Cardiopulmonary Fitness, Depressive Symptoms and Cognitive Performance in Patients with Coronary Artery Disease: Phenomenology and Biomarkers

by

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A thesis submitted in conformity with the requirements for the degree of Doctor of Philosophy
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University of Toronto

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Abstract

Introduction: Coronary artery disease (CAD) has been associated with depressive symptoms and deficits in cognitive performance, both of which have been associated with poorer medical prognoses and poorer psychosocial outcomes. Physical activity can improve cognitive and depressive symptoms, and, for those with CAD, improve medical prognoses. It was hypothesized that depressive symptoms and poorer cognitive performance would be associated with poorer cardiopulmonary fitness in patients with CAD, and that these sequelae would be associated prospectively with noncompletion of cardiac rehabilitation (CR). The benefits of physical activity are thought to result, in part, from decreased inflammatory activity and increased adaptive neural plasticity, to which the ratio of kynurenine to tryptophan (K/T) and brain derived neurotrophic factor (BDNF), respectively, in peripheral blood may pertain. Methods and Results: In a cohort study of patients entering CR, depressive symptoms (Center for Epidemiological Studies Depression scale; CES-D scores) were associated with cardiopulmonary fitness (peak volume of oxygen uptake; VO_{2peak}) during an exercise stress test (B=-.404, p=.001, n=366). The VO_{2peak} was also associated with performance across multiple cognitive domains, but most strongly with performance on tests involving executive function, attention and psychomotor processing speed ($\beta$=.322, p=.002 for composite score, n=81) in a cohort of patients entering CR. In prospective cohort studies, Major Depressive Disorder (adjusted hazard ratio [HR] 2.5, 95% confidence interval [CI] 1.3–4.7, n=195) and poorer performance on a verbal memory test (HR 0.86, 95% CI 0.77-0.96, p=.009, n=131) predicted non-completion of CR. In patients undertaking CR, higher serum K/T ratios were associated with CES-D scores ($\beta$=.322, p=.002, n=95) and with VO_{2peak} ($\beta$=-.391, p<.001, n=95), and in a cohort of patients entering CR (n=88), serum concentrations of BDNF were associated with psychomotor processing speed ($F_{1,87}=9.620, p=.003$), overall cognitive status (Mini Mental Status Exam) scores ($F_{1,87}=15.406, p<.0005$) and VO_{2peak} ($\beta$=.305, p=.013). Conclusions: Depressive symptoms and poorer cognitive performance are clinically important in patients with CAD entering CR and they are both associated with poorer cardiopulmonary fitness. Poorer cardiopulmonary fitness was also associated with higher K/T ratios and with lower BDNF concentrations in serum, which predicted depressive symptoms and poorer cognitive performance, respectively.
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**List of Abbreviations**

- 5-HT: 5-hydroxytryptamine
- ACE: angiotensin converting enzyme
- ACMSD: aminocarboxymuconate semialdehyde decarboxylase
- ACS: acute coronary syndromes
- AD: Alzheimer’s disease
- AHR: aryl hydrocarbon receptor
- ANCOVA: analysis of covariance
- ANOVA: analysis of variance
- ASA: acetylsalicylic acid
- AT_1: angiotensin II receptor type 1
- BDNF: brain derived neurotrophic factor
- BMI: Body mass index
- BVMT-R: Revised Brief Visuospatial Memory Test
- CABG: coronary artery bypass graft
- CAD: coronary artery disease
- CES-D: Center for Epidemiological Studies Depression
- CI: confidence interval
- CNS: central nervous system
- COPD: chronic obstructive pulmonary disorder
- CR: cardiac rehabilitation
- CRP: C-reactive protein
- CVLT-II: California Verbal Learning Test 2nd Ed.
- DDC: dopa decarboxylase
- DSM: Diagnostic and Statistical Manual
- DTI: diffusion tensor imaging
- ECG: electrocardiogram
- eNOS: endothelial nitric oxide synthase
- ERK: extracellular signal-regulated kinase
- FA: fractional anisotrophy
- HAM-D: Hamilton Depression scale
- HAO: 3-hydroxyanthranilate 3,4-dioxygenase
- HDL: high-density lipoprotein
- HIF-1α: hypoxia-inducible factor-1α
- HMG-CoA: 3-hydroxy-3-methyl-glutaryl-CoA
- HPA: hypothalamic-pituitary-adrenocortical
- HPLC: high-performance liquid chromatography
- HR: hazard ratio
- IDO: indolamine 2,3-dioxygenase
- IFN: interferon
- IL: interleukin
- iNOS: inducible nitric oxide synthase
- KAT II: aminotransferase II
- KF: kynurenine formamidase
- KMO: kynurenine monoxygenase
- K/T: kynurenine to tryptophan ratio; arbitrary units of μmol kynurenine per mmol tryptophan
- KYNU: kynureninase
- LDFR: long delay free recall
LDL low-density lipoprotein
LNAAT large neutral amino acid transporter
LPS lipopolysaccharide
MCI mild cognitive impairment
MDD major depressive disorder
MI myocardial infarction
MMP metalloproteinases
MMSE Mini Mental State Examination
MRI magnetic resonance imaging
NAD nicotinamide adenine dinucleotide
NADPH nicotinamide adenine dinucleotide phosphate
NINDS-CSN National Institute of Neurological Disorders and Stroke and Canadian Stroke Network
nNOS neuronal nitric oxide synthase
NMDA N-methyl-D-aspartate
NO nitric oxide
NOS nicotinamide adenine dinucleotide phosphate oxidase
pcASL pseudocontinuous arterial spin labeling
PCI percutaneous coronary intervention
RER respiratory exchange ratio
SD standard deviation
SDFR short delay free recall
SNAT aralkylamine N-acetyltransferase
SSRI selective serotonin reuptake inhibitors
tACS time since most recent acute coronary syndrome
TDO tryptophan dioxygenase
Th1 type 1 helper T
Th17 type 17 helper T
TNF tumor necrosis factor
TPH2 tryptophan hydroxylase 2
TrkB tropomyosin related kinase receptor type B
TRI-Cardiac Toronto Rehabilitation Institute Cardiac Rehabilitation and Secondary Prevention Program
VCAM-1 vascular cell adhesion molecule-1
VEGF vascular endothelial growth factor
VO_{2}\text{peak} peak volume of oxygen uptake
WHtR waist-to-height ratio
I. Introduction

I.i Presentation of coronary artery disease

Coronary Artery Disease (CAD) affects approximately 19.8% of Canadians over the age of 65\(^1\) significantly affecting quality of life; 60% of those with CAD report a reduction in physical activity and 30% report disability and unemployment due to illness\(^2\). CAD involves a narrowing of the arteries that supply blood to the heart through a process known as atherosclerosis. Stenosis of the coronary arteries can restrict oxygen supply to the heart sufficiently to require revascularization such as percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG) and/or result in ischemic damage and myocardial infarction (MI). Thus, the clinical population of patients with CAD includes patients with a history of MI, prior revascularization and/or coronary angiographic evidence of significant (usually at least 50% blockage) in at least 1 major coronary artery.

Vascular risk factors such as dyslipidemia, hypertension, elevated body mass index (BMI), type II non-insulin dependent diabetes are involved in the progression of atherosclerosis and they are highly prevalent in CAD populations. These risk factors are involved in damaging the vascular endothelium under which the atherosclerotic plaque forms\(^3\)-\(^7\). Medications most commonly prescribed to manage these risk factors include 3-hydroxy-3-methyl-glutaryl-CoA (HMG-CoA) reductase inhibitors (or “statins”) for dyslipidemia, beta adrenergic receptor antagonists, calcium channel antagonists, angiotensin converting enzyme (ACE) inhibitors and diuretics for hypertension, peroxisome proliferator-activated receptor gamma agonists, metformin, glyburide or insulin for diabetes, and nitroglycerin for angina\(^8,9\). Commonly, patients who present with coronary stents are treated with anti-platelet agents for 1 year. The majority of patients are treated with a low dose (81 mg) of acetylsalicylic acid. These medical histories, vascular risk factors and concomitant medications are common in the presentation of stable CAD in the setting of comprehensive cardiac rehabilitation (CR). While these medications have established efficacy, additional benefits of rehabilitation and secondary prevention have been consistently described\(^9,10\).

In Ontario, CR is most often a 3-month to 1-year comprehensive intervention. The Toronto Rehabilitation Institute Cardiac Rehabilitation facility operates a 1 year program\(^11\). This program primarily services an estimated catchment area of at least 2.2 million, although Ontarians are accepted from anywhere in Toronto and outreach from more remote areas is increasingly popular. The referral
rate is approximately 1,800 patients per year. Referral is made by physician prescription only, and at least 400 physicians, including cardiologists, family doctors, surgeons, endocrinologists and internists, refer patients to the program\(^1\). Any physician can refer a patient to the Toronto Rehabilitation Institute program via the Physician Referral Form (Appendix I) although cardiologists most frequently refer patients. Physicians are made aware of the program via continuing physician education seminars, invitations to tour the facility, presentations at hospital rounds, various lectures, and workshops run by CR leadership and staff. Funding for the program is provided by the Ontario Ministry of Health, and no cost to the client is associated with the program for residents of Ontario who have a valid Ontario Health Insurance Plan card\(^1\). Patients without contraindications outlined by the Canadian Association of Cardiac Rehabilitation\(^1^2\) are accepted into the program. Absolute contraindications to exercise, such as severe aortic stenosis, uncontrolled heart failure or uncontrolled hypertension would exclude patients from the program while CR can be individualized to accommodate contraindications to particular exercise intensities or modalities\(^1^2\). Subjects may start CR a minimum of 6 weeks post-CABG, 6 weeks post-MI, or 3 weeks post-PCI. Only patients with CAD (as defined above) were studied for the purposes of the present thesis; however, the Toronto Rehabilitation Program also accepts patients with 2 or more vascular risk factors, those with valvular heart disease, peripheral vascular disease, primarily a diagnosis of diabetes, and other indications, who would have been excluded from the studies reported in the present thesis. The Toronto Rehabilitation program structures a separate class for patients with heart failure (New York Heart Association Functional Class II or III)\(^1\).

The Toronto Rehabilitation Institute Cardiac Program as per Canadian Association of Cardiac Rehabilitation evidence-based clinical practice guidelines to identify and modify cardiovascular risk factors\(^1^2\); thus, the Toronto Rehabilitation Institute program involves dietary education and monitoring, smoking cessation, psychosocial supports including depression screening and treatment and stress management classes and/or individual talk therapy, and prescription of a combination of onsite (supervised) and off-site exercise sessions\(^1^1\). The primary clinical targets of CR include reducing body mass and improving cardiopulmonary fitness. Body composition is monitored using waist circumference, percentage body fat and BMI while cardiopulmonary fitness is monitored using the peak volume of oxygen uptake per minute, normalized for body mass (VO\(_{2}\)\(_{\text{Peak}}\) measured in ml•kg\(^{-1}\)•min\(^{-1}\)).

\(^1\) CR participants from the heart failure class (who would have New York Class II or III) were not recruited for the present studies (Chapters 2-6), thus patients currently experiencing symptoms of heart failure, or who had a history of heart failure beyond Class I, were not studied for the purposes of this thesis.
using a standardized exercise stress test\textsuperscript{11}. For the purposes of the studies presented in this thesis, these outcomes were measured in accordance with standard clinical practice at the CR facility. CR programs have been shown to substantially reduce mortality and the recurrence of acute coronary syndromes (ACS), MI and coronary events\textsuperscript{10} and epidemiological studies show that each 1\% increase in VO\textsubscript{2Peak} is associated with a 2\% reduction in the risk of mortality\textsuperscript{13, 14}.

Two central nervous system (CNS) complications common in populations with CAD, depressive symptoms and poorer cognitive performance, are associated with substantially poorer prognoses\textsuperscript{15-17} and with poorer overall quality of life\textsuperscript{18, 19}. Evidence from medically healthy adult populations suggests that both cognitive performance\textsuperscript{20} and depressive symptoms\textsuperscript{21} may be related to physical inactivity, and conversely, that physical activity can prospectively improve these symptoms\textsuperscript{22, 23}. The present thesis explores these associations in patients with CAD entering CR, it examines cognitive and depressive symptoms as potential barriers to exercise intervention in the setting of CR, and it investigates associated biomarkers of potential pathoetiolog\textsuperscript{ical significance.

\textit{I.i Depressive symptoms and CAD}

The prevalence of depression in patients with CAD is at least two-fold higher than general population estimates; while the lifetime prevalence of major depressive disorder (MDD) is estimated to be between 4.4\% and 20\% in the general population\textsuperscript{24}, between 18\% and 45\% of those admitted to hospital for CAD show signs of significant depressive symptoms or suffer from MDD, and subsyndromal depressive symptoms are also highly prevalent\textsuperscript{25-31}. The importance of depression in this population has been well established. Depressive symptoms are associated with CAD severity and progression, as they increase the risk of mortality independently of cardiac risk factors\textsuperscript{15-17} in those with stable CAD\textsuperscript{15, 26, 28, 29, 32-34}, those recovering from CABG\textsuperscript{35} or those recovering from MI\textsuperscript{26, 28, 29, 36, 37}. The negative impact of depressive symptoms increases with their severity\textsuperscript{38}, increasing, for example, the risk of hospitalization due to complications of CAD dose-dependently\textsuperscript{39}. Depressive symptoms have been observed to persist for 1 year following hospitalization for ACS, consistent with common windows of observation\textsuperscript{40, 41}, but studies suggest that they are also common antecedents of an ACS\textsuperscript{42}.

No single mechanism has been identified that can account for the association between depression and CAD, however, a combination of biological and psychosocial factors are likely to be involved. Evidence from the Swedish Twins Registry suggests that the effect of CAD on the onset of major depression was
much stronger than the effect of MDD on CAD onset, suggesting that CAD and associated risk factors may confer vulnerability to depression\textsuperscript{43}. Transient depressive symptoms immediately following a CAD diagnosis or an acute coronary syndrome are common but may subside following revascularization procedures distinguishing these patients from those with MDD\textsuperscript{44}. Psychosocial support may be protective against developing persistent depression\textsuperscript{45} and cognitive factors such as coping and goal-setting are also associated with depressive symptoms\textsuperscript{46}. Personality traits and vital exhaustion share variance with depressive symptoms in predicting inflammatory and behavioural risk factors for CAD\textsuperscript{47, 48}. A possible neurobiological basis stems from the “vascular depression hypothesis” for late-life depression (that which occurs for the first time in late-life, frequently in association with psychomotor retardation, anhedonia, impaired insight and behavioral disability\textsuperscript{49}). Coined by George Alexopoulos and colleagues, this hypothesis suggests that “cerebrovascular disease may predispose, precipitate, or perpetuate some geriatric depressive syndromes”\textsuperscript{50}. This hypothesis was predicated on the clinical association between depressive symptoms and executive dysfunction in older patients, suggesting that ischemic vascular lesions may disrupt prefrontal systems or associated fronto-subcortical white matter circuits\textsuperscript{51-54}. Given multiple genetic, environmental, behavioural and biological risk factors, and potential for interactions between them, the present thesis considers depressive symptoms in the context of a biopsychosocial model.

Physical inactivity has been suggested as one potential behavioural mediator of the association between depression and poorer cardiac prognoses. In one prospective study, Whooley et al. followed a cohort of 1017 stable CAD patients for a mean duration of 4.8 years\textsuperscript{55}. That study replicated the association between depressive symptoms at baseline and future cardiac events (hazard ratio [HR], 1.50; 95% confidence interval, [CI], 1.16-1.95; \(P=.002\)), but further showed that the association could be attenuated to non-significance (HR, 1.05; 95% CI, 0.79-1.40; \(P=.75\)) when controlling for biological and behavioural factors such as left ventricular ejection fraction, serum C-reactive protein (CRP) concentrations and self-reported physical activity levels in the statistical model\textsuperscript{55}. In a fully adjusted model, physical inactivity alone reduced the impact of depression by 31%. While those data are highly informative to the epidemiologist, they are perhaps less so to the clinician. In a practical sense, while physical inactivity may be more closely related to cardiac outcomes than depression, the potential impediment to adherence to physical activity prescriptions imposed by MDD remains unqualified. These data suggest the need to determine first, if cardiopulmonary fitness is related to depressive symptoms in patients entering CR (Chapter 1), and second, if depressive symptoms and a psychiatric diagnosis of
MDD can prospectively predict non-adherence to CR above and beyond effects of cardiopulmonary fitness at baseline (Chapter 2).

Inflammation is intimately associated with the development of atherosclerotic lesions and with the rupture of plaques leading to ACS\textsuperscript{56-59}. Clinically, patients with CAD show higher systemic inflammatory activity than controls as measured by peripheral blood cytokine concentrations such as interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α)\textsuperscript{60}. Physical activity and exercise training in patients with CAD can reduce systemic inflammatory activity as indicated, for example, by reduced circulating concentrations of CRP\textsuperscript{61,62}, soluble TNF-α receptor \textsuperscript{1}\textsuperscript{63,64}, IL-6\textsuperscript{65,66} and interferon-γ (IFN-γ)\textsuperscript{65}. Exercise interventions can also decrease circulating concentrations of vascular cell adhesion molecule-1 (VCAM-1), which is released by endothelial and smooth muscle cells in response to cholesterol accumulation\textsuperscript{67}. VCAM-1 signals the infiltration of innate and adaptive immune cells at the site of an evolving arterial lesion\textsuperscript{67}. Infiltrating monocytes differentiate into macrophages and begin to secrete matrix metalloproteinases (MMPs), nitric oxide (NO) and pro-inflammatory cytokines such as TNF-α and IFN-γ\textsuperscript{68}, which might also be attenuated by physical activity\textsuperscript{65,69-71}. Infiltrating T cells, particularly type 1 helper T (Th1) cells are activated by oxidized cholesterol in the forming lesion, and they produce additional IFN-γ, TNF-α and other Th1-type pro-inflammatory cytokines, which are found abundantly in atherosclerotic plaques\textsuperscript{72-74}. IFN-γ stimulates further release of NO, pro-inflammatory cytokines and pro-thrombotic molecules from macrophages, while TNF-α stimulates the release of reactive oxygen and nitrogen species from endothelial cells, all of which contribute to endothelial dysfunction and plaque expansion\textsuperscript{74}. Consistent with an anti-inflammatory effect, exercise has been shown to regress plaque expansion and improve measures of vascular endothelial function\textsuperscript{75}. As an immunological countermeasure, infiltrating cells which produce the anti-inflammatory cytokine IL-10 can inhibit plaque expansion by quieting the Th1 response\textsuperscript{76}. Clinically, exercise can increase systemic concentrations of IL-10\textsuperscript{63,65}. When a plaque matures, it forms a fibrous cap composed of smooth muscle cells and the collagenous matrix proteins they secrete. This cap may be destabilized by mechanical disruption, by inhibition of smooth muscle cell proliferation by IFN-γ, by direct inhibition of collagen secretion by IFN-γ and by increased expression of MMPs that degrade the collagenous matrix\textsuperscript{56,77-79}. It is usually the rupture of this cap that leads to thrombosis, angina and infarction\textsuperscript{80}. The benefit of exercise in patients with established CAD disease may involve stabilization of the cap by decreasing expression of MMPs or pro-inflammatory cytokines\textsuperscript{81}. 
As described in a recent meta-analysis by our research group, MDD is also associated with higher concentrations of pro-inflammatory cytokines in peripheral blood, particularly IL-6 and TNF-α. As subsequently reviewed, cytokines involved in the cellular immune response, although more difficult to observe in plasma for technical reasons, might also be involved in MDD. Mitogen stimulated assays of peripheral blood mononuclear cells have shown higher synthetic capacity of other cytokines, including IFN-γ, in samples from MDD patients as compared to controls. Clinically, CRP concentrations were more strongly related to heart rate variability in CAD patients with depression than in CAD patients without depression, suggesting a vulnerability to inflammatory processes in depressed patients, which was also suggested in another large study where CRP and depression interacted to predict ACS over 2 years. However, in another study, peripheral blood concentrations of IL-6 and CRP were not higher among depressed patients following hospitalization for an ACS as compared to non-depressed patients suggesting the need to investigate potential mediators of affective vulnerability to inflammatory activity. Dantzer and colleagues have suggested that some depressive symptoms, particularly fatigue and somatic-type symptoms, are reminiscent of the “sickness behaviours” associated with cytokine elevations in animal models, which may or may not transition into more severe cognitive and affective symptoms depending on the presence of certain unknown vulnerability factors.

One potential mediator of vulnerability is the capacity of the pro-inflammatory cytokines to induce the indolamine-2,3-dioxygenase (IDO) enzyme, which catalyzes the rate-limiting step in the synthesis of kynurenine from tryptophan. An elevated plasma kynurenine/tryptophan (K/T) ratio is therefore thought to reflect IDO activity, though tryptophan dioxygenase (TDO) expressed in the liver and possibly brain might also contribute to the K/T ratio. Pro-inflammatory cytokines, including IFN-γ, IL-6 and TNF-α can increase the expression of IDO in both central and peripheral immune cells, including monocytes and macrophages. In addition, recently, vascular endothelial cells have been recognized as an important source of kynurenine, which appears to be a vasodilatory mechanism involved in blood pressure regulation. Kynurenine readily crosses the blood-brain barrier via the large neutral amino acid transporter (LNAAT) in capillary endothelial cells, suggesting that the synthetic capacity of monocytes, macrophages and other peripheral tissues can contribute substantially to central concentrations, normally accounting for 60% of central kynurenine. It was first suggested that IDO activity may contribute to depressive symptoms by reducing the availability of tryptophan, the precursor for the synthesis of serotonin and melatonin. Later, it was also recognized that the microglial metabolites of kynurenine, including quinolinic acid, 3-hydroxykynurenine and 3-hydroxyanthranilic acid, can have appreciable neurotoxicity.
particular importance, quinolinic acid, an endogenous \( N \)-methyl-D-aspartate (NMDA) agonist can overstimulate NMDA receptors found, for example, on hippocampal neurons, leading to depolarization by excessive \( \text{Ca}^{2+} \) influx, excessive free-radical production, and neuronal apoptosis\textsuperscript{96, 105, 108-111}. 
**Figure i. Human tryptophan metabolism (abridged).** Tryptophan, 5-hydroxytryptophan and L-kynurenine can be transported across the blood brain barrier endothelial cells by the large neutral amino acid transporter (LNAAT). Peripheral tryptophan homeostasis is maintained predominantly by hepatic TDO. Glucocorticoids can induce TDO\(^{112}\) and IDO can be induced by pro-inflammatory cytokines, producing N-formylkynurenine (rate-limiting step). L-kynurenine is produced from N-formylkynurenine by kynurenine formamidase (KF). Peripheral L-kynurenine can relax vascular smooth muscle causing vasodilatation\(^99\), while the L-kynurenine metabolites produced by kynurenine monoxygenase (KMO), kynurenine aminotransferase II (KAT II) and kynureninase (KYNU) have various immunoregulatory functions. KYNU can convert 3-hydroxy-L-kynurenine into 3-hydroxyanthranilic acid and L-kynurenine into anthranilic acid. Anthranilic acid can be hydroxylated and subsequently converted into quinolinic acid by 3-hydroxyanthranilate 3,4-dioxygenase (HAO). The enzymatic conversion of 2-amino-3-carboxymuconate semialdehyde by aminocarboxymuconate semialdehyde decarboxylase (ACMSD) into 2-aminomuconate semialdehyde (and subsequent non-enzymatic conversion into picolinic acid) competes for the formation of quinolinic acid. Peripheral synthesis of kynurenine can contribute substantially to central kynurenine concentrations via transport across the blood brain barrier endothelial cells by the large neutral amino acid LNAAT. Peripheral kynurenine and tryptophan crossing via the LNAAT can be taken up and metabolized within the CNS into kynurenic acid by astrocytes or into quinolinic acid by microglia\(^{113}\). Peripheral tryptophan can also be converted by tryptophan hydroxylase 2 (TPH2) into 5-hydroxy-L-tryptophan, which can also cross the blood brain barrier. In the CNS, tryptophan and 5-hydroxy-L-tryptophan give rise to serotonin and melatonin via the activities of dopa decarboxylase (DDC), aralkylamine N-acetyltransferase (SNAT) and acetylserotonin O-methyltransferase (ASMT). 5-hydroxy-L-tryptophan in the periphery can be converted into serotonin by DDC, or into 5-hydroxy-L-tryptophan by IDO, and subsequently into 5-hydroxykynurenamine, which is a potently vasoactive and antithrombotic 5-hydroxytryptamine (5-HT) antagonist\(^{114}\).
Quinolinic acid excitotoxicity is endogenously attenuated by another kynurenine metabolite, kynurenic acid, which acts as an uncompetitive antagonist at NMDA receptors at their glycine site, and \( \alpha_7 \) nicotinic receptors\(^\text{115} \), reducing NDMA activity by both pre- and post-synaptic mechanisms\(^\text{116-118} \). Accordingly, endogenous kynurenic acid concentrations control the vulnerability of hippocampal and striatal neurons to degeneration in the presence of quinolinic acid\(^\text{115,119} \). Under pathological conditions including cerebral ischemia, brain quinolinic acid concentrations can increase 10- to 100-fold\(^\text{120} \) and neuronal damage can be potentiated by the presence of other inflammatory mediators such as IL-1\( \beta \)\(^\text{121} \). In addition, quinolinic acid can induce an increase in glial fibrillary protein and a reduction in vimentin concentrations at physiological concentrations in primary human astrocyte cultures\(^\text{122} \), consistent with astrogliosis and suggestive of potent neuroinflammatory effects.

The involvement of neuroinflammation in depressive symptoms has been suggested by increased concentrations of IL-6 in the cerebrospinal fluid of suicide attempters (which was proportional to the severity of depressive symptoms)\(^\text{123} \), increased expression of IFN-\( \gamma \) and IL-18 in post-mortem brain tissue from MDD patients as compared to age, gender and post-mortem interval matched control subjects\(^\text{124} \), and higher cerebrospinal fluid concentrations of IL-1\( \beta \) and lower soluble IL-2 receptor concentrations in MDD patients as compared to controls\(^\text{125,126} \). Thus, quinolinic acid might also contribute to depressive symptoms secondary to inflammatory activity and to the symptoms of MDD by directly damaging neurons and by perpetuating a neuroinflammatory response. Clinically, increased concentrations of kynurenine and its metabolites have been observed in patients with MDD\(^\text{127-129} \), and correlated with depressive symptoms and incomplete remission of symptoms following therapy\(^\text{130} \). Taken together, this cascade constitutes a neurodegenerative hypothesis of depression\(^\text{86} \).

Wirleitner et al., observed that the K/T ratio was higher in subjects with CAD than in control subjects, and that it increased numerically with the number of arteries involved, reaching the highest levels in those with restenosis of a previously revascularized lesion\(^\text{131} \). In addition, the K/T ratio was found to correlate with risk factors for CAD, including lower HDL cholesterol and higher CRP concentrations in a large cohort of young adults\(^\text{132} \). The K/T ratio was elevated in patients post-stroke (n=50) compared to control subjects (n=35) in a study reported by Darlington and colleagues, remaining higher than control subjects without stroke throughout the study (14 days), which suggests the stability of the K/T ratio as a biomarker\(^\text{133} \). These findings suggest that the vascular and neurodegenerative hypotheses for depression may converge in patients with CAD due to the immune dysfunction associated with atherosclerosis and
susceptibility to cerebral infarction. Thus, patients with CAD may be predisposed to depressive symptoms and this may be indicated clinically by an elevated K/T ratio (Chapter 3).

Novel therapeutics for depression in CAD are a particularly important unmet medical need since a large proportion of CAD patients with depression do not respond to current therapies. While randomized controlled trials have established the safety of currently available serotonergic antidepressants in CAD patients with MDD, their efficacy has been limited, reporting only modest differences between active treatment vs. placebo groups. In one large trial using citalopram, Lesperance and colleagues reported that 64.1% of patients continued to suffer depressive symptoms after 12 weeks of treatment and 52.8% of patients met criteria for response. Non-response to antidepressant therapy may be a particularly important prognostic marker. In one trial using mirtazepine, the incidence of future acute coronary syndromes was higher in non-responders (25.4%) than in responders (7.4%). Mortality rates were comparably increased in patients refractory to sertraline and cognitive behavioral therapy. These findings are particularly intriguing given that concentrations of kynurenine and its metabolites decline only in MDD patients whose depressive symptoms remit, regardless of which of the current therapies are used and that the K/T ratio is predictive of mortality and future acute coronary syndromes in patients with CAD. Thus further exploration of the kynurenine hypothesis may yield attractive additions to the pharmacological armamentarium for the treatment of depression in this population, which might more proximally target the pathoetiology of the symptoms.

I.iii. Cognitive performance and CAD

Cognitive performance is particularly critical in aging populations where it can predict functional decline, progression to dementia and fatality. Measures of CAD including arterial thickening, coronary artery calcification and the presence of atherosclerotic plaques, and vascular risk factors themselves have been associated with cognitive decline, including increased risks of mild cognitive impairment (MCI) and progression to Alzheimer’s disease (AD). In patients with Alzheimer’s disease, indications of white matter damage on magnetic resonance imaging (MRI) scans interact with cerebral atrophy, a hallmark of the disease, predicting a much greater rate of cognitive decline in patients with both indications of pathology.

Common deficits in cognitive performance associated with CAD and vascular risk factors include poorer performance on tests of executive function and verbal memory. Numerous studies of
CAD populations have demonstrated subtle changes at all stages of disease progression; prior to acute cardiovascular events\textsuperscript{162}, pre-operatively but post-MI\textsuperscript{161}, and following CABG surgery\textsuperscript{163, 164}. Longitudinal studies show that cognitive deficits often persist after CABG and that poorer post-operative performance can predict poorer performance 5 years post-CABG\textsuperscript{165}. Cumulative effects of obesity and hypertension, have been observed prospectively on learning, memory and executive function\textsuperscript{166, 167}. Hypertension has been correlated with poorer executive function and memory performance\textsuperscript{168, 169}. Hypertension\textsuperscript{155} and abnormal lipid metabolism, including low HDL cholesterol concentrations\textsuperscript{170} and high total cholesterol concentrations\textsuperscript{171, 172}, have been associated with clinical cognitive decline and dementia, while antihyperlipidemic statins may have protective effects\textsuperscript{171-175}. These associations between measures of cognition and cardiac risk factors or cardiac histories common in the presentation of CAD in CR suggest that these factors, alone or in combination, may contribute to cognitive performance in this population.

In patients with CAD, cognitive function is a significant determinant of overall quality of life\textsuperscript{19} and daily functioning, as exemplified by associations with unemployment, failure to return to work following an acute coronary syndrome, sick leave, early retirement\textsuperscript{176}, mortality\textsuperscript{149, 177, 178} and physical disability\textsuperscript{179}. It has been suggested that atherosclerosis and hypertension may lead to diffuse embolic or hemorrhagic infarctions in, or secondary inflammatory damage to brain regions subserving memory and decision making ability, which could contribute to poorer self-care and therefore result in poorer medical prognoses\textsuperscript{180}; however, little prospective evidence has been obtained in this population. The survival benefit of CR suggests the need to identify independent prospective clinical predictors of noncompletion\textsuperscript{10}; however, the clinical significance of cognitive performance in CR has not been assessed. Because vascular processes that contribute to cognitive dysfunction may also contribute to depressive symptoms\textsuperscript{181, 182}, these two sequelae may be related, necessitating proper statistical attention to determine their independence in predicting clinical outcomes, and the nature of their interaction, if any (Chapter 5).

While the importance of vascular health in the maintenance of cognitive function has been established, it remains unclear why some patients with CAD develop deficits in cognitive performance while others do not, and how these deficits might be prevented or reversed. The efficacy and tolerability of the currently available cognitive enhancing agents, predominantly acetylcholinesterase inhibitors, have been limited in patients with cognitive symptoms that do not meet criteria for dementia, and the evidence does not seem to suggest that these agents can delay cognitive decline\textsuperscript{183-187}. In addition, only small
improvements of uncertain clinical significance are seen with these agents in dementia of vascular origin (reviewed\textsuperscript{188}). However, in medically healthy older adults, a body of epidemiological evidence supporting an association between self-reported physical activity\textsuperscript{189,190} or objectively measured cardiopulmonary fitness\textsuperscript{20} and preservation of cognitive performance is growing. Presently, no studies have focused on a population of patients with CAD. Patients with CAD typically demonstrate lower than average cardiopulmonary fitness\textsuperscript{8,191} and the cognitive deficits described above. The epidemiological evidence suggests the need to determine whether cardiopulmonary fitness is associated with cognitive performance in a population of patients with CAD entering CR. An informative study would consider the VO\textsubscript{2Peak} in models controlling for other common vascular risk factors and comorbidities that have been previously related to cognitive deficits (Chapter 4).

While exercise interventions can bring about cognitive improvement\textsuperscript{23}, improvements in VO\textsubscript{2Peak} have not always been correlated directly with improvements in cognition\textsuperscript{192} suggesting the need to further explore the mechanisms involved. Physical activity is known to improve multiple vascular risk factors including lipid parameters in medically healthy older adults\textsuperscript{193,194} but the mechanisms supporting improved cognitive function in humans are not clearly established. It is possible that the anti-hyperlipidemic and anti-inflammatory effects of exercise might contribute to reduced formation of sclerotic lesions in the carotid arteries that can lead to embolism in the cerebrovasculature, to improved vascular endothelial function improving cerebral perfusion\textsuperscript{195,196}, or to the stabilization of plaques preventing further infarctions of the small cerebral vessels, all of which might result in improved or preserved cognitive function\textsuperscript{197-199}. MRI studies have shown an association between cardiopulmonary fitness and greater volumes of grey and white matter in medically healthy older subjects\textsuperscript{200,201}, and that aerobic exercise can prospectively increase grey and white matter volumes\textsuperscript{202,203}. Preservation of frontal lobe and hippocampal gray matter, and white matter volumes associated with cardiopulmonary fitness would be predicted to spare executive functions and overall memory performance. Increases in cerebral vascularization and increased neurogenesis due to the release of brain derived neurotrophic factor (BDNF) have been proposed as possible mechanisms underlying volumetric brain changes and cognitive improvement associated with physical activity\textsuperscript{203-206}.

Considerable evidence from patients with CAD suggests increased susceptibility to brain insults compromising cerebral tissue, including increased findings of silent infarctions, white matter hyperintensities, and cerebral atrophy in MRI studies\textsuperscript{207-210}. While not necessarily a direct consequence of atherosclerosis in the coronary arteries, the presence of these radiological findings defines CAD as an
important high-risk population, since these changes have been implicated in the development of cognitive impairment, particularly subtle cognitive changes that may be clinically unnoticed\textsuperscript{208, 211-214}. Substantial evidence suggests that cerebral infarction can initiate or exacerbate inflammatory cascades leading to increased neuronal degeneration\textsuperscript{215-220}. Considering ischemic stroke as a model, infarcts in the middle cerebral artery territory can lead to atrophy in territories exceeding the tissue affected by the primary stroke lesion\textsuperscript{221}. The atrophy observed in other vascular territories is suggestive of secondary neurodegenerative processes initiated by the infarction\textsuperscript{221}. Thus, intrinsic degenerative processes might contribute to cerebral atrophy, leading to the development of cognitive impairment in susceptible patients.

