The Role of Endothelial Function in the Relationship between Depression and Cardiovascular Disease

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"Things without all remedy should be without regard."

Contribution of Authors

All manuscripts represent sub-analysis of the MOSMI study, designed by co-investigators André Arsenault, Simon Bacon, Kim Lavoie, and Blaine Ditto. Baseline data was collected prior to my joining the research group by various research assistants and prior graduate students. I played a lead role in the MOSMI year six follow-up, coordinating the selection of questionnaires for this follow-up, supervising data collection, entry, and verification with a team of research assistants and undergraduate honours students, and liaising with research ethics boards.

For manuscript one, I selected the topic. I co-designed the statistical analysis and interpreted the results with my co-supervisor Simon Bacon. I wrote the initial draft of the manuscript, with co-supervisors Simon Bacon and Blaine Ditto providing feedback during the writing process. Co-authors Kim Lavoie, Roxanne Pelletier, Tavis Campbell, and André Arsenault provided additional feedback on later drafts. This manuscript is currently published in Biological Psychology.

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Table of Contents

Abstract

Depression independently and consistently predicts a doubling of risk for developing cardiovascular disease (CVD) and CVD mortality. Despite significant research, the identification of pathways explaining this relationship remains challenging. This thesis explores the role of the endothelium, a layer of cells lining vascular walls that regulate homeostatic functions. Depressive disorders have previously been associated with impaired endothelial function (EF). The first study assessed whether this relationship may have an interaction with anxiety, and whether this relationship could be observed with subclinical continuous measures of depressive symptoms. The second study utilized a structural equation modeling approach to identify mechanisms that may explain the relationship between depression and EF, utilizing a sample of cardiac outpatients. Two significant pathways, one featuring physiological markers of CVD risk and another including behavioural factors, were identified. The third study used longitudinal data to determine if EF would mediate a relationship between depression and CVD outcomes over a six-year time period. EF was found to significantly mediate the relationship between depression and future coronary artery bypass graft surgery, after adjusting for age, sex, and presence of CVD at baseline. Overall, increasing evidence exists to suggest that endothelial health and associated pathways may link depression to CVD.

Résumé

La dépression indépendamment et consistante prédit un doublement du risque de développer une maladie cardiovasculaire (MCV) et une mortalité par MCV. L'identification des parcours expliquant cette relation reste difficile. Cette thèse explore le rôle de l'endothélium, la couche la plus interne des vaisseaux sanguins, qui régulent les fonctions homéostatiques. Des troubles dépressifs ont déjà été associés à une fonction endothéliale (FE) altérée. La première étude a évalué si cette relation peut avoir une interaction avec l'anxiété et si cette relation peut être observée avec des mesures continues sous-cliniques des symptômes dépressifs. La deuxième étude a utilisé la modélisation de l'équation structurale pour identifier les mécanismes qui peuvent expliquer la relation entre la dépression et la FE, en utilisant un échantillon de patients cardiaques. Deux voies significatives, l'une présentant des marqueurs physiologiques du risque MCV et une autre, y compris les facteurs comportementaux, ont été identifiées. La troisième étude a utilisé des données longitudinales pour déterminer si la FE affecterait une relation entre la dépression et les résultats de MCV sur une période de six ans. La FE s'est révélée faire le médiateur significativement la relation entre la dépression et la chirurgie de pontage aorto-coronarien, après ajustement pour l'âge, le sexe et la présence de MCV au départ. Dans l'ensemble, des preuves croissantes existent pour suggérer que la santé endothéliale et les voies associées peuvent relier la dépression à la maladie cardiovasculaire.

General Introduction

Depressive disorders and cardiovascular diseases (CVD) are the two leading causes of disease burden in middle and high income countries (Mathers & Loncar, 2006). Evidence suggests that these conditions are not independent, but have a complex relationship in which depression is a risk factor for the development of CVD, and a marker of prognostic severity in patients with CVD (Hare, Toukhsati, Johansson, & Jaarsma, 2014). Despite a compelling public health interest, and the wealth of studies identifying individual elements of this relationship (Gan et al., 2014; Mendelsohn, 2012; Miller & Raison, 2016), the exact mechanisms that link these disorders remain unclear. The role of the endothelium, a thin layer of cells that line artery interiors, may explain this relationship.

Cardiovascular Disease

CVD represents the leading cause of mortality worldwide, accounting for approximately 32% of all deaths (17.9 million) worldwide in 2015 (Wang et al., 2016). This represents a 12.5% increase since 2010 (Wang et al., 2016), and accounts for nearly half of all deaths due to non-communicable disease (Mendis et al., 2011). In Canada, 25% of deaths in 2013 were due to CVD, totaling 63,291 deaths. This has fallen since 2000, when CVD accounted for 70,646 deaths, 32% of the total that year (Statistics Canada, 2017), likely due to decreasing rates of cigarette smoking (Lee et al., 2009). Despite these high mortality rates, cohort studies have suggested that up to 90% of cases of

CVD may be preventable (Lloyd-Jones et al., 2006; McGill, McMahan, & Gidding, 2008).

An improved understanding of the pathogenesis of CVD is essential not simply due to mortality, but the societal, institutional, and personal burdens of the disease. Approximately 10% of the global disease burden, as measured by disability adjusted life years, is attributable to CVD (Mendis et al., 2011). Individuals with impaired cardiac health report poorer physical and mental quality of life (Allen et al., 2015), while patients recovering from cardiac surgery commonly experience pain, insomnia, fatigue, poor appetite, shortness of breath, and anxiety (Subeh, Salami, & Saleh, 2014). Health-related quality of life is reported to be more strongly impaired in patients with comorbid CVD and major depressive disorder (O'Neil et al., 2013). On a societal level, CVD carries a high cost. In the USA, CVD direct medical costs were $318 billion in 2017, and are projected to rise to $749 billion in 2035 due to aging of the population. Indirect costs due to lost productivity were $237 billion in 2015, and expected to rise by 55% over the same time period (American Heart Association, 2017).

In approximately 80% of CVD deaths, atherosclerosis represents the underlying disease process that results in an eventual myocardial infarction (MI, commonly known as a heart attack) or cerebrovascular accident (CVA, primarily a stroke) (Mendis et al., 2011). Atherosclerosis is a multi-stage process that develops over many years, leading to the formation of a fibrous,

fatty atheromatous plaque (also known as an atheroma). This atheroma causes a hardening of the arteries, damaging their elasticity and impairing their ability to vasodilate and vasoconstrict. It also leads to a narrowing (stenosis) of the lumen (the space within the arteries) which restricts blood flow. An unstable atheroma is at risk of rupture, which may cause the creation of a thrombus (a blood clot). An expanding thrombus is usually asymptomatic until an artery has become so occluded that blood supply becomes insufficient. This creates an ischemia (a restriction in blood supply, leading to a shortage of oxygen and glucose in body tissues) downstream from the thrombus, and potential infarction (tissue death) in the affected area. MI and CVA represent the rapid death of tissue in the heart and brain, respectively (Wang et al., 2012; Weber & Noels, 2011).

Endothelial Function

The process of atherosclerosis is linked to endothelial dysfunction and the initial accumulation of low-density lipoprotein (LDL, a type of cholesterol) in the intima, the innermost layer of an artery (Weber & Noels, 2011). The intima consists of a layer of endothelial cells, one cell thick, supported by a layer of elastic lamina cells. In a healthy artery, endothelial cells respond to physical and chemical signals by producing vasoactive molecules that mediate homeostatic processes (Deanfield, Halcox, & Rabelink, 2007). This process regulates vascular tone (the dilation and constriction of the artery), vessel wall inflammation (immune response), and

cellular adhesion. Following the initial intrusion of LDL into the intima, some of these normally homeostatic processes become pathogenic. Specifically, endothelial cells respond to LDL oxidation by initiating an inflammatory response, attracting monocyte white blood cells to penetrate the intima, transform into a type of macrophage known as a foam cell, and ingest LDL (Ruparelia, Chai, Fisher, & Choudhury, 2017). These foam cells undergo apoptosis (cell death) and together with other cell debris and cholesterol crystals form the necrotic, "fatty-streaked" core of an atheroma (Weber & Noels, 2011). This further damages the endothelium, and stimulates an ever increasing pro-inflammatory response, attracting more white blood cells, and continuing the cycle of plaque development (Ruparelia et al., 2017).

Due to its crucial role in the atherosclerosis disease process, it is unsurprising that a meta-analysis found endothelial function to be a consistent and independent predictor of cardiovascular events, even after adjusting for confounding risk factors (Inaba, Chen, & Bergmann, 2010). Interesting, one analysis revealed that endothelial dysfunction in both the coronary and peripheral arteries had similar predictive power, and that endothelial dysfunction successfully predicted cardiovascular events that occurred remotely from the area where endothelial dysfunction was detected (Lerman & Zeiher, 2005). This implies that although an infarction, for example, may be a localized event in, for example, the heart, underlying endothelial dysfunction is likely systemic throughout the body.

The endothelium's strong prognostic value in predicting cardiovascular events likely has two explanations. First, dysfunction of the endothelium represents an early stage of atherosclerosis that is an asymptomatic phase in the development of CVD (Gonzalez & Selwyn, 2003). Second, healthy functioning of the endothelium is impacted by many traditional risk factors of CVD, leading some to suggest that it represents the integrated effect of multiple risk factors (Widlansky, Gokce, Keaney, & Vita, 2003).

Measurement of Endothelial Function

Endothelial function is generally discussed using two categories: coronary endothelial function, assessed in the coronary arteries; and peripheral endothelial function, assessed using arteries not in the chest, and representing systemic endothelial function throughout the body (Jay Widmer & Lerman, 2014). Different measurement techniques exist to assess each type of endothelial function.

Coronary endothelial function is most often assessed using quantitative coronary angiography. This is an invasive technique, in which a small tube is inserted into the coronary arteries in order to release a radioactive dye. A pharmacological agent such as acetylcholine is then administered to induce vasodilation. The radioactive dye allows for blood and tissue to be observed by an X-ray, allowing this vasodilation to be quantitatively measured. In an artery with impaired endothelial function, the vasodilation response is blunted (Jay Widmer & Lerman, 2014; Lekakis et al., 2011).

Peripheral measures of endothelial function often utilize the brachial artery, located in the forearm. Venous occlusion plethysmography (VOP) tests act by inflating a cuff which allows the inflow of blood, but stops the outflow of blood. This allows for the volume change of blood to be measured. Similar to the previous technique, agents to stimulate vasodilation such as acetylcholine are introduced, and changes in forearm blood flow are assessed (Jay Widmer & Lerman, 2014; Lekakis et al., 2011).

Flow-mediated dilation (FMD) represents a common, non-invasive technique. It utilizes ultrasound to measure changes in the brachial artery diameter, following the administration of a hyperemic challenge (Lekakis et al., 2011). A hyperemic challenge elicits endothelium-dependent vasodilation through the inflation of a blood pressure cuff which blocks blood flow, creating a shortage of oxygen and a buildup of waste products in the arm. Following the release of the blood pressure cuff, a healthy endothelium will respond by relaxing the vascular smooth muscle and increasing the diameter of the artery, in order to increase blood flow to the arm. An impaired endothelium will show less vasodilation following this challenge. As one of the endothelium's primary homeostatic functions is regulating vascular tone (the degree of constriction of an artery), this represents a strong proxy of endothelial function (Corretti et al., 2002).

This current thesis utilizes a nuclear medicine variation of the FMD technique, in which a radioactive tracer is inserted and radiographic imaging

is used to compare vasodilation in a hyperemic arm to regular blood flow in a non-hyperemic arm (Dupuis et al., 2004). This technique, including its reliability and validity data, is discussed in greater detail at a later point in this thesis.

Vasodilation may also be influenced by endothelial-independent factors, such as smooth muscle function in response to exogenous sources of nitric oxide, such as nitroglycerin. Endothelial-independent assessment of vasodilation in adults at risk of atherosclerosis has shown that smooth muscle dysfunction can occur independently of impaired endothelium-dependent dilation (Adams et al., 1998). Endothelial-dependent and independent measures are useful for differentiating between mechanistic pathways (i.e., endothelial dysfunction or smooth muscle dysfunction) that may lead to impaired vasodilation in individuals with atherosclerosis.

Risk Factors of CVD

Decades of research have identified numerous risk factors, quantified their relative importance, and organized these risk factors into theoretical pathways to explain the pathogenesis of CVD. In identifying and organizing these risk factors, it is useful to organize these into two categories: behavioural and physiological markers of CVD risk. Of course behavioural risk factors also work by influencing physiological activity – these categories are not meant to represent a mind-body dichotomy, but simply a means to describe the different pathways.

Physiological Pathways

Dyslipidemia. Hypercholesterolemia – specifically, high levels of LDL cholesterol – usually represent the strongest predictor of future cardiovascular events. A 2007 meta-analysis of 61 prospective cohort studies, with an aggregate sample of 900,000 adults without previous disease, conclusively demonstrates this (Prospective Studies Collaboration, 2007). Increasing total cholesterol was associated with increased levels of CVD-related mortality in this sample, even after adjusting for blood pressure, suggesting cholesterol has an additive effect. This finding is also seen in INTERHEART, a case-control study that recruited 30,000 participants from 52 countries across each inhabited continent, heightening the global generalizability of these results. INTERHEART data demonstrated that a high ratio of LDL cholesterol to HDL cholesterol accounted for 54% of the population attributable risk of MI (Yusuf et al., 2004)

Hypertension. High blood pressure can increase the force required by the heart muscle to pump blood. When there is not enough blood flow to supply the needs of the body and lungs, heart failure occurs, which can lead to further complications such as ischemia and infarction. In 2015, high systolic blood pressure represented one of the largest contributors to global disability adjusted life years (Forouzanfar et al., 2016). INTERHEART demonstrated that hypertension provided 23% of the population attributable risk of MI (Yusuf et al., 2004). Reductions in blood pressure as a

result of medication therapy has the effect of reducing new and recurring cardiovascular events (Law, Morris, & Wald, 2009). A recent meta-analysis showed depression to be risk factor for hypertension (Meng, Chen, Yang, Zheng, & Hui, 2012). This is likely a result of depression's association with autonomic nervous system dysfunction, specifically increased sympathetic activity and poor vagal control (Scalco, Scalco, Azul, & Lotufo Neto, 2005).

Pro-inflammatory processes. In recent decades, inflammatory processes have been identified as a central risk factor for cardiovascular events (Ruparelia et al., 2017). This is unsurprising, due to the key role of chronic inflammation – in concert with endothelial dysfunction – in promoting atherosclerotic plaque development. A recent meta-analysis of over 160,000 people measured C-reactive protein (CRP), a protein produced in the liver and found in blood plasma in response to inflammation. It observed continuous relationships between increasing levels of CRP and greater risk of coronary heart disease, ischemic stroke, and vascular mortality (The Emerging Risk Factors Collaboration, 2010). A separate meta-analysis measured pro-inflammatory cytokines (proteins released by immune cells to stimulate immune response). Higher levels of these cytokines were associated with both non-fatal MI and cardiac-related mortality, independent of traditional risk factors such as hypertension, hypercholesterolemia, and smoking status, highlighting its novel importance as a marker of CVD risk (Kaptoge et al., 2014).

Behavioural Pathways

Smoking. Cigarette use represents a strong and consistent predictor of major adverse cardiac outcomes. In fact, cigarette smoking represents the leading risk factor for disability according to the Global Burden of Disease study (Lim et al., 2012). INTERHEART data found that current and former history of smoking accounted for 36% of the population attributable risk of MI (Yusuf et al., 2004). Even passive smoking is associated with an increase in the risk of coronary heart disease (RR=1.25) compared to individuals not exposed to smoke (He et al., 1999). In a prospective cohort study of 260,000 people, smoking increased coronary heart disease risk across all age groups, and among smokers between 68% to 88% of coronary heart disease risk was attributable to smoking status (Tolstrup et al., 2013). Smoking is believed to specifically damage the endothelium and impair endothelial function, as we know vasodilation is impaired in smokers, and smoking causes damaging alterations to the vascular wall. Smoking also contributes to the oxidation of LDL cholesterol, and activates pro-inflammatory processes, two early steps in the development of atherosclerotic plaques (Messner & Bernhard, 2014).

Physical activity. Inactivity represents a consistent predictor of cardiovascular events, though the specific dose of physical activity required to see a protective effect is still a matter of debate (Warburton & Bredin, 2016). A recent meta-analysis of epidemiological studies found engaging in the equivalent of 150 minutes/week of moderate intensity leisure time

physical activity (LTPA) reduced CVD risk by 14% compared to individuals reporting no activity, and 300 minutes/week reduced rates by 20% (Sattelmair et al., 2011). The INTERHEART study demonstrated that physical inactivity (defined as engaging in moderate activity for less than four hours per week) accounted for nearly 26% of the population attributable risk of MI (Yusuf et al., 2004). A meta-analysis of prospective cohort studies found that high levels of LTPA reduce the risk of CVD by 20 to 30%, and that moderate levels of occupational physical activity reduce risk by 10 to 20%, for both men and women (Li & Siegrist, 2012).

Diet, Alcohol, and Weight. Additional behavioural risk factors for CVD potentially include diet and alcohol intake, although this data lacks some consistency. INTERHEART data revealed that 13% and 14% of the population attributable risk of MI was accounted for by vegetable/fruit and alcohol intake, respectively. Sodium intake generally has an inverse relationship with CVD mortality, although this relationship is not consistently observed among younger (<55 years old), non-white, or obese individuals independent of other risk factors (Cohen, Hailpern, Fang, & Alderman, 2006). A recent meta-analysis showed that dietary sugars are associated with increases in blood serum lipid levels, including cholesterol, independent of the effect of sugar on body weight (Te Morenga, Howatson, Jones, & Mann, 2014). Increasing body weight, as assessed by Body Mass Index and waist circumference, is also associated with higher rates of CVD and CVD-related mortality (Flint et al., 2010; Katzmarzyk et al., 2012). In a recent Cochrane

review, reducing saturated fat led to a 17% reduction in the risk of CVD (Hooper, Martin, Abdelhamid, & Davey Smith, 2015). Certain diets, such as a Mediterranean diet high in plant foods and low in red meat, have been found to be associated with healthier endothelial function (Davis et al., 2017).

Depression as a Risk Factor for CVD

Depression is currently recognized as an independent risk factor for the development of CVD (Gan et al., 2014); however, its strength and interplay with other risk factors remains debated (Cohen, Edmondson, & Kronish, 2015).

It has been six decades since the first pieces of scientific literature began to recognize an association between depression and CVD (Wynn, 1967). Early literature identified the fact that patients who experienced a major adverse cardiac event, such as a MI, afterwards developed depression at rates higher than those observed in the general population (Cay, Vetter, Philip, & Dugard, 1972). Over time, researchers observed that depression was a strong predictor of survival following cardiovascular events. A seminal paper from this era observed that patients who were recovering from a MI and were depressed died at a rate over five times higher than non-depressed post-MI patients over a six month period (Frasure-Smith, Lesperance, & Talajic, 1993). A meta-analysis of prospective cohort studies published ten years later would advance the literature by demonstrating that depression

predicted the development of CVD in initially healthy individuals (Rugulies, 2002a).

Recent meta-analyses have consistently replicated this finding, additionally demonstrating that depression's predictive power is independent of other, traditional risk factors. A large meta-analysis, consisting of nearly 900,000 patients in prospective cohort studies, found depression to predict increased risk of MI and other types of CVD (RR=1.3), independent of smoking, hypertension, physical activity, diabetes, body mass index, and socioeconomic status (Gan et al., 2014). A similar meta-analysis including nearly 320,000 patients found depression to be associated with increased risk of CVA (RR=1.45) and CVA-related mortality (RR=1.55) (Pan, Sun, Okereke, Rexrode, & Hu, 2011). The INTERHEART study computed an index of "Psychosocial factors" that included exposure to depression, perceived stress, low locus of control, and major life events. When compared against other risk factors for MI, the population attributable risk for psychosocial factors (29%) was of a magnitude similar to smoking, physical activity, and obesity (Yusuf et al., 2004). Among those who have already developed CVD, depressed patients were observed to have a mortality rate twice as high as non-depressed patients, according to a meta-analysis (Barth, Schumacher, & Herrmann-Lingen, 2004).

While these large epidemiological studies underscore the importance of depression in relation to CVD, they are limited as they do not explain its

effects. Though studies suggest depression is an independent predictor, it is possible that there are interactions among these risk factors. There may also be bi-directional relationships between these factors and CVD. For example, it is possible that depression is a risk factor that leads to a higher future incidence of CVD in healthy individuals, and also that depression arises as a consequence of an adverse cardiac event, such as an MI, where it has prognostic value by influencing worse outcomes such as a greater risk of mortality (Hare et al., 2014).

Pathways between Depression and CVD

There is little conclusive evidence to explain the causal steps that link depression to CVD, though a number of theorized pathways exist.

