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Psychosocial factors in the development of heart disease in women: current research and future directions

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Abstract

Objective—To review the recent (1995–2009) literature on psychosocial risk and protective factors for coronary heart disease (CHD) among women, including negative emotions, stress, social relationships, and positive psychological factors.

Methods—Articles for the review were identified using PubMed and bibliographies of relevant articles. Eligible studies included at least 100 women and either focused on (a) exclusively female participants or (b) both men and women, conducting either gender-stratified analyses or examining interactions with gender. Sixty-seven published reports were identified that examined prospective associations with incident or recurrent CHD.

Results—In general, evidence suggests that depression, anxiety disorders, anger suppression, and stress associated with relationships or family responsibilities are associated with elevated CHD risk among women, that supportive social relationships and positive psychological factors may be associated with reduced risk, and that general anxiety, hostility, and work-related stress are less consistently associated with CHD among women relative to men.

Conclusions—A growing literature supports the significance of psychosocial factors for the development of CHD among women. Consideration of both traditional psychosocial factors (e.g., depression) and factors that may be especially important for women (e.g., stress associated with responsibilities at home or multiple roles) may improve identification of women at elevated risk as well as the development of effective psychological interventions for women with or at risk for CHD.

Keywords

coronary heart disease; women's health; depression; hostility; psychological stress; social support

Over the past decade, a number of reviews have summarized the growing literature on psychosocial risk factors for coronary heart disease (CHD), which include negative emotional states, psychological stress, and lack of supportive social relationships (1,2,3,4). Although these important reviews note some differences in risk factors for men and women, they do not evaluate the results systematically by gender. The goal of this review is to summarize the results of studies that examine the relationship between psychosocial risk factors and CHD for women specifically.

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Why Focus on Women's CHD?

Rather than generalizing results from studies of men to women, we believe that it is important to examine women separately to determine which psychosocial factors are most significant for their cardiovascular risk. Our reasons for conducting this literature review are fourfold. First, there is emerging evidence that the manifestation and presentation of women's CHD differ from CHD among men (5). The emergence of CHD in women typically lags about 10 years behind men due in part to the cardioprotective effect of endogenous estrogens. As a result, women with CHD tend to be older and have more comorbid conditions, such as arthritis and cancer, relative to men. Women also differ from men in the symptoms and signs of myocardial infarction (MI) with which they typically present, as women are more likely to present with atypical symptoms such as fatigue, nausea, shoulder or back pain, or shortness of breath rather than the classic symptoms of chest and radiating arm pain (6). Women are more likely to experience sudden cardiac events without prior symptoms (7) and are also more likely to experience ischemia and microvascular disease without any evidence of obstructive coronary disease (5). Women with CHD are less likely to be diagnosed and treated efficiently and aggressively, and as a result of these challenges as well as the fact that women with CHD tend to be older and sicker, women generally have a worse medical prognosis than men following MI or revascularization (8). Thus, women with CHD differ from men with CHD in important ways that may interact with psychosocial risk factors.

Second, there are notable gender differences in the prevalence of some psychosocial states that have been identified as coronary risk factors. For example, the lifetime risk for major depressive disorder among women is approximately twice that of men (9,10). Depression is a robust risk factor for both incident and recurrent CHD (11), yet women are not twice as likely as men to develop CHD as a result of their twofold greater risk for depression. This suggests that the strength of the association between certain psychosocial risk factors and CHD may differ across men and women. Given gender role issues, women may also be exposed to psychosocial experiences that are less prevalent among men, such as tension between career and family commitments (12). The effects may also differ by cohort with women in the labor force to a greater extent now than prior generations. Moreover, as described later, the psychosocial interventions studied to date have been demonstrated to be less beneficial for female CHD patients, highlighting a need to better understand gender differences in mechanisms and epidemiology linking psychosocial risk factors for recurrent CHD.

Third, the physiological mechanisms underlying CHD may differ between men and women. For example, diabetes mellitus (13) and the metabolic syndrome (14,15) appear to be more closely linked to CHD among women than men, and adjusting for the presence of diabetes reduces gender differences in risk. Traditional cardiovascular risk algorithms, such as the Framingham risk score, tend to underestimate CHD risk among women, whereas novel risk factors improve prediction (5). One of these novel biomarkers, C-reactive protein (CRP), is a stronger predictor of cardiovascular risk among women than men (16), and circulating CRP levels tend to be higher in women across the life course (17), suggesting that inflammatory processes may play a greater role in the development of women's heart disease. Women without obstructive coronary disease are at risk for left ventricular dysfunction precipitated by severe emotional stress, a phenomenon likely mediated by sympathetic nervous system activity (18). Lastly, data from the Women's Ischemia Syndrome Evaluation (WISE) suggests that stress-induced disruptions in ovulatory cycling may be associated with CHD in premenopausal women (19). This evolving evidence suggests that the pathophysiological mechanisms underlying women's CHD are not fully elucidated and that metabolic abnormalities, sympathetic nervous system dysfunction, inflammation, and endogenous estrogens play an important role. Given that factors such as depression and stress have been linked to each of

these biological processes (20,21,22), understanding the relationship between psychosocial risk factors and CHD outcomes among women is important.