Neurotrophic factors, such as BDNF, induce cell survival pathways and suppress intrinsic cellular apoptotic machinery\textsuperscript{222-224}. Thus, BDNF not only influences neuronal proliferation, survival, and differentiation by well characterized pathways\textsuperscript{225}, but in addition, it is involved in resilience to tissue injury\textsuperscript{226-228}. Both BDNF and its cognate tropomyosin related kinase B (TrkB) receptor are immediate early genes induced by ischemic brain injury\textsuperscript{229-231} and evidence from human and animal studies suggests that BDNF can promote adaptive neuronal plasticity, neuroprotection and functional recovery after focal ischemia\textsuperscript{232-235}. These observations suggest that BDNF may also be involved in important compensatory neuroprotective mechanisms in patients with CAD. If this is true, it is hypothesized that an association between serum BDNF concentrations and cognitive performance may be observable in patients with CAD (Chapter 6).
I.iv Hypotheses

Investigations supporting this thesis concerned two parallel sets of hypotheses. The first set examining depressive symptoms and the second examining cognitive performance, both in relation to physical activity in patients with CAD (a concept map relating these hypotheses can be found in Appendix II). These hypotheses are developed along 3 themes; establishing phenomenology, examining clinical significance prospectively and identifying associated biomarkers:

*Set 1: Cardiopulmonary fitness and depression in CAD*

Chapter 1: Depressive symptoms will be associated with poorer cardiopulmonary fitness in a cohort of patients with CAD entering CR.

Chapter 2: Depressive symptoms and MDD at baseline will be prospectively associated with noncompletion of CR.

Chapter 3: Depressive symptoms will be associated with higher K/T ratios in a cohort of patients with CAD entering CR.

*Set 2: Cardiopulmonary fitness and cognitive performance in CAD*

Chapter 4: Poorer cognitive performance will be associated with poorer cardiopulmonary fitness in a cohort of patients with CAD entering CR.

Chapter 5: Poorer cognitive performance at baseline will be associated with noncompletion of CR.

Chapter 6: Poorer cognitive performance will be associated with lower serum BDNF concentrations in a cohort of patients with CAD entering CR.
I.v Summary of methods and specific aims

The first 3 chapters of this thesis explore the relationships between cardiopulmonary fitness and depressive symptoms. First, a cross-sectional cohort study was used to establish that depressive symptoms are associated with poorer cardiopulmonary fitness among patients with CAD entering CR. Second, a prospective observational cohort study was used to determine whether a clinical diagnosis of MDD could predict non-completion of cardiac rehabilitation, and to contrast the effectiveness of CR for patients with and without MDD. Third, an observational cohort study was used to assess associations between the K/T ratio, depressive symptoms and cardiopulmonary fitness.

The next 3 chapters of this thesis explore the relationships between cardiopulmonary fitness and various measures of cognitive performance in this population. First, a cross-sectional cohort study design was used to qualify cardiopulmonary fitness as an independent predictor of cognitive performance in patients entering CR. Second, a prospective cohort study was used to determine whether performance on a sensitive verbal memory test could predict non-completion of CR. Third, a cross-sectional cohort study of patients entering CR was used to explore serum BDNF concentrations as a biomarker potentially related to cognitive performance and cardiopulmonary fitness naturalistically.
II.

Chapter 1:

The Relationship Between Cardiopulmonary fitness and depressive symptoms in cardiac rehabilitation patients

1.1 Statement of work and disclosure

Published in the Journal of Rehabilitation Medicine (Swardfager W, Herrmann N, Dowlati Y, Kiss A, Oh P, Lanctôt KL. J Rehabil Med. 2008;40(3):213-18.), this study assembled a cohort of patients entering CR in which our group had implemented depression screening using the Center for Epidemiological Studies Depression (CES-D) scale\textsuperscript{236}. This data was collected by the staff of the Toronto Rehabilitation Institute, Cardiac Rehabilitation facility under the direction of Dr. Oh as per this newly established clinical practice. The primary author, under the guidance of Dr. Kiss, assembled the cohort from the database and conducted all statistical analyses. Drs. Lanctôt and Herrmann contributed to the study concept and design. Ms. Dowlati assisted with descriptive statistics. All authors contributed to the writing and/or editing of the manuscript.

1.2 Abstract

Objective: To identify independent predictors\textsuperscript{ii} of depressive symptoms in a cohort of patients with coronary artery disease (CAD) entering cardiac rehabilitation. Design: Cross-sectional cohort study. Patients and Methods: Consecutive patients entering a cardiac rehabilitation and secondary prevention program underwent screening for depressive symptoms using the Center for Epidemiological Studies Depression (CES-D) scale and cardiopulmonary fitness testing to quantify peak oxygen consumption (VO\textsubscript{2} Peak). Results: 22.3\% of patients with CAD (n=366) reported at least mild (CES-D≥16) and

\textsuperscript{ii}The term “predictor” was used in this study only to distinguish an independent variable from a dependent variable in a linear regression model. All associations in this study were cross-sectional and no prospective comparisons were made. The design of the statistical model, with respect to choice of independent vs. dependent variable does not imply an assumption about the direction of causation; the model is chosen to assess the proportion of variance in the dependent variable of interest associated with the independent variables.
10.4% reported significant (CES-D≥23) depressive symptoms. Antidepressant medications were being used by 6.3% of patients. Sociodemographic, cardiopulmonary and cardiac characteristics, and medical comorbidities previously associated with depression accounted for 14.7% of the variance in a multiple linear regression model (F=8.713, p<0.001) predicting CES-D scores. Significant independent predictors of CES-D scores were lower VO$_{2}$Peak, younger age, female sex, lower maximum diastolic blood pressure, angina and antidepressant use. Conclusion: Reduced physical fitness, younger age, female sex and ischemic symptoms of CAD predict higher depressive symptoms in patients entering cardiac rehabilitation.

1.3 Introduction

Coronary artery disease (CAD) is a leading cause of disability, mortality and health care utilization in developed countries. In Canada, one in four men and one in five women suffer from some form of heart disease. Depressive symptoms are common in persons with CAD where they increase the risk of mortality independently of medical risk factors and interfere with cardiac rehabilitation.

Despite demonstrated correlations between depressive symptoms and low activity levels, relatively few investigations have focused on the association between depressive symptoms and cardiopulmonary fitness in patients with CAD. Since a primary focus of rehabilitation is to improve cardiopulmonary fitness, the interaction between fitness and depressive symptoms may be of substantial clinical importance. In addition, CAD is associated with multiple comorbid medical conditions and risk factors. Hypertension, diabetes, COPD, and symptoms of CAD such as angina pectoris have been associated with an increased prevalence of depression and medications used in the management of these conditions such as ß-blockers and statins have been suggested to interact with depressive symptoms.

The goal of this study was to measure the prevalence of depressive symptoms and identify independent predictors of depressive symptoms in patients with stable CAD entering cardiac rehabilitation. Knowing predictors may be useful to clinicians and they can be used to inform future studies designed to understand the etiology of mood complications in this population. The use of psychotropic medications was also characterized in this population. These findings may help to establish strategies to better manage depressive symptoms associated with CAD within the setting of cardiac rehabilitation and to aid in the optimization of rehabilitation for patients suffering depressive symptoms.
1.4 Methods

1.4.1 Setting

This was a cohort study of 366 patients selected from the Toronto Rehabilitation Institute Cardiac Rehabilitation and Secondary Prevention Program (TRI-Cardiac). The TRI-Cardiac is a university-affiliated rehabilitation facility serving an urban population with a catchment area of approximately 2.5 million. Patients recovering from various manifestations of CAD and those with significant cardiac risk factors, various forms of congenital heart defects or diabetes are accepted at the TRI-Cardiac and enrollment is based on physician referral only. All participants provide written informed consent for their clinical data to be used in research investigations in accordance with the Research Ethics Board.

1.4.2 Subjects

Patient demographics, cardiac and other medical morbidities, medical history, cardiopulmonary fitness testing data and concurrent medications were obtained by electronic chart review. A clinical cohort of patients with CAD entering rehabilitation was defined based on a history of myocardial infarction (MI), coronary angiographic evidence of ≥ 50% blockage in at least 1 major coronary artery, or prior revascularization such as percutaneous coronary intervention (PCI) procedures or coronary artery bypass graft (CABG) surgery at the time of enrollment at the TRI-Cardiac (see Figure 1.1). All subjects entered rehabilitation a minimum of 6-8 weeks post-CABG (6 weeks for uncomplicated CABG), a minimum of 6 weeks post-MI, or a minimum of 3 weeks post-PCI. Patients were excluded if they did not perform cardiopulmonary fitness testing, if they were unable to complete the Centre for Epidemiological Studies Depression (CES-D) scale, or if their records were otherwise incomplete.

![Diagram of Cohort with CAD]

Figure 1.1 Definition of a cohort with CAD

366 Participants selected for study
- Evidence of CAD
- Complete medical chart and fitness data
- Completion of the CES-D with 4 or less answers missing

- Insignificant depressive symptoms (CES-D<16)
  - n=284 (77.6%)
- Mild depressive symptoms (CES-D 16-22)
  - n=44 (11.9%)
- Significant depressive symptoms (CES-D>22)
  - n=38 (10.4%)
1.4.3 Methods

1.4.3.1 Depressive symptoms

All patients were screened for depressive symptoms using the CES-D scale. The CES-D scale has been used extensively in CAD populations. The concurrent validity, construct validity and reliability of the CES-D have also been established in community samples. In addition, a cut-off score of 16 on the CES-D has demonstrated high sensitivity (100%) and specificity (88%) for detecting DSM (Diagnostic and Statistical Manual)-IIIR diagnosed depression in older subjects and an adequate sensitivity (60% major depression and 71% minor depression) and specificity (83% and 83% respectively) in community samples. Importantly, increasing rates of medical illnesses are not related to the number of false positives using the CES-D.

1.4.3.2 Cardiopulmonary fitness

As part of standard clinical protocol, a cardiopulmonary fitness assessment was carried out. Clinical assessment was performed under medical supervision by a multidisciplinary team including trained exercise physiologists. The exercise stress test, as previously described, was used to measure cardiopulmonary responses to increasing intensities of exercise. Measures included the anaerobic threshold, peak heart rate, maximum blood pressure and peak oxygen consumption (VO$_{2Peak}$). The VO$_{2Peak}$ is the most reliable and reproducible indicator of cardiopulmonary fitness. Resting physiological measurements including heart rate and blood pressure, and anthropometrics including height, mass, girth, and percentage body fat were recorded. Body mass index (BMI) and waist-to-height ratio (WHtR) were calculated as per standard definitions. Since body mass is a composite of fat and muscle masses, and reduced ratios of muscle to fat have been previously documented in the depressed elderly, BMI may be insufficient as an index of body composition. WHtR is an index of relative central adiposity, which does not rely on measurement of body mass and may therefore demonstrate superiority as a risk factor.
1.4.3.3 Statistical analysis

Descriptive statistics were calculated for all variables of interest. Continuous measures such as age were summarized using means and standard deviations whereas categorical measures were summarized using counts and percentages.

To determine which clinical variables were the most significant independent predictors of depressive symptoms, a backward elimination linear regression model was performed. Variables associated with depression or depressive symptoms in previous studies of CAD patients were entered into the model including the sociodemographic characteristics age, sex, smoking status and marital status, the anthropometric characteristics BMI and WHtR, resting physiology including heart rate, systolic and diastolic blood pressure, and cardiopulmonary fitness parameters including VO$_2$max, maximum heart rate, and maximum systolic and diastolic blood pressures $^{21, 239-243, 250-252}$. Cardiac factors including history of MI, PCI, CABG, congestive heart failure and cardiac arrest, and the presence of hypertension and angina, and the medical comorbidities diabetes, COPD, cancer, renal disease and stroke that have been previously associated with depression or depressive symptoms were also entered $^{18, 240}$. Concurrent use of statins $^{174}$, β-blockers $^{244}$, antidepressant or anxiolytic medications which may affect depressive symptoms was also entered into the model. Parameters below 5% significance were omitted until parameters could no longer be rejected (exit criterion $p>0.05$). All analyses were two-tailed with results considered significant at $p<0.05$. All analyses were performed using SPSS statistical software (version 13.0, SPSS Inc., Chicago, IL.).

1.5 Results

1.5.1 Patient characteristics and incidence of depressive symptoms

The sociodemographic characteristics of patients recruited into this study are summarized in Table I.I. Between September 2004 and June 2005, there were 366 patients enrolled. Seventy-six percent were male and 71% were married. The mean age of patients was 63.6 (SD 10.7) years. Of all patients, 22.3% (n=82) showed at least mild (CES-D≥16) and 10.4% (n=38) showed significant (CES-D≥23) depressive symptoms (see Figure 1.1).

Only 6.3% of patients (n=23) were using antidepressant medication and 9.3% (n=34) were using an anxiolytic. The most common medications included selective serotonin reuptake inhibitor (SSRI).
antidepressants, the serotonin and norepinephrine reuptake inhibitor venlafaxine, and benzodiazpine anxiolytics. Of patients showing significant depressive symptoms (CES-D≥23, n=38), 31 (82%) were not using an antidepressant and of patients showing at least mild depressive symptoms (CES-D≥16, n=82), 71 (87%) were not using an antidepressant.
Table I.I Patient Characteristics

<table>
<thead>
<tr>
<th>Sociodemographic</th>
<th>Prevalence (%)</th>
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<tbody>
<tr>
<td>Age</td>
<td>63.6 (SD 10.7) years</td>
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<tr>
<td>Employment</td>
<td>128 (34.9 %)</td>
</tr>
<tr>
<td>Unmarried/divorced/widowed</td>
<td>105 (28.7 %)</td>
</tr>
<tr>
<td>Sex (female)</td>
<td>88 (24.0 %)</td>
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<tr>
<td>Current Smoking Status</td>
<td>21 (5.7 %)</td>
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<tr>
<th>Cardiac Factors and Diagnoses iii</th>
<th>Prevalence (%)</th>
</tr>
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<tbody>
<tr>
<td>Myocardial Infarction</td>
<td>206 (56.2 %)</td>
</tr>
<tr>
<td>PCI</td>
<td>175 (47.8 %)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>170 (46.4 %)</td>
</tr>
<tr>
<td>CABG</td>
<td>136 (37.2 %)</td>
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<tr>
<td>Valvular Heart Disease</td>
<td>30 (8.2 %)</td>
</tr>
<tr>
<td>Angina</td>
<td>29 (7.9 %)</td>
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<tr>
<td>Conduction Deficit</td>
<td>29 (7.9 %)</td>
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<tr>
<td>Congestive Heart Failure iv</td>
<td>23 (6.3 %)</td>
</tr>
<tr>
<td>Cardiac Arrest</td>
<td>14 (3.8 %)</td>
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<tr>
<td>Pacemaker</td>
<td>9 (2.4 %)</td>
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<table>
<thead>
<tr>
<th>Medical Comorbidities</th>
<th>Prevalence (%)</th>
</tr>
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<tbody>
<tr>
<td>Diabetes</td>
<td>103 (28.1 %)</td>
</tr>
<tr>
<td>COPD</td>
<td>27 (7.4 %)</td>
</tr>
<tr>
<td>Cancer</td>
<td>22 (6.0 %)</td>
</tr>
<tr>
<td>Renal Disease</td>
<td>18 (4.9 %)</td>
</tr>
<tr>
<td>Stroke</td>
<td>15 (4.1 %)</td>
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<tr>
<td>Peripheral Vascular Disease</td>
<td>14 (3.8 %)</td>
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<table>
<thead>
<tr>
<th>Concomitant Medications</th>
<th>Prevalence (%)</th>
</tr>
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<tbody>
<tr>
<td>Statins</td>
<td>335 (91.5%)</td>
</tr>
<tr>
<td>β-blockers</td>
<td>301 (82.2%)</td>
</tr>
<tr>
<td>Nitroglycerin</td>
<td>151 (41.3%)</td>
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<tr>
<td>Antidiabetic agents</td>
<td>77 (21.0%)</td>
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<tr>
<td>Ca²⁺-Channel Antagonists</td>
<td>68 (18.6%)</td>
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<tr>
<td>Antiasthmatic agents</td>
<td>29 (7.9%)</td>
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<table>
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<tr>
<th>Psychotropic Medications</th>
<th>Prevalence (%)</th>
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<tbody>
<tr>
<td>Anxiolytics</td>
<td>34 (9.3%)</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>24 (6.3%)</td>
</tr>
<tr>
<td>Other Classes</td>
<td>5 (1.4%)</td>
</tr>
</tbody>
</table>

SD=standard deviation; COPD=chronic obstructive pulmonary disorder; PCI=percutaneous coronary intervention; CABG=coronary artery bypass graft;

iii The cumulative incidence of PCI and CABG was 302 (82.5%). This variable was associated with lower CES-D scores in bivariate analyses (β=-.140, p=.007) but it was not a significant predictor (β=-.031, p=.588) when forced into a multiple regression model controlling for angina and other variables in Table I.III, although angina remained associated with CES-D scores (β=.178, p=.002). This suggests that a post-surgical alleviation of angina symptoms did not account for the association between CES-D and angina reported in Table I.III.

iv Indicates a lifetime history of heart failure
1.5.2 Physiological and cardiopulmonary characteristics

Patient physiological and exercise characteristics are summarized in Table I.II. The mean VO_2Peak was 17.1 (SD 4.7) ml/kg/min, which is approximately 65% of an age-matched norm and considered very poor for patients of this age. The mean BMI was found to be 28.0 (SD 4.7) kg/m^2 which is associated with an increased risk of cardiovascular complications. Of all patients, 45.1% were classified as overweight (BMI between 25 and 30 kg/m^2) and 27.3% were classified as obese (BMI ≥ 30 kg/m^2). The mean WHtR was found to be 0.569 (SD 0.074) which is classified as overweight and characterizes the risk of cardiovascular complications to be significant.

### Table I.II: Patient Physiological Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anthropometric</strong></td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td>28.0 (4.7) kg/m^2</td>
</tr>
<tr>
<td>Percentage Body Fat</td>
<td>28.8 (9.1) %</td>
</tr>
<tr>
<td>Waist-to-Height Ratio</td>
<td>0.569 (0.074)</td>
</tr>
<tr>
<td><strong>Resting Physiology</strong></td>
<td></td>
</tr>
<tr>
<td>Resting Heart Rate</td>
<td>66.9 (12.7) BPM</td>
</tr>
<tr>
<td>Resting Systolic BP</td>
<td>131.8 (20.2) mm Hg</td>
</tr>
<tr>
<td>Resting Diastolic BP</td>
<td>72.9 (9.6) mm Hg</td>
</tr>
<tr>
<td><strong>Fitness Parameters</strong></td>
<td></td>
</tr>
<tr>
<td>VO_2Peak</td>
<td>17.1 (4.7) ml/kg/min</td>
</tr>
<tr>
<td>Anaerobic Threshold</td>
<td>13.2 (3.0) ml/kg</td>
</tr>
<tr>
<td>Max Heart Rate</td>
<td>113.1 (22.3) BPM</td>
</tr>
<tr>
<td>Maximum Systolic BP</td>
<td>176.6 (28.2) mm Hg</td>
</tr>
<tr>
<td>Maximum Diastolic BP</td>
<td>79.1 (11.9) mm Hg</td>
</tr>
</tbody>
</table>

SD=standard deviation; BMI=body mass index; BP=blood pressure

1.5.3 Predictors of depressive symptoms

When sociodemographic variables, cardiac factors, medical comorbidities, concomitant medications and fitness parameters previously associated with increased depressive symptoms were entered into a backward linear regression, 6 variables remained in the model accounting for 14.7% of the variance (F=8.713, p<.001). Table I.III contains coefficients obtained in the final regression model. This model suggests that a 1 ml/kg/min decrease in VO_2Peak is associated with a 0.424 point increase in CES-D score, that a 1 year decrease in age is associated with a 0.17 point increase in CES-D score, and that a 1 mm Hg decrease in maximum diastolic blood pressure is associated with a 0.105 point increase in CES-
Those with angina had a 5.8-point higher CES-D score on average than those without angina. Females had a 2.8-point higher CES-D score on average than males. Patients using an antidepressant had a 5.6-point higher CES-D score on average than those not using an antidepressant.

Table I.III: Coefficients of Linear Regression Model Predicting CES-D Scores‡

<table>
<thead>
<tr>
<th>Independent variables</th>
<th>Coefficient (B)</th>
<th>Std. Error</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>VO(_{2}) Peak</td>
<td>-.424</td>
<td>.128</td>
<td>.001</td>
</tr>
<tr>
<td>Age</td>
<td>-.170</td>
<td>.053</td>
<td>.001</td>
</tr>
<tr>
<td>Angina</td>
<td>5.848</td>
<td>1.854</td>
<td>.002</td>
</tr>
<tr>
<td>Sex</td>
<td>2.795</td>
<td>1.329</td>
<td>.036</td>
</tr>
<tr>
<td>Max Diastolic BP</td>
<td>-.105</td>
<td>.047</td>
<td>.026</td>
</tr>
<tr>
<td>Antidepressant Use</td>
<td>5.607</td>
<td>2.172</td>
<td>.010</td>
</tr>
</tbody>
</table>

‡R=0.408, R square=.166, adjusted R Square=0.147, Std. Error of the Estimate=8.302, p<0.001

1.6 Discussion

A significant correlation between VO\(_{2}\) Peak and CES-D scores was identified in a population of patients with CAD entering rehabilitation. This finding is consistent with the few available reports of correlations between reduced cardiopulmonary fitness and depressive symptoms in patients with CAD\(^{239,250}\). A correlation between VO\(_{2}\) Peak and depressive symptoms has also been identified in women showing no clinical evidence of cardiovascular disease\(^{249}\) suggesting that the relationship between depressive symptoms and fitness may be of broad clinical importance. The present study demonstrates the importance of the VO\(_{2}\) Peak, as it emerged as the strongest predictor of CES-D scores, independent of age, sex, medical complications and concurrent medications. This finding may have implications for treatment. It is possible that exercise prescriptions aimed at improving cardiopulmonary fitness may also be beneficial for the improvement of depressive symptoms in persons with CAD. Longitudinal studies show that depressive symptoms tend to decrease over the course of cardiac rehabilitation\(^{253}\), though it remains unclear which aspects of rehabilitation may be beneficial and whether this improvement is related to an increase in VO\(_{2}\) Peak. It is also possible that depression and cardiovascular disease share etiologic underpinnings such that, rather than treating sequelae, treatment impacting underlying causal factors will be necessary to improve both cardiac outcomes and depressive symptoms.

It has been speculated that psychological features of depression such as reduced motivation, anhedonia and introversion could result in an ongoing reduction in physical activity levels and contribute to
reduced cardiopulmonary fitness in depressed subjects. Deconditioning could lead to loss or weakening of muscle tissue or affect neuronal pathways that regulate heart rate and cardiac output. As a limitation of this study, psychological variables such as the roles of psychosocial wellbeing and social readjustment were not formally assessed. Cardiac rehabilitation may help to improve VO_{2Peak} by interacting with psychological features of depression, reducing motivational barriers and modifying behaviors not conducive to maintaining both cardiac health and positive affect.

In addition to psychological factors, physiological processes associated with depressive symptoms might interact with physical fitness. Recently, plasma levels of interleukin-6, a circulating pro-inflammatory cytokine, have been inversely correlated with the VO_{2Peak} in asymptomatic men. Elevated levels of these cytokines, indicating activation of the inflammatory system, have also been observed in major depressive disorder where they could directly elicit depressive symptoms and thus contribute to reduced physical activity. As atherosclerosis and poor CAD prognoses have been associated with inflammatory activation, this hypothesis may be particularly relevant. In this report, increased depressive symptoms were found in patients with angina, which has been associated with increased plasma levels of pro-inflammatory cytokines. Elevated pro-inflammatory cytokines have also been associated with feelings of exhaustion which may be related to cardiopulmonary fitness and contribute to depressive symptoms. These potential mechanisms require further investigation.

Only 24% of subjects included in this study were female in agreement with previous reports that female patients are less likely to enroll in cardiac rehabilitation following acute coronary events. This suggests the need to investigate possible gender-biases in patient attitudes towards rehabilitation or in physician referrals to rehabilitation. A significant association between female sex and increased CES-D scores was found, indicating that female sex independently predicted increased depressive symptoms. This is in accord with other reports that females are at increased risk of depressive symptoms among cardiac rehabilitation participants. This may be of particular importance since female patients and those with higher depressive symptoms are less likely to complete cardiac rehabilitation. However, when female patients and those with significant depressive symptoms complete rehabilitation, they show significant improvements in lipid profile, BMI and exercise capacity. This suggests that developing methods to improve adherence to rehabilitation in women and depressed patients may be of substantial clinical benefit. Behavior change theory has been suggested as a guiding principle in the design of novel interventions.

\[\text{\textsuperscript{v}}\text{Specifically, the presence of coronary artery disease and significant deconditioning may be causes or consequences of inflammation but the direction of causation has yet to be resolved.}\]

\[\text{\textsuperscript{v}}\]
individualized physical activity interventions for women, which could be integrated into cardiac rehabilitation. In one small trial, women who were randomized to a self-efficacy based intervention showed improvements in physical activity levels and cardiopulmonary fitness whereas women randomized to a more traditionally structured exercise program did not 259. Follow-up intervention has also been shown to protect against symptoms of anxiety and depression in women while improving long-term risk-factor management 260. Cardiac rehabilitation may be an ideal setting to implement additional female gender-focused support.

Depressive symptoms could also be predicted by younger age. This is consistent with reports of increased psychological distress in younger patients with CAD 261. It is possible that depressive symptoms and CAD share common etiopathological factors which mediate the association between depression and poorer CAD prognosis. Patients presenting at a younger age with complications of CAD therefore may be more severely affected by a process that also predisposes them to depressive symptoms. This hypothesis is supported by the observation of increased coronary risk factors in younger CAD patients 261.

Reduced maximum diastolic blood pressure during fitness assessment was independently correlated with CES-D scores, although a correlation with resting diastolic blood pressure was not observed. In studies of older populations, low resting diastolic blood pressure has been associated with depressive symptoms 252, inciting considerable debate concerning possible consequences of aggressive antihypertensive treatment which may include depressive symptoms and increased risks of cardiac and all-cause mortality 262. However, in this population, the correlation of lower maximum diastolic blood pressure with higher CES-D scores could not be accounted for by controlling for hypertension or the use of antihypertensive medications, and the use of antihypertensives was not associated with low blood pressure. This is consistent with another report associating low resting blood pressure with anxiety and depression independently of antihypertensive treatment 252. Reduced maximal blood pressure during stress testing may be related to depressive symptoms through dysregulation of central neuroendocrine systems. For example, chronic activation of the hypothalamic-pituitary-adrenocortical (HPA) axis in depressed patients could result in abnormal glucocorticoid feedback regulation of the HPA axis, or desensitization of pressor responses by downregulation of adrenergic receptors. This could result in the blunted physiological responses to physical exertion observed in CAD patients with depressive symptoms which is reminiscent of the blunted HPA responses documented in patients with depression secondary to other
Lower maximum diastolic blood pressure was correlated with CES-D scores even when controlling for age and the use of antidepressant medications\textsuperscript{vi}.

The rate of antidepressant use in this population was comparable to that reported in other studies of cardiac rehabilitation patients\textsuperscript{265}. Of patients showing significant depressive symptoms only 18\% were using an antidepressant. This suggests that antidepressant medication may be underutilized in this population and that systematic screening for depression at entry into cardiac rehabilitation could help to fulfill an unmet need. It is possible that treatment of depressive symptoms may improve cardiac rehabilitation outcomes. Antidepressant use has been associated with reduced rates of mortality and recurrent MI in post-MI patients with depression\textsuperscript{266}. Similarly, depression has been associated with a reduced likelihood of completing rehabilitation\textsuperscript{253} and treatment of depressive symptoms may interact with adherence to rehabilitation exercise prescriptions. Conversely, adverse risk profiles have been associated with the use of some antidepressants in certain CAD patients\textsuperscript{266}, cautioning physicians to choose safe and effective treatments\textsuperscript{vii}.

Limitations of this study include lack of a diagnostic interview for depression and a lack of recorded psychiatric history. In these patients, it is not known whether psychiatric symptoms preceded or followed acute coronary events. In future studies, it would be interesting to determine if the clinical characteristics of patients with a premorbid psychiatric condition differ from those who suffer depressive symptoms for the first time following an acute coronary event. A further limitation was the absence of an assessment of CAD severity. However, available indicators such as cardiac risk factors and medical/surgical histories were not correlated with CES-D scores and did not differ significantly between those who used antidepressants and those who did not, suggesting that differences in the severity of CAD do not account for the observed associations between depressive symptoms and cardiopulmonary fitness.

In summary, depressive symptoms are prevalent among stable CAD patients entering cardiac rehabilitation and they are frequently untreated. Of the investigated parameters, the most significant

\textsuperscript{vi} The observed association between depressive symptoms and lower resting diastolic blood pressure may reflect an association with stiff resistance arterioles. In a study of 449 adults with MDD and 169 controls arterial stiffness, as measured by calibrated radial tanometry, was independently associated with current MDD, episode duration, and with the severity of anxious and depressive symptoms\textsuperscript{264}. Seldenrijk A, van Hout HP, van Marwijk HW, et al. Depression, anxiety, and arterial stiffness. \textit{Biological psychiatry}. Apr 15 2011;69(8):795-803.

\textsuperscript{vii} While some studies have suggested an association between antidepressant use and survival, this benefit has not been observed in prospective randomized trials (see discussion).
independent predictor of depressive symptoms was the VO$_2$Peak during cardiopulmonary fitness assessment. Depressive symptoms were also predicted by younger age and female sex. The correlation between depressive symptoms and reduced physiological responses to exercise suggests the need to investigate possible psychological and physiological mechanisms mediating this correlation. An increased focus on psychological/psychiatric screening and intervention may improve the effectiveness of cardiac rehabilitation.

1.7 Significance and Impact

This study established that depressive symptoms are associated with cardiopulmonary fitness independent of other clinical characteristics, vascular risk factors, common comorbidities and the use of HMG-CoA reductase inhibitors and beta adrenergic receptor antagonists in a cohort of patients with CAD entering CR. Understanding the factors that contribute independently to experiencing increased depressive symptoms in this population yielded hypotheses about how these symptoms could be treated. The results of this study suggested further longitudinal studies of how these symptoms might change after an exercise intervention. In addition, establishing depressive symptoms as a correlate of an important CR outcome in this population provided a strong rationale to prospectively investigate depressive symptoms as predictors of cardiopulmonary fitness outcomes over the course of CR. As a limitation, the inconclusive nature of the depressive symptoms measured in this study strongly suggested the need to conduct diagnostic interviews for DSM-IV depression criteria in prospective studies. From this study, it was unclear if the association between poorer cardiopulmonary fitness and depressive symptoms was related to the presence of clinically recognizable MDD.
Chapter 2:

Major Depressive Disorder Predicts Completion, Adherence and Outcomes in Cardiac Rehabilitation: A Prospective Cohort Study of 195 Patients with Coronary Artery Disease

2.1 Statement of work and disclosure

The primary author designed the study established a recruitment strategy under the supervision of Drs. Lanctôt, Herrmann and Oh, actively recruited patients, performed patient interviews, designed the study database and tracked patient progress throughout the study. Some patient recruitment and interviews were performed by Ms. Dowlati, Ms. Saleem and Mrs. Sherman. Ms. Dowlati and Ms. Saleem assisted with data entry. Some attendance data were collected from the site and entered into the database by Mr. Farber. Cardiopulmonary fitness testing was performed by Toronto Rehabilitation Institute staff. Ms. Marzolini assisted with the interpretation of fitness data. All statistical analyses were carried out by the primary author under the guidance of Dr. Kiss.

2.2 Abstract

Objective: To compare completion, adherence and clinical cardiac outcomes between subjects with and without major depressive disorder (MDD) undertaking cardiac rehabilitation (CR). Methods: In a prospective cohort study of consecutive patients with CAD (n=195) entering 1-year outpatient CR between January 2006 and August 2008, rates of non-completion (comprehensive CR criteria) and non-adherence (<70% attendance at scheduled CR visits), and CR outcomes were compared between patients with and without MDD based on a structured clinical interview for DSM-IV criteria. Results: MDD was diagnosed in 22.1% of subjects. Rates of non-completion were 44.2% and 28.9%, and rates of non-adherence were 53.0% and 34.9% for those with and without MDD, respectively. MDD was associated with increased risks of non-completion (multivariate hazard ratio [HR], 2.5; 95% confidence interval [CI], 1.3-4.7) and non-adherence (multivariate HR, 2.4; 95% CI, 1.3-4.2). More subjects with MDD

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viii The research interview during which MDD was diagnosed also involved a complete medical history from the patient and administering the CES-D. Permission was sought at the time of the interview to verify the history and obtain more detailed information using the CR site electronic records.

ix The mean time since most recent coronary event was 13.5±11.1 weeks (excluding 5 patients with only remote histories). Time since most recent event was not associated with noncompletion (B=-.006, p=.529) and it did not warrant inclusion in the model assessing the association between
failed to complete CR for medical reasons than those without MDD (25.6% vs. 12.3%, $p=.031$) in comparisons post-hoc. Subjects with MDD achieved poorer cardiopulmonary fitness increases (change in peak oxygen uptake of $3.3 \pm 3.2$ vs. $6.6 \pm 5.7$ ml/kg/min; $p=.021$) and poorer body fat outcomes (an increase of $2.1 \pm 4.5\%$ vs. a decrease of $0.4 \pm 3.4\%$, $p=.009$) than those without MDD. Conclusion: MDD was associated with poorer rates of completion and adherence in CR and it mitigated improvements in clinical outcomes. Despite depression screening and psychosocial support as structured components of care, MDD remained a significant barrier to effective CR.

2.3 Content

The material comprising this chapter was published (Swardfager W, Herrmann N, Marzolini S, Saleem M, Farber S, Kiss A, Oh P, Lanctôt KL. *J Clin Psychiat*. 2011;72(9):1181-1188; Epub, Nov 2, 2010) and it is copyrighted to the Physicians Postgraduate Press (2010). The content of this chapter can be found on the publisher’s website:


MDD and noncompletion as per prespecified model building criteria. Of the sample, 7 patients had a history of class I heart failure (1 with MDD and 6 non-MDD), but this was not associated with MDD (Chi-square=.236, $p=.528$) or with non-completion ($B=-.825$, $p=.112$) and it did not warrant inclusion in the survival model ($B$ for MDD was adjusted from $-.613$ to $-.597$, remaining significant at $p=.033$).

* Differences in mean changes in $\text{VO}_{2\text{Peak}}$ ($F=4.40$, $p=.038$), percentage body fat ($F=7.75$, $p=.006$) and waist circumference ($F=2.58$, $p=.111$) between MDD and non-MDD patients were not altered in models controlling for the use of antidepressant medications.
2.4 Significance and impact

This study confirmed the results of previous and concurrent studies documenting an association between depressive symptoms and non-adherence to CR\textsuperscript{237, 268-270}. This study qualified previous findings by showing that depressive symptom screening, specifically a cut-off score of 16 on CES-D, can be of clinical utility comparable to a psychiatric diagnosis of MDD based on DSM-IV criteria in the setting of CR. Importantly, depression screening and treatment were included as structured components of care in the CR program studied, but the association between MDD and non-completion of CR was not attenuated by the use of these services. Despite the availability of these services and systematic referral based on screening, psychosocial supports remained underutilized by patients with MDD.

