH CVD IN WOMEN

The Central Illustration summarizes the predominant biological and behavioral pathways through which maladaptive stress responses can lead to CVD in women.

BIOLOGICAL PATHWAYS.

Biological effects of psychosocial stress that are implicated in cardiovascular sequelae among women include dysregulation of the neuroendocrine axis and autonomic nervous system, and their effects on immune function, inflammation, and vascular function (Figure 2).

Neurobiology.

Physiologic responses to stress are regulated by the medial prefrontal cortex, amygdala, and hippocampal areas of the brain. These areas have downstream connections affecting 2 main neuroendocrine stress response systems that work in concert: the hypothalamic-pituitary-adrenal (HPA) axis, with release of cortisol from the adrenal cortex, and the sympathetic-adrenal-medullary system, with release of noradrenaline from peripheral nerves and adrenaline from the adrenal medulla.[80] When stressors become recurrent or chronic, or after traumatic exposures, repeated activation of these systems can lead to alterations of normal physiology, including immune function, blood pressure, vascular function, visceral fat deposition, coagulation, and metabolic effects.[7,81] The HPA axis is also regulated by gonadal hormones, which contribute to sex differences in stress responsitivity.[82] In turn, the sympathetic nervous system, together with the hypothalamus and pituitary gland, are implicated in the regulation of ovarian function through the hypothalamic-pituitary-gonadal axis.[83,84] Ovarian function also is sensitive to psychosocial stress, and this may have implication for the development of CHD in women.[83] The HPA and hypothalamic-pituitary-gonadal axes counterregulate each other and work synergistically to regulate the environmental, reproductive, and genetic responses to stress.[82]

Sex dimorphism in stress-related neurobiologic pathways have been demonstrated at multiple levels. Women (before menopause) have a higher parasympathetic and lower sympathetic tone than men, but are more susceptible to the detrimental effects of sympathetic hyperactivity.[85] However, it is not only exaggerated responses to stress, but also diminished responses that have garnered recognition as indicators of dysregulation.[86] The ultimate adverse consequences of stress on the cardiovascular system are multifactorial and include cardiac electrical instability, myocardial ischemia, microvascular dysfunction, atherosclerotic plaque disruption, and thrombus formation, which are implicated in arrhythmias, MI, cardiomyopathy and stroke.[21]

Whether and how strongly an event is perceived as stressful can drive the stress-response biology. Studies have reported that women generally have a higher perception of stress than men.[19] However, the results are mixed and may be task specific or cycle dependent in young women. Whereas normal men show greater cortisol responses to achievement challenges, women manifest increased cortisol responses to social rejection.[87] Because women tend to experience more daily psychosocial stressors than men, they could have more long-term adverse consequences of HPA activation.

Immune function and inflammation.

It has long been documented that acute mental stress results in an inflammatory cytokine surge through sympathetic nervous system activation.[88] The HPA axis also modulates immune system responses through the glucocorticoid receptor.[89] From an evolutionary standpoint, the stimulation of innate and acquired immunity during acute stress should increase the chances of survival in the face of potentially harmful exposures. However, chronic activation of the immune system from persistent stress can predispose to cardiometabolic diseases.[24] Children who endured early life adversities show higher inflammation 20 years later, even after accounting for other childhood exposures and health behaviors.[43] These findings are especially relevant for women, who have a higher prevalence of these exposures.[90,91] Stress-related mental disorders including depression and PTSD, which are more prevalent among women, have also been associated with higher levels of inflammatory biomarkers and evidence of immune dysregulation.[92,93] Women have a more pronounced inflammatory response to acute mental stress than men of similar age and CHD status, particularly interleukin-6.[94,95] Furthermore, women manifest decreased glucocorticoid sensitivity after an acute stressor compared with men, leading to more protracted inflammation,[96] and heightened platelet aggregation both at rest and with mental stress.[97] These responses can contribute to the risk of subsequent CVD events. Indeed, among individuals with CHD, an increased inflammatory response to stress was associated with an elevated risk of adverse cardiovascular outcomes among women, but not among men.[98] Thus, the sexual dimorphism in the inflammatory response to stress may help explain the pathophysiology and prognosis of CHD in women.

Vascular function.

