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REVIEW

Psychosocial Stress, the Unpredictability Schema, and Cardiovascular Disease in Women

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Abstract

Depression/anxiety-related disorders and psychosocial stress have been implicated as cardiovascular disease (CVD) risk factors. Women are at considerable risk for affective disorders and report greater severity from psychosocial stress, compared to men. Affective disorders and cardiovascular disease likely share underlying pathophysiological mechanisms that are potentiated among women – especially younger women. Environmental stressors that threaten the safety, security, and status of an individual are appraised by the brain, producing a cascade of evoked physiological and cognitive responses. In the short term, these processes overcome stressors, but come with long-term health implications. Chronic psychosocial stress leads to a dysregulation of the stress response systems that can lead to a heightened stress appraisal schema called the *unpredictability schema*, a construct that might arguably place women at heightened risk for CVD.

Keywords: cardiovascular disease; psychological stress; depression; anxiety; Women; unpredictability schema; life history theory; psychosocial stress

Introduction

Women's cardiovascular health is in part impacted by: (1) physiological and biological systems and (2) the societal and community demands unique to the female gender [1, 2]. Women have higher prevalence of stress-related mental disorders such as depression or anxiety than men [3–5]. It is increasingly acknowledged that the relationship between cardiovascular disease (CVD) and depression/anxiety-related disorders is highly prevalent in women, especially in younger women [6–9]. Thus, this review focuses on CVD and affective disorders (e.g., anxiety, post-traumatic stress disorder (PTSD), and depression) as end-products that potentially result from overcoming a lifetime of environmental and psychosocial stress. Stressors may serve as cues that convey key information about the condition and availability of resources in the immediate environment that are processed by the brain and conveyed to the circulatory system and the rest of the body via the autonomic nervous system, hypopituitary-adrenal axis, and inflammatory processes [10]. Individuals identify the level of predictability, controllability, and safety present in the environment through a cognitive perceptual and appraisal system called the *unpredictability schema* [11]. The influence of environmental stressors spans across physiology, development, behavior and, ultimately, health. We provide a conceptual explanation of the unpredictability schema, followed by short sections defining psychosocial stress and reviewing its impact on CVD risk in women.

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The Unpredictability Schema: Affect and Cardiovascular Disease

The brain has been characterized as the "central organ of stress" [12, 13] because it perceives, appraises, and labels external environmental stimuli as either safe or threatening (see Figure 1). Contingent on the assessments of the brain appraisal system, bio-energetic resources are mobilized across physiological systems to create a coordinated stress response [10, 12–14]. For instance, the autonomic nervous system – notably the vagal nerve – is hypothesized to be an organizer for social behavior across phylogenetic time [15]. When an individual perceives themselves to be in an unsafe or threatening situation, the stressor evokes a physiological response that activates the sympathetic nervous system [15]. Sympathetic activation creates a cascade of coordinated responses within the circulatory system (among others) designed to overcome the stressor. Because the circulatory system is designed to attend to urgent threats to health (e.g., wounds, viral/bacterial infections etc.) and to mobilize and transport resources and defenses (i.e., nutrients, oxygen, hormones, cytokines) across tissues, the coordinated response includes increased heart rate, vasodilation and mobilization of oxygenated blood to the extremities with diversion of resources away from vital organs. Blood during a stress response becomes increasingly coagulated and the immune system is mobilized. These physiological responses were designed to facilitate adaptive behaviors that would quickly overcome environmental challenges in the short term.

Over time, repeated exposure to stress and stress response activation results in physiological, neurological, and brain re-organization that canalize stress responses and cognitive adaptations in ways that help individuals *specialize* and *sensitize* to the features of their immediate environment [10, 14, 16–18]. Chronic stress alters brain anatomy by increasing amygdala functioning (e.g., vigilance), decreasing ventral striatal reward sensitivity (e.g., reward-seeking behavior), and decreasing executive functioning of the prefrontal cortex (e.g., impulsive behavior) [14, 17]. Pervasive and long-term activation of these brain and stress response systems from chronic stress results in dysregulation of the stress response system [12, 19] and greater vigilance and impulsive behavior [10, 20]. These adaptations, however, come with upstream costs. These adaptations manifest as decrements in mental