This study further showed that even among patients who remained adherent to CR over 1 year, those with MDD showed smaller gains in cardiopulmonary fitness and less loss of abdominal girth compared to those without MDD over 1 year. These observations demonstrate the evolution of differential cardiometabolic risk profiles over the course of a long-term fitness intervention, i.e. a “cardiometabolic toll” of MDD in this population. These findings will be of interest to clinical psychiatrists and CR staff as they consider the management of patients with CAD and comorbid MDD\textsuperscript{271, 272}. The data are consistent with epidemiological studies showing co-occurrence of the cardiometabolic syndrome with MDD\textsuperscript{273}.

For the purposes of the present study, reasons for dropout/discharge were recorded. Interestingly, the increase in attrition from CR associated with MDD was attributable to an increased impact of medical morbidity. This suggests that, among patients with CAD and comorbid MDD who are motivated and physician-selected to take part in CR, “lack of interest” per se may be less important as a barrier than medical morbidity. Targeted support to ensure adequate control of vascular risk factors and/or monitoring/treating medical morbidity may be required in order to ensure continued ability to participate. These findings are analogous to observations from the workforce, where subjects with MDD were more susceptible to disability due to chronic medical conditions (reviewed\textsuperscript{274}). The increased rates of morbidity in subjects with MDD warrant further attention.
Chapter 3:

Indoleamine 2,3-dioxygenase Activation and Depressive Symptoms in Patients with Coronary Artery Disease.

3.1 Statement of work and disclosure

This work was published in Psychoneuroendocrinology (Swardfager W, Herrmann N, Dowlati Y, Oh P, Kiss A, Walker S, Lanctôt KL. Psychoneuroendocrinology. 2009;34(10):1560-6)\textsuperscript{275}. The primary author designed the study and actively recruited patients under the supervision of Drs. Lanctôt, Herrmann and Dr. Oh, performed patient interviews, performed phlebotomy and blood sample preparation, designed the database and entered the data. Some patient recruitment and interviews were performed by Ms. Dowlati and Mrs. Sherman. Ms. Dowlati also assisted with data entry. HPLC assays were performed by the Pharmacy Department in the laboratory of Professor Walker. Cardiopulmonary fitness testing was performed by Toronto Rehabilitation Institute staff. All statistical analyses were carried out by the primary author under the guidance of Dr. Kiss. Drs. Lanctôt and Herrmann oversaw and contributed to the study concept, design and analysis.

3.2 Abstract

An increase in immune-stimulated synthesis of kynurenine from tryptophan by indoleamine 2,3-dioxygenase (IDO) has been observed in patients with coronary artery disease (CAD). However, neuropsychiatric correlates of IDO activation remain unexplored. We hypothesize that IDO activation, as measured by the kynurenine to tryptophan (K/T) ratio, is associated with depressive symptoms in those with CAD. This cross-sectional study recruited subjects with CAD (n=95) from a cardiac rehabilitation facility. Demographic, anthropometric and cardiac data were obtained by chart review. Patients using an antidepressant were excluded. The presence of a major depressive episode or minor depression was assessed using a structured clinical interview for depression based on Diagnostic and Statistical Manual 4\textsuperscript{th} edition criteria. The Center for Epidemiological Studies-Depression Scale (CES-D) was used to quantify depressive symptoms. A standardized exercise stress test was used to assess cardiopulmonary fitness as summarized using the peak volume of oxygen consumption (Peak VO\textsubscript{2}). Kynurenine and tryptophan were assayed from fasting plasma samples to obtain the K/T ratio. Higher K/T ratios were significantly associated with higher CES-D scores (β=.322, p=.002) in a linear
regression controlling for time since most recent acute coronary syndrome (tACS), age and sex. Twenty-four patients met criteria for depression (16 major depression; 8 minor depression). There was a trend towards higher K/T ratios in depressed vs. non-depressed patients (45.6±20.0 vs. 38.5±15.7 umol/mol, F=3.778, p=.055) when controlling for age, sex and tACS. Activation of IDO is associated with the severity of depressive symptoms among patients with CAD.

3.3 Introduction

The prevalence of major depressive disorder (MDD) in patients with coronary artery disease (CAD) is roughly twice that of the general population. In addition, many other CAD patients suffer from minor depression, and still others suffer from subsyndromal depressive symptoms that do not meet diagnostic criteria for depression. Major and minor depression have been associated with poorer quality of life and cardiac mortality, while subsyndromal depressive symptoms have been associated with poorer cardiopulmonary fitness.

Studies of patients with CAD have associated depressive symptoms with peripheral pro-inflammatory markers such as IL-6 and C-reactive protein. Pro-inflammatory cytokines can upregulate the expression of indoleamine 2,3-dioxygenase (IDO) which catalyzes the rate-limiting step in the synthesis of kynurenine from tryptophan, increasing the plasma kynurenine to tryptophan (K/T) ratio. Elevated plasma K/T ratios have been observed in patients with CAD compared to controls where they have been correlated with other markers of immune activation and disease progression. Thus the K/T ratio may be an important pathophysiological biomarker in those with CAD.

Previous studies have variably reported evidence of IDO activation in medically healthy depressed patients as compared to controls and recently, the severity of depressive symptoms has been associated with the production of kynurenine and its metabolites in patients with major depression. The possibility of a causal relationship between tryptophan catabolism and depressive symptoms was suggested by Maes, Bonaccorso, et al. (2001) in a study of hepatitis C patients administered IFN-α. The resultant increase in depressive symptoms was correlated with inflammatory markers, and in susceptible patients, major depressive episodes were induced. A more recent study failed to replicate this finding, but not without presenting post-hoc analyses implicating an imbalance of kynurenine metabolites further down the degradation pathway.
The present study tests the hypothesis that IDO activation, as measured by K/T ratios, is associated with depressive symptoms in those with CAD. This study also explored relationships between the K/T ratio and cardiac factors previously associated with depressive symptoms such as obesity\textsuperscript{284}, poorer cardiopulmonary fitness\textsuperscript{236, 239} and specific symptoms of depression in \textit{post-hoc} analyses.

3.4. Method

3.4.1 Participants

Patients with CAD participating in a one year cardiac rehabilitation program involving supervised aerobic and resistance training were recruited. The Toronto Rehab Cardiac Program accepts patients recovering from ACS or cardiac procedures by physician referral. Patients were included based on histories of myocardial infarction (MI), angiographic evidence of $\geq 50\%$ blockage in at least one major coronary artery, or prior revascularization such as percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG) surgery. Patients enter rehabilitation a minimum of six–eight weeks post-CABG, six weeks post-MI, or three weeks post-PCI. Patients were excluded if they could not complete cardiopulmonary fitness testing, the Center for Epidemiological Studies-Depression (CES-D) scale or a structured clinical interview, if they were using an antidepressant, or if their medical records were otherwise incomplete. Patients were also excluded based on the presence of neurodegenerative illness, heart failure, acute viral or bacterial infection, cancer, or psychiatric diagnoses other than depression. Participants provided written informed consent in accordance with local Research Ethics Boards. Consecutive patients were approached until 95 eligible patients agreed to participate (Figure 3.1).
3.4.2 Materials

Depressive symptoms were quantified using the CES-D scale, a 20-item questionnaire scored between 0 and 60 used extensively in CAD populations\textsuperscript{35,244}. Major and minor depression were diagnosed based on a structured clinical interview for Diagnostic and Statistical Manual 4\textsuperscript{th} edition criteria (SCID-IV) criteria\textsuperscript{285}. The Mini Mental State Examination (MMSE) was used to exclude cognitively impaired patients (MMSE < 24).

A standardized exercise stress test was used to measure peak oxygen consumption ($\text{VO}_{2\text{Peak}}$)\textsuperscript{11}, a reliable and reproducible indicator of cardiopulmonary fitness\textsuperscript{248}. Resting and maximal physiological measurements including heart rate and blood pressure, and anthropometrics including height, mass, waist circumference, and percentage body fat were recorded. Body mass index (BMI) was calculated as per standard definition.
3.4.3 Procedure

All participants were approached from among cardiac rehabilitation patients as they performed an exercise stress and they were briefed concerning study procedures. After obtaining informed consent, subjects were administered the SCID-IV and MMSE by a trained researcher and asked to complete the CES-D. Subjects were then asked to return in order to provide a fasting blood sample within the next week. Blood samples were collected in EDTA vacutainer tubes at 0930h ± 30 min following a 12-hour overnight fast. Patients were asked to abstain from all food, beverages and alcohol except they were permitted to drink water and to take their medications. Blood samples were centrifuged at 1000 g for 10 min at 4°C and plasma was separated and stored at -80°C until the time of assay.

3.4.4 Plasma assays

Tryptophan and kynurenine concentrations were determined by high-performance liquid chromatography (HPLC), as described elsewhere\textsuperscript{286, 287}. Tryptophan was measured by isocratic reverse phase HPLC without derivatization and fluorescence detection. For kynurenine, an equal volume of 3% perchloric acid was used for protein precipitation. After centrifugation, the concentration of L-kynurenine in the supernatant was measured by HPLC with UV detection at 258 nm. The mobile phase consisted of 9% acetonitrile in 0.05 M potassium phosphate mono basic, pumped through a reverse phase 5 µm ODS column, 250 mm x 4.6 mm (Symmetry; Waters Corporation, Milford, Massachusetts, United States of America).

3.4.5 Statistical analysis

Continuous measures were summarized using means and standard deviations whereas categorical measures were summarized using percentages. Tryptophan and kynurenine were determined by mass and converted to molar units. Their quotient was multiplied by 1000 to obtain the K/T ratio in units of mmol/µmol.

Two analyses were performed to test our hypothesis. First, an analysis of covariance (ANCOVA) was used to test the association between depression diagnosis and K/T ratios. Age, sex and time since most recent ACS (tACS) were included as covariates \textit{a priori}\textsuperscript{265, 288-291}. Next, a multiple linear regression
model was used to examine the association between K/T ratios and CES-D scores controlling for age, sex and tACS\(^{265, 288-291}\). These analyses were adjusted for multiple comparisons with results considered significant at \(p<.025\).

Several exploratory analyses were also performed \textit{post-hoc}. Associations between other categorical characteristics (e.g. ASA use) and the K/T ratio were assessed \textit{post-hoc} using analyses of covariance (ANCOVA) controlling for age and sex. Linear regression models controlling for age and sex were used to assess correlations between plasma assay results and continuous patient characteristics (e.g. \(\text{VO}_2\text{Peak}\)). In addition, the relationships between K/T ratios and individual CES-D items were explored using Pearson correlations.

All analyses were two-tailed and performed using SPSS statistical software (version 16.0, SPSS Inc., Chicago, Illinois, United States of America).

### 3.5 Results

#### 3.5.1 Clinical characteristics

The sociodemographic characteristics of the 95 subjects are summarized in Table III.I. The time since most recent ACS (tACS; mean± SD) was 36.7 ± 67.4 weeks and the K/T ratio was inversely correlated with tACS (\(r=-.225, p=.030\))\(^{\text{xi}}\). Most patients were using daily low-dose aspirin (92%) and lower K/T ratios were found in these patients (\(F=3.992, p=.049\)) when controlling for age and sex (overall model \(F(3,94)=2.651, p=.038\)). No other associations between K/T ratios and sociodemographic factors, cardiac factors/diagnoses, lipid levels, medical comorbidities or concomitant medications could be identified.

\(^{\text{xi}}\) This time represents the time since most recent cardiac surgery, MI or acute coronary syndrome.
Table III.I: Characteristics of the Study Population

<table>
<thead>
<tr>
<th>Sociodemographic</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs) (mean ± SD)</td>
<td>63.8 ± 11.6 years</td>
</tr>
<tr>
<td>Employed (%)</td>
<td>48</td>
</tr>
<tr>
<td>Unmarried/widowed/divorced (%)</td>
<td>6/6/14</td>
</tr>
<tr>
<td>Sex, male (%)</td>
<td>85</td>
</tr>
<tr>
<td>Past Smoking/Current Smoker (%)</td>
<td>54/1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Psychometric</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Depression, major/minor (%)</td>
<td>24 (16/8)</td>
</tr>
<tr>
<td>CES-D Score (mean ± SD)</td>
<td>11.8 ± 10.8</td>
</tr>
<tr>
<td>MMSE Score (mean ± SD)</td>
<td>28.8 ± 1.7</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cardiac Factors and Diagnoses[^{xii}]</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension (%)</td>
<td>55</td>
</tr>
<tr>
<td>PCI (%)</td>
<td>51</td>
</tr>
<tr>
<td>Myocardial Infarction (%)</td>
<td>51</td>
</tr>
<tr>
<td>CABG (%)</td>
<td>35</td>
</tr>
<tr>
<td>Angina[^{xiii}] (%)</td>
<td>34</td>
</tr>
<tr>
<td>Valvular Heart Disease (%)</td>
<td>6</td>
</tr>
<tr>
<td>Pacemaker (%)</td>
<td>1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Lipids</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Cholesterol (mean ± SD)</td>
<td>3.89 ± 1.19 mmol/L</td>
</tr>
<tr>
<td>HDL Cholesterol (mean ± SD)</td>
<td>1.14 ± 0.41 mmol/L</td>
</tr>
<tr>
<td>LDL Cholesterol (mean ± SD)</td>
<td>2.05 ± 0.78 mmol/L</td>
</tr>
<tr>
<td>Triglycerides (mean ± SD)</td>
<td>1.45 ± 0.84 mmol/L</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Medical Comorbidities</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes (%)</td>
<td>24</td>
</tr>
<tr>
<td>COPD (%)</td>
<td>5</td>
</tr>
<tr>
<td>Cerebrovascular Accident (%)</td>
<td>5</td>
</tr>
<tr>
<td>Peripheral Vascular Disease (%)</td>
<td>4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Concomitant Medications</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Statins (%)</td>
<td>97</td>
</tr>
<tr>
<td>ASA (%)</td>
<td>92</td>
</tr>
<tr>
<td>β-blockers (%)</td>
<td>73</td>
</tr>
<tr>
<td>Antihypertensive (%)</td>
<td>66</td>
</tr>
<tr>
<td>Nitroglycerin (%)</td>
<td>54</td>
</tr>
<tr>
<td>Antidiabetic agents (%)</td>
<td>20</td>
</tr>
<tr>
<td>Ca(^{2+})-Channel Antagonists (%)</td>
<td>16</td>
</tr>
<tr>
<td>Diuretics (%)</td>
<td>16</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Psychotropic Medications</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Anxiolytics (%)</td>
<td>7</td>
</tr>
</tbody>
</table>

CES-D, Center for Epidemiological Studies-Depression Scale; MMSE, Mini Mental State Examination; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; HDL, high-density lipoprotein; LDL, low-density lipoprotein; COPD, chronic obstructive pulmonary disorder; ASA; acetylsalicylic acid. n=95.

\[^{xii}\] No patients with a history of heart failure were included in this study.

\[^{xiii}\] Indicates patients with a history of angina that has required medical treatment, not necessarily those with current symptoms of angina.
3.5.2 Association of the K/T ratio with depressive symptoms

Plasma assay results are summarized in Table III.II. The K/T ratio was a significant independent predictor of CES-D scores ($\beta=.322$, $p=.002$) in a linear regression model controlling for age, sex and tACS (overall model $F(4,90)=4.067$, $p=.005$, adjusted $R^2=.120$). Individual CES-D items found to correlate significantly ($p<.05$) with K/T ratios were 3, 6, 9, 14, 17, 18 and 20, which pertain to “the blues”, depressed mood, “failure” feelings, loneliness, crying, sadness and inability to “get going”. None of the classes of concomitant medications (see Table III.I) significantly altered the association between the K/T ratio and CES-D scores when included in linear regression. A trend was identified ($F=3.778$, $p=.055$) towards a higher mean K/T ratio in depressed (45.6±20.0 umol/mol) compared to non-depressed subjects (38.5±15.7 umol/mol) in ANCOVA controlling for age, sex and tACS (overall model $F(5,92)=2.55$, $p=.033$).

Table III.II Plasma Measures and Adjusted Regression Coefficients in Relation to CES-D Scores

<table>
<thead>
<tr>
<th>Relationship with CES-D Scores Adjusted for Sociodemographic Variables(^1)</th>
<th>Standardized Regression Coefficients(^2)</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kynurenine (mean ± SD) 2.01 ± 0.78 mmol/L</td>
<td>.255</td>
<td>.018</td>
</tr>
<tr>
<td>Tryptophan (mean ± SD) 50.96 ± 8.67 mmol/L</td>
<td>-.196</td>
<td>.068</td>
</tr>
<tr>
<td>K/T ratio (mean ± SD) 40.28 ± 17.04 µmol/mmol</td>
<td>.322</td>
<td>.002</td>
</tr>
</tbody>
</table>

\(^1\)Adjusted for age, sex and time since most recent ACS.
\(^2\)Individual linear regression models between plasma assays and CES-D Scores, n=95

3.5.3 Associations of the K/T ratio with fitness characteristics

In analyses *post-hoc*, the K/T ratio was associated with measures of body composition, resting heart rate and cardiopulmonary fitness in linear regression models controlling for age and sex (Table III.III). The use of concomitant medications (Table III.I) did not significantly alter associations between the K/T ratio and any of these characteristics.
Table III. III: Physiological Characteristics and Adjusted Regression Coefficients in Relation to K/T Ratios

<table>
<thead>
<tr>
<th>Standardized Regression Coefficients</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anthropometric</td>
<td></td>
</tr>
<tr>
<td>BMI (mean ± SD)</td>
<td>28.0 ± 4.5 kg/m²</td>
</tr>
<tr>
<td>Percentage Body Fat (mean ± SD)</td>
<td>27.6 ± 7.1%</td>
</tr>
<tr>
<td>Waist Circumference (mean ± SD)</td>
<td>97.9 ± 13.7 cm</td>
</tr>
<tr>
<td>Resting Physiology</td>
<td></td>
</tr>
<tr>
<td>Resting Heart Rate (mean ± SD)</td>
<td>55.7 ± 22.4 BPM</td>
</tr>
<tr>
<td>Resting Systolic BP (mean ± SD)</td>
<td>131 ± 18.8 mm Hg</td>
</tr>
<tr>
<td>Resting Diastolic BP (mean ± SD)</td>
<td>73.9 ± 10.9 mm Hg</td>
</tr>
<tr>
<td>Fitness Parameters</td>
<td></td>
</tr>
<tr>
<td>VO_{2peak} (mean ± SD)</td>
<td>20.2 ± 6.8 ml/kg/min</td>
</tr>
<tr>
<td>Anaerobic Threshold (mean ± SD)</td>
<td>6.9 ± 2.5 ml/kg</td>
</tr>
<tr>
<td>Max Heart Rate (mean ± SD)</td>
<td>121.9 ± 22.4 BPM</td>
</tr>
<tr>
<td>Maximum Systolic BP (mean ± SD)</td>
<td>178.1 ± 27.8 mm Hg</td>
</tr>
<tr>
<td>Maximum Diastolic BP (mean ± SD)</td>
<td>79.7 ± 11.1 mm Hg</td>
</tr>
</tbody>
</table>

BMI, body mass index; BP, blood pressure.

1 Adjusted for age and sex.
2 Individual linear regression models between physiological characteristics and K/T ratios

3.6. Discussion

The present study reports a mean K/T ratio of 40.3 ± 17.0 mmol/µmol, which is comparable to that of a previous CAD cohort and higher than that of controls\textsuperscript{131}. In the Maes et al. (2001) study of interferon-treated patients, the mean K/T ratio increased from 39±14 to 51±25 mmol/µmol, over 2-4 weeks and depressive symptoms were precipitated\textsuperscript{282,283}. Plasma K/T ratios above 51 mmol/µmol were observed in 29% of patients in the present study, suggesting the probable clinical significance of endogenous IDO activation in CAD. Accordingly, the present study describes a significant association between the K/T ratio and degree depressive symptoms and identifies a trend towards higher mean K/T ratios in those with clinical depression. The presence of a trend yet lack of a clear difference in this study could result from a lack of statistical power due to a limited number of depressed patients (observed power .360). Previous studies in patients with CAD suggest that the individual items of the CES-D cluster into three component dimensions encompassing “somatic” symptoms and those of “depressive affect” and “low positive affect”\textsuperscript{292}. The items found to be associated with the K/T ratio in this study belong exclusively
to Contrada’s dimension of “depressive affect”, representing six out of the seven items grouped in that dimension.

The mechanisms behind these associations remain speculative. Inflammatory activation of IDO in peripheral white blood cells could precipitate depressive symptoms by reducing the availability of tryptophan to the CNS. Additionally, cross-talk between the peripheral and central immune systems can propagate a pro-inflammatory signal across the blood brain barrier into the CNS where pro-inflammatory cytokines synthesized de novo can upregulate IDO in blood brain barrier pericytes and cells derived from the hypothalamic-pituitary-adrenal (HPA) axis. Within the CNS, kynurenine metabolism may cause neuronal damage by producing quinolinic acid, a potentially excitotoxic NMDA receptor agonist, and the oxidative neurotoxins 3-hydroxykynurenine, 3-hydroxyanthranillic acid and 5-hydroxyanthranillic acid. A fifth kynurenine metabolite, kynurenic acid, is an endogenous neuroprotective NMDA antagonist and its abundance relative to other metabolites has been associated with fewer depressive symptoms. The observed association between the K/T ratio and depressive symptoms may relate to these mechanisms; however, while kynurenine can cross the blood brain barrier, the plasma concentrations measured in this study do not necessarily reflect the central activity of kynurenine metabolites.

Regardless of the mechanisms by which the K/T ratio is associated with depressive symptoms, it is interesting to speculate as to the potential importance of this pathway. For example, clinical trials document poor response rates and residual symptoms following treatment with selective serotonin reuptake inhibitors (SSRIs) in patients with CAD. In the Cardiac Randomized Evaluation of Antidepressant and Psychotherapy Efficacy trial, 64.1% of depressed patients continued to suffer depressive symptoms (Hamilton Depression scale [HAM-D] ≥ 8) after 12 weeks and only 52.8% of patients responded with a 50% reduction in HAM-D scores following treatment with citalopram. Symptoms associated with K/T elevation may contribute to these residual symptoms. In a recent prospective study of MDD patients, no changes were found in kynurenine over the course of SSRI treatment as a group, but patients who showed a decline in kynurenine and its metabolites experienced a more complete recovery. Thus IDO activation may be distinct from the serotonergic dysfunction that can be manipulated with SSRIs. Treatment of residual symptoms is of particular interest, since patients nonresponsive to antidepressants are at increased risk of mortality. Alternative or adjunctive treatments might target consequences of chronic inflammation in patients with atherosclerosis.
It has been suggested that treatment with anti-inflammatory therapies such as aspirin might reduce the K/T ratio\(^{295}\). In the present study, aspirin use was associated with a lower K/T ratio; however, the mean population K/T ratio remained elevated compared to that of previously reported control groups\(^{131}\) and a correlation between the K/T ratio and depressive symptoms could still be demonstrated, suggesting that aspirin cannot fully mitigate the effect. Similarly, the corticosteroid anti-inflammatory prednisolone failed to normalize changes in the kynurenine pathway found in subjects with rheumatoid arthritis\(^{296}\).

In this study, a higher K/T ratio was associated with poorer cardiopulmonary fitness as measured by VO\(_{2\text{Peak}}\), an important predictor of survival in CAD\(^{297}\). Poorer VO\(_{2\text{Peak}}\) has been associated with elevated inflammatory markers\(^ {254}\) and exercise can improve VO\(_{2\text{Peak}}\), producing a corollary reduction in IFN-\(\gamma\)\(^ {65}\), a particularly potent IDO inducer\(^ {97}\). Studies in other populations have also associated elevated K/T ratios with BMI\(^ {281}\) and obesity\(^ {298}\). However, changes in body composition following bariatric surgery did not significantly reduce the K/T ratio\(^ {298}\), suggesting that VO\(_{2\text{Peak}}\) may be a more viable target for intervention. It remains to be seen whether improvement in fitness over the course of cardiac rehabilitation might be associated with reduction in K/T ratios and improvements in depressive symptoms. Subjects with greater tACS had lower K/T ratios, suggesting possible recovery or rehabilitation related effects. However, all patients were undertaking cardiac rehabilitation and repeated interviews before and after rehabilitation were not performed for the purposes of this report, precluding assessment of the effect of rehabilitation on K/T ratios. This may be of particular interest since depressive symptoms can predict future ACS in patients with CAD\(^ {55}\) and K/T ratios have also been associated with mortality\(^ {288}\).

A limitation of this study was its naturalistic design, which yielded only 24 depressed patients. As a result, this study may have failed to demonstrate a significantly elevated mean K/T ratio in depressed subjects due to a lack of statistical power. Second, patients presenting with symptomatic inflammatory or infectious diseases were excluded, but it is possible that presymptomatic acute conditions may account for a component of the variance in K/T ratios. Third, the time since event in this population varied considerably and its association with K/T ratios remains poorly understood. Fourth, plasma kynurenine concentrations may not correlate with central concentrations. Finally, BMI and VO\(_{2\text{Peak}}\) could not be directly associated with depressive symptoms as in larger cohort studies, limiting our ability to comment on the K/T ratio as a potential mediator of the associations between these parameters and depressive symptoms.
In conclusion, IDO activation is associated with depressive symptoms in patients with CAD. Poorer cardiopulmonary fitness and body composition may contribute to elevated K/T ratios in this population.

3.7 Role of the funding sources

Funding for this study was provided by the Drummond Foundation, Québec, Canada, and the Physicians’ Services Incorporated Foundation, Ontario, Canada. These funding agencies had no further role in the study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

3.8 Significance and Impact

The association between depressive symptoms and kynurenine synthesis is consistent with mechanisms proposed based on preclinical studies relating inflammation to the evolution of depressive symptoms (reviewed\textsuperscript{87}). Although a diagnosis of MDD was associated with higher K/T ratios only at trend level, depressive symptoms increased linearly with the K/T ratio among all patients. These data support the hypothesis that inflammatory activity may contribute to the severity of depressive symptoms in this population even though other inflammatory biomarkers have not consistently shown the association\textsuperscript{60}.

This biomarker is of particular interest because kynurenine can directly cross the blood-brain-barrier where it gives rise to neurotoxic metabolites. As such, peripheral tryptophan metabolism along the kynurenine pathway may represent a target suitable for pharmacotherapeutic intervention. Recently, peripherally acting kynurenine aminotransferase II inhibitors have shown the ability to decrease symptoms in animal models of neurodegeneration\textsuperscript{299} suggesting that the adverse effects of this pathway on the brain might soon be manageable with emerging therapies. This study provides a clinical rationale to test these therapies in this population when they become available for clinical development.
Chapter 4:

Cardiopulmonary Fitness is Associated with Cognitive Performance in Patients with Coronary Artery Disease

4.1 Statement of work and disclosure

This study was published in the Journal of the American Geriatrics Society (Swardfager W, Herrmann N, Marzolini S, Saleem M, Kiss A, Shammi P, Oh P, Lanctôt KL. J Am Geriatr Soc. 2010;58(8):1519-1524). The primary author designed the study and actively recruited patients under the supervision of Drs. Lanctôt, Herrmann and Oh, performed patient interviews including cognitive testing, scored cognitive tests, designed the study database and entered cognitive data into the database. Some patient recruitment and interviews were performed by Ms. Dowlati and Mrs. Sherman. Ms. Saleem assisted with scoring of cognitive tests and with data entry. Cardiopulmonary fitness testing was performed by Toronto Rehabilitation Institute staff. Ms. Marzolini assisted with fitness data collection and interpretation prior to data entry. Dr. Shammi provided detailed training and guidance on the interpretation of cognitive test data. All statistical analyses were carried out by the primary author under the guidance of Dr. Kiss. Drs. Lanctôt and Herrmann oversaw and contributed to the study concept, design and analysis.

4.2 Abstract

Objectives: To investigate the association between cardiopulmonary fitness and cognitive performance in subjects with coronary artery disease (CAD). Design: Cross-sectional observational study. Setting: Outpatient cardiac rehabilitation. Participants: 81 subjects with CAD. Measurements: Cardiopulmonary fitness was assessed by measuring peak oxygen uptake (VO₂Peak) in a standardized exercise stress test. The fraction of the predicted age and gender norm for VO₂Peak was computed for each patient. A battery of neuropsychological tests including the Stroop, Trail Making Test B, Digit Symbol Coding, Revised Brief Visuospatial Memory Test, California Verbal Learning Test 2nd Ed. and the Mini Mental Status Exam (MMSE), was administered from which composite Z-scores were computed for tasks involving executive function and memory. Results: Executive function, memory and MMSE scores were
correlated with VO$_{2\text{Peak}}$ but only performance in the executive domain was independently associated with VO$_{2\text{Peak}}$ in multiple linear regression. In a multiple linear regression model controlling for potential clinical confounders, VO$_{2\text{Peak}}$ ($\beta$=.666, p<.0005) and covariates accounted for 36% of the variance in executive function scores. Conclusions: Poorer VO$_{2\text{Peak}}$ is associated with poorer cognition, particularly executive function, in subjects with CAD independent of other cardiac risk factors. Cardiopulmonary fitness may be a protective factor for cognition in patients with CAD.

4.3 Introduction

Cardiovascular disease and cardiovascular risk factors have been associated with increased cognitive decline in studies of older adult populations$^{150}$. In patients with coronary artery disease (CAD), changes in cognition pose significant detriments to quality of life$^{19}$ and daily functioning$^{176}$. Furthermore, cognitive changes can place older patients at an increased risk of developing dementia$^{301}$. Epidemiological studies suggest a beneficial effect of physical activity on cognitive function$^{302}$ and physical activity is associated with decreased rates of incident dementia in the general population$^{303}$. Notably, Barnes et al. confirmed that cardiopulmonary fitness is associated with cognition in medically healthy patients over 55 years of age, and that direct measurement of cardiopulmonary fitness is more reliable than a validated exercise frequency questionnaire$^{20}$.

Cardiopulmonary fitness is an important clinical determinant of cardiac prognosis and mortality in subjects with CAD$^{297}$ but its association with cognitive function has not been explored in this population. Patients with CAD often exhibit poorer performance on tests involving executive function and memory$^{153,162}$. Therefore, the present study sought to determine whether these aspects of cognition were associated with cardiopulmonary fitness. Moreover, in addition to poorer cardiopulmonary fitness, other vascular risk factors highly prevalent in subjects with CAD, such as hypertension, diabetes and dyslipidemia, have been individually associated with cognitive decline in medically healthy population samples$^{304,305}$. Therefore, the present study sought to determine whether associations between cardiopulmonary fitness and cognitive function could be demonstrated independent of other vascular risk factors in subjects with CAD.
4.4 Methods

4.4.1 Participants

Consecutive patients were approached at entry into a cardiac rehabilitation program. Inclusion criteria included a documented history of CAD (myocardial infarction, MI; angiographic evidence showing ≥50% blockage in at least one major coronary artery; percutaneous coronary intervention, PCI; or coronary artery bypass graft surgery, CABG) and a minimum of 6 weeks post-CABG or MI, or 3 weeks post-PCI. Participants were interviewed by a trained study researcher and excluded if they could not complete cognitive testing or if their medical records were otherwise incomplete. Demographic information (e.g. age, gender, education), cardiac history (e.g. PCI, CABG, MI), vascular risk factors (e.g. body mass index, hyperlipidemia, diabetes, hypertension, waist circumference, smoking), concomitant medications and medical/psychiatric comorbidities, anthropometrics and fitness data were ascertained during the patient interview or by chart review as possible confounders affecting fitness or cognitive testing. In addition, some cardiac medications have been associated with preservation of cognitive function\(^ {171}\) and cardiac surgical history may be relevant to the degree or course of cognitive changes\(^ {306}\).

Patients were excluded on the basis of a previously diagnosed neurodegenerative disorder, schizophreniform or bipolar psychiatric illness. Depression (including major or minor depression) was diagnosed by study personnel based on a structured clinical interview for Diagnostic and Statistical Manual 4\(^ {th}\) Edition criteria and the Center for Epidemiological Studies Depression (CES-D) scale was used to quantify depressive symptoms as per the National Institute of Neurological Disorders and Stroke and Canadian Stroke Network (NINDS-CSN) harmonized standards for the investigation of vascular cognitive impairment\(^ {307}\). Depression was assessed as a possible confounder based on a previously established association with cardiopulmonary fitness in this population\(^ {236}\).
4.4.2 Cognitive testing

A battery of cognitive tests was used to measure executive function, memory and global cognition\textsuperscript{xiv}. Tasks involving an executive component included the Trail Making Test B, the Victoria version of the Stroop test, and the Digit Symbol Coding task, a measure of complex attention and psychomotor speed from the Wechsler Adult Intelligence Scale 3\textsuperscript{rd} Edition. Verbal memory tasks included immediate, short and long delayed free recall of the California Verbal Learning Test 2\textsuperscript{nd} Ed. (CVLT-II) word list. General cognitive status was assessed using the Mini-Mental Status Examination (MMSE). These instruments were chosen based on NINDS-CSN harmonized standards\textsuperscript{307}. The Revised Brief Visuospatial Memory Test (BVMT-R) was added as a visuospatial memory task. All cognitive testing was carried out at a standardized time (0930 hr ± 30 min) and subjects refrained from eating or drinking any caffeine-containing beverages for at least 4 hours prior.

For each cognitive task, a Z-score was determined based on published age and gender matched norms. The Z distribution maps the population mean of the test variable to 0, with better performance being more positive and poorer performance being more negative based on a normal distribution. The Z-scores of related tests can be summed to avoid multiple comparisons\textsuperscript{308}. For executive function, the Z-scores of the Stroop, Trail Making B and Digit Symbol tasks were summed. For memory, three Z-scores from the CVLT-II (short and long delayed verbal recall and verbal learning) and two from the BVMT-R (visuospatial learning and recall) were summed.

4.4.3 Cardiopulmonary fitness

Cardiopulmonary fitness was assessed by cycle ergometer (Ergoline 800 EL) symptom-limited graded exercise test. Work load was increased by 16.7 Watts every minute and breath-by-breath gas samples were collected and averaged over a 20 second period via calibrated metabolic cart (Vmax SensorMedics 2900)\textsuperscript{11}. The peak volume of oxygen uptake (VO\textsubscript{2Peak}) was recorded and normalized for body mass (VO\textsubscript{2Peak} reported in ml/kg/min). The VO\textsubscript{2Peak} thus obtained represents a measure of ventilatory capacity at peak effort and it is a highly reliable and reproducible measure of cardiopulmonary fitness\textsuperscript{248}. The respiratory exchange ratio (RER), an indicator of metabolic effort\textsuperscript{309}, was calculated as the ratio of

\textsuperscript{xiv}Cognitive assessments were performed by research staff blinded to information from the CR site concerning cardiopulmonary fitness testing; however, medications, demographics and medical histories were obtained at the time of the cognitive interview by the same researcher.
CO₂/O₂ in gas breath samples at the time of VO₂Peak measurement. For each subject, the VO₂Peak measured from exercise stress testing was divided by his or her expected VO₂Peak and this fractional VO₂Peak was determined. The expected VO₂Peak was calculated from established age and gender norms:

Expected VO₂Peak = 60 -(0.55 × Age) ml/kg/min for male subjects and

Expected VO₂Peak = 48 -(0.37 × Age) ml/kg/min for female subjects

The fraction of the predicted VO₂Peak norm provides a clinically meaningful measure of cardiopulmonary fitness that can be compared across age and gender.

