Přehledový článek | Review article

Depression, cardiovascular disease, and related pathophysiologic mechanisms in women

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SOUHRN

Kontext: Ačkoliv na depresi se v doporučeních AHA a EACPR již pohlíží jako na rizikový faktor kardiovaskulárních onemocnění (KVO), k dispozici máme málo genderově zaměřené literatury. Studie prokázaly, že prevalence deprese může být v určitém věku u žen vyšší a predisponuje ženy k úmrtí z kardiovaskulárních (KV) příčin významněji než muže.
Cíl: Cílem našeho článku bylo podat přehled současných důkazů svědčících pro prevalenci KVO a deprese u žen, nalézt spojitost mezi depresí a KVO u této populace a určit možné biologické mechanismy, které zodpovídají za tento vztah.
Metody: Procházeli jsme původní sdělení a metaanalýzy publikované před 20. 4. 2019.
Výsledky: Náš přehledový článek rozpoznal konzistentní spojitost mezi depresí a KVO u žen a prediktivní hodnotu deprese u mortality z KV příčin, také jsou zde zdůrazněny některé možné patofyziologické mechanismy zodpovědné za tento vztah zvláště u žen.
Závěry: Ženy častěji zažívají nedostatečnou sociální podporu a sociální integraci stejně jako depresi, která vede k nežádoucím parametrům týkajícím se KVO a zesiluje riziko úmrtí z kardiálních příčin, časné hodnocení psychosociálních rizikových faktorů i u žen s nízkým rizikem KVO bude prvořadé pro to, abychom se vyhnuli budoucím komplikacím a definovali efektivní načasování kognitivně založené intervence.

Keywords:
Cardiovascular mortality in women
Depression

ABSTRACT

Background: Although depression is already elevated to the status of a risk factor for CVD in AHA and EACPR guidelines and recommendations, there is lack of gender specific information. Studies have proven that depression can be more prevalent in women at specific age and more significantly predisposes cardiovascular mortality compared to men.
Purpose: The goal of our manuscript was to review current evidences suggesting prevalence of cardiovascular disease and depression in women, to find out the link between depression and cardiovascular disease in this particular population and determine plausible biological mechanism to account for this relationship.
Methods: We reviewed original manuscripts and meta-analysis published before Apr 20, 2019.
Results: Our review identified consistent association between depression and cardiovascular disease in women and predictive value of depression on cardiovascular mortality, also there are underlined some plausible pathophysiologic mechanisms responsible for this relation especially in women.
Conclusions: Women are more frequently experiencing lack of social support and social integration, as well as presence of depression leading to adverse CVD outcome and enhanced risk of cardiac death, early assessment of psychosocial risk factors even in low CVD risk female patients will be paramount to avoid future complication and define effective timing for cognitive-based intervention.

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Introduction

In recent years prevalence of cardiovascular disease (CVD) has been increased in women to close to men's rate[1] and we are facing reality when the absolute numbers of women living with and dying of CVD and stroke exceed those of men.[2] Because traditional risk factors do not account for all of the variance of CVD, there has been growing interest in nontraditional risk factors, including psychosocial variables. Studies have shown, that psychological factors are associated with CVD and psychosocial interventions has been suggested as adjuvant to more traditional treatment.[3,4]

Depression is a novel and independent risk factor for cardiovascular disease, which despite extensive support in the literature has been underestimated and regardless of studies, evaluating and proving link between depressive disorders and traditional cardiovascular disease risk factors, is still neglected.