Women with CHD manifest more pronounced peripheral microvascular vasoconstriction both at rest and after mental stress than do men,[99] a response that is related to vascular dysfunction at the coronary level.[100] Stress-induced abnormal vasomotion can impair microvascular flow owing to failure of the small coronary arteries to dilate and increased afterload from an elevated systemic vascular resistance.[101,102] Women with ischemia and nonobstructive coronary artery disease (INOCA) exhibit enhanced peripheral vasoconstriction with mental stress.[100] Coronary microvascular dysfunction in women likely contributes to mental stress–induced myocardial ischemia (MSIMI),[102,103] and is also a feature of stress-induced cardiomyopathy,[17] which is typically triggered by strong emotions.[104] Notably, similarly to inflammation,[98] microvascular changes with mental stress have been linked to adverse cardiac events in women but not in men.[99] In contrast to microvascular function, young premenopausal women have similar or better macrovascular

function (brachial artery endothelial function and arterial stiffness) compared with men, with no sex differences in response to stress.[99,105]

BEHAVIORAL PATHWAYS.

Psychologic well-being has been linked with cardiovascular health–related behaviors identified by the American Heart Association's "Life's Essential 8," including smoking, excess adiposity, diet, physical activity,[106] and sleep.[107]

Smoking.

Psychosocial stress is associated with an increased desire to smoke, higher smoking rates, and nicotine dependence.[108] High levels of stress are also associated with greater odds of continued smoking and a lower ability to quit.[109] Women are more likely to smoke as a coping strategy for stress than men, have more difficulty quitting smoking, and are more likely to relapse after quitting, possibly owing to a higher level of withdrawal symptoms.[110] Smoking is a major risk factor for CVD and is more hazardous for women than for men,[111] especially at young ages.[112] Smoking also has an antiestrogenic effect, which adversely affects the lipid profile of women.[111]

Excess adiposity and dietary behavior.

Exposure to social stressors during early childhood (1–3 years of age) is associated with an increased risk of excess adiposity at 5 years of age in female but not in male children.[113] Emotional eating, the tendency to eat in response to emotions, is one of the mechanisms through which stress and depression leads to excess adiposity in both men and women.[114] Emotional eating is more prevalent in women, who are more likely than men to experience eating disorders.[115] Among women, daily stressors are especially implicated in this behavior.[116] Other stress-coping eating patterns, such as binge eating, commonly start at an earlier age in women than men.[117]

Physical inactivity.

Sedentary behavior disproportionately affects women, with only 20% of adult women (vs 28% of adult men) meeting the physical activity guidelines established by the U.S. Department of Health and Human services.[118] Stress is inversely related with physical activity in both men and women, but reverse causation is also possible, as some individuals use exercise to cope with stress.[119] Active women exercise more when stressed, whereas those who rarely exercise tend to become less active.[119] Leisure-time physical activity is associated with a reduced risk of CVD and all-cause mortality,[111] and women derive greater benefits than men from physical activity.[120] Even daily walking, is protective in a dose-dependent fashion, whereas sedentary behavior is associated with elevated CVD risk.[121] Exercise improves cardiorespiratory fitness[122] and has cardioprotective effects for both primary and secondary CVD prevention in both sexes. Furthermore, it improves autonomic nervous function by increasing resting vagal tone and heart rate variability, and has the additional benefit of alleviating stress and anxiety through endorphin release.[122]

Sleep disturbances.

Women are at high risk of experiencing poor sleep quality and insomnia[123] during pregnancy and postpartum,[124] across the menopause transition, and in the postmenopausal period.[125] Women are more likely than men to experience sleep disturbances after traumatic stress exposures.[126] Caregiving, a role predominantly undertaken by women, is associated with sleep disturbances, and female caregivers report worse sleep-related problems than male caregivers.[127] Any divergence from the recommended 7 to 8 hours of sleep, poor sleep quality,[128] and sleep-disordered breathing[129] are associated with a higher risk of mortality and cardiovascular events in adults. Insomnia, when persistent or occurring with short sleep, has been associated with a higher CVD risk in women.[123] Sleep-disordered breathing is also more common among individuals with mental health disorders.[130] Thus it is possible that sleep affects CVD risk in women, but more data are needed.

SPECIFIC CARDIOVASCULAR CONDITIONS

Cardiovascular disorders that are intricately linked to stress are presented in Table 1. MSIMI, stress-induced cardiomyopathy, and SCAD are discussed below.

STRESS-INDUCED ISCHEMIA.