Finally, there is a burgeoning literature on women's incident and recurrent CHD. The last systematic review of the literature on women was based on articles published between 1980 and 1994 (23). With a few notable exceptions (24,25), studies prior to 1995 often enrolled too few women to conduct gender-stratified analyses or merely adjusted for gender rather without examining potential interactions between gender and psychosocial predictors, limiting the information available about psychosocial risk factors for women's CHD specifically. In the past decade, large prospective epidemiological studies of women (e.g. Women's Health Initiative (WHI), Nurses' Health Study (NHS)) with significant follow-up intervals have been conducted, and more researchers have examined gender differences by conducting gender-segregated analyses or examining gender by predictor interactions.

The goal of this paper is to review literature from 1995–2009 on psychosocial factors in women's CHD. We have chosen to focus this review on emotional states and disorders, psychological stress, social support, and personality factors (1,2,4). Thus, this paper does not review the literature on health behaviors, such as smoking, or on links between socioeconomic status and CHD. Given our interest in psychosocial states and traits as risk factors for CHD, we use the term "gender" throughout this review (26). After summarizing the current state of the field, we highlight promising areas for future research.

Approach to the Literature Review

Articles for the current review were identified with PubMed using the Medical Subject Heading (MeSH) term *myocardial ischemia* (which included *acute coronary syndrome, coronary disease*, and *myocardial infarction*) and at least one of the following: *life change events; stress, psychological; emotions; social support; mood disorders; anxiety disorders; personality; adaptation, psychological*. The searches were limited to studies using human subjects and available in English language. Bibliographies of relevant articles also were used to identify additional studies that had not been identified by the database search. Because we were interested in predictors of CHD events during follow-up, we excluded studies with fewer than 100 female participants on the basis that these studies likely captured too few CHD events among women to yield reliable results. Eligible studies included focused either on (a) exclusively female participants or (b) both men and women, conducting either gender-stratified analyses or examined interactions with gender. Studies that focused exclusively on men or that adjusted for gender without reporting results separately for men and women or that did not test interactions with gender are not reviewed here because they do not allow for estimates of effects for women. We focus our discussion on studies that adjusted for at least a subset of known CHD risk factors and potential confounds, including age, smoking, and socioeconomic status. In studies of incident and recurrent CHD, we limit our review to studies with the endpoints of death (verified by public or hospital records) or cardiac events and excluded studies with the primary endpoints of angina, stroke, or congestive heart failure outcomes. See Table 1 for the methodological details of studies that yielded three or more reports included in this review.

Although we were predominantly interested in prospective risk factors for incident or recurrent CHD events or mortality, the burgeoning literature on indices of subclinical atherosclerosis could inform our discussion of mechanisms and potential prevention strategies. Advances in noninvasive imaging techniques permit quantification of subclinical atherosclerosis, including thickness of the common carotid artery intima-media complex (IMT) or the presence of coronary or aortic calcification. Although they are not strongly interrelated, each of these subclinical markers is significantly predictive of clinical coronary events (27,28) and provide an opportunity for investigators to examine the risk conferred by psychosocial factors early in

the progression of atherosclerosis, before symptoms emerge. This may be particularly important for studies of women, as many studies do not include adequate follow-up time to observe sufficient events given the older age at which women tend to manifest events. Most studies in this area are cross-sectional and provide limited information about the temporal association between psychosocial factors and subclinical atherosclerosis, but we include the few studies with longitudinal designs in our discussion of each psychosocial construct.

Overall, we identified 67 reports for inclusion in the current review. This includes 24 reports (from 10 independent studies) with exclusively female samples and 43 reports (from 27 independent studies) conducting gender-stratified analyses. The majority of studies in the current review (n = 53) focused on the prediction of incident CHD among initially healthy individuals. Sample sizes for these studies ranged from 312 to 97,253 women (median = 3,413), with 4 to 27 years of follow-up (median = 10 years). We also report the findings of investigations of psychosocial risk factors for recurrent CHD or mortality among female cardiac patients (n = 14). Sample sizes for studies of patients ranged from 106 to 792 women (median = 292), with 1 to 19 years of follow-up (median = 5 years). Given significant heterogeneity in psychosocial predictors, CHD outcomes, and other study characteristics, this systematic review does not employ meta-analytic methods to estimate aggregated effect sizes. We have organized this review by psychosocial risk factor, focusing first on associations with incident CHD, then recurrent CHD.

Negative Emotional States and Traits

Depression

Depression and incident CHD—Eighteen studies investigated the association between depressed mood, depressive disorders, or psychological distress and incident CHD among women. Three were prospective studies examining this relationship in exclusively female samples. In one study, more severe depressive symptoms were associated with increased risk of cardiovascular death, following a dose-response relationship (29). Findings from the NHS were consistent with this, with fully adjusted models indicating that depressive symptoms were associated with fatal CHD but not nonfatal events (30). A report from WHI included some women with CHD at baseline, and the association between depressive symptoms and mortality was significant only for women who did not report a history of CHD at study entry (31). Thus, results from these three large studies of women support the hypothesis that depressive symptoms predict CHD mortality among initially healthy women.

