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WOMEN AND ISCHEMIC HEART DISEASE (J.M. PEÑA AND F. LIN, SECTION EDITORS)

A Narrative Review of the Association Between Depression and Heart Disease Among Women: Prevalence, Mechanisms of Action, and Treatment

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Abstract

Purpose of Review Sex and gender differences exist with regard to the association between depression and cardiovascular disease (CVD). This narrative review describes the prevalence, mechanisms of action, and management of depression and CVD among women, with a particular focus on coronary heart disease (CHD).

Recent Findings Women versus men with incident and established CHD have a greater prevalence of depression. Comorbid depression and CHD in women may be associated with greater mortality, and treatment inertia. Proposed mechanisms unique to the association among women of depression and CHD include psychosocial, cardiometabolic, behavioral, inflammatory, hormonal, and autonomic factors.

Summary The literature supports a stronger association between CHD and the prevalence of depression in women compared to men. It remains unclear whether depression treatment influences cardiovascular outcomes, or if treatment effects differ by sex and/or gender. Further research is needed to establish underlying mechanisms as diagnostic and therapeutic targets.

Keywords Coronary heart disease · Cardiovascular disease · Depression · Women · Gender differences · Sex differences

Introduction

Cardiovascular disease (CVD), defined here as coronary heart disease (CHD), peripheral vascular disease (PVD), and stroke, is the leading cause of morbidity and mortality

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among women in the USA and globally [1, 2]. In the general population and among patients with CVD, women are nearly twice as likely to have depression compared to men and have higher rates of depression across all age groups [3, 4]. An association between CVD and depression has been established in the literature, and depression is recognized as a modifiable risk factor for CVD, particularly CHD [5••]. Data suggest that this association is bidirectional; CHD is associated with a higher risk of developing depressive symptoms, and depression is associated with increased risk of incident and recurrent CHD [6, 7]. The bidirectional associations of depression and CHD, and response to depression treatment, may differ by sex/gender [8].

To address sex/gender differences with regard to CVD and depression, it is necessary to understand the current state of the literature, most of which has focused on CHD, and make actionable recommendations for addressing risk factors. There are several prior reviews on the association between depression and heart disease in women [5••, 9••]; however, few have simultaneously described differences in prevalence rates, management, and mechanistic differences. We conducted a narrative review of the recent (i.e., over the last 5 years) CVD literature, focused on CHD, to address several aims. First, to report the latest data on sex/gender differences across the lifespan in the prevalence of depression in CHD; second, to describe evidence on the differential relationship between depression and incident and recurrent CHD by sex/gender; third, to discuss proposed mechanisms underlying the association of depression and CHD among women; and lastly, to explore whether current interventions for depression in CHD are informed by known insights on sex/gender differences in depression and CHD risk. Because the literature rarely distinguishes sex from gender, we use both terms throughout unless otherwise specified in a given study.

Methods

A narrative review was performed focused on studies published in the last 5 years, with older publications included for landmark studies and topics for which recent literature was limited. The PubMed, PsycINFO (EBSCO), and Embase databases were searched on 15 December 2021, using the terms "cardiovascular disease," "cardiovascular diseases," "CVD," "coronary artery disease," "coronary disease," "heart disease" and "depression," "major depressive disorder," "major depression," or "MDD" and "women" or "woman" or "female" (Appendix 1). The search was limited to the last 5 years, covering the period of 1 January 2017 to 15 December 2021. To ensure all recent literature was considered, the search was re-run on 19 January 2022 and again on 8 February 2022.

Epidemiology of Depression and CHD in Women

Depression and Risk of Incident CHD Among Women

Depression appears to be a risk factor for incident CHD among women. A prospective cohort study of nearly 2,000 healthy women in the USA found that a positive depression screen at year 2 of the study was associated with a significantly greater risk of one or more incident CHD events at year 10 compared to controls (13.0% versus 6.5%, $p < 0.001$) [10]. In logistic regression models, depression was the only risk factor predictive of CHD in women younger than 65 (OR = 6.56, 95% CI 1.07–40.09, $p = 0.042$) and was not a significant risk factor among women 65 and older. These data suggest that differences in depression and CHD risk may vary across the lifespan, with a greater risk among young women specifically. However, in a prospective study of 690,335 women in the UK (mean age 59.8), depression was not an independent risk factor for hospitalization or death from MI [11].

