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Psychological health and ischemic heart disease in women: A review of current evidence and clinical considerations across the healthspan

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Abstract

PURPOSE OF THE REVIEW: Psychological health encompasses a constellation of negative and positive factors – i.e., psychosocial stress, depression, anxiety, trauma, loneliness and social isolation, anger and hostility, optimism, and a sense of purpose. This narrative review presents current evidence for the intersection of psychological health, risk of ischemic heart disease (IHD), and IHD-related outcomes, with an emphasis on associations in women.

Recent Findings: For women, relations between psychological health and IHD reflect important sex and gender differences in biological and psychosocial factors. Although efforts devoted to understanding psychological health and IHD risk have varied by psychological factor – scientific evidence is strongest for depression, while anxiety, trauma, and positive psychological factors warrant more investigation – less optimal psychological health was consistently associated with an earlier and greater risk of IHD morbidity and mortality in women. Still, many past prospective studies of psychological factors and IHD risk had a limited representation of women, did not include analyses by sex, or failed to account for other influential, sex-specific factors. Thus, there are multiple pathways for further, rigorous investigation into psychological health-IHD associations, mechanisms, and empirically-supported psychological interventions to mitigate IHD risk among women.

Summary: Given the robust evidence linking psychological health with women's risk for IHD, implementing routine psychological assessment is recommended. Significant life events, developmental milestones specific to women, and IHD diagnoses or events could cue

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additional psychological assessment, which will mutually strengthen the evidence for integrated psychological and IHD care and delivery of that care to this vulnerable group.

Keywords

heart; ischemic heart disease; mental health; psychological health; women

Introduction

The World Health Organization defines psychological health as “a state of well-being in which an individual realizes his or her own potential, can cope with the normal stresses of life, can work productively and fruitfully, and is able to make a contribution to his or her community” [1]. Also often referred to as mental health, psychological health is evaluated on a multidimensional spectrum from positive dimensions and well-being (e.g., happiness, optimism, sense of purpose and meaning) to negative dimensions and ill-being (e.g., depression, anxiety, hopelessness, pessimism) [2]. Psychological health encompasses both short-term emotional states and subclinical symptoms (e.g., psychological distress) and more lasting symptoms that meet diagnostic criteria for psychiatric disorders. Importantly, psychological health is a critical component of cardiovascular health (CVH), as it confers risk for ischemic heart disease (IHD) and other types of cardiovascular disease (CVD), especially among women [2–6]. Negative dimensions of psychological health are associated with the onset of cardiovascular risk factors (e.g., hypertension, obesity) and IHD (e.g., angina, acute myocardial infarction [MI]), greater risk for IHD incidence and progression, adverse outcomes following major acute cardiovascular events (MACE), and premature mortality [7–13]. In contrast, positive dimensions of psychological health are associated with better CVH and recovery following acute ischemic events [2, 14, 15].

The connection between psychological health and IHD among women is in part due to important sex and gender differences in women’s vulnerability to these conditions. Such differences are likely due, in part, to genetics, neurobiological factors including sex hormones, dopaminergic, noradrenergic, and serotonergic systems, and regulation of those systems [16]. Simultaneously, the intersectionality of sex, gender, culture, and race that informs women’s lived experiences also influences psychological health, health behaviors, and social interactions, thus setting the stage for women’s health risk, outcomes, and quality of life. In contrast with sex, which is a biologically-determined category, the construct of gender refers to a person’s relationships and interactions based on their gender identity (i.e., marital/relationship status, family or local network, social support) [17]. Compared to men, women tend to be more disadvantaged in education, income, health literacy, and access to healthcare [18]. Women from socially and racially disadvantaged backgrounds have distinct experiences of stigma, stereotyping, and discrimination [19, 20]. Social and structural disparities due to sex and gender-related roles also directly and indirectly affect women’s psychological health and subsequent IHD risk [7, 21–23].

