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RACE AND ETHNICITY DISPARITIES (M ALBERT, SECTION EDITOR)

# Cumulative Psychological Stress and Cardiovascular Disease Risk: A Focused Review with Consideration of Black-White Disparities

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## Introduction

Psychosocial stressors are social or environmental exposures or demands that place a burden on the adaptive capacities of an individual, and can result in physiological "wear and tear" that may lead to illness [1••]. Several lines of evidence point to stressors as having a key role in the development and progression of cardiovascular disease (CVD) [1••, 2, 3]. To date, a majority of studies on psychosocial stressors and CVD have concentrated on the relationship between single domains of stress, such as job stress [4] or social support [5], and studies of psychosocial stressors in relation to surrogate CVD biomarkers or symptoms of CVD and CVD death as outcomes are often limited by small sample sizes. At present, there are significant gaps in the literature with regard to the prospective relationship between the accumulation of multiple types of stressor exposure (i.e., "cumulative stressors") and CVD outcomes. In the present review, we discuss the importance of examining the cumulative effects of psychosocial stressors, potential mechanisms for associations between psychosocial stressors and elevated CVD risk, and provide suggestions for future research and practice.

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## Multiple Psychological Stressors and Cardiovascular Disease Outcomes

Research suggests that an individual's perceived stress (i.e., self-report of the extent to which situations in life are appraised as stressful [6]) has implications for CVD risk [7••]. For example, the Malmo Preventive Population Based Cohort, including 13,609 individuals (80 % male, mean age 45 years), showed that over two decades, high perceived stress was independently associated with CVD, and particularly, fatal stroke (relative risk 2.0, 95 % confidence interval, CI, 1.1 – 3.9) [8]. The Copenhagen City Health Study is another large-scale study that has examined generalized perceived stress and CVD. This study found a strong relationship between high perceived stress, all-cause and ischemic heart disease mortality in men <55 years old (hazard ratio, HR, 2.6, 95 % CI 1.2 – 5.6), but not in women [9]. These findings are supported by a recent meta-analysis of six prospective observational cohort studies that measured perceived stress and incident coronary heart disease at least 6 months later, which estimated an aggregate risk ratio of 1.27 (95 % CI 1.12 – 1.45) for the relationship between high perceived stress and incident coronary heart disease [7••]. Table 1 provides examples of large studies (>2,000 subjects) that evaluated the association between general perceived stress and CVD events.

While it is valuable to study the impact of perceived stress on CVD risk, self-report of exposure to a range of psychosocial stressors also have relevance for CVD risk. Table 2 provides examples of the types of individual stressors that researchers have evaluated in relation to a range of CVD outcomes with large-scale epidemiological cohorts. Importantly,

**Table 1** Examples of large studies (>2,000 subjects) that evaluated the association between general perceived stress or composite stress score measures and CVD events

| Reference | Study/cohort | Stress domains | | Gender | Age (years)[b] | CVD outcome (approximate RR)[c] |
|---|---|---|---|---|---|---|
| | | No. measured | Type | | | |
| [49] | Copenhagen cohort of 8,365 men born in 1953 and living in Denmark in 1968 | 2 | Job; personal relationship | 100 % male | 28 – 39 | MI (1.2 – 1.3) |
| [50] | Workers in Scotland, 2,623 subjects | 1 | Perceived stress | 100 % male | 48.0 | CVD mortality (0.9 – 1.0) |
| [8] | Malmo Preventive Project, 13,609 subjects | 1 | Perceived stress | 80 % male | 45 | Fatal + nonfatal CVD (1.1), stroke (2.0) |
| [51] | Multifactor Primary Prevention Trial, 6,935 subjects | 1 | Perceived stress | 100 % male | 47 – 55 | CAD (1.5), stroke (1.8), CVD mortality (1.7) |
| [52] | Japanese Collaborative Cohort Study, 73,424 subjects | 1 | Perceived stress | 41 % male | 40 – 79 | Men: CHD (1.1[d]), stroke (1.1[d]). Women: CHD (2.3), stroke (2.2) |
| [9, 53, 54] | Copenhagen City Heart Study, about 12,000 subjects | 1 | Perceived stress | About 56 % male | 56.0 | Men: IHD (1.3), CVD mortality (1.0-1.2). Women: IHD (1.2), CVD mortality (1.6 – 3.4) |
| [11••] | INTERHEART[a], 24,767 subjects | 5 | Home; job; financial; life events | 73.5 % male | 57.5 | MI (2.0) |
| [55] | Australian longitudinal study of women's health, 6,994 subjects | 7 | Perceived stress related to: own health, health of other family members, living arrangements, money, relationship with spouse/ partner, relationship with children, relationship with other family members | 100 % female | 70 – 75 | New onset of CHD (1.7) |

