Therapeutic Advances in Cardiovascular Disease

Inflammation, depression and cardiovascular disease in women: the role of the immune system across critical reproductive events

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Abstract: Women are at increased risk for developing depression and cardiovascular disease (CVD) across the lifespan and their comorbidity is associated with adverse outcomes that contribute significantly to rates of morbidity and mortality in women worldwide. Immune-system activity has been implicated in the etiology of both depression and CVD, but it is unclear how inflammation contributes to sex differences in this comorbidity. This narrative review provides an updated synthesis of research examining the association of inflammation with depression and CVD, and their comorbidity in women. Recent research provides evidence of pro-inflammatory states and sex differences associated with alterations in the hypothalamic–pituitary–adrenal axis, the renin–angiotensin–aldosterone system and the serotonin/kynurenine pathway, that likely contribute to the development of depression and CVD. Changes to inflammatory cytokines in relation to reproductive periods of hormonal fluctuation (i.e. the menstrual cycle, perinatal period and menopause) are highlighted and provide a greater understanding of the unique vulnerability women experience in developing both depressed mood and adverse cardiovascular events. Inflammatory biomarkers hold substantial promise when combined with a patient’s reproductive and mental health history to aid in the prediction, identification and treatment of the women most at risk for CVD and depression. However, more research is needed to improve our understanding of the mechanisms underlying inflammation in relation to their comorbidity, and how these findings can be translated to improve women’s health.

Keywords: cardiovascular diseases, depression, inflammation, menopause, menstrual cycle, pregnancy, sex differences, women

Introduction

A complex relationship exists between depression and cardiovascular disease (CVD), both of which are chronic conditions that have significant detrimental effects on women’s health. The burden of illness and prognosis is far worse in women with comorbid depression and CVD compared with either alone, despite advances in the recognition and treatment of these disorders. These conditions independently and concurrently are associated with staggering healthcare costs and are the top contributors to morbidity and mortality rates of women in developed countries. The comorbidity of these disorders arises as a result of a range of factors, including the activation of shared etiological pathways. Much of the recent research in these areas has focused on the role of the immune system and inflammation in both depression and CVD, though few studies have examined the comorbidity of these conditions and how women are affected during...
reproductive life events. The aim of this paper is to provide a narrative review of inflammatory states associated with alterations in biological systems and female reproductive life events that may contribute to the development of comorbid depression and CVD in women.

Depression disproportionally affects women worldwide at a rate that is nearly twofold greater than men, with sex differences emerging as early as adolescence. Depression in women is a significant risk factor for the development of CVD events (i.e. myocardial infarction, stroke, coronary heart disease, etc.) and cardiovascular mortality, and women who have experienced a cardiac-related event are more likely to be depressed than men. Despite a growing awareness of these issues in women, and initiatives aimed at improving outcomes in those with CVD and depression independently, more research is needed to assist in the prevention, identification and treatment of comorbid CVD and depression in women.

Evidence supports a bidirectional relationship between depression and CVD, whereby depression is a predictor for the development of CVD, and vice versa. Indeed, midlife patients with diagnosed major depressive disorder are twice as likely to have a cardiac event, defined as a fatal or non-fatal myocardial infarction, angina pectoris, congestive heart failure or cardiac arrhythmia. In women, coronary disease rates are strongly predicted by a diagnosis of depression over periods up to 20 years. Moreover, female patients are also more likely than males to experience depressive symptoms after diagnosis of acute myocardial infarction, and there is a nearly threefold greater risk for cardiac readmission in those who develop a depressive episode after an acute coronary syndrome event. Similarly, the first-ever onset of depression in patients following an acute coronary event significantly increases the risk of another cardiac-related event within 2 years. Despite these findings, the mechanisms contributing to the greater risk for developing both of these disorders in women are likely multifactorial and remain poorly understood.

Immune-system dysregulation has been implicated in both the development of depression and CVD, highlighting the possibility of a common etiological basis. In fact, chronic low-grade inflammation has been hypothesized to contribute to the development of both disease states. Individuals with comorbid depression and CVD may also have imbalances in homeostatic regulation of different biological systems, with alterations observed in the hypothalamic-pituitary-adrenal (HPA) axis, renin-angiotensin-aldosterone system (RAAS), and serotonin/kynurenine pathways that are accompanied by inflammation and endothelial dysfunction. Disruption to these systems, in combination with risk factors and periods of hormonal fluctuation associated with reproductive events, is hypothesized to promote a state of inflammation in women that may contribute to the development and reinforcement of a cycle linking depression and CVD.

Here, we build on previous work in this area, with the first section of the review focusing on inflammation and sex differences associated with alterations of key biological systems (HPA axis, RAAS, and serotonin/kynurenine pathway) implicated in the pathogenesis of depression and CVD. The remainder of the review examines immune-system functioning during vulnerable reproductive periods surrounding menstruation, the perinatal period, and menopause, in order to better understand how these events might contribute to the significant depression and CVD comorbidity observed in women. Lastly, we conclude with a brief discussion on future directions within the field.

**Inflammation in CVD and depression**

**Measuring inflammation**

Inflammatory biomarkers are an important feature of immune dysregulation in depression and CVD. Several of the most studied markers of inflammation in both disease states include the interleukin (IL) cytokine group, specifically IL-1β, IL-6, IL-8, IL-10, and IL-12. Of particular interest is IL-6, which is produced at the site of inflammation in response to tissue injury and functions as both a pro- and anti-inflammatory cytokine responsible for regulating cellular processes. Tumor necrosis factor alpha (TNF-α) also plays an important role as an early mediator of the inflammatory response, and is responsible for the production and recruitment of pro-inflammatory cytokines. Within the endothelium, both TNF-α and IL-1β can upregulate IL-6 gene expression. IL-6 is also responsible for stimulating expression of the acute-phase protein...
C-reactive protein (CRP) and the production of cortisol via effects on the HPA axis. The pro-inflammatory cytokine, interferon gamma (IFN-γ), is another immune-response mediator that is primarily produced by activated T lymphocytes in response to inflammation.