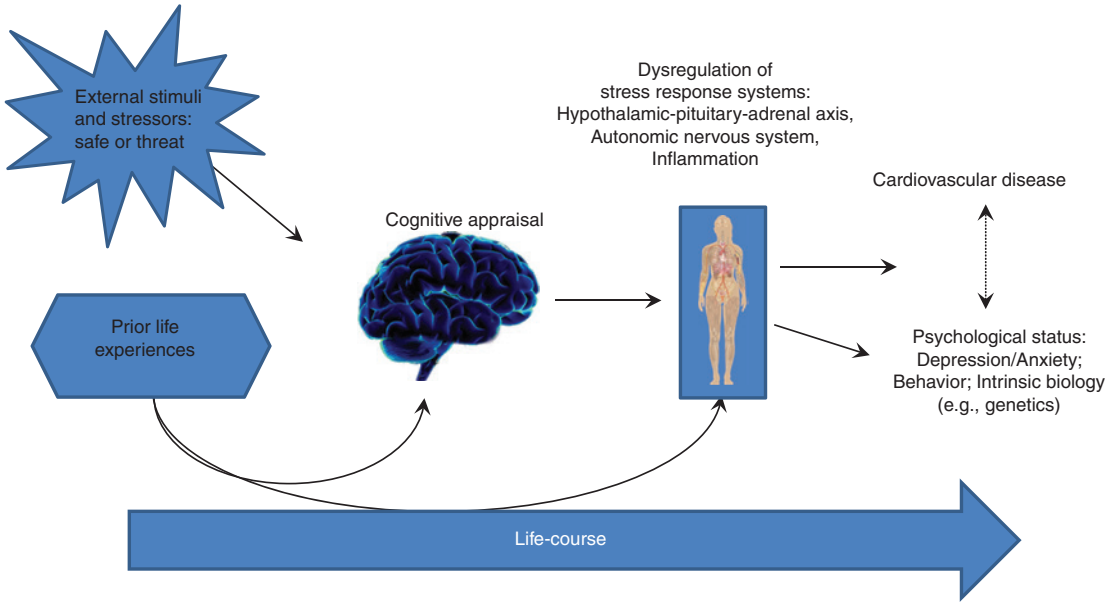

Figure 1 Potential Life-Course Pathways of Cardiovascular Disease and Mental Psychological Stress.
The brain is the focal point of stress response in that it cognitively appraises external stimuli/stressors and situations as benign or threatening, which produces of concerted cascade of responses across different physiological systems – notably dysregulation of the Hypopituitary Adrenal/Gonadal Axes, Sympathetic Adrenal Medullary Axis, and the immune system. Over time, this results in both increased cardiovascular disease risk and reduced mental health.

and physical health – such as depression and CVD – through *exogenous* (i.e., dysregulation of the stress response systems) and *endogenous* pathways (i.e., increased risk-taking, decreased health-maintaining behavior, and decreased interoceptive awareness) [13, 21] (Figure 2).

Evidence suggests that early and repeated exposure to stressful or threatening environments can shape worldviews and perceptions in a manner that orients individuals toward perceiving society and the environment as unpredictable, unreliable, threatening, and hostile, and discounting the future [11, 16, 22]. This cognitive orientation has been called the *unpredictability schema* [11, 23] and includes behavioral and affective components of decreased perceptions of control, increased pessimism, hostility, and vigilance (see Table 1 for additional components of the unpredictability schema).

The unpredictability schema and its components have been linked to greater anxiety and depressive symptoms, increased reward-seeking and risk-taking and poor health-maintaining behavior (e.g., over-eating) [24, 26–28]. Indeed, research documents increased drive for reward-seeking behavior, following chronic stress exposure [14, 21]. Further, brain systems calibrated by chronic stress response such as the ventral striatum are implicated in increasing health-harming, reward-seeking behaviors [14]. For example, smoking is one traditional health-harming/reward-seeking behavior both implicated in cardiovascular risk and associated with exposure to higher levels of stress [29–31]. Torres and O'Dell [30], using extensive research from animal models, propose that females are especially sensitive to nicotine, with stress heightening nicotine sensitivity in neuro-reward pathways and increasing intensity of withdrawal.

Table 1 Description of the Unpredictability Schema.

Unpredictability Schema Components (Adapted by Ross and Hill [11])
Self
External Locus of Control
↓ Sense of Control/Mastery
↓ Self-Efficacy
↑ Helplessness
↑ Pessimism
↑ Hopelessness
↑ Future Discounting
People
↓ Interpersonal Trust
↑ Cynical Hostility
↑ Vigilance
World
↑ Causal Uncertainty
↓ Poor Sense of Coherence
Measures of the Unpredictability Schema
Scale of Unpredictability Beliefs [23]
Unpredictability Schema Scale [24, 25]

In addition to increased reward-seeking, risk-taking and decreased health-maintenance, the unpredictability schema may produce a reduction in interoceptive awareness [24]. Interoceptive awareness is the perceptual processing of internal bodily states such as pain and hunger; conversely, exteroceptive awareness is the perceptual processing of external stimuli situated outside of the body [32].

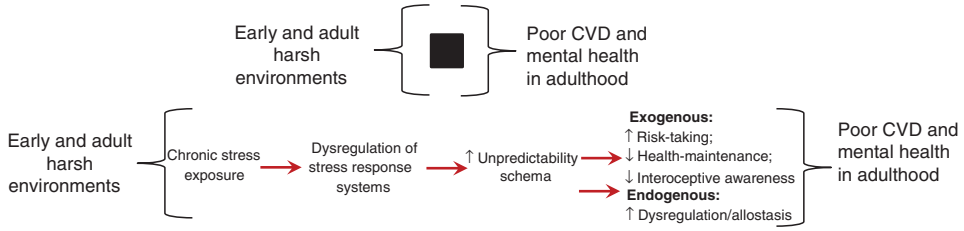

Figure 2 The "Black Box" of Harsh Environments and Poor CVD Health in Adulthood.
The figure demonstrates the different levels in which harsh and unpredictable environments may influence cardiovascular health. (1) Harsh environments increase the likelihood of chronic stress exposure, which increases the dysregulation of the stress response system. (2) Dysregulation of the stress response system increases antagonistic or opportunistic socioemotional social strategies that include increased vigilance, pessimism, hostility and decreased perceived control. Over time, the combination of the up-regulated stress response systems, coupled with opportunistic/antagonistic social strategies, creates endogenous (i.e., somatic) alterations such as physiological dysregulation or allostasis; exogenous (i.e., behaviorally) alterations include increased risk-taking behavior, decreased health-maintaining behavior, and decreased interoceptive awareness.

Evidence suggests that activation of one perceptual system may supersede the other [32]. Recent work on the unpredictability schema has proposed that early experiences of systemic chronic stress may orient individuals toward vigilance, which may alter perceptual systems to focus on exteroceptive awareness (external stimuli), foregoing interoceptive awareness (internal bodily sensations) [24]. As predicted, the association between a heightened unpredictability schema was associated with *decreased* interoceptive awareness and over-eating [24]. Thus, it is possible that increased exteroceptive awareness, as a result of hyper-vigilance and stress response, may cause people to be less aware of bodily sensations.

