

**DEPRESSIVE SYMPTOMS AND CARDIOVASCULAR HEALTH
DURING PREGNANCY**

THE ASSOCIATION OF PLASMINOGEN ACTIVATOR INHIBITOR-1
AND ANTEPARTUM DEPRESSIVE SYMPTOMS:
CONSEQUENCES FOR CARDIOVASCULAR HEALTH

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ABSTRACT

Major Depressive Disorder (MDD) is one of the most common psychiatric conditions affecting adults and afflicts approximately 5% of the world's population. MDD is highly co-morbid with cardiovascular disease, a major source of morbidity and mortality. Although a number of pathological changes observed in MDD may impact cardiovascular health, no single mechanism has been identified that can explain this association. Both MDD and CVD are more common in women, and pregnancy may represent a period of elevated risk for both depression and changes in cardiovascular health that may never fully resolve in the years following pregnancy. This study of 61 pregnant women during their third trimester of pregnancy investigated whether depressive symptoms (as measured by the Edinburgh Postnatal Depression Scale, or EPDS) are associated with decreased heart rate variability, a well-known marker of cardiovascular risk. Additionally, this study will investigate whether Plasminogen Activator Inhibitor-1 and 2 (PAI-1 and PAI-2) mediate this association. These pro-thrombotic proteins have long been linked to the presence and severity of cardiovascular disease, and an emerging body of evidence suggests that plasma concentrations of these proteins may also be elevated in Major Depressive Disorder. Heart rate variability was significantly reduced among participants who had clinically significant depressive symptoms during the third trimester (EPDS >14), although adjustment for age, body mass index, smoking, education level and use of psychiatric medication fully attenuated this relationship. PAI-1 and PAI-2 measured via ELISA assay in a subset of the study population (n=23) was found to not mediate this association. This study is the first of its kind to evaluate the role of PAI-1 in

psychiatric illness during pregnancy, and may serve as the impetus for further research aimed at elucidating the relationship between mental health and cardiovascular risk during gestation.

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ABBREVIATIONS

ASDNN	Average Standard Deviation of NN Intervals
BMI	Body Mass Index
CIDI-V	Composite International Diagnostic Interview- Women
CRP	C- Reactive Protein
CVD	Cardiovascular Disease
ELISA	Enzyme Linked Immunosorbant Assay
EPDS	Edinburgh Post/Peri-natal Depression Scale
HPA-Axis	Hypothalamic-Pituitary-Adrenal Axis
HRV	Heart Rate Variability
MDD	Major Depressive Disorder
PAI-1/2	Plasminogen Activator Inhibitor (1 and 2)
SDANN	Standard Deviation of Averaged NN Intervals
SDNN	Standard Deviation of NN Intervals

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CHAPTER 1

1.0 General Introduction

High rates of co-morbidity have been observed between Major Depressive Disorder (MDD) and Cardiovascular Disease (CVD). Current epidemiological research asserts that both conditions are more frequent in women than in men (Statistics Canada, 2008a). Depression also occurs more frequently during pregnancy than at other times in life (Payne, Palmer, & Joffe, 2009), while cardiovascular complications during gestation are also relatively common, and account for a large proportion of maternal mortality and morbidity during the antepartum and early postpartum period (Bowers et al., 2013). A number of pathological changes observed in MDD are believed to affect cardiovascular health, although no single mechanism has been identified.

The primary aim of this thesis is to investigate the relationship between maternal depressive symptoms in the third trimester of pregnancy and cardiovascular health. As a secondary objective two potential mediators of this association; Plasminogen Activator Inhibitor-1 (PAI-1) and 2 (PAI-2), will be examined. The first chapter of this thesis is a general background of the relationship between cardiovascular disease and Major Depressive Disorder, followed by an overview of how pregnancy may further exaggerate this association. Next, a review paper describing the proposed biological mechanisms supporting PAI-1 and PAI-2 as putative mediating factors is included. Chapter two outlines the study design and methodology of my investigation of this model. Chapter

three describes the results of this study, while chapter four describes the implications, limitations and future directions of this work.

1.1 Major Depressive Disorder During Pregnancy as a Potential Risk Factor for Cardiovascular Disease in Later Life

1.1.1 Introduction

Major Depressive Disorder (MDD) and cardiovascular disease (CVD) among the most prevalent chronic health conditions in the world. CVD is responsible for 50% of all global deaths not due to communicable disease and approximately 1 in 3 people will die of CVD in the United States (Mozaffarian et al., 2015). Lifetime prevalence of depression is 16.9% in the United States (Kessler & Bromet, 2013); with approximately 6.6% of the public experiencing MDD within the past year (Center for Behavioral Health Statistics and Quality, 2015). Major Depressive Disorder has been identified as a potent risk factor for cardiovascular disease development (Elderon & Whooley, 2013; Hare, Toukhsati, Johansson, & Jaarsma, 2014). Patients with MDD experience an over 2-fold risk increase for developing cardiovascular disease (Schulz et al., 2000; B. W. Penninx et al., 2001; van Marwijk, van der Kooy, Stehouwer, Beekman, & van Hout, 2015). Depression in otherwise healthy children has been associated with decreased cardiovascular health in adolescence (Rottenberg et al., 2014), suggesting that this co-morbidity is present even in segments of the population least at risk for developing CVD. Pathological processes such as monoamine dysfunction, HPA-axis dysregulation, sympathoadrenal hyperactivity and inflammation have been observed in depression and may contribute to this co-morbidity.

Women are almost twice as likely as men to experience MDD at some point in their lives (Kessler, McGonagle, Swartz, Blazer, & Nelson, 1993; Hasin et al., 2005), while women may also be at a higher risk for CVD-related death than men (Statistics

Canada, 2008a). Depressive episodes commonly occur during reproductive milestones associated with hormonal fluctuation, with pregnancy representing a time of particularly high risk (Payne et al., 2009). One in five women experience clinically significant depressive symptoms during both antepartum (Marcus, Flynn, Blow, & Barry, 2003) and postpartum (Gavin et al., 2005). Additionally concerning, gestational complications such as pre-eclampsia are more common among women experiencing antepartum depression (Kurki, Hiilesmaa, Raitasalo, Mattila, & Ylikorkala, 2000a), and appear to increase the likelihood of developing cardiovascular pathology in later life (Bellamy, Casas, Hingorani, & Williams, 2007). Because even healthy pregnancies induce vast (though temporary) physiological changes in a woman's body, it is posited that the compounded effect of MDD pathology may trigger more severe consequences for cardiovascular health than would be observed in non-gestational MDD, or in pregnancy uncomplicated by depression.

In this review, five potential sources of the MDD-CVD co-morbidity are examined: health behaviours and risk-factor clustering, serotonin function and metabolism, HPA-axis dysregulation, sympathoadrenal hyperactivity and inflammatory processes. Finally, the potential compounding effect of antepartum depression upon cardiovascular health is examined.

Health Behaviours and Risk-Factor Clustering

Cognitive and affective aspects of Major Depressive Disorder can directly impact health behaviours and influence patient lifestyle. These in turn can increase the likelihood

of CVD development, and increase severity as well as mortality rates. For instance, patients with depression are more likely to smoke (Pasco et al., 2008; Anda et al., 1990) and less likely to successfully quit smoking (Brown, Pamela A. F. Madden, Deena R, Madden, Palenchar, & Cooper-Patrick, 2000) than those without depression. Smoking is a causative agent in the development of CVD, and one of the single largest predictors of age of onset, severity and mortality due to CVD (Doyle, Dawber, Kannel, Kinch, & Kahn, 1964; R. B. D'Agostino et al., 2008). Depression is also associated with increased obesity and central adiposity (Cizza, 2011). Moreover, food choice and eating behavior is closely tied to mood (Singh, 2014). Obesity is a potent risk factor for cardiovascular disease (Poirier et al., 2006), as are dietary practices that increase LDL cholesterol and triglyceride intake (Wilson et al., 1998). Finally, sleep disruption and insomnia are often-reported symptoms of MDD, and chronic sleep disruption also negatively impacts cardiovascular health (Mullington, Haack, Toth, Serrador, & Meier-Ewert, 2009).

1.1.2 Serotonin, Depression and Cardiovascular Disease

Serotonin (5-hydroxytryptamine, or 5-HT) is a monoamine neurotransmitter synthesized from the amino acid tryptophan and widely distributed throughout the central nervous system. 5-HT also facilitates a myriad of cell-signaling processes in endothelial cells throughout the circulatory system, among other sites. In the brain, 5-HT modulates such disparate cortical processes as cognition, reward processing and behaviour formation. It is also an important regulator of mood, although the mechanism by which it exerts these effects is not entirely understood (Berger, Gray, & Roth, 2009). Indeed, depletion of the serotonin precursor tryptophan has been observed to produce transient

dysthymia among participants with no history of depression (S. N. Young, Smith, Pihl, & Ervin, 1985).

Reduced 5-HT Function and MDD

Synaptic 5-HT deficiency or loss of function is closely tied to the mood and cognitive symptoms of Major Depressive Disorder; 5-HT has been the primary target of the vast majority of antidepressants in clinical use. The most commonly used medications today are "specific serotonin reuptake inhibitors" (SSRIs), that function as antagonists to the serotonin transporter (SERT), a receptor responsible for reabsorbing 5-HT from the synapse and transiting back into the bouton of the pre-synaptic cell. By reducing the efficiency of SERT, 5-HT remains in the synapse for a longer average period of time and therefore binds to more postsynaptic serotonin receptors (Coplan, Gopinath, Abdallah, & Berry, 2014). The comparatively high efficacy of 5-HT mediated antidepressant treatment has further encouraged research into 5-HT synthesis, metabolism, mechanisms of action and receptor function and expression. Although a comprehensive review of serotonin's involvement in the etiology of MDD is beyond the scope of this review, a recent meta-analysis by (Kato & Serretti, 2010) elaborates on major fields of investigation. Although there is extensive evidence implicating 5-HT in MDD pathology, it is not yet known whether this is a cause or consequence of other processes, and by which mechanism 5-HT regulates mood.

5-HT in the Periphery: Involvement in Depression

Serotonin is an important cell-signaling molecule throughout the circulatory system, and 5-HT receptors are widely distributed on platelets. 5-HT at these sites also appears to be implicated in MDD. Platelet 5-HT_{1a} receptor expression is inversely correlated with MDD (Zhang et al., 2014), while 5HT₂ receptors may be elevated in depressive states (Hrdina et al., 1995). The ability of platelets to aggregate and form thrombus is regulated by serotonin, and these processes are also over activated in MDD, then attenuated by SSRI administration (Lopez-Vilchez et al., 2014). However, there does not appear to be a direct relationship between brain 5-HT receptors and platelet 5-HT receptors (Yatham et al., 2000), further complicating the role of 5-HT in MDD.

5-HT and Cardiovascular Disease

Because serotonin is directly responsible for regulating blood pressure, myocardial inotropy, vascular resistance and platelet aggregation, serotonin activation can profoundly affect cardiac health (Berger et al., 2009). Elevated levels of plasma 5-HT have observed in patients with cardiovascular disease (Vikenes, Farstad, & Nordrehaug, 1999). Abnormal patterns of platelet activation in response to serotonin exposure have been observed in patients with cardiovascular disease (Kim, McClure, Neighoff, Vaidya, & Williams, 2014). Furthermore, 5-HT mediated platelet activation has been associated with aortic stenosis (Rouzaud-Laborde et al., 2014) and in atherosclerotic plaque formation (Patzelt, Verschoor, & Langer, 2015).

1.1.3 HPA Axis Dysregulation in Depression and Cardiovascular Disease

The Hypothalamic-Pituitary-Adrenal (HPA) axis is the primary homeostatic mechanism for regulating the body's stress response. While the exact relationship between stress and depression is not fully understood, it is thought that overactive or inappropriate responses to stressors may trigger, exacerbate or occur in Major Depressive Disorder (Belmaker & Agam, 2008). Indeed, dysregulation of the HPA axis in depression (Fischer & Cleare, 2015), as well as anxiety disorder (Dieleman et al., 2015) have been extensively documented, supporting the chronic stress hypothesis. Furthermore, behavioural models of depression in animals involve HPA axis dysregulation (Ménard, Hodes, & Russo, 2015). Ideally, the HPA axis functions as a series of self-limiting feedback loops in which the appraisal of a threat triggers corticotropin (CRH) release from the hypothalamus onto the anterior pituitary. This results in adrenocorticotrophic hormone (ACTH) secretion from the pituitary, in turn triggering cortisol release from the adrenal glands. Following the release of cortisol, a negative feedback loop occurs in which cortisol inhibits the release of CRH at the hypothalamus (Pariante & Lightman, 2008). Cortisol is the body's primary endogenous glucocorticoid and has a wide array of physiological effects, both central and peripheral. Cortisol modulates metabolic function in a concentration and circadian rhythm-dependant manner (for instance; paradoxically inducing hepatic gluconeogenesis while inducing insulin insensitivity) but appears to directly contribute to obesity and abdominal adiposity among patients with high serum cortisol levels(Condren, 2002). Cortisol is also a potent anti-inflammatory and immune-suppressant via its activation of immune-cell associated glucocorticoid receptors

(GCRs)(Padgett et al., 2003) (Jia, Niu, Cong, Zhang, & Zhao, 2014). Additionally, cortisol regulates circadian rhythmicity, with morning spikes in serum cortisol associated with increased wakefulness, and HPA axis dysregulation implicated in poor sleep (Buckley & Schatzberg, 2005). Cortisol also regulates blood volume, heart rate, electrolyte balance and membrane permeability in tissues throughout the body. A comprehensive review of cortisol synthesis, function and metabolism may be found in *Physiologic and Pharmacologic Effects of Corticosteroids* (McKay & Cidlowski, 2003).