Measurement of inflammatory cytokine levels is not only an effective tool for generating an individual’s inflammatory profile and assessing immune-system activity, but also has the potential to be used as a readily available test for identifying individuals at risk of developing inflammatory-related conditions.

**Evidence of inflammation in CVD and depression**

Elevated levels of similar pro-inflammatory cytokines have been found in individuals with depression and in those with cardiovascular conditions. For example, a recent large meta-analysis reported that levels of IL-6 and CRP are higher in those with depression. These same inflammatory markers are also elevated in patients with coronary heart disease and in those with heart failure, though the sensitivity of CRP in heart failure has recently been called into question.

Given the number of studies that have reported associations of inflammation with depression and CVD independently, it is surprising that so few have investigated inflammatory markers in relation to concurrent depression and CVD. There has been a report of increased CRP levels and IL-6 messenger ribonucleic acid expression in depressed coronary heart disease patients, compared with those with heart disease alone, raising the possibility that CRP and IL-6 could eventually serve as a useful risk marker for this comorbidity.

**Sex differences: inflammation in CVD and depression**

Well-documented sex differences in inflammation in the general population have been reported, including higher CRP levels in adult...
women that result from accelerated increases in CRP levels during late adolescence. Within the context of cardiovascular health, pro-inflammatory markers may help predict cardiac outcomes in females. Specifically, CRP was found to be a predictor of myocardial infarction, stroke and cardiovascular death in women. In healthy women with no history of CVD, higher levels of CRP and IL-6 are associated with the presence of other cardiovascular risk factors, such as high body mass index, blood pressure, and smoking status, suggesting that increases in cardiovascular risk in women may be accompanied by increases in inflammation.

When comparing cytokine levels in heart failure patients by sex, age also appears to play a significant role. Specifically, lower and more stable levels of TNF-α were reported in women with heart failure under the age of 50, which was followed by a sharp increase after this age. Furthermore, this pattern of age-related change in TNF-α in women differs from the linear increase observed in men, suggesting that cytokine secretion is affected by age and sex. The inflammatory change observed in women may be related to physiological and hormonal alterations that accompany reproductive life events, such as menopause. In line with this reasoning, the cardiovascular effect of the sex hormone estradiol, which declines during the menopausal transition, has been shown to vary based on menopausal stage and the extent of atherosclerosis present in arteries. Additional evidence from preclinical animal models suggests that the cardio-protective effects of estradiol are negated in cases of severe atherosclerosis. Cumulatively, these reports provide evidence for unique inflammatory and physiological states in women that vary across the lifespan, which change based on age, fluctuations of reproductive life events, such as menopause, and so a closer examination of the inflammatory changes that occur following disruption to these systems may help elucidate the complex relationship linking inflammation to comorbid depression and CVD in women.

**Stress and HPA axis**
Chronic stress and communication between the neuroendocrine and immune systems may be one link between depression and CVD. Stress often accompanies and can precede comorbid depression and CVD in women. For example, older, single, and hospitalized non-White females receiving cardiovascular care were more likely to have depressive symptoms and experience greater stress.

**HPA axis and inflammation**
Several inflammatory cytokines, specifically IL-1β, IL-6 and TNF-α, also have the ability to activate the HPA axis, and this modulation of stress response is greater in female mice models. Sex-specific regulation of the HPA axis and immune system is also found in relation to depressive symptoms in human participants; where females with higher depressive symptom severity had lower cortisol to high-sensitivity CRP (hsCRP) ratios, suggesting heightened inflammation and homeostatic dysregulation among these two systems. The connection between inflammation and stress can be further modified by early exposure to external factors, such as childhood maltreatment.

**Childhood maltreatment and inflammation**
One form of early-life exposure that has significant effects on developmental and health trajectories is childhood maltreatment. Some have argued that early-life exposure to adversity leads to low-grade, chronic inflammation *via* changes to the
signaling mechanisms between the peripheral immune system and the brain. This altered state, which persists into adulthood, likely predisposes individuals to several poor health outcomes that are accompanied by high-risk behaviours such as cigarette smoking, alcohol consumption, substance abuse, obesity, and physical inactivity. These same behaviours often accompany depression and predispose risk for development of CVD, and may be involved in associations between childhood adversity and inflammation later in life.

The immune system is also affected by adverse childhood experiences. Studies have repeatedly detected increased levels of IL-6, TNF-α and CRP associated with exposure to adversity in childhood. Elevated levels of CRP have also been described in depressed children and adults exposed to maltreatment during childhood, but not in depressed individuals with no history of childhood adversity. Therefore, inflammation could potentially mediate the effects of childhood abuse on mental health, with higher levels of immune system responses being linked to depression, and potentially increasing subsequent risk for CVD.

**Sex differences: childhood adversity in CVD and depression**

Individuals with depression and lower levels of education are more likely to report past exposure to childhood adversity (i.e. financial difficulties, family conflicts, etc.) and females who specifically experienced adverse childhood events were more likely to have depression, as well as coronary heart disease or cerebrovascular disease in adulthood. A sex-specific dose–response relationship has been demonstrated in the CVD literature, showing that women who reported more than two childhood adversities were at risk for developing heart disease or cardiovascular mortality three times greater than those with no exposure to childhood adversity.

**RAAS in CVD and depression**

Angiotensin II and aldosterone are involved in the pathogenesis of CVD and its risk factors including hypertension, heart failure, coronary artery disease and metabolic syndrome. Treatment studies have best illustrated how the RAAS is implicated in CVD. Drugs blocking angiotensin function appear to decrease morbidity and mortality in patients with heart failure, coronary artery disease, myocardial infarction, and stroke, further establishing the involvement of the RAAS system with cardiovascular events. Beneficial effects from the addition of aldosterone antagonists to treatments for heart failure with reduced ejection fraction have also been reported.