Pro-Inflammatory Processes. Inflammation represents a likely pathway to explain this connection. As previously discussed, inflammation is a key process in the development of arthrosclerosis and CVD, aiding in the creation of plaques and arterial blockages. Research pointing to a link between depression and inflammation is extensive, although its directionality is still debated (Miller & Raison, 2016). Individuals with major depression show elevated levels of inflammatory cytokines, small signaling molecules in the body that promote immune response. This relationship is seen even in the absence of other medical conditions that would stimulate an inflammatory response, among medically healthy depressed individuals. (Miller, Maletic, & Raison, 2009). Specifically, meta-analyses have identified

IL-1β, IL-6, Tumor Necrosis Factor and C-reactive protein (CRP) as reliable biomarkers of inflammation in depressed individuals (Miller & Raison, 2016). It is important to note that inflammation is not simply associated with the somatic symptoms of depression - such as fatigue, insomnia, and changes in appetite - which one would expect to observe in individuals who are physically ill. Inflammation is also associated with cognitive and emotional symptoms of depression, such as depressed mood, low feelings of self-worth, anhedonia, concentration difficulties, and suicidal ideation (Jokela, Virtanen, Batty, & Kivimäki, 2016).

Studies conflict when attempting to identify the directionality of the relationship, making it hard to conclude whether depression induces inflammation, inflammation induces depression, or if the causal pathways are bidirectional. A prospective study attempting to clarify this observed that baseline scores of depressive symptoms predicted six year change in levels of IL-6, a pro-inflammatory cytokine. Baseline IL-6, however, did not predict levels of depressive symptom (Stewart, Rand, Muldoon, & Kamarck, 2009). However, a small meta-analysis of 11 papers noted that inflammatory markers such as CRP and IL-6 had a small but significant association with the future development of depressive symptoms (Valkanova, Ebmeier, & Allan, 2013). Additionally, a recent randomized controlled trial found that healthy young adults injected with an endotoxin – a substance which stimulates an inflammatory response in individuals – showed significant increases in

feelings of depressed mood over a six hour time period, compared to a placebo control group (Eisenberger, Inagaki, Mashal, & Irwin, 2010).

Alternatively, both depression and inflammation may also be induced by a third variable that is known to stimulate immune response, such as such as medical illness, environmental factors, gut micro-organisms, or adipose tissues (Felger & Lotrich, 2013; Shimbo, Chaplin, Crossman, Haas, & Davidson, 2005). The hyperactivity of the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic nervous system observed in depression may represent an additional third variable, as this activity stimulates a pro-inflammatory response. Chronic over-activation of the HPA axis may also reduce glucocorticoid receptor function, which inhibits the homeostatic ability of cortisol to suppress inflammation, thus leading to a vicious cycle of chronic inflammation (Miller et al., 2009).

Health Behaviours. Depressed individuals tend to engage in more negative and fewer protective health behaviours than non-depressed individuals. Depressed people are twice as likely to smoke and show a higher nicotine dependence after quitting than non-depressed people (Mendelsohn, 2012). High comorbidities exist between depression and alcohol use disorder across the lifespan (Brière, Rohde, Seeley, Klein, & Lewinsohn, 2014). A meta-analysis found that depression is a strong risk factor for decreased levels of physical activity (Roshanaei-Moghaddam, Katon, & Russo, 2009). Conversely, undertaking physical activity is

consistently associated with improved mood in depressed individuals (Knapen, Vancampfort, Moriën, & Marchal, 2015).

In cardiac patients specifically, health behaviours are known to be associated with certain psychological factors (Mercer et al., Submitted). Following a MI, depressed patients are less likely to adhere to a low-fat diet, to engage in regular exercise, or to take medications as prescribed, as compared to non-depressed patients (Bauer et al., 2012; Ziegelstein et al., 2000). This may explain why depression following a cardiovascular event is associated with worse prognosis and increased risk of mortality.

Depression and Endothelial Function

Endothelial function – a homeostatic process that is both influenced by these previously discussed physiological and behavioural factors, and a prognostic indicator of cardiovascular events – may play an important role in mediating the pathway between depression and CVD.

Potential relationships between depression and endothelial function represent a novel and growing area of literature. A cross-sectional study noted that endothelial function is impaired in cardiac outpatients with major depressive disorder, as compared to cardiac outpatients who are not depressed (Lavoie, Pelletier, Arsenault, Dupuis, & Bacon, 2010). The same pattern of impaired endothelial function is also seen among healthy young adults who have major depressive disorder, as compared to non-depressed

healthy adults (Rajagopalan et al., 2001). Impaired endothelial function is even seen in individuals who have received antidepressant treatment and whose depressive symptoms are in remission, as compared to healthy controls (Broadley, Korszun, Jones, & Frenneaux, 2002; Rybakowski, Wykretowicz, Heymann-Szlachcinska, & Wysocki, 2006).

Some studies have measured depressive symptoms using continuous scales on self-report questionnaires. Higher depressive symptom scores have been associated with impaired endothelial function among CVD patients (Aydin Sunbul, Sunbul, & Gulec, 2017; Chen et al., 2013; Sherwood, Hinderliter, Watkins, Waugh, & Blumenthal, 2005). Increasing depressive symptom scores are also associated with impaired endothelial function in non-cardiac cohorts of the general elderly population (van Sloten et al., 2013). A recent meta-analysis has provided the strongest evidence to date that depression is associated with lower rates of vasodilation, suggesting that endothelial function – particularly the ability to regulate vasodilation and vasoconstriction – is impaired in depressed individuals (Cooper et al., 2011).

Pro-inflammatory processes. Inflammation is a possible pathway for the relationship between depression and endothelial function, though few studies have directly assessed these three factors, and none to date have examined them longitudinally in order to establish potential causation. It is possible that due to behavioural and physiological changes associated with chronic idiopathic depression (absent of other medical conditions that

influence immune function) a chronic pro-inflammatory response is stimulated in the body (Felger & Lotrich, 2013). This inflammation would then damage the endothelium through mechanisms discussed earlier, supporting the development of an atherosclerotic plaque and impairing the homeostatic functions of the endothelium. Atherosclerosis and major adverse cardiac outcomes would be the end product of this process.

A recent population-based cohort study examined associations of depression, endothelial function, and inflammation in the same sample. It was found that inflammation and endothelial function were both associated with depressive disorder, independent of lifestyle factors, however these associations were not assessed longitudinally (van Dooren et al., 2016).

Health Behaviours. Depression's characteristic association with negative health behaviours could also explain its relationship with endothelial function. Depression is associated with a number of negative health behaviours, such as smoking, physical inactivity, and lack of medication adherence among cardiac patients (Bauer et al., 2012; Knapen et al., 2015; Mendelsohn, 2012; Roshanaei-Moghaddam et al., 2009; Ziegelstein et al., 2000). Many of these negative health behaviours may directly impair endothelial function, or promote changes that lead to endothelial damage.

Cigarette smoking is consistently associated with impaired endothelial function, possibly in a dose-response relationship (Celermajer et al., 1993). This is possibly due to the fact that long-term smoking leads to an increase in

the oxidation of LDL cholesterol (Heitzer et al., 1996). It is the accumulation of LDL cholesterol in the intima of blood vessels that initiates the process of atherosclerosis. Physical inactivity may also play a negative role, as a recent meta-analysis has demonstrated that physical activity plays a dose-response role in enhancing endothelial function. Both aerobic and resistance exercise was found to improve endothelial function in a dose-dependent manner, possibly through enhancing the bioavailability of nitric oxide, a signaling molecule used by the endothelium to induce relaxation of the smooth muscle and vasodilation (Ashor et al., 2015).

Measurement of Depression

One difficulty inherent in this area of research is the measurement of depression. While the lay term is easily understood, clinical diagnostic labels, thresholds for classification, and measurement tools may vary wildly from study to study.

The Diagnostic and Statistical Manual of Mental Disorders (DSM-5) outlines multiple "Depressive Disorders" (labeled Mood Disorders in earlier editions) (APA, 2013). Commonly, this label will be applied to Major Depressive Disorder (both current and in partial remission) and Persistent Depressive Disorder (Dysthymia). Major Depressive Disorder is defined as the presence of five symptoms over a two week period, one of which must be either 1/ depressed mood or 2/ loss of interest or pleasure. The remaining symptoms may be: 3/ significant weight loss or gain, or decrease or increase

in appetite, 4/ insomnia or hypersomnia, 5/ psychomotor agitation or retardation, 6/ fatigue or loss of energy, 7/ feelings of worthlessness or guilt, 8/ diminished ability to concentrate or indecisiveness, or 9/ recurrent thoughts of death, suicidal ideation, or a suicide attempt. Additionally, there must be clinically significant distress or impairment in important areas of functioning, and these symptoms cannot be attributable to the effects of a substance or other medical condition. Persistent Depressive Disorder, in contrast, does not require symptoms to be present during a two-week period, but rather that they be present for at least 50% of the days over a two year period. Additionally, fewer symptoms are required to be present.

Difficulties in the measurement of depression extend to the diagnostic tools utilized. In order to meet DSM-5 criteria for a Depressive Disorder, a clinical interview delivered by trained personnel is required. A dichotomous label is then assigned, indicating the absence or presence of a diagnosis. This method is time consuming and expensive. It limited as it does not capture the presence of sub-clinical symptoms that do not pass the threshold required for diagnosis, and or the difference in magnitude of symptoms which can vary greatly in clinical populations. Due to this, many research projects measure depressive symptoms using a self-report, multiple choice questionnaire. Usually a standardized, well validated questionnaire such as the Beck Depression Inventory-II will be utilized (Beck, Steer, Ball, & Ranieri, 1996). While these tools are considerably more efficient and provide continuous measurement of depressive symptoms, they are not without their

own limitations. Specifically, they may be unable to differentiate between symptoms due to depression versus another medical condition.

Diagnosing depression in cardiac patients represents a particular challenge, as many of the symptoms of CVD are similar to symptoms of depression. Patients recovering from cardiac surgery commonly experience insomnia, fatigue, and poor appetite (Subeh et al., 2014). Some of these somatic symptoms may also be side effects of medications often prescribed to cardiac patients (McDonagh, 2014; Rossi, 2006). A trained clinician delivering a structured interview may be able to use clarifying questions to differentiate between symptoms of depression and CVD. However, a self-report questionnaire may incorrectly capture these CVD symptoms as symptoms of depression, and incorrectly report a higher level of depressive symptoms than the patient is truly experiencing. This is particularly troublesome for research studies attempting to link depression to CVD, as measurement error would inflate the strength of any observed relationship.

Anxiety, Endothelial Function, and CVD

When measuring depression, it is important to remain cognizant of potential anxiety disorders. Anxiety and depression are highly comorbid among samples of both psychiatric and cardiac patients (Frasure-Smith & Lespérance, 2008; Hirschfeld, 2001). Additionally, questionnaire measures of anxiety and depressive symptoms show high correlations (Endler, Denisoff, & Rutherford, 1998; Stulz & Crits-Christoph, 2010). This is

particularly troublesome, as it suggests that when a study measures only one set of symptoms, while not measuring or adjusting for the other, the questionnaire may not be adequately differentiating between each (Karagözoğlu, Masten, & Baloğlu, 2005; McWilliams, Cox, & Enns, 2001). For example, a study utilizing an anxiety self-report questionnaire could identify a weak association between anxiety symptom scores and an outcome variable of interest. However, the association was actually being driven by the symptoms of depression that overlap with those measured by the anxiety questionnaire. This problem could have been solved by measuring both anxiety and depressive symptoms and adjusting for each, or utilizing a clinical interview with better discriminant validity.

Proper discrimination is important because anxiety and depression seem to act on different physiological pathways, and potentially have qualitatively different effects on the cardiovascular system. For example, anxiety may potentially act on sympathetic physiological pathways elicited by active coping tasks (Ditto & Miller, 1989), while depression is possibly more associated with passive coping styles. While the associations between depression and CVD are consistent and replicable, the anxiety literature is considerably unclear.

A recent six-year prospective study found that depression and comorbid depression and anxiety were associated with increased CVD incidence, while anxiety was not associated (Seldenrijk et al., 2015). In a

meta-analysis, anxiety was associated with cardiac mortality, but it was not associated with nonfatal MI (Roest, Martens, de Jonge, & Denollet, 2010a). Contradicting this is an older study of 5000 cardiac outpatients. This study observed that while depressive symptoms were associated with greater mortality rates, anxiety symptoms actually had a protective effect, and were associated with lower rates of mortality (Herrmann, Brand-Driehorst, Buss, & Ruger, 2000).

There is a very limited literature studying relationships between anxiety and endothelial function. A few studies with small sample sizes have demonstrated some cross-sectional associations between anxiety and endothelial function (da Silva et al., 2015; Narita, Murata, Hamada, Takahashi, Kosaka, et al., 2007; Narita, Murata, Hamada, Takahashi, Omori, et al., 2007). However, these studies utilized self-report questionnaire assessments of anxiety symptoms, and did not adjust for potential comorbid depressive symptoms, suggesting they may be vulnerable to the discriminant validity limitations discussed previously.

The Current Thesis

A mature body of research has established that relationships exist between depression and CVD, yet much of the mechanisms that explain these relationships remain unclear, while conflicting studies provide results that may seem contradictory. Endothelial function represents a plausible mediator for this relationship, yet few studies have examined these three

variables in the same population. This current thesis was designed to advance our understanding of the relationship between depression and CVD by modeling potential pathways that may connect these variables, and assessing the role of endothelial function as a mediator. Utilizing a sample of typical cardiac outpatients referred for exercise stress testing, three inter-related studies were designed.

Manuscript One attempts to determine if endothelial function is associated with measures of depressive symptoms, anxiety symptoms, or the interaction between depressive and anxiety symptoms. This study aimed to determine if anxiety has a qualitatively different effect on endothelial function than depression, and provide methodological improvements on previous studies by better discriminating between these two commonly co-occurring symptom sets. Additionally, when contrasted with a previous paper by Lavoie et al. (2010), this study would determine if it is more appropriate to assess relationships between endothelial function and depression using continuous self-report measures of depressive symptoms, or dichotomous clinician-administered screening interviews.

Manuscript Two aimed to utilize a structural equation modeling approach not previously seen in this literature to model pathways between depression and endothelial function. Two latent variables were constructed, representing traditional physiological markers of CVD risk (such as pro-inflammatory processes and dyslipidemia) and behavioural risk factors for

CVD (including smoking and physical activity). Models were constructed using these latent variables to demonstrate potential pathways between depression and endothelial function, and the relative strength and salience of each of these pathways was compared.

Manuscript Three utilizes longitudinal data over a six-year period to assess if endothelial function represents a useful mediator of potential relationships between depression and a number of adverse coronary artery disease outcomes, including MI, percutaneous coronary intervention procedures, and coronary artery bypass graft surgery. In doing so, an attempt was made to demonstrate some directionality to this overall relationship between depression and CVD.

The use of the same sample in each of these manuscripts allows for one overarching model to be theorized and constructed, based on the relationships and pathways identified in each of these studies. See Figure 1 for a visual representation of this model, including pathways studied in this current thesis, in addition to some theoretical pathways believed to exist based on previous literature.

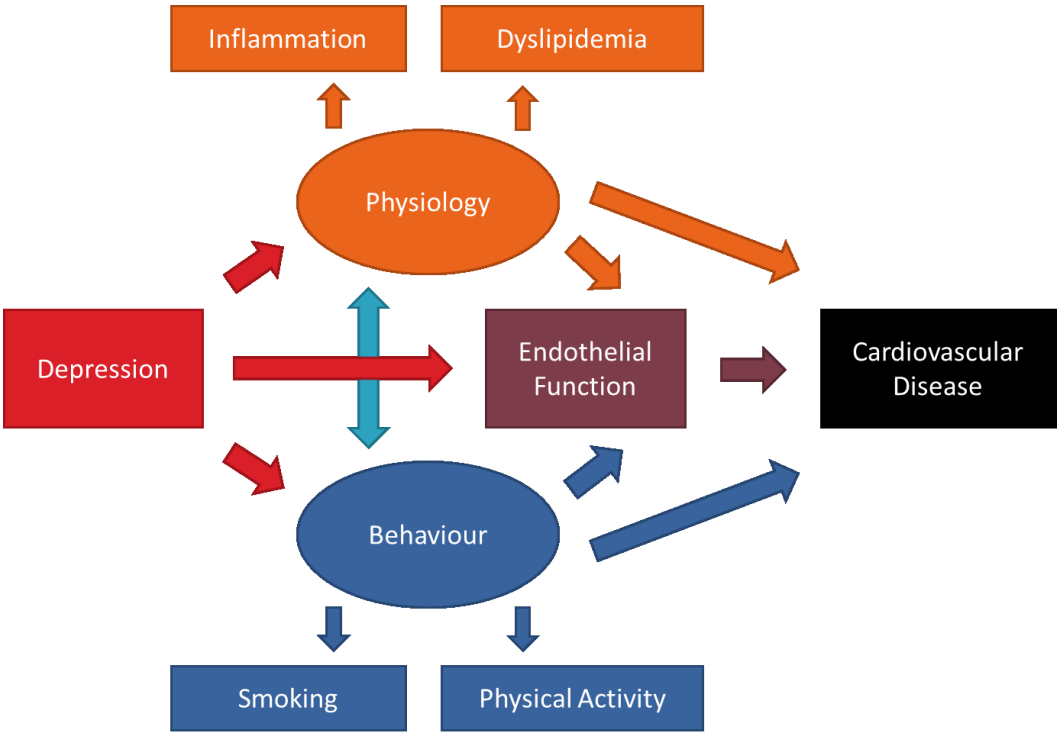

Figure 1. Theorized pathways between depression, endothelial function, and cardiovascular disease outcomes.

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Manuscript One

The interaction between anxiety and depressive symptoms on brachial artery reactivity in cardiac patients

Mercer, D. A., Lavoie, K. L., Ditto, B., Pelletier, R., Campbell, T., Arsenault, A., & Bacon, S. L. (2014). The interaction between anxiety and depressive symptoms on brachial artery reactivity in cardiac patients. *Biological psychology, 102*, 44-50.

Abstract

The association between anxiety, depression, and endothelial function (EF) was assessed in a sample of 295 cardiac outpatients (n=222 men; mean age=59). Patients were administered the Beck Depression Inventory-II and the State-Trait Anxiety Inventory, trait scale. EF was assessed through forearm hyperemic reactivity, a nuclear medicine variation of the flow-mediated dilatation technique, which calculates the rate of uptake ratio (RUR) between hyperaemic and non-hyperaemic arms. No main effect for anxiety (F=1.40, p=.24) nor depression (F=2.66, p=.10) was found in models for EF, however there was an interaction (F=4.11, p=.04). Higher anxiety and lower depressive symptoms were associated with superior RUR compared to lower anxiety and lower depressive symptoms. Anxiety had no influence on RUR in those patients with higher depressive symptoms, who generally displayed the lowest levels of RUR, i.e., poor function. It is speculative whether this potential protective role of anxiety may be guided by behavioural or physiological mechanisms.

Psychological variables, including affective states such as depressed mood and anxiety are risk factors for the development of cardiovascular disease (CVD) (Kubzansky, Kawachi, Weiss, & Sparrow, 1998; Lesperance, Frasure-Smith, Juneau, & Theroux, 2000; Suls & Bunde, 2005). Findings from meta-analyses suggest that the presence of increased depressive symptoms are associated with a doubling of risk for developing CVD and risk for CVD mortality compared to individuals with low levels of depressive symptoms (Barth et al., 2004; Rugulies, 2002b). Associations between anxiety and CVD have also been examined in a recent meta-analysis, showing elevated anxiety symptoms to be associated with a greater risk of developing CVD (HR: 1.26, 95% CI: 1.15-1.38) and cardiac death (HR: 1.48, 95% CI: 1.14-1.92) (Roest, Martens, de Jonge, & Denollet, 2010b).

Unfortunately, the bio-behavioral mechanisms underlying these relationships remain unclear, though processes such as hypothalamic-pituitary-adrenal (HPA) axis hyperactivity, sympathomedullary hyperactivity, and proinflammatory cytokine activation have been implicated (Gonzalez & Selwyn, 2003; Joynt, Whellan, & O'Connor, 2003; Musselman, Evans, & Nemeroff, 1998). Interestingly, all of these mechanisms have been associated with dysfunction of the nitrous oxide pathway (Rajagopalan et al., 2001), a messenger released by the endothelium that regulates vasodilation (Lowenstein, Dinerman, & Snyder, 1994), suggesting a link between psychological factors and endothelial dysfunction.

The endothelium is a dynamic layer of cells lining the vascular walls which regulates many homeostatic processes (Vita & Keaney, 2002). These include the production of vasodilators (e.g., nitrous oxide) and vasoconstrictors (Gonzalez & Selwyn, 2003), and the regulation of blood fluidity and inflammation. Endothelial dysfunction is strongly and independently associated with increased risk of CVD development, (Lerman & Zeiher, 2005; Quyyumi, 2003; Schachinger, Britten, & Zeiher, 2000), as it is considered to reflect a composite of many factors affecting cardiovascular health (e.g., dyslipidemia, hypertension, smoking, diabetes, and inflammation) (Bonetti, Lerman, & Lerman, 2003; Lekakis et al., 2011).