Of the 15 studies that examined both women and men, six reported a relationship between depression and elevated risk for CHD events or mortality that was significant for both genders (32,33,34,35,36,37) and did not significantly differ in magnitude. Five other studies reported a significant association between depression and incident CHD for women but not men. These reports included a study of healthy older adults (38), two studies of middle-aged adults (39, 40), and two studies of adults with chronic conditions that confer elevated risk for CHD, specifically hypertension (41) and insulin-dependent diabetes (42). The remaining four studies reported an association between depression and incident CHD for men but not women (43, 44,45,46). Thus, of 15 studies, depression was related to incident CHD in women in 75% of them. One other report examined relationships between general negative affect and incident CHD, reporting that negative emotion was independently associated with elevated CHD risk for both genders (47).

Depression and recurrent CHD—Seven studies examined the association between depression and recurrent CHD. Four reports focused on samples of female cardiac patients. In their study of women 3–6 months after hospitalization for an acute coronary event, Horsten and colleagues (48) reported that endorsing two or more depressive symptoms doubled risk

for recurrent events, suggesting that even low levels of depression may have prognostic significance for female patients. In WISE, women with suspected coronary artery disease who reported both current depressive symptoms and a history of treatment for depression had significantly increased risk for death or recurrence (49). This effect was partially mediated by elevations in systemic inflammation (i.e., CRP; 50). A recent paper based on this same sample examined categories of depressive symptoms and reported that somatic (e.g., fatigue, difficulty sleeping) but not affective or cognitive symptoms of depression were associated with increased CHD risk (51), consistent with other analyses in mixed gender samples (52). Three additional studies examined the association between depression and recurrent CHD in women compared to men, and all three reported that depressive symptoms were significantly associated with coronary mortality among both male and female patients recently hospitalized for CHD (53, 54,55). Taken together, these studies suggest that depressive symptoms in the aftermath of a cardiac event are associated with increased risk for recurrent events or death in women.

Summary—Depression, which is twice as common among women relative to men, is a relatively consistent predictor of both incident and recurrent CHD among women. Twenty-five studies provide suggestive evidence that depression may be most strongly related to CHD outcomes among women when depression is chronic and severe. Recent longitudinal analysis of subclinical athersoclerosis measures in the Study of Women's Health Across the Nation further supports this hypothesis, as results revealed that recurrent depression (but not a single episode of depression) was a risk factor for progression of coronary calcification in midlife women (56). For both genders, the somatic symptoms of depression such as fatigue may be more closely related to clinical CHD events. These somatic symptoms may be a marker of early CHD, poor general health, and/or sickness behavior related to systemic inflammatory processes (57). Consistent with this finding is a longitudinal analysis from the Pittsburgh Healthy Heart Project, which found that depressive symptoms, particularly somatic symptoms, predicted increasing carotid IMT for both men and women (58).

Anxiety

Anxiety and incident CHD—Another negative emotion that may be a risk factor for CHD is anxiety. Several anxiety-related constructs have been examined in research, ranging from single items tapping anxiety (e.g., "Are you often troubled by feelings of tenseness, tightness, restlessness, or inability to relax?") to clinical anxiety disorders. We identified seven prospective studies that examined the role of anxiety in predicting incident CHD. All four of the women-only studies reported a significant increase in CHD risk associated with anxiety symptoms and disorders, including symptoms of phobia (particularly claustrophobia), posttraumatic stress disorder, and panic disorder (59,60,61) as well as general anxiety (e.g., "being anxious/worried"; 62). Of three studies including both men and women, two used brief measures of anxiety and indicated that, although anxiety was significantly more common among women, anxiety predicted five- (but not ten-year) incident CHD and mortality in men but not women (63) and that, although anxiety was associated with total mortality for both genders, tension was associated with increased risk of incident CHD for men only (64). One other study conducting gender-segregated analyses used a well-validated measure of anxious mood, the General Well-being Schedule, and reported that elevated anxiety was associated with risk for both men and women (40).

Anxiety and recurrent CHD—Of two separate prospective studies of cardiac patients conducted by Frasure-Smith and colleagues, one reported that anxiety predicted cardiac mortality over the year after MI for men but not women (54), while the other reported that anxiety two months after cardiac catheterization predicted recurrent disease in both men and women over two years (55).

Summary—Available literature is small and mixed, with only nine studies identified for inclusion. Anxiety disorders are associated with increased CHD risk among initially healthy women, but studies of both incident and recurrent CHD report that general anxiety is a more consistent coronary risk factor for men than women. Only one longitudinal study has examined anxiety and subclinical atherosclerosis, reporting that anxiety was not related to IMT progression for either gender (58).