Though much of the research examining RAAS activity has focused on its relation to CVD risk and outcomes, recent research has implicated RAAS dysfunction in depression, as well. Findings from both human and nonhuman animal studies have linked aldosterone to depression. Depressed individuals have greater aldosterone levels when...
coupled with a social stressor, and individuals with primary aldosteronism, a condition where excessive amounts of aldosterone are produced, have increased rates of psychiatric problems like depression and anxiety. In animal models, rats treated with aldosterone also display depressive-like symptoms.

Evidence connecting angiotensin II to depression primarily comes from preclinical studies. Genetically mutated mice missing the gene responsible for producing angiotensin demonstrate fewer depressive-like behaviors and antidepressant-like effects have been observed in mice treated with drugs that block the angiotensin-converting enzyme or the ATR1. Collectively, these reports from both human and animal models provide compelling evidence of the involvement of RAAS dysfunction with cardiovascular complications and depressed mood.

**RAAS and inflammation**

Even though it is known that the RAAS influences inflammation, there are few studies examining the association of RAAS hormones with inflammatory markers. Early reports have shown that angiotensin-receptor blockers or angiotensin-converting-enzyme inhibitors can modify levels of TNF-α and CRP, and more recently, aldosterone has been linked to vascular inflammatory markers such as pentraxin-3, an acute-phase protein. In a sample of patients with endocrine disorders, serum pentraxin-3 levels were negatively correlated with plasma aldosterone concentrations, suggesting that aldosterone may be a negative regulator of pentraxin-3. However, there is conflicting evidence regarding the influence of pentraxin-3 on CVD due to pentraxin-3 having both beneficial and detrimental cardiovascular effects that are context dependent.

**Serotonin/kynurenine pathway**

**Serotonin/kynurenine pathway and inflammation**

Several pieces of evidence have pointed to the involvement of altered tryptophan metabolism in inflammation and the development of mood disorders. The amino acid tryptophan can be converted to the neurotransmitter serotonin by tryptophan hydroxylase, or kynurenine via the actions of indoleamine 2,3-dioxygenase (IDO) and tryptophan 2,3-dioxygenase (TDO). Several molecules such as cortisol can promote TDO, whereas the most potent activator of IDO expression is the pro-inflammatory cytokine IFN-γ. Under stress or increased inflammatory conditions, both IDO and TDO enhance activation of the kynurenine pathway. Activation of the kynurenine pathway following chronic inflammation is modified to increase the production of neurotoxic metabolites and release reactive oxygen species, resulting in lipid peroxidation and neurodegenerative brain changes.

**Sex differences: RAAS in CVD: case of preeclampsia**

The unique case of preeclampsia, a condition characterized by high blood pressure in pregnancy, offers insights into how the RAAS and inflammation may be contributing to CVD risk in women. Dysfunction of the RAAS, in particular changes to angiotensin II, during pregnancy is implicated in preeclampsia. Inflammation (as measured by CRP levels) in pregnant women exhibiting altered utero–placent al function was associated with an insertion/deletion polymorphism in the angiotensin-converting-enzyme gene responsible for the conversion of angiotensin II from angiotensin I. Lasting changes to endothelial function are also observed in postpartum women with a past history of preeclampsia who display enhanced vasoconstriction sensitivity to angiotensin II, suggesting that increased sensitivity to angiotensin II may contribute to persisting vasculature dysfunction and increase risk for future CVD.

To date, there have been no studies looking at the association of the immune system and RAAS dysfunction in women with comorbid depression and CVD. However, the above reports suggest a link between inflammation and the RAAS hormones aldosterone and angiotensin II, which are implicated in cardiovascular health and mood. Therefore, RAAS dysfunction may confer greater risk to subsets of women during reproductive events.
serum kynurenine compared with tryptophan (KYN/TRP ratio), a measure of IDO activity, have been demonstrated in CVD patients, such as those with coronary heart disease\textsuperscript{72} and ischemic stroke,\textsuperscript{73} and provide evidence for altered kynurenine synthesis. Furthermore, the KYN/TRP ratio, as well as other kynurenine metabolites, are strongly associated with increased risk of poor outcomes following stroke\textsuperscript{74} and cardiovascular-related mortality in the general population.\textsuperscript{75}

Depressed coronary heart disease patients show greater serum KYN/TRP ratio compared with those without depression,\textsuperscript{23} suggesting that depression coupled with CVD leads to increased activation of the kynurenine pathway. In the case of depression caused by immunotherapies, patients receiving high-dose IFN-\(\alpha\) treatment experience greater amounts of depressive symptoms, which further lends support to the involvement of kynurenine pathway dysfunction in the emergence of depressive symptoms.\textsuperscript{71,76}

The serotonin hypothesis of depression originally posited that mood changes occur as a result of serotonin deficiency, although it is now understood that a multitude of factors are implicated.\textsuperscript{77} Even though increased kynurenine activation may be associated with depression via decreased serotonin synthesis, accumulating evidence suggests that depressive symptoms may arise due to an imbalance of kynurenine metabolites, with the production of neurotoxic metabolites being favoured.\textsuperscript{78} A meta-analysis of the relationship between kynurenine metabolite levels in relation to mood disorders reported lower levels of kynurenine in unipolar major depression; yet the results with other metabolites, such as the KYN/TRP ratio, were inconclusive, however.\textsuperscript{79}

**CVD risk factors in women**

Well-characterized sex differences exist among traditional risk factors that contribute to CVD risk. In women, these factors include: older age, abnormal lipid profiles (i.e. elevated low-density lipoprotein cholesterol and triglycerides, and decreased high-density lipoprotein cholesterol), hypertension, diabetes mellitus, smoking, physical inactivity and obesity.\textsuperscript{83} Women with depression are also more likely to have CVD risk factors related to metabolic dysregulation,\textsuperscript{84} and many of these CVD factors also increase the risk for depression. A large body of evidence also supports the involvement of inflammatory processes with these traditional CVD risk factors.