The HPA Axis in Major Depressive Disorder

HPA axis dysregulation has been consistently observed in patients with Major Depressive Disorder (Pariante & Lightman, 2008). Pathological changes in HPA axis function may occur at any level of the axis(Herman, Ostrander, Mueller, & Figueiredo, 2005), and numerous hypotheses have been forwarded to explain the mechanism underlying mood modulation and HPA axis function (Turecki, 2014). For instance, an inappropriate appraisal of everyday stressors may induce heightened cortisol release (Raz & Leykin, 2015), or the negative feedback loop regulating the axis may be impaired due to the loss of glucocorticoid receptors in the hypothalamus (Dedovic, Duchesne, Andrews, Engert, & Pruessner, 2009). Alternatively, CRH may be basally elevated in patients with MDD, suggesting that the HPA axis may be constitutively hyperactive (Ménard et al., 2015). A growing body of research suggests that antidepressant therapy may attenuate HPA-axis dysregulation in patients with depressive or anxiety symptoms, although the mechanism behind this effect is not well understood (Barden, 2004). It is possible that the cognitive effects of antidepressant use alone can reduce the perceived

magnitude of stressors, producing a concomitant decrease in HPA-axis activation. Alternatively, modulation of CNS serotonin metabolism may directly influence hypothalamic activation, reducing HPA axis activity (Gotlib, Joormann, Minor, & Hallmayer, 2008). HPA Axis dysregulation may also account for elevated rates of obesity (Cizza, 2011; Lasserre et al., 2014) and sleep disturbances (Buckley & Schatzberg, 2005). Chronically elevated cortisol (although an acute anti-inflammatory) may also induce a compensatory down-regulation of glucocorticoid receptors, which may contribute to systemic inflammation observed in MDD (Padgett et al., 2003).

The HPA-Axis in Cardiovascular Disease

HPA axis dysregulation has been identified as a significant individual risk factor for cardiovascular disease (Rosmond & Bjorntorp, 2000). As cortisol directly mediates blood pressure, lipid metabolism, insulin resistance and immune system function, its involvement in cardiovascular pathology is unsurprising (Walker, 2007). The most striking example of the contributory role played by the HPA axis in CVD may be observed in patients with Cushing's syndrome, a condition characterized by chronically elevated plasma cortisol (Erem et al., 2009). These patients have a four-fold increase in the risk for cardiovascular mortality compared to the general population (Whitworth, Mangos, & Kelly, 2000), largely due to cortisol induced obesity, hypercholesterolemia, hypertension and hyperglycemia (Frustaci et al., 2016). In patients without Cushing's disease or other HPA axis pathology, HPA axis over-activity has been associated with cardiovascular risk factors (Le-Ha et al., 2016). Most convincingly, HPA-axis hyperactivity has been directly identified as a partial mediator of cardiovascular-

associated morbidity and mortality among a population of patients with mood disorders (Jokinen & Nordström, 2009).

1.1.4 Sympathoadrenal Hyperactivity in Depression and CVD

Another consequence of elevated cortisol is the induction of sympathoadrenal hyperactivity via the release of catecholamines like epinephrine (Epi) or norepinephrine (NE) from the adrenal medula (Maes, Minner, Suy, Vandervorst, & Raus, 1991). This imbalance between sympathetic and parasympathetic activity may impair the regulation of heart rate and rhythm, with adverse consequences for cardiovascular health (Curtis & O'Keefe, 2002). One common measure of sympathetic function is heart rate variability (HRV), where differences in heart-beat are assessed over a period of time. Subtle inconsistencies in duration and timing of heart beats are a normal part of heart function, as the cardiovascular system (and its innervations) compensate for changes in posture, activity level, vascular diameter and pressure changes in the thoracic cavity due to respiration (Quintana & Heathers, 2014). Reduced HRV is suggestive of cardiovascular pathology and/or sympathetic overactivation (as the parasympathetic signals that "delay" heart beat are drowned out). Two modalities of this measure exist; either the number of beats at a given frequency over a given recording-time are counted ("frequency domain") or measures of the variance between beats (such as standard deviation) are calculated ("time domain") (van Ravenswaaij-Arts, 1993). Heart rate variability has been extensively utilized psychometric research, and as a tool for measuring cardiovascular health.

Sympathoadrenal Hyperactivity in Depression

Heart rate variability has been observed to be reduced in depressed patients with no history of cardiovascular disease (Quintana & Heathers, 2014), suggesting that an imbalance in sympathetic and parasympathetic activity occurs in patients with depression. Furthermore, this reduction in heart rate variability may be attenuated by efficacious antidepressant therapy (Kemp et al., 2010). Depression is also thought to increase the risk for premature ventricular contraction, a specific type of asymptomatic arrhythmia often observed during 24-HRV recording (Grippe & Johnson, 2009). Additionally, sympathetic overactivation has been observed in depressed patients through increased activity of circulating catecholamines (Janowsky, El-Yousef, & Davis, 1974), and via suppression of the parasympathetic nervous system (Agelink et al., 2001).

Sympathoadrenal Hyperactivity in Cardiovascular Disease

Heart rate variability has been identified as a robust predictor for risk of future cardiac events (Tsuji et al., 1996a), as well as for sudden death and ventricular arrhythmias in patients with previously diagnosed cardiovascular disease (Curtis & O'Keefe, 2002). Incidence of cardiac rhythm disturbance is also higher amongst patients with depression, and this may predispose them to sudden cardiac arrest (Watkins et al., 2006). Finally, the presence of premature ventricular arrhythmia dramatically increases the risk of cardiac mortality (Joynt, Whellan, & O'Connor, 2003).

1.1.5 Inflammation in Depression and Cardiovascular Disease

Systemic inflammation refers to an innate immune response implicating a vast array of cell-signalling molecules, immune cells and cytokines, triggering the release of acute-phase proteins such as C-Reactive Protein (CRP- a common clinical measure on non-specific inflammation) (B. W. J. H. Penninx, 2016). This non-specific immune response is accompanied by significant physiological distress, with accompanying mood and cognitive effects. Inflammation has consistently been observed to co-occur in depression, and it is likely that a bidirectional relationship exists (Harrison, 2016). In animal research, induced inflammation is used to model depressive behaviour (Bakunina, Pariante, & Zunszain, 2015), while numerous human studies have identified systemic inflammation in MDD. Chronic inflammation is also a causative agent in cardiovascular disease development, and inflammatory markers such as CRP are utilized as biomarkers for assessing risk and severity of cardiovascular pathology.

Inflammation in Major Depressive Disorder

Numerous meta-analyses have observed that circulating pro-inflammatory cytokines (IL-6, TNF-a) are significantly elevated in Major Depressive Disorder (Howren, Lamkin, & Suls, 2009; Liu, Ho, & Mak, 2012; Dowlati et al., 2010). Complicating the relationship between MDD and inflammation, IL-6 has also been observed to be elevated in people experiencing chronic stress, suggesting that inflammation may be a physiological response to psychological stress that may include depression, but is not necessarily specific to the condition. Reduced serum concentration of circulating pro-inflammatory cytokines appear to predict improved efficacy of cognitive behavioral therapy (CBT) in patients with MDD (Moreira et al., 2015),

although this may also be due to improved stress-management and appraisal among CBT treatment responders. However, observations of significant depressive symptoms among patients experiencing systemic inflammation due to underlying illness suggest that the inflammatory cascade is itself implicated in aspects of depressive illness (Joynt et al., 2003). Additionally, some research suggests that inflammation is specific to depression rather than anxiety, implying that stress appraisal may play only a minor role (Baune et al., 2012). A newly emerging avenue of investigation considers the role of the CNS immune system in depressive etiology. Some evidence suggests that microglia (CNS immune cells) may be in an overactive state during episodes of depression, and that this may be due to or coincide with systemic inflammation, although the mechanisms underlying the interplay between the CNS and peripheral immune systems must be investigated further (Réus et al., 2015).

Inflammation in Cardiovascular Disease

Chronic inflammation is a significant contributor to cardiovascular pathology, so much so that CRP is a commonly utilized biomarker for assessing cardiovascular mortality (Ridker, Hennekens, Buring, & Rifai, 2009). Patients with pre-existing inflammatory illness (such as rheumatoid arthritis or lupus) have much higher risk of cardiovascular disease development, and worse outcomes on average than the general population (Kao, Sabatine, & Manzi, 2003). Atherosclerotic plaque formation requires macrophage proliferation at the site of the plaque, a process mediated by pro-inflammatory cytokines (Libby, 2002). These cytokines may also activate platelets, as well as prothrombotic proteins, producing circulating thrombi, leading to myocardial

infarction, deep vein thrombosis and ischemic disorders (Samad & Ruf, 2013). Given the direct association between inflammation and cardiovascular disease, anti-inflammatory therapies are currently being evaluated for treating and preventing CVD (Ridker et al., 2014).

1.1.6 Perinatal Depression May Compound Cardiovascular Risk

Pregnancy is a period of unique and significant physiological stress and is accompanied by dramatic changes to the endocrine and cardiovascular systems (Buss et al., 2012). Cortisol increases throughout gestation, as does blood pressure (Voltolini & Petraglia, 2014). Likewise, maternal immune function during pregnancy is altered to privilege the placenta and fetus. Pro-thrombotic factors are also elevated as pregnancy progresses, a phenomenon hypothesized to protect the mother during childbirth (de Boer, ten Cate, Sturk, Borm, & Treffers, 1989). Typically these adaptations are very transient and resolve in the early post-partum. However, given the potential effects of MDD upon these systems, coupled with the elevated incidence of mood disorders during antepartum, it is plausible that the combination of pregnancy-stressors and MDD pathology might produce cardiovascular damage that persists into the decades beyond childbirth.

Gestational Complications, Depression and CVD

Major Depressive Disorder may predispose women for development of gestational complications such as pre-eclampsia (PE); gestational hypertension accompanied by proteinuria (Palmsten, Setoguchi, Margulis, Patrick, & Hernández-Díaz, 2012; Kurki, Hiilesmaa, Raitasalo, Mattila, & Ylikorkala, 2000b). PE has serious

consequences for both maternal and fetal health, and can potentially develop into eclampsia, a life-threatening medical emergency. PE is thought to be a consequence of abnormal placenta formation, although the mechanism behind this is unclear (Al-Jameil, Aziz Khan, Fareed Khan, & Tabassum, 2014), although some evidence suggests that systemic inflammation may directly contribute to the development of pre-eclampsia (Duley, 2009). Likewise, alternations in platelet 5-HT function have also been observed in cases of PE and in gestational hypertension without proteinuria (Sabolovic Rudman et al., 2014). Sympathetic overactivation may also be implicated in PE (Logue et al., 2016). Pre-eclampsia is also a potent independent risk-factor for the development of CVD in mid-life (Bellamy et al., 2007), an association particularly potent when predicting mid-life hypertension (Garovic & Hayman, 2007).

The HPA-Axis, Estrogen and Endocrine Function During Gestation

Although cortisol (and CRH) are elevated in healthy pregnancies, it may be further compounded by the presence of Major Depressive Disorder. Women with prenatal depression exhibit a blunted cortisol response after a dexamethasone challenge (similarly to depression outside of pregnancy), although average circulating cortisol was higher as an effect of pregnancy (Meltzer-Brody, 2011). Additionally, increasing plasma estrogen concentration during pregnancy may modulate peripheral and CNS serotonin activity (Kammerer, Taylor, & Glover, 2006). Estrogen may act as a neuromodulator via synaptic estrogen receptors, directly influencing 5-HT function (Joffe & Cohen, 1998). The

relationship between estrogen and mood is multi-factorial and not generally thought to be related to either elevated or reduced levels of estrogen. Rather, change in basal levels of estrogen appear to be indicative of mood disturbance.

1.1.7 Conclusion

Depression and cardiovascular disease are highly co-morbid conditions, that are among the most prevalent illnesses in North America. MDD is thought to be a potent independent risk factor for the development of CVD, while also increasing mortality and morbidity in patients with CVD. Numerous potential mechanisms have been identified; chiefly serotonergic activity, HPA-axis dysregulation, sympathoadrenal hyperactivity, and inflammation. Both CVD and MDD pose a particularly high risk to women, who are significantly more likely to develop both conditions. Additionally, the perinatal period has even higher rates for depression, and cardiovascular gestational complications are more prevalent among women with MDD. These in turn increase the risk of CVD in later life. It is possible that depression during pregnancy may have a particularly severe effect upon cardiovascular health in later life, while also providing the clinician an opportunity to predict and avert cardiovascular pathology while these women are still healthy. Longitudinal follow-up studies are necessary to assess the risk of perinatal depression upon subsequent cardiovascular health.

1.2 **Is Plasminogen Activator Inhibitor-1 a Physiological Bottleneck Bridging Major Depressive Disorder (MDD) and Cardiovascular Disease (CVD)?**

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Abstract

Major Depressive Disorder (MDD) is estimated to affect one in twenty people worldwide. MDD is highly co-morbid with cardiovascular disease (CVD), itself one of the single largest causes of mortality worldwide. A number of pathological changes observed in MDD are believed to contribute to the development of cardiovascular disease, although no single mechanism has been identified. There are also no biological markers capable of predicting the future risk of developing heart disease in depressed individuals. Plasminogen Activator Inhibitor 1 (PAI-1) is a pro-thrombotic plasma protein secreted by endothelial tissue and has long been implicated in CVD. An expanding body of literature has recently implicated it in the pathogenesis of Major Depressive Disorder as well. In this paper we review candidate pathways implicating MDD in CVD and consider how PAI-1 might act as a mediator by which MDD induces CVD development; chiefly through sleep disruption, adiposity, Brain Derived Neurotrophic Factor (BDNF) metabolism, systemic inflammation, and Hypothalamic-Pituitary-Adrenal (HPA) axis dysregulation. As both MDD and CVD are more prevalent in women than men, and both incidence of either condition is dramatically increased during reproductive milestones, we also explore hormonal and sex specific associations between MDD, PAI-1 and CVD. Of special interest is the role PAI-1 plays in perinatal depression and in cardiovascular complications of pregnancy. Finally, we propose a theoretical model whereby PAI-1 might serve as a useful biomarker for CVD risk in those with depression, and as a potential target for future treatments.

*Keywords: Cardiovascular Disease, Major Depressive Disorder, Pregnancy,
Thrombosis, Women's Health*

Introduction

Robust epidemiological, clinical, and experimental evidence links Major Depressive Disorder (MDD) and cardiovascular disease (CVD) (Elderson & Whooley, 2013)(Wright, Simpson, Van Lieshout, & Steiner, 2014). It is estimated that 350 million people suffer from depression worldwide, however its burden of illness is 50% greater for women than for men (Ferrari et al., 2013). Approximately 25% of women will meet diagnostic criteria for MDD at some point in their lives, and up to 40% will develop CVD (Government of Canada, Health Canada, Public Affairs, 2009). Cardiovascular disease is a leading cause of mortality for women, accounting for up to 30% of all female deaths (Statistics Canada, 2008b), and women appear to be at greater risk for cardiovascular specific death than men (Statistics Canada, 2008b). Major Depressive Disorder seems to increase the risk for, and severity of cardiovascular disease but no single mechanism has been able to conclusively explain this link (Charles B Nemeroff & Goldschmidt-Clermont, 2012). Depressive symptoms have prognostic value for patients with CVD (Nakamura et al., 2013) while pre-existing CVD is a potent risk factor for depressive symptoms above that which might be expected with any chronic illness (Hare et al., 2014). Many biological and psychosocial factors may contribute to this co-morbidity. For instance, Major Depressive Disorder has been associated with increased inflammation, Hypothalamic-Pituitary-Adrenal (HPA) axis dysregulation, impaired Brain Derived Neurotrophic Factor (BDNF) metabolism, sleep disturbance, and obesity. Likewise, dysregulation of female sex hormones observed in MDD may account in part, for the disparity in prevalence between men and women. Each of these pathways have in turn

been implicated in cardiovascular disease development. However, integration of these disparate findings has remained elusive.