It is not clear whether the association between depression and incident CHD varies by sex/gender based on studies to date. A recent meta-analysis found that while depression is significantly associated with incident ischemic heart disease overall, there was no significant difference between women and men [12]. The authors noted that studies reporting results on women only were underrepresented compared to those on men only. In addition, the included studies mainly involved obstructive coronary artery disease (CAD), which is a more common disease pattern in men than women.

The diagnostic modality used to establish depression diagnosis, including self-report versus direct measurement, may also play a role in sex/gender differences. In an analysis of two prospective epidemiologic studies, depressive symptoms (measured using validated self-report scales) were an independent risk factor for both first (HR = 2.72, 95% CI 1.50–9.12) and recurrent CVD events (HR = 1.31, 95% CI 1.01–1.69) in women only [13]. In a cross-sectional study based on the National Health and Nutrition Examination Survey, a diagnosis of depression on self-reported questionnaire was associated with the development of CVD in both women and men (AOR = 2.46, 95% CI 1.13–5.36 versus AOR = 1.80, 95% CI 1.09–2.92) [14]. A retrospective cohort study of patients admitted for psychiatric disorders, including depression, found that the relative but not absolute risk of CVD associated with depression was greater among women [15]. Of note, this study did not include patients with less severe depression (i.e., those diagnosed using

self-reported measures, not requiring hospitalization, or community-based populations).

Prevalence of Depression Among Women with CHD

Depression prevalence varies across the lifespan. Data from the National Health and Nutrition Examination Survey found rates of depression in the USA to be 10.1% among women and 5.5% among men for adults 20 to 39 years, 11.5% versus 5.2% for 40 to 49 years, and 9.6% versus 6.1% for 60 years and above (all $p < 0.05$) [3]. Below, we describe the latest evidence on sex/gender differences in prevalence of depression with regard to CHD populations and the diagnostic modality used to measure depressive symptoms, given variability in the methods utilized (Table 1). Recent studies demonstrate a greater prevalence of depression among women compared to men hospitalized with myocardial infarction (MI) [16–20] and CHD events (i.e., coronary artery bypass graft surgery (CABG), percutaneous coronary intervention (PCI), or unstable angina, in addition to MI) [21–28] (Table 1). These studies show differences in the prevalence of depressive symptoms among women versus men ranging from 4.5 [16] to 23.0% [19].

In terms of MI, in a large retrospective analysis of hospitalizations for acute MI, the prevalence of depression was 9.2% among women (median age 77) versus 4.7% among men (median age 70) ($p < 0.001$) [16]. In younger age groups, where gaps in depression rates are greatest overall, there was a similarly significant difference between men and women aged 18 to 45 years admitted with MI (12.7% versus 4.8%, $p < 0.001$) [17]. In a cohort of post-MI patients under the age of 60, women were more likely to have elevated depressive symptom scores than men at baseline (49% versus 26%, $p < 0.001$) and at 6 months (40% versus 27%, $p = 0.039$) [19].

Regarding any CHD event, data also demonstrates a greater prevalence of depressive symptoms among women than men. A systematic review of longitudinal studies (2019) in women hospitalized for an index CHD event found that depressive symptoms (mainly assessed using validated self-report scales; one included study utilized diagnostic interview) ranged from 27.9 to 40.3% [29•]. Women had a higher prevalence of depressive symptoms than men at baseline (35.8% versus 23.5%), and over 24 months (22.7% versus 19.8%). A cross-sectional survey of nearly 8,000 patients previously admitted for any CHD event found a prevalence rate of depressive symptoms of 30.6% in women and 19.8% in men ($p < 0.001$) [21]. A similarly elevated risk of depression in women compared to men following CABG has been described in a recent review of the literature (2020) [25]. One included study found that patients readmitted with concurrent depression between 14 and 90 days after CABG were more likely to be women (41.5% versus 31.9%, $p < 0.0001$) [26].