**Hypertension and inflammation**

Hypertension is one CVD risk factor that affects a large proportion of postmenopausal women and is linked to CVD mortality.\textsuperscript{85,86} In a large-scale longitudinal study, women with hypertension and elevated hsCRP levels experienced a greater risk of developing a stroke compared with normotensive women,\textsuperscript{87} implicating both hypertension and inflammation in the development of stroke in women. Women are also vulnerable to the development of hypertension during other reproductive events, such as preeclampsia during pregnancy, which may be associated with lasting inflammatory changes. A systematic review and meta-analysis found that a majority of studies assessing CVD risk markers in complicated pregnancies reported higher levels of inflammatory biomarkers, such as IL-6, TNF-\(\alpha\), intracellular...
adhesion molecule, vascular cell adhesion molecule, and IL-10, among women following pregnancy with preeclampsia, but these did not reach statistical significance. It’s important to note that the meta-analysis was not performed for all markers due to the limited number of published studies, and those included in the quantitative analyses may have failed to reach significance due to small sample sizes.

**Diabetes mellitus and inflammation**
Diabetes, a metabolic disorder characterized by insulin resistance and high blood glucose levels, also appears to increase CVD risk to a greater degree in women than men. A large amount of evidence supports the role of chronic low-grade inflammation in the etiology of type 2 diabetes mellitus. A prospective study revealed that a heightened pro-inflammatory state in women, as evidenced by higher levels of CRP, IL-6 and TNF-α, is associated with an increased risk for developing type 2 diabetes mellitus. Women experience a unique risk for developing diabetes during pregnancy, known as gestational diabetes mellitus, which is also associated with immune system activation, resulting in increased levels of pro-inflammatory markers and decreased levels of anti-inflammatory markers.

**Obesity and inflammation**
Obesity is another CVD risk factor that triggers a pro-inflammatory immune response that contributes to the increased risk women have for developing type 2 diabetes mellitus, preeclampsia, gestational diabetes mellitus, and depression. Several inflammatory markers, including CRP, IL-1β, and IL-6, are positively associated with body composition and measures of adipocyte size. In obese women, CRP and IL-10 levels are greater than nonobese controls, with the highest levels observed in those with comorbid type 2 diabetes mellitus, suggesting that there is a greater inflammatory response in women with more than one CVD risk factor. Additionally, depressed individuals are more likely to be obese, and obese women are more likely to experience depression. Inflammation may help to explain this relationship in women, as higher levels of TNF-α and leptin, a hormone linked to obesity, were reported in women with depressive symptoms.

**Physical inactivity and inflammation**
Sedentary lifestyle is also often present in obese individuals and can further promote CVD development in women. Overweight women with the least amount of physical activity energy expenditure display greater hsCRP levels, suggesting that lack of physical activity contributes to a heightened inflammatory profile in overweight women. Furthermore, it is well known that increasing physical activity has beneficial effects in reducing inflammation and mild-to-moderate levels of depression in women. Taken together, several of the traditional risk factors that contribute to CVD risk in women are associated with a state of increased inflammation.

It is important to note that these CVD risk factors and altered physiological states are not unique to women, and therefore are not fully able to explain how inflammation may be contributing to depression and CVD comorbidity due to sex differences. To further our understanding of why women are at greater risk for developing comorbid depression and CVD, inflammatory processes and physiological features associated with female reproductive events and sex hormones will now be discussed (Figure 2).

**Sex hormones and inflammation**
Inflammatory profiles in women appear to fluctuate based on reproductive events across the lifespan, with estradiol (17β-estradiol) exposure playing a significant role. Estradiol is the primary sex hormone of the three endogenous estrogens (which also include estriol and estrone) that drives sexual development and regulates reproductive processes, such as menstruation in females. The influence of estradiol on the immune response includes alterations to cytokine secretion that varies based on immune cell type, estradiol concentrations and expression of estrogen receptors. Estrogens can induce an inflammatory reaction via their effects on neutrophils, likely via estrogen receptors α and β. In general, estradiol appears to be linked to suppression of pro-inflammatory cytokine production, such as reduced expression of IL-6 and TNF-α, and increased production of anti-inflammatory cytokine IL-10, though effects on IL-10 levels change depending on location in the nervous system. Further complicating this relationship is estradiol dose, as higher concentrations are
linked to anti-inflammatory responses, whereas low concentrations are associated with pro-inflammatory responses. Progesterone is another sex hormone that can bind to its receptors on a variety of immune cell types, but the effects are predominantly anti-inflammatory. Changes to the natural fluctuation of estrogen and progesterone during reproductive events in women may impact the immune system and subsequently trigger development of CVD and depression.

It has long been known that a woman’s reproductive history can alter their health trajectory. Earlier age of menarche and menopause has been consistently linked to higher CVD risk, including coronary heart disease, electrocardiogram abnormalities, and cardiovascular-related mortality. Limited research has been conducted examining inflammation related to age of menarche or menopause onset, but some evidence supports the involvement of inflammation in their timing. Increased levels of CRP and adiposity measures in female children at age 5 was correlated with decreased levels of sex hormone binding globulin, which predicted earlier menarche. Recently, it has been shown that earlier menopause onset is associated with higher CRP levels in postmenopausal women, with stronger associations noted for African-American women. Complications that arise during these pivotal time periods can reveal subclinical syndromes and provide insight into future risk of cardiovascular and other chronic diseases.

**Figure 2.** A summary of female-specific reproductive events and physiological features that contribute to a pro-inflammatory state in women. It is hypothesized that alterations to circulating levels of sex hormones, endothelial dysfunction and exposure to vascular stress during unique reproductive events promote an inflammatory response in women that likely contribute to the development or exacerbation of depression and cardiovascular disease.