In this review we propose a novel link between MDD and CVD; the prothrombotic factor Plasminogen Activator Inhibitor-1 (PAI-1). Serum PAI-1 has been observed to be elevated in MDD, is strongly associated with cardiovascular disease development, and most convincingly, acts within each of the biological and psychosocial mechanisms already proposed to explain MDD and CVD co-morbidity. Although each of these pathways act independently of one another PAI-1 represents a convergence point. PAI-1 elevation in MDD induces further dysregulation, prompting the proliferation of vascular changes that culminate in CVD. Likewise, PAI-1 may influence the development of MDD, producing a positive feedback loop whereby proliferation of depressive symptoms increases PAI-1, in turn increasing CVD risk and the severity of MDD symptoms. Given its significant involvement in both MDD and CVD etiology, it is hoped that PAI-1 will have unique potential as a biomarker capable of predicting later cardiovascular health in patients with MDD.

PAI-1: Function and Expression

Plasminogen Activator Inhibitor-1 is a circulating protein synthesized by platelets, hepatocytes, adipocytes, vascular smooth muscle cells and various epithelial cells (Ha, Oh, & Lee, 2009). Additionally, it is present in the central nervous system, secreted by neurons and astroglia. It increases coagulation by inhibiting the breakdown of formed clots. After secretion, PAI-1 may be either active, inactive or latent. Active form may be

converted to latent (which may then be reactivated) or into a permanently inactive form, which is then degraded further (Cale & Lawrence, 2007). While in the systemic circulation, PAI-1 prevents clot degradation via inhibition of two key precursors to plasmin: tissue- and urokinase-type plasminogen activator (tPA and uPA respectively) (Binder et al., 2002). Tissue type plasminogen activator is secreted by endothelial cells as part of a negative-feedback loop regulated by fibrin (Figure 1).

Figure 1: PAI-1 Synthesis and Function

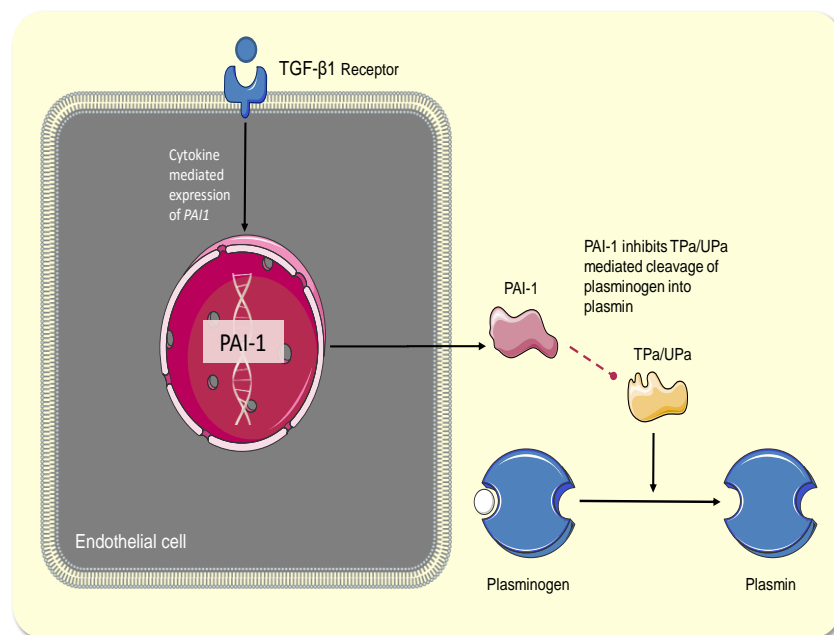


Figure 1: PAI-1 Synthesis and Function

Conversely, serum uPA concentration is controlled by the membrane bound urokinase receptor (uPAR) found on epithelial cells (Yasar Yildiz, Kuru, Toksoy Oner, & Agirbasli, 2014). Both tPA and uPA are highly potent plasmin activators and are

administered clinically as thrombolytics- clot busting agents used to treat thrombotic occlusive diseases such as myocardial infarction or ischemic stroke (Wechsler, 2011). Plasmin degrades fibrin in a process known as fibrinolysis (Nicholl, Roztocil, & Davies, 2006) . Fibrin is the end product of a complex signalling pathway known as the coagulation cascade. This pathway is responsible for the induction of clotting following trauma to blood vessels- one of the first steps of tissue repair (Loof, Deicke, & Medina, 2014). However, such a pathway must be closely managed to ensure that blood clotting only occurs at the specified location. Faulty or unregulated coagulation is a hallmark of many serious illnesses (Lipets & Ataullakhanov, 2015; Mego et al., 2015; Wada, Matsumoto, & Yamashita, 2014). Fibrinolysis counters coagulation, ensuring that formed clots are well localized to the site of injury. During coagulation, thrombin triggers the release of PAI-1 from platelets and surrounding epithelial tissue, which prevents clot degradation. Ideally, PAI -1 is tightly regulated to balance coagulation and fibrinolysis. Should PAI-1 become over activated or expressed (as is observed in MDD), thrombotic and fibrotic cardiovascular disease may occur (Figure 2).

Figure 2: PAI-1 Induces Atherothrombus Formation

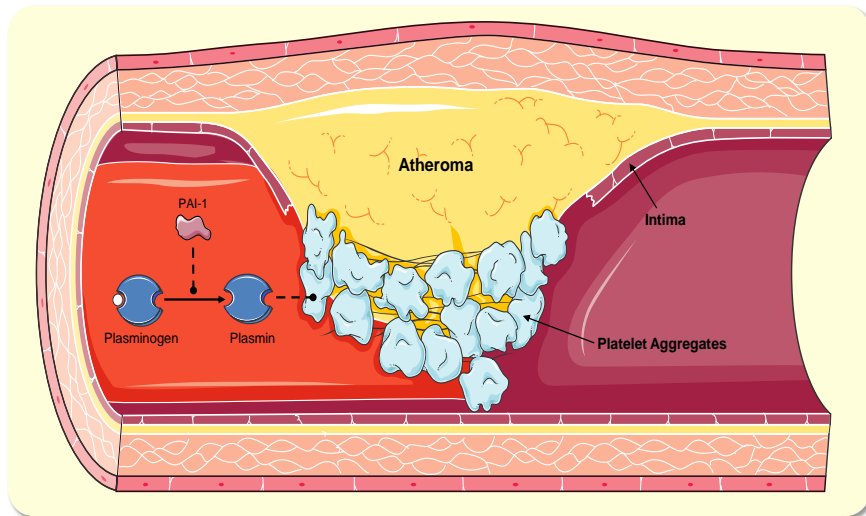


Figure 2: PAI-1 induces Atherothrombus formation

PAI-1 inhibits the conversion of plasminogen to plasmin, inducing platelet aggregation, promoting thrombogenesis. Inhibition of thrombi degradation is also the chief mechanism by which PAI-1 contributes to other ischemic cardiovascular diseases such as myocardial infarction. PAI-1 indirectly contributes to atherosclerotic plaque formation by inhibiting plasmin formation, reducing compensatory vascular remodelling.

Indeed, increased plasma concentrations of PAI-1 have been documented in numerous cardiovascular disorders, most notably atherosclerosis (Vaughan, 2005) (Schneiderman et al., 1992) (Massot et al., 2014) and myocardial infarction (Eriksson, Kallin, van 't Hooft, Båvenholm, & Hamsten, 1995).

Plasminogen Activator Inhibitor 1 expression is induced chiefly by TGF- β 1 (McCaffrey, 2000)(Z. Jiang et al., 2003), although TNF- α and interleukin 1 are also responsible for PAI-1 expression, among other cytokines (Swiatkowska, Szemraj, & Cierniewski, 2005)(Ha et al., 2009). A number of common polymorphisms of SERPINE1 have been identified, of which the removal of a single guanine (in a series of five) found in the SERPINE1 promotor region has been most heavily studied. The 4G/4G and 4G/5G polymorphisms elevate serum concentration of PAI-1 (Liang, Jiang, Ouyang, & Yang,

2015). The 4G polymorphism is associated with elevated rates of coronary artery disease, myocardial infarction and pre-eclampsia (Boekholdt et al., 2001; Liang et al., 2015; Morgan, Bombell, & McGuire, 2013; Parpugga et al., 2015).

Both PAI-1 and tPA are widely expressed in neurons of the hippocampus (Salles & Strickland, 2002), hypothalamus and amygdala (Pawlak, Magarinos, Melchor, McEwen, & Strickland, 2003), as well as astrocytes throughout the central nervous system. Additionally, systemic PAI-1 may cross the blood brain barrier via low density lipoprotein receptor related protein (Gabathuler, 2010). In the medial and central amygdala, PAI-1 interacts with tPA to regulate stress related neural remodelling (Pawlak et al., 2003). Because this brain region strongly projects onto the hypothalamus, it appears that PAI-1 can regulate the physiological response to external stress via the HPA- axis. PAI-1 is also influential in synaptic plasticity (Melchor & Strickland, 2005) via regulation of N-methyl-D-aspartate (NMDA) receptor functionality and expression on the synapse (Chevilley et al., 2015)(Robinson, Lee, Christie, & Birch, 2015). The nature of these interactions are still being elucidated and it appears that both tPA and PAI-1 may be variably neurotoxic or neurotrophic depending on dose and region of interest. Finally, PAI-1 directly inhibits tPA mediated cleavage of the precursor pro-BDNF to mBDNF (mature BDNF) (Rodier et al., 2014). These findings point to tPA and PAI-1 being implicated in emotion, memory formation, stress appraisal and response and learning.

Depression, Thrombogenesis and PAI-1

Major Depressive Disorder is characterized by a depressed mood or loss of interest in daily activities for at least two weeks. Although its most obvious symptoms are primarily psychiatric it might be understood as a systemic disease and many seemingly disparate biological systems have been implicated in MDD development, variability in symptom severity and treatment response. There is strong evidence to suggest that MDD influences many PAI-1 regulatory pathways (Figure 3), yet direct investigation of PAI-1 in depressed populations is a fairly recent avenue of research. In an otherwise healthy population, there was a significant association between serum PAI-1 concentration and depressive symptoms (Doulalas et al., 2006). Likewise, PAI-1 was also observed to be associated with anxiety symptoms in a healthy population (Geiser et al., 2008). A five year study of over three thousand peri-menopausal women reported a significant correlation between elevated plasma PAI-1 concentration and severity of depressive symptoms. This association persisted after controlling for confounds such as health history, age and medication use (Matthews et al., 2007). Another study of depressed pre-menopausal women found that plasma concentrations of PAI-1 were significantly elevated in depressed women compared to controls (Eskandari et al., 2005). Additionally, serum PAI-1 concentrations was observed to be elevated in patients with MDD, independent of whether they were diagnosed with co-morbid cardiovascular disease (Lahlou-Laforet et al., 2006). To further elucidate the mechanisms underpinning the relationship between MDD and PAI-1, we will review MDD induced obesity/adiposity, sleep disruption, BDNF metabolism impairment, inflammation and HPA axis dysregulation and consider how PAI-1 is implicated in each of these pathways.

Additionally, we will address the increased incidence of MDD in women by considering female hormonal dysregulation, and its associated consequences for PAI-1 and fibrinolysis.

ADIPOSITY, DEPRESSION AND PAI-1

Epidemiological evidence strongly suggests that Major Depressive Disorder has been associated with increased rates of adiposity and obesity (Hawkins & Stewart, 2012; Kessler & Bromet, 2013; Lasserre et al., 2014). This symptom may be a manifestation of the psychological implications of MDD; anhedonia, sleep disruption and depressed mood may reduce physical activity levels and discourage healthy lifestyle habits. Because adipose cells secrete PAI-1, increased adiposity directly elevates serum PAI-1 concentration (Ahirwar, Jain, Goswami, Bhatnagar, & Bhattacharjee, 2014; Ghosh & Vaughan, 2012; Landin et al., 1990; Shimomura et al., 1996). Consequently, findings by Eskandari et al suggest that women with MDD had both increased abdominal adiposity, and elevated PAI-1 compared to non-depressed controls; a finding that persisted after accounting for body mass Index (Eskandari et al., 2005).

SLEEP DISTURBANCE, DEPRESSION AND PAI-1

Sleep disturbance, insomnia and delayed sleep onset are common symptoms of Major Depressive Disorder (Baglioni et al., 2011), and may worsen existing symptoms of MDD (Ohayon, 2002). Sleep disturbance is also an independent risk factor for the development of Major Depressive Disorder in a healthy population (Baglioni et al., 2011). Sleep disruption is also a risk factor for non-psychiatric co-morbidities of

depression, including cardiovascular disease (Schwartz et al., 1999). Sleep disturbance is closely associated with chronic stress, and with over-activation of the hypothalamic-pituitary-adrenal axis, the body's primary stress regulation mechanism (Buckley & Schatzberg, 2013). In this sense, sleep disturbance appears to be both a risk factor for, and symptom of depression. It has also been observed that self-reported sleep disturbance is a more powerful predictor of somatic co-morbidity than absolute measures of sleep time and quality, further complicating the sleep-depression interaction. This effect may be due to the significant variation in required sleep within a population, which impedes our ability to produce general benchmarks for what constitutes healthy sleep. Elomaa and colleagues observed that self-reported sleep disturbance is associated with elevated PAI-1 serum concentration in otherwise healthy patients with a history of Major Depressive Disorder, after controlling for smoking and use of sleep medication (Elomaa et al., 2013). Likewise, mild sleep disturbance in a population without a history of mental illness also produced a concomitant increase in serum PAI-1 concentration (Tosur et al., 2014), suggesting that PAI-1 expression is influenced by sleep disturbance in the absence of depressive symptoms. However, as sleep disturbance appears to impact cytokine (Cho, Eisenberger, Olmstead, Breen, & Irwin, 2016) and BDNF expression (Giese et al., 2014), complex interactions between these systems may be responsible for producing a net increase in serum PAI-1.