While psychological health is an important component of cardiac and vascular health, it is often overlooked during women’s healthcare interactions. Clinicians may feel rushed or lack the skills to assess psychological health. Patients, too, may feel uncomfortable or

uncertain about sharing psychological concerns with their providers [24]. Specific to IHD management, patients may not think it is appropriate to discuss psychosocial stress, other dimensions of their psychological health, psychiatric diagnoses, or treatment history with their cardiologist, and may worry that they will be judged or treated differently. The need for greater awareness of the psychological-CVH intersection among women and integration into cardiovascular care encourages this state-of-the-science review. We first review the most relevant studies and meta-analyses published in the last 10 years that included women, stratified by different psychological attributes. In the second section, we review evidence-based psychological treatment strategies and suggest approaches for incorporating psychological health into clinical practice. Ideally, the conclusions and identified questions will inspire further scientific advances and encourage the inclusion of psychological health in recommendations for IHD management across women's life course.

Negative Psychological Factors

Psychosocial Stress—Psychosocial stress is a normal aspect of daily life and more than half of patients with a diagnosis of IHD and other types of CVD report high levels of stress [25]. Women report greater stress burden than men – with more daily stress and chronic stress exposure (e.g., sex-based discrimination, socio-culturally constructed roles and identities, multiple role burden – as a partner, primary caregiver, financial provider, and a single and/or working parent [26–28]), and greater cumulative stress across the lifespan [29–33] – which may increase risk for IHD [34]. Additionally, standardized mental stress paradigms often provoke differential responses to stress among women. In some studies, women show distinct hormonal responses to acute stress [35, 36], and stress-induced myocardial ischemia (MSIMI) – assessed with myocardial perfusion imaging – is twice as common among women than men [10, 37–41]. Interestingly, MSIMI may go undetected among women (i.e., occur in a subclinical manner) as it is often not associated with anginal symptoms, electrocardiographic abnormalities, or the degree of atherosclerotic disease [42]. Sex-specific observational studies also demonstrate the contribution of MSIMI to future IHD risk. Women who showed peripheral microvascular dysfunction in response to a mental stressor at baseline had a 50% greater risk of MACE over 5 years compared to both women without this response and to men with a positive mental stress-induced response [10], underscoring the potential role of mental stress in women's distinct stress-related vulnerability to IHD. Still, more robust prospective investigations are required to determine how MSIMI and other acute physiological changes in response to mental stress predict IHD risk development among women.

Substantial observational evidence also highlights the importance of chronic psychosocial stress in vulnerability to IHD among women. An estimated 58% of patients with CVD report high levels of psychosocial stress. Prospective analyses from 6,508 participants in the Multi-Ethnic Study of Atherosclerosis (MESA; 53% women), revealed that lifetime discrimination in 2 areas compared with no reported discrimination was associated with a 28% greater risk for incident CVD [43]. Cross-sectional analyses from two cohorts of women with ischemia and no obstructive coronary artery disease (INOCA; n = 551 and 376, respectively) revealed that home and work stress in the first cohort, and financial stress in the second cohort, were associated with anginal or anginal-equivalent symptoms and functional impairment [44].

Other large prospective studies have corroborated the importance of job strain in predicting incident CVD, especially for women with low control or occupational skill [28, 45]. In the Variation In Recovery: Role of Gender on Outcomes of Young AMI Patients (VIRGO) study of young adults with a history of MI, marital stress was more commonly reported by women than men, and marital stress was associated with worse cardiac-specific quality of life, health status, and greater odds of angina and all-cause readmissions at 1-year post-MI, although results did not differ by sex [46]. Related to caregiving stress, a meta-analysis of 41 studies with a high proportion of women in the samples (52% to 100%), indicated that caregivers have a 2x greater vulnerability to incident CVD than non-caregivers, although sex-specific analyses were not reported [47]. Overall, psychosocial stress likely contributes to women's vulnerability to IHD, but further prospective research by sex is needed – particularly concerning relationships, caregiving, and discrimination – to determine the independent and cumulative contributions of social and structural stressors that adversely affect women, and which stress management or other interventions can mitigate risk for women.