*CAD* coronary artery disease, *CHD* coronary heart disease, *CVD* cardiovascular disease, *IHD* ischemic heart disease, *MI* myocardial infarction

[a] Case-control study

[b] Range given if mean age not provided

[c] Sex-stratified effects presented when effects are conditional on sex

[d] Not statistically significant; all others are significant

few large-scale epidemiological studies linking chronic stress to CVD have focused on the relationship between CVD and combined measures of stress. Even in studies that have collected information on multiple types of stressors, it is common for researchers to have analyzed each type of stressor individually, without attention to the way that these stressors may accumulate to influence risk, or interact with each other, which may have led to underestimates of the impact of psychosocial stressors on CVD outcomes. For example, a long-term follow-up study of chronic stress from Quebec, Canada, involving 869 men aged 40 to 60 years [10] showed no relationship between chronic stress and ischemic heart disease or CVD mortality. Of note, while this study included 13 questions about psychological stress, the combined impact of these measures over time on CVD risk was not assessed.

The INTERHEART study, a large study consisting of 24,767 individuals from 52 countries, provided evidence to support the importance of considering multiple psychosocial factors in relation to atherosclerotic risk [11••]. This study found that persistent psychological stressors related to work, finances, home and life events were associated with a twofold increased risk of acute myocardial infarction (MI), accounting for a population risk attributable to chronic stress of 33 % [11••]. However, the INTERHEART study was limited due to the case-control design and the possibility of recall bias, particularly among persons who have experienced an MI. Thus, there remains an important need for research that assesses the joint effect of multiple acute and chronic stressors in longitudinal studies with well-characterized CVD outcomes.

**Table 2** Examples of large studies (>2,000 subjects) evaluating single domains of stress and CVD outcomes

| Reference | Stress domain | CVD outcomes |
|---|---|---|
| [56–58] | Caregiving/ home stress | MI, CVD mortality, total CVD |
| [49, 59–73] | Acute stress events | MI, stroke, CVD mortality, total CVD |
| [35, 74–76] | Social support, relationships, and family stress | IHD, CVD mortality, total CVD |
| [5, 32, 77–79] | Social networks/ isolation | MI, stroke, CVD mortality, total CVD |
| [80] | Discrimination | Total CVD |
| [81–88] | Early life adversity | IHD, CVD mortality, total CVD |
| [67, 76, 89–106] | Job stress | MI, stroke, CVD mortality, total CVD |

*IHD* ischemic heart disease, *total CVD* fatal and nonfatal MI, stroke, CVD mortality

## Potential Biological Mechanisms Linking Psychological Stress to Cardiovascular Disease

Experiences throughout an individual's life related to emotional stress, unhealthy behavior and environmental insults contribute to the progression of atherosclerosis over time [12]. At the experimental level, several lines of evidence link psychological stress to (1) dysregulation of the hypothalamic–pituitary axis (HPA), (2) excessive inflammation, and (3) sympathetic nervous system overdrive resulting in catecholamine production [13]. Figure 1 illustrates potential mechanisms by which cumulative stress may increase CVD risk. As shown, the brain plays a central role in the physiological effect of cumulative stressors on the heart [14••]. Central to this brain–heart connection is *allostasis* and *allostatic load*. Allostasis refers to the homeostatic or adaptive processes that occur due to changes in the body as a result of acute psychological stress or other insults, whereas allostatic load represents the "wear and tear" or detrimental physiological effects that promote disease over time [14••]. While controlled laboratory animal and human studies modeling acute stress support these mechanisms [15], similar work related to cumulative psychosocial stressors at the population level is limited.