In approximately 1 in 6 patients with clinically stable CHD, acute mental stress in the laboratory can trigger myocardial ischemia detectable with the use of myocardial perfusion imaging. Compared with ischemia provoked by a conventional stress test, such as exercise or pharmacologic stress, MSIMI is usually silent, occurs at a lower hemodynamic workload, and can manifest even after successful revascularization.[131,132] MSIMI is associated with a 2-fold increased risk of adverse cardiovascular events that is independent from conventional stress ischemia and other standard risk indicators.[133] Acute hemodynamic, vascular, and platelet reactivity to mental stress has been associated with MSIMI, along with inflammation, metabolic risk factors, and psychologic distress.[131,134–138]

Women, especially younger women, are more likely to develop MSIMI than are men of similar age.[15,16] For women, microvascular reactivity has a more pronounced role in MSIMI,[16,103,135] whereas obstructive coronary disease and increases in blood pressure and heart rate have a larger role in men.[132,135] Furthermore, women with MSIMI, but not men, are more likely to report angina in everyday life than their counterparts without MSIMI, even though MSIMI is usually silent in the laboratory.[139] Some of these features are reminiscent of the INOCA syndrome. Like MSIMI, INOCA is more common in women and is related to psychosocial stress, daily angina and microvascular disease.[139,140] Moreover, women with INOCA have more microvascular vasoconstriction in response to mental stress than do asymptomatic women without INOCA.[100] Thus, at least among women, MSIMI and INOCA could be manifestations of the same phenomenon.

STRESS-INDUCED CARDIOMYOPATHY.

Stress-induced (takotsubo) cardiomyopathy, or apical ballooning syndrome, is an acute reversible dysfunction of the left ventricle that commonly occurs after an episode of intense emotional or physical stress in the preceding 1 to 5 days.[17,141] It is characterized by the

presence of apical hypokinesis, akinesis, or dyskinesis co-existing with basal hyperkinesis in the absence of epicardial coronary artery disease.[17] It occurs mostly among postmenopausal women.[142] Chronic stressors, pre-existing mental disorders, and exposure to trauma are important risk factors for this condition.[142]

A common theory for the etiology of this condition is myocardial stunning by supraphysiologic levels of plasma catecholamines, which is supported by histopathologic findings of catecholamine toxicity.[142] More recent hypotheses implicate altered microvascular perfusion, myocardial inflammation, and electrophysiologic derangements secondary to intense sympathetic activation as contributory mechanisms.[17] The increased prevalence of stress-induced cardiomyopathy after menopause has been linked to estrogen depletion, which causes alterations in the autonomic nervous system, including an increase in the expression of beta-adrenergic receptors on cardiac cells, augmented sympathetic drive, and endothelial dysfunction.[17] Neuroimaging testing has shown structural and functional changes in the corticolimbic system, a brain area that regulates emotions, the autonomic nervous system, and cardiovascular response to stress.[143,144]

Spontaneous coronary artery dissection.

SCAD is a significant cause of MI and sudden death among young adults with few traditional CVD risk factors, especially women (mostly perimenopausal), who represent 90% of SCAD cases.[145] SCAD is an epicardial coronary artery dissection that is not iatrogenic or associated with atherosclerosis or trauma[18] and causes coronary artery luminal obstruction owing to an intramural hematoma or intimal disruption.[18] SCAD accounts for approximately 35% of acute coronary syndromes in women younger than 50 years[146] and is the most common cause of MI during pregnancy and postpartum.[18] Psychosocial stress can play a role, because SCAD is commonly triggered by intense emotional stress.[147,148] Survivors of SCAD have significant rates of PTSD, depression, and anxiety[146] and are at increased risk of recurrent SCAD and cardiovascular events.[148] Recurrence is possible on re-exposure to the emotionally stressful conditions that occur with pregnancy.[18]

SCREENING FOR PSYCHOSOCIAL STRESS AMONG WOMEN FOR CVD PREVENTION

Preventive health care has a crucial role in improving women’s health through the delivery of services that promote psychologic well-being and behavioral health.[149] Although there has been growing attention to the importance of the psychosocial sphere in cardiovascular health,[150] there is a reluctance to incorporate psychosocial aspects into guideline recommendations.[151] Part of this hesitation may derive from inconclusive data on the beneficial effect of interventions targeting psychosocial stress on CVD outcomes.[152] In addition, stress is a complex multi-dimensional construct that is challenging to assess. Although several short questionnaires for psychologic distress, such as scales of perceived stress, anxiety, and depression, used alone or in combination, are predictive of cardiovascular events,[153,154] there is lack of agreement on the best practices for screening implementation, and there is little data specific for women.[150] A composite measure of psychologic distress was recently shown to significantly improve risk prediction in patients

with CHD beyond traditional risk indicators, suggesting its potential for translation to the clinical setting.[154] On the other hand, advanced imaging protocols that identify biological responses to stress are currently limited to the research domain, and their clinical utility is uncertain.[8,81] While robust clinical trials are needed on the utility of screening modalities and optimal clinical decision support systems for psychosocial stress among women, current evidence supports recognizing psychosocial factors in the clinical care of women, and alleviating such factors remain a priority in patient-centered cardiovascular care.[81]

MANAGEMENT OF PSYCHOSOCIAL STRESS IN WOMEN

The ideal framework for improving psychosocial well-being should promote recognition of a patient's needs, adjust care to personal circumstances, and connect patients to appropriate community resources.[155] Interventions that can be used to mitigate psychosocial stress in women are presented in Table 2.