Sex and gender differences in depression among people with CVD also have been characterized in ambulatory settings. In a study of the electronic health record of primary care patients in the UK with incident CVD (angina, MI, transient ischemic attack, or stroke), the age-standardized prevalence of depression in women was 31.1%, more than double that of men [30]. A cross-sectional survey in Poland found that depressive symptoms were more prevalent in women with prior MI (76.9% versus 32.9%, $p < 0.001$) and with no significant difference observed among men [31]. In a study of community-dwelling patients in Korea with CAD, the association of CAD with depression was significant in women only, and this risk was stronger in those diagnosed more recently and at a younger age (≤ 64 years) [32]. These differences in depression rates by sex/gender appear to persist longitudinally; patients with angiographically determined coronary artery disease CAD followed over an average of 10 years who developed depression were more likely to be women (37% versus 24%, $p < 0.0001$) [33].

Depression and Risk of Recurrent CHD and CVD/All-Cause Mortality by Sex/Gender

Next, we discuss the differential prognostic impact of depression by sex/gender. Among CHD patients, depression is associated with greater in-hospital, all-cause mortality following acute MI in women than men; however, the evidence to support sex/gender differences in the association between depression and CHD mortality is mixed overall. Recent data demonstrates significantly greater in-hospital [34] and 30-day [35•] all-cause mortality rates among women with acute MI compared to men, which is consistent with prior research [36]. These findings were in younger women (< 60 years old) who tend to have higher rates of depression; as such, depression has been proposed as a potential mediator in the relationship between sex/gender and mortality in post-MI populations [37].

Regarding stable CHD, a study of 14,577 patients across 39 countries found that depressive symptoms are similarly associated with 4-year CVD mortality, non-fatal MI, and non-fatal stroke in both women and men (mean age 65 years) [38]. In a similarly aged population of patients with stable CHD, women had a lower risk of the composite outcome of cardiovascular death, non-fatal MI, and non-fatal stroke than men. However, there was a statistically significant increase in the risk of the CHD mortality among women as the severity of depressive symptoms increased, such that the differences in event rates between men and women were no longer significantly different [22]. Therefore, the cardiovascular risk advantage conferred by female sex was lost as depressive symptoms emerged, leaving women with depression facing a similar risk for CHD as men overall

Table 1 Prevalence of depression among women with CVD and CHD

Authors (reference number)	Population	Prevalence of depression			Size of study population	Age range	Time of data capture	Geographical setting	Diagnostic modality
		Women	Men	*p*					
Matetic et al. (2021) [16]	Hospitalization for acute MI	9.2%	4.7%	< 0.001	7,026,432	≥ 18 years	2004–2015	United States	Retrospective chart review: ICD-9[1] and Clinical Classification Software codes
Bandyopadhyay et al. (2020) [17]		12.7%	4.8%	< 0.001	156,018	18– < 45 years	2010–2014	United States	Retrospective chart review
Saelee et al. (2019) [19]		49.1% (baseline) 40.2% (6-month follow-up)	26.3% 27.2%	< 0.001 0.039	313	18–60 years	August 2012–March 2016	United States (Atlanta, Georgia)	Self-report: BDI-II[2] ≥ 14
Serpytis et al. (2018) [18]		54.2%	47.5%	0.413	160	> 18 years	1 November 2012–31 May 2013	Lithuania	Self-report: HADS-D[3]
Pogosova et al. (2017) [21]	Hospitalization for any CHD event	30.6%	19.8%	< 0.001	7,998	18– < 80 years	2012–2013	Europe (24 countries)	Self-report on interview: HADS-D
Guimaraes et al. (2017) [22]		19.2%	10.1%	< 0.0001	15,828	≥ 60 years	1 December 2008–1 October 2013	Global (39 countries)	Self-report: "Have you felt down/depressed?"; "often" or "always"
Figueiredo et al. (2017) [24]		37.8%	14.8%	< 0.0001	356	> 20 years	N/A	Brazil	Diagnostic interview: Structured Clinical Interview of the DSM–IV Axis I Disorders-Patient Edition
Kim et al. (2021) [32]	Community-based patients with CAD	22.0%	5.5%	0.012 (un-adjusted) 0.016 (age-adjusted)	10,771	≥ 40 years	2014, 2016, 2018	Korea	Self-report: PHQ-9[4] ≥ 10
Tran et al. (2018) [30]	Community-based patients with CVD (angina, MI, transient ischemic attack, and stroke)	31.1% [95% CI 28.3–35.5%]	15.0% (14.3–16.5%)		4,198,039	16–113 years	2004–2014	United Kingdom	Chart review: ICD-10[5] and primary care (Read) codes
Piwonski et al. (2019) [31]	Community-based patients with MI or stroke	76.9%	32.9%	$p < 0.001$	2413	18–79 years	2011	Poland	Self-report: BDI[6] score ≥ 10