We have previously shown the presence of major depressive disorder in cardiac outpatients to be associated with poorer forearm hyperemic reactivity, a proxy measure for endothelial function (Lavoie et al., 2010). Separate studies have demonstrated impaired endothelial function to be associated with depressive symptoms in CVD patients (Sherwood et al., 2005) and major depressive disorder in healthy individuals with no CVD risk factors (Rajagopalan et al., 2001). This inverse association between depressive symptoms and flow mediated dilation, another proxy measure of endothelial function, has been supported by a recent meta-analysis which identified a combined effect size correlation coefficient of $r = 0.19$ ($p = .001$) (Cooper et al., 2011). Additionally, major depressive disorder has been found to be associated with decreased nitric oxide synthase activity (Chrapko et al., 2004). This association may represent a part of the mechanism

underlying the relationship between depression and endothelial dysfunction.

Anxiety and depression are highly comorbid, as evidenced by high concurrence in both psychiatric & cardiac samples (Frasure-Smith & Lespérance, 2008), and high correlations between questionnaire measures (Endler, Denisoff, & Rutherford, 1998; Stulz & Crits-Christoph, 2010). In contrast to the depression literature, there is a limited amount of data looking at the potential associations between endothelial function and anxiety. However, it would appear that there is a negative correlation between trait anxiety and brachial artery flow-mediated dilation (Narita, Murata, Hamada, Takahashi, Omori, et al., 2007). Despite the well-documented comorbidity of anxiety and depressive symptoms, to our knowledge only one study has examined an interaction between anxiety and depression on endothelial function. This study observed less vasodilation in postmenopausal women with elevated anxiety and depression (Harris, Matthews, Sutton-Tyrrell, & Kuller, 2003).

This study sought to better understand the relationships between anxiety, depressive symptoms and endothelial function by assessing the interaction of anxiety and depressive symptoms on brachial artery reactivity, in a sample of cardiac patients referred for myocardial perfusion imaging. Based on previous findings, it was hypothesized that patients displaying elevated levels of depressive and anxiety symptoms would have worse reactivity, thus indicating the greatest amount of endothelial dysfunction.

Materials and Methods

Participants

The current study represents a sub-analysis of the Cross-sectional Mechanisms and Longitudinal Outcomes of Silent Myocardial Ischemia (MOSMI) study, which was designed to assess the relationship between blood pressure and silent myocardial ischemia (Gordon et al., 2012; Pelletier et al., 2011). A total of 906 outpatients referred for a single photon emission computed tomography (SPECT) perfusion exercise stress test in the outpatient nuclear medicine service of the Montreal Heart Institute between May 2005 and December 2006 were recruited. Approximately one-third (n = 330) were recruited for the forearm hyperaemic reactivity (FHR) test. Due to limited camera availability, these patients were recruited consecutively from the total sample until three available testing slots per day were filled. Patients were included if they were at least 18 years of age, and spoke either English or French. Patients were excluded from the MOSMI study if they suffered from a pain disorder other than angina; used a prescription or non-prescription analgesic on the day of exercise testing; used a non-steroidal anti-inflammatory agent (NSAID), coxibs, or anti-neoplastic agent within the last 7 days; were pregnant; had a severe or co-morbid condition and were not expected to survive for 12 months (e.g., cancer); had a history of drug or alcohol abuse; or had a mental condition (determined via self-report and chart review of prescribed medications) rendering the participant unable to

understand the nature, scope, and possible consequences of the study. Patients were excluded from the FHR test if they reported having smoked within 6 hours, or eaten within 4 hours, prior to the test. The human ethics committee of the Montreal Heart Institute approved the protocol, and all patients provided written, informed consent prior to participation.

Procedure

Patients presenting for exercise stress testing at the Nuclear Medicine Service of the Montreal Heart Institute were invited to participate. On the first day of the SPECT perfusion imaging testing, patients began with a standard treadmill exercise stress test (modified Bruce protocol) followed by standard SPECT imaging (Anagnostopoulos et al., 2004). Patients were administered a battery of self-report questionnaires assessing sociodemographic and medical history information which were provided to them after they had completed the exercise stress test. On the following day, patients who had accepted to enter the FHR sub-study had their fasting blood drawn and resting blood pressure taken (using a manual sphygmomanometer) (Tycos-767 series, Welch Allyn, Skaneateles Falls, NY) by an experienced nuclear medicine technician. Patients then completed the FHR test, followed by the rest scan according to the SPECT protocol. Patients were asked to maintain all usual medications, but asked to refrain from taking β blockers due to the SPECT test.

Brachial Artery Reactivity. Reactivity was assessed using a nuclear

medicine variation of the well-established flow-mediated dilation protocol (Corretti et al., 2002), a technique developed in our laboratory (Dupuis et al., 2004). Participants were seated with both arms extended over a large field of view gamma-camera (Seintronix, London, UK) facing upward, hands prone. A blood pressure cuff (Adult First Responders, B&A Instruments, New York, NY) was placed over the right arm, and inflated to 50 mmHg above systolic blood pressure for 5 minutes, creating a hyperemic challenge. Thirty seconds after sudden cuff release, a tracer in the form of technetium-99m-tetrofosmin was injected as a bolus (15.5 MBq/kg) via a small catheter positioned in the bend of the left arm, with the injection trajectory masked using a lead lining between the arm and the tubing. Dynamic imaging of the forearms was taken and sustained for ten minutes, using 128 x 128 matrices at a sampling rate of one frame per second. Comparing activity-time curves over identical regions of interest in the hyperemic right arm and the non-hyperemic control left arm using custom software (SyGeSa, Montreal, Canada) allowed for the derivation of a relative-uptake-ratio (RUR), a unit-less index of maximum rise in activity. A higher ratio reflects greater endothelial reactivity and better endothelial function. This technique has been shown to predict the presence of CAD using a cutoff RUR of 3.55 with a sensitivity of .70 and a specificity of .60 (Arsenault, Bacon, Lavoie, & Meloche, 2005; Dupuis et al., 2004). This technique has shown to have excellent measurement properties, including high test-retest reliability (r=.89) (Bacon, Meloche, Lavoie, & Arsenault, 2012) and very good inter- and intra-rater reliability (r=.98)

(Veldhuijzen van Zanten et al., 2006), and is comparable to other similar techniques (Karacalioglu et al., 2006).

Depressive Symptoms Assessment. The Beck Depression Inventory-II (BDI) is a self-report measure of 21 multiple-response items, each which relate to a depressive symptom (Beck et al., 1996). Each response is rated on a scale of 0 to 3, allowing for total scores ranging from 0 to 63. Cutoffs exist to differentiate minimal depression (0-13), mild depression (14-19), moderate depression (20-28, and severe depression (29-63), however as this study was concerned with depression as a continuous, not categorical variable, these cutoffs were not utilized. An example of an item, relating to pessimism, would provide the following four response options (with scores in parenthesizes): I am not discouraged by my future (0); I feel more discouraged about my future than I used to be (1); I do not expect things to work out for me (2); I feel my future is hopeless and will only get worse (3). The BDI-II has been used in previous research assessing associations between depressive symptoms and endothelial function (Sherwood et al., 2005)

Anxiety Symptoms Assessment. The State-Trait Anxiety Inventory, trait scale (STAI-T) is a self-report measure of 20 items, each rated on a scale of 1 to 4 (Spielberger, Gorsuch, & Lushene, 1970). Scores range from 20 to 80, with higher scores indicating greater anxiety. An example of an item would include "I feel nervous and restless," onto which participants are asked to

indicate how they generally feel using the responses Almost Never (1), Sometimes (2), Often (3), or Almost Always (4). The STAI-T scale has been shown to possess high test-retest reliability (r = .86) (Spielberger et al., 1970), and acceptable concurrent validity when correlated with other scales of anxiety, including the Anxiety Scale Questionnaire (r = .73) and the Manifest Anxiety Scales (r = .85) (Spielberger, Ritterband, Sydeman, Reheiser, & Unger, 1995). The STAI-T is believed to be useful in the differentiation of anxiety from depression (Tilton, 2008), and has been utilized in previous studies assessing associations between anxiety and endothelial function (Narita, Murata, Hamada, Takahashi, Kosaka, et al., 2007; Narita, Murata, Hamada, Takahashi, Omori, et al., 2007).

Statistical Analyses

Two general linear model analyses were conducted to assess the association between BDI-II scores and STAI-T scores on forearm hyperemic reactivity (RUR). The first model assessed the main effects of depressive and anxiety symptoms, while the second included an interaction term. Both models were adjusted for previous history of CAD (including myocardial infarction, coronary artery bypass graft surgery, and percutaneous coronary intervention), age, sex, smoking status, self-reported leisure-time physical activity, body mass index (BMI), prescription of ACE inhibitor (yes-no) and statin (yes-no), hypertension (yes-no), and dyslipidemia (yes-no). These covariates were chosen a-priori due to their known associations with the

main variables of interest (Furberg, 1999; Kinlay, Libby, & Ganz, 2001; Lavoie et al., 2010; Narita, Murata, Hamada, Takahashi, Omori, et al., 2007; Rajagopalan & Harrison, 1996). Statistical significance was set at .05 for each analysis. All analyses were performed using SAS version 9.3 (SAS Institute, Cary, NC).

Results

Sample characteristics

Demographic details are presented in Table 1. For the current analyses, a total of 295 (75% male) outpatients, with a mean age of 59 ± 9.5 years, who had complete data were included. In Table 2, medical and clinical characteristics are summarized. The sample was found to be on average overweight (mean BMI = 28 ± 4.4), with a history of smoking (58% were previous smokers), although only 10% were current smokers. A history of coronary artery disease (CAD) was reported by 41% of the sample. Over half of the sample was prescribed statins (51%), while just over a quarter were prescribed ACE inhibitors (26%). Mean RUR was 4.10±1.71, just above the cutoff of <3.55 used to indicate the presence of CAD (Dupuis et al., 2004).

Effects of depressive and anxiety symptoms on endothelial function

As seen in Table 3, analyses revealed no statistically significant main effect for BDI-II or STAI-T scores in models with forearm hyperemic reactivity after adjustment for covariates. However, there was a statistically

significant interaction effect between BDI-II and STAI-T scores on forearm hyperemic reactivity. As shown in Figure 1, which depicts upper and lower quartiles of BDI-II and STAI-T scores for illustrative purposes, higher levels of anxiety and lower levels of depressive symptoms were associated with higher RUR's compared to lower anxiety and higher depressive symptoms. Anxiety was not associated with RUR in participants with higher depressive symptoms, who generally displayed the lowest RUR's.

Post-hoc analyses

Three general linear models were performed, to determine the association between anxiety, depressive symptoms, and an interaction term on smoking status, physical activity, and BMI, three potential mechanisms that may explain the findings of the main analyses. All previously defined covariates were also used for these analyses. These results are summarized in Table 4. No significant main effects or interaction was identified for any of the dependent variables.

Discussion

In our sample of 295 cardiac patients referred for SPECT exercise stress testing, higher anxiety with lower depressive symptoms was associated with superior forearm hyperemic reactivity, compared both to participants with higher depressive symptoms, and participants with lower depressive symptoms and lower anxiety. These results suggest that higher levels of

anxiety, in the absence of higher depressive symptoms, may be protective of poor forearm hyperemic reactivity or endothelial dysfunction.

Whilst our interaction result is novel in the context of the endothelium, it may be compared with the results of a previous study that examined these relationships in the context of CVD. In a large sample of over 5,000 patients referred for exercise testing, it was demonstrated that anxiety and depression had independent, opposite predictive effects on CVD mortality over five years. While anxiety was associated with decreased mortality, depression was associated with increased mortality after adjusting for anxiety (Herrmann et al., 2000). Overall, our findings suggest that it is not merely the presence of anxiety, but the interaction of anxiety and low depressive symptoms, that may provide some protective role, which may be through superior endothelial function.

Research examining physiological response to mental stress may explain these findings. It is well known that stressors that project the possibility of escape or avoidance (often referred to as active coping stressors) can elicit qualitatively different patterns than stressors that are entirely uncontrollable (passive coping stressors) (Obrist, 1981). Challenging tasks eliciting active coping have been associated with vasodilation in the large muscles (Ditto & Miller, 1989). In contrast, tasks eliciting passive coping, helplessness, and frustration are associated with vasoconstriction (Miller et al., 1995). Active coping, a state of arousal in response to a

situation that provides some chance of escape, may be analogous to high trait anxiety with low depressive symptoms, while passive coping, which features stress that is uncontrollable, may be analogous to a state of learned helplessness, featuring high depressive symptoms (Snow-Turek, Norris, & Tan, 1996). This pattern of vasodilation among higher anxiety with lower depressive symptom individuals, and vasoconstriction among individuals with higher depressive symptoms would be consistent with the results of our study.

Our findings identified no main effect for either anxiety or depressive symptoms independent of the interaction term. While our use of an interaction term was novel, this contrasts with some previous studies that observed associations between endothelial function and either depressive symptoms (Sherwood et al., 2005) or diagnoses of a mood disorder (including major depression and minor depression) (Lavoie et al., 2010; Rajagopalan et al., 2001; Rybakowski et al., 2006). These studies did not adjust for anxiety, unlike our own. Our findings also contrast with two small studies that observed high levels of anxiety to be related to worse brachial artery flow-mediated dilation in smaller samples of healthy elderly males (Narita, Murata, Hamada, Takahashi, Kosaka, et al., 2007; Narita, Murata, Hamada, Takahashi, Omori, et al., 2007). Once again, unlike our study, depression was not adjusted for in this previous research.

Our measurement of anxiety and depressive symptoms in the same

sample represents a significant advantage to our study for two reasons. First, it is well established that anxiety and depressive symptoms commonly co-occur, including in cardiac samples (Frasure-Smith & Lespérance, 2008). Second, there is psychometric evidence that self-report scales of anxiety and depressive symptoms, such as those utilized in this study, assess some common features, representing a potential confound (Karagözoğlu et al., 2005; McWilliams et al., 2001). Results such as those identifying high levels of anxiety to be related to worse brachial artery flow-mediated dilation (Narita, Murata, Hamada, Takahashi, Kosaka, et al., 2007; Narita, Murata, Hamada, Takahashi, Omori, et al., 2007) may have been driven by comorbid and unmeasured depressive symptoms identified by the STAI-T. It is possible that this scale, utilized in these previous two studies, was not differentiating between participants with anxiety independent of depressive symptoms, and comorbid anxiety and depressive symptoms. As our study suggests that these two groups would have opposing relationships with forearm hyperemic reactivity, this represents a significant confound in the previous literature.

The mechanisms of a possible protective effect of anxiety are unclear. Research examining health behaviours in cardiac patients has observed that anxiety has not been as strongly associated with smoking, unhealthy diets, and physical inactivity as depressive symptoms (Benninghoven et al., 2006; Bonnet et al., 2005; Strine, Chapman, Kobau, & Balluz, 2005). Additionally, some evidence has suggested that depression, but not anxiety, is associated

with nonadherence to medication (DiMatteo, Lepper, & Croghan, 2000). Although our study was not designed to examine the mechanisms underlying the association between anxiety and depressive symptoms and brachial artery reactivity, some post-hoc tests were performed to examine the possible role of health behaviours as a mechanism. Leisure time physical activity, smoking status, and body mass index were not associated with anxiety, depressive symptoms, or their interaction. This lack of an association suggests that it is unlikely these health behaviours represent a mechanism to explain this study's primary finding.

Strengths and Limitations

Our study did not directly measure endothelial function, but assessed FHR using a nuclear medicine variation (Dupuis et al., 2004) of the well-established FMD protocol. However, the FMD protocol is recognized and accepted as a popular, valid proxy of endothelial function (Cooper et al., 2011; Corretti et al., 2002; Lekakis et al., 2011; Lerman & Zeiher, 2005). Our FHR variation of this protocol, in particular, is strengthened by its validity, demonstrated by its ability to predict the presence of CAD (Arsenault et al., 2005; Dupuis et al., 2004), as well as its excellent reliability (Meloche, Arsenault, Lavoie, & Bacon, 2005; Veldhuijzen van Zanten et al., 2006).

For the current study we did not define anxiety or depression via cutoff points that are suggestive of clinically important levels. It is believed that this represented a strength for two reasons. First, it recognized and assessed

the effect of anxiety and depressive symptoms in the sub-clinical or non-diagnosable range. Through the process of dichotomization, individuals with sub-clinical levels of depressive symptoms may be incorrectly categorized into a control group with individuals experiencing limited or no depressive symptoms. However, previous research has suggested that even subclinical levels of depressive symptoms may be associated with CVD risk factors (Rubin et al., 2010). Second, it allowed for each of these constructs to be measured continuously, not simply dichotomously, increasing the statistical power of our analyses (Peacock, Sauzet, Ewings, & Kerry, 2012).

Study Implications & Future Directions

Findings from this study imply that higher anxiety, in the presence of lower levels of depressive symptoms, may have a protective effect on brachial artery reactivity, a proxy of endothelial function and a prognostic indicator of cardiovascular health. Future research should attempt to determine whether a protective role of anxiety, absent of depression, is seen in association with other cardiovascular risk factors, and in the prediction of CVD events and mortality. Additional research should examine potential mechanisms, including biological and behavioural routes, which may underlie this relationship. The identification of these mechanisms may have clinical implications, through the identification of positive health behaviours to promote cardiovascular and endothelial health among at-risk individuals, and the general population.

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Table 1: Sociodemographic Data

	n (%) or Mean (SD)
Age	59.17 (9.50)
Sex (male)	222 (75%)
Ethnicity (white)	287 (98%)
Cohabitating (yes)	222 (75%)
Employed (FT or PT)	176 (60%)
Education (≥ 12 years)	193 (65%)

Table 2: Medical & Clinical Characteristics

	Mean (SD) or n (%)
BMI (kg/m^2)	28 (4.4)
Smoker (previous)	171 (58%)
Smoker (current)	29 (10%)
Pack-years	15.9 (19.7)
Resting SBP (mmHg)	129 (18.5)
Resting DBP (mmHg)	74 (9.3)
Hyperlipidemia (yes)	185 (63%)
Hypertension (yes)	182 (62%)
STAI-T score	37.3 (9.4)
BDI score	8.6 (7.6)
Any CAD (yes)	121 (41%)
Previous MI (yes)	68 (23%)
Previous PTCA (yes)	79 (27%)
Previous CABG (yes)	40 (14%)
Previous Stroke (yes)	4 (2%)
Previous CHF	15 (7%)
ACE inhibitors (yes)	77 (26%)
BP lowering meds (yes)	155 (53%)
Statin (yes)	149 (51%)
Anti-depressant meds (yes)	29 (10%)

Table 3: Association between STAI-T and BDI-II scores and RUR

	F	p	Beta (SE)
Main Effects Model			
STAI-T	.02	.886	.0023 (.0162)
BDI	.46	.496	-.0137 (.0201)
Interaction Model			
STAI-T	1.40	.238	.0225 (.0190)
BDI	2.66	.100	.0885 (.0542)
Interaction (STAIxBDI)	4.11	.044	-.0021 (.0010)

Table 4: Association between STAI-T and BDI-II scores and potential mechanisms

	F (p)		
	Smoking Status	Physical Activity	BMI
STAI-T	3.42 (.07)	.76 (.38)	.05 (.83)
BDI	1.02 (.31)	1.23 (.27)	1.58 (.21)
Interaction	3.14 (.08)	.68 (.41)	1.91 (.17)

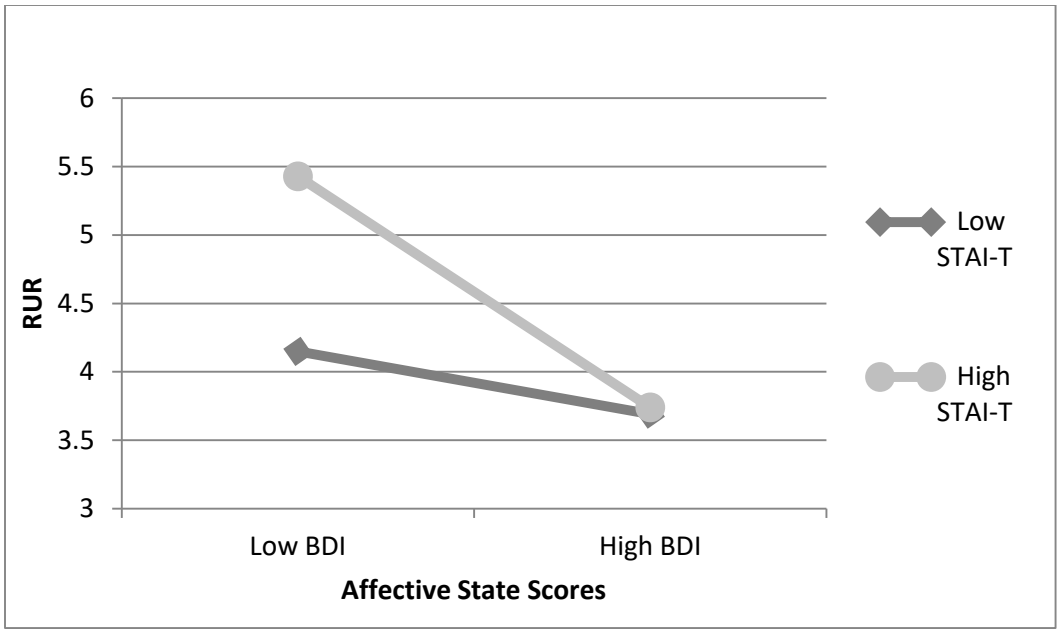

Figure 1: Interaction of upper and lower quartiles of BDI-II and STAI-T symptom scores on RUR.