Resting and maximal physiological measurements (e.g. heart rate and blood pressure) and anthropometrics (e.g. height, body mass, waist circumference) were measured and recorded. Body mass index (BMI) was calculated as per standard definition.

4.4.4 Statistics

Pearson correlations and univariate analyses of variance, as appropriate, were used to identify patient characteristics associated with composite Z-scores, MMSE scores, or VO₂Peak. A linear regression model predicting VO₂Peak was used to identify cognitive domains associated with cardiopulmonary fitness.

To assess the association between cardiopulmonary fitness and cognitive domains of interest independent of clinical characteristics, cardiopulmonary fitness was entered as a key predictor into a linear regression model predicting composite Z-scores. Possible confounders (subject characteristics from Table IV.I) were entered individually into the unadjusted model and their effects on the association between the key predictor and the dependent variable were determined. In addition, to test the cumulative risk factor burden as a possible confounder, the number of vascular risk factors (as in Table IV.I; hypertension, smoking, diabetes, BMI>30 kg/m², waist circumference>102 for men or >88 cm for women and dyslipidemia) were summed for each subject. All variables found to influence the main effect of their key predictor (B coefficient altered by greater than ±10%) were entered into a final multiple linear regression model. While backward elimination multiple linear regression can reveal more significant independent predictors, the described method is associated with less bias when seeking to explore the independent effect of a particular predictor variable. Multicollinearity was assessed among
predictors using the tolerance statistic (tolerance ≤ 0.4) and if multicollinearity was identified, only one variable identified as part of a multicollinear set was included in the final model. All analyses were carried out in SPSS (version 16.0) and all statistics were two-tailed.

4.4.5 Standard protocol approvals and patient consents

Institutional research ethics boards approved the study protocol. Subjects provided written informed consent to participate.

4.5 Results

4.5.1 Recruitment

Study personnel contacted 122 cardiac rehabilitation participants meeting inclusion criteria, as determined by clinical personnel, at their intake into cardiac rehabilitation. Subsequently, 25 declined to be interviewed. Cognitive testing was carried out in all but 16 subjects; 10 met further exclusion criteria, 4 were unable to schedule an appointment, 1 had a language barrier, 1 was unable to complete the study tasks due to inadequate visual acuity. There were therefore 81 subjects in the study and their characteristics are summarized in Table IV.1.

4.5.2 Subject characteristics and cardiopulmonary fitness

Exercise stress testing results are summarized in Table IV.1. Of all subjects, 42% presented with VO2Peak below average (≤73% of their predicted VO2Peak) based on age and gender norms. A mean RER ± standard deviation of 1.18±0.11 was observed, indicating the involvement of anaerobic metabolism at the time of VO2Peak measurement309 (only 6 subjects failed to achieve RER ≥1.1). In bivariate comparisons, VO2Peak was negatively associated with age (r = -.354, p = .001), beta-blocker use (F1,79 = 5.725, p = .019), and diuretic use (F1,79 = 8.019, p = .006), and associated positively with dyslipidemia (F1,79 = 5.770, p = .019) and MMSE scores (r = .241, p = .030). VO2Peak was not associated with other sociodemographics, psychometrics, vascular risk factors, concomitant medications or resting physiological measures.
### Table IV.I: Characteristics of Study Participants\textsuperscript{ xv}

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Value</th>
<th>F or r*</th>
<th>P-Value\textsuperscript{†}</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sociodemographic</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, mean ± SD, yr</td>
<td>62.5±11.0</td>
<td>-0.354</td>
<td>0.001</td>
</tr>
<tr>
<td>Employed, n (%)</td>
<td>45 (55.6)</td>
<td>1.773</td>
<td>0.187</td>
</tr>
<tr>
<td>Partnered, n (%)</td>
<td>61 (75.3)</td>
<td>0.902</td>
<td>0.467</td>
</tr>
<tr>
<td>Sex, male, n (%)</td>
<td>70 (86.4)</td>
<td>1.519</td>
<td>0.221</td>
</tr>
<tr>
<td>Caucasian, n (%)</td>
<td>71 (87.7)</td>
<td>0.045</td>
<td>0.992</td>
</tr>
<tr>
<td>Total education, mean ± SD, yr</td>
<td>16.5±3.4</td>
<td>0.210</td>
<td>0.855</td>
</tr>
<tr>
<td><strong>Psychometric</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depressive episode, n (%)</td>
<td>26 (32.1)</td>
<td>0.410</td>
<td>0.665</td>
</tr>
<tr>
<td>History of depressive episode, n (%)</td>
<td>16 (19.8)</td>
<td>1.098</td>
<td>0.298</td>
</tr>
<tr>
<td>CES-D score, mean ± SD</td>
<td>12±11</td>
<td>0.037</td>
<td>0.743</td>
</tr>
<tr>
<td>MMSE score, mean ± SD</td>
<td>29±3</td>
<td>0.241</td>
<td>0.030</td>
</tr>
<tr>
<td><strong>Vascular Risk Factors\textsuperscript{xvi}</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>48 (59.3)</td>
<td>1.134</td>
<td>0.290</td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Past Smoker, n (%)</td>
<td>43 (53.1)</td>
<td>0.265</td>
<td>0.608</td>
</tr>
<tr>
<td>Cigarettes per day, mean ± SD</td>
<td>10±11</td>
<td>-0.025</td>
<td>0.827</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>15 (18.5)</td>
<td>2.717</td>
<td>0.103</td>
</tr>
<tr>
<td>BMI, mean ± SD, kg/m\textsuperscript{2}</td>
<td>28.5±4.6</td>
<td>-0.173</td>
<td>0.123</td>
</tr>
<tr>
<td>Waist circumference, mean ± SD, cm</td>
<td>100.3±10.2</td>
<td>-0.190</td>
<td>0.092</td>
</tr>
<tr>
<td>Dyslipidemia, n (%)</td>
<td>27 (33.3)</td>
<td>5.770</td>
<td>0.019</td>
</tr>
<tr>
<td>Total No. Vascular Risk Factors, mean ± SD</td>
<td>2.9±1.1</td>
<td>0.027</td>
<td>0.813</td>
</tr>
<tr>
<td><strong>Cardiac History</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCI, n (%)</td>
<td>48 (59.3)</td>
<td>0.601</td>
<td>0.441</td>
</tr>
<tr>
<td>Myocardial Infarction, n (%)</td>
<td>42 (51.9)</td>
<td>1.985</td>
<td>0.163</td>
</tr>
<tr>
<td>CABG, n (%)</td>
<td>26 (32.1)</td>
<td>0.678</td>
<td>0.413</td>
</tr>
<tr>
<td>Peripheral Vascular Disease, n (%)</td>
<td>4 (4.9)</td>
<td>2.207</td>
<td>0.142</td>
</tr>
<tr>
<td><strong>Concomitant Medications</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Statins, n (%)</td>
<td>78 (96.3)</td>
<td>1.078</td>
<td>0.302</td>
</tr>
<tr>
<td>ASA, n (%)</td>
<td>78 (96.3)</td>
<td>0.849</td>
<td>0.360</td>
</tr>
<tr>
<td>β-blockers, n (%)</td>
<td>63 (77.8)</td>
<td>5.725</td>
<td>0.019</td>
</tr>
<tr>
<td>Antihypertensive, n (%)</td>
<td>53 (65.4)</td>
<td>0.445</td>
<td>0.507</td>
</tr>
<tr>
<td>Nitroglycerin, n (%)</td>
<td>50 (61.7)</td>
<td>1.356</td>
<td>0.248</td>
</tr>
<tr>
<td>Diuretics, n (%)</td>
<td>14 (17.3)</td>
<td>8.019</td>
<td>0.006</td>
</tr>
<tr>
<td>Ca\textsuperscript{2+}-Channel Antagonists, n (%)</td>
<td>11 (13.6)</td>
<td>1.535</td>
<td>0.219</td>
</tr>
<tr>
<td>Anxiolytics, n (%)</td>
<td>11 (13.6)</td>
<td>0.064</td>
<td>0.801</td>
</tr>
<tr>
<td>Antidiabetic agents, n (%)</td>
<td>10 (12.3)</td>
<td>3.278</td>
<td>0.074</td>
</tr>
<tr>
<td>Antidepressants, n (%)</td>
<td>6 (7.4)</td>
<td>2.174</td>
<td>0.144</td>
</tr>
<tr>
<td><strong>Resting Physiology</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resting Heart Rate, mean ± SD, BPM</td>
<td>67.4±11.7</td>
<td>0.042</td>
<td>0.710</td>
</tr>
</tbody>
</table>

\textsuperscript{ xv} Time since most recent coronary event was 14.4±8.9 weeks, excluding 2 outliers with only remote histories. This variable was not associated with VO\textsubscript{2Peak} (r=−.072, p=.541) or any measure of cognitive performance (−.049<r<.063, .599<p<.986).

\textsuperscript{xvi} No patients had a history of heart failure in this study sample.
Table IV. I continued

<table>
<thead>
<tr>
<th></th>
<th>Mean ± SD, mm Hg</th>
<th>F</th>
<th>r</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resting Systolic BP</td>
<td>127.4±16.4</td>
<td>-0.140</td>
<td>0.211</td>
</tr>
<tr>
<td>Resting Diastolic BP</td>
<td>74.2±9.7</td>
<td>0.106</td>
<td>0.348</td>
</tr>
</tbody>
</table>

**Fitness Parameters**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean ± SD, ml/kg/min</th>
<th>F</th>
<th>r</th>
</tr>
</thead>
<tbody>
<tr>
<td>VO$_{2\text{Peak}}$</td>
<td>20.06±5.10</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Fraction of norm VO$_{2\text{Peak}}$</td>
<td>0.82±0.23</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>RER, mean ± SD</td>
<td>1.18±0.11</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Maximum Heart Rate, mean ± SD, BPM</td>
<td>121±22</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Maximum Systolic BP, mean ± SD, mm Hg</td>
<td>180±28</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Maximum Diastolic BP, mean ± SD, mm Hg</td>
<td>80±10</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

*F* represents the F statistic in one-way analyses of variance (ANOVA) comparing VO$_{2\text{Peak}}$ between categorical subject characteristics and *r* represents the Pearson correlation between VO$_{2\text{Peak}}$ and continuous subject characteristics, as appropriate.

†P-value represents the two-sided significance in one-way ANOVA or Pearson correlations.

ASA = acetylsalicylic acid; BP = blood pressure; BPM = beats per minute; CABG = coronary artery bypass graft; CES-D = Center for Epidemiological Studies-Depression Scale; MMSE = Mini Mental Status Exam; PCI = percutaneous coronary intervention; RER = respiratory exchange ratio, VO$_{2\text{Peak}}$ = peak volume of oxygen uptake.

4.5.3 Subject characteristics and cognition

Cognitive testing results are summarized in Table IV.II. In univariate comparisons, executive function composite Z-scores were associated negatively with diabetes ($F_{1,79}=6.293$, *p*=.014) and the use of antidiabetic medications ($F_{1,79}=4.472$, *p*=.038), and positively with VO$_{2\text{Peak}}$ (r=.307, *p*=.005), maximum heart rate (r=.256, *p*=.021) and maximum systolic blood pressure (r=.286, *p*=.010) during fitness testing.

In univariate comparisons, memory composite Z-scores were associated positively with years of formal education (r=.219, *p*=.049), the use of an antidepressant medication ($F_{1,79}=4.594$, *p*=.035), and with VO$_{2\text{Peak}}$ (r=.281, *p*=.011) and maximum heart rate (r=.244, *p*=.028) during fitness testing.

Scores on the MMSE ranged from 23 to 30 with 9 subjects scoring below 28. In univariate comparisons, MMSE scores were associated positively with years of formal education (r=.362, *p*=.001), being Caucasian ($F_{1,79}=7.734$, *p*=.007), and in addition to VO$_{2\text{Peak}}$, maximum heart rate (r=.282, *p*=.011) and maximum systolic blood pressure (r=.230, *p*=.040) during fitness testing. MMSE scores were associated negatively with diabetes ($F_{1,79}=5.000$, *p*=.028) and history of MI ($F_{1,79}=4.111$, *p*=.046).
Table IV.II: Cognitive Testing Results and Correlations with Cardiopulmonary Fitness

<table>
<thead>
<tr>
<th>Raw Scores</th>
<th>Raw Scores vs. VO\textsubscript{2Peak}</th>
<th>Normalized Scores</th>
<th>Z-Scores vs. Fractional VO\textsubscript{2Peak}</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Raw Score, mean ± SD</td>
<td>r</td>
<td>P-Value</td>
</tr>
<tr>
<td>Executive Function (Composite)*</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Stroop</td>
<td>28.6±9.3 sec</td>
<td>-.324</td>
<td>.003</td>
</tr>
<tr>
<td>Trail Making B</td>
<td>88.2±42.0 sec</td>
<td>-.320</td>
<td>.004</td>
</tr>
<tr>
<td>Digit-Symbol Encoding</td>
<td>61.3±16.7 sym.</td>
<td>.476</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Memory (Composite)*</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>CVLT-II Learning</td>
<td>43.2±12.2 words</td>
<td>.296</td>
<td>.007</td>
</tr>
<tr>
<td>CVLT-II Short Delay Recall</td>
<td>9.0±3.6 words</td>
<td>.238</td>
<td>.033</td>
</tr>
<tr>
<td>CVLT-II Long Delay Recall</td>
<td>9.3±3.5 words</td>
<td>.225</td>
<td>.044</td>
</tr>
<tr>
<td>BVMT-R Learning Score</td>
<td>3.7±2.7 points</td>
<td>.350</td>
<td>.001</td>
</tr>
<tr>
<td>BVMT-R Recall Score</td>
<td>8.0±3.6 points</td>
<td>.322</td>
<td>.003</td>
</tr>
<tr>
<td>Overall Cognition (MMSE score)†</td>
<td>28.9±1.7 points</td>
<td>.241</td>
<td>.030</td>
</tr>
</tbody>
</table>

*For composite or individual test Z-scores, correlation represents Pearson correlations (r) between the fraction of expected VO\textsubscript{2Peak} based on age and gender matched norms and Z-score based on age matched norms and P-Value represents the associated two-tailed significance

†For MMSE scores, correlation represents the association (β) between VO\textsubscript{2Peak} and MMSE score in multiple linear regression controlling for age and gender; sig. represents the associated two-tailed significance (p), n=81

BVMT-R = Revised Brief Visuospatial Memory Test; CVLT-II = California Verbal Learning Test 2\textsuperscript{nd} Ed.; MMSE = Mini Mental Status Exam; SD = standard deviation.

4.5.4 Cardiopulmonary fitness and cognition

Significant bivariate associations were identified between VO\textsubscript{2Peak} (in ml/kg/min) and raw scores for all cognitive tests (p<.05; see Table IV.II). Fractional VO\textsubscript{2Peak} (normalized for age and gender) was associated with Z-scores for the Trail Making B, Digit Symbol, and BVMT-R tasks (p<.05; see Table IV.II). MMSE scores were associated with VO\textsubscript{2Peak} in linear regression controlling for age and gender (p=.011; see Table IV.II). Subjects who attained average or above average VO\textsubscript{2Peak} also attained higher executive function composite Z-scores scores (F\textsubscript{1,80}=17.059, p<.0005) and non-significantly higher memory composite Z-scores scores (F\textsubscript{1,80}=2.846, p=.096) and MMSE (F\textsubscript{1,80}=1.847, p=.178) scores than those who attained below average VO\textsubscript{2Peak}.

In a multiple linear regression model (F\textsubscript{3,80}=7.672, p<.0005, Adj. R\textsuperscript{2}=.200), executive composite Z-scores (β=.552, p<.0005) were associated with fractional VO\textsubscript{2Peak} independently of performance in the other two domains but memory composite Z-scores (β=-.066, p=.583) and MMSE scores (β=-.086, p=.477) were not.
In a linear regression model that included clinical characteristics (from Table IV.I) found to modify the association between executive function composite Z-scores and fractional VO$_{2\text{Peak}}$ by at least 10% ($F_{4,77}=12.001$, $p<.0005$, adjusted $R^2=.358$), cardiopulmonary fitness was strongly and independently associated with executive function ($B=6.723$, $\beta=.666$, $p<.0005$; Figure 4.1$^{xvii}$), as were resting heart rate ($B=.062$, $\beta=.303$, $p=.002$) and gender ($B=1.756$, $\beta=.255$, $p=.008$) but not waist circumference ($B=.034$, $\beta=.147$, $p=.120$). This model suggests that attaining a VO$_{2\text{Peak}}$ 20% lower than the norm was associated with a decrease in executive function equivalent to over one half of the observed standard deviation in composite Z-scores. Excluding the 6 patients with RER<1.1 did not significantly alter this association.

Figure 4.1 Association between cardiopulmonary fitness and executive function in 81 subjects with CAD

Open circles represent subjects with diabetes, closed circles represent subjects without diabetes.

$xvii$ As depicted, VO$_{2\text{Peak}}$ (as a fraction of the age and gender norm) was associated with executive function (composite Z score) in a linear regression model ($B=4.818$, $\beta=.470$, $p<.0005$), alone accounting for 21.1% of the variance in executive function ($R^2=.221$, adjusted $R^2=.211$).
4.5.5 Cognitive domains and MMSE scores

Executive ($\beta=.547$, $p<.0005$) and memory ($\beta=.391$, $p<.0005$) composite Z-scores were strongly associated with overall cognition in analyses post-hoc, accounting for 29.0% and 14.2% of the variance in MMSE scores, respectively. When both domains were entered into a multiple linear regression model ($F_{2,80}=17.735$, $p<.001$), the executive composite Z-score remained significant ($\beta=.473$, $p<.001$) but the composite memory Z-score did not ($\beta=.139$, $p=.215$). Very little more variance in MMSE scores could be predicted by the model including composite memory Z-scores (adjusted $R^2=.295$) than could be predicted by executive composite Z-scores alone (adjusted $R^2=.290$).

4.6 Discussion

The present study demonstrates a significant association between cardiopulmonary fitness and cognition, particularly executive function, in subjects with symptomatic cardiovascular disease. This finding is consistent with previous studies in other settings, including a study by Barnes et al., which reported that poorer cardiopulmonary fitness was most strongly associated with executive decline in healthy older adults\textsuperscript{20}. The present study demonstrates that the association between fitness and executive function was independent of other cardiovascular risk factors, despite their extensive co-occurrence in this population. For instance, while a univariate association between diabetes and poorer executive function was observed (Figure 4.1) as in previous reports\textsuperscript{308}, the presence of diabetes and the use of antidiabetic agents did not affect the association between cardiopulmonary fitness and executive function.

Cardiopulmonary fitness was also associated with performance on the MMSE, the instrument most commonly used to screen for overall cognition in clinical practice. This correlation was not significant when controlling for executive function, suggesting that the executive domain may largely account for the relationship between fitness and overall cognition in subjects with CAD. In analyses post-hoc, the executive domain predicted more variance in MMSE scores than did memory, and the contribution of memory to MMSE scores was not significant when controlling for executive function. This is particularly intriguing given that the MMSE does not specifically test the executive domain\textsuperscript{307}. Other studies have shown executive dysfunction to be particularly prominent in the presentation of clinical MCI when vascular risk factors are present\textsuperscript{312}. Although infrequently assessed in clinical practice, decline in executive function can precede memory decline and increase the risk of decline on the MMSE, even in medically and cognitively healthy older subjects\textsuperscript{301}.
While not routinely assessed as a component of care, poorer cognitive function is a key determinant of quality of life\textsuperscript{19} and it can pose a significant barrier to maintaining function in subjects with CAD. Specifically, poorer subjective cognitive function has been associated with unemployment, failure to return to work following an acute coronary syndrome, sick leave and early retirement, independent of other cardiac factors\textsuperscript{176}. Though the direction of causation cannot be inferred from these associations, cognitive decline could lead to a decline in physical activity, resulting in poorer cardiopulmonary fitness. Conversely, physical activity might protect against cognitive decline. In controlled clinical trials involving medically and cognitively healthy older adults, exercise can improve aspects of frontal lobe function, including attention and executive function\textsuperscript{23, 192, 313}. Volumetric magnetic resonance (MR) imaging studies suggest that aerobic exercise might increase grey\textsuperscript{203} and white matter volumes\textsuperscript{202} in medically healthy older adults. Selective losses of frontal lobe grey\textsuperscript{314} and white\textsuperscript{315} matter have been observed in subjects with CAD compared to medically healthy controls, suggesting the need to explore possible protective factors. The sparing of executive function associated with cardiopulmonary fitness observed in the present study may be related to preservation of frontal lobe volume in more active CAD patients. In addition, the frontal lobes can effect memory performance by exerting attentional control via reciprocal white matter connections with the hippocampi\textsuperscript{316}. A protective effect of fitness on the frontal lobe would be consistent with the observed association between memory and fitness that shares variance with executive function.

A meta-analysis by Angevaren et al. found that subjects randomized to fitness interventions improved reliably in measures of processing speed and attention compared to controls, but that the majority of comparisons, considering all cognitive outcome measures assessed, failed to demonstrate a consistent effect\textsuperscript{23}. Angevaren et al. point out a lack of high-quality controlled studies and a lack of consistency in the choice of outcome measures. Choosing cognitive assessments based on the domains most likely to be affected could considerably strengthen the evidence. In that regard, the present study identifies a robust correlation between VO\textsubscript{2Peak} and composite Z-scores computed from tasks involving psychomotor speed, complex attention and executive function in subjects with CAD. Choosing study populations most likely to benefit could also strengthen the evidence. For instance, interventions showing no effect of exercise on executive function\textsuperscript{313} have not focused on subjects most vulnerable to these deficits such as those with symptomatic cardiovascular disease.

The present study was strengthened by the use of objective fitness measures, adding to a body of epidemiological evidence that has relied heavily on subjective reports of exercise frequency, by the use
of composite Z-scores encompassing important cognitive domains, and by using linear regression models controlling precisely for clinical confounders. Importantly, cardiac risk factors did not attenuate the association between cardiopulmonary fitness and executive function. Limitations of the study include a small sample size relative to epidemiological studies, a lack of structural MR imaging to determine possible neuroanatomical correlates of the observed associations, and a cross-sectional study design precluding the assessment of causal relationships. Exploring the relationships between cognition, cardiopulmonary fitness and other cardiovascular parameters (e.g. left ventricular ejection fraction) might have suggested mechanistic aspects worthy of exploration in future studies. Similarly, while only 4 subjects presented with a diagnosis of peripheral vascular disease, and this was not found to account for the observed associations, it cannot be ruled out that subclinical peripheral vascular disease may have contributed to limiting exercise tolerance in some subjects; however subject RERs suggest that most were able to exert adequate physiological effort at the time of peak measurements. As a further limitation, other cognitive domains such as episodic memory were not assessed. Well-designed randomized prospective interventions are needed in this population to determine the direction of cause and effect, and the appropriate clinical application of these results. Nonetheless, the present study was adequate to detect a robust association between cardiopulmonary fitness and aspects of cognition, emphasizing the potential importance of this modifiable risk factor to cognitive aging in subjects with CAD.

4.7 Significance and impact

Although cardiopulmonary fitness has been associated with cognitive performance in medically healthy older adults\textsuperscript{20}, this association had not been clearly demonstrated in a population of patients with CAD. Many vascular risk factors themselves have been associated with poorer performance in various cognitive domains, including memory and executive function, suggesting the need to establish whether an association between cognitive performance and cardiopulmonary would be independent of these risk factors. Cardiopulmonary fitness, measured objectively using a standardized exercise stress test, was independently associated with tasks depending heavily on executive function, attention and psychomotor processing speed, adding evidence to a body of literature that has relied heavily on self-reported exercise frequency questionnaires\textsuperscript{302, 303}.
5.1 Statement of work and disclosure

This study will be published in a September issue of Psychosomatic Medicine (Swardfager W, Herrmann N, Marzolini S, Oh PI, Saleem M, Shammi P, Kiss A, Cappell J, Lanctôt KL. Psychosomatic Med. Sep;73(7):580-7)\textsuperscript{317}. The primary author designed the study under the supervision of Drs. Lanctôt, Herrmann and Oh (recruitment strategy as established in Chapter 1, Section 2), actively recruited patients, performed patient interviews including cognitive testing, scored cognitive tests, designed the database and entered cognitive data into the database. Some patient recruitment and interviews were performed by Ms. Dowlati and Mrs. Sherman. Ms. Saleem assisted with scoring of cognitive tests and with data entry. Cardiopulmonary fitness testing was performed by Toronto Rehabilitation Institute staff. Ms. Marzolini facilitated fitness and CR program attendance data collection and assisted with the interpretation of fitness data. Dr. Shammi provided detailed training for neuropsychological testing and guidance on the interpretation of cognitive data. All statistical analyses were carried out by the primary author under the guidance of Dr. Kiss. Ms. Cappell assisted with some descriptive statistics. Drs. Lanctôt and Herrmann oversaw and contributed to the study concept, design and analysis.

5.2 Abstract

Objective: To assess cognitive performance as a predictor of non-completion of cardiac rehabilitation (CR) using a standardized verbal memory test. Methods: This was a prospective cohort study of consecutive patients with coronary artery disease (CAD; n=131) entering 1-year outpatient CR between April 2007 and May 2009. Verbal memory performance was assessed using the California Verbal Learning Test 2\textsuperscript{nd} Ed. (CVLT-II). Attendance at weekly CR sessions was recorded and completion or non-completion was determined according to comprehensive CR criteria. Depression was diagnosed according to DSM-IV criteria as a possible confounder. Results: Verbal memory performance at entry into CR differed significantly ($F_{1,130}=7.80$, $p=.006$) between non-completers and completers (mean...
cumulative CVLT-II score -1.15±2.59 vs. 0.47±3.12) in analysis of covariance controlling for pertinent clinical confounders. Better verbal memory performance predicted a reduced risk of non-completion (hazard ratio [HR], 0.86; 95% confidence interval [CI], 0.77-0.96, p=.009) in time-to-event analysis adjusted for depression (HR 2.62, 95% CI 1.33-5.17, p=.006) and smoking history (HR 2.03, 95% CI, 0.98-4.22, p=.06). A post-hoc analysis suggested that better verbal memory performance predicted a reduced risk of non-completion for medical reasons (HR 0.83, 95% CI .70-.99; p=.03). Conclusion: Poorer verbal memory performance was associated with an increased risk of non-completion of CR among participants with CAD. Further studies exploring practical methods for screening and targeted support might improve rehabilitation outcomes.

5.3 Introduction

Comprehensive cardiac rehabilitation (CR) involves exercise training, education, lifestyle modification and psychosocial support and it is highly effective in reducing long-term mortality and the recurrence of acute coronary syndromes. However, many participants are unable to adopt the prescribed lifestyle changes or adhere to structured exercise regimes, limiting their effectiveness.

Coronary artery disease (CAD) is associated with poorer cognitive performance and with an increased rate of decline in verbal memory. For patients with CAD, subjective cognitive factors are significant determinants of quality of life and daily functioning and poorer cognitive performance has been associated with physical disability and mortality. It has been suggested that cognitive processes may be particularly important determinants of adherence to risk factor management; however, to our knowledge, verbal memory performance has not been explored as a predictor of adherence to CR.

The present study sought to determine if poorer performance on a standardized verbal memory test can predict non-completion of CR. Vascular risk factors and depression are highly prevalent in patients with CAD and they have been associated with cognitive decline and with an increased risk of CR non-completion. Therefore, the present study sought to determine if an association between verbal memory performance and non-completion of CR could be demonstrated independent of other established predictors.
5.4 Methods

5.4.1 Participant screening and recruitment

Local Research Ethics Boards approved this study. Consecutive patients entering the Toronto Rehabilitation Institute 1 year CR program between April 2007 and April 2009 were screened at intake. Patients who completed cardiopulmonary fitness testing having sufficient medical information to determine cardiac and related diagnoses were referred to the study. Referred participants who provided written informed consent were subsequently interviewed to formally assess inclusion/exclusion criteria. Participants with documented CAD (myocardial infarction, angiographic evidence of ≥ 50% blockage in at least one major coronary artery, or prior revascularization) were included. Patients were excluded in the presence of any previously diagnosed neurodegenerative illness, active cancer, surgery planned within 12 months, or premorbid psychiatric diagnoses other than depression. Participants were screened for dementia using the Mini Mental Status Examination (MMSE) and patients with MMSE<24 were excluded \(^{322, 323}\).

5.4.2 CR protocol

Participants started CR at least 6 weeks post coronary artery bypass graft surgery or post myocardial infarction or 3 weeks post percutaneous coronary intervention. Participants attended supervised exercise sessions weekly for six months, followed by monthly visits for an additional two months \(^{11}\). An additional 4 aerobic sessions and 1 to 2 resistance sessions away from the centre were prescribed weekly and tracked via exercise log. Resources offered to all participants included information sessions regarding risk factor management (e.g. medication use, weight control, diet and smoking cessation). Standard practice included screening for depressive symptoms using the Center for Epidemiological Studies Scale for Depression (CES-D) \(^{246}\). Participants screening positive for depressive symptoms (CES-D≥16), showing signs of depression during weekly visits or voicing subjective feelings of depression were referred to a staff psychologist for assessment, counseling and/or psychiatric referral.
5.4.3 Completion of CR and attendance

Participants were followed throughout the standard CR protocol and completion or non-completion of CR was determined based on the case manager’s comprehensive assessment of compliance with individualized program expectations (a combination of daily exercise prescriptions, attendance to scheduled CR sessions and completion of exercise tests). Attendance at each visit and the date of completion or premature withdrawal were recorded along with the reason for dropout/discharge where appropriate.

5.4.4 Study assessments

A trained researcher administered the California Verbal Learning Test 2nd Ed. (CVLT-II) at a standardized time (0930 hr ± 30 min) under the supervision of an experienced clinical neuropsychologist. The CVLT-II was chosen because it has demonstrated sensitivity to deficits across cognitive domains frequently affected in patients with cardiovascular disease and it is included in harmonized standards for the investigation of vascular cognitive impairment [180, 307, 324]. The CVLT-II word list consists of 16 words that are read to and recalled orally by the participant 5 times. The CVLT-II words fall into 4 categories so that strategic aspects of cognition contribute to overall verbal memory performance [324]. The sum of the words recalled over the 5 trials is recorded as a measure of encoding. A distractor list is then read to the participant and repeated back by the participant after which time recall of the original word list is prompted by the examiner, constituting short delayed free recall. After 20 minutes, during which time intervening assessments are administered, the participant is asked to recall the original word list (i.e. long delayed free recall). Z-scores were calculated from established age and education matched norms and overall memory performance was calculated as the sum of encoding, short and long delayed free recall Z-scores. The Z distribution maps the population mean of the test variable to 0, with better performance being more positive and poorer performance being more negative based on a normal distribution, allowing individual Z-scores to be quantitatively combined to generate a cumulative score [308]. To avoid possible postprandial effects, participants refrained from eating for 4 hr prior to administration of the CVLT-II [325] and caffeine containing beverages were not permitted on the morning of testing.

A structured clinical interview was administered to ascertain whether participants met Diagnostic and Statistical Manual 4th Edition depression criteria. Participants meeting criteria for minor depression were
categorized as depressed because both major and minor depression are associated with increased mortality among those with CAD 278 and with poorer cognitive performance in older persons 326. A clinically experienced psychiatrist conducted researcher training and quality assurance for interview skills and diagnostic accuracy, and reviewed results.

Sociodemographic information, cardiac factors, and medications were ascertained during the patient interview and by chart review. Cardiopulmonary fitness was assessed using a standardized symptom-limited graded exercise test on a cycle ergometer (Ergoline 800 EL). Peak volume of oxygen uptake (VO$_{2peak}$) was assessed by breath-by-breath gas samples via calibrated metabolic cart (Vmax) 11. Resting and peak physiological measurements were recorded. Percentage body fat was assessed by bioelectric impedance (Tanita TBF-300A, Tokyo, Japan), waist circumference was measured and body mass index (BMI) was calculated per standard definition. In addition, the number of vascular risk factors (as in Table V.I; hypertension, smoking, diabetes, BMI>30 kg/m$^2$, waist circumference>102 for men or >88 cm for women and dyslipidemia) were summed for each participant as a measure of cumulative risk factor burden. Coronary angiography reports were reviewed for indices of CAD severity including the involvement of each major coronary artery (>50% stenosis) and the presence of restenosis in any previously revascularized lesion.

5.4.5 Statistical analyses

All analyses were two-tailed and they were performed using SPSS statistical software (version 16.0.1, SPSS Inc., Chicago, Illinois, United States of America). Baseline cumulative verbal memory scores were assessed for associations with participant characteristics using Pearson Chi-square or univariate analyses of variance (ANOVA) as appropriate. Differences in baseline characteristics between completers and non-completers were assessed in Pearson Chi-square (using Fisher’s exact test where appropriate) or univariate ANOVA.

Cumulative verbal memory scores were compared between completers and non-completers in analysis of covariance (ANCOVA). Characteristics associated with non-completion of CR in previous studies were selected as covariates a priori (e.g. body composition, depression, the use of antidepressants, smoking history, VO$_{2peak}$, not living with a spouse or equivalent, and age) 8, 237, 268-270, 321. Characteristics associated with cognitive performance or non-completion in the present population were also included as covariates.
Cox proportional hazards models were used to explore the association between verbal memory performance and time in CR. Participants not meeting completion criteria were treated as censored observations at their last week of attendance. Characteristics found to influence the main effect of verbal memory (i.e. change in B of ±10% or greater) were entered into an adjusted Cox regression model. While backward elimination multiple linear regression can reveal more significant predictors, the described method is associated with less bias when seeking to explore the independent effect of a particular predictor variable. Hazards models adjusted with other potentially relevant covariates were also explored. Subgroup analyses were planned in depressed and non-depressed participants.

5.4.6 Sample size and study power

At a two-sided significance of 0.05, a sample size of 130 achieves 80% power to detect a difference in verbal memory scores between completers and non-completers in a two independent samples t-test with a medium effect size (Hedge’s g=0.5) assuming a standard deviation of 4.5 in cumulative verbal memory scores and a 30% rate of non-completion.