Hostility

Hostility and incident CHD—Another category of negative emotions that have been examined as psychosocial risk factors includes hostile attitudes, behaviors, and emotions. Six studies investigated the link between such hostility-related constructs and incident CHD in women. In WHI, cynical attitudes (mistrust of others) increased risk of death but not incident cardiac events, particularly among African-American women (65). Five prospective studies conducted gender-segregated analyses. With the exception of one study of hostile attitudes in older Danish adults (66), which reported significant associations with MI and mortality for both genders, all studies found that the relationship between angry emotional states and incident CHD was significant among men but not women. Of note, studies that compared mean hostile attitudes or angry emotion scores between men and women reported higher scores for men. These four studies reported a positive association among men, suggesting that greater trait anger (67,68), "CHD-prone personality" (tendency to experience anger, aggression, and arousal when faced with relational problems; 69), and hostile attitudes (70) predict CHD in middle-aged men but not in women. Taken together, these five studies suggest that the association between hostile attitudes or anger and CHD in initially healthy adults is not apparent in women and is stronger for men, a conclusion consistent with the effects of a recent meta-analysis (71).

Hostility and recurrent CHD—Two studies of women with suspected or documented CHD found that hostile attitude scores predicted significantly increased risk for future cardiac events (72,73).

Summary—Results from these eight studies suggest that hostile attitudes predict clinical outcomes for African-American women or for women who already have CHD. Experience of anger is less strongly associated with incident CHD in women relative to men. Trait anger has also been associated with progression of subclinical carotid atherosclerosis in women in one longitudinal report from the Healthy Women Study (HWS; 74), although hostility showed no association with IMT progression in another sample of both men and women (58). Of note, there is some evidence that hostility may consist of multiple dimensions that are differentially associated with CHD (e.g., neurotic vs. non-neurotic hostility; 75), a possibility which was infrequently appreciated in the studies meeting our criteria.

Anger suppression

Anger suppression and incident CHD—In addition to the frequency or severity of angry feelings, the expression or suppression of hostility and related emotions may also be associated with CHD risk. Three reports examined prospective associations between anger suppression and incident CHD for both men and women. One report from the Framingham Offspring Study found that the Anger-In subscale of the Spielberger Trait Anger Expression Inventory was not associated with CHD risk for either men or women (67). However, another analysis of the same cohort reported that self-silencing (i.e., keeping feelings to oneself during conflicts with spouse) was associated with fourfold increased risk for CHD among women but was unrelated to CHD outcomes among men (76). The Tecumseh Community Heart Study used a hypothetical anger-provoking scenario to assess tendency to suppress anger, reporting that anger suppression was associated with CHD mortality for women but not men (77). In a fourth

study examining a potentially related construct, submissiveness (defined as a preference to stay in the background and let others dominate), Whiteman and colleagues found that greater submissiveness was associated with reduced CHD risk among women but not men (78).

Anger suppression and recurrent CHD—In a recent study of women hospitalized for an acute cardiac event, suppression of angry feelings was significantly associated with risk for a recurrent event or cardiac death (79). However, a study of one-year prognosis after MI reported that Anger-In was not associated with outcomes for either men or women (54).

Summary—The Anger-In scale did not show consistent associations with coronary risk; two additional longitudinal reports indicated that Anger-In was unrelated to IMT progression over three years (58,74). However, studies that employed alternative, study-specific measures of suppressed anger demonstrated that this construct may predict outcomes both among healthy women and women who have had cardiac events. Self-report assessments of anger-in are limited by participants' awareness of and willingness to report on their tendencies to suppress anger. Based on these six studies, links between anger suppression and cardiovascular health among women warrants additional study.

Stress

Stress and incident CHD

Another psychosocial risk factor that has been linked to CHD in men is stress, most commonly work-related psychological stress (80,81). Three studies examined the relationship between work stress and incident CHD in samples of women only. Two of these reported no significant association between job strain (defined as high demand and low control), passive jobs (defined as low demand and low control), or active jobs (defined as jobs that are both high in demands and high in control) and CHD (82,83). Another report from the NHS found no relationship between job security and total CHD, although job insecurity was associated with increased risk of nonfatal MI over two years but not four years of follow-up (84). Three other studies conducted gender-segregated analyses. Two analyses conducted with the Whitehall II cohort found that both job strain and effort-reward imbalance were associated with incident CHD for men and women (85,86). An analysis of the Framingham Offspring study reported that for women but not men, active jobs characterized by both high demand and control increased risk of incident CHD (87).

In addition to these studies of work-related stress, two studies examined the relationship between general daily stress and incident CHD among men and women. While Iso and colleagues reported that relationships with total CHD were stronger among Japanese women than men (88), Nielsen and collaborators reported that perceived stress predicted CHD mortality for young, healthy Danish men but not women (89).

Stress and recurrent CHD

Two reports from the Stockholm Female Coronary Risk Study (FemCOR) reported that work stress alone had no significant relationship with recurrent events in women after a coronary event (90) but that the combination of work and marital stress was associated with a nearly sixfold increased risk for recurrent disease (91). Another study of male and female MI patients reported that job strain did not predict recurrent events or mortality for either gender (92).