Transition

An interpretation of the results from this first manuscript must be made in context with a recent paper by Lavoie et al (2010), which analyzed the relationship between depression and endothelial function in the same sample of individuals. In contrast to the first manuscript of this dissertation, which attempted to observe a main effect of depression using a continuous measure of symptoms from a self-report questionnaire, the Lavoie et al (2010) paper utilized a diagnostic interview (the Primary Care Evaluation of Mental Disorders, or PRIME-MD) and assigned patients a dichotomous diagnosis based on mood disorder criteria according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV).

Interestingly, while the first manuscript did not identify a significant main effect of depressive symptoms on brachial artery reactivity, the Lavoie et al (2010) paper utilizing the same sample did identify a main effect of Mood Disorder (MD) on brachial artery reactivity. Patients with a MD had significantly lower brachial artery reactivity than patients without a MD.

Due to this different pattern of results, some conclusions can be inferred based on the two measurement techniques utilized. It seems that the relationship between depression and endothelial function does not operate on a dose-response principle, as a significant relationship was not observed when utilizing a continuous measure of depressive symptoms. Rather, the relationship seems to operate according to a threshold, as the

main effect was observed when utilizing a dichotomous measure of mood disorder diagnosis. It appears that adverse effects on endothelial health do not tend to occur with rising levels of subclinical depressive symptoms, but rather only have a significant negative effect when the patient experiences enough clinically significant symptoms to qualify for a diagnosis of mood disorder.

It is also relevant to note that, in a cardiac sample as was utilized in this study, it is common for symptoms of cardiovascular disease, such as lethargy and low appetite, to appear similar to symptoms of depression. It is possible that the trained graduate students who administered the PRIME-MD diagnostic interview accurately differentiated between symptoms of depression and cardiovascular disease, while the self-report questionnaire of depressive symptoms (Beck Depression Inventory-II) misattributed these cardiac symptoms to depression.

These findings implicate the PRIME-MD diagnostic interview as potentially the more valid and clinically relevant measure of depression to use, when analyzing relationships between depression and cardiovascular processes, such as endothelial function. Future research into the mechanisms of this relationship between depression and endothelial function would be advised to utilize a diagnostic interview delivered by a clinician or other individual trained to appropriate differentiate between symptoms of depression and cardiovascular disease.

Manuscript Two

Exploring pathways between depression and endothelial function: A structural equation modeling approach

Mercer, D. A., Lavoie, K. L., Ditto, B., Arsenault, A., & Bacon, S. L. Exploring pathways between depression and endothelial function: A structural equation modeling approach. (In-preparation).

Abstract

Depression has been associated with impaired endothelial function (EF). Multiple physiological (e.g., inflammation) and behavioural (e.g., physical activity and smoking) factors are hypothesized to underlie this relationship; however the exact pathways are unclear. Using a structural equation modeling approach, pathways between depression and EF were explored in a sample of 328 cardiac outpatients (n=245 men; mean age=60). Patients were administered the PRIME-MD, a brief psychiatric screening interview to assess the presence of a DSM-IV-TR mood disorder (MD). EF was assessed through forearm hyperemic reactivity, a nuclear medicine variation of the flow-mediated dilatation technique, which calculates the rate of uptake ratio between hyperaemic and non-hyperaemic arms. Blood serum samples were collected to assess pro-inflammatory markers and lipids, and patients completed health behavior questionnaires self-reporting physical activity and smoking status. Two well-fitting models indicating pathways between MD and EF were identified. The first model indicated a significant physiological pathway linking presence of mood disorder (γ=.57, $p<.001$) and EF (β=-.34, $p<.001$). The second model showed significant pathways from mood disorder to separate physiological (γ=.34, $p<.05$) and behavioural (γ=-.47, $p<.05$) latent variables, but only the behavioural variable showed a significant pathway to EF (β=.36, $p<.001$). This suggests physiological and behavioural factors provide useful mechanisms to explain the relationship

between MD and EF, however behavioural mechanisms may provide a more direct relationship.

In the past two decades, depression has been well established as an independent risk factor for the development of cardiovascular disease (CVD) (Kubzansky, Kawachi, Weiss, & Sparrow, 1998; Lesperance, Frasure-Smith, Juneau, & Theroux, 2000; Suls & Bunde, 2005). Meta-analyses show the presence of depressive symptoms is associated with a doubling of risk for developing CVD and risk for CVD mortality compared to individuals with low levels of depressive symptoms (Barth, Schumacher, & Herrmann-Lingen, 2004; Rugulies, 2002). Unfortunately, the bio-behavioral mechanisms underlying this relationship remain unclear, though EF may play a role (Cooper et al., 2011; Lerman & Zeiher, 2005).

The endothelium is a dynamic layer of cells lining the vascular walls that regulate many homeostatic processes (Vita & Keaney, 2002). These include the production of vasodilators (e.g., nitrous oxide) and vasoconstrictors (Gonzalez & Selwyn, 2003), and the regulation of blood fluidity and inflammation. Endothelial dysfunction is strongly and independently associated with increased risk of CVD development, (Lerman & Zeiher, 2005; Quyyumi, 2003; Schachinger, Britten, & Zeiher, 2000), as it is considered to reflect a composite of many factors affecting cardiovascular health, such as hyperlipidemia, hypertension, smoking, diabetes, and inflammation (Bonetti, Lerman, & Lerman, 2003; Lekakis et al., 2011).

We have previously shown the presence of major depressive disorder in cardiac outpatients to be associated with poorer brachial artery reactivity,

a proxy measure for EF (Lavoie, Pelletier, Arsenault, Dupuis, & Bacon, 2010). Separate studies have demonstrated impaired EF to be associated with depressive symptoms in CVD patients (Sherwood, Hinderliter, Watkins, Waugh, & Blumenthal, 2005) and major depressive disorder in healthy individuals with no CVD risk factors (Rajagopalan et al., 2001). This inverse association between depressive symptoms and flow mediated dilation, another proxy measure of EF, has been supported by a recent meta-analysis that identified a combined effect size correlation coefficient of $r = 0.19$ ($p = .001$) (Cooper et al., 2011).

EF represents an important marker of cardiac health (Lerman & Zeiher, 2005; Quyyumi, 2003). Studying its relationship with depression may help us better understand why depression is strongly associated with adverse cardiovascular disease outcomes. Two potentially related pathways may be proposed, based on previous literature, to explain this relatively consistent relationship between depression and EF.

The first pathway represents physiological factors influencing endothelial health, such as inflammation and lipid levels. Depression is associated with dysregulated proinflammatory cytokine activation (Joynt, Whellan, & O'Connor, 2003; Musselman, Evans, & Nemeroff, 1998). This is relevant, as proinflammatory processes are a crucial step in the development of atherosclerosis, a chronic disease that leads to a thickening of the artery

wall and a hardening of the endothelium, impairing healthy endothelial functioning (Gonzalez & Selwyn, 2003).

The second pathway represents behavioural factors believed to be associated with endothelial health, including physical activity and smoking (Gordon, Lavoie, Arsenault, Ditto, & Bacon, 2008). Individuals with depression are twice as likely to smoke as those non-depressed (Mendelsohn, 2012) and at risk for decreased levels of physical exercise and the development of a sedentary lifestyle (Roshanaei-Moghaddam, Katon, & Russo, 2009). Though we conceptualize these pathways separately, it is possible that elements overlap, with behavioural factors influencing physiological changes.

This study sought to use a structural equation modeling approach to explore potential mechanisms that may explain this relationship between depression and EF. It was hypothesized that physiological factors, such as proinflammatory processes and hypercholesterolemia, and behavioural factors, such as physical activity and cigarette smoking, may represent potential mechanisms in this relationship. This study attempted to model these pathways using a sample of cardiac outpatients referred for myocardial perfusion imaging.

Materials and Methods

Participants

The current study is a sub-analysis of the cross-sectional mechanisms and longitudinal outcomes of silent myocardial ischemia (MOSMI) study, initiated to assess the relationship between blood pressure and silent myocardial ischemia (Gordon et al., 2012; Pelletier et al., 2011). A total of 906 outpatients referred for a single photon emission computed tomography (SPECT) perfusion exercise stress test in the outpatient nuclear medicine service of the Montreal Heart Institute between May 2005 and December 2006 were recruited. Approximately one-third (n = 328) were recruited for the forearm hyperaemic reactivity (FHR) test. These patients were recruited consecutively from the total sample until three available testing slots per day were filled, due to limited personnel and camera availability. Patients were included if they were at least 18 years of age, and spoke either English or French. Patients were excluded from the MOSMI study if they suffered from a pain disorder other than angina; used a prescription or non-prescription analgesic on the day of exercise testing; used a non-steroidal anti-inflammatory agent (NSAID), coxibs, or anti-neoplastic agent within the last 7 days; were pregnant; had a severe or co-morbid condition and were not expected to survive for 12 months (e.g., cancer); had a history of drug or alcohol abuse; or had a mental condition (determined via self-report and chart review of prescribed medications) rendering the participant unable to understand the nature, scope, and possible consequences of the study. Patients were excluded from the FHR test if they reported having smoked within 6 hours, or eaten within 4 hours, prior to the test. The human ethics

committee of the Montreal Heart Institute approved the protocol (#05-748), and all patients provided written, informed consent prior to participation.

Procedure

Patients presenting for exercise stress testing at the Nuclear Medicine Service of the Montreal Heart Institute were invited to participate. On the first day of the SPECT perfusion imaging testing, patients began with a standard treadmill exercise stress test (modified Bruce protocol) followed by standard SPECT imaging (Anagnostopoulos et al., 2004). Patients underwent a brief, structured psychiatric interview (Primary Care Evaluation of Mental Disorders [PRIME-MD]), and were administered a battery of self-report questionnaires assessing sociodemographic and medical history information which were provided to them after they had completed the exercise stress test. On the following day, patients who had accepted to enter the FHR sub-study had their blood drawn (following fasting) and resting blood pressure taken (using a manual sphygmomanometer) (Tycos-767 series, Welch Allyn, Skaneateles Falls, NY) by an experienced nuclear medicine technician. Patients then completed the FHR test, followed by the rest scan according to the SPECT protocol. Patients were asked to maintain all usual medications, but asked to refrain from taking β blockers due to the SPECT study.

Brachial Artery Reactivity. Reactivity was assessed using a nuclear medicine variation of the well-established flow-mediated dilation protocol (Corretti et al., 2002), a technique developed in our laboratory (Dupuis et al.,

2004). Participants were seated with both arms extended over a large field of view gamma-camera (Seintronix, London, UK) facing upward, hands prone. A blood pressure cuff (Adult First Responders, B&A Instruments, New York, NY) was placed over the right arm, and inflated to 50 mmHg above systolic blood pressure for 5 minutes, creating a hyperemic challenge. Thirty seconds after sudden cuff release, a tracer in the form of technetium-99m-tetrofosmin was injected as a bolus (15.5 MBq/kg) via a small catheter positioned in the bend of the left arm, with the injection trajectory masked using a lead lining between the arm and the tubing. Dynamic imaging of the forearms was taken and sustained for ten minutes, using 128 x 128 matrices at a sampling rate of one frame per second. Comparing activity-time curves over identical regions of interest in the hyperemic right arm and the non-hyperemic control left arm using custom software (SyGeSa, Montreal, Canada) allowed for the derivation of a relative-uptake-ratio (RUR), a unit-less index of maximum rise in activity. A higher ratio reflects greater endothelial reactivity and better EF. This technique has been shown to predict the presence of CAD using a cutoff RUR of 3.55 with a sensitivity of .70 and a specificity of .60 (Arsenault, Bacon, Kavoie, & Meloche, 2005; Dupuis et al., 2004). This technique has shown to have excellent measurement properties, including high test-retest reliability (r=.89) (Meloche, Arsenault, Lavoie, & Bacon, 2005) and very good inter- and intra-rater reliability (r=.98) (Veldhuijzen van Zanten et al., 2006).

Mood Disorder Assessment. The Primary Care Evaluation of Mental Disorders (PRIME-MD) is a brief psychiatric screening instrument based on Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) criteria, initially designed to allow physicians to efficiently diagnose common mental disorders in a primary care setting (Spitzer et al., 1994). The mood disorder module of the structured interview was used to assess the presence of Major Depressive Disorder, Dysthymia, or Minor Depression (Depressive Disorder Not Otherwise Specified). All interviews were administered by clinical psychology graduate students or research associates, systematically trained and verified by licensed clinical psychologists. Previous research has shown high agreement between PRIME-MD and independent mental health professional diagnoses (kappa = 0.71) (Spitzer et al., 1994). Previously published literature with the MOSMI sample have utilized PRIME-MD diagnoses (Lavoie et al., 2010).

Serum Assays. On the second day of the SPECT perfusion image testing, following fasting, serum was drawn. Assays were conducted using the Dimension Vista system with a CardioPhase Flex reagent cartridge (Siemens Healthcare Diagnostics, Newark, Delaware, USA). The high sensitivity C-reactive Protein (CRP) measurement by the system provides an analytical measurement range of 0.016-0.96 mg/dL, for undiluted samples. Samples above 0.95 mg/dL were repeated with increasingly high dilutions to obtain a measurement. Lipid measurements have an analytical measurement range of 1.29-15.54 mmol/l for undiluted samples. Levels of high-density

lipoprotein (HDL), low-density lipoprotein (LDL), and triglycerides (TG) in the serum samples were measured.

Health Behaviours. Questions were adapted from the Physical Activity Recall questionnaire (Sallis et al., 1985) and the Health Practices Index (Berkman, Breslow, & Wingard, 1983). Patients self-reported frequency and duration of regular LTPA over the past year, which was classified as moderate (e.g., brisk walking), high (e.g., doubles tennis), or very-high (e.g., jogging) intensity exercise. This data was converted to metabolic equivalent of task (MET) hours per week. Smoking status was measured by patient self-report, and defined categorically as 0 = non-smoker, 1 = past smoker, and 2 = present smoker.

Statistical Analyses

Two main structural equation models were fitted to examine pathways between presence of a mood disorder, latent variables of interest, and brachial artery reactivity. The first incorporated a latent variable representing physiological measurements of traditional cardiovascular risk factors, with CRP, LDL, HDL, and Triglycerides tested as potential factors loading onto this variable (physiological latent variable). The second model incorporated two latent variables. CRP and total cholesterol were tested to load onto the physiological latent variable in this model, while LTPA and smoking status were tested to load onto the new behavioural latent variable (Gordon et al., 2008). Due to sample size and limited power, one measure of

total cholesterol was used in this model, rather than multiple measures of separate lipids as was used in the first model. This one compositie measure was chosen based on the characteristics and loadings of lipids in the first model.

Acceptable fit statistics for the models to be tested were set a priori, and based on well-accepted values indicated in other literature. Models were assessed using three fit statistics: 1) the Adjusted Goodness of Fit Index (AGFI), with > .9 indicating acceptable fit (Baumgartner & Homburg, 1996); 2) the Standardized Root Mean Square Residual (SRMR), with .08 or less indicating acceptable fit (Hu & Bentler, 1999); and 3) the Root Mean Square Error of Approximation (RMSEA), with .06 or less indicating acceptable fit (Hu & Bentler, 1999). All analyses were performed using SAS v9.3 (SAS Institute, Cary, NC).

Results

Sample characteristics

Demographic details are presented in Table 1. Patients with a mood disorder were significantly younger and less educated than non-depressed patients. In Table 2, Medical & Clinical characteristics are summarized. Patients with a mood disorder had a lower relative uptake ratio, our measure of brachial artery reactivity, than those without a mood disorder. Those with a mood disorder were significantly more likely to be current smokers, and had significantly higher levels of CRP and Triglycerides.

Model 1: Physiological Latent Variable

This model is illustrated in Figure 1. A significant pathway with a positive coefficient was identified between mood disorder and the physiological latent variable, suggesting that having a mood disorder was associated with higher levels of negative physiological markers. A significant pathway with a negative coefficient was identified between the physiological latent variable and brachial artery reactivity, suggesting that higher levels of negative physiological markers were associated with worse brachial artery reactivity. The physiological latent variable contained significant loadings of CRP and Triglycerides. All three fit statistics described earlier indicated acceptable model fit (AGFI = .981; SRMR = .033; RMSEA <.001) (see: Statistical Analyses in Methods & Materials for a priori defined cutoffs).

Model 2: Physiological and Behavioural Latent Variables

This model is illustrated in Figure 2. A significant pathway with a positive coefficient was identified between mood disorder and the physiological latent variable. A significant pathway with a negative coefficient was identified between mood disorder and the behavioural latent variable, suggesting the presence of a mood disorder was associated with lower tendency towards positive health behaviours. With both latent variables in the model, only the behavioural variable had a significant pathway to brachial artery reactivity. This pathway was positive, suggesting that positive health behaviours were associated with better brachial artery

reactivity. The pathway between physiological factors and brachial artery reactivity was no longer significant; though it did retain a negative coefficient as seen in Model 1, but the magnitude of this coefficient was much smaller.

The physiological latent variable contained a significant loading of CRP, and a loading of total Cholesterol that trended towards significance ($p = .05$). The behavioural latent variable contained a significant loading of smoking status; however the loading of leisure time physical activity was not statistically significant.

Two of the fit statistics described earlier indicated acceptable model fit (AGFI = .945; SRMR = .048). However, the RMSEA statistic of .065 bordered on the cutoff set a priori (< .06). Overall, it was determined that this model fit was acceptable.

Additional Models

Additional models were tested, incorporating latent variables that might represent potential confounding variables (i.e., demographic characteristics, previous history of cardiovascular disease status) and additional pathways between the behavioural and physiological latent variables. Each of the additional models either did not converge using our statistical software, or did not satisfy our acceptable model fit statistics. This was likely due to the limited sample size available for these analyses, the complexity of incorporating multiple pathways between up to three latent variables, and the constraints of using some dichotomous manifest variables.

Discussion

In our sample of 328 cardiac patients referred for SPECT exercise stress testing, two models were fit to explain the pathways between depression, as indicated by the presence of mood disorder, and EF, measured using brachial artery reactivity. The use of a structural equation modeling approach to explore the research question offered multiple advantages over a traditional multiple regression approach. It allowed for the examination of composite, inferred variables such as health behaviours and physiological markers of cardiovascular risk. Additionally, it permitted the modeling of a multi-step relationship, elucidating potential mechanisms at play in the relationship between depression and EF.

Our first model showed significant pathways from mood disorders to the physiological CVD risk factor latent variable and from the physiological latent variable to brachial artery reactivity. This physiological latent variable contained significant loadings of CRP and Triglycerides. This is consistent with theories that posit proinflammatory processes, identified through the presence of markers such as CRP, may be a mechanism to explain the relationship between depression and EF (Joynt, Whellan, & O'Connor, 2003; Musselman, Evans, & Nemeroff, 1998, Gonzalez & Selwyn, 2003).

According to this theory, depression would lead to dysregulated psychoneuroimmunological functioning, including chronic elevations of proinflammatory processes. This relationship has been well established in

previous literature (Dowlati et al., 2010). Inflammation then initiates the atherosclerotic process, as monocyte white blood cells are attracted to the endothelium and ingest cholesterol and triglycerides to create foam cells, the building blocks of the plaque buildup characteristic of atherosclerosis. This narrowing of the arteries and hardening of the endothelium produces impairment of EF, and heightens the risk of future adverse cardiovascular disease events (Lerman & Zeiher, 2005).

Our second model incorporated both physiological and behavioural latent variables. There were significant pathways linking mood disorders to both latent variables, however only the behavioural latent variable then showed a significant pathway to brachial artery reactivity. The magnitude of the coefficent for the pathway between the physiological latent variable and brachial artery reactivity was of a smaller magnitude, as compared with the same pathway in Model 1. This decrease in magnitude, combined with the presence of a significant pathway incorporating the behavioural latent variable, could suggest that behavioural factors have a more salient pathway to endothelial health, or may offer a more direct ability to predict endothelial functioning, than the physiological latent variable utilized in this model.