**Oral contraceptive use**

Women may use oral contraceptives for a variety of reasons throughout their reproductive lifetime, including for preventing pregnancy, reducing abdominal menstrual pain, and as part of treatment for conditions such as polycystic ovarian syndrome (PCOS) and endometriosis.

**Oral contraceptive use, CVD and depression**

The use of certain oral contraceptive formulas may increase CVD risk in women. For example, combination oral contraceptives containing exogenous estrogen and progestin are linked to the development of CVD risk factors, such as hypertension, as well as thromboembolism and ischemic stroke (even though the overall risk in healthy women of reproductive age is relatively low). Other formulations of oral contraceptives, specifically those containing progestin-only, are associated with reduced risk of CVD when compared with women taking the combination type. However, women with a history of using both the progestin-only and combined oral contraceptives had twice the odds.
of developing heart disease or stroke compared with women who only took the combined oral contraceptive.120

While there is no conclusive evidence supporting the link between oral contraceptive use and depression, there appears to be a small proportion of women who are vulnerable to developing negative mood following combination contraceptive use.121 In the case of premenstrual dysphoric disorder (PMDD), an oral contraceptive formula containing drospirenone, a form of progestin, and ethinyl estradiol has been shown to be clinically effective in treating premenstrual mood symptoms, such as depression.122 Therefore, it is possible that some women may be more susceptible to mood alterations following oral contraceptive use based on the type of progestin used.

**Oral contraceptive use and inflammation**

In terms of inflammation, a small amount of research has shown that oral contraceptive use in healthy young women is linked to increased CRP levels,123–125 though findings have been inconsistent.126 In nonhuman animal models, administration of combination oral contraceptives led to increased blood pressure and greater endothelial dysfunction associated with elevated circulating levels of CRP, uric acid and plasminogen-activator inhibitor 1 (PAI-1) pro-inflammatory mediators in female rats.127 Uric acid is related to several cardiometabolic risk factors, such as hypertension and diabetes, and can increase pro-inflammatory cytokine expression,128 whereas the protein PAI-1 is stimulated by several pro-inflammatory cytokines.129 In the case of women with PCOS, oral contraceptive use was associated with increased CRP, whereas no significant change in IL-6 or TNF-α levels was found, and PAI-1 levels tended to be decreased depending on the type of oral contraceptive used.130 Taken together, there is some evidence supporting altered inflammatory state in women taking oral contraception that may contribute to risk of depression and CVD, but more research is needed before conclusive findings may be drawn.

**Perinatal depression and inflammation**

Vulnerable populations may experience alterations to the cytokine-glucocorticoid feedback circuit during the perinatal period, leading to decreased regulation of cytokine production and cortisol secretion, and increased depression susceptibility.135 One possible mechanism by which the immune system influences mood during pregnancy is through activation of toll-like receptors and NLRP3 inflammasome from immune placental cells, causing an inflammatory shift which may trigger depression in pregnancy.136

Increased levels of pro-inflammatory cytokines have been demonstrated in perinatal women with major depression, but the literature is mixed.137 One study investigating serum levels of inflammatory markers prior to delivery found lower levels of 40 markers of inflammation (including IL-10) linked to postpartum depression.138 However, another recent study found no association between cytokine levels and perinatal depression in plasma, but noted that higher levels of IL-1β, IL-23 and IL-33 in cerebrospinal fluid were associated with an increased odds of developing perinatal depression.139 A cross-sectional study found increased pro-inflammatory markers, specifically IL-6, IL-15 and chemokine ligand 3 (CCL3), in women with depressive symptoms during the third trimester, but these results varied based on ethnicity and timepoint examined during the perinatal period.140

In a sample of Swedish women, several peripheral inflammatory biomarkers, including IL-18, was increased in women with postpartum depression.141 The variability of findings observed among studies investigating inflammatory markers with perinatal depression likely reflects the different psychiatric problems and cardiovascular events. Global pooled prevalence rates demonstrate that 11.9% of women experience perinatal depression.131 Similar rates of antenatal depression have been described across the gestational period, with higher rates observed in the second and third trimester.132,133

Pregnancy has been described as a ‘stress test’ that can reveal a woman’s underlying vascular health.116,134 Complications that arise during pregnancy, such as depression, preeclampsia, gestational diabetes and preterm delivery, can indicate women who have an increased risk for developing CVD or depression later in life.
study designs employed and highlights the importance of timing and source of sample collection.

The protein PAI-1 may provide a plausible link for how inflammation is associated with perinatal depression and CVD risk. PAI-1 is secreted by various endothelial cells and its production is increased during pregnancy. An increase in several inflammatory cytokines, such as CRP, IL-1β, IL-6, and TNF-α, which may occur as a result of perinatal depression or HPA axis dysfunction, can lead to increased expression of PAI-1 and subsequently increase risk for the development of atherosclerosis and myocardial infarction.

Based on the evidence described above, there is strong support for the involvement of pro-inflammatory cytokines with perinatal depression, but more research is needed to determine a reliable inflammatory profile associated with developing mood symptoms in the perinatal period. Perinatal depression may contribute to increased CVD risk in women through inflammatory changes that promote hypertension in the form of preeclampsia and the development of gestational diabetes, but this has yet to be directly tested. The following two sections will summarize the recent advances in the literature pertaining to depression and CVD risk in gestational diabetes and preeclampsia.

Gestational diabetes mellitus

Gestational diabetes mellitus, CVD and depression

A relationship exists between depression in pregnancy and gestational diabetes mellitus (GDM), as depression in the first trimester of pregnancy has been shown to predict the development of GDM. In the general population, depression and type 2 diabetes are comorbid conditions, with higher prevalence observed in females; however, there are conflicting reports on the directionality of the relationship between depression and GDM. Regardless, the association between depression and GDM may be explained by a shared pro-inflammatory state that results in the inability to produce enough insulin, and puts women at risk for adverse cardiovascular outcomes.