Conceptualization of Psychosocial Stress and Stressors

An extensive literature exists that describes the conceptualization and measurement of stress and stressors [33, 34]. A *stressor* is conceptualized as an environmental stimulus or event that threatens the security, autonomy, status, and, survival of an organism. Broadly, there exists three domains of stressors [33]: (1) *negative life events*, discrete events that individuals experience such as losing a job or death of a loved one, (2) *chronic difficulties*, sustained and long-term stressful situations, such as caring for a loved one or living in a disadvantaged neighborhood, and (3) *cumulative stress exposure* (lifetime stress) which is also known as the sum-total or culmination of chronic and acute life stressors across the lifespan. Stressors are further distinguished across development, whereby stressors experienced prenatally or in childhood/adolescence are categorized as early adversity and stressors following those developmental stages are adult stressors.

Harshness – defined as "external sources of disability and death" that are independent of age and health [16] – and *unpredictability* – defined as "spatial variation in harshness" [16] – have been suggested as relevant dimensions of environmental risk (i.e., life stressors) that convey key information about the safety, security, and controllability about the immediate environment and the reliability and trustworthiness of individuals present in the environment. Indeed, harshness and unpredictability help inform and link the disparate literature between mood disorders and CVD risk in women.

Women CVD and Psychosocial Stressors in Women

Psychosocial stress and its underlying components negatively impact cardiovascular health and mortality [35] (see Figure 1). The INTERHEART study showed that psychosocial factors were as potent to CVD risk (Odds Ratio (OR): 2.67, 95% Confidence Intervals (CI): 2.21–3.22) as smoking (OR: 2.87, 95% CI: 2.58–3.19) as other traditional risk factors, like Type II diabetes (OR: 2.37, 95% CI: 2.07–2.71) [36]. Disaggregation of psychosocial stress in INTERHEART revealed that, compared to age- and sex-matched controls, patients with reported myocardial infarction had elevated psychosocial stress from different measured stress domains, including home and work stress, financial stress, stressful life events, and depression [37]. Additionally, patients had lowered perceived locus of control. A series of meta-analytic and pooled-analyses work continues to find support for an association between psychosocial stress and CVD, including hypertension [38], stroke (with greater risk in women) [39], coronary heart disease [40], and CVD death [41].

The examination of the relationship between assorted domains of life stress (e.g., work, relationship, health, jobs) among middle-aged and older adults (45–84 years old) on markers of endothelial dysfunction, a precursor to CVD, found that reporting two or more stressful life events compared to no life events were associated with greater endothelial dysfunction, as evidenced by decreased flow-mediated dilation and higher levels of I-CAM1 [42]. The sequelae of work stress have been an extensively studied stress domain. Meta-analyses have found an association between work stress and CVD [43], including stroke risk [44]. Specifically focusing on women, prospective work in the Women's Health Study (WHS) highlighted the significance of psychosocial stress [45], by examining the effects of job strain on incident CVD risk [46]. Both high strain, characterized by a combination of low control and high demands, and active strain, characterized by high control and high demands, were associated with greater risk of acute cardiovascular events [46].

Caregiver burden has also been implicated in CVD risk. Current [HR: 1.35, 95% CI: 1.06–1.68] and long-term care of a spouse [HR: 1.95, 95% CI: 1.19–3.18] have found strong associations between caregiving and CVD risk [47]. Caring for an ill spouse at ≥9 hours a week (RR: 1.82, 95% CI: 1.08–3.05) compared to 0 hours a week was associated with greater CVD risk in the Nurse's Health Study [48].

Women hospitalized for *Takotsubo or stress-induced cardiomyopathy*, a diagnosis more prevalent in women, were more likely to report experiencing greater negative life events than unexposed women [49]. Other work in middle-aged adult men and women with stable coronary heart disease demonstrates that women (particularly younger women, e.g., ≤50 years old), compared to men, are at greater risk for mental stress-induced myocardial ischemia [50]. In this study, women experienced higher levels of myocardial ischemia in response to mentally-induced stress compared to men (OR: 2.06, 95% CI: 1.12–3.79). These findings were more potent in younger women (e.g., ≤50 years old) where women had a 4-fold higher likelihood of mentally-induced stress ischemia compared to their male counterparts. This work may have relevance for the observed phenomenon in women afflicted with chest pain and without epicardial coronary artery disease. Additional work suggests that mental health status may moderate the association between life stressors and cardiovascular health. In a sample of 28,583 US men and women (mean age = 44.8; female = 57.6%), the association between negative life events and CVD incidence was stronger in participants who reported a history of depression [51], suggesting that psychological status may amplify the effects of negative life events. Furthermore, early adversity has been implicated in the progression of CVD risk [52]. Some research suggests that the effects of early adversity may be more potent in women, as well as heightened in women with stressful life experiences in adulthood [53]. Table 2 outlines studies of psychological status with a focus on stress and CVD in women.

Psychological Status and CVD Risk: Intersection of Sex and Race/Ethnicity

As reviewed by Mehta and colleagues [1], women of color, including Hispanic/Latinas and black women, experience more severe physical and mental comorbidities and greater cardiovascular complications at younger ages than other women. Although not only limited to U.S. women belonging to racial/ethnic minority groups, earlier progression of CVD in women is more pronounced in women with depression or anxiety disorders [1, 58]. Further, because racial/ethnic minority women are more likely to reside in harsh, unpredictable, and uncontrollable environments, they are more likely to encounter chronic stress exposure across the lifespan, potentially making ethnic and racial minority women more susceptible to CVD as a result of their life experiences. Additionally, nativity status is another important CVD factor to consider among racial/ethnic minorities. For example, foreign-born Hispanics/Latinos have greater risk of CVD death than US-born Hispanic/Latinos, the risk is highest among Cubans, then Puerto Ricans, and Mexicans [59].