[1]International Classification of Diseases, Ninth Revision

[2]Beck Depression Inventory-II

[3]Hospital Anxiety and Depression Scale–Depression

[4]9-Item Patient Health Questionnaire

[5]International Classification of Diseases, Tenth Revision

[6]Beck Depression Inventory

(who traditionally have higher mortality rates than women). These data are in contrast to a prior meta-analysis, which found that depression was associated with CHD death in men but not women ($p = 0.08$); the study used a narrower definition of MI or coronary death and included studies that spanned a wide age range with nearly half including only patients aged 65 and older [39].

Mechanisms Linking Depression and CHD in Women

Previous reviews have proposed mechanisms for the link between depression and CHD in the general population [5••] and among women [9••]. These mechanisms, including psychosocial, mental stress-induced ischemia, cardiometabolic, behavioral, inflammatory, hormonal, and autonomic factors, are likely multi-directional and work synchronously to influence the development of depression and CHD (Fig. 1). Below, we discuss recent studies that specifically examine whether and how these mechanistic factors relate to depression and CHD by sex/gender.

Psychosocial Stress

Acute and chronic stress are associated with development of major depression and other psychiatric disorders and can predict future CVD events [40]. Psychosocial stress is implicated in the sex/gender differences in cardiovascular risk, as women have a greater prevalence of psychosocial stressors than men and appear to be more susceptible to the effects of stress on CHD [40]. In general, women experience greater exposure to life stressors linked to CVD including childhood neglect, physical and sexual abuse, domestic violence, socioeconomic disadvantage, discrimination, and family-related stress; and have a greater prevalence of stress-related psychiatric disorders (i.e., major depression and post-traumatic stress disorder) [40–42]. The landmark INTERHEART study found that an aggregate exposure of psychosocial and mental health factors, including depressive symptoms, was a key component of the population attributable risk for MI and that psychological stress was greater in women than men (40% versus 25%) [43]. Psychosocial and emotional stress can directly induce myocardial ischemia, are also associated with unhealthy behaviors such as smoking, alcohol use, and poor diet, and can trigger inflammation, neurohormonal activation, endothelial dysfunction, and platelet activation which are predisposing to CHD [5••, 40].

Mental Stress-Induced Ischemia

Among patients with CHD, psychological distress can provoke an imbalance in coronary blood flow causing transient perfusion deficits and resultant ischemia in an entity known as mental stress-induced MI, which can be induced in a laboratory using a standardized public speaking task [40]. Given its significant association with CVD events and mortality, mental stress-induced MI may explain the association between psychological distress, such as depression, and adverse cardiovascular outcomes. Prior studies of patients with CHD demonstrate that depressive symptoms may be associated with a greater likelihood of mental stress-induced MI [44], and young women are especially susceptible to mental stress-induced MI [45]. Furthermore, women with recent MI are twice as likely to develop mental stress-induced MI than men [46].