Depression—Of the psychological health dimensions studied in association with IHD, the largest body of research pertains to the role of depression. Depression is one of the most common psychological conditions, which is distinguished by symptoms of persistent low mood, loss of interest or pleasure in normal activities, hopelessness, and undesirable changes to energy, appetite, weight, and sleep [48]. About 18% of adults will meet diagnostic criteria for depression in their lifetime, and depression is 2x more prevalent among women than men [49, 50]. Depression is observed in 1 out of 3 adults with IHD and the prevalence of depression is again at least 2x greater for women [51]. In addition to increased biological and psychosocial vulnerability to depression among women, depression is a well-known factor in women's risk for IHD [16, 52, 53], particularly among those who are younger [54]. In a prospective investigation of 3237 patients undergoing coronary angiography to diagnose CAD (34% women), women who were aged 55 years and who reported higher baseline symptoms of on the Patient Health Questionnaire (PHQ)-9 showed a greater risk of incident CAD and death across 3 years compared to same-aged women with lower depression symptoms. Furthermore, this association was more robust for younger women compared with same-aged men or women >55 years old [55]. Depression may also impact the uptake of guideline-concordant medical therapies among women. In a cohort study of 124,443 patients who underwent a percutaneous coronary intervention (33% women), adults with depression were 10-20% less likely to reach optimal adherence to guideline-directed medical therapies than those without depression. While there is significant observational research concerning depression and IHD among women, there is an underrepresentation of women in randomized clinical trials (RCT) of depression and IHD. In future trials, researchers should also consider the factors shared by women who are mutually at risk for depression, IHD, and adverse cardiovascular outcomes [56].

Anxiety—Anxiety is another prevalent psychological condition that an estimated 1 in 3 women and 1 in 5 men experience in their lifetime [57]. Like depression, anxiety is more common among patients who are diagnosed with CVD: 1 in 3 adults show clinically-significant symptoms of anxiety [25], and the prevalence is 2x greater in women versus

men [53, 58]. Moreover, women with INOCA may be more likely to have anxiety than those with other CVD [12, 58–60]. Although anxiety is highly comorbid with depression, it should be viewed as an independent risk factor for IHD among women and men. An investigation with data from 431,973 participants in the UK Biobank (55% women) showed that patients who were diagnosed with an anxiety disorder had a 72% greater independent risk of IHD and other CVD, and anxiety was associated with comparable risk to having a depression diagnosis [52]. Among women with IHD, anxiety appears to predict future adverse health outcomes. Based on a narrative review, women with elevated anxiety symptoms following MI show an increased risk for morbidity, rehospitalization, mortality, and worse quality of life [53]. While other findings concerning anxiety and IHD risk have been mixed [58], sex-specific analyses were often not conducted, which is problematic given the greater prevalence of anxiety in women versus men [61]. Although anxiety appears to be a risk factor for IHD among women, the underlying biological and psychosocial factors underlying these relations, require further study. Relatedly, investigations into anxiety as an aggregated category, may obscure important differences in specific types of anxiety disorders or subclinical anxiety symptoms that may affect IHD risk and prognosis [22]. Thus, our current knowledge about anxiety and IHD in women is only “the tip of the iceberg,” and more sex-specific studies are necessary to understand the influence of anxiety and related treatments in cardiovascular medicine [58].

Trauma and Posttraumatic Stress Disorder—Trauma – including adverse experiences in childhood (e.g., abuse, neglect) and adulthood (e.g., sexual harassment, assault, military sexual trauma) – is common among women [62], and is also associated with a greater likelihood of CVD [63–65]. Posttraumatic stress disorder (PTSD) is defined as the experience of a psychologically distressing event or trauma that produces feelings of intense fear and helplessness [57]. PTSD may similarly attributable to one’s social circumstances or context [66]. Symptoms include negative mood changes or cognitions, hyperarousal, intrusive thoughts and memories, avoidance of reminders and activities associated with the trauma, and sensations of re-experiencing traumatic events (e.g., via flashbacks and nightmares). Like trauma, a PTSD diagnosis or clinically significant self-reported symptoms of PTSD are each associated with increased risk for IHD and other CVD compared to adults without a PTSD diagnosis or with low symptoms [64, 67–71], and the magnitude of attributable risk appears to be similar by sex. Few studies of PTSD and incident IHD have been pursued with women exclusively. Among these is a retrospective cohort study of 398,769 U.S. women Veterans with and without PTSD, in which a PTSD diagnosis was associated with a 44% increased risk of incident IHD over 17 years [72]. Altogether trauma and PTSD are likely involved in women’s distinct risk for IHD. Yet, as women are disproportionately affected by trauma and PTSD, replicating, and extending this work is paramount. If and how treatment for PTSD affects women’s IHD risk is also unknown.

