THE RELATIONSHIP BETWEEN PHYSICAL ACTIVITY AND FITNESS LEVEL, AND PHYSIOLOGICAL AND PSYCHOLOGICAL STRESS IN INDIVIDUALS WITH SPINAL CORD INJURY

by

Gabriel Ursus Dix

B.H.K., University of British Columbia Okanagan, 2019

A THESIS SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF

MASTER OF SCIENCE

in

THE COLLEGE OF GRADUATE STUDIES

(Health and Exercise Sciences)

THE UNIVERSITY OF BRITISH COLUMBIA

(Okanagan)

April 2021

© Gabriel Ursus Dix, 2021
The following individuals certify that they have read, and recommend to the College of Graduate Studies for acceptance, a thesis/dissertation entitled:

Impact of physical activity and fitness level on physiological and psychological stress in individuals with spinal cord injury

submitted by Gabriel Dix in partial fulfillment of the requirements of

the degree of Master of Science.

Dr. Kathleen Martin Ginis, Faculty of Health and Social Development & Faculty of Medicine

**Supervisor**

Dr. Jonathan Little, Faculty of Health and Social Development

**Supervisor**

Dr. Tanya Forneris, Faculty of Health and Social Development

**Supervisory Committee Member**

Dr. Christopher West, Faculty of Medicine

**University Examiner**
Abstract

Introduction: Although research involving able-bodied individuals has explored the relationships between cardiorespiratory (CR) fitness, cortisol, perceived stress, and leisure time physical activity (LTPA), limited research has investigated these relationships in people with a SCI. This study examined the relationships between LTPA, CR fitness and psychological (i.e., perceived) and physiological (i.e., circulating cortisol) stress in adults with chronic SCI. It was hypothesized that LTPA and CR fitness would negatively correlate with 1) perceived stress, and 2) circulating cortisol.

Methods: Nine men with chronic (>1-year post injury) traumatic SCI (M=18.4 years post-injury; 4 tetraplegia; 5 AIS-A) participated in this cross-sectional study. Participants arrived at the lab fasted (≥ 12 hours) and completed the Perceived Stress Scale and a self-report measure of LTPA-SCI prior to performing a graded \( \dot{V}O_2 \) peak test. Blood samples were taken in the fasted state prior to the \( \dot{V}O_2 \) peak test. Cortisol concentration was assessed using a cortisol ELISA.

Results: Hypothesis 1 received partial support as \( \dot{V}O_2 \) peak (i.e., CR fitness) was only trivially negatively correlated with perceived stress \( (r=-.076) \) whereas a small negative correlation was observed between total LTPA and perceived stress \( (r=-.187) \). Hypothesis 2 was supported as both \( \dot{V}O_2 \) peak \( (r=-.306) \) and total LTPA \( (r=-.475) \) demonstrated a medium-large negative correlation with levels of cortisol. Forced regression analysis indicated \( \dot{V}O_2 \) peak and LTPA together explained 23.2% of the variance in cortisol \( (R^2_{adj}=.232, F[2,5] = 0.755, p=.517) \) and 3.5% of the variance in perceived stress \( (R^2_{adj}=.035, F[2,5]=0.091, p=.914) \).
**Conclusions:** Both LTPA and CR fitness showed a medium-large negative correlation with cortisol, suggesting that as physical activity and fitness increase, cortisol levels decrease. More variance in cortisol is explained by a combination of LTPA and fitness than by either variable alone, suggesting that a combination of physiological adaptation (i.e., fitness) and behaviour (i.e., LTPA) may play a role in cortisol secretion. Interestingly, LTPA and CR fitness explained less variance in perceived stress than cortisol, suggesting that additional factors not examined in the present study likely contribute to variations in perceived stress.
Lay Summary