## Socioeconomic Status and CVD Risk: The Unexamined Role of Psychosocial Stressors

Cumulative stress may also contribute to the socioeconomic status (SES) gradient in CVD. There is now clear evidence that CVD risk varies by SES, with lower SES associated with elevated CVD risk [16]. For example, in the landmark Whitehall Study of British civil servants, increasing employment grade was inversely associated with all-cause and CVD mortality, a relationship that was attenuated by 29 % after adjustment for health behaviors [17, 18]. Similarly, studies on the relationship between SES and CVD risk from the US, Latin America, Europe, Japan, the Middle East and Asia also show a "gradient effect" between SES and health [19, 20]. In the Women's Health Study (WHS) cohort, a large prospective study of female health professionals, the relationship between SES (defined by education, occupation and family income) and verified CVD events also demonstrated a steep inverse gradient of incident CVD events with better education and income [21••]. Intriguingly, in the WHS cohort, the protective effect of SES on CVD risk was not entirely explained by traditional, behavioral or novel biomarkers of CVD risk. These factors only accounted for approximately 50 % of the SES–CVD association, suggesting a potential role for other unmeasured determinants, such as psychological stress, in the SES–CVD relationship. The finding of an SES–CVD gradient among women in the WHS was also replicated in our evaluations of the associations between SES and blood pressure progression [22] and between SES and incident diabetes [23] in this cohort, emphasizing the importance of examining root causes of the gradient at all SES levels.

Despite the longstanding observation of the SES–CVD risk gradient, the full range of factors that determine the gradient remain largely unknown [18, 24]. Possible mechanisms of this SES–CVD gradient include the "drift hypothesis" (i.e., the effect of illness on health that may result in lower social status), health behaviors, psychological status, and exposure to psychosocial stressors [24]. To date, cumulative exposure to psychosocial stressors remains an understudied contributor to the SES–CVD risk gradient. The critical role that psychological stress might play in the SES–CVD relationship is suggested by work from the Whitehall Study indicating the importance of job control as a mediator of the SES–CVD relationship where this factor provided the largest contribution to the gradient [25]. Persons of lower SES are characterized by: (1) more risky health behaviors, (2) greater chronic and acute stress, (3) lower levels of social relationships and support, (4) higher levels of psychological attributes known to be risky for CVD (e.g., higher hopelessness or greater hostility or depression), (5) more adverse environmental exposures including social and biological/chemical/physical, and (6) elevated biological risk factors [26]. Thus, it will be valuable for future research to examine the extent to which cumulative stress, in addition to well-established behavioral and psychological risk factors, is able to account for social inequalities in CVD risk.

## Psychosocial Stress, Psychological Characteristics, Social Ties and Cardiovascular Disease

Cumulative psychosocial stressors must be understood in the context of established psychological characteristics and other