Data also suggest that the pathophysiology of mental stress-induced MI may differ by sex; microvascular dysfunction and peripheral vasoconstriction in response to mental stress specifically are predictive of mental stress-induced MI in women [47]. Coronary microvascular dysfunction, endothelial dysfunction, and coronary vasospasm can be triggered by psychological stress including depression and are implicated in the development of ischemia with non-obstructive CAD, which is more common among women [48]. While mental stress-induced MI is a proposed link between depression and incident and recurrent CHD among women, it is not clear if this relationship is causal rather than correlational. Further studies are also needed to conclude whether stress-induced MI mediates the relationship between depression and CHD among women and whether

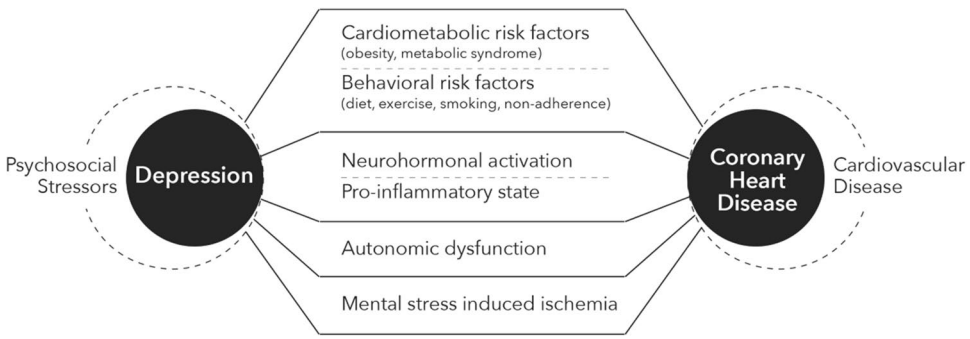

Fig. 1 Proposed pathways in the association between depression and CHD in women

there are sex/gender differences, particularly in the context of cumulative psychosocial stressors highlighted above.

Cardiometabolic Risk Factors

Data supports an association between depression and traditional cardiometabolic risk factors for CVD that may vary by sex/gender. Cross-sectional data from a population-based sample of Danish young adults found that women with depressive symptoms had significantly increased odds of having an overweight BMI, abdominal adiposity, insulin resistance, low high-density lipoprotein, and high low-density lipoprotein compared to non-depressed women; in depressed men, the odds of high blood pressure were significantly increased compared to non-depressed controls, but not other components of metabolic syndrome [49]. In a study of adults aged 50–74, more severe depressive symptoms predicted higher BMI over four assessment points over 10-year follow-up, particularly among women compared to men [50]. A prospective study of African American adults that investigated the role of allostatic load (AL) in the association between depression and incident CHD found that depression score was significantly associated with metabolic AL (quantified by waist circumference, triglyceride to high-density lipoprotein ratio, low-density lipoprotein, and hemoglobin A1c) among women ($p = 0.005$) but not among men in stratified analyses [51]. Metabolic AL mediated 5.79% of the association between depressive symptoms and incident CHD ($p = 0.044$) and was significant among women ($p = 0.016$) but not men. In one study, gender moderated the association between depression and cardiovascular health (defined as a composite of BMI, smoking, physical activity, healthy diet score, blood pressure, fasting plasma glucose, and total cholesterol); in stratified analyses, depressive disorders were significantly associated with poorer cardiovascular health in women [52]. In a population-based survey, the association between depression and lower odds of favorable cardiovascular health was significantly stronger in women than men (OR = 0.72; 95% CI 0.60–0.86 versus OR = 0.92; 0.64–1.32, p-interaction = 0.03) [53].

Overall, these findings suggest that the association between depression and certain cardiometabolic factors is more pronounced among women than men. While there are signals that depression affects certain cardiovascular risk factors more strongly in women, it is not clear whether these factors directly mediate the relationship between depression and CHD or rather represent concomitant comorbidities driven by another common process such as behavioral factors. More studies are needed to clarify if obesity and metabolic syndrome are key mediators linking depression and CHD/CVD in women.

Behavioral and Lifestyle Factors

Another proposed explanation for the association between depression and CVD are modifiable behaviors that predispose the development of CHD/CVD, such as sedentary lifestyle, smoking, overeating, and adherence to medications and lifestyle modifications [5••, 21]. Recent women-only studies demonstrate that those with depression are less likely to be physically active and have lower adherence to smoking cessation and healthy diet than non-depressed counterparts [54] but do not include sex/gender comparisons. In a cross-sectional study of patients admitted with CHD, physical inactivity partially explained the gap in prevalence of depression symptoms among women versus men [55]. In another analysis, moderate recreational activity modified and mediated the effect of CVD on depression, with the mediation effect statistically significant in women only [56]. Conversely, one study of a primary care population found that the association between depressive symptoms and physical inactivity was not modified by gender or comorbid CVD [57].