Loneliness and Social Isolation—Loneliness is defined as the subjective distressing feeling of being alone or separated. Social isolation is characterized as having few social relationships or infrequent social interactions [73]. Extensive research shows that loneliness, social isolation or even just inadequate social support, are associated with a greater risk for incident IHD [59, 74–77]. Social isolation and loneliness are also significant factors among

women with IHD. In cross-sectional studies of patients with CAD, low perceived social support from women's friends and family was associated with mental and physical fatigue [78], social isolation was related to less self-care [77, 79], low social support reported by patients in cardiac rehabilitation reported worse health-related quality of life [80], and women who reported loneliness had a nearly 3x greater risk of 1-year, all-cause mortality versus those who did not report loneliness [81]. The type of social support received is also critical. In a national study of 3,006 men and women aged 75+ who were hospitalized for MI (44% women), low versus high informational support (i.e., knowledge or advice) was associated with a 22% greater risk of readmission and low versus high emotional support (i.e., receiving expressions of empathy and caring) was associated with a 43% greater risk of mortality [82]. In patients with established CVD, social isolation has been associated with an increased risk of all-cause mortality for women and men [74, 83]. Other prospective findings have been mixed, with no relations among women [84]. Thus, social isolation and loneliness appear to be detrimental to women and men with IHD, but further sex-specific analyses should be pursued in demographically diverse samples.

Anger and Hostility—Anger “consists of feelings that vary in intensity, from mild irritation or annoyance to intense fury and rage”[85] and is measured as a state, trait, or one's ability to express their anger. Hostility is, “a complex set of feelings and attitudes that motivate aggressive and often vindictive behavior.”[86] Anger and hostility are related constructs, which are likely involved in the onset of acute cardiovascular events [87]. Clinical research studies including myocardial perfusion imaging show that anger provokes MSIMI among both women and men [88]. Based on data from the multinational INTERHEART Study, out of 12,461 patients with a history of MI (24% women), 14% reported experiencing anger or emotional upset in the 1 hour before their event, comparable to the proportion who engaged in physical activity prior to MI [89]. Those who experienced anger or emotional upset had a >2x greater odds of MI, with no effect modification by sex. Prospective investigations have yielded some evidence supporting the roles of anger and hostility in predicting IHD risk. Data from a 10-year prospective study of 1,593 U.S. adults (54% women) showed that baseline hostility and anger expression were associated with CVD-related mortality, but sex did not moderate this association [90]. There is also speculation that anger and hostility affect IHD risk less for women than men [91–94], or not at all [13], although studies have often included a higher proportion of men or failed to assess for differences by sex. As observed with other dimensions of psychological health, further prospective analyses of anger, hostility, and IHD risk should be conducted with women.

Positive Psychological Factors: An Emerging Area

Contemporary approaches to investigating psychological health and CVH have increasingly focused on positive psychological dimensions – optimism, well-being, purpose, gratitude, happiness, sense of purpose, positive affect, and ikigai (i.e., a Japanese concept meaning a motivating force that provides a sense of purpose) – to determine the potential salubrious effects [14, 15, 95–99]. Despite disparate definitions, optimism is consistently and independently related to IHD risk and related-mortality, and these associations are robust for women and men [14, 100]. For example, using 8 years of prospective data from

70,021 women participating in the Nurses' Health Study, optimism was associated with a 38% lower risk of CVD-related mortality [101]. In another prospective study of 664 men and women aged 65 years (15% women), optimism during MI-related hospitalization was associated with a lower risk of mortality over the next 20 years [102]. Unfortunately, sex-stratified analyses were not conducted. Moreover, it is not clear if people who are healthier or recovering more optimally post-MI are simply more optimistic. Evidence reflecting other positive constructs and IHD risk is more sparse, and associations by sex are often not pursued. In a prospective investigation of 126,255 participants in the U.K. Biobank who were free of IHD at baseline (55% women), those with the lowest psychological wellbeing score (based on happiness, life satisfaction, depression, and neuroticism) had the greatest risk for CAD 12 years later, with a stronger association in women [103]. As observed with other negative, psychological constructs, additional longitudinal data will help to determine which positive psychological factors protect women's CVH.