European guidelines of cardiovascular disease prevention state that low socio-economic status, lack of social support, stress at work and in family life, hostility, depression, anxiety and other mental disorders contribute to the risk of developing CVD and a worse prognosis of CVD.[5] Psychosocial risk factors act as barriers to treatment adherence and efforts to improve lifestyle, as well as to promoting health in patients and populations. Psychosocial risk factor assessment, using clinical interview or standardized questionnaires, in individuals at high CVD risk or with established CVD belongs to class IIa, level B recommendation according to European guidelines of cardiovascular disease prevention.[5]

The American Heart Association (AHA) recently released a scientific statement elevating depression to the status of a risk factor for patients with acute coronary syndromes,[6] however released guidelines and recommendations are experiencing lack of gender specific information in high or low CVD risk group. Numerous prospective studies, systemic reviews and meta-analyses have shown link between mood disorder and excess cardiovascular mortality after acute coronary syndrome (ACS).[7] The prevalence of major depression is two times higher in postmenopausal women than in men, older women much more likely than older men to have recurrent episodes,[8] fluctuating hormonal levels from menstrual cycle and reproduction, and psychosocial factors may contribute to these gender differences.[9] Clinical features of depression in women include more atypical symptoms, anxiety and eating disorders, and longer and more recurrent depressive episodes.[8] Studies also have shown that higher prevalence of depressive symptoms in women modestly contributes to their higher rates of rehospitalization and angina compared with men.[10] Depression rates are doubled in the presence of diabetes and are considerably higher in diabetic women compared with diabetic men,[11] and depressed diabetic women have more rapid development of CVD compared with non-depressed diabetic women.[12]

The goal of our manuscript is to review current evidences suggesting prevalence of cardiovascular disease and depression in women, to find out the link between depression and cardiovascular disease in this particular population and determine plausible biological mechanism to account for this relationship.

Literature search strategy

We searched PubMed, MEDLINE databases to identify relevant peer-reviewed studies on or before Apr 20, 2019 for combination of the following terms: "Depression, cardiovascular disease in women", "Depression and cardiovascular mortality in women", "Pathophysiologic mechanisms linking depression to cardiovascular disease".

Gender specific pathophysiology linking depression to cardiovascular disease

Several studies have examined and are giving insights into the pathophysiology linking depression to cardiovascular disease in gender specific group. In one experimental model of stress, the social stress of subordination caused hypothalamic–pituitary–adrenal and hypothalamic–pituitary–ovarian dysfunction in adult female cynomolgus monkeys.[13] After the induced stress female cynomolgus monkeys developed more atherosclerosis than non-stressed females and also they developed signs of depression and poor ovarian function, which along with hypercortisolemia, increases cardiovascular reactivity and metabolic syndrome. These pathophysiological pathways can be responsible for the enhanced atherosclerosis in women, where the level of social stress at any age is significantly high.[14,15] It is proposed that both social and hormonal influences stimulate affiliative needs for girls during puberty, this gender-specific predisposition may account for the increased risk of depression when an adolescent female is stressed by negative life events.[9]

A meta-analysis of 361 studies involving 18,454 individuals reported that depression induces elevations in cortisol which can lead to activation of inflammation pathways. There were not found differences in terms of gender.[16] Inflammation represents one mechanism that can directly accelerate atherosclerosis.[17] Pro-inflammatory states can be triggered by sympathetic activity and are associated with a dysregulated hypothalamic–pituitary–adrenal (HPA) axis.[18] Big case-control studies and meta-analysis have demonstrated excesses in pro-inflammatory markers for both major depression and bipolar disorder showing that patients with bipolar disorder have higher concentrations of soluble interleukin-2 receptor (sIL-2R), interleukin-6R receptor (sIL-6R), tumor necrosis factor alpha (TNF-α), soluble tumor necrosis factor receptor type 1 (sTNFR1), and interleukin-4 (IL-4), studies have not performed gender specific analysis, although majority of them included more women than men.[19] Studies also show that all three, C-reactive protein (CRP), IL-1, and IL-6 were significantly associated with depression[20,21] but very few of them, with small sample size have provided data partitioned by sex.