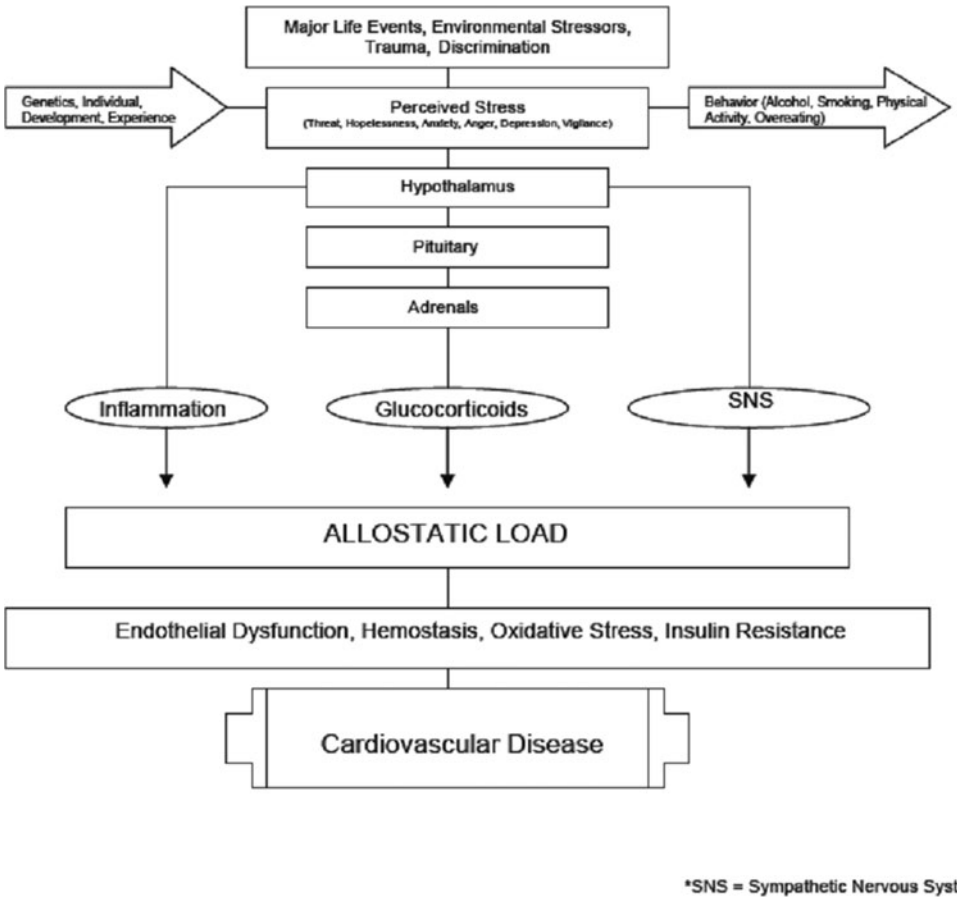


**Fig. 1** Mechanisms by which stress may cause cardiovascular disease

social factors that are associated with CVD risk. Although the pattern is not uniform, studies of general population samples, psychiatric patients, and cardiac patients have found that depression and anxiety are associated with increased risk of CVD [27]. Importantly, these associations persist in well-executed prospective studies that have adjusted for traditional risk factors and potential confounding factors in a broad range of different populations [28]. Hopelessness, a key symptom of depression, has also been shown to predict CVD mortality and MI in men even after adjusting for overall depressive symptoms [29]. Building on earlier research that had identified Type A behavior as a risk factor for CVD, the vast majority of recent research has found that anger and hostility are independent risk factors for CVD [28]. A large body of research has also shown that multiple indicators of social support, social integration and social networks are related to CVD morbidity and mortality [5, 30–33]. This research indicates that the absence of social ties typified by social isolation, the negative aspects of close relationships, and marital stress are strongly related to elevated CVD risk [34–36].

Research on psychosocial stressors or perceived stress in relation to CVD risk that has simultaneously considered other established psychological characteristics and social factors supports the importance of considering the joint influence of individual psychological characteristics and contextual characteristics. For example, prior research has indicated that perceived stress is more strongly associated with CVD functioning among individuals with low levels of social support [37]. Furthermore, another study found that women with high work stress also report elevated levels of hostility, anger, depression, anxiety and social isolation [38]. Given that psychosocial risks tend to co-occur and thus accumulate within the same individuals [39], a better understanding of how psychosocial stressors combine with each other and with individual differences in psychological factors and social ties to affect CVD risk is needed.