The purpose of this thesis was to explore the relationship between physical activity and stress in adults with a spinal cord injury (SCI). Following a spinal cord injury, paralysis might seem like the biggest issue. However, psychological issues like stress might be considered a bigger problem. Two ways to measure stress are through questionnaires or cortisol, a stress hormone found in the blood. Like stress, how active someone is can be measured by asking how much physical activity they engage in, or by completing a fitness test. Physical activity is considered more behavioural, while fitness is typically considered to be a long-term adaption to exercise. Based on the results of this thesis, it seems both the short-term behavioural and long-term adaptive aspects of physical activity play a role in stress, although it seems many factors outside of how physically active someone is might play a role in stress.
Preface

This thesis is based on a worked conducted at the University of British Columbia (Okanagan) by Gabriel Dix, Dr. Jonathan Little, and Dr. Kathleen Martin Ginis. This thesis is a subproject of a larger randomized controlled trial examining the effects of exercise prescribed according to the international scientific spinal cord injury exercise guidelines on chronic pain in adults with a chronic spinal cord injury. An international team headed by Dr. Kathleen Martin Ginis was responsible for the larger randomized controlled trial, however for the present thesis, Gabriel Dix was responsible for the research design, collection and analysis of data, and data interpretation. Further, Gabriel was the phlebotomist for the project and was solely responsible for blood collection and analysis. Dr. Jonathan Little and Dr. Kathleen Martin Ginis provided assistance with the study design, measurement selection, obtaining ethics approval, and the analysis and interpretation of the results. Additionally, the aim of this current thesis shifted dramatically due to SARS CoV-2 (i.e., Covid-19) virus, ensuing global pandemic, and halt to in-person research. As such, the analysis of cortisol was introduced post-hoc as the original aim of this thesis was to analyze the relationship between physical activity, fitness, and immune cell function.

This research study has not yet been published.

This research study was approved by the Clinical Research Ethics Board at the University of British Columbia (Okanagan).

H19-01650. CIHR-funded RCT - Effects of SCI exercise guidelines.
# Table of Contents

*Abstract* ............................................................................................................................ iii  
*Lay Summary* ........................................................................................................................ v  
*Preface* .................................................................................................................................. vi  
*Table of Contents* .................................................................................................................. vii  
*List of Tables* .......................................................................................................................... ix  
*List of Figures* ......................................................................................................................... x  
*List of Abbreviations* ............................................................................................................... xi  
*Acknowledgements* ................................................................................................................ xii  
*Dedication* ............................................................................................................................... xiv  

## 1.0 Introduction .................................................................................................................... 1  
1.1 The Spinal Cord, Anatomy ............................................................................................... 1  
1.2 Spinal Cord Injury ............................................................................................................. 2  
  1.21 Spinal Cord Injury, Pathophysiology .............................................................................. 2  
  1.22 Spinal Cord Injury, Classification .................................................................................. 2  
  1.23 Spinal Cord Injury, Epidemiology .................................................................................. 3  
1.3 Spinal Cord Injury, Secondary Consequences of Injury ................................................... 5  
1.4 Stress .................................................................................................................................. 7  
  1.41 What is stress? .................................................................................................................. 7  
  1.42 The stress response pathways (SAM and HPA axis) ........................................................ 9  
  1.43 The nervous system and stress ....................................................................................... 10  
  1.44 Spinal Cord Injury and Stress ....................................................................................... 12  
1.5 Physical Activity and Fitness: Defining Key Concepts ..................................................... 14  
  1.51 The Effects of PA, Exercise, and Fitness on Cortisol and Perceived Stress .................... 17  
    Cortisol ............................................................................................................................... 17  
    Perceived Stress ................................................................................................................ 21  
  1.52 Potential explanations for relationships between Perceived Stress, Cortisol, and Physical  
    Activity/Physical Fitness ..................................................................................................... 23  

## 2.0 Summary and Significance ............................................................................................ 26  
2.1 Addressing the Gap .......................................................................................................... 26  
2.2 Purpose ............................................................................................................................... 27  
2.3 Hypothesis ......................................................................................................................... 27  