INDIVIDUAL-LEVEL INTERVENTIONS.

Stress management and behavioral interventions such as mindfulness,[156] biofeedback,[157] and collaborative care approaches that incorporate psychologic care[158] can be delivered at the individual level. Although trials on behavioral interventions that have targeted stress were typically small with few data specific to women, benefits have been shown for psychologic endpoints, such as reduction of perceived stress and reinforcement of positive psychologic constructs and healthy behaviors. However, the benefits on clinical endpoints have not been firmly established.[150] Stress management programs can be used in conjunction with established recovery programs, such as cardiac rehabilitation, to promote relaxation and improve stress-coping skills,[150] and should capitalize on established models of integrated care delivery using team-based approaches.[159] Trials in patients with CVD have also supported the value of cognitive behavioral approaches in improving symptoms of anxiety and depression[160,161] that are often consequences of stressful exposures, promoting adherence to care recommendations and reducing hospital admissions.[161]

COMMUNITY-LEVEL INTERVENTIONS.

Targeting psychosocial stress at the community level, such as schools, workplaces, churches, and neighborhoods, could provide even greater benefits than individual-level interventions,[106] but must incorporate a comprehensive understanding of social determinants of health, which include economic, social, environmental, and psychosocial factors that influence health,[155] and a coordinated effort to engage the entire community,[30] including women. An example of a successful approach implemented in the REACH US (Racial and Ethnic Approaches to Community Health Across the United States) study, included tailored, culturally sensitive neighborhood coalitions, health education, and outreach programs administered by local health workers with indigenous ties to the community.[162] Task shifting roles within the health workforce team can increase mental health access for women by redistributing responsibilities from physicians to community health workers.[30] Establishment of structural and functional support networks in marginalized communities can promote stress reduction and positive coping mechanisms.[162] The B-SWELL (Midlife Black Women's Stress and Wellness) intervention is an example of an ongoing community-

based intervention that was designed to target stress and healthy lifestyle behaviors among a high-risk population of Black women.[163] Geomapping can be used to identify disadvantaged communities[30] that could benefit most from these interventions.

IMPACT OF PSYCHOSOCIAL STRESS ON GENDER INEQUITY IN CVD AND FUTURE DIRECTIONS

Gender inequities in cardiovascular care refer to differences in CVD prevention, diagnosis, and management between men and women that are unnecessary and unjust and are potentially driven by gendered bias.[2] To appropriately address gender inequities in cardiovascular health, cardiologists should recognize that psychosocial stress negatively affects cardiovascular health and is unequally distributed between men and women.[164] Addressing psychosocial stress could mitigate CVD risk among women.[8] Programs and policies should focus on structural and environmental conditions that affect psychosocial health.[164] We have identified the following action items:

- Adequately powered randomized trials should be designed to inform the development of guidelines for screening and management of psychosocial stressors to improve patient outcomes. Strategies specific for women should be tested. Clinical trials should identify the best implementation practices and optimal patient support systems. With these data, screening and management of psychosocial stress can eventually be adopted as a performance measure, using pay-for-performance models of care to promote adoption into clinical practice. For example, in diabetes, carefully designed pay-for-performance programs have achieved modest but significant improvements in diabetes care and control.[165]
- Epidemiologic and mechanistic studies are needed to clarify the impact of psychosocial stress on CVD risk in women according to a life course approach that begins in childhood. This approach is congruent with an international initiative that has proposed the 2030 Sustainable Development Goals for childhood development.[166]
- Intervention trials and community-level studies should target factors in the social environment that contribute to psychosocial distress[30] among women. These include structural determinants of equity, such as racial and gender discrimination, socioeconomic adversity, gender earnings gaps, health care access, and neighborhood environment, as well as community factors, such as social cohesion, housing instability, food insecurity, limited transportation, and personal experience.[155] Gender earnings gaps are an important focus for future research.
- Efforts should be directed toward addressing psychosocial barriers to women's participation in cardiovascular research by providing adequate support and resources, because representation by women is essential to ensure gender equity in cardiovascular care.