5.5 Results

5.5.1 Participant characteristics

Analyses included 131 participants (Figure 5.1). Participant characteristics are summarized in Table V.I. Included participants were similar in age (64.5±11.2 yr), gender (81.0% male) and rate of CR completion (71.6%) to patients from the centre database (mean age 61.0±10.5 yr, 81.6% male, 70.0% completing CR, n=5922) and the proportion of participants screening positive for depressive symptoms (25.6%) was comparable to that of patient samples from the centre database (22.3%, n=366).
Figure 5.1 Participant Characteristics and study design
Table V.I: Participant Characteristics and Associations with Non-completion of CR

<table>
<thead>
<tr>
<th>Participant Characteristics</th>
<th>Completers</th>
<th>Non-Completers</th>
<th>( \chi^2 ) or F</th>
<th>P Value (^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sociodemographic</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, mean ±SD, yr</td>
<td>65.4± 11.3</td>
<td>62.8± 11.3</td>
<td>1.36</td>
<td>.25</td>
</tr>
<tr>
<td>Employed, No. (%)</td>
<td>45 (48)</td>
<td>21 (57)</td>
<td>0.84</td>
<td>.36</td>
</tr>
<tr>
<td>Living with spouse or equivalent, No. (%)</td>
<td>75 (80)</td>
<td>23 (62)</td>
<td>4.38</td>
<td>.04</td>
</tr>
<tr>
<td>Male, No. (%)</td>
<td>77(82)</td>
<td>28 (76)</td>
<td>0.65</td>
<td>.42</td>
</tr>
<tr>
<td><strong>Ethnicity</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian, No. (%)</td>
<td>84 (89)</td>
<td>31 (84)</td>
<td>0.77</td>
<td>.38</td>
</tr>
<tr>
<td>Education, mean± SD, yr</td>
<td>16.6 ± 3.3</td>
<td>16.0 ± 3.1</td>
<td>0.86</td>
<td>.36</td>
</tr>
<tr>
<td><strong>Cardiac Risk Factors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension, No. (%)</td>
<td>51 (54)</td>
<td>19 (51)</td>
<td>0.09</td>
<td>.76</td>
</tr>
<tr>
<td>Diabetes, No. (%)</td>
<td>16 (17)</td>
<td>7 (19)</td>
<td>0.07</td>
<td>.80</td>
</tr>
<tr>
<td><strong>Smoking history</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never smoked, No. (%)</td>
<td>48 (51)</td>
<td>10 (27)</td>
<td>6.22</td>
<td>.01</td>
</tr>
<tr>
<td>Current smoker, No. (%)</td>
<td>2 (2)</td>
<td>3 (8)</td>
<td>2.59</td>
<td>.11</td>
</tr>
<tr>
<td>BMI, mean ±SD, kg/m(^2)</td>
<td>27.8± 4.8</td>
<td>29.6±4.9</td>
<td>3.50</td>
<td>.06</td>
</tr>
<tr>
<td>&gt;30 kg/m(^2), No. (%)</td>
<td>24 (26)</td>
<td>13 (36)</td>
<td>1.43</td>
<td>.23</td>
</tr>
<tr>
<td>Dyslipidemia, No. (%)</td>
<td>28 (30)</td>
<td>9 (24)</td>
<td>0.39</td>
<td>.53</td>
</tr>
<tr>
<td>Waist Circumference, mean±SD, cm</td>
<td>97.8±12.7</td>
<td>102.8±12.1</td>
<td>4.15</td>
<td>.04</td>
</tr>
<tr>
<td>&gt;102 (men) or &gt;88 (women) cm, No. (%)</td>
<td>38 (41)</td>
<td>26 (72)</td>
<td>9.89</td>
<td>.002</td>
</tr>
<tr>
<td>No. Vascular Risk Factors, mean±SD</td>
<td>2.2±1.4</td>
<td>2.7 ±1.2</td>
<td>5.22</td>
<td>.02</td>
</tr>
<tr>
<td><strong>Cardiac History</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCI, No. (%)</td>
<td>47 (50)</td>
<td>20 (54)</td>
<td>0.18</td>
<td>.68</td>
</tr>
<tr>
<td>Angina, No. (%)</td>
<td>25 (27)</td>
<td>9 (24)</td>
<td>0.07</td>
<td>.79</td>
</tr>
<tr>
<td>Myocardial Infarction, No. (%)</td>
<td>44 (47)</td>
<td>21 (57)</td>
<td>1.05</td>
<td>.31</td>
</tr>
<tr>
<td>CABG, No. (%)</td>
<td>27 (29)</td>
<td>13 (35)</td>
<td>0.52</td>
<td>.47</td>
</tr>
<tr>
<td><strong>Psychometric</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CES-D score, mean±SD</td>
<td>10.4 ± 9.7</td>
<td>13.7 ± 11.7</td>
<td>2.77</td>
<td>.10</td>
</tr>
<tr>
<td>Current depression, No. (%)</td>
<td>20 (21)</td>
<td>15 (41)</td>
<td>5.03</td>
<td>.03</td>
</tr>
<tr>
<td>Premorbid depressive episode, No. (%)</td>
<td>22 (23)</td>
<td>11 (30)</td>
<td>0.56</td>
<td>.45</td>
</tr>
</tbody>
</table>

\(^b\) Time since most recent coronary event was 15.7±13.7 weeks, excluding 3 outliers with only remote histories. This variable was not associated with noncompletion (B=-.003, p=.832) it did not affect the association between CVLT-II scores and noncompletion as per prespecified prospective model building criteria. Of the sample, 2 patients had a history of class I heart failure (1 with MDD and 6 non-MDD), but this was not associated with non-completion (B=.523, p=.607) and it did not warrant inclusion in the survival model (B for MDD was adjusted from -.136 to -.135, remaining significant at p=.015).
### Table V.I continued

**Coronary Angiographic Data (n=124)**

<p>| | | | | |</p>
<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td><strong>No. vessels involved, mean ±SD</strong></td>
<td>1.9 ± 1.1</td>
<td>2.1 ± 0.9</td>
<td>0.33</td>
<td>.57</td>
</tr>
<tr>
<td><strong>Percent cumulative stenosis, mean ±SD</strong></td>
<td>133.1 ± 78.2</td>
<td>147.2±81.9</td>
<td>0.78</td>
<td>.38</td>
</tr>
<tr>
<td><strong>Restenosis, No. (%)</strong></td>
<td>7 (8)</td>
<td>6 (18)</td>
<td>2.56</td>
<td>.11</td>
</tr>
</tbody>
</table>

**Concomitant Medications**

<p>| | | | | |</p>
<table>
<thead>
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</thead>
<tbody>
<tr>
<td><strong>Statin, No. (%)</strong></td>
<td>90 (96)</td>
<td>33 (89)</td>
<td>1.99</td>
<td>.16</td>
</tr>
<tr>
<td><strong>ASA, No. (%)</strong></td>
<td>86 (92)</td>
<td>36 (97)</td>
<td>1.40</td>
<td>.22</td>
</tr>
<tr>
<td><strong>β-blockers, No. (%)</strong></td>
<td>68 (72)</td>
<td>32 (87)</td>
<td>2.94</td>
<td>.09</td>
</tr>
<tr>
<td><strong>Antihypertensive, No. (%)</strong></td>
<td>59(63)</td>
<td>26 (70)</td>
<td>0.66</td>
<td>.42</td>
</tr>
<tr>
<td><strong>Nitroglycerin, No. (%)</strong></td>
<td>51 (54)</td>
<td>23 (62)</td>
<td>0.68</td>
<td>.41</td>
</tr>
<tr>
<td><strong>Antidiabetic agents, No. (%)</strong></td>
<td>12 (13)</td>
<td>6 (16)</td>
<td>0.27</td>
<td>.61</td>
</tr>
<tr>
<td><strong>Ca²⁺ Channel Antagonists, No. (%)</strong></td>
<td>15 (16)</td>
<td>7 (19)</td>
<td>0.17</td>
<td>.68</td>
</tr>
<tr>
<td><strong>Diuretics, No. (%)</strong></td>
<td>22 (23)</td>
<td>4 (11)</td>
<td>2.65</td>
<td>.10</td>
</tr>
<tr>
<td><strong>Anxiolytics, No. (%)</strong></td>
<td>11 (12)</td>
<td>3 (8)</td>
<td>0.36</td>
<td>.55</td>
</tr>
<tr>
<td><strong>Antidepressants, No. (%)</strong></td>
<td>8 (9)</td>
<td>3 (8)</td>
<td>0.01</td>
<td>.94</td>
</tr>
</tbody>
</table>

**Physiological Parameters**

<p>| | | | | |</p>
<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td><strong>Resting Heart Rate, mean ± SD BPM</strong></td>
<td>66.8 ± 11.5</td>
<td>66.9 ± 12.3</td>
<td>0.00</td>
<td>.97</td>
</tr>
<tr>
<td><strong>Resting Systolic BP, mean ±SD, mm Hg</strong></td>
<td>128.8 ± 16.4</td>
<td>127.9±18.3</td>
<td>0.08</td>
<td>.78</td>
</tr>
<tr>
<td><strong>Resting Diastolic BP, mean ± SD, mm Hg</strong></td>
<td>73.8±10.2</td>
<td>73.0 ± 9.4</td>
<td>0.16</td>
<td>.69</td>
</tr>
<tr>
<td><strong>VO₂peak, mean ±SD, ml/kg/min</strong></td>
<td>19.53±5.58</td>
<td>19.09±5.62</td>
<td>0.17</td>
<td>.68</td>
</tr>
</tbody>
</table>

*a abbreviations: ACS, acute coronary syndrome; CES-D, Center for Epidemiological Studies-Depression Scale; PCI, percutaneous coronary intervention; CAGB, coronary artery by-pass graft; COPD, chronic obstructive pulmonary disorder; ASA; acetylsalicylic acid.*

*b two-tailed significance in Pearson χ² or one-way ANOVA; completers (n=94) and non-completers (n=37)*

### 5.5.2 Cognitive performance

Cognitive results are summarized in Table V.II. MMSE scores ranged from 24 to 30 (median=30, mode=30). In univariate comparisons, cumulative verbal memory scores were associated positively with hyperlipidemia (F₁,₁₃₀=8.45, p=.004), resting heart rate (r=.23, p=.009) and VO₂peak (r=.22, p=.01).

Participants with and without depression did not differ in verbal memory scores (F₁,₁₃₀=0.94, p=.34), though a trend was detected towards better verbal memory performance in participants using an antidepressant (F₁,₁₃₀=3.38, p=.07) and participants using an anxiolytic showed better verbal memory performance (F₁,₁₃₀=4.47, p=.04). Coronary angiographic data were available for 124 participants. Verbal memory performance was not associated with the total number of arteries involved (r=-.14, p=.12), the cumulative percentage stenosis in all 4 major coronary arteries (r=-.10, p=.27) or with
restenosis ($F_{1,123}=.19, p=.66$). Other sociodemographics, cardiac risk factors, cardiac histories, physiological parameters and medication prescriptions were not associated with verbal memory performance ($p>.05$).

5.5.3 Associations between verbal memory performance and non-completion of CR

Over 48 weeks, 29.4% of participants failed to meet comprehensive CR criteria for completion. Verbal encoding and recall, and cumulative verbal memory performance scores were lower in participants who failed to complete CR compared to completers but MMSE scores were not (Table V.II). Associations between participant characteristics and non-completion are summarized in Table V.I; as compared to those who would complete CR, non-completers were more likely to live alone, to have a history of smoking, to have an elevated waist circumference, to have more vascular risk factors, and to have depression at the time of entry into CR. In an ANCOVA model controlling for potential confounders ($F_{13,130}=3.69, p<.001$, adjusted $R^2=0.21$ for the overall model), cumulative verbal memory scores differed significantly between completers and non-completers ($F_{1,130}=7.80, p=.006$). An alternative model that also included sex, years of formal education and hypertension as covariates was explored to further rule out possible confounding effects, but the association between lower cumulative verbal memory scores and non-completion of CR was unaltered ($F_{1,130}=9.42, p=.003$).
In time-to-event analysis, higher cumulative verbal memory scores were associated with lower non-completion hazards ratios (Table V.III). This association was also significant when adjusting the Cox regression model with covariates that most influenced the association between verbal memory and non-completion, i.e. depression and smoking history (Table V.III). The adjusted model suggests that a cumulative decrease of 1 Z-score unit was associated with a 14% decrease in the likelihood of completing CR. A history of premorbid depressive episode(s) and CES-D scores also influenced the effect of verbal memory on non-completion (change in B≥10%) but less so than a current depressive episode and their inclusion in the model did not modify the association between non-completion and verbal memory performance (HR 0.84, 95% CI .75-.94, p=.005). The association between cumulative verbal memory scores and completion of CR was significant in models adjusted with each of the characteristics from Table V.I (p<.05). Repeating the adjusted model including the 3 participants with MMSE<24 did not suggest that excluding these participants introduced appreciable bias (verbal memory performance HR 0.86, 95% CI .77-.96, p=.008).

Table V.III: Coefficients of Cox Proportional Hazards Models showing Associations between Verbal Memory Performance and Non-completion of CR

<table>
<thead>
<tr>
<th>Relative Risk (95% CI)</th>
<th>B</th>
<th>SE</th>
<th>Wald</th>
<th>Sig. a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unadjusted model b</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Verbal memory performance</td>
<td>.87 (.78-.97)</td>
<td>-.14</td>
<td>.055</td>
<td>6.04</td>
</tr>
<tr>
<td>Adjusted model c</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Verbal memory performance</td>
<td>.86 (.77-.96)</td>
<td>-.15</td>
<td>.058</td>
<td>6.87</td>
</tr>
<tr>
<td>Current depression</td>
<td>2.62 (1.33-5.17)</td>
<td>.96</td>
<td>.35</td>
<td>7.68</td>
</tr>
<tr>
<td>Smoking history</td>
<td>2.03 (.98-4.22)</td>
<td>-.71</td>
<td>.37</td>
<td>3.59</td>
</tr>
</tbody>
</table>

a two-tailed significance  
b overall model Chi-Square=6.07, df=1, p=.01  
c model contains variables found to influence the unadjusted B for verbal memory performance by ≥10%; overall model Chi-Square=17.23, df=3, p=.001

5.5.4 Subgroup analyses in depressed and non-depressed participants

Of all participants, 35 (26.7%) met DSM-IV diagnostic criteria for major or minor depression. Participants with major depression (n=21) or minor depression (n=14) did not differ in verbal memory scores (F1,34=0.67, p=.40) or in likelihood of non-completion (9/21 and 6/14, respectively). The proportion of non-completers was higher among depressed participants than among non-depressed participants (42.9% vs. 22.9%, Chi-square=5.03, p=.025).
Among depressed participants, poorer verbal memory scores predicted non-completion (HR 0.80, 95% CI .66-.97, p=.02), even when controlling for depressive symptom severity (HR 0.80, 95% CI .66-.97, p=.02). Among depressed participants, those with negative cumulative verbal memory scores were older (F1,34=8.46, p=.006) and more likely to have had CABG (50.0% vs. 9.5%, Fisher’s Exact test, p=.01) though neither age (F1,34=0.10, p=.75) nor the proportion of participants with CABG (33.3% vs. 20.0%, Fisher’s Exact test, p=.45) differed between completers and non-completers who were depressed at study entry.

In non-depressed participants (n=96), a trend persisted towards poorer verbal memory scores predicting non-completion (HR 0.87, 95% CI .76-1.00, p=.06), which was significant when adjusted for depressive symptoms (HR 0.86, 95% CI .74-1.00, p=.04). Among non-depressed participants who also had no prior history of depression (n=84) poorer cumulative verbal memory scores were significantly associated with non-completion (F1,83=4.33, p=.04), even when including depressive symptoms as a covariate (F1,83=4.84, p=.03).

5.5.5 Dichotomous time-to-event analyses

In time-to-event analyses, participants with cumulative verbal memory scores in the negative range (n=63) were 2.37-fold more likely not to complete CR than participants with cumulative verbal memory scores in the positive range (p=.02; Figure 5.2A). The relative risk associated with having a cumulative verbal memory score in the negative range was comparable to that observed for depression (2.17-fold more likely not to complete CR, p=.02; Figure 5.2B). The co-occurrence of depression and a negative cumulative verbal memory score was associated with a greater risk of non-completion; participants who presented with both depression and a cumulative verbal memory score in the negative range (n=14) were 4.04-fold more likely than others to not complete CR (HR 4.04, 95% CI 1.89-8.60, p<.001).

To investigate the interaction between depression and poorer verbal memory performance, participants were stratified based on having no depression and a positive cumulative verbal memory score, either depression or a negative cumulative verbal memory score, or both depression and a negative cumulative verbal memory score. As compared to participants presenting with no depression and a verbal memory score in the positive range, participants presenting with either depression or a cumulative verbal memory score in the negative range showed an 2.60-fold increased risk of non-completion (p=.05; Figure 5.2C),
while those having both depression and a negative cumulative verbal memory score had an 8.13-fold increased risk as compared to those who had neither (p<.001; Figure 5.2C).

5.5.6 Association between verbal memory performance and non-completion for medical reasons

In a *post-hoc* comparison, participants who withdrew from CR prematurely for medical reasons (n=16) showed significantly poorer verbal memory at baseline ($F_{1,130}=5.04$, $p=.03$). In Cox regression analysis, better verbal memory performance predicted a lower risk of non-completion for medical reasons (HR 0.83, 95% CI 0.70-0.99; $p=.03$).
Figure 5.2 Time in CR with values right-censored for non-completers at the time of their last CR session attendance.

Survival patterns shown for:

A) Participants who presented with a cumulative verbal memory score in the negative (n=68; dashed line) or positive (n=63; solid line) ranges (unadjusted HR 2.37, 95% CI 1.17-4.79, p=.02)

B) Participants who presented with (n=35; dashed line) and without (n=96; solid line) depression (unadjusted HR 2.17, 95% CI 1.12-4.19, p=.02)

C) Participants who presented with no depression and a positive cumulative verbal memory score (n=42; solid line), those who presented with either depression or a negative cumulative verbal memory score (n=75; dashed line; HR 2.60, 95% CI 0.99-6.85, p=.05), or those who presented with both depression and a negative cumulative verbal memory score (n=14; long-dashed line; HR 8.13, 95% CI 2.72-24.34, p<.001).
5.6 Discussion

In the present study, poorer verbal memory performance predicted non-completion of CR. Although CAD has been associated with poorer verbal memory performance, to our knowledge, an association between poorer verbal memory performance and non-completion of CR had not been assessed systematically. In previous studies, detrimental effects of clinical depression or depressive symptoms on completion rates have been documented. These observations have led to the inclusion of depression screening and psychosocial supports as structured components of care in CR programs. In the present study, the association between poorer verbal memory performance and non-completion was independent of clinical depression and depressive symptom severity; poorer cognitive performance and depression contributed additively to the risk of non-completion.

Although the cumulative burden of vascular risk factors was associated with non-completion and with verbal memory performance, verbal memory performance remained an independent predictor of non-completion when controlling for vascular risk factors both cumulatively and individually. Verbal memory scores were significantly associated with cardiopulmonary fitness at entry into CR, suggesting that participants with better cognition may have had higher baseline physical activity levels, and hence less difficulty adopting CR exercise prescriptions; however, poorer verbal memory performance was associated with non-completion independently of cardiopulmonary fitness. These findings are consistent with a path analysis presented by Elias and colleagues, in which physical ability was more closely related to verbal memory performance than diastolic blood pressure, with verbal memory acting as a mediator between the vascular risk factor and the functional outcome.

It has been suggested that vascular damage to brain regions that subserve memory and decision-making might interact with self-care and therefore poorer adherence to risk factor management might contribute to increased medical burden. In the setting of CR, the post-hoc association between poorer verbal memory performance and non-completion of CR for medical reasons is consistent with this hypothesis, and with reports of increased mortality associated with poorer cognitive performance in other community samples. Processes which contribute to both atherosclerosis and poorer verbal memory performance, might also contribute to adverse medical outcomes. Although coronary angiographic measures did not attenuate the association between poorer verbal memory and non-completion, other measures of CAD severity, cerebrovascular disease and inflammatory activity were not explored.
The present study suggests that cognitive screening might be of clinical utility in this population. Completers of CR differed from non-completers in all three CVLT-II measures, suggesting that aspects of memory performance associated with non-completion may originate at the encoding trials and subsequently affect recall. This may have implications for screening. The encoding trials not only engage the hippocampus, but they also rely on the integrity of the frontal lobe and of the interconnecting white matter in order to sustain attention and engage strategic aspects of memory. Cerebrovascular lesions and volumetric changes in each of these structures have been associated with CAD and vascular risk factors.

Although mean Z-scores of non-completers were lower than those of completers on each CVLT-II metric, the mean Z-scores of both completers and non-completers were within the “normal” range, suggesting the clinical importance of subtle relative deficits. While sufficiently sensitive to these deficits, the CVLT-II is an impractical screening instrument. By contrast, the MMSE was not adequately sensitive. For screening, brief instruments such as the 5 minute Montreal Cognitive Assessment might be explored, whereas the CVLT-II might be used in subgroups of patients at particularly high risk of non-completion. For instance, while depression can be effectively screened in the setting of CR, identification of depression in CR participants has not translated into quantifiable improvements in medical outcomes.

Subgroup analyses of the present data suggest that verbal memory testing might differentiate depressed participants who are particularly at risk of non-completion.

The existing infrastructure for psychosocial support in many CR programs might be suitable to investigate cognitive screening and intervention. In the present study, a trend was observed towards better verbal memory performance in participants using antidepressants, consistent with other evidence that antidepressants can improve cognitive performance in those with CAD; however, low rates of antidepressant utilization in the present cohort resulted in inadequate power to detect associations between antidepressant use and adherence to CR. Additionally, cognitive training can improve long-term cognitive performance and daily function though it remains to be tested whether such gains might translate into better adherence to risk factor management for CR participants with CAD.

This study was strengthened by a prospective design, the use of a sensitive verbal memory test, and by exploration of time-sensitive analyses controlling for potential clinical confounders. Though potential confounders did not impact the clinical significance of verbal memory performance, the study was not powered to detect their specific effects. As a potential limitation, CAD severity was assessed only by coronary angiography and cardiac history; however, these data do not suggest that CAD severity is...
likely to account for the observed associations. Though largely representative of the population at the CR centre, the possibility that the sample was biased at the level of recruitment cannot be ruled out. Moreover, CR participants may be more motivated or perceived by their physicians to be more amenable to CR and therefore they may not represent all patients with CAD. As a further potential limitation, determination of time in CR relied on attendance to visits at the centre and this may not accurately reflect the length of time a participant remained adherent to offsite exercise prescriptions. It should also be considered that the length, intensity and cost to the consumer of CR programs and associated care vary significantly. In the present study, 48-week CR and related care were publicly funded by national health coverage, which may limit the generalizability of the results. Although publicly funded care may have reduced potentially confounding socioeconomic effects, such effects were not assessed.

5.7 Conclusion

Poorer verbal memory performance was associated with increased rates of non-completion and an increased impact of medical morbidity among CR participants with CAD. Participants with depression and poorer verbal memory performance were particularly at risk. Further studies might seek to optimize clinical outcomes by exploring practical methods for screening and by developing additional structured supports.

5.8 Significance and impact

Although a considerable body of evidence now documents the strength of depressive symptoms as a predictor of non-completion of CR, no prospective study had assessed the impact of cognitive function. The present study identifies a new risk factor for non-completion of CR, documenting a relative risk comparable in magnitude to, but independent of, that associated with depression. Importantly, an interaction was identified between depression and poorer verbal memory performance, such that patients affected by both of these brain-related risk factors were the most severely affected. This suggests the potential clinical utility of cognitive testing for identifying patients at higher risk of non-completion among patients who also screen positive for depressive symptoms.
This study establishes that subtle deficits in cognitive performance are clinically significant in patients with CAD entering CR. The data provide a strong rationale to investigate the etiology of these deficits and to better understand how they pose a barrier to participation in CR. Post-hoc analyses suggest that, much like the effect of depression (Chapter 1, Section 2), these deficits were associated with non-completion due to an increased impact of medical morbidity, even though the association was independent of baseline measures of CAD severity and vascular risk factor burden. These findings are in agreement with other reports wherein cognitive performance acted as a statistical mediator of the effect of vascular risk factors on physical ability\textsuperscript{179}. 
Chapter 6:

Brain Derived Neurotrophic Factor, Cardiopulmonary Fitness and Cognition in Patients with Coronary Artery Disease

6.1 Statement of work and disclosure

This study has been published in Brain, Behaviour, and Immunity (Swardfager W, Herrmann N, Marzolini S, Saleem M, Shammi P, Oh PI, Albert PR, Daigle M, Kiss A, Lanctôt KL. Brain Behav Immunity. 25(2011);1264-71)\(^{336}\). The primary author designed the study and recruited patients under the supervision of Drs. Lanctôt, Herrmann and Oh (recruitment strategy as established in Chapter 1, Section 3), performed patient interviews including cognitive testing, performed phlebotomy, collected genetic samples, scored cognitive tests, designed the study database and entered data. Some patient recruitment and interviews were performed by Ms. Saleem and Mrs. Sherman. Ms. Saleem assisted with scoring of cognitive tests and with data entry. Cardiopulmonary fitness testing was performed by Toronto Rehabilitation Institute staff. Ms. Marzolini facilitated fitness data collection and assisted with the interpretation of fitness data. Dr. Shammi provided guidance on the interpretation of cognitive data. All statistical analyses were carried out by the primary author under the guidance of Dr. Kiss. Genotyping was performed by Ms. Daigle in the laboratory of Dr. Albert. Serum IL-6 and BDNF concentrations were assayed by Li Mei and Betty Wong in the laboratory of Dr. David Cole at Sunnybrook Health Sciences Centre. Drs. Lanctôt and Herrmann oversaw and contributed to the study concept, design and analysis.

6.2 Abstract

Objective: To assess serum brain derived neurotrophic factor (BDNF) concentrations as a correlate of cardiopulmonary fitness and as a predictor of cognitive performance in subjects with coronary artery disease (CAD).

Methods: Serum BDNF concentrations were assayed by ELISA and fitness was assessed using a standardized exercise stress test. The Mini Mental Status Examination (MMSE), California Verbal Learning Test 2nd Ed., Stroop, Trail Making Test B and the Digit Symbol-Coding task were administered. The val66met BDNF genotype and serum interleukin-6 (IL-6) and tumor necrosis factor-α...
(TNF-α) concentrations were determined as potential confounders. Results: In subjects with CAD ($n=88$; 85.2% male, mean age 62.8±10.5 yr), cardiopulmonary fitness was associated with higher serum BDNF concentrations ($\beta=.305$, $p=.013$). Higher serum BDNF concentrations were associated with higher MMSE scores ($F(1,87)=15.406$, $p<.0005$) and better performance on the Digit Symbol-Coding task ($F(1,87)=9.620$, $p=.003$). IL-6, TNF-α and the val66met genotype did not influence these results. Conclusion: Serum BDNF concentrations were associated with cardiopulmonary fitness, psychomotor processing speed and overall cognition in subjects with CAD.

6.3 Introduction

Cardiopulmonary fitness has been associated with better cognitive performance in older adults. Consistent with this observation, physical activity can improve performance on tests of processing speed, attention, executive function and memory. Physical activity can also increase brain derived neurotrophic factor (BDNF) concentrations in peripheral blood. Evidence suggests that BDNF may be involved in the beneficial effect of cardiopulmonary fitness on cognitive performance. In the CNS, BDNF can support neuronal growth and survival and attenuate inflammatory damage to axons and midbrain dopaminergic neurons. In medically and neurologically healthy older adults, higher serum BDNF protein concentrations have been variably associated with better cognitive performance.

In subjects with coronary artery disease (CAD), the association between cardiopulmonary fitness and cognitive performance has been observed independent of other vascular risk factors, demographics, cardiac histories and concomitant medications, suggesting that fitness may be a clinically important factor protecting against cognitive decline. However, peripheral blood BDNF protein concentrations have not been assessed as a predictor of cognitive performance, nor as a correlate of cardiopulmonary fitness in this population.

Previous literature suggests several factors that may influence these relationships. A single nucleotide polymorphism at codon 66 of the BDNF gene, which results in an amino acid substitution (val66met) in the pro-region of the protein, has been associated with poorer cognitive performance. The val66met genotype has also been associated with variation in peripheral blood BDNF protein concentrations, suggesting the need to assess the val66met genotype as a potential confounder. Moreover, serum BDNF concentrations have been associated with inflammatory biomarkers in subjects with CAD. Exercise-
responsive inflammatory biomarkers, notably IL-6 and TNF-α\textsuperscript{65, 349}, have been associated with the progression of CAD\textsuperscript{350, 351} and with poorer cognitive function\textsuperscript{329, 352} suggesting the need to explore systemic inflammatory activity as a potential confounder.

The present study sought to determine whether peripheral blood BDNF protein concentrations were associated with cardiopulmonary fitness and cognitive function in subjects with CAD independent of two inflammatory markers, a common polymorphism in the BDNF (val66met) genotype, and other clinical characteristics.

6.4 Methods

The present study assessed cross-sectional associations between 1) serum BDNF concentrations and cardiopulmonary fitness and 2) serum BDNF concentrations and cognitive performance in a cohort of consecutive patients with CAD entering cardiac rehabilitation.

6.4.1 Participants

Institutional research ethics boards at Sunnybrook Health Sciences Centre and the Toronto Rehabilitation Institute approved the study protocol. Consent to participate was sought from consecutive patients with a documented history of CAD (myocardial infarction, MI; angiographic evidence showing ≥50% blockage in at least one major coronary artery; percutaneous coronary intervention, PCI; or coronary artery bypass graft surgery, CABG) entering a cardiac rehabilitation (CR) program. Subjects began CR a minimum of 6 weeks post-CABG or MI, or a minimum of 3 weeks post-PCI. Participants were interviewed by a trained study researcher and excluded if they could not complete cognitive testing or if their medical records were otherwise incomplete. Demographics (e.g. age, gender, education), cardiac history (e.g. PCI, CABG, MI), vascular risk factors (body mass index, hyperlipidemia, diabetes, hypertension, waist circumference, smoking), concomitant medication use, medical/psychiatric comorbidities and anthropometrics were ascertained by CR staff or chart review and confirmed by patient interview. Where available, coronary angiography reports were reviewed for indices of CAD severity including the involvement of each major coronary artery (>50% stenosis) and the presence of restenosis in any previously revascularized lesion.
Patients were excluded on the basis of any previously diagnosed neurodegenerative disorder or schizophreniform or bipolar psychiatric illness. As a possible confounder, major or minor depression were diagnosed by study personnel using the Structured Clinical Interview for Diagnostic and Statistical Manual 4th Edition criteria. The Center for Epidemiological Studies Depression (CES-D) scale was used to quantify depressive symptoms based on demonstrated utility in patients with CAD.

6.4.2. Cognitive testing

A battery of cognitive assessments encompassing processing speed, executive function, memory and global cognition were administered, including the Trail Making Test B, the Victoria version of the Stroop test, and the Digit Symbol-Coding task, a measure of complex attention and psychomotor processing speed from the Wechsler Adult Intelligence Scale 3rd Edition. Verbal memory was assessed as immediate, short and long delayed free recall of the California Verbal Learning Test 2nd Ed. (CVLT-II) word list. Global cognitive status was assessed using the Mini-Mental Status Examination (MMSE). These instruments were chosen based on the National Institute of Neurological Disorders and Stroke and Canadian Stroke Network (NINDS-CSN) harmonized standards. All cognitive testing was carried out at a standardized time (0930 hr ± 30 min) and participants refrained from eating or drinking any caffeine-containing beverages for at least 4 hours prior and from extensive physical activity. For each cognitive task, a Z-score was determined based on published norms. The Z distribution maps the mean of the test variable to 0 with 1 Z-score unit equal to 1 standard deviation (better performance is more positive and poorer performance is more negative).

6.4.3 Serum collection and assays

Blood samples were drawn at 0930 h ± 30 min following a 12 h overnight fast and centrifuged at 1000 g for 10 min at 4°C. Serum was separated and stored at -80°C until the time of the assay. IL-6 and TNF-α (Alpco Diagnostics, Salem NH, USA) and BDNF (R&D Systems Inc., Minneapolis, MN, USA) were assayed by ultrasensitive enzyme-linked immunosorbant assay according to manufacturers’ instructions with sensitivities of 0.16, 0.5 and 20 pg/mL, respectively.
6.4.4 Genetic sample collection and genotyping

Genomic DNA was extracted from Dacron buccal swabs using the Qiamp DNA mini kit (Qiagen, Missisauga, Ontario, Canada). The Val66Met (rs6265) genotype was determined by polymerase chain reaction (PCR) restriction fragment length polymorphism analysis. The PCR reaction was performed in a final volume of 25 ml containing 1X Phusion HF buffer (Finnzymes, Finland), 2 pmol of each PCR primer, 200 mM dNTP, 50 ng of genomic DNA and 0.625 units of Phusion (Finnzymes, Espoo, Finland). The primers used for amplification were 5’-CCCAAGGCAGGTTCAAGAG-3’ (forward) and 5’-CGTTACCCACTCAACTAATCTGTA-3’ (reverse). The PCR conditions used were: 30 s, 98°C; 35 cycles of 10 s, 98°C; 20 s, 68°C; 10 s 72°C; and 5 min, 72°C. PCR was followed by digestion of amplicons using NlaIII (New England Biolabs, Pickering, Ontario, Canada) at 37°C for 3 h, yielding fragments of 81 and 222 bp (G allele), 81, 54, and 167 bp (A allele) or 81, 54, 167 and 222 bp (heterozygous). Genotypes were confirmed by automated sequencing using the primer: 5’-TGCCCCCATGAAAGAAGC-3’.

6.4.5 Physical assessments

At the patients’ CR intake visit, blood pressure and heart rate were measured by CR staff. Anthropometric measurements were also made; percentage body fat was assessed by bioelectric impedance (Tanita TBF-300A, Tokyo, Japan), waist circumference was measured and body mass index (BMI) was calculated per standard definition.

6.4.6 Cardiopulmonary fitness assessment

Cardiopulmonary fitness was assessed by a cycle ergometer (Ergoline 800 EL) symptom-limited graded exercise test. Work load was increased by 16.7 Watts every minute and breath-by-breath gas samples were collected and averaged over a 20 second period via calibrated metabolic cart (Vmax) 11. The peak volume of oxygen uptake (VO$_2$Peak) was recorded and normalized for body mass (VO$_2$Peak reported in ml/kg/min). The VO$_2$Peak thus obtained represents a measure of ventilatory capacity at peak effort and it is a highly reliable and reproducible measure of cardiopulmonary fitness 248. The respiratory exchange ratio (RER), an indicator of metabolic effort 309, was calculated as the ratio of CO$_2$/O$_2$ in gas.
breath samples at the time of VO$_{2\text{Peak}}$ measurement. For each subject, the VO$_{2\text{Peak}}$ measured from exercise stress testing was divided by his or her expected VO$_{2\text{Peak}}$ to provide a clinically meaningful measure of cardiopulmonary fitness that can be compared across age and gender.$^{310}$ The expected VO$_{2\text{Peak}}$ was calculated from established age and gender norms$^{310}$ as:

$$\text{Expected VO}_{2\text{Peak}} = 60 - (0.55 \times \text{Age}) \text{ ml/kg/min for male subjects and}$$
$$\text{Expected VO}_{2\text{Peak}} = 48 - (0.37 \times \text{Age}) \text{ ml/kg/min for female subjects}$$

6.4.7 Statistical analyses

All analyses were carried out in SPSS (version 16.0) and considered significant at a two-tailed $\alpha$ of 0.05. Pearson correlations and univariate analyses of variance (ANOVA), as appropriate, were used to identify patient characteristics associated with serum BDNF concentrations. Serum protein concentrations were log-transformed as necessary, and linearity was assessed using P-P plots. Bonferroni correction was applied to comparisons between the val66met genotypes because there are three genotypes (val/val, val/met and met/met), and hence inherent multiple comparisons between them.