Summary

Results from these fifteen studies suggest that traditional measures of job strain based on perceptions of high demand and low control at work may be less important for women relative to men. Consistent with this, a longitudinal analysis using daily diary data reported that ratings

of high demand and low control in daily life were associated with IMT progression over three years for men but not women (93). Rather than traditional measures of job stress increasing risk, women who have both high demand and high control at work may be at elevated risk for CHD, along with women exposed to psychological stress both at work and at home. Inconsistent relationships between CHD and nonspecific stress underscore the need for future research to examine specific sources of psychological stress relevant to women's lives when investigating women's cardiovascular risk.

Social Relationships

Social relationships and incident CHD

Social relationships, size and diversity of networks, and positive support from others have also received empirical attention as psychosocial factors linked to CHD. Studies examining social support or stress in social relationships were more likely than studies of more traditional psychosocial risk factors to use study-specific measures rather than well-validated scales. Of the two women-only studies linking social relationships to incident CHD, one study examining social support at work and home cited null results (82) while another reported that larger social networks and being married were each associated with reduced risk of mortality (94). Five studies examined associations between social relationships and incident CHD in men and women separately, with mixed results. Two found that perceived social support was not associated with incident CHD for either gender (68,95). Two studies reported that the presence of a partner was associated with reduced risk of incident CHD for men but not for women (76,96). The remaining two studies found significant relationships for women only between CHD risk and low social support at work (97) and loneliness (98).

Stress related to interpersonal relationships and family responsibilities has received less attention in relation to CHD in men but may be significant for women's CHD. In two papers from the NHS, Lee and collaborators reported increased risk for incident CHD associated with hours spent caring for children or grandchildren (99) and hours spent caring for a disabled or ill spouse (100). However, neither report found a relationship between the perceived stress or reward associated with caregiving and CHD. Two additional studies examined gender-specific associations. One reported that greater conflict in close relationships predicted MI for both genders (101), while an analysis of the Whitehall II cohort found that perceived control at home was associated with reduced risk for incident CHD for women but not men (102).

Social relationships and recurrent CHD

Two studies of female patients with documented or suspected coronary disease reported that low levels of social integration were associated with increased risk for recurrent events and mortality (48,103). A study of men and women that survived to discharge following MI found no association between perceived social support and survival for either gender (54).

With respect to the stressful aspects of relationships, the Stockholm Female Coronary Risk Study reported that marital stress nearly tripled the risk for recurrent events (90), and a follow-up analysis concluded that it was the combination of work and marital stress that was the strongest predictor of recurrent disease (91).

Summary

Evidence from these studies suggests that the presence of social relationships may be important for the cardiovascular health of both disease-free women and coronary patients. While the mere presence of a spouse or partner may be protective for men, the presence of positive, reciprocal social relationships may be more important for women. In the HWS, high marital satisfaction predicted less IMT progression (104). Another study found that frequent interactions with one's

spouse in the context of a satisfactory marriage predicted less IMT progression for men only (105). For women, more frequent social interactions predicted greater increases in IMT, leading the authors to hypothesize that frequency of social interactions may reflect greater role overload among women. Given methodological variations in how the presence, quantity, and quality of social relationships were assessed, more research clarifying the kind of social support most important for women's CHD is warranted. Preliminary data further suggest that psychological stress in interpersonal domains may be more important risk factors for women's CHD than work-related stress and that cumulative stress from multiple roles may be an important risk factor for women.

Positive Psychological Factors

Positive psychological factors and incident CHD

Relative to negative psychological factors, positive factors have received relatively little study in relation to CHD. We identified four studies that examined the relationship between positive states or traits and incident CHD in women. First, optimism, a dispositional tendency to expect positive outcomes, was associated with reduced risk for MI, incident CHD, and CHD mortality in the WHI (65). In a sample of elderly Dutch adults, however, optimism was associated with coronary death among men but not women (106). Positive affect was not associated with incident CHD for either women or men in Whitehall II (47), while greater emotional vitality (a sense of vitality, positive well-being, and emotional control) was related to lower risk for incident CHD for both genders in NHANES I (107).

Positive psychological factors and recurrent CHD

To our knowledge, no prospective studies to date meeting our inclusion criteria have that examined whether optimism or other positive psychological factors are associated with prognosis among female CHD patients.

Summary

Preliminary data from six studies in this area suggest that optimism and other positive psychological attributes may be associated with lower risk of incident CHD among women. In HWS, optimism was also associated with less IMT progression over three years (108).

Overall Summary of Women's Risk Factors

Table 2 presents a summary of our findings on psychosocial factors for women's CHD. Although women's CHD differs from men's disease in important ways, our review highlights more gender similarities than differences with respect to psychosocial risk factors for incident or recurrent disease. With respect to negative emotions as a risk factor for CHD, our findings suggest that depressive symptoms are related to CHD and that severe, worsening, or recurrent clinical depression and somatic rather than cognitive/affective symptoms of depression may be particularly important risk factors. Anxiety requires further investigation, although some studies indicate that it is more consistently related to CHD risk among men than women. However, the presence of specific anxiety disorders (i.e., panic disorder, claustrophobia, and posttraumatic stress disorder) appears to be associated with elevated risk among healthy women. Limited evidence exists for anger being associated with increased risk for incident CHD among healthy women, though hostile attitudes may be important for African-American women and female CHD patients. Some data support the hypothesis that suppression of angry feelings is associated with adverse outcomes for both healthy and clinical female samples.