The physiological latent variable contained significant loadings of CRP, and a marginally significant loading of total cholesterol. The behavioural latent variable contained a signficant loading of smoking status, however leisure time physical activity did not significant load onto the latent variable.

This is consistent with previous literature showing individuals with depression to be more likely to smoke than those non-depressed (Mendelsohn, 2012), and the well established relationship between cigarette usage and cardiovascular disease (Ockene & Miller, 1997).

It is unlikely that these models represent the only important pathways between depression and EF. Indeed, the generalizability of these results should be tempered by the recognition that these models do not incorporate common covariates often employed when studying these relationships, such as age, sex, and previous history of cardiovascular disease (Mercer et al., 2014). Due to limited sample size and power, the complexity of models able to be constructed using this data set was constrained, and no models incorporating additional demographic or medical history data were able to be acceptably fit. However, in spite of these caveats, these models do suggest the presence of a physiological mechanism centered on proinflammatory processes, and a behavioural mechanism centered on smoking, that may provide some utility in explaining the relationship between depression and EF, and the broader link between depression and cardiovascular health.

Strengths and Limitations

The use of a proxy measure of EF should be acknowledged as a potential limitation. Our study did not directly measure EF, but assessed FHR using a nuclear medicine variation (Dupuis et al., 2004) of the well-established FMD protocol. However, the FMD protocol is recognized and

accepted as a popular, valid proxy of EF (Cooper et al., 2011; Corretti et al., 2002; Lekakis et al., 2011; Lerman & Zeiher, 2005). Our FHR variation of this protocol, in particular, is strengthened by its validity, demonstrated by its ability to predict the presence of CAD (Arsenault et al., 2005; Dupuis et al., 2004), as well as its excellent reliability (Meloche et al., 2005; Veldhuijzen van Zanten et al., 2006).

The use of cross-sectional data must also be recognized as a limitation, as the pathways constructed in these models imply a directionality that may not be present. However, the use of longitudinal data would not necessarily satisfy this requirement for directionality, as many of the processes discussed (mood disorders, pro-inflammatory processes, EF impaired by atherosclerosis) represent chronic, long-term impairments. Even a longitudinal design would not necessarily allow for the identification of an accurate date of onset for these disorders, or length of time required for their effects to manifest (MacCallum & Austin, 2000). While bi-directional pathways could have alleviated this concern, limitations on the complexity of models, due to sample size and power, meant that bi-directional pathways could not be incorporated into these models while retaining acceptable fit parameters.

Study Implications & Future Directions

These findings represent an initial step in observing and modeling mechanisms to explain the relationship between depression and EF. Future

research should build on these initial findings in two specific ways. First, research should attempt to replicate these findings using data sets with larger sample sizes, which would allow for the inclusion of more complex pathways (such as bidirectional pathways, additional latent variables, and pathways between the latent variables). Second, these findings should be extended to additional adverse cardiovascular disease outcomes, in order to establish if EF is a useful mediator of the relationship between depression and cardiovascular disease, and to identify additional pathways in greater connection between depression and cardiovascular health.

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Table 1: Sociodemographic Data by Mood Disorder (MD)

	n (%) or Mean (SD)		F or χ^2	p
	No MD (n=273)	MD (n=52)		
Age	60.09 (9.16)	56.50 (10.68)	6.24	.01
Sex (male)	206 (75%)	37 (71%)	.43	.51
Ethnicity (white)	255 (96%)	46 (98%)	2.21	.70
Cohabitating (yes)	202 (76%)	36 (77%)	.01	.92
Employed (FT or PT)	154 (58%)	33 (70%)	2.35	.13
Years of Education	13.74 (4.26)	12.24 (3.88)	4.51	.03

Table 2: Medical & Clinical Characteristics by Mood Disorder (MD)

	Mean (SD) or n (%)		F or χ^2	p
	No MD (n=273)	MD (n=52)		
Relative-uptake-ratio	4.23 (1.75)	3.39 (1.34)	10.8	.001
Smoker (previous)	158 (58%)	28 (56%)	7.57	.02
Smoker (current)	25 (9%)	11 (22%)		
Leisure-time physical activity (MET hours/week)	6.74 (19.67)	5.26 (12.84)	.27	.60
BMI (kg/m^2)	28 (4.5)	29 (4.2)	3.81	.05
Resting SBP (mmHg)	129 (19.1)	127 (21.3)	.43	.51
Resting DBP (mmHg)	74 (9.8)	74 (7.9)	.00	.97
C-reactive Protein (mg/L)	1.97 (2.30)	3.13 (3.61)	8.02	.01
HDL (mmol/L)	1.69 (6.69)	1.18 (.36)	.28	.59
LDL (mmol/L)	2.53 (0.93)	2.62 (.80)	.44	.51
Triglycerides (mmol/L)	1.44 (0.87)	1.74 (.89)	4.96	.03
Any CAD (yes)	106 (39%)	22 (42%)	.20	.65
Previous MI (yes)	62 (23%)	11 (21%)	.07	.80
Previous PTCA (yes)	68 (25%)	15 (29%)	.32	.57
Previous CABG (yes)	36 (13%)	8 (15%)	.16	.69
Previous Stroke (yes)	3 (1%)	2 (5%)	2.43	.12
Previous CHF (yes)	14 (7%)	3 (8%)	.09	.77
BP lowering meds (yes)	142 (53%)	24 (47%)	.64	.42
Statin (yes)	132 (49%)	25 (49%)	.003	.96
Anti-depressants (yes)	21 (8%)	8 (17%)	3.88	.05

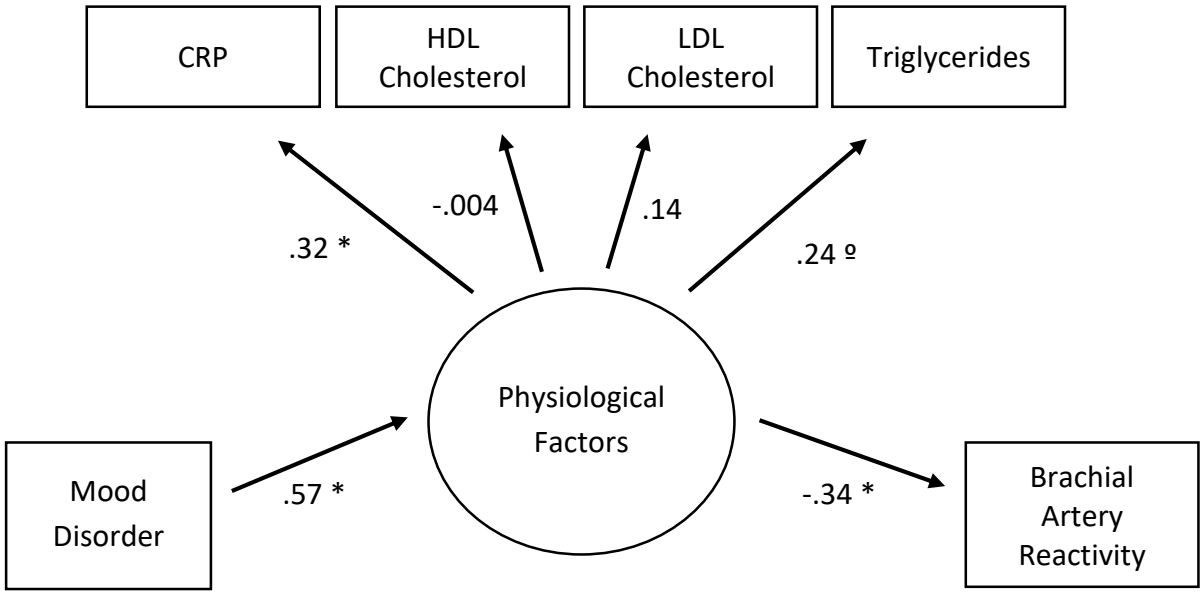

Figure 1. Structural equation model including physiological factors, with parameter estimates indicated. Square boxes indicate manifest variables, circles represent latent variables. * indicates significance at *<.001*; º indicates significance at *<.01*.

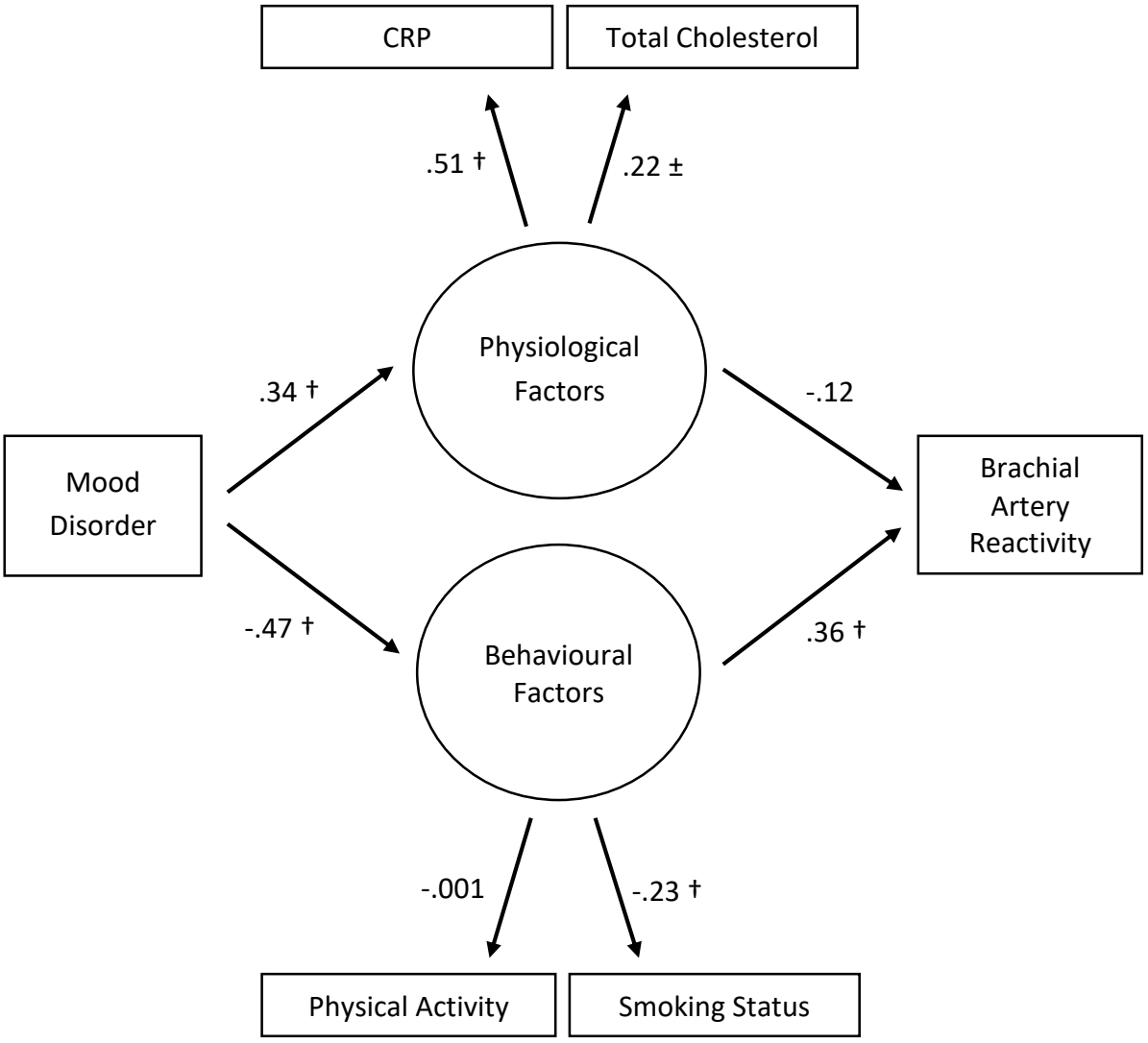

Figure 2. Structural equation model including physiological and behavioural factors, with parameter estimates indicated. Square boxes indicate manifest variables, circles represent latent variables. † indicates significance at *<.05*; ± indicates significance *=.05*.

Transition

The second manuscript extended upon previous research by identifying not only relationships between depression and endothelial function, but by modeling bio-behavioural pathways that may explain the underlying mechanisms for this relationship. Salient pathways relying on behavioural and physiological risk factors for cardiovascular disease were identified to link depression and endothelial function, however the second manuscript provided no longitudinal data, or evidence that impaired endothelial function predicts adverse cardiac events.

The third manuscript aimed to address these two limitations by utilizing follow-up data collected six years after the baseline data that has been used in the first and second manuscript. This longitudinal data was used to assess if endothelial function was able to mediate a relationship between depression at baseline, and incidence of a major adverse cardiac event over a six-year time period.

Manuscript Three

The interaction between anxiety and depressive symptoms on brachial artery reactivity in cardiac patients

Mercer, D. A., Lavoie, K. L., Ditto, B., Arsenault, A., & Bacon, S. L. Exploring pathways between depression and endothelial function: A structural equation modeling approach. (In-preparation).

Abstract

Depression independently predicts increased risk of developing cardiovascular disease (CVD). However, mediators of the relationship are unclear. Endothelial function represents a sensitive marker of cardiac health which is known to be impaired in depressed individuals. This study assessed if endothelial function would mediate an indirect relationship between depression and adverse cardiac outcomes over a period of six years in a sample of 204 cardiac outpatients. Patients were administered the PRIME-MD, a brief psychiatric screening interview to assess the presence of a DSM-IV-TR mood disorder (MD). Endothelial function was assessed through forearm hyperemic reactivity, a nuclear medicine variation of the flow-mediated dilatation technique. Medical history was assessed at baseline and six years following, using a combination of structured interview and self-report. Endothelial function did not mediate a relationship between MD and a composite index of any coronary artery disease event (.18, 95% CI [-.06, .54]), however it did mediate a relationship between MD and coronary artery bypass graft surgery (1.68, 95% CI [.16, 6.22]), after adjusting for age, sex, years of education, and history of cardiac disease at baseline. Conclusions drawn from this data should be tempered, due to the small sample size and low rate of cardiac events over the six-year period of study. However, one can speculate that endothelial function may mediate relationships between depression and some major adverse cardiac events. Future research should

replicate these methods with larger sample sizes and explore potential mechanisms.

Depression has been well established as an independent risk factor for the development of cardiovascular disease (CVD) (Cohen, Edmondson, & Kronish, 2015; Hare, Toukhsati, Johansson, & Jaarsma, 2014; Kubzansky, Kawachi, Weiss, & Sparrow, 1998; Lesperance, Frasure-Smith, Juneau, & Theroux, 2000; Seldenrijk et al., 2015; Suls & Bunde, 2005). Those with increased depressive symptoms have been shown to have double the risk for developing CVD and CVD mortality compared to individuals with low levels of depressive symptoms, according to meta-analyses (Barth, Schumacher, & Herrmann-Lingen, 2004; Rugulies, 2002).

While this relationship is strong and relatively consistent, potential mediators are still in the process of being identified. Endothelial function is consistently associated with both cardiac health outcomes (Lerman & Zeiher, 2005; Park & Park, 2015; Quyyumi, 2003) and depressive symptomatology (Cooper et al., 2011; van Dooren et al., 2016). This raises the possibility that endothelial function may represent a useful mediator for understanding this relationship between depression and CVD (Barth et al., 2004; Hare et al., 2014; Rugulies, 2002).

The endothelium is a dynamic layer of cells lining the vascular walls that regulate many homeostatic processes (Vita & Keaney, 2002), such as the production of vasodilators and vasoconstrictors, inflammation, and the regulation of blood fluidity (Gonzalez & Selwyn, 2003). The endothelium is impaired by diseases such as atherosclerosis, a fibro-fatty plaque

development that leads to a thickening of the artery wall and a hardening of the endothelium, impairing healthy endothelial functioning (Gonzalez & Selwyn, 2003). Endothelial health is susceptible to multiple bio-behavioural processes, such as hyperlipidemia, hypertension, smoking, diabetes, and inflammation. Due to this, it is considered to reflect a composite of many factors affecting cardiovascular health (e.g.,) (Bonetti, Lerman, & Lerman, 2003; Lekakis et al., 2011; Park & Park, 2015).

Multiple studies have demonstrated impaired endothelial function to be associated with mood disorders or depressive symptoms in cardiac patients (Lavoie, Pelletier, Arsenault, Dupuis, & Bacon, 2010; Sherwood, Hinderliter, Watkins, Waugh, & Blumenthal, 2005) and major depressive disorder in healthy individuals with no CVD risk factors (Rajagopalan et al., 2001). This is confirmed by a recent meta-analysis of 12 studies that identified a combined effect size correlation coefficient of $r = 0.19$ ($p = .001$) between depressive symptoms and flow mediated dilation, another proxy measure of endothelial function (Cooper et al., 2011).

This relationship may be due to depression's association with dysregulated proinflammatory processes, a crucial step in the development of atherosclerosis (Joynt, Whellan, & O'Connor, 2003; Musselman, Evans, & Nemeroff, 1998). It may also involve the connection between depression and negative health behaviours that represent traditional risk factors for CVD. For example, depressed individuals show higher rates of smoking

(Mendelsohn, 2012), lower levels of physical exercise, and a more sedentary lifestyle (Roshanaei-Moghaddam, Katon, & Russo, 2009) than non-depressed individuals.

Endothelial dysfunction has been shown to be associated with adverse cardiovascular events, including myocardial infarction, need for revascularization, and cardiac-related mortality (Quyyumi, 2003; Schachinger, Britten, & Zeiher, 2000). Dysfunction of both coronary and peripheral endothelium have similar predictive power, even in cases where the coronary event occurs remotely from the peripheral site where dysfunction was initially detected (Lerman & Zeiher, 2005), suggesting endothelial function may be a sensitive marker of cardiac health.

This study sought to use a mediation analyses to explore whether endothelial function would mediate a relationship between depression and adverse coronary artery disease (CAD) outcomes over a six-year period, including myocardial infarction and need for revascularization through percutaneous coronary intervention or coronary artery bypass graft surgery. It was hypothesized that the mediation models would show significant indirect pathways between depression and adverse CAD outcomes through endothelial function.

Materials and Methods

Participants

The current study is a sub-analysis of the Cross-sectional Mechanisms and Longitudinal Outcomes of Silent Myocardial Ischemia (MOSMI) study, originally designed to examine the relationship between blood pressure and silent myocardial ischemia (Gordon et al., 2012; Pelletier et al., 2011). A total of 906 outpatients referred for a single photon emission computed tomography (SPECT) perfusion exercise stress test in the outpatient nuclear medicine service of the Montreal Heart Institute between May 2005 and December 2006 were recruited. Approximately one-third (n = 328) were recruited for the forearm hyperaemic reactivity (FHR) test. These patients were recruited consecutively from the total sample until three available testing slots per day were filled, due to limited personnel and camera availability. At a six-year follow-up, 204 of the initial 328 patients were successfully contacted by telephone and completed the follow-up procedure.

Patients were included if they were at least 18 years of age, and spoke either English or French. Patients were excluded from the MOSMI study if they suffered from a pain disorder other than angina; used a prescription or non-prescription analgesic on the day of exercise testing; used a non-steroidal anti-inflammatory agent (NSAID), coxibs, or anti-neoplastic agent within the last 7 days; were pregnant; had a severe or co-morbid condition and were not expected to survive for 12 months (e.g., cancer); had a history of drug or alcohol abuse; or had a mental condition (determined via self-report and chart review of prescribed medications) rendering the participant unable to understand the nature, scope, and possible consequences of the

study. Patients were excluded from the FHR test if they reported having smoked within 6 hours, or eaten within 4 hours, prior to the test. The human ethics committee of the Montreal Heart Institute approved the protocol (#05-748), and all patients provided written, informed consent prior to participation.

Procedure

Patients presenting for exercise stress testing at the Nuclear Medicine Service of the Montreal Heart Institute were invited to participate. On the first day of the SPECT perfusion imaging testing, patients began with a standard treadmill exercise stress test (modified Bruce protocol) followed by standard SPECT imaging (Anagnostopoulos et al., 2004). Patients underwent a brief, structured psychiatric interview (Primary Care Evaluation of Mental Disorders [PRIME-MD]), and were administered a battery of self-report questionnaires assessing sociodemographic and medical history information which were provided to them after they had completed the exercise stress test. On the following day, patients who had accepted to enter the FHR sub-study had their blood drawn (following fasting) and resting blood pressure taken (using a manual sphygmomanometer) (Tycos-767 series, Welch Allyn, Skaneateles Falls, NY) by an experienced nuclear medicine technician. Patients then completed the FHR test, followed by the rest scan according to the SPECT protocol. Patients were asked to maintain all usual medications, but asked to refrain from taking β blockers due to the SPECT study.