A linear regression model was used to determine if cardiopulmonary fitness was a significant predictor of serum BDNF protein concentrations. Possible confounders were chosen $a$ priori, including depression,$^{353}$ age,$^{356}$ gender,$^{345,356,357}$ val66met genotype$^{347}$ and serum inflammatory markers$^{348}$ for inclusion in the model. Clinical characteristics associated with BDNF concentrations were also included as covariates. As a possible covariate, the number of vascular risk factors (i.e. hypertension, smoking, diabetes, BMI>30 kg/m$^2$, waist circumference>102 for men or >88 cm for women and dyslipidemia) were summed to account for cumulative vascular risk factor burden.

Z-scores from individual cognitive tests were entered into a multiple linear regression model to assess their independent associations with the fraction of the VO$_{2\text{Peak}}$ norm. Performance in one cognitive domain can affect performance on tests designed to measure other domains, so a multiple linear regression approach was used. Z-scores from individual cognitive tests were also entered into a multiple linear regression model to assess their independent associations with serum BDNF concentrations. In linear regression models, multicollinearity was assessed among predictors using the tolerance statistic.
(tolerance \leq 0.4) and if multicollinearity was identified, only one variable identified as part of a multicollinear set was included in the final model.

A multivariate general linear model was used to assess the associations between serum BDNF protein concentration and cognitive test results that were independently associated with BDNF concentrations. Age, gender, angiographic CAD severity measures, cardiac risk factors or other subject characteristics associated with serum BDNF concentrations or cognitive test results were explored as potential confounders.

Subgroup analyses were planned in male subjects due to possible differential effects in males and females \textsuperscript{345, 356, 357}, and in non-depressed subjects who were also free of any antidepressant medication due to an association between depression and lower BDNF concentrations or possible effects of antidepressant medications \textsuperscript{353}.

6.4.8 Sample size

A sample size of $n=90$ was considered sufficient (80% power) to detect a clinically meaningful relationship (0.3 standard deviations per one standard deviation change) between serum BDNF concentrations and cardiopulmonary fitness at a two-sided significance of $\alpha=0.05$.

6.5 Results

6.5.1 Recruitment

Study personnel contacted 139 patients at their intake CR visit who met inclusion criteria as determined by clinical personnel. Subsequently, 34 patients declined to be interviewed. Cognitive testing was carried out in all but 18 patients who consented to be interviewed; 11 met further exclusion criteria, 5 were unable to schedule an appointment, 1 screened positive for significant cognitive impairment (MMSE<24), 1 could not complete cognitive testing because of insufficient English language skills and 1 was unable to complete study tasks due to inadequate visual acuity. There were therefore 88 subjects studied (Table VI.I).
Table VI.I: Characteristics of Study Participants and Associations with Serum BDNF Protein Concentrations

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Association with serum BDNF concentrations</th>
<th>$F$ or $r^a$</th>
<th>Sig.$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sociodemographic</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, mean ± SD, yr</td>
<td>62.79±10.47</td>
<td>$r=.114$</td>
<td>.292</td>
</tr>
<tr>
<td>Employed, n (%)</td>
<td>49 (55.6)</td>
<td>$F(1,87)=.189$</td>
<td>.665</td>
</tr>
<tr>
<td>Partnered, n (%)</td>
<td>68 (77.3)</td>
<td>$F(1,87)=.004$</td>
<td>.952</td>
</tr>
<tr>
<td>Sex, male, n (%)</td>
<td>75 (85.2)</td>
<td>$F(1,87)=1.315$</td>
<td>.255</td>
</tr>
<tr>
<td>Caucasian, n (%)</td>
<td>79 (89.8)</td>
<td>$F(1,87)=.066$</td>
<td>.798</td>
</tr>
<tr>
<td>Total education, mean ± SD, yr</td>
<td>16.4±3.4</td>
<td>$r=-.038$</td>
<td>.724</td>
</tr>
<tr>
<td><strong>Psychometric</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depressive episode, n (%)</td>
<td>26 (29.5)</td>
<td>$F(1,87)=.102$</td>
<td>.751</td>
</tr>
<tr>
<td>History of depressive episode, n (%)</td>
<td>24 (27.3)</td>
<td>$F(1,87)=.002$</td>
<td>.964</td>
</tr>
<tr>
<td>CES-D score, mean ± SD</td>
<td>11.70±11.34</td>
<td>$r=-.102$</td>
<td>.345</td>
</tr>
<tr>
<td><strong>Vascular Risk Factors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>52 (59.1)</td>
<td>$F(1,87)=.054$</td>
<td>.817</td>
</tr>
<tr>
<td>Past smoker, n (%)</td>
<td>53 (60.2)</td>
<td>$F(1,87)=.080$</td>
<td>.778</td>
</tr>
<tr>
<td>Years smoked, mean ± SD</td>
<td>12.92±14.80</td>
<td>$r=.015$</td>
<td>.890</td>
</tr>
<tr>
<td>Cigarettes per day, mean ± SD</td>
<td>10.28±11.6</td>
<td>$r=-.021$</td>
<td>.844</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>14 (15.9)</td>
<td>$F(1,87)=1.036$</td>
<td>.312</td>
</tr>
<tr>
<td>BMI, mean ± SD, kg/m²</td>
<td>28.73±4.67</td>
<td>$r=-.124$</td>
<td>.257</td>
</tr>
<tr>
<td>BMI&gt;30 kg/m² (%)</td>
<td>29 (33.0)</td>
<td>$F(1,87)=1.581$</td>
<td>.212</td>
</tr>
<tr>
<td>Waist circumference, mean ± SD</td>
<td>101.5±10.8</td>
<td>$r=-.040$</td>
<td>.715</td>
</tr>
<tr>
<td>Waist circumference &gt;88 (female) or &gt;105 (male)</td>
<td>47 (53.4)</td>
<td>$F(1,87)=.086$</td>
<td>.770</td>
</tr>
<tr>
<td><strong>Cardiac History</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCI, n (%)</td>
<td>53 (60.2)</td>
<td>$F(1,87)=.361$</td>
<td>.549</td>
</tr>
<tr>
<td>Myocardial Infarction, n (%)</td>
<td>43 (48.9)</td>
<td>$F(1,87)=.082$</td>
<td>.775</td>
</tr>
<tr>
<td>CABG, n (%)</td>
<td>28 (31.8)</td>
<td>$F(1,87)=.922$</td>
<td>.340</td>
</tr>
<tr>
<td>Angina, n (%)</td>
<td>25 (28.4)</td>
<td>$F(1,87)=.011$</td>
<td>.918</td>
</tr>
<tr>
<td>Peripheral Vascular Disease, n (%)</td>
<td>4 (4.5)</td>
<td>$F(1,87)=.347$</td>
<td>.557</td>
</tr>
<tr>
<td>No. Vessels Involved, mean ± SD</td>
<td>2.03±0.96</td>
<td>$r=-.071$</td>
<td>.533</td>
</tr>
<tr>
<td>Time since event, mean ± SD, weeks</td>
<td>14.2±8.1</td>
<td>$r=-.031$</td>
<td>.785</td>
</tr>
<tr>
<td><strong>Concomitant Medications</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Statins, n (%)</td>
<td>86 (97.7)</td>
<td>$F(1,87)=2.342$</td>
<td>.130</td>
</tr>
<tr>
<td>ASA, n (%)</td>
<td>84 (95.5)</td>
<td>$F(1,87)=.059$</td>
<td>.808</td>
</tr>
<tr>
<td>β-blockers, n (%)</td>
<td>66 (75.0)</td>
<td>$F(1,87)=2.256$</td>
<td>.137</td>
</tr>
<tr>
<td>ACE inhibitor, n (%)</td>
<td>55 (62.5)</td>
<td>$F(1,87)=4.725$</td>
<td>.032</td>
</tr>
<tr>
<td>Nitroglycerin, n (%)</td>
<td>51 (58.0)</td>
<td>$F(1,87)=.248$</td>
<td>.620</td>
</tr>
<tr>
<td>Diuretics, n (%)</td>
<td>14 (15.9)</td>
<td>$F(1,87)=.359$</td>
<td>.551</td>
</tr>
<tr>
<td>Ca$^{2+}$-Channel Antagonists, n (%)</td>
<td>13 (14.8)</td>
<td>$F(1,87)=.167$</td>
<td>.684</td>
</tr>
<tr>
<td>Anxiolytics, n (%)</td>
<td>9 (10.2)</td>
<td>$F(1,87)=.088$</td>
<td>.768</td>
</tr>
</tbody>
</table>

$^a$No patients had a history of heart failure in this study sample.
Table VI.1 continued

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<tr>
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<tr>
<td>Antidiabetic agents, n (%)</td>
<td>9 (10.2)</td>
<td>(F(1,87)=1.565)</td>
<td>.214</td>
</tr>
<tr>
<td>Antidepressants, n (%)</td>
<td>6 (6.8)</td>
<td>(F(1,87)=1.211)</td>
<td>.274</td>
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Resting Physiology

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<tbody>
<tr>
<td>Resting Heart Rate, mean ± SD, BPM</td>
<td>67.66±110.20</td>
<td>(r=.079)</td>
<td>.465</td>
</tr>
<tr>
<td>Resting Systolic BP, mean ± SD, mm Hg</td>
<td>127.91±17.04</td>
<td>(r=-.138)</td>
<td>.202</td>
</tr>
<tr>
<td>Resting Diastolic BP, mean ± SD, mm Hg</td>
<td>74.93±11.17</td>
<td>(r=-.103)</td>
<td>.342</td>
</tr>
</tbody>
</table>

Fitness Parameters

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<tbody>
<tr>
<td>Fraction VO(_{2}\text{Peak norm}), mean ± SD</td>
<td>.858±.263</td>
<td>(r=.252)</td>
<td>.019</td>
</tr>
<tr>
<td>Maximum Heart Rate, mean ± SD, BPM</td>
<td>122.61±20.56</td>
<td>(r=.009)</td>
<td>.933</td>
</tr>
<tr>
<td>Maximum Systolic BP, mean ± SD, mm Hg</td>
<td>181.08±26.49</td>
<td>(r=-.035)</td>
<td>.752</td>
</tr>
<tr>
<td>Maximum Diastolic BP, mean ± SD, mm Hg</td>
<td>79.93±10.39</td>
<td>(r=-.083)</td>
<td>.450</td>
</tr>
</tbody>
</table>

\(^a\)F represents the \(F\) statistic in one-way analyses of variance (ANOVA) comparing serum BDNF protein concentrations between categorical subject characteristics and \(r\) represents the Pearson correlation between serum BDNF protein concentrations and continuous subject characteristics, as appropriate

\(^{b}\)P-value represents the two-sided significance in one-way ANOVA or Pearson correlations

\(n=88\)

ASA = acetylsalicylic acid; ACE = angiotensin converting enzyme; BP = blood pressure; BPM = beats per minute; CABG = coronary artery bypass graft; CES-D = Center for Epidemiological Studies-Depression Scale; PCI = percutaneous coronary intervention; VO\(_{2}\text{Peak}\) = peak volume of oxygen uptake.

6.5.2 Serum assays and genotyping

Mean serum concentrations of BDNF, IL-6 and TNF-\(\alpha\) are presented in Table VI.II. For parametric analyses serum IL-6 concentrations were log-transformed due to skew and kurtosis. One third of TNF-\(\alpha\) concentrations were below the limit of detectability; therefore, for analysis, patients were stratified into tertiles, with non-detectable samples comprising the lowest tertile. The coefficients of variation for BDNF, IL-6 and TNF-\(\alpha\) were 3.5%, 11% and 24%, respectively. Higher serum concentrations of IL-6 were associated with higher BDNF concentrations (Table VI.II). The time since most recent acute coronary syndrome was not associated with serum IL-6 (\(p=.559\)) or TNF-alpha (\(p=.890\)) concentrations suggesting that the population may have been relatively “stable” with respect to inflammatory markers after acute events.

Genotype frequencies for the val66met polymorphism are presented in Table VI.II. Serum BDNF concentrations were numerically higher in subjects carrying at least one copy of the met allele (\(17193\pm7931\) pg/ml) than in subjects of the val/val genotype (\(14798\pm7931\) pg/ml) in agreement with previous findings \(^{347}\), but this difference was not significant (\(F(1,83)=1.724, p=.193\)). The two subjects of the met/met genotype had serum BDNF concentrations of 13334 and 22580 pg/ml.
6.5.3 Cardiopulmonary fitness and serum BDNF protein concentrations

The mean VO$_{2peak}$ of the present cohort was 14.2% below expected age and gender norms (range 45% below to 67% above their predicted VO$_{2peak}$) and 38.4% of subjects presented with VO$_{2Peak}$ below average (<73% of their predicted VO$_{2Peak}$). Of all subject characteristics, poorer cardiopulmonary fitness, the use of an antihypertensive medication, and lower serum concentrations of IL-6 were associated with lower BDNF concentrations (Tables VI.I and VI.II) in bivariate comparisons.

In a linear regression model ($F(7,85)=3.173, p=.005$, adjusted $R^2=.152$) controlling for age, sex, antihypertensive use, depression, antidepressant use, and serum IL-6 concentrations, better cardiopulmonary fitness was a significant independent predictor of serum BDNF concentrations ($\beta=.305, p=.013$). Of all covariates, only serum IL-6 concentrations also independently predicted higher serum BDNF concentrations ($\beta=.304, p=.006$). Including the val66met genotype, angiographic CAD severity measures, or the number of vascular risk factors in this model did not significantly influence the strength of this association between fitness and serum BDNF concentrations ($p<.02$). In planned subgroup analyses, fitness and serum BDNF concentrations remained associated when excluding depressed subjects or subjects using an antidepressant medication ($\beta=.276, p=.041, n=59$) and among male subjects ($\beta=.329, p=.011, n=75$).

Table VI.II: Results of Serum Assays and Genotyping

<table>
<thead>
<tr>
<th>Serum Biomarkers (n=88)</th>
<th>Association with serum BDNF protein concentration</th>
<th>$F$ or $r^a$</th>
<th>Sig.$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>BDNF, mean±SD, pg/ml</td>
<td></td>
<td>15347±7989</td>
<td>-</td>
</tr>
<tr>
<td>IL-6, mean±SD, pg/ml</td>
<td>r=.322</td>
<td>2.97±3.61</td>
<td>.002*</td>
</tr>
<tr>
<td>TNF-α, mean±SD, pg/ml</td>
<td></td>
<td>1.73±3.49</td>
<td>-</td>
</tr>
<tr>
<td>TNF-α, tertile</td>
<td>$F(2,87)=2.578$</td>
<td>-</td>
<td>.082</td>
</tr>
<tr>
<td>BDNF val66met Polymorphism (n=84)</td>
<td>$F(2,83)=.861$</td>
<td>-</td>
<td>.651</td>
</tr>
<tr>
<td>val/val, n (%)</td>
<td>55 (65.5)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>val/met, n (%)</td>
<td>27 (32.1)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>met/met, n (%)</td>
<td>2 (2.4)</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

$^aF$ represents the $F$ statistic in one-way analyses of variance (ANOVA) comparing serum BDNF protein concentrations between categorical subject characteristics and $r$ represents the Pearson correlation; IL-6 concentrations were log-transformed; Bonferroni correction was applied to the val66met genotype comparison

$^bP$-value represents the two-sided significance in one-way ANOVA or Pearson correlations
6.5.4 Cardiopulmonary fitness and cognitive performance

Cognitive test results are summarized in Table VI.III. Significant associations were identified between cardiopulmonary fitness and all cognitive Z-scores except CVLT-II short and long delayed free recall Z-scores in Pearson correlations (Table VI.III). MMSE scores were significantly associated with cardiopulmonary fitness when controlling for age and gender ($\beta=0.240, p=.028$); however, in a multiple linear regression model (overall model $F(5,85)=3.414, p=.008$, adjusted $R^2=.124$), only Digit Symbol-Coding Z-scores were associated with cardiopulmonary fitness independently of performance on the other cognitive tests ($\beta=0.285, p=.023$; Table VI.III).

### Table VI.III: Cognitive Testing Results and Associations with Cardiopulmonary Fitness

<table>
<thead>
<tr>
<th>Cognitive Test</th>
<th>Raw Score</th>
<th>Z-Score</th>
<th>r</th>
<th>Sig.</th>
<th>B</th>
<th>SE</th>
<th>$\beta$</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroop</td>
<td>28.6±9.3 sec</td>
<td>0.36±1.02</td>
<td>.281</td>
<td>.009</td>
<td>.032</td>
<td>.033</td>
<td>.118</td>
<td>.118</td>
</tr>
<tr>
<td>Trail Making B</td>
<td>88.2±42.0 sec</td>
<td>-0.05±0.90</td>
<td>.248</td>
<td>.021</td>
<td>.022</td>
<td>.037</td>
<td>.074</td>
<td>.554</td>
</tr>
<tr>
<td>Digit Sym.-Coding</td>
<td>61.3±16.7 sym.</td>
<td>0.18±1.07</td>
<td>.380</td>
<td>&lt;.001</td>
<td>.073</td>
<td>.031</td>
<td>.285</td>
<td>.023</td>
</tr>
<tr>
<td>CVLT-II Encoding</td>
<td>43.2±12.2 words</td>
<td>0.17±1.2</td>
<td>.243</td>
<td>.024</td>
<td>.022</td>
<td>.026</td>
<td>.096</td>
<td>.407</td>
</tr>
<tr>
<td>CVLT-II SDFR</td>
<td>9.3±3.4 words</td>
<td>.25±1.1</td>
<td>.100</td>
<td>.360</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>CVLT-II LDFR</td>
<td>9.3±3.5 words</td>
<td>0.14±1.1</td>
<td>.162</td>
<td>.136</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>MMSE score</td>
<td>28.9±1.7 points</td>
<td>-</td>
<td>.240</td>
<td>.028</td>
<td>-.018</td>
<td>.026</td>
<td>-.078</td>
<td>.489</td>
</tr>
</tbody>
</table>

*a* Pearson correlations ($r$) between the fraction of age and gender predicted VO$_{2\text{Peak}}$ (see Methods; Cardiopulmonary fitness assessment) and Z-score; for MMSE scores, correlation represents the association ($\beta$) between VO$_{2\text{Peak}}$ and MMSE score in multiple linear regression controlling for age and gender

*b* coefficients of a multiple linear regression model predicting the fraction of expected age and gender VO$_{2\text{Peak}}$ norm with Z-scores on cognitive tests and MMSE scores entered as independents; CVLT-II measures exceeded tolerance for multicollinearity so only the encoding score was entered in the final linear regression model

$n=88$

CVLT-II = California Verbal Learning Test 2nd Ed.; LDFR=long delay free recall; MMSE = Mini Mental Status Exam; SD = standard deviation; SDFR=short delay free recall.
6.5.5 Serum BDNF protein concentrations and cognitive performance

In bivariate comparisons, serum BDNF concentrations were associated with all cognitive measures except CVLT-II short and long delayed free recall and Stroop Z-scores (Table VI.IV). To identify cognitive domains independently associated with serum BDNF concentrations, all cognitive test scores were entered as independent variables into a multiple linear regression model (overall model $F(5,87)=7.937$, $p<.0005$, adjusted $R^2=0.285$). In this model, BDNF concentrations were associated with higher Digit Symbol-Coding Z-scores, higher MMSE scores, and lower Stroop Z-scores (Table VI.IV).

In a multivariate general linear model predicting Digit Symbol-Coding Z-scores (corrected model $F(5,87)=4.345$, $p=.001$, adjusted $R^2=.187$), Stroop Z-scores (corrected model $F(6,87)=1.220$, $p=.304$, adjusted $R^2=.015$) and MMSE scores (corrected model $F(6,87)=3.617$, $p=.003$, adjusted $R^2=.153$), and controlling for age, gender, serum IL-6 concentrations, depression and antidepressant use, higher serum BDNF concentrations were associated with higher Digit Symbol-Coding Z-scores ($F(1,87)=9.620$, $p=.003$) and higher MMSE scores ($F(1,87)=15.406$, $p<.0005$). In this model, higher serum IL-6 concentrations were associated with lower MMSE scores ($F(1,87)=4.035$, $p=.048$). The associations between serum BDNF concentrations and Digit Symbol-Coding Z-scores ($p=.002$) and MMSE scores ($p<.001$) were unchanged when repeating the model with the val66met genotype included as a covariate ($n=84$). Similarly, angiographic CAD severity measures, the use of an antihypertensive medication and cardiac risk factors (cumulatively or individually) did not affect the strength of the observed associations when explored as covariates in the multivariate model ($p<.005$ for all associations between serum BDNF concentrations and MMSE scores or Digit Symbol-Coding Z-scores). In the planned subgroup analysis of non-depressed and antidepressant medication free subjects ($n=59$), serum BDNF concentrations remained associated with MMSE scores ($F(1,58)=13.028$, $p=.001$) and Digit Symbol-Coding Z-scores ($F(1,58)=9.136$, $p=.004$). In the planned subgroup of male subjects ($n=75$), serum BDNF concentrations remained associated with MMSE scores and ($F(1,74)=14.281$, $p<.0005$) and Digit Symbol-Coding Z-scores ($F(1,74)=8.342$, $p=.005$).
Table VI.IV: Associations Between Cognitive Testing and Serum BDNF Protein Concentrations

<table>
<thead>
<tr>
<th>Cognitive Test</th>
<th>Correlation with Serum BDNF Protein Concentration&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Coefficients of a Multiple Linear Regression Model Predicting Serum BDNF Protein Concentrations&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>r</td>
<td>Sig.</td>
</tr>
<tr>
<td>Stroop</td>
<td>-.059</td>
<td>.586</td>
</tr>
<tr>
<td>Trail Making Test B</td>
<td>.212</td>
<td>.047</td>
</tr>
<tr>
<td>Digit Symbol-Coding</td>
<td>.412</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>CVLT-II</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Encoding</td>
<td>.253</td>
<td>.017</td>
</tr>
<tr>
<td>Short Delayed Free Recall</td>
<td>.096</td>
<td>.376</td>
</tr>
<tr>
<td>Long Delayed Free Recall</td>
<td>.135</td>
<td>.210</td>
</tr>
<tr>
<td>MMSE</td>
<td>.342</td>
<td>.001</td>
</tr>
</tbody>
</table>

<sup>a</sup>Pearson correlations (r) between serum BDNF concentrations and cognitive test Z-scores; for MMSE scores, the association (β) between serum BDNF concentration and MMSE score in multiple linear regression systematically controlling for age and gender is presented.

<sup>b</sup>Coefficients of a multiple linear regression model predicting serum BDNF concentrations with Z-scores from cognitive tests entered as independents; CVLT-II measures exceeded tolerance for multicolinearity so only the encoding score was entered in the final linear regression model.

n=88

CVLT-II = California Verbal Learning Test 2nd Ed.; MMSE = Mini Mental Status Exam; SD = standard deviation.

6.6 Discussion

An association between cardiopulmonary fitness and cognitive function was observed in this cohort of subjects with CAD, consistent with previous reports from CAD and medically healthy older subject populations<sup>20, 300</sup>. Of the cognitive tests examined, cardiopulmonary fitness was independently associated with performance in the Digit Symbol-Coding task, which is predominantly a test of psychomotor processing speed and complex attention. This result is consistent with previous studies showing that physical activity reliably improved performance on cognitive tests involving these domains<sup>23</sup>. Poorer performance on the Digit Symbol-Coding task is clinically important in older adults because it has been prospectively associated with incident disability and increased risks of coronary syndromes, stroke and mortality<sup>358-360</sup>.

In a model explaining 15.2% of the variance in serum BDNF protein concentrations, a significant association with cardiopulmonary fitness was observed. This is consistent with reports that physical activity can increase peripheral blood BDNF concentrations in medically healthy subjects<sup>338, 361</sup>. However, since this effect has not been consistent in younger medically healthy and physically active subjects, the present study focused on an older and largely sedentary patient population<sup>362</sup>. The VO<sub>2peak</sub>
of the present cohort was 14.2% below expected age and gender norms, consistent with low self-reported habitual physical activity in patients entering this cardiac rehabilitation program. Due to this and the decline in serum BDNF concentrations associated with age, cardiopulmonary fitness may have been a more relevant predictor of serum BDNF concentrations in this population.

In the present cohort, bivariate comparisons suggested associations between serum BDNF concentrations and better performance across multiple cognitive domains. However, like cardiopulmonary fitness, serum BDNF concentrations were most strongly associated with better performance on the Digit Symbol-Coding task in multiple linear regression analysis and in a multivariate model. In older subjects, a decline in performance on this test has been associated with vascular risk factors such as diabetes and hypertension. Higher peripheral BDNF concentrations also predicted higher scores on the MMSE, the instrument most commonly used to screen for cognitive status in clinical practice. These findings are in agreement with a correlation between MMSE scores and serum BDNF concentrations observed in subjects with vascular dementia, suggesting the involvement of BDNF along a continuum of vascular cognitive impairment. These findings may be clinically important because vascular risk factors can be managed clinically, and their effects on cognitive outcomes might be partially mitigated by physical activity.

Previous associations between circulating BDNF concentrations and vascular risk factors have been identified, but it remains unclear whether this suggests a role in their pathogenesis or in an adaptive physiological response. In diabetic mouse models, BDNF modulates central control of energy balance and chronic administration of BDNF can improve glucose metabolism. Spontaneously hypertensive rats show deficits in hippocampal neurogenesis that can be restored by treatment with oestradiol, which normalizes BDNF expression in the dentate gyrus. Clinically, vascular risk factors lead to dysfunction of the vascular endothelium, which synthesizes and releases BDNF. Vascular endothelial function can be improved by physical activity, which might therefore attenuate the effects of vascular risk factors on neuroprotection and neurogenesis. Increased brain volumes observed in older subjects undertaking regular physical activity would be consistent with the associations between cardiopulmonary fitness, BDNF concentrations and cognitive function observed in the present study.

As reviewed by Zhang and colleagues, physical activity can improve cerebral ischemic tolerance by enhancing blood brain barrier function and increasing cerebral small vessel number. CAD patients are susceptible to subtle cerebral ischemic damage that appears on magnetic resonance images as white
matter hyperintensities. These are an important mediator of the effects of vascular risk factors on cognitive performance, and Digit Symbol-Coding scores in particular. The response to cerebral ischemia involves angiogenesis and neurogenesis, which interact to salvage and remodel affected tissue. This “neurovascular niche” contributes to functional recovery from stroke and possibly to mitigating subtle cognitive deficits resulting from disease of the smaller vessels. Roles of BDNF in the dynamic interactions between neurogenesis and angiogenesis have been described, but remain to be fully characterized. The clinical impact of BDNF signaling on cerebrovascular disease has been suggested by greater white matter hyperintensity volumes in carriers of the met BDNF allele 60 years of age or older. While the significance of peripheral BDNF concentrations in this process is not known, early angiogenic vessels are known to be highly permeable to intravascular components.

The present study did not identify any significant independent predictors of serum BDNF concentrations in addition to cardiopulmonary fitness, with the exception of serum IL-6 concentrations. This may reflect a previously observed correlation between plasma BDNF concentrations and activated mononuclear cell number in medically healthy adults and the stimulatory effect of IL-6 on BDNF secretion from peripheral mononuclear cells. In the present study, BDNF was assayed from serum, which largely reflects activation-dependent release of BDNF from platelets. An association between serum BDNF and soluble P-selectin, a platelet pro-coagulant inflammatory marker, has been observed previously in subjects with CAD. In the present study, serum BDNF and IL-6 concentrations were correlated, but higher BDNF concentrations were associated with higher MMSE scores while higher serum IL-6 was associated with lower MMSE scores. These clinical data would be consistent with pleiotrophic inflammatory effects, which might both exacerbate neural insult and promote compensatory BDNF signaling, a possible role of “neuroprotective immunity” previously described.

As a potential limitation of the present study, physical activity was not quantified; however cardiopulmonary fitness has been more reliably associated with cognitive performance than self-reported metrics of physical activity. In the present cohort, depression and depressive symptom severity were not associated with lower serum BDNF concentrations, contrasting findings in younger adult populations; however, these findings are consistent with other studies of older patients and of those with cardiovascular disease. As a potential limitation, depressive symptom severity was measured by a self-report instrument rather than by clinician rating. This study was also not powered to detect associations between BDNF serum concentrations and the val66met genotype or other clinical
characteristics; however, these covariates did not mitigate the associations between serum BDNF concentrations and study outcomes. While concentrations of IL-6 and BDNF in serum were correlated, the clinical significance of this association is unclear, other inflammatory markers were not explored and many TNF-α assay results were below the limit of detectability. Since BDNF serum assays reflect the release of BDNF from platelets, it is unclear whether plasma concentrations, thought to reflect more immediate systemic BDNF availability, would have been similarly associated with cardiopulmonary fitness or cognitive function. As a further limitation, the antibody used to detect BDNF by ELISA was not necessarily specific for the mature BDNF peptide and concentrations of pro-BDNF were not determined. The observational study design precludes causal inferences. Finally, this cohort of subjects entering cardiac rehabilitation may have been more motivated or perceived to be more amenable to rehabilitation by prescribing physicians, potentially introducing some selection bias and limiting the generalizability of results.

In conclusion, serum BDNF protein concentrations were associated with better cardiopulmonary fitness, better psychomotor processing speed/complex attention and better overall cognition in subjects with CAD. These relationships were independent of IL-6 concentrations and the val66met polymorphism despite the observed association between IL-6 and BDNF concentrations in serum. These findings suggest the clinical relevance of BDNF production as a fitness-related neuroprotective mechanism in subjects with cardiovascular disease.

6.7 Significance and impact

This study found that higher serum BDNF concentrations were associated with superior cardiopulmonary fitness and superior cognitive function in subjects with CAD prior to CR. The study design precludes any inferences of causality; however, naturalistic observation in the setting of current clinical management is useful in that the results can be discussed with respect to other observed phenomena. For instance, larger epidemiological studies have reported that digit symbol-coding scores are predictive of future cardiovascular and cerebrovascular events. The specific associations between cardiopulmonary fitness and BDNF with digit symbol-coding scores suggest their investigation as potential mediators of this effect in future studies. Since the digit symbol-coding test is very sensitive to vascular cognitive impairment, a role of BDNF in preserving cerebrovascular function is suggested in this population. Such clinical correlations may help to direct further investigations. In humans, much
about the regulation of BDNF synthesis, stimulated release, transport and tissue targets in the periphery and brain remains to be clarified, but such investigations may uncover potential pharmacological and nonpharmacological targets.
III.
Discussion of Results and Implications for Future Studies

III.i Phenomenology of MDD and depressive symptoms in CAD

Inflammation has been suggested as a potential mediator of the association between CAD and increased depressive symptoms\(^{390}\). The cross-sectional association between kynurenine concentrations and depressive symptoms (Chapter 3) agrees with findings from the Heart and Soul Study reported by Duivis and colleagues, which found that baseline depressive symptoms prospectively predicted higher concentrations of IL-6 and CRP over 6 years\(^{391}\). That study, also demonstrated that health behaviours could attenuate these associations; thus the effect of depression on inflammatory biomarkers may be mediated by these health behaviours, including physical activity (Figure iiA)\(^{xx}\). This is in agreement with the association between depressive symptoms and VO\(_{2}\text{Peak}\) observed in patients entering CR (Chapter 1). The observations presented by Duivis and colleagues build on previous data from the same study suggesting that health behaviours, including physical activity, can affect the relationship between depression and cardiac prognoses\(^{55}\); however, while sufficiently explanatory in an epidemiological sense, these findings do not predict the clinical utility of exercise intervention in this population\(^{xxi}\).

The present data (Chapter 2) add to this literature, showing that depressive symptoms or MDD pose a significant barrier to exercise intervention independent of baseline CAD severity, vascular risk factors and commonly used medications (for example, the effect was independent of the use of beta-blockers and ACE inhibitors). Thus, the mediating effect can operate, at least partially, in a direction that leads from MDD to decreased physical activity. Moreover, the study demonstrated that a standardized 1 year exercise intervention was less effective for patients with MDD even when they remained adherent to the

\(^{xx}\) Note that the models presented in figures ii.a and ii.c show that the associations between depressive symptoms, physical activity and medical morbidity (which could include CAD severity, left ventricular function, and side-effects of more intensive pharmacotherapy, for example) can be established without considering inflammatory activity. Medical morbidity associated with CAD could result in lower cardiopulmonary fitness and depressive symptoms (e.g. “trouble getting going”, inattention, appetite changes, etc.) and the models allow for the possibility that inflammatory biomarkers may be non-causally or coincidentally associated.

\(^{xxi}\) In addition, the association between lower K/T ratios and the use of daily low dose ASA observed in Chapter 3 suggests the need to further explore the possible roles of concommittant medications with anti-platelet or anti-inflammatory activities. Specifically, failure to use or to adhere to ASA use could be related to depressive symptoms, which could then be related to higher K/T ratios and medical outcomes; however, CES-D scores were not associated with failure to use ASA in the population reported in Chapter 2 (F\(_{1,94}=.053, p=.8\).
program (Chapter 2; Figure iiB). This may be related to lower energy expenditure due, for example, to less time spent exercising at home or to increased perception of fatigue leading to submaximal exertion during exercise, or to dysregulation in metabolic pathways that have often been described in patients with MDD\textsuperscript{272,273}. The latter might result in less physiological adaptation at a given amount of energy expenditure or intensity. The etiology of such changes remain to be clarified, but endocrine abnormalities described in clinical studies and in animal models suggest plausible mechanisms related to perturbations of glucose and lipid homeostasis\textsuperscript{392-396}.

The present investigations provide some additional observations that should be considered in light of other recent reports. Reduced risks of MI and mortality have been associated with the use of antidepressant treatment of at least 12 weeks among depressed patients in a retrospective cohort analysis\textsuperscript{397}; however, even among patients motivated to take part in a CR program who have access to onsite psychosocial support in the context of a universal health care system, the majority of patients with MDD were not using an antidepressant medication. Moreover, it should be cautioned that it remains unclear whether antidepressant use may be causally related to mortality due to a reduction in depressive symptoms that improves health behaviours, or whether antidepressant use may simply constitute a marker of medically compliant behaviour regardless of any psychotropic effect. Additional prospective randomized studies will be needed to provide further evidence, especially since, at present, the survival benefits of depression screening and antidepressant use in patients with CAD remain unclear in randomized studies\textsuperscript{333,398,399}.

There have been six randomized controlled trials of SSRIs (4 using sertraline\textsuperscript{134,400-402}, 1 using fluoxetine\textsuperscript{137} and 1 using escitalopram\textsuperscript{135}) in patients with CAD from which their effects on readmission to hospital for CAD and mortality can be inferred. The follow-up periods in these trials ranged from 12 weeks\textsuperscript{137} to 6 months\textsuperscript{402}. The risks of readmission and mortality were significantly lower in only the largest trial, a single-blind sertraline study reporting data from an observational subgroup of the ENhancing Recovery in Coronary Heart Disease randomized trial\textsuperscript{401}. Trends were also reported in other studies and a meta-analysis of these studies by Pizzi and colleagues\textsuperscript{399} showed that the rates of readmission (available from 5 trials) and mortality (available from 3 trials) were lower in SSRI treated patients. This effect did not remain significant when considering only trials appropriately randomized to SSRIs vs. placebo that were analyzed according to randomization. Thus the most compelling evidence of an overall medical benefit of treatment remains observational in nature and further large prospective
randomized controlled trials of SSRIs with mortality and CAD-related medical outcomes are still needed.