PAI-1 IN THE CENTRAL NERVOUS SYSTEM AND DEPRESSION

Synaptic dysfunction, impaired synaptogenesis and reduced hippocampal volume (Stockmeier et al., 2004) have all been associated with Major Depressive

Disorder,(Duman & Aghajanian, 2012). It has been posited that disruption of neural circuitry associated with emotion regulation, stress response and mood underlies MDD pathology (Price & Drevets, 2010). Brain derived neurotrophic factor (BDNF) is a neurotrophin implicated in neuron survival, and synaptic plasticity (Molendijk et al., 2014). Numerous studies have investigated the role of BDNF in the development and severity of Major Depressive Disorder (Brunoni, Lopes, & Fregni, 2008). BDNF also appears to be modulated in successful treatment of MDD (B.-H. Lee & Kim, 2010). Most of this research has revolved around the impaired conversion of precursor pro-BDNF into mature mBDNF in MDD, particularly in the hippocampus (Warner-Schmidt & Duman, 2006). Direct administration of BDNF into the hippocampus produce antidepressant effects in a rat behavioural model of depression (Shirayama, Chen, Nakagawa, Russell, & Duman, 2002). Cleavage of proBDNF into mBDNF is accomplished by tPA (Rodier et al., 2014), and inhibited by CNS PAI-1 (Pang et al., 2004)(S. J. Tsai, 2005), suggesting that PAI-1 may be implicated in the production of depressive symptoms through its modulation of BDNF expression. Indeed, this has been observed in a rat model of depression, in which chronic stress induced increased expression of both hippocampal proBDNF and PAI-1, When an antidepressant was applied, mBDNF levels increased, as did tPA, although PAI-1 did not decrease, suggesting that tPA mediated conversion of proBDNF to mBDNF can be rescued with antidepressant therapy, while PAI-1 is more resistant to treatment (Tang et al., 2015).

Besides directly cleaving BDNF, PAI-1 may influence BDNF signalling indirectly, by inhibiting BDNF synthesis within the neuron. hippocampal BDNF is

regulated by glutaminergic signalling via N-methyl-D-aspartate (NMDA) receptors. tPA modulates NMDA receptor activity by cleaving the gluN1 receptor subunit, increasing calcium influx into the cell and thereby inducing the release of BDNF (Robinson et al., 2015), and tPA in turn is inhibited by PAI-1. Given the link between impaired synaptogenesis and depressive symptoms, it is expected that successful antidepressant therapy might restore synaptic plasticity in the form of long term potentiation (LTP). Indeed, this effect has been observed in a murine model of anxiety (Bath et al., 2012).

INFLAMMATION, DEPRESSION AND PAI-1

An association between elevated circulating pro-inflammatory cytokines and current depressive symptoms (Baune et al., 2012) as well as past history of depressive episodes (J. J. Young, Bruno, & Pomara, 2014) has been consistently observed. Additionally, inflammatory state has been found to be predictive of efficacy of treatment of depression (O'Brien, Scully, Fitzgerald, Scott, & Dinan, 2007), with more severe inflammation associated with poor treatment response. Conversely, anti-inflammatory drugs have been investigated for their anti-depressant properties (Schmidt, Kirkby, & Lichtblau, 2016), and pro-inflammatory agents such as interferon are recognized for their potential to induce depressive symptoms (Capuron et al., 2002). CRP (Chang et al., 2016), Il-6, Il-1 TNF- α , and TGF- β 1 have all been associated with depressive symptoms and represent potential biomarkers for evaluating the inflammatory milieu in MDD (Goldsmith, Rapaport, & Miller, 2016). Likewise, each of these cytokines serve to upregulate the expression of PAI-1 (Birgel, Gottschling-Zeller, Rohrig, & Hauner, 2000;

Devaraj, 2003; Swiatkowska et al., 2005), suggesting a robust bridge between depression induced inflammation and elevated PAI-1 serum concentration.

SERPINE1 AND DEPRESSION

A few preliminary investigations into the relationship between SERPINE1 and Major Depressive Disorder have yielded encouraging findings. Perhaps most convincingly, a number of SERPINE1 genetic variants have been observed to be associated with depression, and may play a role in response to antidepressant treatment (S.-J. Tsai, Hong, Liou, Yu, & Chen, 2008). However, these results have not yet been replicated in other populations, and more research is required to conclusively identify the role of SERPINE1 variants in MDD.

HPA-AXIS DYSREGULATION, DEPRESSION AND PAI-1

The hypothalamic-pituitary-adrenal (HPA) axis is the primary mechanism by which the body reacts to stress (Pariante & Lightman, 2008). Stressor recognition from the cortex triggers corticotropin releasing hormone (CRH) from the hypothalamus, inducing adrenocorticotrophic hormone (ACTH) release from the anterior pituitary, in turn triggering cortisol secretion from the adrenal cortex. Cortisol then elicits more tailored physiological changes from tissues throughout the body. Dysregulation of this pathway, producing elevated or inappropriate cortisol release has long been implicated in MDD etiology (Belmaker & Agam, 2008; Nestler et al., 2002; Roy, 1992)(C B Nemeroff et al., 1984). Due to the HPA-axis' broad scope of effect, it is difficult to evaluate its specific effect upon fibrinolysis and specifically, PAI-1 activity. However, observations from

patients diagnosed with Cushing's syndrome (hypercortisolemia) suggest that cortisol may be directly involved (Erem et al., 2009), although other pathways cannot be ruled out. Expression of the SERPINE1 gene is regulated by stress exposure, indicating that the HPA-axis is probably exerting some influence on serum PAI-1 concentration (Yamamoto et al., 2002).

DEPRESSION AND FEMALE SEX HORMONES

Major Depressive Disorder is prevalent at rates of 2:1 amongst women compared to men (Ferrari et al., 2013; Silverstein, 2002). Mood disorder episodes are also more prevalent at reproductive milestones, suggesting that sex hormone fluctuations may be implicated (Payne et al., 2009). HPG axis dysregulation is also observed in MDD with additional ramifications for PAI-1 activity in women. Estrogen is an important regulator of the stress response, and is reduced in MDD (Jacobs et al., 2015). It also appears that estrogen is capable of regulating PAI-1 gene expression through two oppositional estrogen receptors ($ER\alpha$ and $ER\beta$), although the clinical implications of this relationship are not yet fully understood (Smith et al., 2004). However, epidemiological findings support the relationship between estrogen and fibrinolysis, as women with increased estrogen appear to experience a cardioprotective effect, with reduced serum PAI-1 (Gebara et al., 1995).

Figure 3: PAI-1 in Major Depressive Disorder

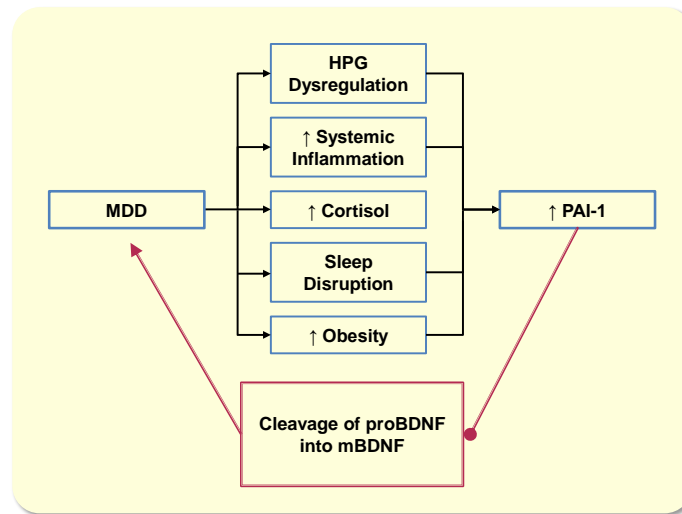


Figure 3: PAI-1 in Major Depressive Disorder

The Role of Plasminogen Activator Inhibitor-1 in Cardiovascular Disease

Development

Increased inflammation, HPA and HPG axes dysregulation, and hypercoagulation are all associated with an increased risk for the development of cardiovascular disease (Elderon & Whooley, 2013). In particular, increased serum concentration of coagulation factors is observed in a wide range of cardiovascular conditions (Vasan, 2014).

Independent of MDD, there is robust evidence for dysregulation of PAI-1 in CVD. A 1998 study by Thogersen et al. found elevated serum concentrations for both PAI-1 and tPA to be associated with first acute myocardial infarction (AMI) in both men and women (Thogersen et al., 1998). While tPA was associated with first AMI independent of other established risk factors, PAI-1 was not. Elevated plasma PAI-1 concentrations have also

been linked to progressive coronary artery disease in young men who have experienced myocardial infarction (Båvenholm et al., 1998). A prothrombotic state (as characterized by increased fibrinogen, induced by elevated PAI-1) is also an observed risk factor for left-ventricular hypertrophy in patients who are hypertensive but with no evidence of ischemic heart disease (Catena, Colussi, Fedrizzi, & Sechi, 2013). There is also some evidence suggesting that expression of PAI-1 mRNA is positively correlated with severity of atherosclerosis (Schneiderman et al., 1992) (Ghosh & Vaughan, 2012). An independent association between PAI-1 and other measures of cardiovascular health has also been observed in a healthy population (Raiko et al., 2012).

ADIPOSITY, PAI-1 AND CVD

Obesity is an important risk factor for cardiovascular disease development, and is associated with increased morbidity, mortality and reduced life expectancy in patients with CVD. Obesity brings with it a host of associated conditions such as hyperlipidemia, hypertension, glucose intolerance and inflammation (Poirier et al., 2006). As such it represents a crossroads in cardiovascular disease development, increasing the severity of multiple distinct mechanisms. Obesity has a profound effect upon PAI-1 secretion due to larger numbers of PAI-1 secreting adipocytes, coupled with up-regulated pathways responsible for inducing PAI-1 secretion, such as inflammation.

SLEEP, PAI-1 AND CVD

Sleep deprivation elevates risk of cardiovascular disease development by exacerbating pre-existing pathological changes; elevating blood pressure, increasing

systemic inflammation and deregulating hormonal signaling (Mullington et al., 2009). As previously discussed, sleep disturbance also increases PAI-1 expression, which is further exacerbated by activation of these other pathways.

BDNF, PAI-1 IN THE CNS AND CVD

It has been noted that BDNF may have a potent cardioprotective effect insofar that patients with CVD have lower blood BDNF than healthy controls (Hashimoto, 2013). Additionally, BDNF receptors are found on many peripheral tissues, including the heart and vasculature, suggesting that the protein may be able to directly influence circulation (Bhuiyan & Fukunaga, 2011). As PAI-1 inhibits the formation of mBDNF, this suggests a potential indirect mechanism by which PAI-1 induces cardiovascular disease that must be explored further. INFLAMMATION, PAI-1 AND CVD

A relationship between cardiovascular disease and inflammation has long been known. IL-6 is a stimulator of macrophage development, which are involved in atherosclerotic plaque formation (Mullington et al., 2009). Likewise, CRP is a non-specific inflammatory protein that accurately predicts cardiovascular health and is a useful clinical tool for evaluating risk of future cardiovascular events. These pro-inflammatory cytokines directly upregulate PAI-1 expression, and as such can impact fibrinolysis.

PAI-1 GENETICS AND CARDIOVASCULAR DISEASE

Polymorphisms of the SERPINE1 gene have been associated with an increased risk for thrombotic disease, of which the 4G/5G insertion/deletion mutation has been most rigorously studied (Ha et al., 2009) and is associated with a higher plasma concentration of PAI-1 (Kathiresan et al., 2005) (Margaglione et al., 1998). This polymorphism has been observed to increase the odds of coronary artery occlusion by more than 1.6 times compared to the homozygous gene variant (Parpugga et al., 2015). An observational study of patients who experience myocardial infarction before age 45 found that they are more likely to carry the 4G allele than the general population (Eriksson et al., 1995). Subsequent meta-analyses support these findings although magnitude of effect has yet to be established (Boekholdt et al., 2001) (Liang et al., 2015). More recent evidence suggests that the 4G/5G polymorphism is a significant factor in persistence of thrombosis in patients experiencing post-thrombotic syndrome, even in the presence of anticoagulant therapies (Incalcaterra et al., 2014). Likewise, 4G SERPINE1 is associated with an increased rate of occurrence of hypertension-hypercholesterolemia (AlBacha et al., 2015) as well as increased mortality in patients experiencing septic shock (Lorente et al., 2015).

PAI-1 and 2 in Pregnancy

Normal pregnancy is associated with considerable modification of maternal coagulation and fibrinolysis (Abdul Sultan et al., 2013), ostensibly as an evolutionary defence against haemorrhage during childbirth (Bonnar, McNicol, & Douglas, 1970). However, this process also increases a pregnant woman's susceptibility to thrombotic and fibrotic disorders such as (pre)- eclampsia (Stegers, von Dadelszen, Duvekot, &

Pijnenborg, 2010), deep- vein thrombosis and gestational hypertension (de Boer et al., 1989) (Parunov, Soshitova, Ovanesov, Pantelev, & Serebriyskiy, 2015). One of the main causes of hypercoagulation in pregnancy is the dramatic increase in plasma concentration of PAI-1, peaking during third trimester. This effect is heightened during pre-eclampsia, where PAI-1 levels are significantly elevated in comparison to trimester-matched healthy controls (Estellés, Gilabert, Aznar, Loskutoff, & Schleef, 1989) (Morgan et al., 2013). Estelles et al. reported a third trimester mean serum PAI-1 concentration of 34.86 ng/ml (S.D. = 11.79) in healthy controls, versus 136.5 ng/ml (S.D.= 130) in patients with severe pre-eclampsia (Estellés et al., 1989). Likewise, plasma PAI-1 was elevated during pregnancies with hypertension that did not fit the strict definition of pre-eclampsia [absence of proteinuria and edema, or women with pre-existing hypertension that was not significantly elevated during pregnancy (Steegers et al., 2010) (Estellés et al., 1989). A second isoform of plasminogen activator inhibitor (PAI-2) is secreted by placental trophoblasts and macrophages during pregnancy (J. A. Lee, Cochran, Lobov, & Ranson, 2011). PAI-2 is a potent inhibitor of uPA, further contributing to hypercoagulation (Chen et al., 2011). Unlike PAI-1, PAI-2 plasma concentration decreases in pre-eclampsia, probably due to impairment of placental growth and function, although this theory requires further evaluation (Gerald & Davis, 2000).