GDM affects 9% of all pregnancies in North America, with even higher rates in the Middle East and North Africa. GDM increases risk for pregnancy complications and unfavourable outcomes, such as preeclampsia, and later development of type 2 diabetes and CVD, including acute myocardial infarction, stroke, and coronary artery disease. In uncomplicated pregnancies, insulin resistance increases midgestation, but women are able to retain normal blood glucose levels during this time through compensatory mechanisms that result in greater insulin secretion. Failure to adequately compensate the increase in insulin resistance leads to the development of gestational diabetes.

Gestational diabetes mellitus and inflammation

Multiple studies have shown altered immune cytokine levels associated with GDM, specifically increased levels of serum pro-inflammatory cytokines, IL-1β, IL-6, CRP, and TNF-α, and lowered levels of anti-inflammatory marker IL-10; however, cytokine levels in women with GDM vary based on time of sampling in pregnancy and not all results reached statistical significance. Altered secretion of cytokines from adipose cells, known as adipokines, are also implicated in GDM and play a role in promoting inflammation, insulin resistance and endothelial dysfunction. Even though these results have been replicated, a recent study failed to detect any noticeable cytokine differences among women with GDM or normal glucose tolerance pregnancies, possibly because the study was not adequately powered to detect differences between groups. It currently remains uncertain whether the associated inflammatory response is a causal factor or consequence of GDM. Even though the nature of this relationship has yet to be fully explored, the pro-inflammatory state associated with GDM may help explain the increased prevalence of comorbid depression in pregnancy and be a contributor toward CVD development later on.

Preeclampsia

During pregnancy, physiological changes take place to ensure that the woman’s body is able to meet the increased demands of a developing fetus. Preeclampsia is thought to develop as a result of several factors, including abnormal vascular remodeling leading to placental ischemia, endothelial dysfunction and oxidative stress, a systemic inflammatory response generated from...
toll-like receptors in the placenta, and (c) genetic vulnerability. A balance between pro-oxidative and antioxidative responses is required for regulating embryogenesis, whereby healthy women display increasing levels of oxidative stress that peak during the second trimester. It is hypothesized that disruption to this balance can promote an inflammatory response that may lead to the development of preeclampsia. Furthermore, exposure to factors contributing to cardiovascular risk prior to pregnancy may also contribute to inflammation and create a lowered threshold for managing vascular stress during pregnancy, which can result in preeclampsia.

**Preeclampsia, CVD and depression**

Preeclampsia affects roughly 5–8% of pregnancies worldwide and is a significant contributor to maternal and fetal morbidity and mortality despite advancements in perinatal care. Preeclampsia is characterized by hypertension, edema and proteinuria, with normotensive women developing new-onset hypertension at around 20 weeks’ gestation. The adverse effects of preeclampsia extend beyond the perinatal period, putting women at greater risk for future adverse cardiovascular events, with risk levels that are proportional to preeclampsia severity. Preeclampsia is linked to CVD risk factors such as chronic hypertension, metabolic disorders, renal disease, as well as stroke in women, and preterm-born offspring with low birth weight. Even though the exact causal mechanism for preeclampsia is unknown, it is plausible that physiological alterations leading to a state of heightened inflammation may help explain why women are at risk for developing preeclampsia in pregnancy.

Depression may also contribute to increases in inflammation and oxidative stress associated with preeclampsia and CVD later in life in women. Depression or anxiety in early pregnancy is associated with a greater risk for developing preeclampsia, and a diagnosis of hypertensive disorder during pregnancy is associated with higher levels of postpartum depression. Furthermore, pregnant women taking antidepressants, especially serotonin–norepinephrine reuptake inhibitors (SNRIs) and tricyclic antidepressants (TCAs), are at increased risk of developing preeclampsia but it has not yet been established if this association is due to these medications or is a result of depression itself. A recent review of the literature further provides support that antidepressant use in pregnancy is associated with moderately increased risk for both preeclampsia and gestational hypertension; however, methodological limitations and differences between studies reduce the ability to draw clear conclusions.

**Preeclampsia and inflammation**

The literature examining the association between preeclampsia and inflammatory biomarkers is mixed. Multiple recent studies have demonstrated increased serum levels of IL-1β, IL-6, IL-8, IL-10, CRP, TNF-α and IFN-γ in women with preeclampsia compared with women with normotensive pregnancies; however, these results remain inconclusive. From all of the inflammatory biomarkers investigated, CRP, IL-6, IL-8, and TNF-α hold the most promise for early identification of women with preeclampsia yet there is not enough evidence supporting the prognostic ability of individual inflammatory markers in predicting the development of preeclampsia, which may be due to discrepancies among gestational timepoints and population studied. The combination of several biomarkers may afford greater predictive ability for identifying preeclampsia onset or prognosis, but more research is needed.

An increased susceptibility for developing preeclampsia during pregnancy may be in part due to genetic influences on the immune system. Several reports highlight the association of cytokine gene polymorphisms with preeclampsia, such as IFN-γ (A874T), IL-6 (G-174C), IL-10 (A-592C) and TNF-α (G-308A), however, these results are still inconclusive and may only be reflective of specific ethnic groups. A recent review of meta-analyses examining genetic risk factors for preeclampsia found strongest evidence for PAI-1 4G/5G polymorphism. Future studies using larger sample sizes are warranted.

Alterations to the endothelium prior to pregnancy may better explain the inflammatory response observed in women with preeclampsia. Plaque erosion and endothelium dysfunction more frequently develops in women and is associated with up to 44% of fatal coronary thrombosis events; however, this was observed in a small sample of
older-aged women and may not be reflective of females in the general population. When the physiology and function of the vascular endothelium is altered, a pro-inflammatory response is activated, resulting in increased cytokine release, leukocyte adhesion and permeability of the endothelium. In the case of preeclampsia, increased macrophage activation is observed within the placenta of women. Alterations to the vascular system following preeclampsia may be long lasting, as one study found vascular dysfunction associated with women who had preeclampsia over 5 years previously, which correlated with measures of hsCRP. Enduring inflammatory states are also reported within women who developed preeclampsia, as increased levels of plasma CRP and IL-6 were found approximately 17 years after their first pregnancy. These results suggest long-lasting changes to a woman’s inflammatory state observed almost 2 decades after giving birth in those with a history of preeclampsia, which may contribute to the development of depression and CVD.