Exposure to adversity among racial/ethnic minorities begins early in life. Racial/ethnic minorities, and economically-disadvantaged children have been reported to experience more adversity than white and economically-privileged children [60]. Evidence suggests that a dose-effect of early adversity on adult cardiovascular health exists. Men and women who reported 3 or more early adverse (ACE) events compared to no events had greater CVD risk (OR: 2.14, 95% CI: 1.56–2.94) and the effect was most potent in individuals who reported 2 or more adult life events (OR: 3.00, 95% CI: 1.74–5.20) [53]. When stratified by sex, the association was only significant among women [53]. This trend continues into later adulthood and may be partially attributed to socioeconomic status.

Data from the Women's Health Study (WHS) showed that markers of economic prestige (higher education and income) were protective against prospective cardiovascular events over 10 years, even after control for traditional cardiovascular risk factors and novel CVD surrogate biomarkers markers such as C-reactive protein [61]. Emerging work from WHS demonstrates that cumulative psychosocial stress, a composited measure consisting of acute negative life events and chronic stressors was significantly higher among Blacks, Hispanics, and Asians when compared to White women, even when after accounting for SES and

Table 2 Selected Summary of Psychosocial Status Papers with a Focus on Stress and Cardiovascular Disease Risk.

Authors	n	Female	Study Design	Psychological Factor	Outcome	Parameter Estimate	95% CI
Garad et al. [53]	4408	50.8%	Prospective	1–2 Child Adversity events	Incident CVD	1.96*	1.26–3.06
Garad et al. [53]	4408	50.8%	Prospective	3+Child Adversity events	Incident CVD	3.02*	1.87–4.88
May-Ling et al. [54]	3392	100%	Prospective	History of Trauma Exposure	CHD	1.54	1.29–1.83
Sumner et al. [8]	49,978	100%	Prospective	Trauma Exposure/0 PTSD Symptoms	Incident CVD	1.38	1.09–1.75
Hendrickson et al. [55]	1021	18%	Prospective	Traumatic Events (4th Quartile)	Incident CVD	1.38	1.06–1.81
Yusuf et al. [36]	12,461†	24.1%†	Case-Control	Psychosocial Factors (Composite)	Myocardial Infarction	3.49*	2.41–5.04
Liu et al. [38]	5696	n/a	Meta-analysis	Psychosocial Stress	Hypertension	2.40	1.65–3.49
Booth et al. [39]	154,938	n/a	Meta-analysis	Psychosocial Stress	Stroke	1.90*	1.40–2.56
Russ et al. [41]	68,222	55.9%	Pooled-analysis	Psychosocial Distress (GHQ-12 Score)	CVD Death	1.17	1.12–1.22
Richardson et al. [40]	118,696	n/a	Meta-analysis	Perceived Stress	CHD	1.27	1.12–1.45
Gallo et al. [56]	5313	62.1%	Cross-Sectional	Chronic Stress	Prevalent CHD	1.22	1.10–1.36
Rosengren et al. [37]	11,119†	n/a	Case-Control	Stressful Life Events (1 Event)	MI	1.30*	1.11–1.52
Rosengren et al. [37]	11,119†	n/a	Case-Control	Stressful Life Events (2+Events)	MI	1.37*	1.12–1.68
Bernston et al. [51]	28,583	57.6%	Prospective	Stressful Life Events (Past Year)	Incident CVD	1.15	1.11–1.19
Mathews et al. [57]	9056	74%	Cross-Sectional	Stress	ICH (6–7 components)	0.65*	0.54–0.79
Mathews et al. [57]	9056	74%	Cross-Sectional	Low Life Satisfaction	ICH (6–7 components)	0.66*	0.45–0.97
Mathews et al. [57]	9056	74%	Cross-Sectional	Anxiety	ICH (6–7 components)	0.65*	0.45–0.95
Rosengren et al. [37]	11,119†	n/a	Case-Control	Feeling Depressed (Last 2 Weeks)	MI	1.60*	1.37–1.88
Whooley et al. [7]	7518	100%	Prospective	Depression	CVD Death	1.80	1.2–2.50
May-Ling et al. [54]	3392	100%	Prospective	Depression	CHD	1.56	1.20–2.04
May-Ling et al. [54]	3392	100%	Prospective	Depression and Anxiety	CHD	1.79	1.38–2.32
Capistrant et al. [47]	8472	52.3%	Prospective	Current Spousal Caregiving (≥14 h/week)	Incident CVD	1.35	1.06–1.68
Capistrant et al. [47]	8472	52.3%	Prospective	Long-term Spousal Caregiving (≥14 h/week – 2 years)	Incident CVD	1.95	1.19–3.18

Table 2 (continued)

Authors	n	Female	Study Design	Psychological Factor	Outcome	Parameter Estimate	95% CI
Lee et al. [48]	54,412	100%	Prospective	Spousal Caregiving (≥9 h/week)	CHD	1.82	1.08–3.02
Rosengren et al. [37]	11,119†	n/a	Case-Control	Home Stress (Several Periods)	MI	1.53*	1.23–1.90
Rosengren et al. [37]	11,119†	n/a	Case-Control	Home Stress (Permanent)	MI	1.88*	1.31–2.69
Rosengren et al. [37]	11,119†	n/a	Case-Control	Financial Stress (Moderate)	MI	1.22*	1.05–1.41
Rosengren et al. [37]	11,119†	n/a	Case-Control	Financial Stress (Severe)	MI	1.33*	1.08–1.64
Slopen et al. [46]	22,086	100%	Prospective	Active Job Strain (High Demand/High Control)	Incident CVD	1.38	1.07–1.77
Slopen et al. [46]	22,086	100%	Prospective	High Job Strain (High Demand/Low Control)	Incident CVD	1.38	1.08–1.77

*Parameter estimate disaggregated by women. †Cases only.
CVD, cardiovascular disease; PTSD, post-traumatic disease; CHD, coronary heart disease; ICH, ideal cardiovascular health.

depression/anxiety [62]. Other work in a sample of over 9000 men and women similarly finds that poorer psychological quality is related with decrease likelihood of attaining ideal or intermediate cardiovascular health status [57]. Trauma exposure [54, 55] and PTSD symptoms arising from trauma [8] are also substantial CVD risk factors [8, 63].