Lipid level abnormalities in women with the symptoms of depression

Previous studies have evaluated the association between lipid level abnormalities depression or schizophrenia[22–25] but sex differences were not taken into account in most of them. High density lipoprotein cholesterol (HDL-C) was reported to be a more significant cardiovascular disease risk factor in women than men, whereas low density lipoprotein cholesterol (LDL-C) is more significant in men.[26] Ancelin et al. in ESPRIT study (analyzed 1040 female patients) demonstrated that increased prevalence of depression among women was associated with HDL-C level.[27] Wysokinski et al. in 760 female patients showed that in unipolar depression group women were characterized with higher total cholesterol and LDL level, lower HDL level compared to men of the same group.[28]

Kim et al. showed that in females prevalence of metabolic disturbance increased from the minimal depressive symptom group (12.1% for hypertriglyceridemia, 9.2% for metabolic syndrome [MetS]) to persistently-severe depressive symptom group (19.6% for hyper-triglyceridemic, 14.4% for MetS), this trend was weaker in males.[29]

In a meta-analysis López-León et al. reported significant evidence for five major depressive disorder susceptibility genes, two of them also being associated with lipids, apolipoprotein E (ApoE), and serotonin transporter (5-HTT).[30] Apolipoprotein E (ApoE) is a major determinant in lipoprotein metabolism, cardiovascular disease, and immunoregulation, each of which is implicated in major depression. Regarding the linked promoter region of 5-HTT (5-serotonin transporter gene linked promoter region [5-HTTLPR]), LDL-C levels have been found to be higher in persons with the long polymorphism (*l*/*l*) than those with short polymorphism (*s*/*s*),[31,32] although not systematically.[33]

Prevalence of depression and cardiovascular disease in women

Studies are experiencing lack of gender specific evidences but in general depression appears to increase the risk of development of CVD in men and women alike.[34] Stockholm Female Coronary Risk study showed that depressive symptoms were significantly associated with angina pectoris in female patients,[35] Vaccarino et al. in WISE study confirmed that depression was a significant predictor of CVD in female patients.[36] Studies are showing controversial results assessing association between depression and traditional cardiovascular disease risk factors in women. Anderson et al. showed that depression rates are doubled in the presence of diabetes and are considerably higher in diabetic women compared with diabetic men,[11] Clouse et al. showed that depressed diabetic women have more rapid development of CVD compared with non-depressed diabetic women.[12] Wagner et al. observed that lifetime major depressive disorder is associated with endothelial dysfunction regardless of diabetes status.[37]

Depression and cardiovascular mortality in women

Studies have shown that persistent depressive symptoms after acute coronary syndrome are common and increase the risk of recurrent cardiac events and mortality (Table 1)[38].

In total depression increases the risk of mortality in patients with established coronary heart disease.[39] Women with acute myocardial infarction (AMI) have more severe depression compared with men, and depressive symptoms persist longer.[40,41] Women also have a greater prevalence of depression as well as more severe depressive symptoms than men after coronary artery bypass graft surgery (CABG).

EPPI, M-HART study have demonstrated that depression is independent predictor for CVD mortality for both gender,[42] PREMIER study also showed that depression symptoms were significantly and similarly associated with cardiovascular outcomes in both men and women.[10]

In women who present with AMI or unstable angina, lack of social support and social integration, as well as presence of depression, are strong predictors of adverse CVD outcome and both independently enhance the risk of cardiac death, recurrent AMI, or revascularization by 2- to 2.5-fold.[35]

It has been suggested that the higher prevalence of depression in women may contribute to this gender difference in post-AMI prognosis.[43]

Summary

Although gender specific approaches is not taken into account in AHA and EACPR guidelines and recommendations, they have elevated depression to the status of a risk factor for CVD, however psychosocial risk factor assessment, using clinical interview or standardized questionnaires is recommended just in individuals at high CVD risk or with established CVD. There is increased recognition that depression delays recovery post-AMI and after CABG in women. Women are more frequently experiencing lack of social support and social integration, as well as presence of depression leading to adverse CVD outcome and enhanced risk of cardiac death,[44] future studies with precise focus on gender specific pathophysiology leading to cardiovascular disease in depressed women can clarify the usefulness of early assessment of psychosocial risk factors even in low CVD risk female patients to avoid future complication and define effective timing for cognitive-based intervention.