CONCLUSIONS

Psychosocial stress is a key modifiable risk factor for women, especially for young and midlife women and those in underrepresented groups. Consideration of the psychosocial milieu is essential to improve cardiovascular health in women and decrease their future risk. For maximum impact, psychosocial adversity must be considered using a multipronged approach that addresses various sources of stress at the individual and community levels.

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ABBREVIATIONS AND ACRONYMS

CHD	coronary heart disease
CVD	cardiovascular disease
HFpEF	heart failure with preserved ejection fraction
HPA	hypothalamic-pituitary-adrenal
INOCA	ischemia with nonobstructive coronary artery disease
MI	myocardial infarction
MINOCA	myocardial infarction with nonobstructive coronary artery disease
MSIMI	mental stress–induced myocardial ischemia
PTSD	posttraumatic stress disorder
SCAD	spontaneous coronary artery dissection

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HIGHLIGHTS

- Psychosocial stress contributes to cardiovascular disease through multiple pathways, and young and midlife women, especially those from marginalized groups, are particularly vulnerable to the adverse effects of psychosocial stress.
- A multipronged approach to psychosocial adversity at the individual and community levels is needed to reduce the impact of stress on women's cardiovascular health.
- Clinical trials should explore the benefits of targeting psychosocial stress to improve women's cardiovascular health.

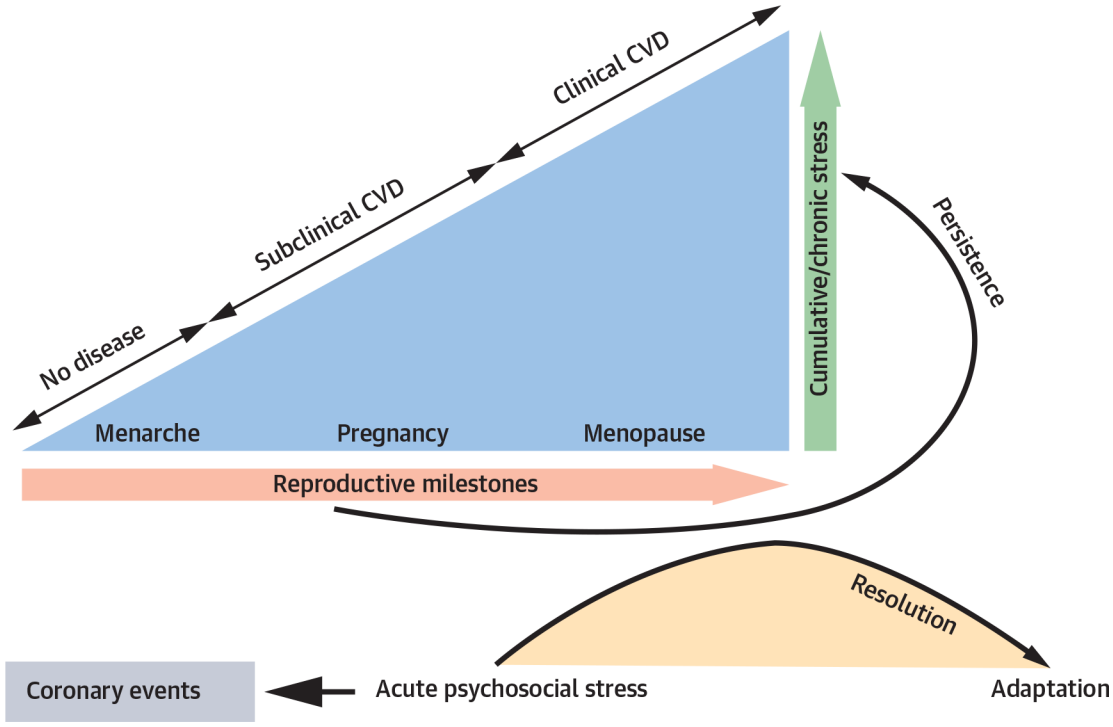


FIGURE 1. Schematic Presentation of Psychosocial Stress and Cardiovascular Disease (CVD) in Women

Acute psychosocial stress can trigger coronary events in women with underlying coronary disease or undergo resolution to create adaptation. Chronic stress can contribute to progression of coronary atherosclerosis and other chronic risk pathways for cardiovascular disease. Reproductive events can worsen stress responses favoring adverse cumulative effects of stressful exposures.