Unique Global Environmental Threats Faced by Women

Across the globe, women encounter distinct life experiences that may amplify the risk of mental illness and cardiovascular disease. At birth and infancy, some groups experience a greater "loss" of female babies than is expected [64]. Additionally, young girls in select cultures and environments may experience reduced access to health care, increasing risk of child mortality [65]. Early stressful experiences marked by sexual, emotional and physical abuse are more likely to be reported by women and individuals from disadvantaged economic backgrounds [66]. Women are also disproportionately at risk for increased poverty than men [67, 68]. As such, greater poverty increases the likelihood that women will be exposed to or reside in harsh and unpredictable neighborhoods [69, 70] or will report more negative life events [71], with U.S minority women and their offspring experiencing higher levels of poverty than white women [68]. For example, in 2015, Black women had the highest levels of poverty (23.1%), followed by Native American (22.7%), Hispanic/Latinas (20.9%), and Asian women (11.7%) [68]. Furthermore, women will be more likely to sustain households with minimal resources [72, 73]. Overall, thus, women, across their life span, may potentially encounter adverse environments and experience negative life events that may impact mental and cardiovascular health.

Sex, Environmental Appraisal, and Processing

In addition to unique lived experiences of some women, evidence suggests potential differential processing of environmental information by sex; differences that may emerge at puberty [74]. Humans have an evolutionary history of cooperation and reliance on others for security, resources

and survival [75]. For this reason, humans, among other social animals, have an intense drive for connection and need to belong [76], which emerges early in life through the attachment to caregivers and persists in adulthood through romantic relationships and familial/friendship bonds. As such, any stressor that deprives an individual of social connection, threatens an individual's status, and/or ostracizes an individual from a group, can result in marked negative physiological responses [77–79]. Perceptions of stress are also influenced by social connections. Individuals who report depression, lower social support, a recent relationship dissolution, or family conflict report higher levels of perceived stress [71]. The impact of psychological stress on health may be contingent on the appraised level of social support available to the individual in their immediate environment. In particular toxic stress [80], defined by adverse experiences without social support and unhealthy brain architecture results in illness compared to both positive or tolerable stress which are both associated with good social support and healthy brain architecture [81]. Indeed, evidence shows heightened diastolic blood pressure reactivity to acute stress in lonelier individuals, with the effect particularly more potent in women [82]. Loneliness has been linked with lower quality support networks (i.e., smaller support networks, less emotional and practical support) [82]. Indeed, a study by Steptoe et al. found that social isolation/loneliness contributes to increased stroke and coronary artery disease risk, as well as all-cause mortality among 6500 participants of the English Longitudinal Study of Ageing (ELSA) [83].

Some research suggests that differences in estrogen and oxytocin levels by sex may differentially modulate the stress response [84–86]. Elevated levels of sustained inflammation, as measured by surrogate inflammatory biomarkers like C-reactive protein, may be the result of a dysregulated glucocorticoid stress response and reduction in anti-inflammatory effects [87].

Finally, the relationship between stressful life experiences and CVD progression may also be implicated by telomere attrition. Telomeres are nucleoprotein sequences that serve as protective caps that conserve the cellular integrity of chromosomes and have been demonstrated to be shorter in women with elevated psychosocial stress and in individuals with recent stressful life events [88, 89]. Furthermore, individuals afflicted with affective disorders had significantly shorter telomeres when compared to age-matched controls [90], and other evidence suggests that chronicity of affective disorders is also linked with shorter telomeres [91]. In totality, emerging evidence suggests an interplay between psychosocial stressors, the unpredictability schema and chronic diseases such as cardiovascular disease.

Conflict of Interest

The authors declare no conflict of interest.

REFERENCES

1. Mehta LS, Beckie TM, DeVon HA, Grines CL, Krumholz HM, Johnson MN, et al. Acute myocardial infarction in women: a scientific statement from the American Heart Association. Circulation 2016;133:916–47.
2. O'Neil A, Scovelle AJ, Milner AJ, Kavanagh A. Gender/sex as a social determinant of cardiovascular risk. Circulation 2018;137:854–64.
3. Salk RH, Hyde JS, Abramson LY. Gender differences in depression in representative national samples: meta-analyses of diagnoses and symptoms. Psychol Bull 2017;143:783–822.
4. Tolin DF, Foa EB. Sex differences in trauma and posttraumatic stress disorder: a quantitative review of 25 years of research. Psychol Bull 2006;132:959–92.
5. Palanza P, Parmigiani S. How does sex matter? Behavior, stress and animal models of neurobehavioral disorders. Neurosci Biobehav Rev 2017;76:134–43.
6. Van der Kooy K, van Hout H, Marwijk H, Marten H, Stehouwer C, Beekman A. Depression and the risk for cardiovascular diseases: systematic review and meta analysis. Int J Geriatr Psychiatry 2007;22:613–26.
7. Whooley MA. Association between depressive symptoms and mortality in older women. Arch Intern Med 1998;158:2129.
8. Sumner JA, Kubzansky LD, Elkind MSV, Roberts AL, Agnew-Blais J, Chen Q, et al. Trauma exposure and posttraumatic stress disorder symptoms predict onset of cardiovascular events in women: clinical perspective. Circulation 2015;132:251–9.
9. Vaccarino V, Bremner JD. Behavioral, emotional and neurobiological determinants of coronary heart disease risk in women. Neurosci Biobehav Rev 2017;74:297–309.