In the present investigation (Chapter 2), the reasons for noncompletion of CR associated with MDD were medical (CAD-related and other) as opposed to motivational (noncompletion due to “lack of interest” was not significantly different between MDD and non-MDD patients). In fact, 57.9% of all non-completion observed in patients with MDD was due to medical reasons, as compared to 43.2% in non-MDD patients. This suggests that among patients sufficiently motivated to undertake CR, the burden of MDD was due, at least partly, to its impact on medical morbidity and suggests that antidepressant medications might not directly impact medical morbidity based on biological mechanisms of action independent of their behavioral effects. Conversely, this might also suggest an increased impact of medical morbidity on mood that was not accounted for in the medical confounders assessed. Regardless of the direction of causation of this association, adjunctive strategies might involve increased monitoring of compliance with cardiac medications\textsuperscript{403}, more aggressive management of vascular risk factors and comorbidities and increased allocation of resources to investigate potential complications in patients who present with MDD. To examine these hypotheses, prospective studies might randomize patients who screen for depressive symptoms to “usual CR” versus “increased monitoring” that would involve pill counts, assessment of compliance with other medical management (e.g. treatments for musculoskeletal conditions\textsuperscript{404}, non-cardiac medications, etc.), more detailed assessment of diet (e.g. intake of omega-3 fatty acids\textsuperscript{405, 406}) and further investigations such as sleep studies to detect possible sleep apnea\textsuperscript{407}, the use long-term electrocardiogram to detect possible arrhythmias that may have not manifested in previous clinical assessments and ambulatory blood pressure monitoring to detect abnormal changes in blood pressure\textsuperscript{408-xxii}. From a broader perspective, it would be interesting to see, in such studies, if attempts to reduce medical burden can have antidepressant effects in this population. Success in lowering depressive symptoms by improving medical management would support the theory

that medical morbidity can lead to depressive symptoms rather than the converse (Fig iiA and iiB). The exploration of additional antidepressant medications targeting underlying biological factors (Fig iiC), potentially inflammatory and neurodegenerative, might also be efficacious.
Figure ii. A biopsychosocial model for depression in CAD. A. A model is proposed based on previous literature suggesting that depressive symptoms are related to inflammatory activity and medical morbidity through an impact on physical activity levels. B. The present studies in CR patients show that depressive symptoms before entering CR are prospectively associated with poorer cardiac outcomes, confirming that the temporality of the effect can go in a direction that leads from depressive symptoms to less physical activity, with increased medical morbidity as a barrier. C. An integrated model that includes the K/T ratio as a correlate of decreased physical activity, body composition and depressive symptoms. Since kynurenine may be psychoactive, the direction of causation between inflammatory activity and depressive symptoms is brought into question, and prospective intervention trials are warranted. Single headed arrows used to denote the temporal directionality of associations, not the establishment of causation. Thesis chapters referenced as indicated.
The association between kynurenine concentrations and depressive symptoms (Chapter 3, Fig iiC) extends the inflammatory hypothesis beyond the cytokines, suggesting the involvement of a neurodegenerative mechanism downstream of pro-inflammatory cytokine signaling. Not only are kynurenine metabolites neuroactive, but the K/T ratio has been associated with mortality and recurrent acute coronary syndromes in a large sample (n=2380) of subjects with stable CAD\textsuperscript{141}. Subtle elevations in IL-6 and CRP have been suggested to be a result of physical inactivity rather than to cause physical inactivity in depressed subjects because cytokine concentrations did not predict future depression but depression predicted future IL-6 and CRP concentrations in a manner dependent on physical inactivity\textsuperscript{391} (Fig iia). However, the role of kynurenine as a potential cause or consequence of depressive symptoms in this model remains considerably less clear.

Subjects with hepatitis C treated with peripheral injections of interferon-\(\alpha\) for 12 weeks showed increases in kynurenine in plasma and cerebrospinal fluid consistent with the induction of IDO, and increased concentrations of the kynurenine metabolite quinolinic acid in plasma and cerebrospinal fluid, each of which correlated with depressive symptoms\textsuperscript{412}. In both the periphery and in the brain, kynurenine is metabolized principally by two enzymes, kynurenine amino transferase II (KAT II) and kynurenine 3-monooxygenase (KMO), the former giving rise to the neuroprotective kynurenic acid and the latter giving rise to 3-hydroxykynurenine, which is further metabolized into quinolinic acid (Figure i). Unchecked, the metabolites along the KMO branch impose oxidative stress\textsuperscript{105, 107, 413}, which, as discussed, can be further pro-inflammatory and neurodegenerative. In animal models, cerebral ischemia increases KMO activity in a manner spatially consistent with secondary brain injury\textsuperscript{414} without producing a proportional increase in KAT II activity, or any increase in the synthesis of kynurenic acid, to oppose this effect\textsuperscript{415}. In interferon-\(\alpha\) treated hepatitis C patients, the plasma concentration of kynurenine correlated with the cerebrospinal concentrations of quinolinic acid\textsuperscript{412}, supporting the clinical utility of peripheral kynurenine concentrations, or K/T ratios, as relevant biomarkers. This evidence would be consistent with the observed association between the K/T ratio and depressive symptoms in CAD patients (Chapter 3). It is suggested that kynurenine, produced in response to atherogenic pro-inflammatory cytokines in the presence of ischemic brain changes, might precipitate or perpetuate depressive symptoms by the central neuroactivities of its metabolites (Figure iv). This mechanism may be particularly relevant to late life cognitive and mood disorders, since K/T ratios have been found to increase with age, and to correlate with depressive symptoms in older adults\textsuperscript{416}. Therefore, the findings
of Chapter 3 have implications for treatment.

Pharmacological manipulation of kynurenine metabolism has been suggested as a target for intervention\(^{417}\). However, IDO itself has been aptly described as a “double-edged sword”\(^{418}\). On one hand, as discussed above (Introduction; Chapter 3), microglial metabolism of kynurenine gives rise to a series of oxidative, excitotoxic and otherwise neuroactive metabolites associated with neuronal damage and depressive symptoms, but on the other hand, kynurenine is used by astrocytes in brain to produce the neuroprotective kynurenic acid. In animal models of cerebral ischemia, administration of kynurenine sulfate dramatically increases cerebral concentrations of kynurenic acid, exerting neuroprotective effects\(^{419,420}\). In addition, the induction of IDO constitutes a physiologically essential immunoregulatory mechanism. Specifically, kynurenine directly activates the aryl hydrocarbon receptor (AHR), persuading certain subsets of T lymphocytes to take on a “regulatory” phenotype instead of a pro-inflammatory cytokine secreting phenotype\(^{421-423}\). Regulatory T cells utilize IL-10 to curb the inflammatory activity of Th1 and Th17 cells\(^{76}\). Similarly, via the AHR, kynurenine curtails the ability of dendritic cells resident in the CNS to support pro-inflammatory cytokine secretion, implicating kynurenine as a regulator of both peripheral inflammation and central neuroinflammation\(^{422,424,425}\). Thus, the predictive effect of IL-6 and CRP concentrations on the development of depression in previous studies of CAD populations\(^{426}\) may have been masked by negative feedback regulation of cell-mediated inflammatory pathways by kynurenine, which can produce depressive symptoms as a side-effect. In the present study, the K/T ratio was inversely associated with cardiopulmonary fitness (Fig iiC), suggesting that exercise may reduce IDO activity by reducing pro-inflammatory cytokine expression as previously discussed\(^{65,66,349,427,428}\). Future studies in this population might seek to qualify whether kynurenine, as opposed to the cytokines that it regulates, can prospectively predict the development of depressive symptoms, and whether exercise interventions can reduce the K/T ratio in conjunction with pro-inflammatory cytokines. Longitudinal associations between changes in depressive symptoms and changes in peripheral blood kynurenine concentration would further strengthen the evidence.

Evidence that kynurenine synthesis may cause depressive symptoms has been provided in an elegant study by O’Connor and colleagues, showing that the development of depressive symptoms following lipopolysaccharide administration can be effectively blocked by the IDO inhibitor 1-methyltryptophan in mice\(^{429}\). However, due to neuroprotective and immunoregulatory effects of kynurenine, inhibiting IDO directly might carry substantial risks of inflammatory, autoimmune and oncogenic consequences. Developing a clinically useful pharmacological strategy will depend on preserving kynurenine.
concentrations in the brain and periphery, while selectively reducing the concentrations of harmful kynurenine metabolites in brain. Cerebral 3-hydroxykynurenine and quinolinic acid concentrations can be selectively manipulated by inhibition of KMO\textsuperscript{430}, currently under investigation as a neuroprotective strategy. Inhibiting central KMO increases brain concentrations of kynurenine and kynurenic acid, while reducing quinolinic acid biosynthesis\textsuperscript{299, 431}. The KMO inhibitors nicotinylalanine\textsuperscript{432, 433}, meta-nitrobenzoylalanine\textsuperscript{434, 435} and Ro61-8048\textsuperscript{299, 434} have demonstrated neuroprotection in epileptic\textsuperscript{435}, neurodegenerative\textsuperscript{299, 433}, autoimmune\textsuperscript{431}, peripheral immune (pokeweed mitogen) stimulated\textsuperscript{436} and ischemic\textsuperscript{434, 437} models in vivo. In particular, Ro61-8048 can reduce neuronal loss in ischemic models, and reduce concentrations of 3-hydroxykynurenine and quinolinic acid in the CNS\textsuperscript{431, 437}.

The clinical use of KMO inhibitors, however, has been delayed by unfavorable pharmacokinetics, sedative effects\textsuperscript{435} and uncertainty as to their tissue distribution when administered orally\textsuperscript{299}; however, JM6, a pro-drug of Ro61-8048 currently in preclinical testing, may have appropriate plasma kinetics. This KMO inhibitor does not cross the blood brain barrier, but rather, it capitalizes on the selective permeability of the blood brain barrier, and most likely of astrocyte feet at the glia limitans, to kynurenine as compared to its metabolites\textsuperscript{101}. Thus, peripheral inhibition of KMO reduces peripheral kynurenine breakdown, increasing the central uptake of kynurenine by astrocytes. This increases central concentrations of kynurenic acid and ameliorates neuronal damage in multiple mouse neurodegenerative models\textsuperscript{299}. While the regulation of the various enzymes of the kynurenine pathway in brain remain incompletely understood, the arms of the pathway initiated by KAT II in astrocytes and KMO in microglia seem to be regulated independently\textsuperscript{430} resulting in a substantial increase in the ratio of neuroprotective kynurenic acid to neurotoxic quinolinic acid in brain with administration of JM6. The association between the K/T ratio and depressive symptoms in patients with CAD (Chapter 3) suggests that peripheral KMO inhibition might be explored in CAD patients with depression and high serum kynurenine concentrations as an alternative or adjunctive treatment.

Since central KMO is regulated independently of kynurenic acid, it could be hypothesized that brain NAD biosynthesis and feedback inhibition of central IDO by nicotinamide adenine dinucleotide (NAD) would be unaffected by JM6\textsuperscript{438-440}. Regardless, any feedback inhibition of central IDO would be circumvented by the influx of kynurenine from the periphery, maintaining adequate central NAD biosynthesis\textsuperscript{441}. However, peripheral inhibition of KMO might theoretically decrease peripheral NAD synthesis, and peripheral concentrations contribute substantially to brain concentrations due to high blood brain barrier permeability\textsuperscript{442}. Niacin has shown neuroprotective effects in recovery from
ishemia\textsuperscript{442-444} and a beneficial role in maintaining HDL concentrations\textsuperscript{445}. In a rat model, administration of niacin, for 14 days beginning 24 hours post-stroke increased synaptic plasticity and axon growth by increasing BDNF expression and Trk-B activation\textsuperscript{443}. Due to the theoretical risk of decreased NAD synthesis associated with KMO inhibition, it might be prudent to monitor niacin plasma concentrations and supplement with extended release niacin as necessary in future studies, although mice treated with JM6 did not show any changes in plasma or brain quinolinic acid concentrations\textsuperscript{299}. It should also be acknowledged that an increase in plasma kynurenine concentrations with the use of a peripheral KMO inhibitor might increase competition for tryptophan in crossing the blood brain barrier via the LNAAT (see Figure i)\textsuperscript{446}. This may affect central serotonin concentrations, making KMO inhibition most safe and effective when used in conjunction with an SSRI. Clinical data will be necessary to confirm the potential for hyposerotonergic side-effects. In addition, while JM6 may be neuroprotective, and clinical evidence suggests protective effects of increased peripheral kynurenic acid concentrations against depressive symptoms\textsuperscript{110, 127}, this may also inhibit hippocampal glutamatergic\textsuperscript{447} and striatal dopaminergic\textsuperscript{116} systems involved in memory, psychomotor function and reward pathways. Monitoring for related side-effects in clinical development is recommended; however, psychomotor and behavioural impairments suggestive of these potential side-effects were not observed in the animal neurodegenerative models\textsuperscript{299}.

While most current antidepressant therapies are believed to function by manipulating the biogenic monoamines, most commonly serotonin, a hyperglutamatergic hypothesis for depression has also been proposed. This was initially based on the observation that NMDA antagonists mimicked the behavioural effects of antidepressants in the mouse inescapable stress model\textsuperscript{448}, and these results have since been replicated in other animal models used to screen antidepressant compounds (reviewed\textsuperscript{449}). There remain very few centrally-penetrating orally active NMDA antagonists free of dissociative side-effects at doses that could produce antidepressant effects\textsuperscript{450-454}. Of the currently available agents dextromethorphan and minocycline, the latter can produce antidepressant-like behavioural effects\textsuperscript{455}, normalize glutamate reuptake\textsuperscript{452}, reduce the brain K/T ratio during systemic inflammatory challenge\textsuperscript{429} and reduce post-ischemic brain damage\textsuperscript{453}. The most clinically promising agent, ketamine, infused at a low doses (0.5 mg/kg), can rapidly induce a reduction in depressive symptoms that persists for 3-7 days\textsuperscript{456-459}. It is possible that kynurenic acid, by virtue of NMDA antagonism, may produce similar antidepressant effects directly, particularly in the setting of inflammatory activity; a hypothesis supported by resistance to the depressogenic effects of interferon-\(\alpha\) in patients with hepatitis C who had higher peripheral blood ratios of kynurenic acid to kynurenine\textsuperscript{110}. 
In considering the evidence presented in this thesis, limitations with regard to the measurement of both the biomarkers and depressive symptoms might be considered, for instance, the lack of a diagnostic interview for DSM-IV depression criteria or ascertainment of psychiatric history in the cohort study presented in Chapter 1 limited that study from determining how these factors interacted with VO\textsubscript{2Peak} to predict depressive symptoms at the time of entry into CR. This limitation was improved upon in subsequent prospective evaluations reported in subsequent chapters. A comparison of noncompletion HRs associated with CES-D scores or a diagnosis of MDD in Chapter 2 (Table II.III), however, suggests that the two constructs may be of comparable clinical utility in this population. Regardless, there remain many unresolved issues concerning the nature of depressive symptoms post-ACS that were not addressed in the present datasets. Although a history of MDD did not affect the association between current depressive symptoms and CR outcomes, the sample sizes reported in the prospective studies reported in Chapters 2 and 5 would not have been adequate to show differential effects of recurrent MDD as compared to first episode MDD controlling for covariates such as age, gender and CAD severity. In addition, underutilization of psychosocial supports in this population precluded assessment of their potential impact on CR and psychiatric outcomes.

Some studies have suggested the utility of dimensional analyses of depressive symptoms in patients with CAD. In the present studies, hypotheses were not formulated based on dimensional analyses, but they might be considered in further post-hoc analyses of these data sets. Particularly, as larger sample sizes are obtained, it may be interesting to explore whether specific symptom dimensions might be associated with poorer outcomes in patients undertaking CR. For instance, somatic type symptoms may be more closely associated with higher risks of mortality than cognitive type symptoms. In a study of patients with unstable angina (n=913), a principle component analysis of Beck Depression Inventory scores suggested that a factor consisting of somatic type affective symptoms predicted Killip class and 12-month all-cause mortality independent of other clinical confounders whereas Beck Depression Inventory items that factored into a cognitive dimension did not\textsuperscript{460}. Similar results were obtained in a sample of 550 women from the Women’s Ischemia Syndrome Evaluation study\textsuperscript{461}. These studies suggest that certain depressive symptoms may be manifestations of physical symptoms of cardiac disease (symptoms of lassitude and fatigue, for example, are common to both). Therefore, somatic type symptoms may account, at least in part, for the association between cardiopulmonary fitness and depressive symptoms (Chapter 1), as both reduced cardiopulmonary fitness and somatic depressive symptoms could be symptoms of either MDD or of cardiac function (left ventricular dysfunction, for example), neither of
which were assessed for the purposes of that study. It might also be suggested that unmeasured cardiac
variables could account for the association between depressive symptoms and non-completion of CR in
previous studies, and between MDD and non-completion in the study presented in Chapter 2. A post-hoc
analysis did not suggest that heart failure could account for the association between MDD and non-
completion; however a trend towards an association between heart failure and non-completion suggested
that left ventricular function, had it been available as a continuous variable, may have accounted for
some of the variance in non-completion independently of MDD. A diagnosis of MDD requires the
presence of at least one cardinal symptom (sadness or anhedonia) while MDD may or may not include
the somatic type symptoms in various combinations. The cardinal symptoms can also predict recurrent
ACS; in particular, two recent studies have suggested that anhedonia, can be strongly and independently
associated with recurrent MI and mortality.\textsuperscript{462, 463} It might also be suggested that sadness or anhedonia
may be reactive to a recent ACS, MI or surgery, while some somatic symptoms may be residual from or
consequential of surgery; however little remission of depressive symptoms over 1 year was observed in
subjects diagnosed at baseline with MDD in the present study (Chapter 2), which is not suggestive of
transient symptoms associated with adjustment disorders. Therefore, it is suggested that MDD was
present and, in addition to purely somatic symptoms, that MDD was clinically important in this
population. Moreover, in the reported biomarker study (Chapter 3), particular symptoms were identified
as correlates of the K/T ratio. Previously, Contrada and colleagues confirmed a 3-factor structure for the
CES-D among 570 patients undergoing cardiac surgery, consisting of positive affect, negative affect and
somatic/vegetative type symptoms.\textsuperscript{292} The K/T ratio in the present study population was associated
exclusively with symptoms that grouped into the negative affect component (Chapter 3). Importantly,
the association between the K/T ratio and depressive symptoms other than those of fatigue and lassitude
suggests that an elevated K/T ratio is not simply associated with somatic symptoms common to both
heart disease and MDD, but rather with the more cardinal affective symptoms of depression. In their
study, Contrada and colleagues observed a decline in depressive symptoms over 1 year, with a more
pronounced decline in somatic symptoms, the majority of which occurred within the first month post-
operatively.\textsuperscript{292} By comparison, symptoms of positive and negative affect were relatively stable, showing
less pronounced, but nonetheless significant, decline. The recruitment of patients into the present studies
would have occurred predominantly after 1 month post MI or intervention, which may have allowed
time for somatic symptoms to have stabilized. This might account for the observed sensitivity and
specificity of the CES-D to detect MDD, and thus to predict non-completion of CR comparably to a
diagnosis of MDD, in the present population (Chapter 2). Similarly, the time elapsed between an acute
coronary event or revascularization and the measurement of depressive symptoms may have improved the ability of the present studies (Chapter 3) to detect the association between negative affective symptoms (more stable over time) with peripheral blood biomarkers by removing noise due to somatic symptoms. However, there remains the possibility that both inflammatory biomarkers and depressive symptoms may coincidentally decline on a similar schedule in this population, and this should be acknowledged as a potential limitation in the biomarker data despite attempts to control for time since the most recent ACS, MI or revascularization in between-subjects comparisons. To establish causality in humans, pharmacological intervention trials will be needed to compliment the manipulations of IDO activity reported in animal models.429.

The observation that sickness behaviours induced by inflammation in animal models can transition over time into symptoms more closely resembling human depression would be consistent with the hypothesis that the pro-inflammatory cytokines may produce certain symptoms while longer-term downstream effects of kynurenine metabolites, or coincident deficits in serotonergic neurotransmission may produce others.87 However, as a limitation, it should be considered that other inflammatory markers or tryptophan metabolites were not measured concurrently with the K/T ratio in the present studies. As discussed, IDO activity is a pleiotrophic part of an inflammatory cascade with the potential for multifactorial psychoactivities (reviewed82,464). Therefore, the biomarker associations found in Chapter 3, while consistent with animal data88,429,465, must be interpreted conservatively - as an association between depressive symptoms and the activation of a broad inflammatory cascade, and not necessarily indicative of any particular causal relationship. In addition, while the K/T ratio remained stable for at least 14 days post-stroke in a previous study of patients post-stroke133, serial measurements were not performed in the present population to formally assess the ratio of between vs. within subjects variance. However, recruitment into a neuroimaging sub-study (n=60), involving repeated blood tests at the time of an MRI (within 2 weeks of baseline cognitive assessment), will facilitate this assessment in future work. These measures will be helpful in determining if the K/T ratio can be developed as a clinically useful biomarker, for instance as a predictor of chronicity of depressive symptoms when MDD presents in late-life, of response to a particular class of antidepressants, or of developing cognitive impairment as a complication as per a working neurodegenerative hypothesis (Fig. iv).
III.iii Phenomenology of cognitive performance in CAD

Although the clinical importance of depression in the context of CAD has entered into the evidence base from which physicians practice, as discussed, this knowledge has failed to bring about measurable improvements in clinical outcomes in this population. Further investigation of the possible pathoetiolo,gy of these symptoms and possible clinical modifiers of the associations between depressive symptoms and recurrent ACS may be informative. Like depressive symptoms, poorer verbal memory performance was associated with non-completion of CR specifically for medical reasons, suggesting that poorer verbal memory performance may be related to underlying disease processes, which also worsened medical outcomes (Chapters 2 and 5, Figure iiiA). In the present study (Chapter 5) about 25% of participants screened positive for depression, showing a 2.5-fold increased risk of non-completion, and about half of those, 11% of all patients, presented with a combination of poorer memory performance and depression. These patients were at an 8-fold increased risk of non-completion, suggesting an additive interactive effect. These observations suggest that development of a more rapid cognitive screening technique could be used to evaluate risk. Specifically, a cognitive screen could be performed in those who screen positive for depression based on the CES-D as a more clinically efficient strategy to target resources on those most severely at risk of poorer outcomes as indicated by the presence of subtle cognitive deficits. However, focusing attention on these patients prior to beginning CR may be more effective. For instance, if patients could be screened in primary care, integrated support could be offered sooner, perhaps in the context of a collaborative care model. This may help to improve continuity of care, increase adherence to primary medical management, and to ensure that secondary prevention is prescribed and adhered to.

A path analysis from the Maine-Syracuse Study presented by Elias and colleagues (n=1025 participants, mean age 61.1 years) showed that cognitive function can act as a statistical mediator between physical ability and vascular risk factors in older patients, suggesting that further investigation of the biological underpinnings of cognitive deficits may help to understand how vascular risk factors translate into physical disability in patients with CAD (Figure iiiA). Like that path analysis, the present findings would suggest that cognitive performance can predict incident disability in the context of CR, independently of depression or vascular risk factors individually or cumulatively. While lower baseline VO_{2peak} can predict noncompletion of CR in larger studies, this effect was not replicated in the present study, possibly because the effect size was too small to be observed (n=131), although the effect of verbal memory performance was observable, and independent of baseline VO_{2peak} (Figure iiiB).
As a potential limitation, assessment of CAD severity was performed by angiography alone. As assessed by angiography, the number of coronary arteries involved, the cumulative percentage stenosis and the presence of restenosis in a previously revascularized lesion may not have been sufficient to describe the severity of CAD and therefore insufficient to fully control for it in analyses. Moreover, the presence of carotid stenosis has been suggested to mediate the effect of atherosclerosis on tests of attention, executive function and psychomotor processing speed\textsuperscript{467} but carotid intima-media thickness was not measured in the present study.

As a further limitation, the patients recruited into the present studies reported more years of formal education than expected based on other Canadian population samples, suggesting a potential source of bias in the patient samples studied. For example, subjects in the Canadian Study of Health and Aging reported 10±4 years for those who did not develop Alzheimer’s disease and 9±4 years for those who did\textsuperscript{148}, while subject samples in the present studies (Chapters 4-6) reported between 16 and 17 (±3) years of education. It is likely that patients who were more highly educated were not only more likely to enter CR, but also more likely to volunteer to participate in research studies. These potential selection biases require further qualification in order to understand the scope of patients to whom the present results may be pertinent. For the purposes of the present studies, years of education were not ascertained in CAD patients who declined to participate in CR, or in CR patients who declined to participate in the studies. From a theoretical perspective, education can be protective against cognitive impairment in Alzheimer’s disease, vascular dementia\textsuperscript{468} and normal aging, an effect described as “cognitive reserve” (reviewed\textsuperscript{469}). Thus more educated patients with extensive neural pathology may present with cognitive performance similar to less educated patients with less neural pathology. This may confound measurement of memory and executive functions insofar as these measures can be used to infer the extent of neural pathology\textsuperscript{470}. As a further limitation, premorbid cognitive ability\textsuperscript{471}, occupational attainment and participation in leisure time activities\textsuperscript{472} were not quantified for the purposes of the present studies, but these may also confer cognitive reserve\textsuperscript{469, 470}. Mechanistically, risk factors for cognitive decline may lead directly to pathological insults (e.g. amyloid deposition, subcortical infarction or white matter damage) or confer vulnerability to such insults\textsuperscript{471}, while some factors might also impair resilience to such insults. Thus the contribution(s) of the various risk factors to overall cognitive performance may be multifactorial. On the other hand, clinical factors conferring cognitive reserve, such as cardiopulmonary fitness or education, may interact with these risk factors at multiple stages. For example, exercise may increase gray and white matter volume or cerebral vascularization, reducing both the propensity for vascular insults and their net effect on cognitive performance, or enhance recovery of tissue from these insults. These
considerations must be taken into account when considering the cross-sectional associations between cardiopulmonary fitness, cognitive performance and biomarkers (Chapters 3 and 6) even though these associations were independent of years of formal education. In addition, although independent of years of formal education, the association between poorer verbal memory performance at entry into CR and non-completion of CR (Chapter 5) may reflect contributions of cognitive reserve and of risk factors for cognitive decline. Based on the principle of cognitive reserve, it could be speculated that extensive vascular neural pathology was present in this well-educated population despite verbal memory performance largely in the normal range. This hypothesis, testable in future MRI studies, might explain why relatively subtle cognitive deficits were strongly predictive of CR non-completion in this population.

As a further potential limitation of the prospective cognitive study (Chapter 5), only performance on the CVLT-II and MMSE scores were assessed as possible predictors of non-completion of CR. However, Stanek and colleagues suggested recently in a small study, that performance in other cognitive domains can predict less improvement in cardiopulmonary fitness over a 12 week CR program. That study, however, employed only the Trail Making Test B and the MMSE. Collectively, the evidence suggests that the MMSE was insufficiently sensitive to detect changes associated with poorer CR outcomes in populations of patients with CAD, but that more sensitive tests may be useful. Future studies might seek to localize this effect to a particular cognitive domain by employing a more comprehensive cognitive battery (as presented in Chapters 4 and 6). It should be acknowledged that even the more comprehensive datasets presented in Chapters 4 and 6 were still limited by the breadth of the cognitive batteries performed. For instance, the NINDS-CSN harmonized standards were abbreviated, omitting, for example, the controlled oral word association task. This verbal fluency task has shown clinical utility in distinguishing patients with subcortical ischemic vascular dementia from Alzheimer’s disease, suggesting that it may have provided additional insight.

Viewed more broadly, the results presented in Chapter 5 and those presented by Stanek and colleagues suggest that cognitive function would be expected to have an effect on cardiopulmonary fitness in this population (Figure iii.B), in addition to the effect that cardiopulmonary fitness can have on cognitive function (Figure iii.A). Of particular relevance, recent evidence from a longitudinal study of CR participants has documented improvements in multiple cognitive domains after 12 weeks of CR. However, if patients with certain cognitive deficits are less likely to complete these interventions, then a bidirectional interaction between physical activity and cognitive function is suggested (Figure iii.C).
Thus, the results presented in Chapter 5 would be consistent with the hypothesis that deficits in cognitive performance due to vascular brain changes may lead to poorer self-care\textsuperscript{180} and subsequently increased medical morbidity. In cognitively impaired older adults, performance in recognition memory, executive function and conceptualization tasks were found to predict physical injury, property loss or emergency interventions due to neglect of self-care\textsuperscript{477} but no such data are available for patients with CAD entering CR, who are largely high-functioning (MMSE≥24). As a further limitation of the present studies, clinical MCI was not formally diagnosed according to Peterson criteria\textsuperscript{478} but this construct has been associated with poorer scores on the Self-Care of Heart Failure Index in patients with heart failure\textsuperscript{327}. Exploring MCI as a construct and specific indices of self-care in this population may have provided additional insight into how cognitive performance may lead to adverse outcomes in CR.

Despite much investigation, a particular organic etiology for the increased cognitive decline observed in patients with CAD remains undefined. The “vascular depression” hypothesis proposed that depressive symptoms in older populations may be secondary to vascular brain changes\textsuperscript{182} and, as discussed, deficits in cognitive performance, particularly deficits in executive function, are likely to have such an etiology. These suggestions, together with the increased prevalence of depressive and cognitive symptoms in patients with CAD prompted the present investigations. The overlap between depressive and cognitive symptoms in late life is so prominent in the clinical presentation of “vascular cognitive impairment”, that the CES-D is recommended in the NINDS-CSN harmonized standards for the investigation of vascular cognitive impairment\textsuperscript{307}. Interestingly, the relative memory deficits associated with non-completion of CR seemed to have originated in the encoding trials of the CVLT-II, which rely on attention and executive functions in addition to encoding and retrieval (Chapter 5). In the included cross-sectional cohort studies (Chapters 4 and 6), cardiopulmonary fitness was associated with performance across multiple cognitive domains (Chapter 4); however, independent associations could only be demonstrated for the Digit Symbol-Coding test, which relies most heavily on attention and psychomotor processing speed (Chapter 6). The association between Digit Symbol-Coding scores and fitness showed a correlation coefficient of $r=0.380$, accounting for approximately 15% of the variance. This represents a substantially robust association for a single independent variable in a clinical population. This is consistent with the results of multiple studies, suggesting cumulatively that performance in these domains is most reliably improved over the course of exercise intervention trials in patients without established CAD\textsuperscript{23}. These domains engage structures sensitive to vascular neural insult such as the frontal lobes, brain structures more classically thought of as memory centres such as the hippocampi and
interconnecting white matter tracts\textsuperscript{324}. Accordingly, frontal lesions have been shown to affect performance on the CVLT-II\textsuperscript{324}.

Future studies will employ structural MRI to evaluate volumes and microstructural integrity (using diffusion tensor imaging; DTI) in important brain regions, i.e. frontal or medial temporal regions\textsuperscript{479}, and the extent of changes in the interconnecting white matter, as predictors of performance on tests of memory, processing speed, attention and executive function. In patients with amnestic MCI, volumes of the hippocampus and of the parahippocampal white matter were associated with declarative memory performance\textsuperscript{480}. In patients with Alzheimer’s Disease and MCI, a DTI measure, mean diffusivity, in the hippocampus correlated with delayed verbal recall\textsuperscript{481, 482} and demonstrated higher diagnostic accuracy\textsuperscript{483} and superior power to predict conversion to AD than hippocampal volume alone\textsuperscript{484}. In a small preliminary study, fractional anisotropy (FA), a measure of white matter integrity, in frontolimbic white matter structures, specifically the left middle cingulum segment, was associated with VO\textsubscript{2Peak} in 15 older adults suggesting that cardiopulmonary fitness may be a protective factor\textsuperscript{485}. Estimates of regional cerebral perfusion using pseudocontinuous arterial spin labeling (pcASL) techniques will also be used to refine associations between structural and microstructural MRI markers and cognitive performance as has been done in other population groups\textsuperscript{486-488}.

Recent DTI studies of patients with late-life depression have been particularly informative. For instance, FA was lower in several frontolimbic regions of 27 depressed elders as compared to controls in a voxel-based analysis covarying for age and mean diffusivity\textsuperscript{489}. Poorer frontolimbic white matter integrity was also significantly associated with non-remission of depressive symptoms in a study of 48 depressed elders\textsuperscript{490}. In 41 depressed older patients, blood pressure was significantly correlated with FA in frontolimbic and frontostriatal white matter\textsuperscript{491}. In depressed elders, deficits in executive function were associated with lower white matter FA in these regions\textsuperscript{492}. Altogether, these findings suggest that white matter disruptions in distributed networks due to vascular risk factors may confer cognitive vulnerability, particularly in patients with late-life depression. The hypothesis that physical activity may protect against neurodegeneration in these networks should be investigated in further studies of vulnerable populations, such as those with CAD and depression. In the present studies, Digit Symbol-Coding scores were particularly associated with cardiopulmonary fitness (Chapters 3 and 4). In traumatic brain injured and post-stroke cohorts, the Digit Symbol-Coding test was particularly sensitive to reduced white matter FA in the long association fibers passing through parietal and temporal lobes and the left middle frontal gyrus\textsuperscript{493}. Specifically, fiber-tracking of DTI data from that study suggested
consistency between lesions producing reduced performance with the trajectories of frontolimbic (inferior occipito-frontal fasciculus) and frontostriatal circuits (superior longitudinal fasciculus connecting the dorsolateral prefrontal and superior parietal cortices)\textsuperscript{493,494}. A particular association between FA in right uncinate fasciculus, a white matter tract connecting the anterior temporal lobe with the inferior frontal gyrus and the ventral prefrontal cortex\textsuperscript{495}, and depressive symptoms late in life\textsuperscript{496-498} might also imply the importance of this tract in the evolution of cognitive and depressive symptoms in CAD. In rats, lesions that disconnect the medial prefrontal cortex from the dorsomedial striatum (caudate-putamen) impair visual attention without affecting classical conditioning, locomotor or motivational abilities\textsuperscript{499}. Similarly, lesions that disconnect the medial prefrontal cortex from the ventral striatum (nucleus accumbens) impaired affective modulation of attention\textsuperscript{500}. These studies suggest that the subtle damage to frontolimbic and frontostriatal networks may limit performance in time- and attention-sensitive cognitive tasks, and that FA in these tracts should be assessed as correlates of cardiopulmonary fitness in patients with CAD.