A New Model

We hypothesize that PAI-1 may be a bridge between depression and earlier onset CVD, and that this association will be particularly apparent during pregnancy. MDD's subtle influence on numerous physiological pathways suggests that a single, discrete

biochemical pathway that directly influences the cardiovascular system is unlikely. This is where the strength of the PAI-1 model lies. PAI-1 is potentially a "physiological bottleneck". Many of the physiological changes associated with depression can subtly influence PAI-1 expression. For instance, sub-clinical inflammation in depression raises IL-1 and TNF- α . Simultaneously, HPA-axis dysregulation leads to increased serum cortisol, aldosterone and angiotensin II (Forhead, Broughton Pipkin, & Fowden, 2000). Each of these hormones increases PAI-1 concentration. While individually insubstantial, each of these pathways can sum to increase PAI-1 and therefore cardiovascular disease risk. PAI-1 is also highly sensitive to behavioural and lifestyle factors such as obesity (Netto et al., 2015), which are also highly co-morbid in depression (Singh, 2014). Furthermore, increased PAI-1 activity due to these disparate mechanisms may induce PAI-1 mediated inhibition of proBDNF cleavage into mBDNF. This may further elevate MDD symptoms, producing a positive feedback loop (Figure 4). This model can also explain why CVD risk may be associated with severity of depression (Lesperance, 2002), as proliferation of this loop would produce an concomitant increase in PAI-1 concentration and therefore cardiovascular pathology. Protective factors such as a diet rich in antioxidants, absence of the SERPINE1 4G genotype and low behavioural/lifestyle risks for CVD (Ralph B D'Agostino et al., 2008) (ie: non-smoker, frequent exercise) will help mitigate risk.

Figure 4: PAI-1 May Mediate MDD and CVD

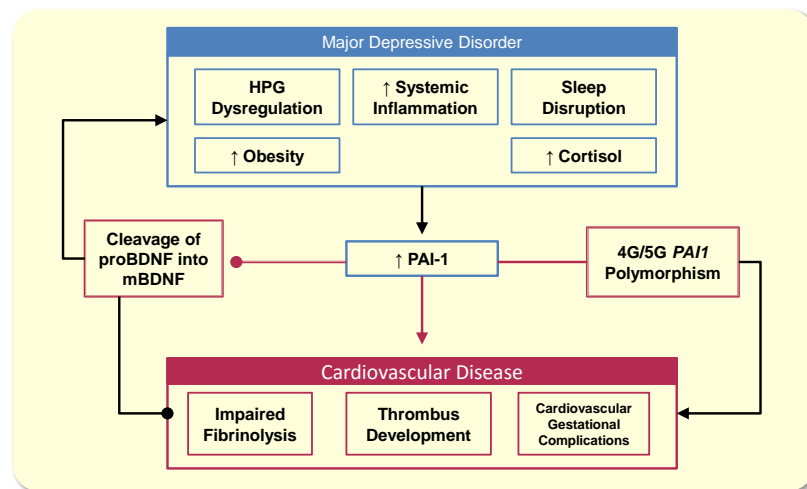


Figure 4: PAI-1 May Mediate MDD and CVD

Proposed cascade of pathophysiological mechanisms and events by which PAI-1 may mediate the MDD-CVD association.

Because of the elevated incidence of perinatal depression, coupled with an elevation of plasma PAI-1, pregnancy represents an ideal opportunity to investigate this model. One limitation of this model is that it doesn't adequately predict what role PAI-2 plays in the co-morbidity between MDD and CVD during pregnancy itself. It is possible that depression related inflammation may increase PAI-2 secretion from placental macrophages. Alternatively, because PAI-2 concentration is so transient (after birth its concentration drops to below physiological values) it has no bearing upon cardiovascular disease risk. Further research to evaluate PAI-2's role in CVD and MDD is warranted. We acknowledge that MDD will not influence all prothrombotic factors, nor are all cases of MDD associated with a prothrombotic state, but if instances of MDD in which hypercoagulation occurs are more likely to result in CVD, then this may be a useful biomarker for directing patient care.

Conflict of Interest

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1.3 Study Objectives and Hypothesis

This study has three major objectives. First, it aims to establish a correlation between perinatal depressive symptoms and reduced cardiovascular health during the third trimester of pregnancy. Next, the link between plasma PAI-1 concentration and MDD symptom severity during the perinatal period must be assessed. Finally, this study will test the hypothesis that plasma PAI-1 concentration mediates perinatal MDD symptoms and CVD risk. Depressive symptoms will be measured via Edinburgh Postnatal Depression Scale score, both continuously and dichotomously, using linear and logistic regression. Twenty-four hour heart rate variability recordings via holter monitor are the primary measure of cardiovascular health. As an ancillary objective, this study will investigate the potential role placenta-derived PAI-2 as a pregnancy specific pro-thrombotic mediator of depressive symptoms and heart rate variability.

CHAPTER 2 : PARTICIPANTS AND METHODS

2.1 Participants and Study Design

2.1.1 Study Population

Sixty-One pregnant women in the third trimester of pregnancy (28-40 weeks gestation) were recruited through the Women's Health Concerns Clinic (WHCC) and the Mood Disorders Research Unit at St. Joseph's Healthcare Hamilton and via the Community Midwives of Hamilton between February 2014 and April 2016.

2.1.2 Inclusion and Exclusion Criteria

Upon registration with the WHCC, women complete a consent to contact form in which they disclose their interest in learning about research being conducted through the WHCC. Potential participants were identified by reviewing their intake notes and chart. They were then contacted by telephone. Inclusion/exclusion criteria, study background and visit protocol were read to them and they were provided an opportunity to ask any questions about the study. A visit time was then scheduled for consenting participants. Community volunteers contacted the clinic themselves through phone and email from recruitment flyers. These potential participants completed the same phone screen as women contacted through the WHCC. Participants who are enrolled in the study had to be over 18 years of age, understand English in written and verbal form, and able to provide informed consent to participate in research. They must have had an absence of symptoms or past history of psychiatric conditions other than depression and anxiety disorders including obsessive compulsive disorder and post-traumatic stress disorder. Past

or present diagnoses of schizophrenia, autism or any DSM-IV Axis II disorders were exclusionary criteria. Participants must also have no current substance use disorder, or cognitive disorders. Participants must have had no chronic medical conditions including pre-existing cardiovascular disease, coagulopathies or congenital cardiac malformations, as well as autoimmune disorders such as lupus, or endocrine disorders such as Addison's disease.

2.1.3 Ethics

All aspects of this study (procedure, screening, data storage and consent) were approved by the Hamilton Integrated Research Ethics Board. All participants provided informed consent. Participant information was anonymized by assigning a unique study ID number for each participant. Binders of hardcopy participant information such as completed questionnaires were stored in a locked cabinet in a private study room.

2.1.4 Study Procedure

This project utilized an observational prospective cohort study design. Participants completed the single study visit during weeks 28-40 (third trimester) of pregnancy. All study data were collected during a single half-day visit, commencing with a single fasting blood draw. To control for circadian rhythmicity (and increase participant comfort), this blood draw was scheduled for between 8:00 and 9:00 AM. Following veinipuncture, participants were given an opportunity to eat while they completed a battery of self-report questionnaires (outline in the following section). The Composite International Diagnostic Interview-Venus (CIDI-V) was then administered by trained interviewers. Finally, blood pressure measurements and Holter monitor placement were conducted at approximately

12:00 pm. The holter monitor recorded for 24 hours. Participants were compensated and arrangements were made to collect the Holter monitor for subsequent analysis. Holter monitors were usually dropped off by the participant to the clinic, although occasionally they were retrieved from the participants' homes or workplaces.

2.2 Psychiatric Measures and Scales

2.2.1 Composite International Diagnostic Interview -Venus

The World Health Organizations' Composite International Diagnostic Interview (CIDI) is a structured, comprehensive diagnostic interview for assessing mental disorders, gathering demographic and socioeconomic history, and generating a detailed physical health history (Haro JM et al., 2006). The CIDI is divided into the following sections: demographics, physical health history, anxiety disorders, depression, bipolar disorder, obsessive compulsive disorder, schizophrenia, current and past substance abuse and post-traumatic stress disorder. The CIDI generates diagnoses in accordance with both ICD and DSM-IV criteria. The CIDI has been validated against the DSM-IV Structured interview (SCID) and found to possess good validity, reliability, sensitivity and specificity across diagnostic modules when administered by trained interviewers (Haro JM et al., 2006).

In this study, an enhanced version of the CIDI was utilized in which additional reproductive, gestational and women's health questions were included, assessing whether psychiatric symptoms assess in the CIDI followed menstrual cycles, appeared or changed during pregnancy and the postpartum, or were associated primarily or increased in severity during menopause. (Martini, Wittchen, Soares, Rieder, & Steiner, 2009).

2.2.2 Edinburgh Postnatal Depression Scale

The Edinburgh Postnatal Depression Scale (EPDS) is a ten item self-report questionnaire for assessing depressive symptoms during the perinatal period. It is the most frequently used tool for quantifying current mood symptoms in this population, and is frequently used to screen women for perinatal or postnatal depression (Cox, Holden, & Sagovsky, 1987). While there is some debate regarding the most appropriate score cut-off to distinguish probable depression from limited depressive symptoms, this research project uses a cut point of 14 indicating probable antepartum depression, in agreement with previous literature assessing antepartum depressive symptoms (Adewuya, Ola, Dada, & Fasoto, 2006; Felice, Saliba, Grech, & Cox, 2006). A recent meta-analysis suggests that this cut-point in antenatal samples produced a positive predictive value (PPV) of 80-81% and a negative predictive value (NPV) of 93-95% for combined major and minor depression (Gibson, McKenzie-McHarg, Shakespeare, Price, & Gray, 2009). The EPDS has also been investigated as a potential tool to assess anxiety symptoms in this population, by producing an anxiety-specific subscale from questions 3,4, and 5 (Matthey, 2008).

The EPDS was utilized as the primary predictor in our study because it produces a continuous score that confers more statistical power to our model. Additionally, it excludes physical symptoms of depression. The EPDS has also been used more extensively in previous research, conferring more comparability between past literature. In this study, a cronbach's α of 0.9, indicating a high degree of internal consistency between scale questions.

2.3 Biological Measures

2.3.2 C-Reactive Protein

C-Reactive Protein (CRP) is a circulating protein of hepatic origin, which is secreted in response to elevated circulating interleukin-6 (IL-6), a cytokine produced by T-cells and macrophages. CRP is utilized clinically as a measure of inflammation and is a useful tool for assessing risk of cardiovascular disease development (Vasan, 2014) CRP is also modestly elevated during healthy pregnancy, as well in cases of gestational hypertension including eclampsia and pre-eclampsia (Steegers et al., 2010). An emerging body of literature has suggested that CRP is elevated in Major Depressive Disorder (Azar & Mercer, 2013) and bipolar disorder II (Chang et al., 2016), potentially as a component of systemic inflammation long associated with these mood disorders (Lang & Borgwardt, 2013). CRP can also provide convergent evidence for the mediating association between depression and cardiovascular disease; it triggers PAI-1 expression (Devaraj, 2003) and may be inhibited by circulating BDNF (Noren Hooten, Ejiogu, Zonderman, & Evans, 2015).

2.4 Measures of Cardiovascular Risk

2.4.2 Heart Rate Variability

Heart Rate Variability (HRV) was measured via 24-hour Holter monitor using time domain measures of intervals between the peak of the QRS complex (R-R intervals) of the cardiac cycle. These intervals were normalized (N-N intervals) to ensure that

variance during periods of high frequency heart rate (for instance, during exercise) did not disproportionately impact the averaged HRV values (Sacha, 2013).

In this study, three cardinal measures of HRV were compiled. The first, SDNN is simply the standard deviation of N-N intervals gathered over 24 hours. While it assesses the largest possible number of discrete intervals, it is thought to be more sensitive to incidents of premature ventricular or atrial contraction (benign and highly common arrhythmias that may be due to minor fluctuations in electrolyte concentration in myocardium) (Billman, Huikuri, Sacha, & Trimmel, 2015). These measures of heart rate variability are robust measures of cardiovascular health and provide good prognostic value for the risk of future cardiovascular disease (Tsuji et al., 1996b).

The Average standard deviation of N-N intervals (ASDNN) creates an average standard deviation from 5 minute blocks of N-N intervals. Conversely the Standard deviation of average N-N intervals (SDANN) generates a single standard deviation from 5 minute averages of N-N intervals. These two measures produce less discrete comparisons than SDNN, but are more robust to the presence of focal arrhythmias.

Reduced heart rate variability is associated with adverse cardiovascular events, and HRV measures have demonstrated prognostic ability above traditional risk factors such as smoking status or presence of left-ventricular hypertrophy (Tsuji et al., 1996b). There is a natural variation in beat to beat frequency in healthy hearts compensate for posture, changes in thoracic pressure associated with breathing and changes in vascular elasticity and volume. An observed reduction in HRV may be due to impaired input of the

autonomic nervous system; indicative of cardiovascular pathology (van Ravenswaaij-Arts, 1993).

Heart rate variability is sensitive to many medications including atypical antipsychotics used to treat Major Depressive Disorder, although SSRI use does not appear to influence HRV (Huang et al., 2016). Additionally, (healthy) pregnancy may mildly reduce heart rate variability, although the clinical significance of this phenomenon is not well understood (Chamchad, Horrow, Nakhamchik, & Arkoosh, 2007). To control for this phenomenon, psychotropic medicine usage will be controlled for in this study.

2.4.3 Framingham Risk Assessment

The Framingham Risk Assessment is a sex-specific formula that estimates 10-year cardiovascular risk (as percent probability for developing cardiovascular disease) for an individual patient, based on presence and severity of lifestyle risk factors, as well as biological measures. This algorithm assigns risk points based upon patient age, total cholesterol, smoking status, HDL-cholesterol, and systolic blood pressure at time of visit (Wilson et al., 1998). The Framingham risk assessment is validated in US and Canadian populations, based upon data gathered via the Framingham Heart Study (Ralph B D'Agostino et al., 2008).

2.4.4 Lipid Profile

A fasting lipid profile was collected as part of the Framingham Cardiovascular Risk Assessment Score. This panel assesses serum levels of low-density lipoprotein

cholesterol (LDL), high-density lipoprotein cholesterol (HDL), triglycerides and total cholesterol. As LDL cholesterol is associated with increased incidence of cardiovascular disease, as well as increased rates of mortality and morbidity amongst patients with cardiovascular disease (Toth, 2016), this panel is a useful additional assessment of participant health.