10. Del Giudice M, Ellis BJ, Shirtcliff EA. The adaptive calibration model of stress responsivity. Neurosci Biobehav Rev 2011;35:1562–92.
11. Ross LT, Hill EM. Childhood unpredictability, schemas for unpredictability, and risk taking. Soc Behav Personal Int J 2002;30:453–73.
12. McEwen BS. Neurobiological and systemic effects of chronic stress. Chronic Stress 2017;1:1–11.
13. Ginty AT, Kraynak TE, Fisher JP, Gianaros PJ. Cardiovascular and autonomic reactivity to psychological stress: neurophysiological substrates and links to cardiovascular disease. Auton Neurosci Basic Clin 2017;207:2–9.
14. Nusslock R, Miller GE. Early-life adversity and physical and emotional health across the lifespan: a neuroimmune network hypothesis. Biol Psychiatry 2016;80:23–32.
15. Porges SW. The polyvagal theory: phylogenetic substrates of a social nervous system. Int J Psychophysiol 2001;42:123–46.
16. Ellis BJ, Figueredo AJ, Brumbach BH, Schlomer GL. Fundamental dimensions of environmental risk: the impact of harsh versus unpredictable environments on the evolution and development of life history strategies. Hum Nat 2009;20:204–68.
17. Figueredo AJ, Vásquez G, Brumbach BH, Schneider SM, Sefcek JA, Tal IR, et al. Consilience and life history theory: from genes to brain to reproductive strategy. Dev Rev 2006;26:243–75.
18. Ellis BJ, Bianchi J, Griskevicius V, Frankenhuis WE. Beyond risk and protective factors: an adaptation-based approach to resilience. Perspect Psychol Sci 2017;12:561–87.
19. Ellis B, Jackson J, Boyce W. The stress response systems: universality and adaptive individual differences . Dev Rev 2006;26:175–212.
20. Cabeza de Baca T, Wahl RA, Barnett MA, Figueredo AJ, Ellis BJ. Adversity, adaptive calibration, and health: the case of disadvantaged families. Adapt Hum Behav Physiol 2016;2:93–115.
21. Penninx BWJH. Depression and cardiovascular disease: epidemiological evidence on their linking mechanisms. Neurosci Biobehav Rev 2017;74:277–86.
22. Cabeza de Baca T, Ellis BJ. Early stress, parental motivation, and reproductive decision-making: applications of life history theory to parental behavior. Curr Opin Psychol 2017;15:1–6.
23. Ross LT, Short SD, Garofano M. Scale of unpredictability beliefs: reliability and validity. J Psychol 2016;150:976–1003.
24. Proffitt Leyva RP, Hill SE. Unpredictability, body awareness, and eating in the absence of hunger: A cognitive schemas approach. Health Psychol 2018;37:691–699.
25. Cabeza de Baca T, Barnett MA, Ellis BJ. The development of the child unpredictability schema: regulation through maternal life history tradeoffs. Evol Behav Sci 2016;10:43–55.
26. Ross LT, Hood CO, Short SD. Unpredictability and symptoms of depression and anxiety. J Soc Clin Psychol 2016;35:371–85.
27. Ross LT, Hill EM. Drinking and parental unpredictability among adult children of alcoholics: a pilot study. Subst Use Misuse 2001;36:609–38.
28. Hill EM, Ross LT, Low BS. The role of future unpredictability in human risk-taking. Hum Nat 1997;8:287–325.
29. Slopen N, Dutra LM, Williams DR, Mujahid MS, Lewis TT, Bennett GG, et al. Psychosocial stressors and cigarette smoking among African American adults in midlife. Nicotine Tob Res 2012;14:1161–9.
30. Torres OV, O'Dell LE. Stress is a principal factor that promotes tobacco use in females. Prog Neuropsychopharmacol Biol Psychiatry 2016;65:260–8.
31. Slopen N, Kontos EZ, Ryff CD, Ayanian JZ, Albert MA, Williams DR. Psychosocial stress and cigarette smoking persistence, cessation, and relapse over 9–10 years: a prospective study of middle-aged adults in the United States. Cancer Causes Control 2013;24:1849–63.
32. Mirams L, Poliakoff E, Brown RJ, Lloyd DM. Interoceptive and exteroceptive attention have opposite effects on subsequent somatosensory perceptual decision making. Q J Exp Psychol 2012;65:926–38.
33. Shields GS, Slavich GM. Lifetime stress exposure and health: a review of contemporary assessment methods and biological mechanisms. Soc Personal Psychol Compass 2017;11:e12335.
34. Monroe SM. Modern approaches to conceptualizing and measuring human life stress. Annu Rev Clin Psychol 2008;4:33–52.
35. Brezinka V, Kittel F. Psychosocial factors of coronary heart disease in women: a review. Soc Sci Med 1996;42:1351–65.
36. Yusuf S, Hawken S, Ôunpuu S, Dans T, Avezum A, Lanas F, et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. Lancet 2004;364:937–52.
37. Rosengren A, Hawken S, Ôunpuu S, Sliwa K, Zubaid M, Almahmeed WA, et al. Association of psychosocial risk factors with risk of acute myocardial infarction in 11 119 cases and 13 648 controls from 52 countries (the INTERHEART study): case-control study. Lancet 2004;364:953–62.
38. Liu M-Y, Li N, Li WA, Khan H. Association between psychosocial stress and hypertension: a systematic review and meta-analysis. Neurol Res 2017;39:573–80.
39. Booth J, Connelly L, Lawrence M, Chalmers C, Joice S, Becker C, et al. Evidence of perceived psychosocial stress as a risk factor for stroke in adults: a meta-analysis. BMC Neurol 2015;15:233.
40. Richardson S, Shaffer JA, Falzon L, Krupka D, Davidson KW, Edmondson D. Meta-analysis of perceived stress and its association with incident coronary heart disease. Am J Cardiol 2012;110:1711–6.
41. Russ TC, Stamatakis E, Hamer M, Starr JM, Kivimaki M, Batty GD. Association between psychological distress and mortality: individual