Tobacco use is a key behavioral mechanism that may relate depression and CVD in women. In a study of women consecutively enrolled at cardiac rehabilitation following revascularization, smoking was associated with depressive symptoms among women (OR = 4.37, 95% CI 1.53–12.52, $p = 0.006$) but not among age- and diagnosis-matched men in bivariate and multivariate regression analyses [58]. In an analysis of a 10-year longitudinal dataset of women who endorsed regular smoking, depression was significantly associated with increased likelihood of continued smoking and relapse [59]. Meta-analytic data shows that smoking is less prevalent in women than men, yet the relative risk of CHD associated with smoking is 25% greater in women, even after adjustment for other cardiovascular risk factors [60]. However, only one of the studies included adjusted for depression. The etiology of why smoking confers a greater risk for CHD in women is not clear, and further studies are needed to examine smoking as a mediator in the relationship between depression and CHD in women compared to men.

Overall, some data suggest that women with depression are more sedentary than men, and among CHD patients, physical inactivity may predispose patients to developing depressive symptoms. Smoking is another potential mediator of depression and CHD in women. Further studies are needed on whether other lifestyle factors including diet and medication adherence mediate the association between depression and CHD in women, and are thereby additional targets for intervention.

Inflammation

Inflammation is a proposed mechanism linking depression and CVD, as depression is associated with a state of increased inflammatory cytokines, which are also related to the development of atherosclerosis and CVD [61]. Mattina et al. [62] described available data on the association between pro-inflammatory states and the development of depression and CVD in women, proposing that cardiometabolic risk exposures not only result in inflammation directly but also affect the hypothalamic–pituitary–adrenal (HPA) axis, renin–angiotensin–aldosterone system, and serotonin/kynurenine pathway that result in further inflammation that contributes to the pathogenesis of both depression and CVD [62]. For instance, C-reactive protein (CRP) is elevated in both CVD and depression; CRP is a predictor of MI, stroke, and CV mortality; and the presence of cardiovascular risk factors such as obesity, hypertension, and smoking increases the levels of CRP in women [62].

Inflammation associated with depression appears to differ by sex/gender. In one study, inflammatory markers such as interleukin-8, interferon gamma, and leptin were significantly elevated in women with major depression compared to controls; alternatively, there was no significant difference in inflammatory markers among men with and without depression [63]. When comparing women and men with major depression, women had significantly higher levels of interleukin-6 ($p < 0.05$) and leptin ($p < 0.01$), which persisted after adjusting for BMI. Additionally, there was a positive correlation between interleukin-1 beta and tumor necrosis factor alpha with depression score and specific depressive symptoms in women, with no significant difference among men. In a separate study, young women with CAD had significantly higher concentrations of interleukin-6 at rest and 90 min after mental stress, compared to similarly aged men [47]. However, associations between inflammation, depression, and CVD may be confounded by lifestyle factors. In an observational cohort study of patients with non-obstructive CAD, women had significantly higher levels of high-sensitivity CRP than men, which dissipated after adjustment for age, BMI, smoking, and physical activity [64]. In terms of the relationship between inflammation and mortality, a longitudinal study of adults aged 52 to 89 found that men but not women with both depressive symptoms and elevated CRP had increased risk of CVD mortality (HR = 3.89; 95% CI 2.04–7.44), which was greater than the risk of CVD mortality for elevated CRP alone; depressive symptoms alone were not associated with increased risk of CVD mortality among men; and neither depressive symptoms nor high CRP conferred an increased risk of CVD mortality among women [65].

Overall, inflammation does not fully explain the pathway between depression and CHD. While sex/gender differences in the inflammatory responses that may be related to depression and CHD have been demonstrated, this association is likely complex and influenced by cofounding factors that can also produce a pro-inflammatory state. The interplay between inflammation, depression, and CHD is likely multidirectional, and depression and inflammation may influence CHD risk in women through independent mechanisms, given that depression and inflammation independently predicted CVD incidence in a prospective study of women at risk for coronary ischemia [66].