## Psychological Stress and Potential Contribution to US Black–White Disparities in Cardiovascular Disease

The potential role of cumulative stress in black–white disparities in CVD is also under-studied. The life expectancy for African-Americans (blacks) continues to lag behind that of their white American counterparts, by an average of 4 years in women and 5 years in men [40••]. It is important to understand the potential contribution of psychosocial stress to these statistics, especially since cardiovascular ailments are the leading cause of mortality. Considerable evidence indicates that social determinants of health including neighborhood, unemployment/

underemployment, financial difficulties, relationship problems, childhood adversity, racial/ethnic discrimination and a myriad of other stressors individually and jointly affect cardiovascular disability, morbidity and mortality beyond the effects of access to healthcare [41••]. A study by Duru et al. that utilized the National Health and Nutrition Examination found that measures of allostatic load were significantly higher in blacks than in whites in both genders such that the higher allostatic load score associated with blacks corresponded to at least a 2.5-fold greater mortality compared to whites [42]. Increasing evidence also suggests that racial/ethnic discrimination, a psychological stressor, influences blood pressure levels/hypertension in blacks [43•]. Interestingly, emerging research adds potential biological credence to a relationship between stress and hypertension in blacks. In a pilot analysis, Barksdale et al. found associations between increased exposure to stress with a lack of blood pressure dipping with sleep, and elevated cortisol levels among black women [44].

Psychological stress also appears to be associated with subclinical atherosclerosis. In a study of 629 white and 164 black male veterans, a moderate or high-risk nuclear imaging finding and corresponding evidence of high-grade coronary obstruction at angiography were related to perceived discrimination in blacks but not in whites (OR 1.3, 95 % CI 1.1 – 1.5; OR 1.0, 95 % CI 0.83 – 1.10, respectively) [45]. By contrast, results from the Jackson Heart Study, an ongoing cardiovascular cohort of blacks living in Mississippi, show differential mediation effects of psychological stressors (e.g., global perceived stress, negative life events and weekly stress inventory scales) on cardiovascular risk factors based on gender. In a cross-sectional analysis, stress mediated the association between SES and CVD risk factors including diabetes, hypertension and obesity among black women; however, no association was noted in black men [46]. No relationship was observed between stress and the presence of carotid plaque in either gender. A popular hypothesis related to psychological stress and the differential manifestation of disease risk is that active coping strategies positively influence an individual's disease risk. In this regard, an evaluation of blacks and whites who displayed defensive coping revealed that only among blacks was there a relationship between defensive coping, and higher stress scores, hypertension, lower levels of salivary 3-methoxy-4-hydroxyphenolglycol (a biomarker of sympathetic activation), higher inflammation and increased carotid intimal thickness [47].

At present, limited information exists about stress interventions among blacks, a critical area for further research. To this end, Schneider et al. assessed the role of transcendental meditation in blacks with known coronary artery disease [48••]. Specifically, in a randomized controlled trial of stress reduction utilizing transcendental meditation compared to health education in 201 black men and women, they observed a 48 % reduction in the composite endpoint of all-cause mortality, stroke or MI after 5.4 years of follow-up. These findings are encouraging and support the concept of psychological stress as a risk factor for vascular disease that warrants further research, not only related to identification of potential stressors but also of key interventions that might decrease CVD risk, particularly in black individuals.

## Future Directions

As described above, most research to date on psychosocial risks and CVD risk has focused on one or two psychosocial characteristics [28] or perceived stress [7••]. While these studies have provided an important first step toward an increased understanding of the social determinants of CVD risk, emerging evidence from cardiovascular medicine suggests that failure to study psychosocial stressors and relevant psychological or contextual characteristics comprehensively may underestimate the role of psychosocial stressors in CVD outcomes, or miss important interactions between psychosocial stressors and individual or contextual characteristics. Moving forward, it will be valuable for research to extend our current understanding of the role of cumulative stress in CVD risk. From a practice perspective, it is important to educate clinicians on psychosocial stressors as risk factors, and to draw on existing research to develop effective stress management techniques that can be integrated into CVD prevention programs.

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**Compliance with ethics Guidelines**

**Conflict of Interest** Natalie Slopen and David R. Williams declare no conflict of interest.

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- •• Of major importance

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