Although there is significant conceptual and measurement overlap between depression, anxiety, and anger (4), our review of the evidence examining each of these emotions as separate

constructs suggests that depression and, to a lesser extent, anxiety are reliable predictors of elevated CHD risk among women whereas anger is not. To isolate the risk conferred by specific negative emotions and to clarify how negative emotional risk factors may work together (e.g., the risk of CHD among women with comorbid depression and anxiety), future studies should measure negative emotions so that these complex relationships can be better understood. Our findings further suggest that measurement of emotion regulation constructs such as suppression and expression may account for additional variance in CHD risk in women.

With respect to other psychosocial factors, work-related stress is not consistently predictive of incident CHD among women, while stress at home or in relationships, alone or in combination with work stress, is related to adverse outcomes for both healthy women and female CHD patients. Supportive social relationships are associated with reduced CHD risk in women as in men. Finally, preliminary findings suggest that some positive psychological factors (e.g., optimism) may be associated with decreased CHD risk among healthy women. Whether the benefits of these positive traits and states are independent of negative emotions, stress, and social relationships remains unknown.

Interventions

Clarifying psychosocial risk factors for CHD in women is important to the extent that it identifies women who may be at risk for coronary events and guides prevention and intervention efforts to reduce the burden of women's CHD. To date, however, psychological interventions have had limited success with female CHD patients. We discuss the results of several interventions aimed at reducing psychosocial risk factors in women.

First, the Montreal Heart Attack Readjustment Trial (M-HART; 109) was a randomized controlled trial of monthly telephone monitoring of psychological distress combined with home-nursing visits in response to high levels of distress. Participants were 1376 post-MI patients (34% women) who were assigned to either the intervention or usual care for one year. Overall, the intervention had no significant survival benefit and only marginal effect on depression and anxiety for men. However, women in the intervention group showed no psychological benefit and had *higher* cardiac and all-cause mortality than the control group.

The Enhancing Recovery in Coronary Heart Disease trial also reported gender differences. In this trial, 2481 MI patients with depression and/or low perceived social support (44% women) were randomized to cognitive behavioral therapy (plus antidepressant medication as necessary) or usual care. All intervention groups showed an improvement in their depressive symptoms and perceived social support. However, post-hoc analyses revealed that only white men benefited from the intervention with respect to cardiac mortality or nonfatal MI (110). Furthermore, minority women in the intervention arm had marginally higher mortality than control participants. Again, the reasons for the differential impact of the intervention by race/ethnicity and gender are unclear, although the authors note that white men received more intensive medical treatment than either women or minorities.

Finally, a recent trial randomized 302 post-coronary artery bypass graft patients with depression (41% women) to telephone-delivered collaborative care or usual care. At 8-month follow-up, men randomized to the intervention reported a significant improvement in depressive symptoms and health-related quality of life whereas women did not (111).

These findings highlight a lack of understanding about how to effectively intervene with distressed female CHD patients to optimize cardiovascular outcomes. Psychological interventions studied to date have tended to be focused on symptom reduction and directive advice rather than emotional expression and social support. Secondary analysis of the patient-nurse interactions from M-HART revealed that educational and reassurance/encouragement

approaches tended to predict reductions in distress among men but worse outcomes for women, whereas listening to concerns about non-cardiac physical symptoms and treatment burden was related to better psychological outcomes for women (112). Women may also benefit from group-based interventions with other female patients rather than mixed gender groups, as women with CHD tend to be older, have lower socioeconomic status and more medical comorbidity, are more likely to live alone, have greater household responsibilities, report lower self-esteem and quality of life following a cardiac event, and may face particular barriers to recovery, including poor exercise capacity and low self-efficacy regarding exercise, transportation problems, and lack of social and spousal support (113). Two pilot studies provide preliminary evidence that women-only CHD rehabilitation (114) and stress management (115) tailored to the concerns and challenges of women may be well-accepted. Investigators in Sweden recently published the results of a randomized controlled trial of group-based stress reduction vs. usual care among 237 female CHD patients (116). Consistent with the literature highlighting home stress, unsupportive social relationships, and suppression of negative emotions as particularly important risk factors for women, the yearlong intervention included focus on coping with stress at home and at work and on social relationships as well as opportunities for emotional expression and the formation of supportive social bonds within the group. Relative to women in the control group, women randomized to the intervention were three times less likely to die after 7 years of follow-up, even after adjusting for clinical prognostic factors. These encouraging results require replication, and additional research in this area is needed to determine which specific strategies will be most effective to reduce psychosocial risk factors and affect cardiac outcomes, both for women with CHD and those at risk.

Summary and Recommendations for Future Research

Accumulating evidence suggests that the biological risk factors, pathophysiology, manifestation, and prognosis of women's CHD differ from men's heart disease. The aim of this review was to summarize the existing literature on psychosocial risk factors for CHD among women. The number of studies including large samples of women has grown significantly in the past 15 years, and we reviewed 67 reports, including prospective epidemiological studies following healthy women and large longitudinal studies of CHD patients.