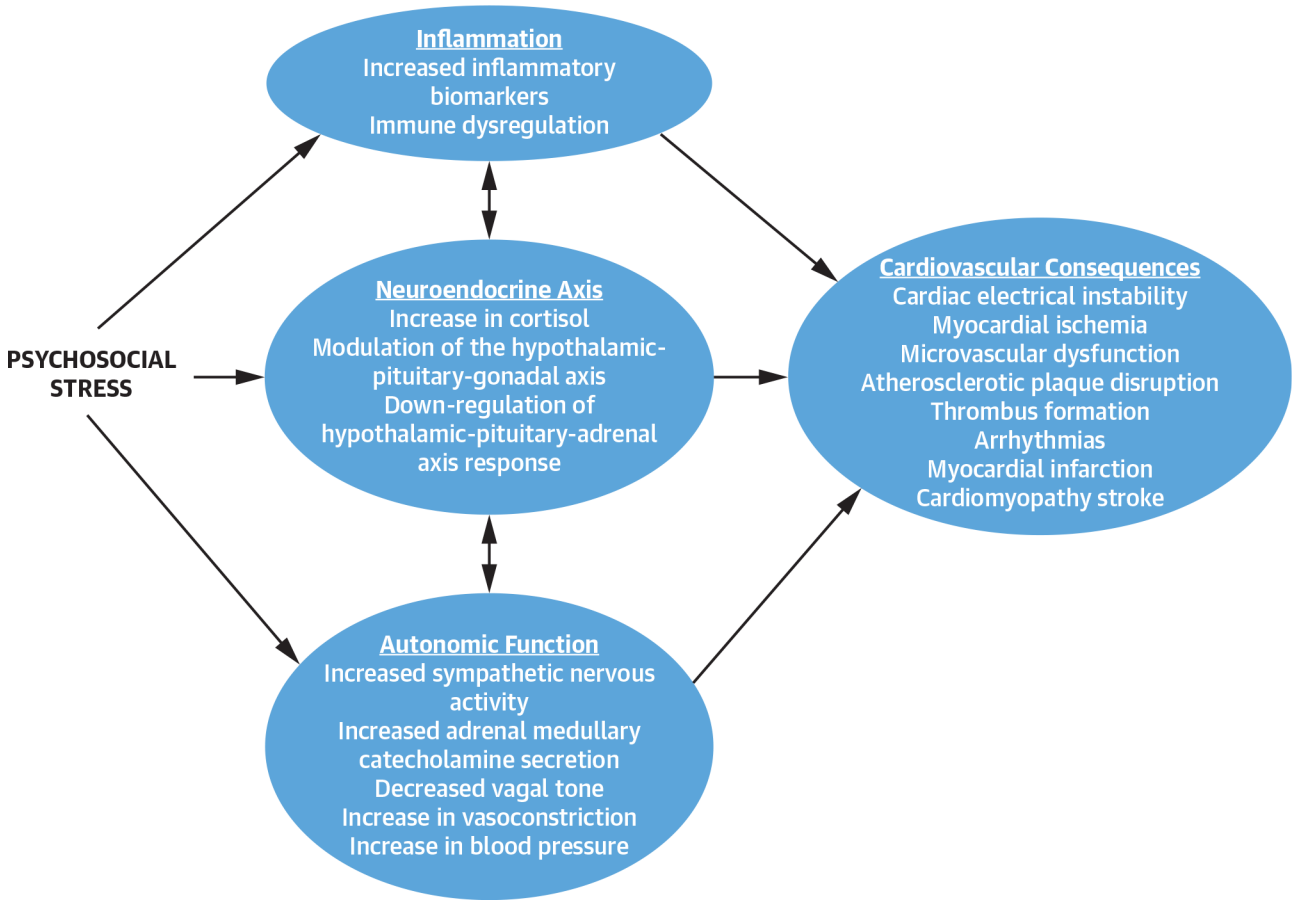
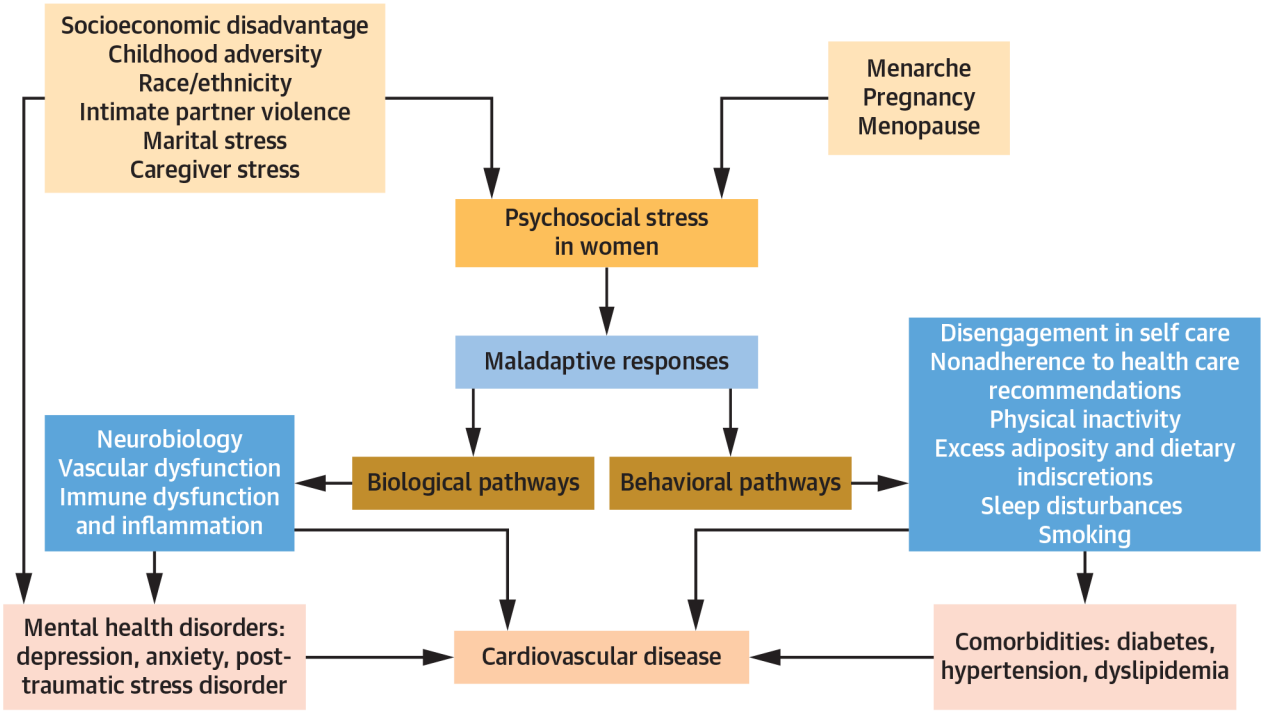