## 3.0 Methods ......................................................................................................................... 28  
3.1 Participants ......................................................................................................................... 28  
3.2 Protocol Overview ............................................................................................................. 29  
  3.21 Blood Collection ............................................................................................................. 31  
  3.22 Cortisol Assay Protocol .................................................................................................. 32  
  3.23 Perceived Stress Scale .................................................................................................... 33  
  3.24 Leisure time Physical Activity Questionnaire ............................................................... 34  
  3.25 Cardiorespiratory fitness testing .................................................................................... 35
3.3 Statistical Analysis ........................................................................................................... 36
  3.31 Data Cleaning and Treatment ....................................................................................... 36
  3.32 Descriptive Statistics, Assumption Testing .................................................................. 37
  3.33 Statistical Significance and effect sizes ...................................................................... 37
  3.34 Testing covariates ....................................................................................................... 38

4.0 Results .............................................................................................................................. 39
  4.1 Correlations .................................................................................................................... 40
    4.11 Correlations between cortisol and perceived stress, total LTPA and VO2peak ........... 40
    4.12 Hypothesis 1: physical activity levels and cardiorespiratory fitness will negatively correlate with levels of perceived stress ................................................................. 41
    4.13 Hypothesis 2: physical activity levels and cardiorespiratory fitness will negatively correlate with levels of circulating cortisol ................................................................................. 41
  4.2 Results of covariate testing ........................................................................................... 41
  4.3 Regressions ..................................................................................................................... 42
    4.31 Predicting Levels of Perceived Stress ....................................................................... 42
    4.32 Predicting Levels of Cortisol .................................................................................... 43
    4.33 Regression Assumption Testing ................................................................................. 44

5.0 Discussion .......................................................................................................................... 46
  5.1 Perceived Stress, LTPA and CR Fitness ......................................................................... 46
  5.2 Cortisol, LTPA and CR Fitness ....................................................................................... 52
  5.3 Strengths of the Study .................................................................................................... 54
    5.31 Measures .................................................................................................................... 54
    5.32 Community Engagement ......................................................................................... 55
  5.4 Limitations ...................................................................................................................... 56
    5.41 Study Design .............................................................................................................. 56
    5.42 Sample Size ............................................................................................................... 57
    5.43 Injury Characteristics ................................................................................................ 57
    5.44 Unexplained Variance .............................................................................................. 58
    5.45 Cortisol and Diurnal Variation .................................................................................. 58
  5.5 Implications .................................................................................................................... 59
  5.6 Future Directions .......................................................................................................... 60

6.0 Conclusion ......................................................................................................................... 63
References ............................................................................................................................... 64
Appendices ............................................................................................................................. 84
Appendix A ............................................................................................................................. 84
List of Tables

Table 1: Participant characteristics ......................................................... 29
Table 2: Participants’ VO\textsubscript{2}peak, circulating cortisol, perceived stress, and activity levels .......................................................... 40
Table 3: Pearson’s \( r \) correlation matrix ...................................................... 42
List of Figures

Figure 1: The Chronic Pain Processing Model.........................................................25
List of Abbreviations

ACTH – Adrenocorticotropic-releasing hormone
ADL – Activities of Daily Living
AIS – American Spinal Injury Association Impairment Scale
ASIA – American Spinal Injury Association
CR - Cardiorespiratory
CRH – Corticotropin releasing hormone
cSCI – Cervical Spinal Cord Injury
CPET – Cardiopulmonary Exercise Testing
CV – Coefficient of Variability
CVD – Cardiovascular Disease
EDTA – Ethylenediaminetetraacetic acid
ELISA – Enzyme-linked Immunosorbent Assay
EPIC-SCI – Exercise Guidelines Promotion and Implementation in Chronic Spinal Cord Injury
HPA – Hypothalamic-Pituitary-Adrenocortical axis
IKT – integrated Knowledge Translation
ISNCSCI – International Standards for Neurological Classification of Spinal Cord Injury
L/min – Litres per minute
LTPA – Leisure Time Physical Activity
LTPAQ-SCI – Leisure Time Physical Activity Questionnaire for people with a Spinal Cord Injury
Ng/ml – nanograms per millilitre
NLI – Neurological Level of Injury
PA – Physical Activity
PSS – Perceived Stress Scale
RER – Respiratory Exchange Ratio
RCT – Randomized Controlled Trial
SAM – Sympathetic-Adrenal-Medullary axis
SCI – Spinal Cord Injury
SNS – Sympathetic Nervous System
SOP – Standard Operating Procedures
SWB – Subjective Well-being
TSST – Trier Social Stress Test
UBC – University of British Columbia
VIF – Variance Inflation Factor
VO₂max – Maximal Volume of Oxygen
VO₂peak – Peak Volume of Oxygen
Acknowledgements