participant pooled analysis of 10 prospective cohort studies. Br Med J 2012;345:e4933.
42. Kershaw KN, Lane-Cordova AD, Carnethon MR, Tindle HA, Liu K. Chronic Stress and endothelial dysfunction: the multi-ethnic study of atherosclerosis (MESA). Am J Hypertens 2017;30:75–80.
43. Kivimäki M, Kawachi I. Work stress as a risk factor for cardiovascular disease. Curr Cardiol Rep 2015;17:74.
44. Fransson EI, Nyberg ST, Heikkilä K, Alfredsson L, Bjorner JB, Borritz M, et al. Job strain and the risk of stroke: an individual-participant data meta-analysis. Stroke 2015;46:557–9.
45. Albert MA, Durazo EM, Slopen N, Zaslavsky AM, Buring JE, Silva T, et al. Cumulative psychological stress and cardiovascular disease risk in middle aged and older women: rationale, design, and baseline characteristics. Am Heart J 2017;192:1–12.
46. Slopen N, Glynn RJ, Buring JE, Lewis TT, Williams DR, Albert MA. Job strain, job insecurity, and incident cardiovascular disease in the Women's Health Study: results from a 10-year prospective study. Behrens T, editor. PLoS One 2012;7:e40512.
47. Capistrant BD, Moon JR, Berkman LF, Glymour MM. Current and long-term spousal caregiving and onset of cardiovascular disease. J Epidemiol Community Health 2012;66:951–6.
48. Lee S, Colditz GA, Berkman LF, Kawachi I. Caregiving and risk of coronary heart disease in U.S. women. Am J Prev Med 2003;24:113–9.
49. Rosman L, Dunsiger S, Salmoirago-Blotcher E. Cumulative impact of stressful life events on the development of takotsubo cardiomyopathy. Ann Behav Med 2017;51:925–30.
50. Vaccarino V, Wilmot K, Mheid IA, Ramadan R, Pimple P, Shah AJ, et al. Sex Differences in mental stress-induced myocardial ischemia in patients with coronary heart disease. J Am Heart Assoc 2016;5:e003630.
51. Berntson J, Patel JS, Stewart JC. Number of recent stressful life events and incident cardiovascular disease: moderation by lifetime depressive disorder. J Psychosom Res 2017;99:149–54.
52. Suglia SF, Koenen KC, Boynton-Jarrett R, Chan PS, Clark CJ, Danese A, et al. Childhood and adolescent adversity and cardiometabolic outcomes: a scientific statement from the American Heart Association. Circulation 2018;137:e15–28.
53. Garad Y, Maximova K, MacKinnon N, McGrath JJ, Kozyrskyj AL, Colman I. Sex-specific differences in the association between childhood adversity and cardiovascular disease in adulthood: evidence from a national cohort study. Can J Cardiol 2017;33:1013–9.
54. May-Ling JL, Loxton D, McLaughlin D. Trauma exposure and the subsequent risk of coronary heart disease among mid-aged women. J Behav Med 2015;38:57–65.
55. Hendrickson CM, Neylan TC, Na B, Regan M, Zhang Q, Cohen BE. Lifetime trauma exposure and prospective cardiovascular events and all-cause mortality: findings from the heart and soul study. Psychosom Med 2013;75:849–55.
56. Gallo LC, Roesch SC, Fortmann AL, Carnethon MR, Penedo FJ, Perreira K, et al. Associations of chronic stress burden, perceived stress, and traumatic stress with cardiovascular disease prevalence and risk factors in the hispanic community health study/study of latinos sociocultural ancillary study. Psychosom Med 2014;76:468–75.
57. Mathews L, Ogunmoroti O, Nasir K, Blumenthal RS, Utuama OA, Rouseff M, et al. Psychological factors and their association with ideal cardiovascular health among women and men. J Womens Health 2018;25:709–15.
58. Gulati M, Buffomante AA, Wenger NK. Depression and anxiety in women with heart disease. Curr Cardiovasc Risk Rep 2016;10:32.
59. Rodriguez F, Hastings KG, Hu J, Lopez L, Cullen M, Harrington RA, et al. Nativity status and cardiovascular disease mortality among hispanic adults. J Am Heart Assoc 2017;6:e007207.
60. Slopen N, Shonkoff JP, Albert MA, Yoshikawa H, Jacobs A, Stoltz R, et al. Racial disparities in child adversity in the U.S. Am J Prev Med 2016;50:47–56.
61. Albert MA, Glynn RJ, Buring J, Ridker PM. Impact of traditional and novel risk factors on the relationship between socioeconomic status and incident cardiovascular events. Circulation 2006;114:2619–26.
62. Siliki Mbassa RA, Zaslavsky AM, Williams DR, Natalie SB, Buring J, Albert MA. Abstract 18364: cumulative psychosocial stress and ideal cardiovascular health in women: data according to race/ethnicity. Circulation 2016;134:A18364.
63. Sumner JA, Kubzansky LD, Roberts AL, Gilsanz P, Chen Q, Winning A, et al. Post-traumatic stress disorder symptoms and risk of hypertension over 22 years in a large cohort of younger and middle-aged women. Psychol Med 2016;46:3105–16.
64. Urquia ML, Ray JG, Wanigaratne S, Moineddin R, O'Campo PJ. Variations in male-female infant ratios among births to Canadian- and Indian-born mothers, 1990–2011: a population-based register study. CMAJ Open 2016;4:E116–23.
65. Khera R, Jain S, Lodha R, Ramakrishnan S. Gender bias in child care and child health: global patterns. Arch Dis Child 2014;99:369–74.
66. Lee C, Coe CL, Ryff CD. Social disadvantage, severe child abuse, and biological profiles in adulthood. J Health Soc Behav 2017;58:371–86.
67. United States Agency of International Development. Gender and extreme poverty. Getting to zero: a USAID discussion series. 2015 [cited 2017 May 20]. Available from: https://www.usaid.gov/sites/default/files/documents/1870/Gender_Extreme_Poverty_Discussion_Paper.pdf.
68. Tucker J, Lowell C. Income, security, and education national snapshot: poverty among women and families, 2015. National Women's Law Center 2016;1–5. WWW.NWLC.ORG.
69. Slabbert I. Domestic violence and poverty: some women's experiences. Res Soc Work Pract 2017;27:223–30.