Unlike the CR noncompletion study presented in Chapter 5, showing that baseline cognitive deficits predicted future noncompletion (Figure iiiB), it should be acknowledged as a potential limitation that the cross-sectional studies presented in Chapters 4 and 6 do not imply any temporality, and none of the included studies can imply a direction of causation. These associations could be interpreted bidirectionally; that is, cognitive decline might be associated with less motivation to take part in physical activity and physical activity might result in improved cognitive function through neuroprotection and adaptive neural plasticity (Figure iv). Certainly, the latter has been suggested by numerous clinical and preclinical studies showing that physical activity interventions can bring about a variety of adaptive neurophysiologic changes.
Figure iii. A biopsychosocial model for cognition in CAD. A. A model is proposed based on previous literature showing that cognitive performance is related to physical activity and vascular risk factors in the general population. A lack of physical activity might also lead to increased medical morbidity through an impact on vascular risk factors. B. The present studies in CR patients show that cognitive performance when entering CR is prospectively associated with noncompletion of CR, showing that the temporality of the effect can go in a direction that leads from cognitive symptoms to less physical activity, with increased medical morbidity as a barrier. C. An integrated model that includes BDNF as a correlate of decreased physical activity and cognitive performance. Associations between cognitive performance and physical activity were independent of vascular risk factors, suggesting the need to better understand the clinical significance of cognitive function in this population. Single headed arrows used to denote the temporal directionality of prospective associations, not the establishment of causation. Thesis chapters referenced as indicated.
III.iv Exercise and BDNF in cognition

In animal studies, exercise protocols can improve learning and memory\textsuperscript{501, 502} on a time-scale consistent with the release and activity of BDNF\textsuperscript{340}. For example, in a rat model, 1 week of treadmill running was sufficient to increase performance in object displacement and object substitution tasks (measures of spatial and non-spatial learning, respectively) and to increase BDNF expression in the dentate gyrus, hippocampus and perirhinal cortex\textsuperscript{502}. In that study, the effect of exercise on non-spatial learning could be mimicked by intracerebroventricular injection of BDNF\textsuperscript{502}. Studies in aged mice have also shown upregulation of BDNF gene expression in the hippocampus after exercise and improved learning and memory\textsuperscript{503}. These functional improvements would be consistent with the increased proliferation and survival of neural progenitor cells and increased neurite outgrowth in the dentate gyrus observed in middle-aged mice after exercise\textsuperscript{504}, which are mediated, at least in part, by BDNF activation of the TrkB receptor\textsuperscript{505}. The release of BDNF from mature neurons has been described in detail, as has modulation of synaptic formation by BDNF and the trafficking of its cognate TrkB receptor\textsuperscript{506}. During normal learning and memory processes, NMDA receptors can induce neuronal nitric oxide synthase (nNOS)\textsuperscript{507} and upregulate the expression of BDNF\textsuperscript{508, 509} mediating plasticity in response to learning stimuli\textsuperscript{510}. The endothelial nitric oxide synthase isoform (eNOS) also seems to be necessary for the generation of long-term potentiation, or the long-lasting enhancement of signaling between two neurons\textsuperscript{511}. Thus, signaling through synaptic NMDA receptors, and activation of TrkB by BDNF are important for learning and memory\textsuperscript{512}.

The capacity of NMDA receptors to promote learning and memory, in part through BDNF transcription\textsuperscript{508, 509}, may seem to contradict the antidepressant benefits of blocking NMDA receptors, since the antidepressant efficacy of the SSRI antidepressants is suggested to depend on their ability to increase BDNF signaling in the hippocampus\textsuperscript{513-516}. However, this apparent contradiction is resolved by the understanding that signaling through NMDA receptors during an action potential can produce adaptive plasticity, but NMDA activation in the absence of an action potential can sustain the activation of Ca\textsuperscript{2+}-calmodulin dependent kinase III, which phosphorylates (inactivates) eEF2, a mediator of ribosomal translocation during protein synthesis\textsuperscript{517}. Thus, inappropriate NMDA signaling (i.e., that which occurs at rest) prevents BDNF translation and blocking NMDA activity at rest with NMDA antagonists such as ketamine may produce antidepressant effects by restoring BDNF translation\textsuperscript{518}. The effects of ketamine on learning and memory would not be expected to exceed their systemic clearance; however, a temporary increase in BDNF translation and subsequent TrkB-mediated metabotropic effects might account for the prolonged antidepressant effect of ketamine observed clinically. These findings
extend the neurodegenerative hypothesis because quinolinic acid can produce prolonged activity-independent of NMDA activation, which may suppress BDNF secretion. Thus, a functional relationship between the kynurenine pathway and the TrkB pathway mediated by BDNF translation in the adult brain is suggested. Interestingly, our studies found that cardiopulmonary fitness was associated with both lower K/T ratios (Chapter 3) and higher BDNF concentrations (Chapter 6) in peripheral blood. Future preclinical and clinical studies should explore the possibility of a direct relationship between these biomarkers as the basis for a novel neuroprotective strategy.

Current clinical studies lend support for the neurotrophic hypothesis of the benefit of exercise in humans. For instance, in a randomized trial reported by Erickson and colleagues, exercise training increased anterior hippocampal volume and improved spatial memory in older human subjects. In that study, hippocampal volume was associated with serum BDNF concentrations. However, as previously discussed, not all of the evidence from human subjects has supported an association between physical activity and increased peripheral blood BDNF concentrations.

In patients with vascular cognitive impairment, serum BDNF concentrations were associated with MMSE scores, suggesting that BDNF may have a protective effect on cognitive function in this population. Patients with CAD show increased hippocampal atrophy compared to age-matched controls and hippocampal volume has been identified as a correlate of memory and executive function in patients with chronic heart failure. In rats, BDNF concentrations are elevated in fields of the hippocampus after transient ischemia, suggesting that BDNF may have a protective effect in the hippocampus. As discussed, patients with CAD are susceptible to other indicators of vascular cognitive impairment, including the subtle cerebral damage that appears on T2-weighted magnetic resonance images as bright foci in white matter termed “white matter hyperintensities”, decreased FA in frontolimbic and frontostriatal white matter, and small “silent” infarctions which do not produce overt clinical signs. These changes are associated with CAD, and with cognitive deficits in patients with CAD. Together, these findings strongly suggest the importance of strategies to improve brain “ischemic tolerance” in patients with CAD, possibly by reducing infarctions or reducing the amount of tissue affected by an infarction or by decreasing the inflammatory/neurodegenerative reponse or increasing neurovascular remodeling post-infarction. A study by Willey and colleagues reported recently that patients in the upper quartile of self-reported physical activity were less likely to have silent infarctions (adjusted odds ratio 0.6, 95% CI 0.4-0.9) in a cohort of 1238 older patients with no history of overt stroke (mean age 70±9 years, 60% female).
the present study, the observation that cardiopulmonary fitness and BDNF are closely related to psychomotor processing speed and executive functions (Chapter 6, Figure iiiC) would be consistent with protection of frontal and limbic structures, or the frontolimbic and frontostriatal white matter tracts which are sensitive to vascular damage.

III.v Possible mechanisms: improving ischemic tolerance

First observed in a gerbil cerebral ischemia model\textsuperscript{538}, the phenomenon of “preconditioning” suggests that exposure to cell stresses can produce adaptive changes that bring about tolerance, reducing the risk of tissue injury on subsequent exposure to ischemia (reviewed\textsuperscript{372}). In animal models, exercise has been qualified as a preconditioning stimulus capable of reducing infarct size after experimentally induced cerebral ischemia\textsuperscript{539, 540}. Similarly, physical conditioning by CR in patients with CAD may limit the extent of cerebral infarction that results from a given insult. The many effects of exercise affecting the cerebrovasculature might be conceptualized within this framework in order to better understand the relationships between changes in vascular risk factors, inflammatory biomarkers, vascular endothelial function and neurovascular plasticity as they relate to cognitive outcomes\textsuperscript{541-546}.

Adaptive neuroplasticity contributes to spontaneous behavioural recovery from cerebral infarction in humans and ischemia in animal models\textsuperscript{374, 547, 548}. Neurogenesis and angiogenesis are very closely associated in the adult cortex to facilitate remodelling\textsuperscript{375}. Evidence suggests that physical activity can stimulate the formation of new blood vessels in animal models\textsuperscript{549} and in healthy aged human subjects\textsuperscript{550}. While specific evidence for the involvement of BDNF in functional recovery from focal ischemia continues to accumulate\textsuperscript{230, 232, 378, 551}, the systems regulating the production and release of BDNF in its “neurovascular niche” remain incompletely understood.

Newly forming vessels consist of a single endothelial cell layer in close proximity with neural progenitor cells. An in vitro model of these interactions presented by Li and colleagues\textsuperscript{379} suggests that capillary formation is supported by neural progenitor cell release of vascular endothelial growth factor (VEGF), BDNF and NO by eNOS activity\textsuperscript{551}, the latter inducing BDNF release from the endothelial cells\textsuperscript{379, 552}. Release of BDNF and VEGF from the forming capillaries can modulate neural progenitor cell growth, survival and differentiation via TrkB and VEGF receptors\textsuperscript{553}. Activation of TrkB induces VEGF expression via the transcription factor hypoxia-inducible factor-1α (HIF-1α)\textsuperscript{554, 555}, increasingly recognized as an important mediator of protection against ischemia\textsuperscript{556-558}. This model suggests a basis
for how forming microvessels and neural progenitor cells participate in the remodeling of cortex via BDNF and VEGF signaling\textsuperscript{374, 376, 559}.

A related adaptation, activation of eNOS, appears to be beneficial in most ischemic tissue models due to promotion of vasodilation, angiogenesis and neurogenesis in the cortex\textsuperscript{551, 560}. Mice deficient in eNOS (eNOS\textsuperscript{-/-}) showed decreased angiogenesis compared to wild-type mice, in conjunction with reduced response to VEGF and decreased BDNF expression\textsuperscript{551}. Subventricular zone neurosphere cultures from the eNOS\textsuperscript{-/-} mice showed decreased progenitor cell proliferation and decreased neurite outgrowth which could be rescued with BDNF treatment\textsuperscript{551}. These data are consistent with the model proposed by Li and colleagues in which VEGF can induce BDNF expression via eNOS activity\textsuperscript{379}.

Glutamate signaling through NR2A containing NMDA receptors can enhance BDNF release and thus enhance plasticity via activation of neuronal NOS (nNOS)\textsuperscript{561}. This has been demonstrated by decreased BDNF expression in the whisker barrel cortex of nNOS deficient (nNOS\textsuperscript{-/-}) mice\textsuperscript{508}. Activation of NR2A containing NMDA receptors seems to be beneficial under both normal and ischemic conditions\textsuperscript{561}, and NO seems to be a necessary signal to bring about exercise induced adaptive plasticity; inhibiting nNOS can prevent the increase in BDNF expression induced by exercise\textsuperscript{552}. However, activation of extrasynaptic NR2B containing NMDA receptors in ischemic tissue does not confer a similar benefit (reviewed\textsuperscript{562}). Instead, NR2B containing receptors contribute to excitotoxicity by assembling with nNOS in a complex at the extracellular membrane\textsuperscript{xxiii} and releasing excessive NO in response to stimulation\textsuperscript{561, 563, 564}. This damages intracellular components\textsuperscript{565-570}, induces mitochondrial dysfunction\textsuperscript{571, 572} and activates pro-apoptotic pathways\textsuperscript{573-576}. Collectively, these processes contribute to post-ischemic neurodegeneration\textsuperscript{216, 217} and NO generated by nNOS can contribute to neurodegeneration during focal ischemia\textsuperscript{577, 578}. Exercise training may help to counteract excitotoxicity in the striatum by preventing the accumulation of extracellular glutamate, attenuating excitotoxicity\textsuperscript{570}. Agents under development to selectively target the NR2B containing NMDA receptors\textsuperscript{450, 451} or to normalize glial glutamate transporter function\textsuperscript{452}, may eventually lead to neuroprotective strategies.

Under ischemic conditions, even low concentrations of NO such as those generated by microglial inducible nitric oxide synthase (iNOS), can be neurotoxic\textsuperscript{580, 581}. However, in vitro evidence suggests

\textsuperscript{xxiii} Interestingly, small molecule inhibitors of the interaction between nNOS and post-synaptic density protein-95, the scaffolding protein to which it binds in order to interact with the NMDA receptor at the membrane, can attenuate post-ischemic damage in the rat and mouse brain. One lead molecule, ZL006 can readily cross the blood brain barrier without substantially inhibiting adaptogenic NR2A containing NDMA receptors and without any obvious effects on memory or behaviour, suggesting a promising drug target for post-ischemic neurodegeneration (Zho et al., Nat Med. 2010 16(12):1439-43).
that BDNF can prevent the neurotoxicity induced by glutamate or NO in cultures of cortical neurons via TrkB activation\textsuperscript{582-584}. Preservation of cortical neurons would be consistent with the benefit of physical activity observed on processing speed (Chapter 6). In cortical tissue, BDNF might also inhibit excitotoxic NMDA mediated Ca\textsuperscript{2+} influx, possibly by activating the p75 neurotrophin receptor, leading to NF-κB activation\textsuperscript{585}, although this mechanism does not seem to operate in hippocampal neurons\textsuperscript{586}.

Further examination of such differences in gene expression between the hippocampus and other regions may help to explain why the hippocampus is particularly susceptible to atrophy, even though white matter hyperintensities may be more common elsewhere.

In addition to NOS activity, it should be considered that BDNF expression might be stimulated by superoxide generated by nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (NOX) enzymes\textsuperscript{587,588}. Isoforms of NADPH oxidase are constitutively expressed in neurons, astrocytes, microglia and cerebrovascular endothelial cells\textsuperscript{589} and NADPH oxidase has been identified as the primary source of superoxide induced by NMDA activation\textsuperscript{590}. Inhibitors of NADPH oxidase can block LTP in hippocampal slices\textsuperscript{591} and context dependent fear memory is impaired in NADPH oxidase 2 knockout (NOX2\textsuperscript{−/−}) mice\textsuperscript{592} suggesting their potential role in normal cognitive function. However, NOX2 can also damage GABAergic interneurons in the prefrontal cortex, leading to increased glutamate release and downregulation of NR2A containing NMDA receptors, increasing the relative activation of NR2B/NR2A containing receptors and contributing to excitotoxicity\textsuperscript{593}. In response to intermittent hypoxia NADPH oxidase 2 can be upregulated through activation of HIF-1α\textsuperscript{594} and by metabotropic glutamate receptor 1 activation via the PKC pathway, which phosphorylates the ionotropic NMDA receptors leading to increased activity\textsuperscript{595}. Superoxide stress on endothelial cells is known to result in disruption of the blood brain barrier during experimental stroke\textsuperscript{596}. Interestingly, NADPH oxidase 4 knock-out (NOX4\textsuperscript{−/−}) mice were protected from oxidative stress, blood brain barrier breakdown and neuronal apoptosis following cerebral ischemia\textsuperscript{597}. It is unclear which NADPH oxidase subtypes might stimulate BDNF secretion during ischemia, however, specific involvement of the NADPH oxidase types in harmful vs. beneficial processes might eventually be exploited pharmacologically if type specific small molecule inhibitors can be found.

In a study of spontaneously hypertensive rats, blood vessel expression of NADPH oxidase subunits and NADPH oxidase activity increased as hypertension developed\textsuperscript{587}. This was attributed to increased expression of the angiotensin II receptor type 1 (AT\textsubscript{1}) receptor on blood vessels and these changes increased BDNF expression, presumably as part of a compensatory mechanism. In a second rat model,
transcription and release of BDNF from cells in the rat rostral ventrolateral medulla, which participates in maintaining vasomotor tone, could be stimulated by microinjection of angiotensin II\textsuperscript{588}. Consistent with a role of superoxide, BDNF expression could be attenuated by coadministration of the antioxidant apocynin or tempol, a free-radical scavenger\textsuperscript{598}. In that study, BDNF expression seemed to reduce superoxide formation by a mechanism dependent on TrkB signaling. Upregulation of BDNF by superoxide and negative feedback regulation of superoxide production suggest possible additional protective roles of BDNF in certain models, which warrants further investigation.

Collectively, these experiments suggest that deficient secretion of BDNF in response to superoxide or NO would be deleterious to neurons and vascular endothelial cells. Given that the val66met polymorphism in the pro-region of the BDNF protein is associated with failure to localize BDNF to secretory granules and with lower depolarization-induced BDNF secretion\textsuperscript{599}, expression of BDNF from the met allele may not support maintenance of cerebrovascular integrity as efficiently. Accordingly, increased white matter hyperintensity volumes have been observed in older human met allele carriers\textsuperscript{380} and val66met knock-in mice show deficits in endothelial cell proliferation and blood vessel density in the ischemic border region of the infarct post-stroke\textsuperscript{378}, suggesting increased susceptibility and impaired adaptation to damage. While much of this evidence remains preliminary, the models discussed may begin to describe the cell stresses governing BDNF secretion during the formation and function of the neurovascular unit in cerebrocortical and subcortical tissues under ischemic stress.
**Figure iv. Working neurodegenerative hypothesis (integrated biomarker model).** Normally, glutamate induces the release of NO, in part through activation of NMDA receptors, which stimulates adaptive plasticity through the release of BDNF and BDNF activity on TrkB receptors. Inflammation can modulate cholinergic and glutamatergic pathways involved in cognitive processing, mood regulation, learning and memory due, in part, to the activities of kynurenine metabolites quinolinic and kynurenic acids on α7 nicotinic and NMDA receptors. When unbalanced by kynurenic acid, quinolinic acid can overstimulate extrasynaptic NMDA receptors containing the NR2B subunit, resulting in excessive nitrosative and oxidative cell stresses implicated in depression and neurodegenerative disorders. Kynurenine can downregulate inflammatory activity via activating the aryl hydrocarbon receptor on certain inflammatory cell types, but, in animal models, cerebral ischemia can induce microglial KMO, which degrades kynurenine along the quinolinic acid pathway. In humans, ischemia may occur post-infarction, or possibly due to hypoperfusion from microvascular damage. This may exacerbate the neurodegenerative cascade by increasing excitotoxicity, further increasing the release of NO and superoxide, the sources of oxidative and nitrosative stress. Both NO and superoxide may regulate BDNF expression, which confers neuroprotection by activating neuronal TrkB receptors and by decreasing the activities of nNOS and NADPH oxidase isoforms. BDNF may also confer resilience by increasing angiogenesis to remodel damaged cortex post-infarction; BDNF synthesis and release from neurons, neural progenitor cells and capillary endothelial cells at the newly forming neurovasculature stimulates VEGF secretion and angiogenesis, the endothelial cells reciprocate by releasing BDNF which stimulates neural progenitor cell maturation and survival. Physical activity may represent a “preconditioning stimulus” which can stimulate BDNF expression (as above), stimulating neurogenesis and angiogenesis to increase brain ischemic tolerance. Physical activity may also alleviate synergistic neurotoxic effects of ischemia and inflammation in brain by decreasing systemic pro-inflammatory cytokine concentrations, central quinolinic acid synthesis and extracellular glutamate concentrations in brain.
Implications for clinical studies

As a limitation of the evidence provided in the present thesis, it must be considered that the associations between BDNF and psychomotor processing speed and between BDNF and cardiopulmonary fitness do not imply any causative relationship. Moreover, any directionality of causation cannot be inferred from the present studies. While BDNF release stimulated by physical activity may improve or preserve psychomotor processing speed, superior cognitive function may lead to increased physical activity leading to increased BDNF secretion. An incremental advance could be made by recruitment of additional patients into the cohort study reported in Chapter 6, in order to perform a path analysis such as that presented by Elias and colleagues. Such an analysis could be used to assess whether serum BDNF concentrations can act as a mediator of the association between cardiopulmonary fitness and psychomotor processing speed, or whether psychomotor processing speed mediates the association between BDNF concentrations and cardiopulmonary fitness; however, such analyses still would not establish directionality or causality. Moreover, the relationships between peripheral BDNF protein concentrations and cognitive outcomes are likely to be complex and the measurement of BDNF in peripheral blood is likely to be confounded by relationships between BDNF and vascular risk factors.

In the present investigation, superior cardiopulmonary fitness was associated with higher serum BDNF concentrations consistent with the involvement of BDNF in an adaptive response to habitual physical activity, but this explained only a small proportion of the variance. In the Baltimore Longitudinal Study of Aging, plasma BDNF concentrations were obtained from 496 middle-aged to elderly subjects, reporting associations between higher plasma BDNF concentrations and increased vascular risk factors such as fat mass, diastolic blood pressure and total cholesterol in females, and diastolic blood pressure and triglycerides in males. These studies suggest that a portion of the variance in peripheral BDNF concentrations may represent compensatory responses to unfavorable cell stresses brought about by these vascular risk factors (reviewed). These relationships may be further confounded by the use of medications, which were not accounted for in the Baltimore study. For instance, the possible involvement of the AT receptor in initiating BDNF release suggests a hypothetical basis for the clinical association between lower serum BDNF and the use of an ACE inhibitor observed in the present investigation (Chapter 6). A future placebo-controlled study might measure serum BDNF before and after acute and chronic dosing with an ACE inhibitor to determine if this observation can be replicated.

The ability of ACE inhibitors to modulate NF-κB signaling and NO production, and possibly to reduce AT receptor-mediated superoxide production, suggests that they may reduce BDNF concentrations
despite the antihypertensive effects that might improve or delay the progression vascular endothelial dysfunction\textsuperscript{3, 6, 546, 603}.

The Baltimore study also did not appear to account for a diagnosis of depression, or for the use of antidepressant medications in their analyses, both of which can affect peripheral BDNF concentrations\textsuperscript{353}. Although the reproducibility of serum BDNF as a biomarker has been established in depression studies and in some cognitive studies, the biological roles and regulation of concentrations of BDNF in peripheral blood compartments remains unclear, suggesting an important knowledge gap worthy of further research. Concentrations of BDNF in serum tend to be much higher than those measured in plasma\textsuperscript{382, 604} because platelets take up BDNF that has been released from other tissues and release it when they are activated\textsuperscript{384}. The clinical significance of this process is not known; however, platelet factors, such as platelet-derived growth factor, interact with vascular endothelial cells during vascular remodeling\textsuperscript{605, 606}, suggesting that further investigation into the role of BDNF release by platelets is warranted. Several antidepressants can stimulate the release of BDNF from platelets\textsuperscript{607} but this effect is also of unknown significance.

The selective serotonin reuptake inhibitors (SSRIs) can increase hippocampal BDNF\textsuperscript{608}, which is suggested to account for their antidepressant effects\textsuperscript{513-516}. This activity may also confer cerebral ischemic tolerance. In mice, chronic fluoxetine administration improved cognitive deficits induced by focal ischemia in a manner dependent on enhancement of newborn cell survival in the hippocampus\textsuperscript{609}. In a human pilot study, the SSRIs were suggested to improve cognitive function in patients with heart failure\textsuperscript{334} and a trend towards better verbal memory performance in patients with CAD using an antidepressant medication was observed in the present study (Chapter 5). These results suggest that the SSRIs might be evaluated in randomized controlled trials as a strategy to improve or maintain cognitive function in patients with CAD. Evidence from two well-designed randomized placebo controlled trials of fluoxetine\textsuperscript{610-612} and citalopram\textsuperscript{613} suggest that this class of medications can improve motor recovery post-stroke. Importantly, some clinical evidence suggests that SSRIs can improve performance on tests of memory\textsuperscript{614} and executive function independent of their effects on mood\textsuperscript{615} in patients post-stroke. These results suggest the potential for clinical benefit in vascular cognitive impairment.

Serum BDNF was associated with both cardiopulmonary fitness and cognitive function; however, an association between IL-6 and BDNF concentrations in serum was also observed (Chapter 6). The significance of this association is unclear, but taken together with a previously observed association between serum BDNF and activated T cell number in older patients\textsuperscript{382}, it should be cautioned that BDNF
concentrations may share variance with inflammatory biomarkers in clinical samples. This is not surprising given that the pro-inflammatory cytokines are pleiotrophic, having roles in tissue injury and in initiating tissue repair pathways. For instance, IL-6 and TNF-α can stimulate BDNF expression via NF-κB signaling, while IL-6 blocking antibodies can reduce BDNF expression. In these studies, stimulatory effects were consistent in central and peripheral neurons, and in peripheral mononuclear cells. Since these inflammatory biomarkers tend to decline over the course of exercise training in patients with CAD, these changes may partially obscure the exercise induced increase in BDNF expression when relying on peripheral blood BDNF measurement. Exercise may also reduce platelet activation, which, as discussed, may contribute to peripherally measured concentrations. Therefore, the balance between neuroprotective and inflammatory biomarkers might be considered in longitudinal exercise studies. The hypothesis that this interaction may be physiologically important is suggested by the weak but significant negative association between IL-6 and MMSE scores in Chapter 6 that only became apparent when controlling for BDNF concentrations and other possible confounders (Chapter 6). While this observation is not conclusive it warrants further study. Such analyses may be particularly relevant when planning MRI studies because IL-6 concentrations have been shown to vary inversely with hippocampal gray matter volume, but BDNF, which may be correlated with IL-6 in serum, would be hypothesized to increase gray matter volume. The balance of the two factors may provide a superior measure of their respective effects.

III.vii A neuroimmunological perspective

Damage to the cerebrovascular endothelium results in the expression of chemokines and cellular adhesion molecules that trigger the infiltration of neutrophils, macrophages and T cells into from peripheral blood into the brain parenchyma. Evidence suggests that extravasation of T cells is involved in mediating post-ischemic cerebral injury. Infiltrating T cells and macrophages may damage neurons directly by the activity iNOS or activate resident microglia and perpetuate a neuroinflammatory response. Cerebral T cell infiltration following transient ischemia can be ameliorated by habitual exercise in rats, suggesting that this mechanism may constitute an additional preconditioning effect. This effect may be due, in part, to an adaptive cerebrovascular response to exercise that involves decreased chemokine or adhesion molecule expression at the blood brain barrier, or due to a change in the polarization of the peripheral immune system. In addition to the former, the latter has been demonstrated recently in mice using a chronic low-grade Trichuris muris.
infection, which exacerbated cerebral microvascular damage following experimental stroke$^{632}$. This is consistent with the clinical association between respiratory infections post-stroke and poorer recovery$^{633-635}$ and thus, with the hypothesized importance of the pro- and anti-inflammatory balance post-stroke$^{636,637}$.

Flow cytometry might be used to identify particular T cell populations that vary in abundance or activation with exercise as has been done to show increased Th17 cell numbers in patients with Alzheimer’s disease$^{638}$. In stroke patients, a unique subpopulation of IL-17 secreting T cells, the $\gamma$δT-cells, increase in peripheral blood 1-3 days post-stroke and they are associated with the degree of neurological impairment$^{628,639-643}$. Experimental depletion of the $\gamma$δT-cells can significantly attenuate ischemia-reperfusion injury$^{628}$ suggesting that these cells may be of pathological significance. However, no studies have evaluated the effect of these cell populations on white matter disease, silent infarctions or cognitive function in patients with CAD, nor have changes in these cells after exercise intervention been examined. Flow cytometry studies may prove more informative than relying on measurement of non-specific intercellular cytokine messengers, which can be confounded by uncertain tissue sources, highly variable serum half-lives, and the presence of their soluble receptors$^{82,83,630}$. While the particular T cell lines involved in post-ischemic neuroinflammatory lesions and their stimulatory signals remain controversial, further investigation may inform the development of pharmacotherapeutics that can interfere with the expansion of certain T cell lines, or with their infiltration into the parenchyma of the brain following vascular neural insult$^{644-646}$. This may help to improve the long-term outcomes of patients with cognitive impairment due to vascular changes.

As previously discussed, kynurenine concentrations can have profound effects on the proliferation of certain T cell populations that may be harmful post-ischemia$^{421,422}$ and kynurenine is likely found elevated in CAD due to activation by inflammatory signals indicating the need for such a system to be upregulated$^{90,91,647}$. However, this pathway may produce depressive symptoms and exacerbate neurodegeneration by virtue of oxidative and excitotoxic metabolites instigated by KMO during cerebral ischemia$^{105,107,412,413,416,429}$. Increasing kynurenine concentrations while balancing its metabolites reversed cognitive deficits in a mouse model of Alzheimer’s Disease, suggesting promise in preventing neurodegeneration in humans. Acutely, kynurenine concentrations can be elevated by physical activity in rats$^{648}$ and human children$^{649}$, suggesting that this may be an endogenous adaptive response that protects sensitive tissues from innate immune stimulation during acute exercise$^{648}$. 


In addition, animal studies have succinctly demonstrated the involvement of BDNF in protecting against neurodegeneration resulting from systemic inflammatory insults. For instance, Wu and colleagues showed that exercise preconditioning can reduce damage to dopaminergic neurons induced by intraperitoneal lipopolysaccharide (LPS) administration by increasing BDNF signaling at TrkB receptors. Although no difference in the neuroinflammatory response to LPS was found between trained and untrained mice, BDNF release was increased in the substantia nigra after LPS injection in trained mice as compared to untrained mice, suggesting a favorable balance of neuroinflammatory and neuroprotective responses to systemic inflammatory challenge that protected against neurodegeneration. These observations may account for the ability of exercise to attenuate LPS induced deficits in neurogenesis, learning and memory. In a 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced mouse model of Parkinson’s disease, BDNF increased substantially in the substantia nigra after 18 weeks of treadmill exercise, which was associated with reduced imbalance and discoordination and reduced mitochondrial damage. Midbrain dopaminergic neurons can release BDNF via activation of nNOS, which can upregulate BDNF via an Extracellular signal-Regulated Kinase (ERK)-dependent mechanism. Similarly, regular physical activity may confer resilient conditions in the human brain, resulting in preservation of cognitive function in the face of inevitable inflammatory challenges post-infarction.

The observation that depressive symptoms and poorer cognitive performance can interact to produce poorer functional outcomes (Chapter 6) suggests that the associated biomarkers, if measured concurrently, might also interact to predict poorer psychiatric, neurological and functional outcomes consistent with the vascular hypothesis of depression in late life and its association with vascular cognitive impairment (Figure iv). For example, high kynurenine concentrations in concert with low BDNF concentrations might imply a particular vulnerability, since the oxidative and excitotoxic stresses of kynurenine metabolites in concert with decreased resilience to inflammatory or ischemic insults associated with lower BDNF activity might be thus indicated. As in studies of either biomarker individually, prospective epidemiological studies might evaluate whether these biomarkers in combination can better predict the future development of depressive symptoms, cognitive impairment, reduced functional status and mortality due to vascular causes.
A primary limitation of the evidence presented in this thesis concerns lack of causative evidence provided by correlative studies. It must be considered that the natural history of CAD in the context of CR may be associated with changes in both the dependent and independent variables measured in the present studies regardless of the associations described herein. Longitudinal associations were assessed with respect to the clinical significance of MDD (Chapter 2) and cognitive performance (Chapter 5) but not with respect to changes in these symptoms as compared to changes in the biomarkers assayed, which, when assessed in future studies, may strengthen or fail to further support this evidence. Concentrations of these biomarkers may be causal or consequential of underlying CAD severity, other cardiovascular parameters or common comorbidities, and they may be causal or consequential of the mood and cognitive symptoms studied. As stated, the present thesis has focused on patients with CAD undertaking CR as a population of interest, and therefore no control groups, such as patients without CAD or those not undertaking CR, were recruited or studied; it was not within the scope of this thesis to qualify the association between a diagnosis of CAD and any of the dependent or independent variables assessed. The generalizability of the present studies to all CAD patients may be limited by potential biases introduced at the levels of CR referral, self-selection and CR intake, and by the demographics of the geographical catchment area. For instance, in the present studies, a higher number of years of formal education may limit the generalizability of the cognitive data obtained. Demographic data were not collected on patients who declined to participate in the present studies; however, comparisons between the included population samples with large unselected samples from the centre database did not suggest appreciable differences in age, gender and CES-D scores. It is unlikely that bias was introduced at the level of the bioassays as the personnel who preformed the bioassays were blinded to all clinical information; however, medical histories and CES-D scores were obtained at the time of the research interview for MDD and cognition, which unblinded researchers to indicators of disease severity, depressive symptoms and overall health status. It should be acknowledged that records from patients in Chapters 2-6 were housed in the same database and overlap was permitted between cohorts such that all comparisons cannot be considered to be entirely independent of each other; however, none of the cohorts were comprised entirely of patients reported in any other cohort and CR participants were recruited consecutively into cohorts of prespecified sizes according to hypotheses a priori.

With these limitations in mind, the present thesis presents evidence that two common but underappreciated sequelae of CAD, depressive symptoms and poorer cognitive function, were associated
with poorer cardiopulmonary fitness in this population. The co-occurrence of these clinical features would predict a substantially increased risk of mortality based on previous epidemiological studies. Prospective studies demonstrated the clinical significance of these sequelae in predicting noncompletion of cardiac rehabilitation. Thus, the symptoms suggested to benefit from physical activity also posed significant barriers to undertaking an exercise intervention. These findings identify a significant unmet medical need. Cardiopulmonary fitness was associated with two peripheral biomarkers, lower K/T ratios and higher serum BDNF as measured from serum, possibly having roles in neurodegeneration and in resilience thereto. The association between increased kynurenine production and depressive symptoms in this population and strong evidence from preclinical studies suggests that the kynurenine pathway may offer an attractive additional or adjunctive drug target when orally bioavailable agents with appropriate pharmacokinetics become available for clinical trials. The association between BDNF concentrations and cognitive performance implies the need to better understand the regulation of neurotrophin concentrations in humans in order to target this biomarker in this population. Thus, endogenous adaptations to physical activity may inform the future pharmacology of mood and cognitive symptoms in patients with CAD.
IV.

References

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Appendix I:

Physician referral form and program information

Patient information can be located at the following address:

http://www.torontorehab.com/TorontoRehabCorporate/media/Toronto-Rehab-Corporate/cardiac-program_1.pdf

The official public service description can be found at the following address:
REFERRAL FORM

PATIENT INFORMATION

NAME ____________________________ SEX □ M □ F DATE OF BIRTH ____________
(Please Print) Last Name First Name Middle Initial Month/Day/Year

STREET ADDRESS ______________________________________ APT # ________________

CITY ____________________________ PROV __________________ POSTAL CODE ____________

TEL ( ) __________________________ ( ) __________________________ EMAIL __________________________
Home Business

OCCUPATION ____________________________ HEALTH CARD NO __________________________

CLOSEST RELATIVE (or CONTACT PERSON) ____________________________ TEL ( )

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REFERRING PHYSICIAN INFORMATION

NAME ____________________________
(Please Print) Last Name First Name

TEL ( ) FAX ( ) EMAIL __________________________

ADDRESS __________________________________________ POSTAL CODE ____________

(Physician Signature) □ Family Practice □ Cardiology □ C.V. Surgery □ Internist

** PLEASE NOTE: Attaching a12 Lead ECG and Discharge Summary will Expedite the Start of Rehabilitation

PATIENT WAIVER

(Print) Last Name First Name Date Of Birth

I Hereby Authorize ____________________________ to Release to Toronto Rehabilitation Institute any Medical Records or Information Concerning my Admission.

Dated this __________ Day of ___________________ 20 __________

Signature ____________________________ Witness __________________________
Appendix II:

Concept map for hypotheses

Relationships between the hypotheses pertaining to cardiopulmonary fitness, cognitive and affective symptoms, biomarker concentrations and cardiac rehabilitation outcomes can be interrelated according to the framework above (specific hypotheses tested in each chapter as indicated).