As with most, if not all my accomplishments, it would be daft to think I made it here without the guidance, aid, and support of the many people who have had a hand in my successes. I am thankful for and would like to acknowledge the two labs of which I am a part; EMIL, or the Exercise Metabolism and Inflammation Lab run by Dr. Jonathan Little, and the SCI Action Canada Lab run by Dr. Kathleen Martin Ginis. In addition to the time, energy, and general support I have received academically, both of these labs have spent a considerable amount of resources focusing on the issues of equity, diversity, and inclusion both in- and outside of academia. As a result, I am graduating this degree not only with a better understanding of spinal cord injury, but with a better understanding of how I can contribute to society as a whole and what sort of positive impact I can have on those around me.

To the faculty of Health and Exercise Sciences at UBCO, it has been my pleasure to complete both my undergraduate and graduate training under the many wonderful professors you host. Although this list is by no means exhaustive, I would especially like to thank Dr. Tanya Forneris, for your help both academically and in my extra-curriculars. I have no doubt that the many, many reference letters you have written for me have helped along the way. I would like to thank Dr. Jonathan Little, my co-supervisor. I respect your total willingness to allow your students to explore their interests and for providing the resources that allow them to do so. It is your enthusiasm to teach and general flexibility that have allowed me to explore the wonderful (and sometimes frustrating) world of the wet lab to which I owe a large portion of this thesis. To Dr. Kathleen Martin Ginis, when you agreed to take me on for my undergraduate
honour’s thesis, I had no idea just what kind of supportive, caring, and inquisitive lab group you had created. Current and former members alike, Rob, Sarah, Kendra, Delaney, Femke, Joan, Jan, Jasmin and Matt, thank you for your support over these past few years. You have helped me navigate nearly every facet of science (and even some facets of life), that have helped me develop as a researcher and person. To Mr. Tarantino, if taking 8 years to complete a Ph.D results in the kind of sage wisdom you provide, I might be signing up for one. Thanks for everything.

Last and certainly not least I would like to thank my family. To my dad Julian, thank you for the love, support, and never-ending stream of positive affirmation. To my mum Victoria, I cannot believe it has been two years. I miss you dearly and believe you would be proud of me. To my brothers Alex, Noah, and Ethan, thank you for all the love and support. These past few years have been difficult, and it has not been easy to live so far away from you all but the times I have been able to visit and spend time with you have been a some of the highlights. I am truly proud to call you all brothers.
Dedication

This thesis is dedicated to my mum. As a nurse of over 30 years, my mum had a deep desire to connect with and heal people, a desire I believe she passed on to me. As I continue to pursue the health sciences and spend my time trying to enhance the quality of life for those around me, know that I am thinking of you.
1.0 Introduction

1.1 The Spinal Cord, Anatomy

The spinal cord is a column of neural tissue that runs from the base of the skull, exiting through the foramen magnum, and terminating within the final thoracic or first few lumbar vertebrae (T12 – L2) (Kayalioglu, 2009). The spinal cord is housed within a vertebral canal, the collective space created in the center of each of the vertebrae, as well as within three layers of protective tissue referred to as the meninges. The purpose of the vertebral canal is to provide physical structure and protection to the spinal cord, while the meninges form a barrier between the spinal cord and potential pathogens and allow the collection of cerebral spinal fluid which acts to protect and nourish the spinal cord and associated nerve roots (Kayalioglu, 2009; Watson & Kayalioglu, 2009).