Six years following baseline, patients were contacted by telephone using either the most recent telephone number available in MOSMI study records, or using the most recent telephone number listed in the Montreal Heart Institute's administrative database. During a structured telephone interview with a trained research associate or graduate student, patients were asked about cardiac and other medical events that had occurred over the past six years, in addition to other psychological and sociodemographic questions. Patients were also asked to complete and return a package of supplementary questions that would be sent by mail.

Brachial Artery Reactivity. Reactivity was assessed using a nuclear medicine variation of the well-established flow-mediated dilation protocol (Corretti et al., 2002), a technique developed in our laboratory (Dupuis et al., 2004). Participants were seated with both arms extended over a large field of view gamma-camera (Seintronix, London, UK) facing upward, hands prone. A blood pressure cuff (Adult First Responders, B&A Instruments, New York, NY) was placed over the right arm, and inflated to 50 mmHg above systolic blood pressure for 5 minutes, creating a hyperemic challenge. Thirty seconds after sudden cuff release, a tracer in the form of technetium-99m-tetrofosmin was injected as a bolus (15.5 MBq/kg) via a small catheter positioned in the bend of the left arm, with the injection trajectory masked using a lead lining between the arm and the tubing. Dynamic imaging of the forearms was taken and sustained for ten minutes, using 128 x 128 matrices at a sampling rate of one frame per second. Comparing activity-time curves over identical regions

of interest in the hyperemic right arm and the non-hyperemic control left arm using custom software (SyGeSa, Montreal, Canada) allowed for the derivation of a relative-uptake-ratio (RUR), a unit-less index of maximum rise in activity. A higher ratio reflects greater endothelial reactivity and better endothelial function. This technique has been shown to predict the presence of CAD using a cutoff RUR of 3.55 with a sensitivity of .70 and a specificity of .60 (Arsenault, Bacon, Lavoie, & Meloche, 2005; Dupuis et al., 2004). This technique has shown to have excellent measurement properties, including high test-retest reliability (r=.89) (Meloche, Arsenault, Lavoie, & Bacon, 2005) and very good inter- and intra-rater reliability (r=.98) (Veldhuijzen van Zanten et al., 2006).

Mood Disorder Assessment. The Primary Care Evaluation of Mental Disorders (PRIME-MD) is a brief psychiatric screening instrument based on Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) criteria, initially designed to allow physicians to efficiently diagnose common mental disorders in a primary care setting (Spitzer et al., 1994). The mood disorder module of the structured interview was used to assess the presence of Major Depressive Disorder, Dysthymia, or Minor Depression (Depressive Disorder Not Otherwise Specified). All interviews were administered by clinical psychology graduate students or research associates, systematically trained and verified by licensed clinical psychologists. Previously

published literature with the MOSMI sample have utilized PRIME-MD diagnoses (Lavoie et al., 2010).

Cardiac Outcomes. At baseline, medical history was assessed using a structured interview and self-report questionnaire, both developed in-lab. Patients were asked to self-report any previous history of a various cardiac and non-cardiac diseases, medical procedures, and risk factors (such as number and date of most recent episode of myocardial ischemia, coronary artery bypass graft surgery, or diagnosis of hyperlipidemia). Data self-reported by the patients were verified through chart review by a research assistant. At the year-six follow-up, the same structured interview and self-report questionnaire were used to identify new events, diagnoses, and other changes in health status over the previous six years.

Three cardiac events of interest were identified in this sample: an episode of myocardial infarction (MI), a percutaneous coronary intervention with or without a stent (PCI), and a coronary artery bypass graft surgery (CABG). A dichotomous composite outcome variable was created to represent the presence of either of these three events over the six years of this study.

Statistical Analyses

Four mediation analyses were constructed, using the PROCESS framework and macro (Hayes, 2013) with SAS v9.4 (SAS Institute, Cary, NC).

In these regression models, the total effect of an independent variable (X) on a dependent variable (Y) is represented by a direct effect (c') of X on Y, and an indirect effect of X on Y through a Mediator (M). This indirect effect is the product of the effect of X on M (a) and of M on Y (b). All coefficients are the result of bias corrected 95% confidence intervals, resampled from 5000 bootstrap samples. A coefficient is significant at $p<.05$ if this 95% confidence interval does not cross zero.

These models are summarized in Figures 1, 2, 3, and 4. Each analysis included presence of mood disorder (MD) as an independent variable, and endothelial function, assessed through RUR, as a mediator. The first analysis utilized the composite variable representing any CAD event of interest over the past six years as a dependent variable. The next three analyses individually examined MI, PCI, and CABG outcomes as dependent variables. Each of these latter three models were adjusted for age, sex, years of education, history of CAD at baseline, presence of ischemia during the exercise stress test, and use of anti-depressant medication.

Results

Sample characteristics

Table 1 summarizes sociodemographic details. Patients with a mood disorder (MD) were significantly younger than those without a MD ($p=.04$). The mean years of education was also lower for patients with a MD; however,

this difference was not statistically significant (p=.08). In Table 2, Medical & Clinical characteristics are summarized. Patients with a MD had a lower relative uptake ratio, our measure of brachial artery reactivity, than those without a MD (p=.001). Those with a MD also had significantly higher levels of c-reactive protein (p=.001) and triglycerides (p=.03).

At baseline, 46% of the sample had a history of CAD, however there was no difference between patients with or without MD (p=.26). 16% of patients without a MD and 26% of patients with a MD experienced a CAD event in the six years after recruitment, with approximately 5% of the sample experiencing a MI, 3% undergoing a CABG, and 13% undergoing a PCI.

Model 1: Any Coronary Artery Disease outcome

This mediational model is illustrated in Figure 1. A significant a_i effect (-1.12) was identified between presence of a MD and lower RUR, 95% CI [-1.74, -.49], however the b_i effect (-.16) between RUR and CAD outcome was not significant as the confidence interval crossed zero, 95% CI [-.41, .08]. The indirect effect (.18), representing the degree to which RUR mediates a relationship between MD and CAD, was also non-significant, 95% CI [-.06, .54].

Model 2: Coronary Artery Bypass Graft Surgery events

This mediational model is illustrated in Figure 2. A significant a_i effect (-1.08) was identified between presence of a MD and lower RUR, 95% CI [-

1.77, -.39]. A significant b_i effect (-1.72) was also identified between lower RUR and increased likelihood of CABG surgery, 95% CI [-3.39, -.07]. Additionally, the indirect effect (1.87) was significant, 95% CI [.13, 6.15], suggesting that RUR does mediate a relationship between MD and CABG surgery. The c_i effect (-.53) directly between MD and CABG was not significant, 95% CI [-3.28, 2.21].

Model 3: Percutaneous Coronary Intervention events

This mediational model is illustrated in Figure 3. A significant a_i effect (-1.10) was identified between presence of a MD and lower RUR, 95% CI [-1.79, -.41], however the b_i effect (-.04) between RUR and PCI events was not significant as the confidence interval crossed zero, 95% CI [-.37, .28]. The indirect effect (.05), representing the degree to which RUR mediates a relationship between MD and PCI, was also non-significant, 95% CI [-.35, .50].

Model 4: Myocardial Ischemia episodes

This mediational model is illustrated in Figure 4. A significant a_i effect (-1.09) was identified between presence of a MD and lower RUR, 95% CI [-1.77, -.40], however the b_i effect (.12) between RUR and MI episodes was not significant as the confidence interval crossed zero, 95% CI [-.31, .55]. The indirect effect (-.13), representing the degree to which RUR mediates a relationship between MD and MI, was also non-significant, 95% CI [-.90, .60].

Discussion

This study examined whether endothelial function could mediate a longitudinal relationship between depression and adverse CAD outcomes over a period of six years, with a sample of 204 cardiac outpatients referred for SPECT exercise stress testing.

Endothelial function, as measured through brachial artery reactivity, did not significantly mediate a relationship between MD and a composite index of CAD outcomes (presence of either a CABG, PCI, or MI event). However, when examining these outcomes individually in separate models, a significant relationship was observed for CABG. Significant relationships were observed between: 1/ presence of MD and lower RUR, and 2/ lower RUR and increased likelihood of CABG surgery. The indirect effect along this mediational pathway was additionally significant, indicating that endothelial function did significantly mediate a relationship between MD and CABG. This finding logically expands upon previous research that has found depression to be associated with impaired endothelial function (Lavoie et al., 2010; Rybakowski, Wykretowicz, Heymann-Szlachcinska, & Wysocki, 2006), and the well-established literature demonstrating endothelial function to be a predictor of cardiac events (Lerman & Zeiher, 2005; Quyyumi, 2003).

While there was a significant indirect effect of MD on CABG, along the RUR mediational pathway, there was no significant direct effect of MD on CABG. While this is unexpected, as previous research has shown associations

of depression with CVD outcomes, this study was impaired by a low base rate of CABG events, which would have lowered the statistical power of this test to observe a significant direct effect. Despite the lack of a significant direct effect, this does not negate the observation of a significant indirect effect (Hayes, 2013). The direct effect represents a composite of all indirect effects of MD on CABG event. This includes both indirect effects that may increase the likelihood of a CABG surgery, such as impaired RUR, and effects that may decrease the likelihood of CABG surgery, such as the social inhibitory features of depression that may decrease an individual's likelihood to seek treatment. While these indirect effects may be significant, their composite effect may feature positive and negative indirect effects cancelling each other out, to result in an insignificant, small direct effect.

Endothelial function was not found to significantly mediate relationships between MD and PCI or MI. This contrast with the CABG findings is surprising, particularly given that PCI and CABG both represent treatment modalities for revascularization of arteries with impaired blood flow (perfusion). In explaining these contradictory findings, it may be useful to compare the differences in clinical characteristics of patients who are usually recommended for PCI vs CABG treatments. While both PCI and CABG offer alternative approaches for revascularization, PCI offers a more rapid, less invasive procedure. This generally makes PCI the preferred alternative for less complex patients with fewer blockages. In contrast, CABG is recommended for patients with complex cases, multivessel blockages, and in

cases where complete revascularization is required (Deb et al., 2013; Sorana, Manchandab, & Schuelerc, 2009).

It is possible to suggest that endothelial function only mediated a relationship between MD and CAD outcomes in patients with severe, complex blockages who required the more invasive CABG revascularization procedure. It is possible that comorbid depression contributed to this increased severity of blockages. There is overlap among traditional symptoms of depression (APA, 2013) and CAD, such as lethargy, poor appetite, and poor sleep, leading to a difficulty primary care physicians may face when attempting to identify symptoms of CAD in patients with comorbid depression (Mitchell & Harvey, 2014). Depressed patients may have been less likely to have their blockages identified at an earlier point where a PCI would have been a viable intervention. Depressed patients also have lower troponin I levels and a lower likelihood of having an abnormal left ventricular ejection fraction (Pelletier et al., 2014), suggesting some traditional measurements of abnormal cardiac function may be less sensitive in identifying at-risk patients with comorbid depression. Finally, depression is associated with less medication adherence (DiMatteo, Lepper, & Croghan, 2000; Lin et al., 2004), which may increase the severity of blockages even in those who are receiving pharmaceutical treatment.

The contrasting findings between CABG and MI, for the role of endothelial function as a mediator, are less surprising. A revascularization

procedure, such as a CABG, is the direct result of atherosclerosis, the disease process which leads to the formation of blockages. Atherosclerosis is stimulated by the endothelium, which initiates the inflammatory response that leads to the development of a fat-streaked plaque. This plaque buildup also causes damage to the endothelium, impairing healthy endothelial function (Ruparelia, Chai, Fisher, & Choudhury, 2017). Due to these multiple physiological processes that link endothelial function to atherosclerosis, it is logical that endothelial function would mediate a relationship between depression and a cardiac procedure needed due to chronic atherosclerosis, such as CABG.

However, the pathophysiological processes that lead to MI are not the same. Although atherosclerosis contributes to the process of experiencing a MI, atherosclerosis is not the direct cause. Unlike the conditions that would necessitate a CABG procedure, a MI is often the result of a rupture of an unstable fibrous cap. This is a dynamic unplanned event, unlike CABG which requires a physician to investigate and identify necessary factors. Due to the more indirect role endothelial function and atherosclerosis play in this process, it is understandable why endothelial function did not mediate a relationship between depression and MI event.

Strengths and Limitations

The low event rate of the CAD outcomes of interest studied in this paper represents a limitation, particularly for CABG as only approximately

3% of this sample required the procedure over the follow-up. Indeed, only one patient in the MD group and four in the non-MD group received a CABG surgery. Replication in a sample with a higher event rate would be required to increase confidence in these results.

Study Implications & Future Directions

These early findings provide some speculation that endothelial function may mediate relationships between depression and cardiac outcomes, particularly severe outcomes such as the need for CABG surgery. While intriguing, particularly due to the longitudinal nature of this study, these should be viewed as preliminary findings that future investigations may build upon. Particularly, it would be important to replicate these findings using more objective measures of cardiac outcomes that do not rely on self-report. Additionally, due to the relatively low rate of occurrence of some of these cardiac events, it would be useful to replicate this study over a longer timespan or in a larger cohort, in order to capture a greater number of adverse cardiovascular outcomes.

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Table 1: Sociodemographic Data by Mood Disorder (MD)

	n (%) or Mean (SD)		F or χ^2	p
	No MD (n=173)	MD (n=31)		
Baseline Measures				
Age	60.53 (8.44)	57.02 (9.62)	4.35	.04
Sex (male)	131 (76%)	21 (68%)	.88	.35
Ethnicity (white)	166 (98%)	28 (97%)	2.53	.64
Cohabitating (yes)	128 (75%)	22 (76%)	.01	.95
Employed (FT or PT)	95 (56%)	21 (72%)	2.68	.10
Years of Education	13.69 (3.97)	12.23 (3.83)	3.08	.08

Table 2: Medical & Clinical Characteristics by Mood Disorder (MD)

	Mean (SD) or n (%)		F or χ^2	p
	No MD (n=173)	MD (n=31)		
Baseline Measures				
Relative-uptake-ratio	4.24 (1.68)	3.12 (1.22)	12.45	.001
Previous CAD (yes)	76 (44%)	17 (55%)	1.26	.26
Resting SBP (mmHg)	129 (17.9)	129 (21.5)	.00	.97
Resting DBP (mmHg)	74 (9.5)	74 (8.2)	.01	.94
C-reactive Protein (mg/L)	1.86 (2.23)	3.73 (4.26)	12.12	.001
HDL (mmol/L)	1.29 (.44)	1.18 (.42)	1.59	.21
LDL (mmol/L)	2.50 (.92)	2.66 (.94)	.76	.38
Triglycerides (mmol/L)	1.36 (0.68)	1.70 (1.05)	4.96	.03
BMI (kg/m^2)	27 (4.3)	29 (4.3)	3.04	.08
BP lowering meds (yes)	93 (55%)	15 (50%)	.26	.61
Statin (yes)	91 (54%)	14 (47%)	.53	.47
Anti-depressants (yes)	13 (8%)	5 (17%)	2.69	.10
Outcome Measures at Year 6				
Any CAD (yes)	27 (16%)	8 (26%)	1.92	.17
MI (yes)	9 (5%)	2 (6%)	.06	.80
CABG (yes)	4 (2%)	1 (3%)	.09	.77
PCI (yes)	19 (11%)	7 (23%)	3.18	.07

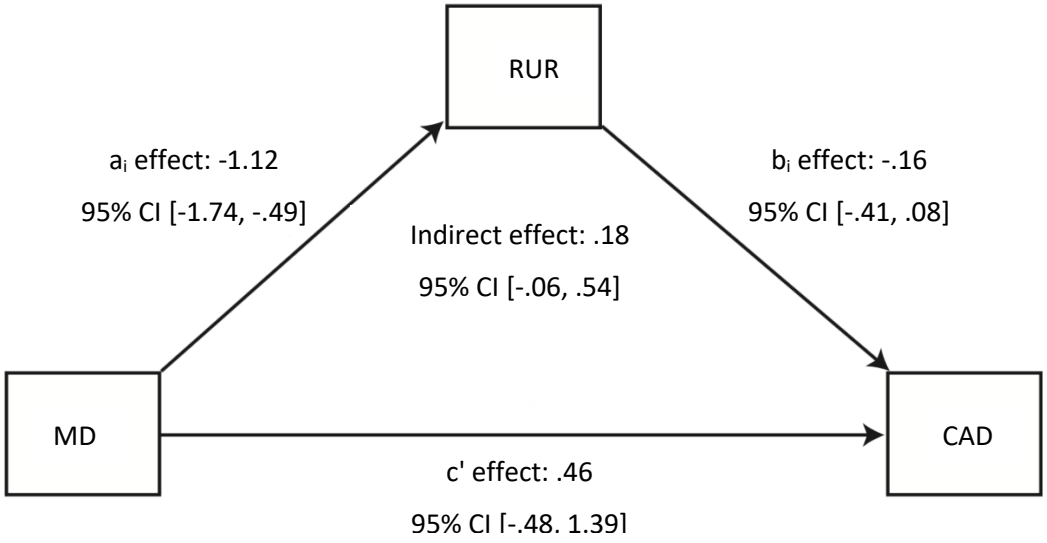

Figure 1. Mediational model for the indirect effect of mood disorder (MD) on any coronary artery disease (CAD) event through brachial artery reactivity (RUR).

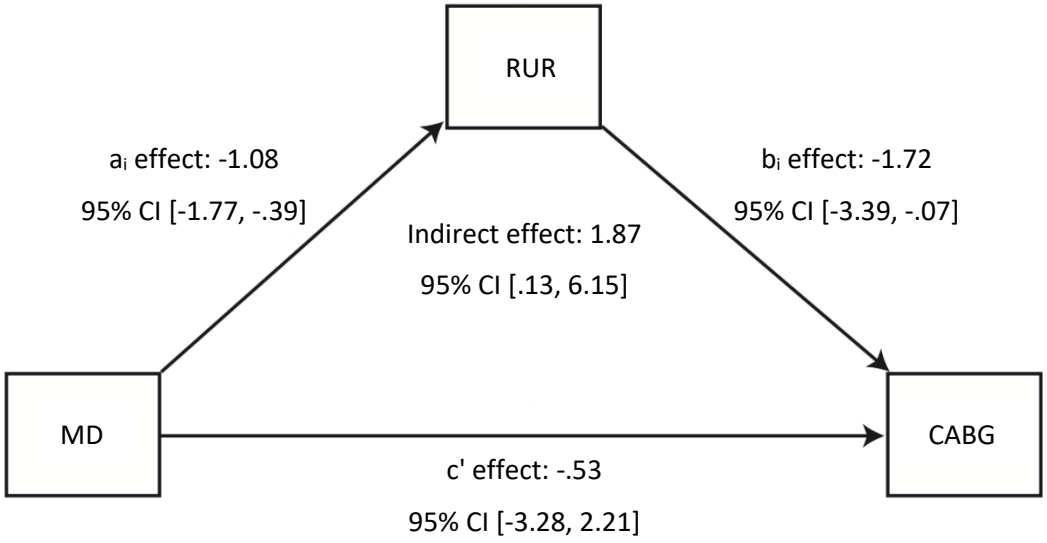

Figure 2. Mediational model for the indirect effect of mood disorder (MD) on a coronary artery bypass graft surgery (CABG) event through brachial artery reactivity (RUR). Model adjusted for age, sex, years of education, history of CAD at baseline, presence of ischemia during the exercise stress test, and use of anti-depressant medication.

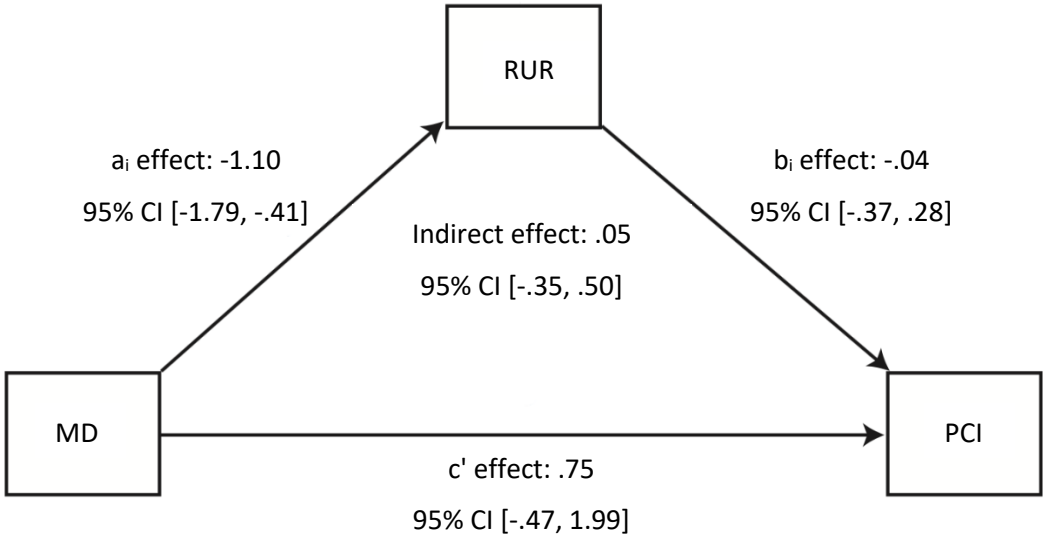

Figure 3. Mediational model for the indirect effect of mood disorder (MD) on a a percutaneous coronary intervention (PCI) event through brachial artery reactivity (RUR). Model adjusted for age, sex, years of education, history of CAD at baseline, presence of ischemia during the exercise stress test, and use of anti-depressant medication.