Hormonal

Fluctuations in inflammatory cytokines during reproductive hormonal events may be implicated in the susceptibility to both depression and CVD in women, with variations in estrogens and progesterone during menstruation, the perinatal period, and menopause impacting the immune system and inflammatory pathways that lead to the development of both depression and CVD [62]. Slavich et al. [67] described the literature on modulation of inflammatory activity by ovarian hormones, leading to greater central nervous system inflammation especially during hormonal transition periods, and blunting of HPA axis reactivity by estrogens that decreases anti-inflammatory signaling [67]. Collectively, sex hormones trigger increased pro-inflammatory cytokines and decreased anti-inflammatory markers across lifetime reproductive events in women that may be implicated in the pathogenesis of both CVD and depression [67]. For instance, changes in circulating sex hormones are associated with development of both depression and CVD during key reproductive events in women, such as perinatal depression and preeclampsia during the perinatal period; or the concurrent increased prevalence of depression and dyslipidemia, hypertension, and endothelial dysfunction in peri-menopausal and post-menopausal women [62]. While hormonal changes are one plausible explanation for sex differences related to depression and CVD, a causative relationship has not been established. Prospective studies of women across reproductive life events could clarify the effect of hormonal changes on depression and CHD/CVD.

Autonomic Dysfunction

Autonomic dysfunction, an imbalance between the sympathetic and parasympathetic nervous systems, is a proposed mechanistic link between depression and CVD [68]. Individuals with CHD and depression have lower heart rate variability (HRV) and higher heart rates than those without depression, and lower HRV is a prognostic risk factor for adverse CHD events, including MI, post-MI mortality, and overall morbidity and mortality, and in patients with stable CHD. Depressed mood and sex/gender may interact

with the central regulation of cardiac autonomic activity in response to negative emotional stimuli. One study found that in women with high levels of depressed mood, but not men or women with low depression levels, lower cardiovagal activity in response to negative affective stimuli was associated with circuitry implicated in the pathophysiology of major depression (greater activation of the hypothalamus and right amygdala, and hypoconnectivity between hypothalamus and right orbitofrontal cortex, amygdala, and hippocampus) [69]. However, a recent review of depression and cardiac autonomic dysfunction (2020) describes a paradox in which depressed women have higher vagally mediated cardiac control than depressed men, which is cardioprotective, yet also have increased CVD risk [70]. Available evidence demonstrates that the association of depressive symptoms with poor cardiac vagal control is stronger in depressed men, who have significantly lower HRV compared to non-depressed controls, whereas no such difference has been observed between women with and without depression [70]. The authors noted a lack of studies in sex-balanced populations and limited longitudinal data. Overall, the association between depression and cardiac autonomic dysfunction appears to facilitate greater CVD risk among men than women. Therefore, elevated rates of CVD prevalence and mortality among women with depression may occur despite protective vagal activity, rather than due to autonomic dysfunction.

Depression and Quality of CHD Management by Sex/Gender

Some data suggest that women with CHD experience clinical inertia and are significantly less likely to undergo coronary angiogram, CABG, PCI overall, and PCI within 24 h compared to men [16, 17]. Depression may affect the care that women with CVD receive. A study of a large database found that all patients with ST elevation MI and comorbid depression were less likely to undergo PCI and CABG [71]; crude rates of PCI and CABG were lower in women than men in general, and lowest among women with depression. A retrospective cohort study of adults hospitalized with first MI found that severe mental illness, including major depression, was associated with decreased rates of coronary revascularization, particularly in women compared to men [72]. In another study, depressed patients had significantly reduced odds of receiving angiography and PCI, and sex/gender was a strong predictor of non-invasive rather than early invasive management across healthy patients and across all subtypes of mental illness studied although this difference was non-significant for major depression alone [73].

CHD and Quality of Depression Management by Sex/Gender

A scoping review of randomized clinical trials on depression treatment in CVD patients found that antidepressants and psychotherapy effectively treated mood symptoms, but did not definitively reduce CVD events or mortality; many of the included studies did not compare men and women [74]. A systematic review and meta-analysis (2018) noted a lack of reviews assessing effects of cognitive-based therapy on depression and CVD by sex/gender, and insufficient data to perform subgroup analyses [75]. Below, we discuss available data describing sex/gender differences in treatment response and impact on CHD.