Based on the current state of the evidence, we advance the following recommendations for future research:

1. The sources of psychological stress important for CHD may be different for women than for men. For women, marital strain, home responsibilities, strain of multiple roles, or lack of reciprocal supportive relationships may be particularly salient, whereas work-related stress may be less important. However, more fine grained analyses are needed as the current cohorts of aging women are markedly different with regard to education, occupation, and social roles, compared to women in earlier cohorts. Ecological momentary assessment of psychological stress could shed light on the types of daily stressors associated with increased CHD risk among women. Given mounting evidence that trajectories to adult CHD begin in childhood (117, 118), research investigating whether early life stress and consequent psychosocial functioning are associated with increased risk for incident CHD is also needed.
2. In addition to research linking frequency or severity of negative emotional experiences to CHD, emotion regulation is a fruitful area for further investigation. Increased attention to individual differences in emotion regulation may result in a better understanding of the role of negative emotion in women's CHD and what constitutes healthy emotional expression in women. For example, the combination of

high levels of anger coupled with a tendency to suppress negative emotions may be particularly cardiotoxic. Given limitations in self-report methodology, researchers in this area should consider techniques such as behavioral assessments (e.g., coding of facial expressions in the laboratory) or obtaining reports about emotional regulation tendencies from spouses or other informants. Investigators should also test the hypothesis that a flexible emotion regulation style, such as the ability to suppress or express negative emotions depending on the context, is cardioprotective (119).

3. Further research is needed to understand whether positive affect and cognitions protect women from CHD, independent of negative affect and cognitions. Positive affect may be particularly important for older women and/or those facing greater stress (120). If positive affect and cognitions prove indeed to be important, it would provide another avenue for intervention in women, i.e. enhancing positive states as opposed to reducing negative states.

4. There is some evidence that gender and race may interact with respect to psychosocial factors and CHD, such that cynical cognitions were more strongly linked to CHD (65) and psychological stress associated with subclinical atherosclerosis (121) in African-American women. Future studies with adequate sample sizes to support these types of analyses should test these three-way interactions between psychosocial variables, gender, and race.

5. Given that women develop CHD later in life than men, the use of subclinical disease measures as tools to examine psychosocial hypotheses in women earlier in the pathogenesis of CHD is important. Longitudinal studies with repeated assessments to permit quantification of progression of subclinical atherosclerosis over time will be especially helpful, as most analyses are cross-sectional and limit causal inference.

6. Although depression is consistently associated with increased cardiovascular risk for both men and women, existing psychological interventions for depression have not benefited women with respect to cardiovascular outcomes. Research to improve the efficacy of psychological interventions for women with or at risk for CHD is needed. In particular, novel interventions targeting some of the psychosocial risk factors identified in this article (e.g., suppression of anger, marital stress, loneliness) may prove to be particularly beneficial for female patients.

7. All large scale clinical trials and observational studies that include women should include a psychosocial assessment of negative emotions, social support, and psychological stress to permit evaluation of psychosocial hypotheses in predicting CHD events. Ongoing research using item-response approaches to developing brief, reliable measures of these constructs would make inclusion of such assessments feasible and cost-effective. Assessment of less commonly studied risk factors, such as anger suppression, caregiving and marital stress, and strain associated with multiple roles at work and at home should also be included in future studies that are in the position to test more speculative concepts.

8. Rather than merely adjusting for gender, investigators examining the association between psychosocial factors and CHD should test hypotheses separately for men and women, either by conducting stratified analyses or by testing interactions with gender.

Given emerging evidence that women's CHD differs from men's disease with respect to epidemiology and pathophysiological mechanisms, we expected at the outset that a systematic review of the literature would reveal significant gender differences in the association between psychosocial factors and CHD. Instead, we identified more similarities than differences between women and men with respect to the psychosocial risk factors associated with increased CHD risk. We also identified several factors that were less (hostility, work stress) or more

(marital stress, anger suppression) important for women than men. Identifying the psychological factors associated with increased CHD risk in women will facilitate the identification of vulnerable women in clinic and inpatient settings. It may inform the development of effective prevention and intervention strategies to improve both quality of life and cardiovascular health among women. Available evidence on the psychosocial predictors of future CHD in women has provided a good start on achieving these goals but much work remains to be done.

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Glossary

CHD	coronary heart disease
CRP	C-reactive protein
HWS	Healthy Women Study
IMT	intima-media thickness
MI	myocardial infarction
NHS	Nurses' Health Study
WISE	Women's Ischemia Syndrome Evaluation
WHI	Women's Health Initiative

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Table 1

Methodology of major studies included in literature review.