Psychological Treatment and Interventions

Building on the vast literature supporting psychological factors in women's IHD risk, there are excellent, evidence-based behavioral and pharmacological treatments for managing stress, depression, anxiety, PTSD and related psychological factors (e.g., cognitive behavioral therapy [CBT], interpersonal therapy [IPT], mindfulness-based stress reduction, selective serotonin reuptake inhibitors [SSRIs] serotonin and norepinephrine reuptake inhibitors [SNRIs]), including in the context of IHD prevention [104]. Among behavioral treatment options, CBT has been the most studied in RCTs of patients at risk for or diagnosed with IHD. CBT is an empirically validated psychotherapy that is efficacious for targeting depression, anxiety, and PTSD in women and men [105–108]. In a recent review and meta-analysis of RCTs among patients with CAD, CBT was effective in reducing depression symptoms, especially in the 1-3 months post-intervention, with promising results for longer follow-up (6 months post-intervention) [109]. CBT is also more effective when delivered at moderate and high frequencies (i.e., defined as 8-12 or >13 sessions). A second meta-analysis showed that CBT is associated with a reduced risk of cardiovascular events, MI, and angina duration and intensity [110]. Finally, a Cochrane review and meta-analysis of RCTs investigating effects of CBT and other varied behavioral interventions among patients with IHD, showed that psychological interventions were associated with a 21% lower risk of cardiovascular mortality across 12 years [111]. While most RCTs have focused on CBT to mitigate psychological concerns, there is growing interest in bolstering positive psychological factors – e.g., targeting optimism, gratitude, resiliency, and happiness. Meta-analyses have shown that positive interventions are effective in improving distress and well-being among women and men with CVD [112, 113], which is certainly an area for scientific growth.

Combining behavioral and pharmacotherapy appears to be most effective for managing psychological health in relation to IHD, and receiving both treatments versus only one type of treatment is associated with lower healthcare utilization and all-cause mortality among patients with IHD [114]. Based on decades of data, SSRIs are well-regarded as safe to use in patients with IHD: SSRIs are less cardiotoxic than the earlier class of tricyclics, and are less likely to cause dependency than benzodiazepines; but there is mixed data

about their short- and long-term cardiovascular effects [105, 115]. A number of well-known RCTs have included combined behavioral and pharmacological interventions, primarily among patients with depression – the Enhancing Recovery in Coronary Heart Disease Patients (ENRICHD) Trial targeted major depression after MI, the Coronary Patients Evaluation Study (COPES)[116] and the Comparison of Depression Interventions after Acute Coronary Syndrome (CODIACS) Vanguard Trial each investigated depression among post-ACS patients [117], the Bypassing the Blues (BtB) Trial was designed to mitigate depression following CABG [118], and the Canadian Cardiac Randomized Evaluation of Antidepressant and Psychotherapy Efficacy (CREATE) Trial focused on patients with CAD and depression [119]. Based on these and other studies of single modalities, the strongest evidence from RCTs supports the use of behavioral treatments – especially CBT, care coordination, and cardiac rehabilitation/exercise combined with pharmacotherapy – together with pharmacotherapy to treat psychological health [105]. Still, there is a paucity of evidence that psychological treatment can prevent IHD overall, including insufficient data from women. Regrettably, many RCTs have small sample sizes and included a low proportion of women and minorities, and the subsequent meta-analyses have often neglected to (or been unable to) report sex-stratified findings [120–123]. Thus, it remains unknown if a given behavioral and/or pharmacological intervention is effective in dually addressing psychological health and IHD risk, and if effects differ by sex. Rigorous trials that dually prioritize both the recruitment of women from diverse racial, ethnic, and socioeconomic backgrounds, and sex-specific reporting of results are needed [111]. To guide these efforts, results from earlier trials must be explored for women and men separately.