FIGURE 2. Biological Effects of Psychosocial Stress and Cardiovascular Sequelae in Women

The neuroendocrine axis interacts in a bidirectional manner with the autonomic nervous system and inflammatory pathways to promote adverse cardiovascular sequelae from stress. Although stress-related risk pathways for cardiovascular disease are multifactorial, the dominant mechanisms for women are inflammation and microvascular dysfunction resulting from neuroendocrine dysregulation and sympathetic nervous system activation.



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CENTRAL ILLUSTRATION. Maladaptive Stress Responses and Cardiovascular Disease in Women

Maladaptive responses to stress that influence cardiovascular disease risk involve biological and behavioral pathways. The coexistence of mental disorders and comorbidities can facilitate cardiovascular disease progression in response to psychosocial stress.

TABLE 1

Cardiovascular Conditions Linked to Stress That Disproportionately Occur Among Women

Condition	Predisposing Factors	Proposed Mechanisms
Mental stress-induced myocardial ischemia (MSIMI)	• Female sex • Younger age • History of ischemic disease • Angina with ordinary activity • Mental health disorders such as depression and post-traumatic stress disorder • Chronic psychosocial stress • Metabolic risk factors	• Microvascular reactivity • Peripheral vasoconstriction • Autonomic dysfunction • Enhanced inflammation • Increased brain activation in the anterior circulate, inferior frontal gyrus, and parietal cortex • Increases in hemodynamic load during mental stress
Spontaneous coronary artery dissection (SCAD)	• Genetic susceptibility • Female sex • Young to middle-aged (perimenopausal) • Emotional and physical stress • Anxiety and depression • Intense exercise and straining • Pregnancy • Hypertension • Connective tissue disorders • Fibromuscular dysplasia • Illicit drugs, such as cocaine	• Leakage of blood from the vessel lumen into the subintima space from an endothelial-intimal disruption • Formation of hematoma in the media from a tear in the microvasculature • Separation of the intima/media from the vessel and compression of the lumen
Stress-induced cardiomyopathy	• Female sex • Older age • Postmenopausal state • Acute intense physical, emotional, or psychosocial stress • Pre-existing mental disorders • Maladaptive stress coping	• Catecholamine storm with intense central and peripheral sympathetic activation • Acute ventricular and hemodynamic load • Activation of negative inotropic signaling in the heart by high catecholamine levels • Microvascular and endothelial dysfunction • Multivessel epicardial coronary spasm • Enhanced inflammation • Altered cardiac metabolism with intracellular lipid accumulation • Action potential and QTc prolongation with increased risk of cardiac arrhythmia • Abnormalities in the corticolimbic system of the brain that regulates emotions
Ischemia with nonobstructive coronary artery disease (INOCA)	• Female sex • Older age • Smoking • Metabolic risk factors such as hypertension, diabetes, and dyslipidemia • Inflammatory disease • Mental health disorders such as anxiety and depression	• Inflammation • Insulin resistance • Oxidative stress • Microvascular dysfunction • Coronary epicardial and microvascular dysfunction • Autonomic dysfunction • Arterial remodeling • Microthrombi and capillary obliteration • Coronary vasospasm
Myocardial infarction with nonobstructive coronary artery disease (MINOCA)	• Female sex • Younger age • Metabolic risk factors such as hypertension • Inflammatory disease • Pulmonary embolism • Severe anemia, sepsis, and hypoxia • Tachyarrhythmia • Platelet disorders • Psychologic stress	• Nonobstructive plaque rupture or erosion • Coronary embolism or thrombosis • Coronary artery vasospasm • Coronary artery dissection • Microvascular disease • Type II myocardial infarction