Name of study	N	Sample	Years of follow-up	Psychosocial predictors	Cardiovascular (CV) outcomes	References
FemCOR	292	Swedish women aged 30–65 admitted for an acute coronary event	5	Depressive symptoms, social integration, job stress, marital stress	CV mortality, acute MI, PTCA CABG	48,90,91
Framingham	1328 to1999	US adults aged 18–77	6–10	Depressive symptoms (CES-D), tension and anxiety, hostility, anger expression, marital status, marital satisfaction, self-silencing, job stress	CHD incidence, all-cause mortality	37,64,67,76,87
NHANES I	1466 to 5007	US adults age 25–75	10–19	Depressed mood (GWB and CES-D), loneliness (item from CES-D), emotional vitality	Nonfatal and fatal CHD events	40,43,98,107
NHS	35038 to 72359	US nurses aged 46–71	4–12	Depressive symptoms (MHI-5), phobia symptoms, job stress, job security, caregiving to spouse/parent, caregiving to children/ grandchildren	Sudden cardiac death, fatal CHD, nonfatal MI	30,59,83,84,99,100
Whitehall II	2897 to 3413	UK civil servants aged 35–55	8–12	Positive and negative affect (Affect Balance Scale), work stress, negative aspects of close relationships, control at home	Fatal CHD, nonfatal MI, definite angina	47,85,86,101,102
WHI	92676 to 97253	US women aged 50–79	4.1–8	Depressive symptoms (items from CES-D), panic symptoms, optimism, hostility	CHF, MI, CABG, angioplasty, CV mortality	31,61,65
WISE	503 to 559	Women referred for coronary angiogram, no recent MI or PTCA or CABG	2.3–5.9	Depressive symptoms (BDI), hostility, social network diversity	MI, CV mortality	49,50,51,73,103

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Table 2

Summary of findings from literature review.

Psychosocial construct		# of reports / studies	Summary of results	Range of significant effect sizes	Range of follow-up	Quality of psychosocial measure(s)	References
Depression	Incident	18 / 16	+ in 12; 0 in 3; +/0 in 3	RR 1.03 (ref 39) to 3.00 (ref 34), most < 2.0	4 – 27 years (median = 9 years)	well-validated measures in 17; single item in 1	29,30,31,32,33,34,35,36,37,38,39,40,41,42,43,44,45,46
	Recurrent	7 / 5	+ in 7	RR 1.37 (ref 54) to OR 3.29 (ref 55)	1 – 19 years (median = 4.9 years)	well-validated measures in 7	48,49,50,51,53,54,55
Anxiety	Incident	7 / 7	+ in 5; 0 in 1; +/0 in 1	RR 1.30 (ref 67) to HR 4.20 (ref 69)	5 – 15 years (median = 10 years)	well-validated measures in 3; minimally validated measures in 4	40,59,60,61,62,63,64,
	Recurrent	2 / 2	+ in 1; 0 in 1	OR 2.58 (ref 56)	1 – 2 years (median = 1.5 years)	well-validated measures in 2	54,55
Hostility	Incident	6 / 6	+ in 1; 0 in 6	RR 1.53 (ref 75)	6 – 27 years (median = 10 years)	well-validated measures in 6	65,66,67,68,69,70
	Recurrent	2 / 2	+ in 2	HR 1.50 (ref 83) to 2.03 (ref 82)	1 – 4 years (median = 3.6 years)	well-validated measures in 2	72,73
Anger Suppression	Incident	4 / 3	+ in 2; − in 1; 0 in 1	RR 1.70 (ref 90) to 4.01 (ref 89)	5 – 17 years (median = 10 years)	well-validated measure in 1; minimally validated measures in 3	67,76,77,78
	Recurrent	2 / 2	+ in 1; 0 in 1	HR 1.19 (ref 92)	1 – 6.4 years (median = 3.7 years)	well-validated measures in 2	54,79
Stress	Incident	8 / 6	+ in 3; 0 in 3; +/0 in 2	HR 1.26 (ref 99) to RR 2.28 (ref 101)	4 to 22 years (median = 11 years)	well-validated measures in 5; single item in 2; minimally validated measures in 1	82,83,84,85,86,87,88,89
	Recurrent	3 / 2	+ in 2; 0 in 1	HR 2.38 (ref 105) to 5.7 (ref 104)	5 to 6 years (median = 5.5 years)	well-validated measures in 3	90,91,92
Social	Incident	12 / 10	− (supportive social relationships) in	HR 1.81 (ref 115) to 2.72 (ref 114)	4 to 19 years (median = 8 years)	well-validated measures in 2; minimally	68,76,82,94,95,96,97,98,99,100,101,102

Psychosocial construct		# of reports / studies	Summary of results	Range of significant effect sizes	Range of follow-up	Quality of psychosocial measure(s)	References
			3; + (caregiving and negative aspects of relationships) in 3; 0 in 5			validated measures in 10	
	Recurrent	5 / 3	−(supportive social relationships) in 2; + (marital stress) in 2; 0 in 1	HR 2.3 for low social integration (ref 49), HR 2.9 for marital stress (ref 103)	1 to 5 years (median = 4.8 years)	well-validated measures in 3; minimally validated measures in 2 reports (same study)	48,54,90,91,103
Positive	Incident	4 / 4	−(optimism, emotional vitality) in 3; 0 in 1	HR 0.91 (ref 74) to 0.22 (ref 123)	8 to 15 years (median = 10.5 years)	well-validated measures in 3; minimally validated measures in 1	47,65,106,107
	Recurrent	0					

Notes. + = positive association; − = negative association; 0 = no significant association; +/0 = mixed results