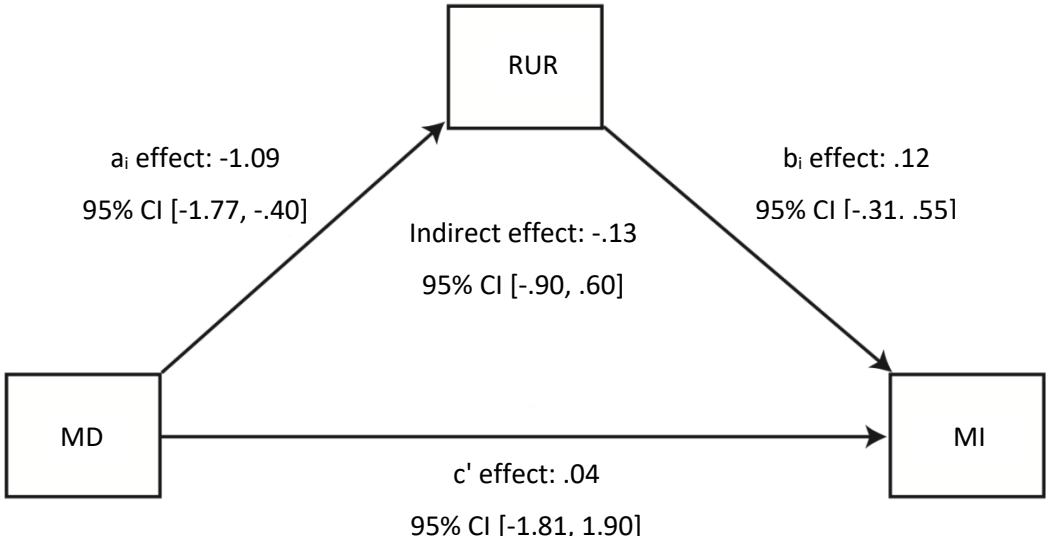

Figure 4. Mediational model for the indirect effect of mood disorder (MD) on a myocardial ischemia (MI) event through brachial artery reactivity (RUR). Model adjusted for age, sex, years of education, history of CAD at baseline, presence of ischemia during the exercise stress test, and use of anti-depressant medication.

General Discussion

This research aimed to improve our understanding of the relationship between depression and CVD, by identifying the role of endothelial function, and modeling potential pathways to explain its effect. Relationships between depression and endothelial function were clarified, behavioural and physiological pathways linking these variables were explored, and endothelial function was found to mediate a relationship between depression and an adverse cardiac outcome over a period of six years. An integrated model of the pathways studied by this current thesis is seen in Figure 1.

Manuscript one assessed associations of endothelial function with depressive symptoms, anxiety symptoms, and the interaction of the two. Previous research has suggested that anxiety may have a qualitatively different effect on cardiovascular health than depressive symptoms, including studies demonstrating that higher anxiety and neuroticism scores are associated with lower rates of cardiovascular mortality (Gale et al., 2017; Herrmann, Brand-Driehorst, Buss, & Ruger, 2000). Despite these potential differences and the high comorbidity of anxiety and depression, previous studies of endothelial function and anxiety failed to adjust for depressive symptoms (Narita, Murata, Hamada, Takahashi, Kosaka, et al., 2007).

This study expanded the previous literature by demonstrating a significant interaction, an effect not previously reported. This highlights different patterns of physiological activation observed in individuals as a

potential result of active coping versus passive coping styles. This finding also highlights the importance of adjusting for depressive symptoms while measuring anxiety, due to their comorbidity (Frasure-Smith & Lespérance, 2008), overlap between depressive and anxiety symptom sets observed on self-report questionnaires assessing each (Karagözoğlu, Masten, & Baloğlu, 2005), and the possibility of unmeasured depressive symptoms dampening an effect of anxiety symptoms. This effect of unmeasured depressive symptoms may explain why our findings contradicted some previous research that identified an association of anxiety symptoms with impaired endothelial function (Narita, Murata, Hamada, Takahashi, Omori, et al., 2007). In contrast, our study observed that anxiety in the absence of depressive symptoms was associated with greater vasodilation, while high anxiety and high depressive symptoms was associated with impaired vasodilation.

Additionally, when contrasted with a previous paper using the same sample (Lavoie, Pelletier, Arsenault, Dupuis, & Bacon, 2010), this study allowed for the comparison of continuous self-report measurements of depressive symptoms against dichotomous clinical interviews of depressive disorders. A significant main effect of depressive disorder status on impaired endothelial function was observed, while the main effect of symptoms measured continuously was not significant. This advanced the literature by suggesting that the relationship between depression and endothelial function may not be a dose-response relationship, but instead may require a threshold of depression severity before endothelial damage occurs.

Manuscript two contributed by utilizing a technique that is novel in this literature to model pathways between depression and endothelial function. A significant pathway was modeled from depressive disorder to a latent variable representing physiological risk factors, and then to endothelial function. When a parallel pathway including a health behaviour latent variable was added to this model, a significant pathway was observed from depressive disorder to health behaviours to endothelial function, but the pathway from physiological factors to endothelial function was no longer significant. In contrast to previous studies that generally examine these pathways individually, this study contributed by assessing these pathways in the same model, and allowing for the comparison of their relative strength. Based on effect size coefficients, it would seem that health behaviours provide a more salient or direct path to endothelial function. Also, pro-inflammatory markers (specifically CRP) and smoking were observed to be the strongest physiological and behavioural loadings, respectively.

Manuscript three expanded the current literature by utilizing a well-accepted statistical technique to assess if endothelial function mediated a relationship between depression and major adverse coronary events over a six year period. This study attempted to identify some directionality in these relationships, by studying future cardiac events. Endothelial function was found to mediate a relationship between depressive disorders and coronary artery bypass grafts, a complex invasive surgery that is a direct result of severe atherosclerosis. Significant mediation effects were not found for a

less severe procedure, percutaneous coronary intervention, or myocardial infarction, an event that relies on different physiological pathways than the other two outcomes of interest. This seems to suggest that endothelial function may mediate some outcomes, specifically those more closely related to atherosclerosis and those of increasing severity and complexity. However, this study was limited by a low incidence rate of cardiac events.

When viewed as a whole, these studies provide some clues regarding the potential factors at play in the relationship between depression and CVD. Endothelial function represents a compelling mediator, through its relationship with depression, the pathological pathways at play in atherosclerosis (such as proinflammatory processes and negative health behaviours), and severe adverse cardiac outcomes. These studies present a plausible pathway, as illustrated in Figure 1, to explain this disease process.

Still, it is important to remember relevant limitations. Manuscripts one and two are limited by the cross sectional nature of the data collected. Inferences of directionality or causation are speculative, as this study design is not equipped to conclude that depression preceded impaired endothelial function, or rule out the possibility that a third variable (such as chronic inflammatory processes) preceded both.

In order to improve confidence in these results, and the theorized model, we suggest replicating and expanding these studies by utilizing a prospective cohort of healthy individuals, with repeated measurements of

depression, endothelial function, inflammatory markers, cigarette smoking habits, and other potential mechanisms. Through this extension of the current research, it would be possible to confirm that depression preceded endothelial impairment, and better understand the directionality between these factors and other potential mechanisms.

Randomized controlled trials that have attempted to treat depression in patients with coronary heart disease have observed little change in CVD morbidity or mortality (Joynt & O'Connor, 2005). The ENRICHD trial included nearly 2500 post-MI patients, incorporating both cognitive behaviour therapy (CBT) and CBT plus selective serotonin reuptake inhibitor (SSRI) antidepressant medication. Despite a greater decrease in depressive symptoms in the treatment groups, there was no difference in event-free survival rates between treatment and usual care groups (Enrichd Investigators, 2003). This current thesis may provide some explanation why intervention studies have thus far had difficulty affecting CVD outcomes.

As manuscripts two and three suggest, depression and CVD outcomes are unlikely to have one simple link, but are likely connected through a series of casual pathways incorporating many intermediate steps. This relationship is also potentially mediated by endothelial function, an important process whose dysfunctions are often asymptomatic. It is possible that endothelial damage, once severe enough, will cause adverse CVD outcomes even if the initial causative factor (potentially depression) is successfully treated. This

may have been the case for ENRICHD patients, who had already experienced a MI, and were likely already suffering from chronic endothelial dysfunction. Future studies should aim to measure not only end-stage outcomes, but also intermediary steps in the atherosclerosis disease process such as endothelial function, to better determine effective points for intervention. It would allow us to study if treating depression would have an effect of slowing or treating endothelial damage, or if intervention should occur at an earlier point before the endothelium has been severely compromised.

Additionally, manuscript one highlights the importance of clinically significant thresholds of depressive symptoms. As seen in this paper, impaired endothelial dysfunction did not have a dose-response relationship with increasing levels of sub-clinical depressive symptoms, but had a relationship with diagnosis of a depressive disorder (as per the Lavoie et al, 2010 paper). This suggests that a certain threshold of depression severity must be reached before adverse CVD outcomes are observed. It is possible that the statistically significant but clinically marginal difference between treatment and control groups in changes of depressive symptoms in the ENRICHD Study explains why there was no difference in CVD outcomes between the groups (Enrichd Investigators, 2003).

Previous research has suggested other pathways, such as autonomic system (ANS) dysfunction via impaired heart rate variability (HRV), may represent factors that link depression to CVD outcomes (Carney & Freedland,

2009). HRV represents variation in the beat-to-beat interval of the heart. It is regulated by the sympathetic and parasympathetic braches of the autonomic nervous system. Low HRV is linked to an increased risk of CVD events (Hillebrand et al., 2013). Depression has been associated with ANS dysfunction and impaired HRV (Carney & Freedland, 2009). This presents a potential pathway from depression to CVD that does not directly implicate endothelial function. While studying ANS dysfunction was beyond the scope of this current thesis, future research should study these two theoretical mediators in tandem, as each represents a potentially different approach to intervention. It is possible that these pathways may be linked by factors such as hypothalamic–pituitary–adrenal axis activity, or that they may represent independent mediators. Clarifying their possible connections should help focus future physiological, epidemiological, and intervention research.

Finally, the differential role of anxiety represents an exciting area of future research that was also beyond the scope of this current thesis. Manuscript one suggested that anxiety may have a qualitatively different effect on endothelial function than depression, while other research literature has not yet come to a consensus on whether anxiety has a positive or negative relationship with CVD outcomes (Herrmann et al., 2000; Roest, Martens, de Jonge, & Denollet, 2010). Future research should model the physiological and behavioural pathways that potentially link anxiety to CVD, in order to contrast those that are also affected by depression from those that represent depression independent pathways.

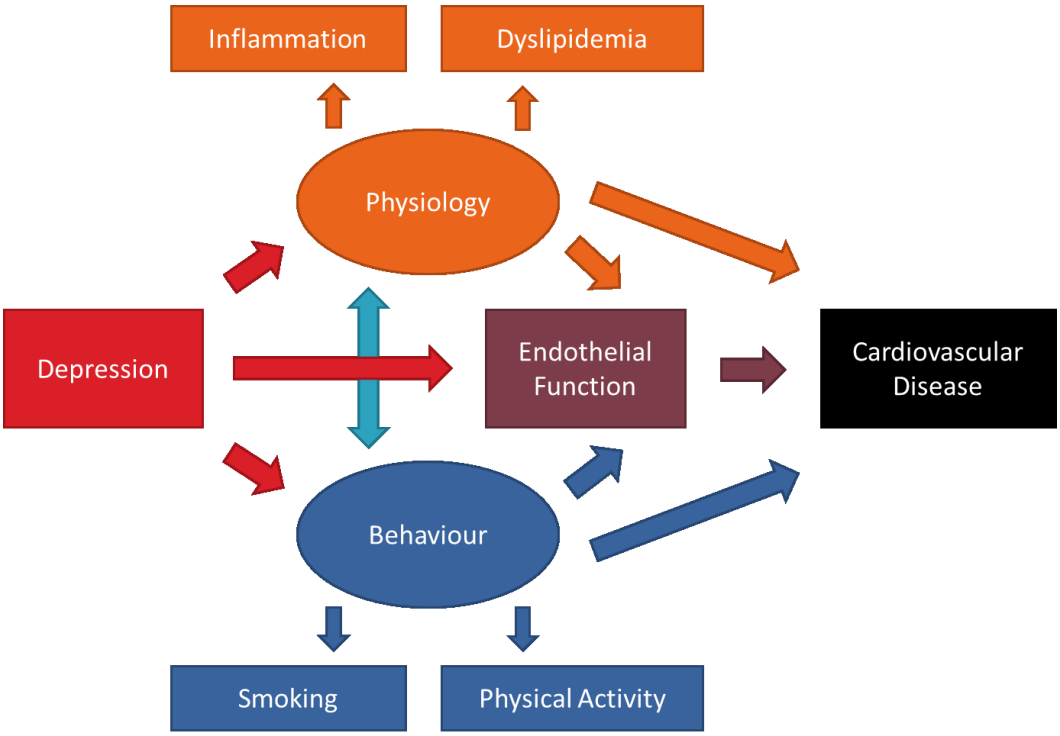

Figure 1. Observed and theorized pathways between depression, endothelial function, and cardiovascular disease outcomes.

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Appendix A

Supplementary Manuscript

Health locus of control is associated with physical activity and other health behaviours in cardiac patients

Mercer, D. A., Ditto, B., Lavoie, K. L., Campbell, T., Arsenault, A., & Bacon, S. L. (Accepted with revisions). Health locus of control is associated with physical activity and other health behaviours in cardiac patients. *Journal of Cardiopulmonary Rehabilitation and Prevention.*

Abstract

Purpose: Physical inactivity, smoking, and excessive alcohol use are well-recognized modifiable risk factors for cardiovascular disease (CVD), yet uptake of strategies to mitigate these poor health behaviours vary widely among CVD patients. Part of this variation may be explained by Health Locus of Control (HLOC), defined as the extent to which individuals believe their health is a consequence of their own actions, chance, or the influence of others (e.g., physicians).

Methods: 599 cardiac out-patients (30% female, 61.4 (9.4) years of age**)** completed the Multidimensional Health Locus of Control questionnaire and a structured health behavior questionnaire assessing physical activity, smoking, and alcohol use, at baseline and a four year follow-up. Relationships between health behaviours and HLOC were assessed cross-sectionally and longitudinally using GLM and logistic regression models adjusting for medical and sociodemographic factors.

Results: Higher internal HLOC was found to be associated with higher levels of leisure-time physical activity (LTPA) (β=.21, p=.0008), while lower internal HLOC was associated with decreasing levels of alcohol consumption over time (β=.26, p=.03). Increasing chance HLOC was related to lower levels of LTPA (β=-.15, p=.047) and increased likelihood of being a smoker (β=.10, p=.01), and increasing physician HLOC was associated with decreased likelihood of being a smoker (β=-.17, p=.01).

Conclusions: Associations between HLOC and multiple health behaviours were observed in a large sample of cardiac outpatients. Results suggest that assessing and targeting HLOC beliefs of cardiac patients may be clinically relevant for behavior change in settings, such as rehabilitation (where behavior change is a goal).

Physical inactivity is a strong, well-established, and modifiable risk factor for cardiovascular disease (CVD) (Miller, Balady, & Fletcher, 1997), (Manson et al., 2002). Meta-analyses have identified a relative risk of CVD associated with physical inactivity to be approximately 1.9, a level comparable to other well-accepted CVD risk factors such as hypertension, cholesterol, and smoking (Berlin & Colditz, 1990; Powell, Thompson, Caspersen, & Kendrick, 1987). The mechanism underlying this effect likely has multiple pathways, as research indicates that exercise training has moderate effects in producing favourable lipid profile changes, lowering blood pressure, increasing quality of life, and improving psychological affect (Joesting, 1981; Miller et al., 1997; Pollock, 1979).

Physical activity levels vary greatly among populations who would benefit from regular exercise, with surveys showing over 50% of Canadian adults are physically inactive (*Canadian Community Health Survey*, 2002-3). It is important to understand the social, environmental, and psychological factors that allow for this variability. Rotter's Social Learning Theory (Rotter, 1954) posits that a specific behaviour is likely to occur if the individual believes that behaviour is likely to lead to a specific reinforcement, and if that reinforcement is valued. Rotter differentiated individuals on the basis of a "locus of control" construct, defining an internal LOC as a belief that a reinforcer is a consequence of an individual's own actions and an external LOC as a belief that a reinforcer is due to events beyond the individual's control (Laffrey & Isenberg, 1983; Norman, 1995). A health-specific

application of this theory has been conceptualized in the Multidimensional Health Locus of Control (HLOC) Scale(Wallston, Stein, & Smith, 1994) in the form of three dimensions: Internal, Chance, and Powerful Others (represented on questionnaires by two separate sub-scales: Physicians and Other People). These dimensions respectively represent the extent to which individuals believe their own health is a consequence of their own actions, chance, or the influence of others.

Reports of associations between HLOC and health behaviours, including physical activity, have been equivocal (Cheng, Cheung, & Lo, 2016; Rod K. Dishman & Mary Steinhardt, 1990; Norman, Bennett, Smith, & Murphy, 1998; Steptoe & Wardle, 2001), though most research has only examined internal HLOC beliefs. Possible explanations for a lack of reported consistency include utilizing small samples, which may be underpowered to detect smaller effect sizes, and overly heterogeneous samples, which introduce excessive uncontrolled variance (Steptoe & Wardle, 2001).

Individuals with an internal HLOC generally are more likely to eat well and exercise regularly (Cobb-Clark, Kassenboehmer, & Schurer, 2014). This relationship was possibly mediated by self-efficacy beliefs and social support (Marr & Wilcox, 2015). Among a sample of internal medicine patients, internal HLOC predicted increased frequency of aerobic exercise at 3 months post discharge (Cramer et al., 2014).

In a study of HLOC beliefs and smoking, individuals who smoked cigarettes were also less likely to endorse HLOC beliefs than a sample of nonsmokers (Strudler Wallston & Wallston, 1978). Additionally, among smokers, higher internal HLOC beliefs were also associated with reductions in smoking (Kaplan & Cowles, 1978; Strudler Wallston & Wallston, 1978). Investigations around relationships between HLOC and alcohol seem to be understudied, though internal HLOC has been shown to be negatively correlated with substance abuse (including alcohol, cigarette, and cannabis use) among adolescents (Dielman, Campanelli, Shope, & Butchart, 1987).

The goal of this prospective longitudinal study was to examine how the dimensions of HLOC were associated with a variety of health behaviours in a sample of cardiac outpatients, a group that does not appear to be specifically studied in the HLOC literature. This study examined overall levels of self-reported LTPA, weekly alcohol consumption, and smoking. Both health behaviours and HLOC were assessed separately at two time-points. In addition, longitudinal change in health behaviours over the four-year design of the study was assessed. It was hypothesized that greater endorsement of internal HLOC beliefs would be associated with increased levels of LTPA, a lower rate of smoking, and lower weekly alcohol consumption, both cross-sectionally at each time-point, and longitudinally.

Methods

Participants

The current study represents a sub-analysis of the MOSMI (Cross-sectional Mechanisms and Longitudinal Outcomes of Silent Myocardial Ischemia) study, which was developed to assess the relationship between blood pressure and silent myocardial ischemia (Gordon et al., 2012; Pelletier et al., 2011). A total of 906 outpatients referred for a single photon emission computed tomography (SPECT) perfusion exercise stress test in the outpatient nuclear medicine service of the Montreal Heart Institute between May 2005 and December 2006 were recruited. This current analysis includes 599 patients for whom data were available at year two (2007-8) and year six (2011-12). There were sex or race restrictions. Patients were included if they were at least 18 years of age and spoke either English or French. Patients were excluded from the MOSMI study if they suffered from a pain disorder other than angina; used a prescription or non-prescription analgesic on the day of exercise testing; used a non-steroidal anti-inflammatory agent (NSAID), coxibs, or anti-neoplastic agent within the last 7 days; were pregnant; had a severe or co-morbid condition and were not expected to survive for 12 months (e.g., cancer); had a history of drug or alcohol abuse; or had a mental condition (determined via self-report and chart review of prescribed medications) rendering the participant unable to understand the nature, scope, and possible consequences of the study. The human ethics committee of the Montreal Heart Institute approved the protocol, and all patients provided written, informed consent prior to participation.