2.5 Putative Mediator: Plasminogen Activator-1 and-2 ELISA

We hypothesize that PAI-1 and PAI-2 may mediate the association between depressive symptoms and cardiovascular risk as measured by heart rate variability. Following collection in EDTA anticoagulant tubes between 8 AM and 9:15 AM on the visit day, samples were stored at -80C prior to analysis. Enzyme- Linked Immunosorbent Assay (ELISA) was utilized to quantify plasma concentration of PAI-1 (RayBio; ELH-PAII-1) and PAI-2 (LifeSpan Biosciences; LS-F467) in participant blood samples. A total of 34 samples were assayed for PAI-1, 25 of which were stored for less than a year, while the remaining 9 had been frozen at -80C for over 18 months. Additionally, these 9 older samples had been thawed and refrozen twice. Only the most recent 25 samples were assayed for PAI-2. Following thawing and dilution, standards and diluents were plated and diluent buffer added (in the PAI-2 ELISA, bovine serum albumin was added to the buffer at a 1:10 dilution); followed by a 2-hour incubation for 2 hours. 100 µl PAI-1 or PAI-2 biotin conjugate solution was added, followed by another 2 hour incubation and

wash. While the PAI-1 plate was incubated at ambient temperature, the PAI-2 plate required a shorter incubation (~30 mins) at 37.5 °C. 100 µl streptavidin-HRP was added, followed by a 30 minute incubation and wash. 100 µl stabilized chromogen was added to each well, followed by a 30 minute room temperature (or 37.5 °C in the case of PAI-2) incubation in darkness. 100 µl Stop solution was added to the well. A 450 nm microtiter plate reader was used to generate standard curve and produce sample measures. Sample measures were conducted in duplicate with a mean concentration derived of these two values. The correlation co-efficient of the kit standards were $R^2 = 0.98$ and $R^2 = 0.99$ for PAI-1 and PAI-2, respectively. Standard curves and sample absorbencies are included in the appendix.

2.6 Covariates

2.7.1 Age

Age may influence the frequency, symptomatology and severity of depressive symptoms in this population, and is also a known risk factor for the development of cardiovascular disease (Ferrari et al., 2013). As there is a relatively wide age-range within the study population (18-40 years), it is important to control for these potential confounding effects.

2.7.2 Smoking Status

Smoking is more frequent among those suffering from mood disorders including anxiety and depression (although the directionality or cause of this association is not yet

fully understood) (Pasco et al., 2008). Smoking is also one of the strongest lifestyle risk factors for cardiovascular disease in the general population (Ralph B D'Agostino et al., 2008). Because many women attempt to quit smoking when they first learn of their pregnancy, this study utilizes past-year (or "pre-partum") smoking status to account for risk accrued prior to smoking cessation. As this is a relatively small cohort, we did not attempt to investigate the differences in years smoking or daily amount of cigarettes smoked. Instead, we classified as whether or not participants had smoked in the past year..

2.7.3 Body Mass Index (BMI)

Pre-pregnancy Body Mass Index is used as a proxy- measure for adiposity not related to pregnancy related weight gain. Major Depressive Disorder is associated with an elevated body mass index. Likewise, BMI is correlated with an increased incidence and severity of cardiovascular illness, particularly in already at-risk groups (Cizza, 2011; Joynt et al., 2003). In this study, BMI was calculated via participant self-report of height and pre-pregnancy body-weight.

2.7.4 Psychotropic Medication Use

Psychotropic medication is defined in this study as any drug prescribed to treat symptoms of mental illness, particularly depression and anxiety. For the purposes of this study, this category includes SSRIs, SNRIs, tricyclic antidepressants, and antipsychotic medications. Additionally, sedatives and hypnotics (such as benzodiazapines) are included in this covariate. Psychotropic medication use was included as a covariate because it can potentially reduce heart rate variability, although it is not thought to

negatively impact long-term cardiovascular health in otherwise healthy patients (Huang et al., 2016; Kemp et al., 2010).

2.7.5 Level of Education

In this study, we used level of education is used as a proxy-measure for socioeconomic status (SES). Because lower SES is associated with an increased risk for both mental illness and cardiovascular disease, it is necessary to control for this potential source of confounding effect (Kessler & Bromet, 2013). Education level was assessed using an 11-point scale ranked by time investment, academic rigor and average earning potential of the stages or programs listed. This list is included below.

Level of Education	
None	1
Some elementary	2
Elementary complete	3
Some high school	4
High school complete	5
Trade/ technical college	6
Some university	7
Bachelors degree	8
Masters degree	9
Doctoral Degree	10
Professional Degree	11

2.7 Statistical Analysis

All statistical analyses were conducted via the open access statistical program R (R version 3.1.3 (2015-03-09) -- "Smooth Sidewalk", Lucent Technologies, 2015). The

Graphical User Interface Rstudio was utilized, as were the following packages: Psych, car, ggplot2, leaps, bstats, pwr, epiR, mediation, and multilevel.

Means and standard deviations were calculated for all demographic data. Data was analyzed both continuously and dichotomously, T tests and Chi-Square tests were used where appropriate to assess group differences. Bartlett's test was used to test homogeneity of variance, Shapiro's test was used to test normality of variable distribution.

For continuous outcomes, linear regression models were utilized to measure the association between predictor (depressive symptoms) and outcome (cardiovascular measure). Multiple linear regression was used after the model was adjusted with the following covariates: age, smoking status, body mass index, use of psychotropic medication, education level and marital status. For dichotomous outcomes, two sample groups were formed from a cut point of 14 on the EPDS: delineating those with or without clinically significant depressive symptoms. ANOVA and ANCOVA were used to evaluate unadjusted and adjusted models, respectively.

Sobel's Test of Mediation was utilized to assess PAI-1's ability to mediate the relationship between depressive symptoms and cardiovascular outcomes, both in continuous analysis and between groups.

CHAPTER 3: RESULTS

3.1 Demographic Information

Sixty-one women in their third trimester of pregnancy completed the study. The average age of participants was 30.7 years old (S.D.=5.7). Age was normally distributed in this sample, and was of equal variance between groups. The average gestational age was 29.9 weeks (S.D.= 5.45). Of the sample population, 52 women completed the EPDS, with an average score of 7.36 (S.D.= 5.85). There were no group differences in rates of past-year smoking ($\chi^2=0.18$, $p= 0.67$), in pre-pregnancy BMI ($t=0.87$, $p= 0.41$), and education level achieved ($t=0.61$ $p= 0.56$). The depressed group did have significantly higher rates of psychotropic medication use.

Women with clinically significant depressive symptoms (EPDS > 14) had a higher gestational age at the time of the visit, more likely to have had a previous pregnancy, and more likely to be on psychotropic medication than their euthymic counterparts. Both populations had equivalent levels of education, equal body mass indexes and similar rates of past-year smoking. Additionally, a family history of mental illness and cardiovascular disease) was collected from 25 participants, although this data is not present for the entire study population. In this study, family history was defined as the presence or absence of either cardiovascular disease or mental illness in a first-degree relative. Of the subset of participants from whom this data was gathered, 3 participants in the depressed group (n=9) reported a family history of cardiovascular disease, as did 9 euthymic participants (n=16). This difference was found to be non-significant ($\chi^2=0.47$, $p= 0.49$). Likewise, 3 participants in the depressed group also disclosed a family history of mental illness, compared to 11 euthymic participants. This difference was also found to be not statistically significant ($\chi^2=0.1$, $p= 0.82$). Although a higher proportion of currently

depressed participants had a 2-year personal history of depressive episodes, this difference was not found to be statistically significant (via Mann-Whitney test). A complete demographic summary is included as figure 3.1.1.

3.1.1 Demographic and Medical History Tables

	Population N=61 Mean (SD)	Euthymic N=52 Mean (SD)	Depressed N=9 Mean (SD)	
Age	30.7 (5.7)	31.6	29.1	$t=1.51, p=0.16$
Weeks Gestation	29.9 (5.45)	29.7*	33.8*	$t=3.41,$ $p=0.005$
% 1 st Pregnancy	24%	29%*	11%*	$\chi^2 =1.17,$ $p=0.28$
BMI	22.8 (13.16)	25.5	26.4	$t=0.87, p=0.41$
% Married	99%	98%	100%	$\chi^2 =1.77,$ $p=0.11$
% Smoking	33%	47%	22%	$\chi^2 =0.18,$ $p=0.67$
Education	6	6	6	$t=0.61, p=0.56$
% Psychotropic Medication Use	13%	6%*	56%*	$\chi^2 =5.81,$ $p=0.02$

* Denotes significant difference ($p=0.05$) between depressed and euthymic group

T-tests and Chi-Square tests utilized where appropriate.

% Smoking defined as past year smoking.

Meds include all psychotropic medications; SSRIs, SNRIs, SARIs, atypical antipsychotics (Quetiapine) etc.

Education level of six corresponds to "technical/vocational college degree, or equivalent"(see 2.7, *Covariates*).

	Population N= 25 Mean (SD)	Euthymic N= 16 Mean (SD)	Depressed N= 9 Mean (SD)	
Positive Family History: CVD	48%	56%	33%	$X^2 = 0.47,$ $p = 0.49$
Positive Family History: Mental Illness	64%	69%	33%	$X^2 = 0.1, p = 0.82$
Past History of Depression	25%	22%	45%	$X^2 = 0.94,$ $p = 0.33$

* Denotes significant difference ($p=0.05$) between depressed and euthymic group
T-tests, Chi-Square tests and Mann-Whitney tests utilized where appropriate.

3.1.2 Predictor Variable: Edinburgh Postnatal Depression Scale

Of the 59 participants who completed an EPDS questionnaire, the mean score was 7.36 (SD= 5.85). After dichotomizing the study sample at a cut point of 14 on the EPDS, the depressed group had a mean score of 17.89 (SD = 3.86), while the euthymic group reported a mean EPDS score of 5.46 (SD=3.75). This difference was found to be statistically significant ($t=8.94, p < 0.001$).

3.1.3 Outcome Variable: Heart Rate Variability

Heart Rate Variability data is summarized in the table below. There were significant differences in SDNN ($t=-3.51, p=0.002$), SDANN ($t=3.84, p<0.001$) and ASDNN ($t=2.16, p=0.05$) between the euthymic and depressed groups.

	Population Mean (SD)	Euthymic Mean (SD)	Depressed Mean (SD)	
SDNN	105.51	109.59*	85.25*	$t=3.51, p=0.002$
SDANN	91.18	94.84*	72.16*	$t=3.84, p<0.001$
ASDNN	48.67	50.59*	40.04*	$t=2.16, p=0.05$

* Denotes significant difference ($p=0.05$) between depressed and euthymic group

3.1.4 Physical Health Measures

A lipid panel and C-Reactive Protein (CRP) assay was collected from each participant on the morning of the study visit, alongside PAI-1 and 2 collection. These tests are taken after a 12 hour fast and are very temporally consistent throughout the population. No significant difference between groups was identified across these panels.

3.1.3 Physical Health Measures: Summary

	Population N=52 Mean (SD)	Euthymic N=43 Mean (SD)	Depressed N=8 Mean (SD)	
Cholesterol	5.3 (6.85)	7.1 (7.51)	6.92 (1.19)	$t=0.15, p=0.88$
Triglyceride	5.1 (0.89)	2.15 (0.91)	2.48 (0.84)	$t=1.01, p=0.33$
HDL	1.73 (0.44)	1.74 (0.44)	1.68 (0.47)	$t=0.34, p=0.74$
LDL	3.56 (0.44)	3.5 (1.21)	3.92 (0.7)	$t=1.34, p=0.19$
TC:HDL	3.7 (1.7)	3.62 (1.02)	4.14 (0.75)	$t=1.70, p=0.11$
C- Reactive Protein	6.22 (4.58)	5.61 (4.41)	7.1 (5.03)	$t=0.63, p=0.54$

3.4 Primary Objective: The Association Between Depressive Symptoms and Heart Rate Variability

3.4.1 Continuous Analysis

Linear regression models were used to assess the relationship between EPDS score and each individual heart rate variability measure (SDNN, SDANN, ASDNN). Before adjustment, these models each had a power level of $\beta = 0.79$. All unadjusted models fulfill assumptions of linearity, independence normality and homoscedasticity. One outlier was identified but as this participant fulfilled all inclusion criteria for the study, their data was included in subsequent analysis.

In unadjusted models, EPDS scores were not associated with reduced SDNN ($R^2 = 0.07$, $B = -1.22$, $p = 0.07$), SDANN ($R^2 = 0.06$, $B = -1.11$, $p = 0.08$), or ASDNN ($R^2 = 0.07$, $B = -0.6$, $p = 0.08$). Model comparison using Akaike information Criterion revealed that the inclusion of EPDS within the model accounted for slightly more variance ($AIC = 417.05$) than a model in which the covariates alone were present ($AIC = 417.33$).

3.4.2 Dichotomous Analysis

An ANOVA was utilized to investigate whether heart rate variability is reduced in participants with significant depressive symptoms ($EPDS \geq 14$) and those without. This model had a power level of $\beta = 0.69$. Prior to analysis, ASDNN and SDANN were found to be non-normally distributed, and were log transformed. Variance was found to not significantly differ between groups. SDNN was found to be lower in the depressed group compared to the euthymic group ($F_{(1,47)} = 5.68$, $p = 0.02$). This observation was replicated

with SDANN ($F_{(1,47)} = 3.45, p = 0.02$) and ASDNN ($F_{(1,47)} = 4.07, p = 0.04$). These results are summarized below (Figures 1-3).

Figure 1.

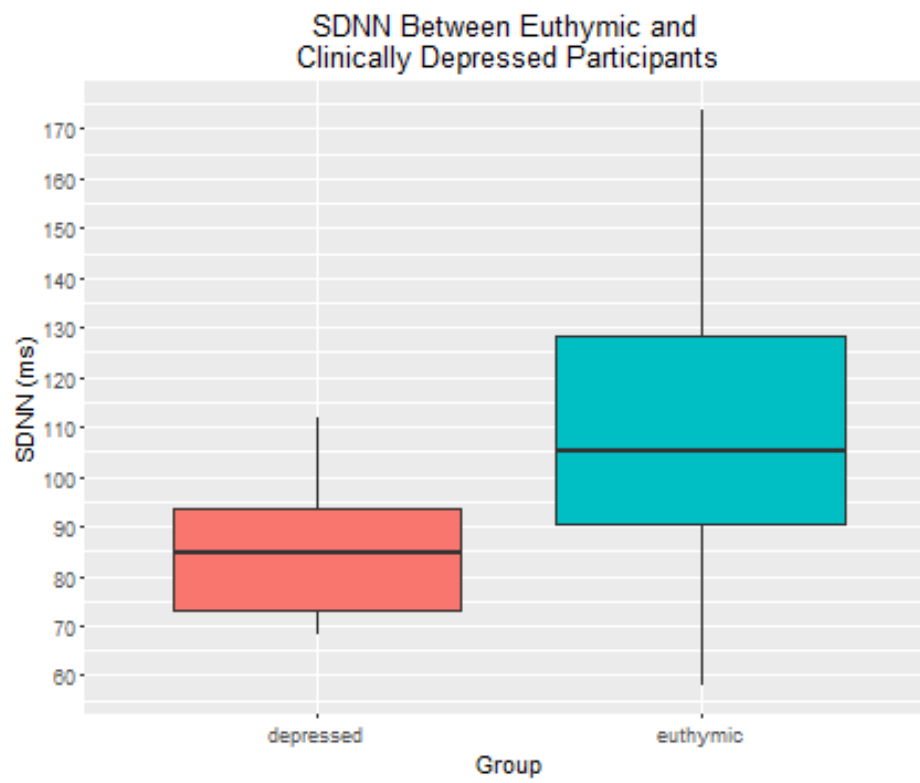


Figure 2.