70. Golin CE, Amola O, Dardick A, Montgomery B, Bishop L, Parker S, et al. Chapter 5 poverty, personal experiences of violence, and mental health: understanding their complex intersections among low-income women. In: O'Leary A, Frew PM, editors. Poverty US Women's Voices. Cham: Springer International Publishing; 2017. pp. 63–91. Available from: https://doi.org/10.1007/978-3-319-43833-7_5.
71. Xu X, Bao H, Strait KM, Edmondson DE, Davidson KW, Beltrame JF, et al. Perceived stress after acute myocardial infarction: a comparison between young and middle-aged women versus men. Psychosom Med 2017;79:50–8.
72. Lange BCL, Dáu ALBT, Goldblum J, Alfano J, Smith MV. A mixed methods investigation of the experience of poverty among a population of low-income parenting women. Community Ment Health J 2017;53:832–41.
73. Barnett MA. Economic disadvantage in complex family systems: expansion of family stress models. Clin Child Fam Psychol Rev 2008;11:145–61.
74. Jackson F, Nelson BD, Meyer A, Hajcak G. Pubertal development and anxiety risk independently relate to startle habituation during fear conditioning in 8–14 year-old females: puberty, anxiety risk, and startle habituation. Dev Psychobiol 2017;59:436–48.
75. Hrdy SB. Mother nature: maternal instincts and how they shape the human species. 1st Ballantine Books ed. New York: Ballantine Books; 2000.
76. Baumeister RF, Leary MR. The need to belong: desire for interpersonal attachments as a fundamental human motivation. Psychol Bull 1995;117:497–529.
77. Slavich GM, O'Donovan A, Epel ES, Kemeny ME. Black sheep get the blues: a psychobiological model of social rejection and depression. Neurosci Biobehav Rev 2010;35:39–45.
78. Eisenberger NI, Moieni M, Inagaki TK, Muscatell KA, Irwin MR. In sickness and in health: the co-regulation of inflammation and social behavior. Neuropsychopharmacology 2017;42:242–53.
79. Dickerson SS, Gruenewald TL, Kemeny ME. When the social self is threatened: shame, physiology, and health. J Pers 2004;72:1191–216.
80. McEwen BS, Bowles NP, Gray JD, Hill MN, Hunter RG, Karatsoreos IN, et al. Mechanisms of stress in the brain. Nat Neurosci 2015;18:1353–63.
81. Cohen S, Hoberman HM. Positive events and social supports as buffers of life change stress1. J Appl Soc Psychol 1983;13:99–125.
82. Steptoe A, Owen N, Kunz-Ebrecht SR, Brydon L. Loneliness and neuroendocrine, cardiovascular, and inflammatory stress responses in middle-aged men and women. Psychoneuroendocrinology 2004;29:593–611.
83. Steptoe A, Shankar A, Demakakos P, Wardle J. Social isolation, loneliness, and all-cause mortality in older men and women. Proc Natl Acad Sci 2013;110:5797–801.
84. Taylor SE, Klein LC, Lewis BP, Gruenewald TL, Gurung RAR, Updegraff JA. Biobehavioral responses to stress in females: tend-and-befriend, not fight-or-flight. Psychol Rev 2000;107:411–29.
85. McEwen BS, Milner TA. Understanding the broad influence of sex hormones and sex differences in the brain: sex hormones affect the whole brain. J Neurosci Res 2017;95:24–39.
86. Bekhbat M, Neigh GN. Sex differences in the neuro-immune consequences of stress: focus on depression and anxiety. Brain Behav Immun 2018;67:1–12.
87. Miller GE, Cohen S, Ritchey AK. Chronic psychological stress and the regulation of pro-inflammatory cytokines: a glucocorticoid-resistance model. Health Psychol 2002;21:531–41.
88. Epel ES, Blackburn EH, Lin J, Dhabhar FS, Adler NE, Morrow JD, et al. Accelerated telomere shortening in response to life stress. Proc Natl Acad Sci USA 2004;101:17312–5.
89. Verhoeven JE, van Oppen P, Puterman E, Elzinga B, Penninx BW. The association of early and recent psychosocial life stress with leukocyte telomere length. Psychosom Med 2015;77:882–91.
90. Simon NM, Smoller JW, McNamara KL, Maser RS, Zalta AK, Pollack MH, et al. Telomere shortening and mood disorders: preliminary support for a chronic stress model of accelerated aging. Biol Psychiatry 2006;60:432–5.
91. Wolkowitz OM, Mellon SH, Epel ES, Lin J, Dhabhar FS, Su Y, et al. Leukocyte telomere length in major depression: correlations with chronicity, inflammation and oxidative stress – preliminary findings. Kiechl S, editor. PLoS One 2011;6:e17837.