Procedure

Patients presenting for exercise stress testing at the Nuclear Medicine Service of the Montreal Heart Institute were invited to participate. On the first day of the SPECT perfusion imaging testing, patients began with a standard treadmill exercise stress test (modified Bruce protocol) followed by standard SPECT imaging (Anagnostopoulos et al., 2004). Following this, patients were administered a battery of self-report questionnaires assessing sociodemographics, health behaviour, psychological variables, and medical history.

Follow up data were obtained at two and six years post-recruitment. At each point, patients were mailed a similar battery of self-report questionnaires, assessing medical, health behaviour, psychological, and personality status. The Multidimensional Health Locus of Control scale (Wallston et al., 1994) was included in each follow up questionnaire battery.

Measures

Health Behaviours. Questions were adapted from the Physical Activity Recall questionnaire (Sallis et al., 1985) and the Health Practices Index (Berkman, Breslow, & Wingard, 1983). Patients self-reported frequency and duration of regular LTPA over the past year, which was classified as moderate (e.g., brisk walking), high (e.g., doubles tennis), or very-high (e.g., jogging) intensity exercise. These data were converted to metabolic

equivalent of task (MET) hours per week. Alcohol use was quantified as the number of alcoholic drinks consumed over an average one week period. Participants were asked to self-report the number of drinks consumed on average each day, for a regular seven day period. Smoking status was defined dichotomously, with participants self-reporting if they currently smoked cigarettes or not.

Health Locus of Control. HLOC was assessed using the Multidimensional Health Locus of Control scales, Form C (Wallston et al., 1994). This scale includes 18 health belief statements, with responses ranging from 1 (strongly disagree) to 6 (strongly agree). HLOC is assessed along four sub-scales: Internal, Chance, Physicians, and Other People. The scores on each subscale represent the degree to which an individual believes their own health is a consequence of each separate factor, with higher scores indicating higher endorsement of each factor. Scores range between 6 and 36 on the Internal and Chance sub-scales, each comprised of 6 items, and between 3 and 18 on the Doctors and Other People sub-scales, each comprised of 3 items. These four scales were identified by the original authors using exploratory factor analysis. Cronbach's alpha scores for each scale range from .71 to .87, suggesting strong internal consistency (Wallston et al., 1994).

Statistical Analyses

A series of general linear model (GLM) analyses were used to determine the effects of HLOC sub-scales on physical activity at each time

point, and change in LTPA across year two and year six measurement points. A second series of GLM model analyses were used to examine the effects of HLOC sub-scales on alcohol use at each time point, and change in alcohol use across both time points. A logistic regression analysis determined the effect of HLOC sub-scales on smoking status. Each model assessed all four of the sub-scales simultaneously as independent variables. These analyses were adjusted for previous history of CVD (including myocardial infarction, coronary artery bypass surgery, and percutaneous coronary intervention), age, sex, and years of education, which were defined a-priori due to their potential to impact the health behaviour-HLOC relationship. Additionally, the physical activity models were adjusted for objective level of fitness (measured in METs, as assessed during the SPECT perfusion exercise stress test).

To compensate for missing data, a multiple imputation (n=20) procedure was utilized. To control for outliers, individual participants was excluded if participants reported over 60 (MET) hours per week of leisure-time physical activity (roughly equivalent to 15 hours of brisk walking per week), or reported consuming more than 70 alcoholic drinks in the past week. To aid in the visualization of three dimensional relationships, such as the change in LTPA by HLOC score over time, quartiles of HLOC scales were constructed only for graphing purposes. These quartiles exist only to provide clarify for visual representations of the relationships, the GLMs being discussed do utilize continuous measures of HLOC scores.

Results

Sample characteristics

Demographic details are presented in Table 1. For the current study, a total of 599 outpatients (69.6% male, 30.4% female), with a mean age of 61.4 ± 9.41 years were included for analysis. Approximately half had a documented history of CVD.

Multicollinearity

To detect multicollinearity among the four sub-scales of the Multidimensional Health Locus of Control questionnaire, variance inflation factors were calculated for each multiple imputation model. Across all models, variance inflation factors for Internal, Doctor, Others, and Chance HLOC sub-scales ranged from 1.00 to 1.50. These are well below standard threshold values (O'brien, 2007), suggesting minimal multicollinearity among the sub-scales.

Internal Consistency

Cronbach's α coefficients, representing internal consistency, were calculated for the HLOC sub-scales at each of the time points. Data are presented in Table 2. Internal and Chance sub-scales demonstrated the highest internal consistency, while Doctor and Other subscales were not as strong. However, it should be noted that these latter two scales each consist

of only three items. The value of α is deflated by scales with fewer numbers of items, suggesting that internal consistency is still acceptable for these scales (Cortina, 1993). It is also noteworthy that internal consistency scores remained relatively similar when comparing year 2 and year 6 data from each sub-scale.

Leisure-time Physical Activity

LTPA averaged 6.41 MET hours/week (SD=8.83) at year two, and declined slightly to an average of 5.54 MET hours/week (SD=9.06) at year six, a decrease that would be expected in an aging sample. Higher Internal HLOC scores were associated with increased overall LTPA levels at year two, β=.21, *SE*=.07, *t*=3.34, *p*=.0008, although at year six this relationship lost statistical significance, β=.12, *SE*=.07, *t*=1.68, *p*=.09. Higher Chance HLOC scores were associated with decreased overall LTPA levels at year two, β=-.15, *SE*=.07, *t*=-1.98, *p*=.047, and at year six this relationship lost significance as well, β=-.12, *SE*=.09, *t*=-1.48, *p*=.14. Others and Physician HLOC scores were not associated with LTPA at either time point. Additionally, none of the four scales were associated with change in LTPA levels between the two time points.

Smoking Status

At year two, 8.9% of the sample were current daily smokers. This decreased slightly to 8.2% at year six. Increasing Doctor HLOC scores were

associated with a decreased likelihood of being a current smoker at year two, β=-.17, *SE*=.07, *t*=-2.54, *p*=.01. At year six, increasing Chance HLOC scores were associated with an increased likelihood of being a smoker, β=.10, *SE*=.04, *t*=2.49, *p*=.01. No other HLOC scales were associated with smoking status at either of the time points. Due to the low number of individuals who reported smoking cessation between year two and year six (n=4), no analyses of change in smoking status were performed.

Alcohol Use

Alcohol use decreased slightly from a self-reported average weekly alcohol consumption of 15.26 drinks (SD=13.83) at year two, to 13.39 drinks (SD=12.39) at year six. These numbers fall at Health Canada low-risk drinking guidelines for men (15 drinks per week) and women (10 drinks per week)(Health Canada, 2011), and are in line with recently reported Statistics Canada averages of alcohol consumption in Quebec (10.14 liters of alcohol per year, the equivalent of 13.92 drinks per week)(Statistics Canada, 2015). Cross-sectionally, at the year two and year six time points, none of the HLOC scales were associated with self-reported average weekly alcohol consumption.

However, associations with change in alcohol consumption were observed longitudinally. Decreasing Internal HLOC scores were associated with lower levels of alcohol consumption between year two and year six, β=.26, *SE*=.12, *t*=2.18, *p*=.03. For every 1 point score decrease in internal

HLOC levels, there was a decrease of ¼ of a unit of alcohol consumed per week. Figure 2 illustrates this association, showing changes of mean weekly alcohol consumption across four quartiles of internal HLOC. As seen in the table, while the highest quartile of internal HLOC maintained a relatively consistent alcohol consumption, individuals in the lower three quartiles showed decreases, on average, of approximately 2 drinks per week.

Additionally, a relationship between increasing Doctor HLOC scores and decreasing levels of alcohol consumption between these two time points showed a tendency towards significance, β=-.45, SE=.24, t=-1.87, p=.06.

Discussion

This study demonstrated associations between beliefs an individual has about sources of control over their own health, and various health behaviours, across a large sample of cardiac patients. The more an individual believed their health was under their own control, the higher physical activity levels tended to be. The less an individual believed they were in control of their own health, the more they tended to decrease their alcohol consumption over four years. The more an individual believed their health was the result of fate or chance, the lower the level of physical activity they tended to engage in, and the higher their likelihood of being a smoker tended to be. Meanwhile, the more an individual believed that their physician was in control of their own health, the less likely they were of being a smoker.

Internal HLOC was cross-sectionally associated with increased LTPA. This association was seen at year-two, but it was not related to longitudinal changes over four years. Physical activity generally showed a decrease over time, as one would expect to see in a sample of older adults. Figure 1 illustrates this relationship using quartiles of internal HLOC scales, for the purpose of clarity to aid in the visualization of this result (though it should be noted that the GLM being discussed utilized a continuous measure of HLOC scores). As seen in the figure, higher levels of internal HLOC showed higher initial levels of LTPA at year two, and accordingly show larger potentially age-related declines between year two and year six. However, the differences across the entire range of internal HLOC scores were not statistically significant, due to large variability of LTPA levels seen in the sample. In contrast to previous studies examining HLOC and LTPA, study is noteworthy for employing a large sample-size, and a statistically powerful longitudinal design. Our results are consistent with a previous, short-term longitudinal study of internal HLOC and LTPA (R. K. Dishman & M. Steinhardt, 1990). It is also relevant to note that there was a secular decrease in LTPA rates between Year 2 and Year 6. This may have implications for long term treatment planning in cardiac rehab services.

These results support the assertion of Rotter's Social Learning Theory (Rotter, 1954) that an individual is more likely to engage in a behaviour if the individual believes that behaviour leads to a specific reinforcement. As this population consisted of cardiac outpatients, it may mean the sample was

more motivated to engage in exercise behavior due to a stronger belief that this behavior leads to a specific reinforcer (i.e., improved cardiovascular health). This study does not address the second factor of Social Learning Theory, that the reinforcement must be valued. We may infer that by presenting for exercise stress testing, this sample demonstrated their cardiac health was valued. A future study should measure this directly as a potential mediator.

Doctor HLOC was cross-sectionally associated with a decreased likelihood of being a smoker at year-two. This may reflect a tendency to comply with direction when an individual places faith and responsibility for their own health in the hands of their health care providers. Shared decision making represents a collaborative approach to healthcare that builds shared responsibility and trust between patients and clinicians. Approaches that include this collaborative style of decision making in order to facilitate and engage intrinsic motivation, such as motivational communication or motivational interviewing, are beneficial for increasing medication and program adherence rates in patients with chronic illness (Lavoie et al., 2014; Parsons, Golub, Rosof, & Holder, 2007; Smith, Heckemeyer, Kratt, & Mason, 1997). It is speculative why this relationship with Doctor HLOC was observed with smoking rates, but not physical activity levels nor alcohol consumption. This may reflect the trend for a higher percentage of physicians to provide smoking cessation counselling to patients (approximately 40%)(Pipe, Sorensen, & Reid, 2009) as compared with

providing exercise prescriptions (about 14%) (Walsh, Swangard, Davis, & McPhee). During the peer review process of this manuscript, it was suggested that patients may also be more likely to comply with recommendations that require giving up an aversive behaviour. They may find it easier to end an aversive behaviour than introducing a time-consuming new behaviour, such as physical activity, into their daily routine.

Chance HLOC was cross-sectionally associated with decreased LTPA at year-two and increased rates of smoking at the year-six time point. Though there are no solid data to support the drivers of these relationships, one might speculate that holding fatalistic beliefs may lead an individual to be resistant to clinical and public health interventions that have aimed to reduce smoking rates and improve physical activity. Alternatively, this relationship may be bidirectional. Individuals with a preexisting history of smoking may believe that their predisposition towards chronic illness associated with cigarette use is already elevated, leading to a diminished sense of control over one's health.

Lower internal HLOC scores were longitudinally associated with decreases in average weekly alcohol consumption between year two and year six. Figure 2 illustrates this relationship using quartiles, however the GLM being discussed utilized a continuous measure of HLOC scores. While average weekly alcohol consumption decreased between year-two and year-six (15.26 vs 13.39: both of which fall within recently reported Quebec

averages (Statistics Canada, 2015)), only lower levels of internal HLOC experienced this drop. In contrast, among individuals with the highest internal HLOC scores, alcohol consumption remained constant over time. This seems counterintuitive, as possessing higher internal HLOC is commonly associated with positive health behaviours. However, unlike health behaviours such as physical activity and smoking, public perception of alcohol consumption is less clear. With smoking, for example, there is little doubt that smoking has negative impacts on cardiac health. This is a strong and consistent research finding (Tolstrup et al., 2013), potentially priming individuals to be more likely to adhere to cessation recommendations. In contrast, a significant body of research, that has increasingly received public attention, suggests that moderate alcohol intake may actually lower the rate of coronary heart disease (Rimm, Williams, Fosher, Criqui, & Stampfer, 1999). It is possible that individuals with higher internal HLOC scores valued the potential health benefits of moderate alcohol consumption, and maintained their weekly alcohol consumption. However, further work on this would be needed to confirm such a hypothesis.

Strengths & Limitations

This study is limited by the accuracy of self-report data. Comparisons of self-report and direct measures of physical activity tend to show weak consistency between methodologies (Prince et al., 2008). However, self-report measures of physical activity are consistently predictive of

cardiovascular outcomes (Warburton, Nicol, & Bredin, 2006), suggesting that although it may represent a different construct, it is still an important measure. It would be useful to replicate these findings using direct measures of physical activity, smoking, and alcohol consumption, such as pedometers, cotinine levels, and ethanol tests, to identify if these relationships replicate using different measurement constructs.

Study Implications & Future Directions

The results of this study suggest that internal HLOC may be a clinically relevant variable for cardiac patients. Future research should examine if assessing this variable at the time of attempted behaviour change (e.g., intake into a cardiac rehabilitation) has utility to predict outcomes. Interventions could also examine the possibility to modify HLOC or design a procedure targeted to those possessing low internal HLOC who may be less likely to engage in health behaviour change programs.

There has been limited research investigating possible interventions to improve HLOC. Some research has suggested that relaxation techniques may improve general internal locus of control, possibly through improving an individual's awareness of their ability to control aspects of themselves, and potentially through reductions in anxiety (Sharp, Hurford, Allison, Sparks, & Cameron, 1997). Older adults have also seen improvements in internal locus of control following cognitive training to improve reasoning and speed of processing skills, suggesting that interventions to improve skills and target

self-efficacy may help individuals feel a greater sense of control over their lives (Wolinsky et al., 2009). It would be interesting to explore if the educational and physical training elements of cardiovascular rehab programs also increase this sense of control, and to identify which elements lead to the greatest change in beliefs.

These findings suggest a relationship between high Doctor HLOC and lower smoking rates. Future studies should examine which aspects of the doctor-patient relationship, such as communication style or respect for patient autonomy, are useful for engendering a high levels of Doctor HLOC in patients. Additionally, it would be useful to study if Doctor HLOC is a useful predictor of change in studies where doctors are directly intervening by providing exercise or behavior change prescriptions to patients.

Finally, smoking cessation and physical activity intervention programs may benefit from tools that identify individuals with a high chance HLOC. These individuals may be resistant to current public health strategies due to a lack of perceived control over their own health. Targeted interventions, aimed at increasing personal responsibility and highlighting the reversibility of modifiable risk factors for CVD, may be beneficial in reaching individuals with a high chance HLOC.

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Table 1. Demographic data

Variable	**Mean (SD)** **Year 2**	**Year 6**
Age (years)	61.39 (9.41)	
Leisure-time Physical Activity (average MET hours/week)	6.41 (8.83)	5.54 (9.06)
Alcohol Consumption (number of drinks per week)	15.26 (13.83)	13.39 (12.39)
Health Locus of Control sub-scales		
Internal (out of 36)	24.7 (5.9)	24.3 (6.0)
Chance (out of 36)	15.7 (5.6)	15.7 (5.5)
Doctor (out of 18)	15.5 (2.4)	15.3 (2.4)
Others (out of 18)	7.9 (3.1)	7.7 (3.2)
Variable	**Percent Frequency** **Year 2**	**Year 6**
Sex	69.6% male 30.4% female	
History of cardiovascular disease*	53.1%	
At least 12 years of education	59.1%	
Current Smoker	8.9%	8.2%

*History of cardiovascular disease includes myocardial infarction, stroke, congestive heart failure, percutaneous coronary intervention, or coronary artery bypass graft.

Table 2. Internal Consistencies for Health Locus of Control sub-scales, reported as standardized Cronbach's α coefficient

Subscale	**Measurement Time Point**	
	Year 2	**Year 6**
Internal	.75	.77
Chance	.68	.68
Doctor	.53	.53
Others	.54	.61

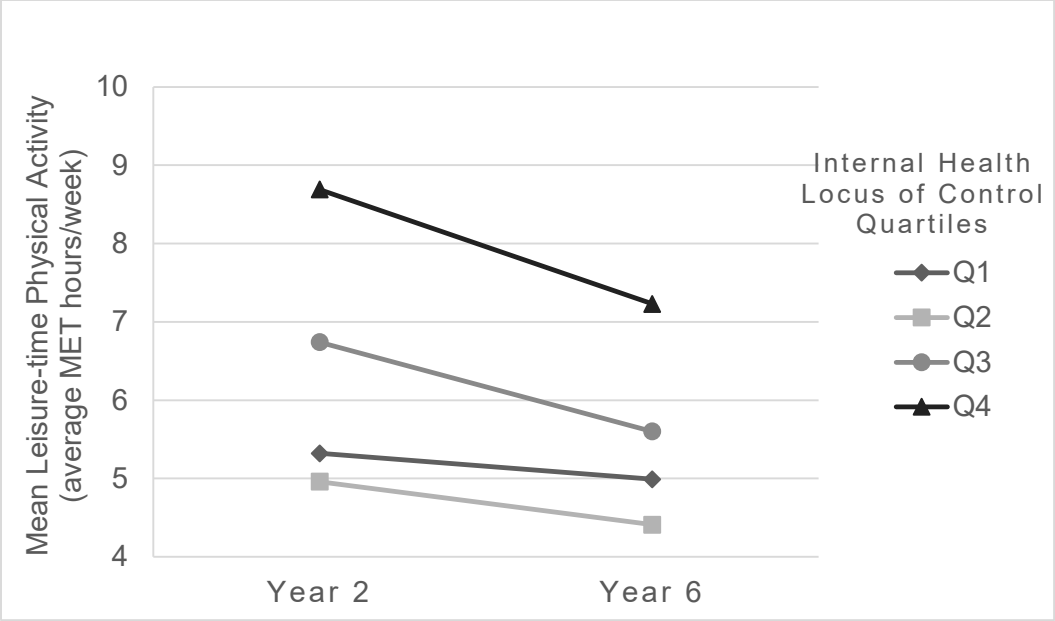

Figure 1. Changes in Mean Leisure-time Physical Activity (average MET hours/week) by internal health locus of control quartiles (measured in year 2)

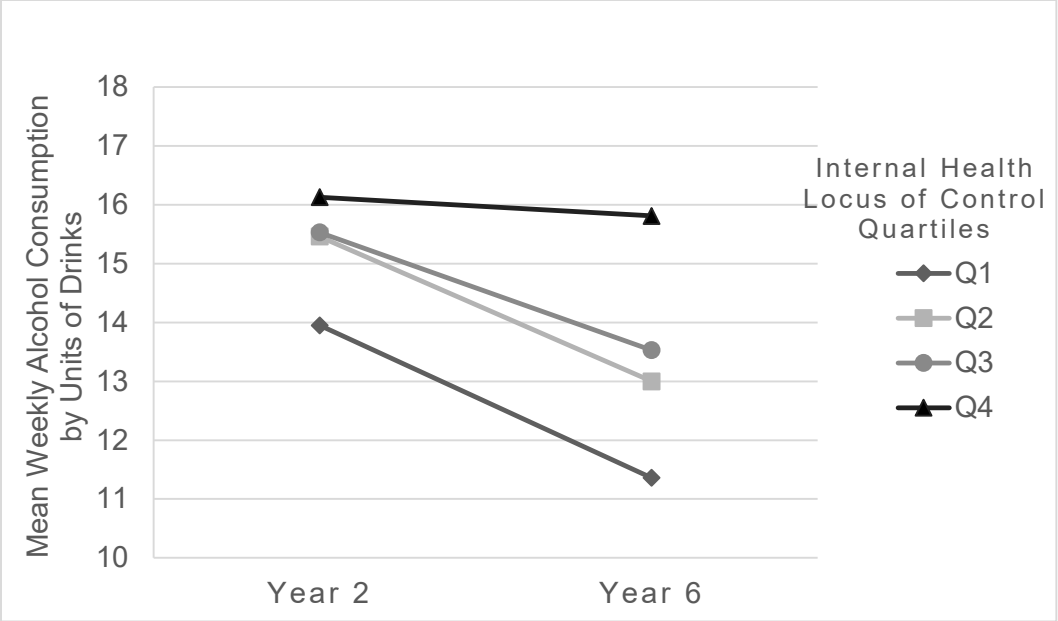

Figure 2. Changes mean weekly alcohol consumption by internal health locus of control quartiles (measured in year 2)