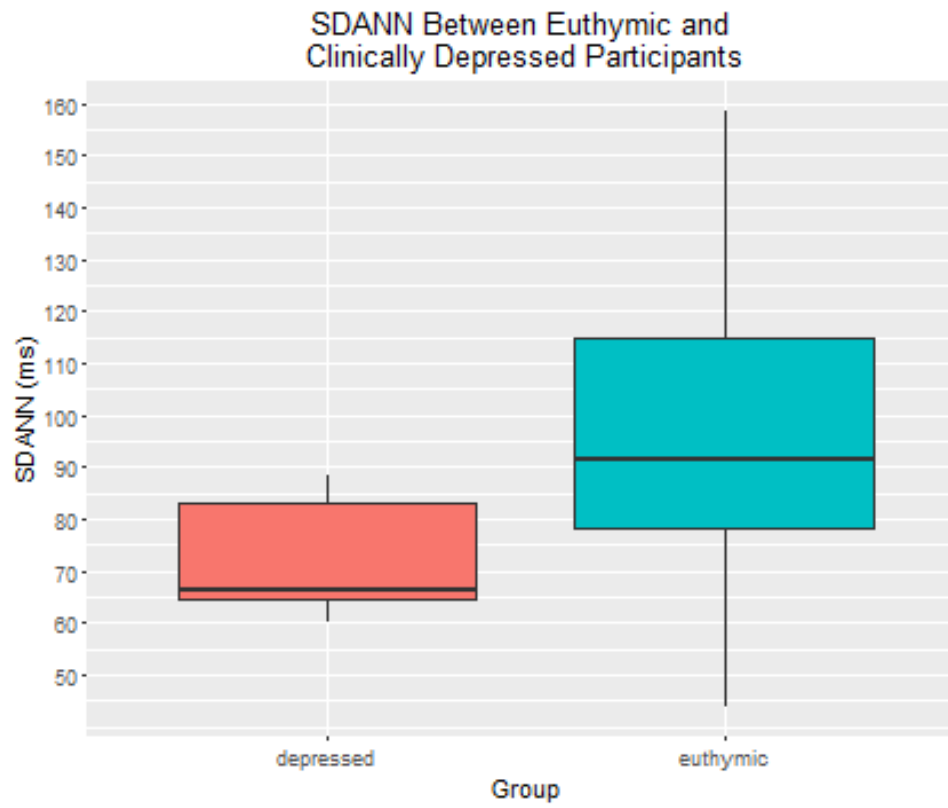
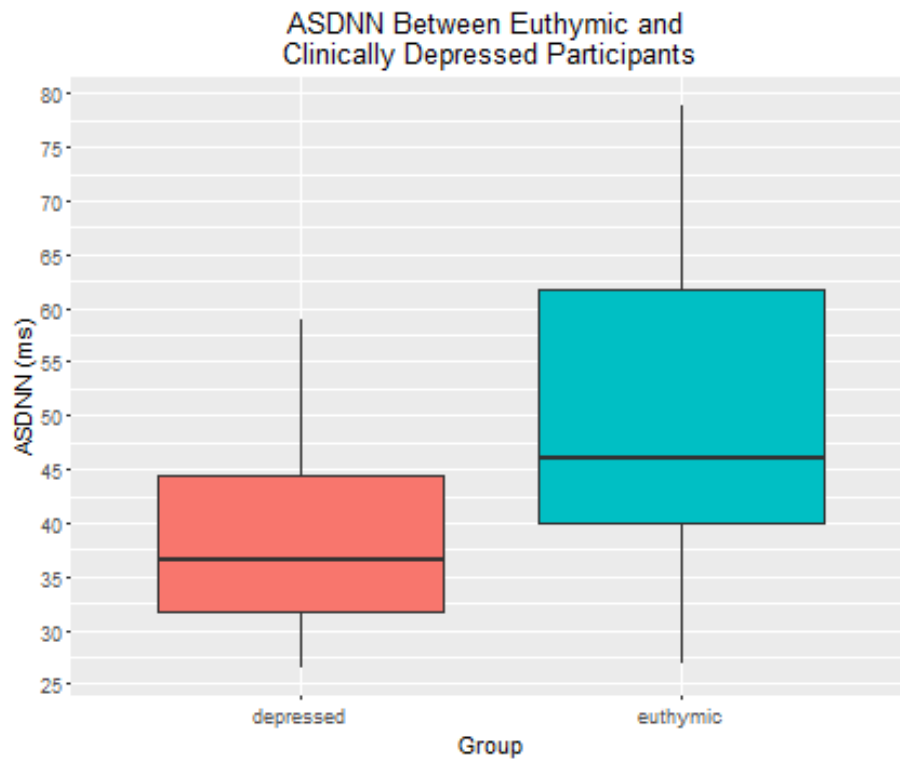


Figure 3.



An ANCOVA was used to control for Age, Smoking Status, Body Mass Index, Psychotropic Medication Use and Level of Education, as between-group differences in these covariates may potentially account for the observed association between clinically significant depressive symptoms and heart rate variability). After adjustment, SDNN ($F_{(1,38)} = 4.05, p = 0.052$) and ASDNN ($F_{(1,38)} = 2.64, p = 0.11$) were no longer associated with clinically significant depressive symptoms. However, SDANN ($F_{(1,38)} = 4.88, p = 0.03$) remained significant after adjustment. Model comparison (via Akaike Information Criterion) suggested that grouping participants by depressive symptom status yielded a stronger model ($AIC = 398.13$) than one in which only the covariates were included ($AIC = 402.72$).

3.5 Association Between PAI-1 and Depressive Symptoms

A general linear model was used to evaluate the relationship between PAI-1 and EPDS scores in 21 participants who completed 24-hour heart rate variability measures, and whose plasma PAI-1 samples were not previously thawed and re-frozen. PAI-1 measurements from the 9 older samples that had been thawed and refrozen were discarded when they were found to be dramatically different from the more fresh 25, and also varied significantly from one another. This model fulfilled linearity, normality and equal variances assumptions. Plasma PAI-1 concentration was not significantly associated with EPDS score prior to adjustment ($R^2 = 0.0, B = 0.36, p = 0.87$), or after introducing the previously established covariates ($R^2 = 0.26, B = -2.45, p = 0.43$).

When comparing plasma PAI-1 concentration between the depressed and euthymic groups, again, no statistically significant association was observed ($F_{(1,24)}=0.002, p=0.97$). A similar result was found after adjustment for covariates were introduced to the model ($F_{(1,24)}=0.41, p=0.53$). A Sobel test of mediation found there to be no statistically significant mediation effect of PAI-1 between any of the heart rate variability metrics and group status. PAI-1 is also not independently associated with heart rate variability in this population ($R^2=0.0, B=-0.01, p=0.98$). Although average PAI-1 plasma concentration was elevated amongst those participants who disclosed a past history of depression, this difference was not significant ($F_{(1,24)}=2.043, p=0.167$).

3.6. PAI-2 And Current Depressive Symptoms

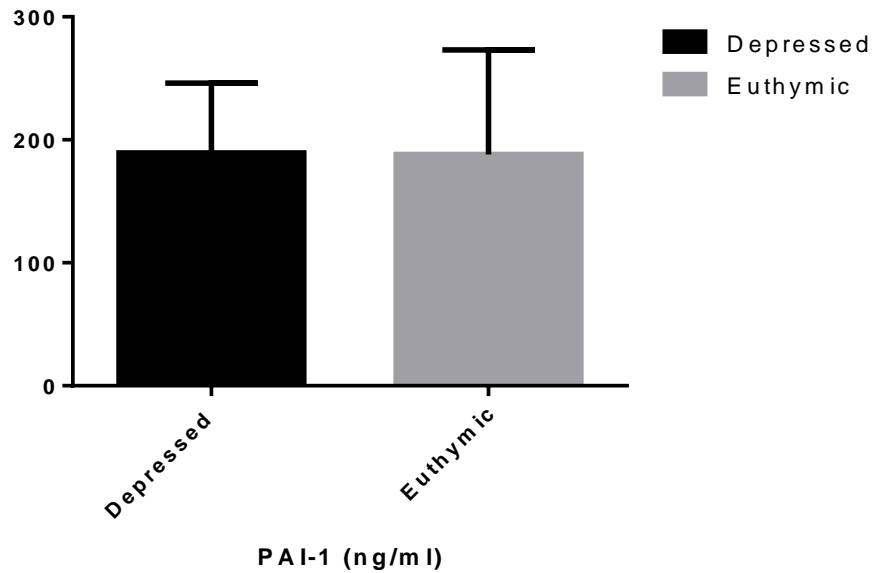
PAI-2 was found to be normally distributed within the population subset that was assayed. Linear regression models fulfilled all assumptions of linearity, normality and homogeneity of variance. PAI-2 was not found to be associated with EPDS score ($R^2=0.03, B=-0.61, p=0.77$), nor did plasma PAI-2 concentration significantly differ between participants with significant depressive symptoms and euthymic participants ($F_{(1,24)}=0.1, p=0.78$). Likewise, PAI-2 was not significantly associated with heart rate variability in this population subset ($R^2=0.03, B=-0.46, p=0.45$). PAI-2 did not mediate the association between EPDS group and any of the heart rate variability measures.

3.6.1 Sobel Test of Mediation Between EPDS Group and HRV Measure for PAI-1 and PAI-2

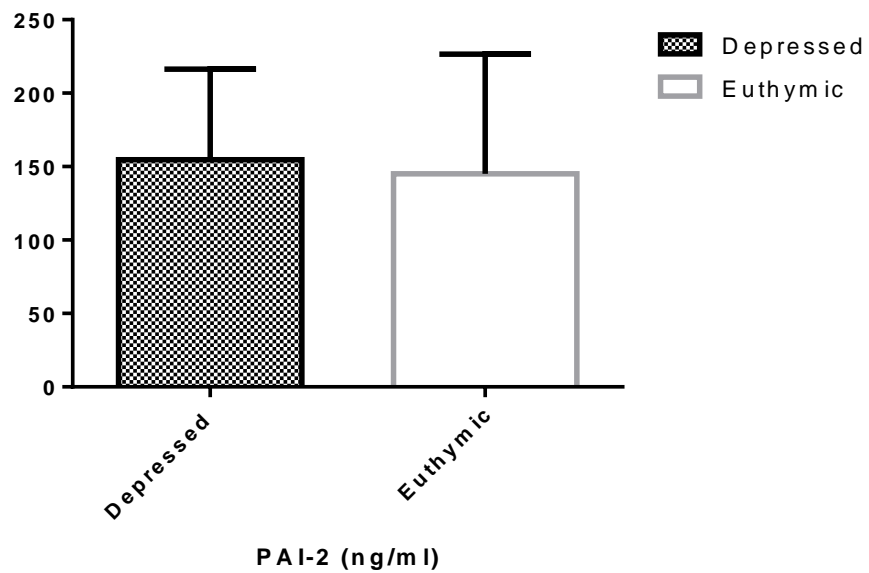
	SDNN	SDANN	ASDNN
PAI-1	($z=0.08, p= 0.9$)	($z=-0.20, p=0.53$)	($z=0.17, p=0.73$)
PAI-2	($z=-0.025, p= 0.69$).	($z=-0.02, p= 0.69$)	($z=-0.02, p=0.15$)

Figures 4 and 5: PAI-1 and PAI-2 Plasma Concentration by Group

PAI-1 Concentration in Depressed Vs. Euthymic Groups



PAI-2 Concentration in Depressed Vs. Euthymic Groups



CHAPTER 4: DISCUSSION

Women are at an elevated lifetime risk for both depression and cardiovascular disease, although the reasons for this comorbidity are not yet well understood. The antenatal period in particular is a time of increased susceptibility to mood disorders, especially depression. Likewise, the dramatic physiological changes associated with pregnancy place additional strain upon the cardiovascular system of the mother. Cardiovascular complications of pregnancy such as gestational hypertension, deep-vein thrombosis and pre-eclampsia may also occur, and appear to be more prevalent among women with depression (Palmsten et al., 2012). Pregnancy is necessarily marked by increased coagulability, likely as an evolutionary adaptation to improve survival during childbirth (Chen et al., 2011)(Hale et al., 2012). Analogous hemostatic changes have been observed in Major Depressive Disorder, and it is hypothesized that this may contribute to its association with cardiovascular disease development (a more detailed review of the biological mechanisms behind this co-morbidity is presented in Chapter 1). One potential factor that may be involved in this association is the pro-thrombotic protein Plasminogen Activator Inhibitor-1. Many of the pathophysiological changes observed in depression may directly increase PAI-1 synthesis, secretion and function. A robust association between PAI-1 and incidence/severity for cardiovascular disease has also been observed. The second isoform of PAI-1, PAI-2 is secreted by the placenta and as such is only biologically active during pregnancy. However, the influence of perinatal depressive symptoms upon PAI-2 activity has not yet been investigated.

In this study we have investigated whether gestational depressive symptoms impact cardiovascular function as measured by 24-heart rate variability. Next, we assessed the relationship between depressive symptoms and plasma PAI-1 concentration, and whether PAI-1

may mediate depressive symptoms and reduced heart rate variability. Finally, we measured PAI-2 plasma concentration to determine whether the concentration of this pregnancy-specific pro-thrombotic protein may be influenced by depressive symptoms. In this chapter the cardinal findings of this study will be interpreted and contextualized in the existing literature. Limitations inherent in this study will also be addressed, and a few potential avenues of further research will be presented.