Some data suggest that women with CHD respond differently to depression treatment than men. In an older randomized clinical trial of cognitive behavioral therapy and serotonin-selective reuptake inhibitors in patients with prior MI, there was no significant reduction in all-cause mortality or recurrent MI in the treatment group compared to usual care, but the data trended towards a more negative effect in women than men (p-interaction = 0.03); this effect was attenuated ($p = 0.20$) after adjustment for age, baseline depression score, and comorbidities [76]. A randomized controlled trial of a program involving virtual problem-solving treatment, pharmacotherapy, or both following an acute coronary syndrome event found that treated women had a greater reduction in depressive symptoms than men (−6.4; 95% CI − 10.1 to − 2.6 versus − 1.6; 95% CI − 6.7–3.6; $p = 0.03$) [77]. In a population-based study, depression increased the risk of CVD in both genders over a median follow-up of 8 years; however, this risk was mitigated when men, but not women, received 10 or more (versus no) outpatient visits for depression [78]. Other studies demonstrate similar responses in men and women to psychotherapy in subjects with CAD [79, 80], and to internet-based cognitive-based therapy in patents with recent MI [81].

Gaps and Future Directions

Our review highlights the need for more analyses on sex/gender differences in depression and CHD, including the impact of social and socioeconomic factors. Intersectionality, the interaction between multiple social identities including gender, race, class, and sexual orientation that confers a unique experience of oppression and discrimination has been applied to the analysis of health disparities in gender-based research [82, 83] and heart disease, specifically [84]. For instance, post hoc analyses by sex and ethnicity of the Enhancing Recovery in Coronary Heart Disease trial found that among white men, there was a significant effect

of depression treatment on cardiac mortality or recurrent non-fatal MI while HRs were non-significant in minority men and women, and white women [85]. Few studies have addressed the link between CVD and depression in women using an intersectional approach, which represents a gap in the literature. Additionally, the studies identified in this review predominantly focus on incident CHD, whereas prior literature has also described an association between depression and recurrent CHD [29•]. Updated studies on the recurrence of CVD among women with depression are necessary to address this gap.

Our review has several limitations. Although we reviewed multiple databases methodically, this is a narrative rather than systematic review, so some topical articles may not be included. Another limitation is reliance on use of the terms "women" and "men" as used in the source literature, which refer to gender rather than biological sex, and neglect nuances in sex and gender identity. Explicit definitions of sex and gender are infrequent in the studies reviewed, and often used interchangeably implying that assigned birth sex always aligns with gender identity [83]. Consideration of gender rather than biological sex is key to understanding mechanisms specific to the risk of CHD incidence and mortality among women [86]. Lastly, our review focuses on CHD, given the broad scope (prevalence, associations, management, and mechanisms) and the fact that the majority of recent studies highlight CHD, and not other CVDs, namely PVD and stroke. This focus on CHD is not only a limitation of our review but also underscores the need to examine sex/gender differences in the association between depression, and PVD and stroke. Importantly, the pathways underlying the association between depression and CVD outside of CHD among women may differ, implying different treatment targets and management considerations.

Conclusions

Recent epidemiological studies, systematic reviews, and meta-analyses describe a strong association in the prevalence of, and link between, depression and incident CHD, as well as mortality among women. We add to prior literature by reviewing unique management and mechanistic considerations. More research is needed to delineate underlying mechanisms of depression and CVD among women, particularly longitudinal studies that may establish a causative rather than correlational association. A clearer understanding of these pathways is crucial for identifying targets for screening, prediction, and treatment. Future research directions include investigating the effects of depression treatment on cardiovascular outcomes among women, and analyses that utilize an intersectional approach.

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Author Contribution Drs. DR and NM had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: DR, NM; acquisition of data: DR, AS, JU; analysis and interpretation of data: DR, AS; drafting of the manuscript: DR, NM; critical revision of manuscript for important intellectual content: RL, JU, TC, CM, KGS, NM; statistical analysis: N/A; obtained funding: NM; study supervision: NM.

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Declarations

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