A complete understanding of the multifaceted relationship between depression, inflammation and preeclampsia requires further research. A major challenge with generalizing results from studies assessing inflammation in relation to perinatal mood has been the large heterogeneity of the samples studied, differences in instruments used to assess mood, and the varying timepoints at which mood and inflammatory state were measured.

**Menopausal transition**

**Menopausal transition, CVD and depression**

The menopausal period is associated with significant hormonal change and increased prevalence of CVD risk factors in women. Women who experience natural or surgical menopause are at higher risk for experiencing a fatal cardiovascular event as compared with younger menstruating women, suggesting that the heightened risk may be related to age or hormonal change that accompanies this time period. Evidence that CVD risk in the menopausal period is associated with timing of hormonal exposure comes from prospective studies showing that women with a shorter reproductive life span, defined as the duration of time from age at menarche to age at menopause, experienced a higher risk of incident coronary heart disease or stroke after menopause. Furthermore, postmenopausal women display more dyslipidemia and hypertension than premenopausal women, which likely results from a combination of hormonal and age-related change.

The menopausal transition and postmenopause periods are associated with greater vulnerability for developing mood symptoms and clinically diagnosed mood episodes. Age of menopausal onset, as well duration of the reproductive period, is associated with postmenopausal depression; whereby earlier-onset menopause was associated with higher risk. The impact of menopause on women’s mental and cardiovascular health may be partially explained by altered sex-hormone production.

The menopausal transition is marked by declining levels of estrogen, which have known neuro- and cardio-protective effects. Results from animal studies on older female rats provide evidence that the protective and anti-inflammatory effects of estradiol are likely age dependent. With older age and menopause, estradiol may no longer be able to exert vascular protection in women as a result of alterations to the estrogen receptor function and expression that occurs in combination with estrogen loss. In postmenopausal women, levels of estradiol, testosterone, and their ratio are associated with CVD incidence, with higher testosterone-to-estradiol ratio increasing risk for CVD, coronary heart disease and heart failure. These results suggest that a woman’s hormone profile following menopause may be indicative of CVD risk.

In addition to lower levels of estrogen, the menopausal period is associated with vascular alterations that significantly impact CVD risk. Across the life span, women display greater endothelial dysfunction postmenopause. Postmenopausal women with hypertension show evidence of systemic inflammation, via neutrophil count, associated with increased arterial stiffness, which provides support for the involvement of inflammation with altered endothelial function in postmenopausal women, leading to greater CVD risk.

**Menopausal transition and inflammation**

When examining the immune system in relation to menopause, changes to several inflammatory
markers have been described and vary based on the stages of the menopausal transition. A 5-year longitudinal study investigating inflammatory markers in premenopausal women who entered the menopausal transition detected notable changes: increased serum IL-8 and soluble TNF-receptor 1 and 2 (sTNFR1 and sTNFR2, respectively), and decreased serum hsCRP. Another study found that women transitioning from pre- to postmenopause displayed an increase in the inflammatory marker glycoprotein acetyls, which has been linked to incident CVD in women in other studies, yet found no changes in CRP levels. A 10-year longitudinal study conducted on premenopausal women found that women who transitioned through menopause experienced elevations in the acute-phase protein haptoglobin, a marker indicative of heightened inflammation, but contrary to other reports, they found reduction in levels of the anti-inflammatory cytokine IL-8. Among nonobese postmenopausal women, increased levels of IL-8 and TNF-α, along with decreased levels of IL-1α and IL-3 have been reported. In sum, longitudinal studies assessing inflammatory markers across the menopausal period have reported differing results that likely reflect methodological disparities among the studies. Nonetheless, the majority of the results provide evidence for greater inflammation associated with the menopausal transition.

There is an increased prevalence of depressive symptoms in peri- and postmenopausal women, which may be related to altered immune-system activity during this time. In midlife-aged women during the menopausal transition, an increase in pro-inflammatory response was observed prior to development of first-onset depression, suggestive of a potential cascading effect. In postmenopausal women, higher CRP levels are found in those with clinical levels of depression and in those taking antidepressants, linking inflammatory status with depression severity in postmenopausal women. Levels of haptoglobin, which is previously shown to be increased in patients with depression and associated with CVD risk, were positively correlated with estradiol levels only in the group of perimenopausal women experiencing a first episode of depression and not taking antidepressants. These results suggest that first-ever-onset depression occurring in the menopausal period may reflect a distinct inflammatory profile, which is negatively influenced by estradiol in this population. Currently, there is not enough consistent evidence supporting the practicality of using one or more inflammatory biomarkers to predict depression during the menopausal transition.

Very few studies have examined the association of inflammatory markers with CVD risk in menopausal women. In a sample of postmenopausal women with higher-than-normal blood glucose levels, higher serum CRP levels were associated with insulin resistance, a physiological condition which promotes dyslipidemia and atherosclerosis development. A more recent study investigating CRP found a positive association with coronary artery calcification, a measure predictive of CVD among African-American midlife women only, which highlights the importance of considering ethnicity differences. Presence of low-grade inflammation has been shown associated with biomarkers of atherosclerosis risk in postmenopausal women; specifically, levels of IL-12 were positively associated with measures of very-low-density-lipoprotein cholesterol.

These studies collectively show that increased inflammation during the menopausal transition and in postmenopause appears to be related to both depression and CVD risk, which is further complicated by the influence of estrogens, or lack thereof.