Mechanisms of Psychological Factors and IHD in Women

The proposed pathophysiological mechanisms that underlie psychological-IHD associations among adults include both behavioral and biological pathways, and sex differences in these pathways have previously been reviewed in depth [54, 124–127]. To summarize, psychological health can influence cardiovascular risk via cardiometabolic metrics and related behaviors (e.g., blood pressure, diet, exercise, sleep, smoking, obesity, adherence), immune system regulation and inflammatory responses, the autonomic nervous system and neuroendocrine system, platelet aggregation and endothelial function, and genetic factors [54]. Among these systems, three mechanistic pathways are notable. First, negative psychological factors may alter primary stress-responsive systems – the hypothalamic-pituitary-adrenal (HPA) axis, sympathetic-adrenal-medullary (SAM) system, and sympathetic nervous system (SNS) – provoking subsequent changes in blood pressure, lipid, and glucose regulation, which can then promote atherosclerosis [128]. In a second pathway, women's psychological risk profile may promote vulnerability to abnormal coronary vasomotion and microvascular disease [129]. Women are more likely to show MSIMI and other distinct physiological changes in response to mental stress [10, 38, 39], which may directly lead to epicardial and microcirculatory dysfunction. Third, women's psychological health may affect their IHD risk via estrogen regulation. Estrogen protects against atherosclerosis by regulating lipid levels, promoting endothelium dependent vasodilation, enhancing bioavailability of nitric oxide from endothelial cells, and contributing to beneficial hemostatic effects [130]. Conversely, circulating estrogens can promote inflammation to a greater extent among women [126]. Women who experience

significant psychosocial stress and other psychological health concerns show changes in estrogen physiology – e.g., ovarian dysfunction and hypoestrogenism [130]. Other emerging cardiovascular risk factors for women include age at menarche; polycystic ovarian syndrome; pregnancy-related factors (e.g., parity, gravidity, and infertility) and conditions of pregnancy (e.g., hypertensive disorders of pregnancy and gestational diabetes); menopause and related symptoms; and autoimmune conditions [131, 132]. Ultimately, this knowledge base evokes more questions than answers about the mechanisms linking women’s psychological health with risk for IHD and further large scale investigations are essential to describe the multisystem biological and behavioral mechanisms specific to women.

Clinical Applications for Psychological Management Across Cardiovascular Health

To optimally assess and support IHD prevention for women, in line with the American Heart Association’s ‘Life’s Essential 8’ approach [3] – i.e., addressing diet, physical activity, sleep, nicotine exposure, weight, blood pressure, lipids, and glucose – equal attention should be paid to a ninth domain – addressing psychological health [2] (see Figure 1).

Primordial and primary IHD prevention could begin in adolescence and young adulthood, when psychological health concerns become more common for younger women versus their male peers [133, 134], and include education about psychological symptoms and awareness along with risk factors for future IHD. Throughout younger, middle, and late adulthood women’s psychological health could then be addressed in concert with CVH, guided by a biological and biographical framework that includes a woman’s family history, lived experiences and current social circumstances, menstrual history, pregnancy, menopause, and changes due to aging [135, 136].

An initial step to address women’s psychological health in IHD prevention and management across their healthspan involves routine and uniform screening, particularly for negative psychological factors – psychosocial stress, depression, anxiety, trauma or PTSD, social isolation or loneliness, or anger [137]. Notably, since 2002 the U.S. Preventive Service Task Force has highlighted the burden of depression in health and healthcare and the importance of depression screening among all adults [138]. More recently, the USPSTF recommended separate screening for anxiety [139]. Although depression and anxiety disproportionately affect women in general and those with IHD [49, 51, 58], regrettably this care remains the exception in cardiovascular medicine rather than the norm. Consideration of positive psychological attributes – happiness, meaning, and purpose – is also valuable for conceptualizing women’s IHD risk profile, factors affecting their motivation and confidence in IHD risk factor management, or adherence to treatment plans [112, 113]; women who show greater psychological well-being are more likely to engage in healthy lifestyle behaviors and are better equipped to manage stressful life events [2]. Brief, validated screeners are available to efficiently assess psychological health among women and their results are associated with IHD incidence and outcomes [73, 137]. Some of the most well-known measures include the 4- or 10-item Perceived Stress Scale [140]; the Patient Health Questionnaire (PHQ-2 or PHQ-9) or the National Institutes of Health’s (NIH) Patient-Reported Outcomes Measurement Information System (PROMIS®) 4-item measure

for depression [141, 142]; the Generalized Anxiety Disorder measure (GAD-2 or GAD-7) or the 4-item PROMIS screener for anxiety [142, 143]; the 8-item Short Post-Traumatic Stress Disorder Rating Interview (SPRINT) [144]; the NIH Toolbox 5-item Loneliness Measure [145]; the 5-item PROMIS Emotional Distress/Anger measure [142]; and the NIH Toolbox's 5-item General Life Satisfaction or 4-item Meaning and Purpose measures [145].