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Conflict of interest
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Table 1 – Summary of studies that examined association of depression and cardiovascular disease (and cardiovascular disease risk factors) in female patients

Study	Age, y	Number of women enrolled in the study	Association of CVD with depression	Instrument for the evaluation of depression	Assessment timing
Waaserteil-Smooller et al. WHI-OS	50–79	93 676	57% of cardiac catheterization, angioplasty, or coronary bypass surgery (ORs, 1.41, 1.57, and 1.28, respectively) was associated with depression in women	CES-D	1 week prior
Frasure-Smith et al. EPPI and M-HART study	50–74	283	Depression is independent predictor for CVD mortality for both gender: $p = 0.30$	BDI	Within few hours after PCI
Horsten et al. Stockholm Female Coronary Risk study	30–65	292	Depressive symptoms were associated with angina pectoris in females, $p = 0.003$	Pearlin et al., BDI	Prior to their visit to research clinic
Parshar et al. PREMIER study	30–65	807	Depression symptoms were significantly and similarly associated with cardiovascular outcomes in both men and women ($p = 0.05$)	PHQ-Primary Care Evaluation of Mental Disorders Brief Patient Health questionnaire	During hospitalization
Vaccarino et al. WISE study	> 18	679	Depression was a significant predictor of CVD ($p < 0.001$)	BDI	Baselin, during hospitalization
ENRICHED study	49–72	1084	Antidepressant drug use was associated with lower risk of death or non-fatal myocardial infarction. Group by sex interaction on the risk of death or recurrent non-fatal MI (unadjusted $p = 0.03$, adjusted $p = 0.2$)	HRSD, DSM-IV	During hospitalization
Wagner et al.	52–69	215	L-MDD is associated with endothelial dysfunction regardless of diabetes status ($p = 0.05$)	DSM-IV, CES-D	Self-reported postmenopausal women, recruited from outpatient primary care clinics
Ancelin et al. ESPRIT study	68–76	1040	Increased prevalence of depression among women was associated with HDL-C level, $p = 0.03$	MINI	Longitudinal study of neuropsychiatric disorder in community-dwelling French elderly
Kim et al.	40–59	5632	In females, metabolic disturbance prevalence increased from the minimal depressive symptom group (12.1% for hypertriglyceridemia, 9.2% for MetS) to persistently severe depressive symptom group (19.6% for hypertriglyceridemia,14.4% for MetS); this trend was weaker in males	BDI	Evaluation during hospital visit
Wysokinski et al.	31–72	760	In unipolar depression group women were characterized with higher total cholesterol and LDL level, low HDL level compared to men of the same group	DSM-IV	Only the first entry for each patient from inpatient care units was used for analysis.
Gil et al. SOPKARD	50–60	477	Metabolic syndrome was observed more frequently in subjects with depressive symptoms compared to those without depressive symptoms in the whole group (35% vs 28%, $p < 0.05$), difference was observed in females (31% vs 28%, ns)	BDI	Patients were selected based on primary prevention of arterial hypertension, diabetes and lipid abnormalities program

BDI – Beck Depression Inventory; CES-D – Center for Epidemiological Studies Depression Scale; CVD – cardiovascular disease; DSM-IV – Diagnostic and Statistical Manual Of Mental Disorders, fourth edition; HDL-C – high density lipoprotein cholesterol; HRSD – Hamilton Rating Scale for Depression; LDL-C – low density lipoprotein, L-MDD – lifetime major depressive disorder; MetS – metabolic syndrome; MINI – Mini-International Neuropsychiatric Interview; PCI – percutaneous coronary intervention.

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