A summary of the evidence describing the inflammatory response in women according to reproductive events that increase risk for depression and CVD can be found in Table 1. Collectively, these reports suggest that increased pro-inflammatory cytokine and immune markers, as well as decreased anti-inflammatory cytokines in women across several reproductive events, are associated with hormonal and physiological change, and that these changes are likely involved in the development of CVD and depression.

Future directions

Use of inflammatory markers in predicting CVD outcomes

Inflammatory markers may be helpful in predicting adverse health outcomes following a cardiac event. Increased levels of IL-6 and TNF-α following heart failure were associated with increased mortality risk among men and women. Similar
results have been found in patients with coronary heart disease, where several adverse outcomes, including cardiovascular and all-cause mortality, myocardial infarction, heart failure hospitalization and cancer mortality, were linked to IL-6 levels. This has also been noted in women presenting with symptoms of ischemia, where higher IL-6 levels were predictive of heart-failure hospitalization and mortality. These results suggest the potential predictive value of IL-6 as an inflammatory marker for adverse outcomes in women with CVD.

Treatment strategies targeting inflammation
At the moment, there are not enough conclusive data to support the use of inflammatory biomarkers in guiding detection or treatment with pharmacotherapies aimed at reducing inflammation associated with depression or CVD within clinical practice. A current promising avenue for treating inflammation associated with depression and CVD is use of antidepressants and drugs with anti-inflammatory properties, specifically nonsteroidal anti-inflammatory drugs, omega-3 polyunsaturated fatty acids and statins, though treatment considerations must be made regarding their use. If dysregulated immune-system functioning plays a primary role in the etiology of these diseases and can be reliably identified, then treatment strategies targeting inflammation may be beneficial (to learn more about recent advances, see Jones and Patel and Zuzarte et al.). With this promising potential comes the need for prospective, randomized-controlled-trial intervention studies in order to determine the effects of anti-inflammatories on long-term outcomes.

Inflammation and the gut microbiome
There is increasing interest in investigating the influence of the gut microbiome on pathophysiology and progression of psychiatric disorders and CVD. Cross-talk between microbiota and the sex hormones of the endocrine system, such as estrogens, may result in changes to inflammation, leading to increased susceptibility for developing depression. Furthermore, there is evidence supporting a link between gut-flora metabolism and CVD risk and pathogenesis. The influence of the gut microbiome on inflammation, mood and CVD risk adds to the complexity of the overall picture. Future research is needed to determine its role in women and in the development of comorbid depression and CVD. If closely associated, examination of the gut bacterial

| Reproductive event associated with greater risk for depression and CVD in women | Change to inflammatory markers |
|---|---|
| Oral contraceptive use | Pro-inflammatory Anti-inflammatory |
| | ↓ CRP, uric acid ↓ PAI-1 |
| Perinatal depression | ↑ IL-1β, IL-6, IL-15, IL-18, IL-23, IL-33, PAI-1, CCL3 ↓ IL-10 |
| Gestational diabetes | ↑ IL-6, IL-12, CRP, TNF-α ↓ IL-4, IL-10 |
| Preeclampsia | ↑ IL-1β, IL-6, IL-8, CRP, TNF-α, IFN-γ ↑ IL-10 |
| Menopausal transition | ↑ sTNFR1, sTNFR2, glycoprotein acetyls, haptoglobin ↓ CRP, IL-1α, IL-3 ↓ IL-8 |

Changes to inflammatory markers vary depending on the population studied, type and timing of sample collection. CCL3, chemokine ligand 3; CRP, C-reactive protein; CVD, cardiovascular disease; IFN-γ, interferon gamma; IL, interleukin; PAI-1, plasminogen-activator inhibitor 1; sTNFR1, soluble TNF-receptor 1; sTNFR2, soluble TNF-receptor 2; TNF-α, tumor necrosis factor alpha.
ecosystem may be beneficial as a diagnostic tool and the development of novel therapeutics targeting diet and changes to the gut flora.

Conclusion
An abundance of research has linked immune-system dysfunction to the development of depression and CVD, with evidence supporting a unique pathogenesis in women. However, there is a scarcity of studies assessing inflammatory profiles in women that also examine depressed mood and CVD simultaneously. Prospective studies focusing on reproductive histories of women are needed, as the majority of investigations completed to date are cross-sectional in design and have failed to consider the effects of sex hormones at several timepoints or focus on reproductive events. Studies conducted with larger female sample sizes will be helpful in determining whether subsets of women are particularly vulnerable to inflammatory changes associated with the development of these conditions.

The likelihood that a single inflammatory marker will be able to reliably predict onset of depression or CVD is unlikely, and future research should embrace investigations that examine multiple inflammatory biomarkers to examine their collective influence or those investigating the balance between pro- and anti-inflammatory states. Additionally, research within this field may help guide future treatment initiatives aimed at targeting inflammatory dysregulation in women with comorbid CVD and depression.

Several methodological limitations have made it difficult to assess sex differences associated with comorbid depression and CVD. The reduced number of female participants and lack of female-specific variables relating to reproductive health in past CVD research has contributed to the difficulty in investigating sex-specific factors that contribute to health outcomes in women. Many reports only examine samples composed primarily of males; therefore, it is difficult to determine whether the results generalize to females.

Overall, it appears that there is likely a subset of women who are more at risk and susceptible to inflammatory changes that in turn leads to the development and reinforcement of a cycle contributing to both depression and CVD. Heightened risk in women is apparent during periods of hormonal fluctuation, suggesting a strong interaction between inflammation and sex hormones. This model is multifaceted and the mechanistic pathways through which the immune system influences these disease states in women have yet to be fully elucidated. As research within this field progresses, it will undoubtedly continue to highlight and bring greater awareness of sex differences that contribute to the development of comorbid depression and CVD in women, improved treatments and superior outcomes in this population.

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Conflict of interest statement
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