While there is no clinical biomarker of psychological distress or well-being, using screeners can prompt discussion, referrals, and interventions to aid and mitigate women's psychological symptoms, efforts that may directly or indirectly improve inflammation and autonomic nervous system regulation, and can then have salutary CVH benefits (e.g., lower blood pressure; better endothelial function) [54, 93, 128]. Symptoms that meet diagnostic criteria for a psychiatric disorder should prompt referral to a behavioral medicine or mental health provider, or to a multidisciplinary integrated prevention team that holistically manages CVH – ideally including a clinician with behavioral health expertise. A whole-person care approach can help patients and providers alike to draw connections between psychological health, cardiovascular risk factors, and anginal symptoms – with attention to underlying genetic, biological, and sociocultural factors that may be sex-specific. As a standard of care, shared decision making should be used to balance any tradeoffs in treatment for psychological health with IHD risk management for women [146, 147].

In addition to regular screening for psychological health, specific milestones in a woman's development should prompt discussion of psychological health in relation to CVD risk and management. For example, a diagnosis of polycystic ovarian syndrome or premature menopause – both risk factors for IHD [148, 149] – can be associated with depression, anxiety, and psychosocial stress [150, 151]. As another example, assessing psychological health in the pre-, ante-, and postpartum periods is helpful to identify and address postpartum stress, depression, anxiety, or PTSD and may help to support healthy lifestyle behaviors throughout adjustment to parenthood and the childbearing years [152]. Women with lower symptoms of antepartum depression are more likely to exercise regularly and throughout pregnancy and have a lower risk for hypertensive disorders of pregnancy [153, 154]. Reciprocally, women who experience hypertension, preeclampsia, or eclampsia are also at risk for postpartum depression, adverse pregnancy outcomes, and future cardiovascular events [155, 156]. Thus, a hypertension diagnosis should flag an in-depth assessment of cardiovascular risk *including* psychological health. In the menopausal years, hormonal shifts can dually promote vulnerability to psychological distress and cardiovascular instability [157, 158]. Blood pressure and cholesterol increase in women, and there is an emergence of endothelial and microvascular dysfunction [159]. How these biological shifts share common pathways with psychological health, or how psychological health and CVH interact with one another, is likely complex [41, 129, 160]. Addressing both factors simultaneously is important for managing new cardiovascular risk factors and symptoms and to support psychological wellbeing through this transitional period. Finally, as women age, there is a higher risk for IHD, as well as diastolic dysfunction complicated by heart failure, and atrial fibrillation [161–163]. Women tend to live longer than men and may find themselves at an increased risk for social isolation [164]. This experience may limit physical activity and social support, increase sedentary time, and lead to symptoms of depression and loneliness. Thus, there are ample, obvious opportunities for assessing and

managing psychological health in tandem with IHD to provide more holistic cardiovascular care and to preserve CVH for women.

Conclusion

The present state of the science concerning psychological health and IHD in women is robust. Substantial data reinforces the important links between various psychological factors and related diagnoses with IHD risk and outcomes [2]. Gaps in this literature are also perceptible. While the behavioral pathways and biological mechanisms are complex and show clear differences for women compared to men [8, 59], many prospective studies of psychological health and IHD have had a limited representation of women, did not include analyses by sex even when powered to do so, or failed to account for sex-specific biological and psychosocial factors. Further investigation into these sex-specific associations, mechanisms, and the effects of empirically supported psychological interventions is required to improve the evidence base for treating interrelated psychological health and IHD outcomes among women. Even without such data, there are already many opportunities to address women's psychological health within the scope of IHD prevention. Significant or adverse life events, pregnancy, parenthood, menopause, retirement, or other aging milestones, along with any new cardiovascular diagnosis or event could cue a brief psychological assessment. Standardizing and implementing uniform and routine clinical assessment of psychological health is required to support this intersection of women's health risk. Finally, establishing integrated team models can lead to more high-value interactions between women who are at risk for IHD and cardiovascular medicine providers, and ultimately, to improved outcomes throughout the course of a woman's healthspan.

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Fig. 1. Psychological health – which consists of interrelated, negative and positive factors – influences women's risk for ischemic heart disease (IHD). Psychological factors with the most robust evidence in relation to IHD risk and outcomes among women are depicted. To help mitigate risk for IHD risk and outcomes, women's psychological health should be assessed and managed in concert with their cardiovascular health.