4.1 Interpretation of Key Findings

4.1.1 Primary Objective: The Relationship Between Heart Rate Variability and Depressive Symptoms

This study observed an association between clinically significant depressive symptoms during the third trimester of pregnancy and reduced 24-hour heart rate variability. However, confounding factors such as BMI, age and education level largely attenuated this relationship. An association between depressive symptoms and reduced heart rate variability has been previously observed in non-pregnant populations. For instance, a study comparing young women with depression and anxiety symptoms to matched controls found a large effect of mood symptoms upon HRV after controlling for nuisance variables (Henje Blom, Olsson, Serlachius, Ericson, & Ingvar, 2010). A recent meta-analysis of this literature base has found that decreases in heart rate variability are proportional to depressive symptom severity (Kemp et al., 2010). In a prospective observational cohort study (of similar methodology to the work presented in this thesis) conducted by Shea, et al. observed that women with depressive symptoms (as measured by an EPDS score >12) were found to have significantly reduced heart

rate variability than controls during the second trimester of pregnancy (Shea et al., 2008). Our research supports these findings and extends them into the third trimester of pregnancy.

A recent study by Rouleau et al. has identified heart rate variability as a mediator of depressive symptoms and gestational hypertension (Rouleau et al., 2016), further validating the hypothesis that antepartum depression can impact cardiovascular functioning. Data gathered from a randomized controlled trial suggests that gestational suggested that the presence of antenatal depressive symptoms was associated with excessive weight gain over the course of pregnancy, which concomitantly impacted cardiovascular health (Perales et al., 2016). Additionally, a recent secondary analysis of a large longitudinal cohort study validated heart rate variability as a useful metric for predicting cardiovascular disease development in the general population, and found that reduced heart rate variability may be indicative of hyperglycemia and hypertension within 12 years (Wulsin, Horn, Perry, Massaro, & D'Agostino, 2015).

4.1.2. PAI-1 and PAI-2 as Mediators of Current Depressive Symptoms and Heart Rate Variability

Plasma concentrations of PAI-1 were not significantly associated with EPDS score, nor were they significantly elevated in participants with clinically relevant depressive symptoms. PAI-1 was also not found to mediate the relationship between heart rate variability and clinically significant depressive symptoms. PAI-2 was found to not be significantly associated with EPDS score, group status or heart rate variability measure. However a recently published study has observed significantly increased PAI-1 serum concentrations among patients currently experiencing a major depressive episode, compared to controls (H. Jiang et al., 2016). These participants were drawn from an inpatient population, and were not receiving drug treatment in

the two weeks prior to PAI-1 measurement. Additionally, this increased PAI-1 serum concentration was not attenuated by the administration of SSRI antidepressants, although subjective depressive symptoms (as measured by the Hamilton Depression Rating Scale) were significantly improved post-treatment (H. Jiang et al., 2016). This supports earlier observations suggesting that PAI-1 is elevated during episodes of depression and anxiety (Lahlou-Laforet et al., 2006; Geiser et al., 2008).

While to date there has been little research directly investigating PAI-1's effect upon heart rate variability in populations with mood disorders or other mental illnesses, PAI-1 serum concentration was found to be associated with reduced heart-rate variability (utilizing frequency domain measures) among a sample of healthy participants representing the general population (von Känel et al., 2007). Furthermore, this study detected a mediation effect of BMI upon the relationship between PAI-1 and heart rate variability. In another study, a sample of women recovering from an acute coronary event (~3-6 months post hospitalization) completed a frequency-domain recording of heart rate variability and had PAI-1 serum concentration measured as part of a battery of blood tests measuring thrombotic state (von Känel & Orth-Gomér, 2008). PAI-1 was found to be significantly associated with reduced heart rate variability, and those participants that had elevated PAI-1 concentrations were also predisposed to elevated rates of thrombosis than those participants who had normal PAI-1 concentrations (von Känel & Orth-Gomér, 2008). These findings are suggestive of a relationship between PAI-1 and heart rate variability that may be further exacerbated by depressive pathology, although this association was not detected in our study.

As PAI-2 is placenta derived, it is only present in serum during pregnancy and therefore may represent a unique biomarker for evaluating placental functioning. A recent study utilizing a

population based prospective cohort study of over 7,000 women has investigated PAI-2 concentration during the first trimester of pregnancy (Coolman et al., 2012). Low first-trimester PAI-2 was associated with a higher risk for pre-eclampsia as well as lower birth weight for the fetus (Coolman et al., 2012), possibly due to impaired placenta function, leading to reduced PAI-2 secretion. As PAI-2 may be a useful measure of placental health, it may be the case that a ratio between PAI-1 and PAI-2 (in which high PAI-1 and low PAI-2 indicate gestational pathology) could have prognostic value for assessing risk and severity of gestational complications.

4.2 Study Limitations

4.2.1 Sample Size and Statistical Power in Fully Adjusted Models

While unadjusted models comparing heart rate variability measures to EPDS scores or presence vs. absence of severe depressive symptoms were adequately powered ($\beta=0.79$ and 0.71 , respectively), the addition of five covariates reduced this dramatically ($\beta=0.51$ and 0.38). Additionally, only a subset of study participants' blood samples were able to be assayed for PAI-1 and PAI-2 ($n=25$), due to degradation from repeated freezing and thawing of plasma. This reduced sample size hindered our ability to detect group differences and accurately evaluate mediation effects. It is important to note that the ELISA conducted on the non-refrozen samples was of excellent quality, with samples run in duplicate, and with the correlation coefficient of the plate standards at $.98$ and $.99$ for PAI-1 and PAI-2 respectively.

4.2.2 Low Numbers of Depressed Participants

This study was comprised of a relatively healthy out-patient population that was currently receiving treatment for their depressive symptoms. Only 9 participants met the EPDS cut-off to be classified as depressed for the purposes of the between group analyses. It is plausible that a study utilizing participants from an in-patient clinic and then compared to matched controls

would be more likely to detect group differences in PAI-1 concentration, or identify PAI-1 as a mediator. A larger study with greater EPDS score variability between participants can also adequately address these limitations. The fairly rigorous exclusion criteria in this study was necessary to ensure that HRV and PAI-1 measures were not being influenced by nuisance variables, but there is the possibility that by excluding participants with chronic health conditions or current substance abuse, the participants included in the study were not entirely representative of most women with antepartum depression. Because of this, it is possible that the findings presented in this study under-estimate the influence of depressive symptoms upon heart rate variability, or the difference in PAI-1 and PAI-2 concentration in those with depression compared to those without.

4.2.3 Heart Rate Variability in Non-Cardiovascular Research

Heart rate variability has been extensively studied in psychiatric research as a measure of autonomic nervous system dysfunction (van Ravenswaaij-Arts, 1993). This research suggests that heart rate variability is sensitive to behavioral, emotional and cognitive states, and that while these may impact cardiovascular health, they may also be indicative of the subjective experiences anxiety and stress (Beckham, Greene, & Meltzer-Brody, 2013). However, much of this research utilizes a frequency domain paradigm in which heart rate variability is recorded in lab over 5 minutes in response to a stressor or task (Quintana & Heathers, 2014). The use of 24-hour time-domain Heart Rate Variability measures is more robust to transient emotive states and therefore should provide a clear measure of cardiovascular risk in this population. Furthermore, heart rate variability as a tool for assessing cardiovascular function (Tsuji et al., 1996b) (Wulsin et al., 2015) has been extensively validated and is an often utilized paradigm in cardiology research; use of this technique allows for more straightforward comparisons to previous research.

4.2.4 Years of Education as a Measure of Socioeconomic Status

Years of education completed was selected as a proxy-measure of socioeconomic status as it was consistently recorded throughout the entire study. Additionally, education level may be a better measure of lifestyle factors, and health behaviors (such as knowledge of nutrition, hygiene and exercise) than simply recording household income. Furthermore, socioeconomic status is heavily influenced by participant age and marital status (an effect particularly pronounced in younger populations). These factors likely do not significantly influence participant health in this relatively young study sample, but could disproportionately affect SES score.

4.3 Future Directions

This study represents a pilot investigation into the impact of mood disorders during pregnancy upon cardiovascular health, although a larger study is required to answer this question more conclusively. This study attempts to measure subtle changes in cardiovascular function during the third trimester under the hypothesis that pregnancy provides "a window into the future"; predicting future cardiovascular health in a population that is young and generally healthy. Ideally, a longitudinal cohort study would follow women from pregnancy until late life and compare cardiovascular health during gestation with incidence of cardiovascular disease in the ensuing decades.

While there is robust evidence in support of depression as a risk factor for cardiovascular disease, the development of a risk-mitigating treatment has not yet been established. Indeed, it is difficult to assess whether successful treatment of depression can mitigate cardiovascular risk in the same way that smoking cessation might, simply because MDD is very difficult to effectively treat. Indeed, SSRIs appear to be efficacious in only 1 in 3 patients (Belmaker & Agam, 2008).

Additionally, recurrence rates after a first episode of depression are estimated to exceed 50% (Burcusa & Iacono, 2007) and may approach 90% (Stewart, 2011). It is not yet known whether a subjective improvement in mood due to successful antidepressant therapy actually coincides with improved cardiac outcomes (Whooley et al., 2006). A longitudinal study evaluating whether patients who were effectively treated for depression (including recurrent depressive episodes) are at a similar risk for CVD than the general population is necessary to address this question. Moreover, if pregnancy specific depression proves to be a period of elevated cardiovascular risk, then perhaps aggressive treatment during this period may represent an important first step in addressing this co-morbidity.

While investigating the relationship between depressive symptoms and PAI-1 during pregnancy represents an entirely novel avenue of research, assessing PAI-1, depressive symptoms, and other measures of cardiovascular health in the general population is also warranted. Besides heart rate variability, other measures of cardiovascular function may be utilized, and these may provide additional insights into changes in cardiovascular function during episodes of antepartum depression. One such measure is carotid-intima media thickness (CIMT), an ultrasound procedure in which the common carotid artery is scanned bilaterally, inferior to the carotid bifurcation (Bots, Hoes, Koudstaal, Hofman, & Grobbee, 1997; Lorenz, Markus, Bots, Rosvall, & Sitzer, 2007). Measurement of the intimal layer of this artery provides an assessment of early atherosclerotic plaque formation, as the common carotid is one of the first sites in which plaque formation develops (De Korte, Fekkes, Nederveen, Manniesing, & Hansen, 2016). Use of this measure may provide a more specific assessment of cardiovascular health in the context of atherosclerosis. Another newly developed technique is peripheral arterial tonometry (PAT). This non-invasive measure assesses pulse-volume amplitude in the left and

right index fingers following brachial artery occlusion with a sphygmomanometer (Mitchell et al., 2010). PAT provides an assessment of endothelial function and has been extensively used in thrombosis research (Hamburg & Benjamin, 2009).

4.4 Conclusion

This study attempted to characterize the relationship between depressive symptoms and cardiovascular risk, as assessed by heart rate variability. In keeping with existing literature, an association between clinically significant depressive symptoms and reduced heart rate variability was observed. However, this effect was attenuated after controlling for nuisance variables. Nonetheless, it is plausible that a larger sample with greater depressive symptom variance would have improved our ability to detect this association after adjustment. There is a growing body of literature implicating PAI-1 in both Major Depressive Disorder and cardiovascular disease, although to date little research exists investigating PAI-1 during pregnancy. While this study did not detect any association between PAI-1 and either heart rate variability or depressive symptoms during gestation, it is possible that further research may more conclusively assess this relationship. Indeed, studies previously reviewed have identified associations between PAI-1 and MDD, and PAI-1 and HRV independently. Given PAI-1's potential as a biomarker, or as a target for therapeutic intervention, additional research may directly improve patient care, as well as shed light on the shared pathophysiology of Major Depressive Disorder and cardiovascular disease.

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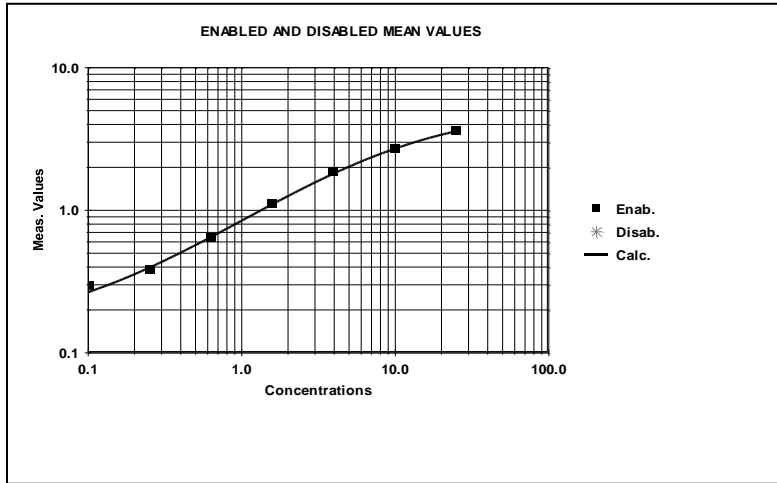
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CHAPTER 6: APPENDIX

PAI-1 Standard Curve



N/A

Status:

Remark:

Bold values are extrapolated
 Four parameter logistic: $y = b + (a - b) / (1 + xc)^d$

Fit type:

Meas.

transformation:

Linear

Conc.

transformation:

Linear

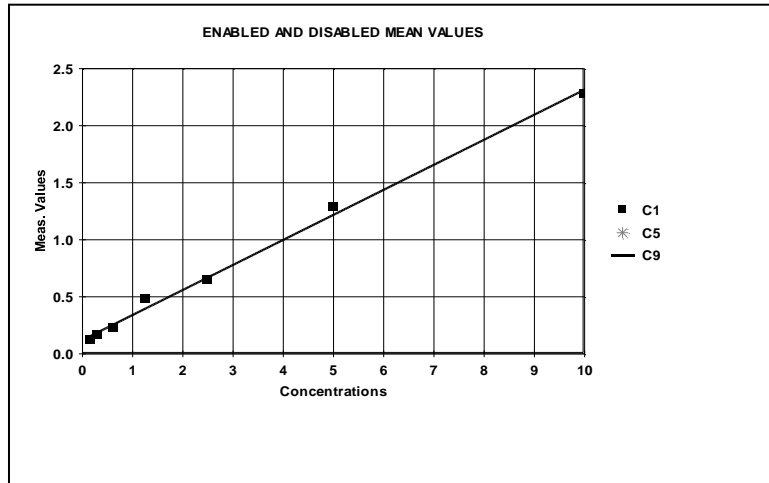
Parameters:

	a	b	c	d
	0.143	5.145	0.107	0.810

Corr. coeff. R2:

0.999

PAI-2 Standard Curve



Mean Blank	N/A	
Status:		
Remark:		
Fit type:	Linear regression (SVD): $y = a + b \cdot x$	
Meas. transformation:	Linear	
Conc. transformation:	Linear	
Parameters:	a	b
	0.122	0.219
Corr. coeff. R2:	0.991	