Condition	Predisposing Factors	Proposed Mechanisms
Heart failure with preserved ejection fraction (HFpEF)	• Female sex • Postmenopausal • Older age • Comorbidities such as hypertension, diabetes, obesity, renal dysfunction, coronary artery disease, atrial fibrillation, autoimmune disease, and iron deficiency • Perceived stress	• Inflammation • Insulin resistance • Oxidative stress • Endothelial dysfunction • Coronary microvascular or macrovascular ischemia • Neurohormonal activation • Decreased secretion of natriuretic peptides • Activation of the renin-angiotensin-aldosterone system • Concentric left ventricular remodeling • Diastolic dysfunction • Decreased aortic and left ventricular compliance • Abnormal ventricular-arterial coupling

TABLE 2

Interventions That Can Be Used to Mitigate Psychosocial Stress in Women

Intervention	Type	Benefits
Cognitive-behavioral therapy	Individual	Alleviates anxiety and depression, and promotes self-efficacy and adherence to health care recommendations
Mindfulness, meditation	Individual	Improves sleep, cognitive appraisal, and positive attitudes, and lowers blood pressure
Biofeedback techniques	Individual	Relieves anxiety and depression, and improves coping skills, self-regulation, and control of emotions and behavior
Stress management and lifestyle coach	Individual	Promotes resilience and relaxation, ability to deal with negative outcomes, and participation in cardiac recovery programs
Stress education	Individual	Promotes self-efficacy, behavioral capability, and adoption of healthy lifestyle practices
Interpersonal (couples) therapy	Individual	Reduces marital discord, physical abuse, and domestic violence; improves satisfaction in marital relationships
Sleep hygiene education	Individual	Reduces insomnia and improves sleep quality
Preventive health care	Individual and community	Promotes health lifestyle and allows early diagnosis of mental health disorders and cardiovascular disease
Tailored neighborhood coalitions	Community	Enhance communal efficacy and collective programs to address specific stressors such as crime and homelessness
Culturally sensitive community support networks	Community	Promote observational learning and positive coping among group members
Task-shifting roles from physicians to community health workers within the health workforce team	Community	Improves communal access to mental and cardiovascular care, and promotes investment in indigenous community workers and organizations
Geomapping	Community	Identification of disadvantaged neighborhoods that can be targeted with appropriate resources
Provision of affordable housing and safe neighborhood environment	Policy	Encourages social cohesion, safety, physical activity, and healthy lifestyle
Development of effective transportation networks	Policy	Encourages mobility and access to community and human resources
Institution of food security programs	Policy	Ensures the availability of nutritious food in sufficient quantity to all individuals
Countering of structural racism and discrimination	Policy	Creates equal opportunities for marginalized women and reduces health disparities
Provision of affordable health care insurance	Policy	Improves access to mental and cardiovascular care for women
Establishment of poverty alleviation programs	Policy	Alleviates socioeconomic disadvantage for vulnerable women
Promoting inclusion of women in clinical trials	Policy	Improves availability of evidence and guidelines recommendations that are specific to women
Involving indigenous women in developing policies that are designed to improve their mental and cardiovascular health	Policy	Provides precise interventions that address the needs of women in the specific community