The primary role of the spinal cord is to relay sensory and motor information between the central and peripheral nervous systems. The central nervous system refers to all the tracts and nuclei of the brain and spinal cord while the peripheral nervous system refers to the nerves and ganglia outside of the central nervous system, including the 12 cranial nerves and all nerve roots exiting the spinal cord (Vilensky et al., 2015). Blood supply and adequate circulation are critical for the human body, and the brain and spinal cord are no different. In addition to nourishment, the clearance of waste, and the facilitation of neurotransmitter gradients, blood supply to the brain and spinal cord act to dissipate heat that may otherwise impede synaptic ability (Koizumi et al., 1954; Watson et al., 2009). In addition to the various central and radicular arteries, the anterior, or front aspect of the spinal cord is supplied blood from the anterior spinal
artery, while the posterior aspect is supplied blood from both of the posterior spinal arteries (Martirosyan et al., 2011).

1.2 Spinal Cord Injury

1.21 Spinal Cord Injury, Pathophysiology

Spinal cord injury is defined as damage or insult to the spinal cord resulting in a loss of neural connection between the brain and periphery (World Health Organization [WHO], 2013). A spinal cord injury can result from either traumatic or non-traumatic causes and be classified as either tetraplegia, damage to the cervical segments of the spinal cord, or as paraplegia, damage to the thoracic, lumbar or sacral regions of the spinal cord (McDonald & Sadowsky, 2002). Non-traumatic causes of a spinal cord injury can include degenerative, vascular, infectious, inflammatory or other disease related factors (Kretzer, 2016; McDonald & Sadowsky, 2002). Globally, the most common causes of traumatic spinal cord injury are motor vehicle accidents and falls (Kumar et al., 2018), a fact that is mirrored in Canada where, varying by age group, motor vehicle accidents and falls are responsible for approximately 35% and 31% of traumatic spinal cord injuries, respectively (Pickett et al., 2006).

1.22 Spinal Cord Injury, Classification

Traumatic spinal cord injuries can be further classified using the radiographic level of injury or the neurological level of injury. The radiographic or skeletal level signifies the level at which the spinal column has been fractured or insulted. However, SCIs are more commonly classified by their neurological level of injury, or the level at which the spinal cord ceases ‘normal’ neurological sensory and motor function (Kirshblum et al., 2011). For example, if an individual experiences a spinal cord injury and fractures the
sixth cervical vertebrae but has no 'normal' sensory perception or motor function below the level of the fourth cervical vertebrae, they would be considered to have a C6 radiographic or skeletal injury, and a C4 neurological level of injury (NLI).

Injury completeness or preserved function is tested by performing the International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI) American Spinal Injury Association (ASIA) Impairment Scale (AIS) examination (Kirshblum et al., 2011). The full grading scheme for the sensory (0 = absent to 2 = normal sensation) and motor (0 = total paralysis to 5 = normal function) test can be found in Appendix 1.

1.23 Spinal Cord Injury, Epidemiology

Incidence and Prevalence

The most recent data regarding global traumatic SCI incidence, or the number of new cases of traumatic SCI, suggests that as of 2007 there are an estimated 23 cases per million worldwide, with approximately 40 cases per million in North America (Lee et al., 2014). Global figures, however, may not be an accurate indicator of incidence for many reasons, one of which is that the lack of globally standardized methods of assessment for SCI may interfere with accurate record keeping and comparison (Singh et al., 2014). A more comparable indicator of incidence is country-specific data. As of 2010 the Canadian discharge incidence, or the number of patients who survived a traumatic SCI and were discharged from hospital, was around 41 cases per million. In comparison, the annual discharge incidence of non-traumatic SCI was around 68 cases per million (Noonan et al., 2012). These numbers, however, may be grossly
misrepresentative as individuals who succumb to their injuries prior to or during hospitalization may not be counted in the totals. This has been evidenced in Canadian epidemiological data where the inclusion of fatal traumatic SCIs increased the incidence from 41 to 52.5 cases per million people (Noonan et al., 2012). In terms of prevalence, or the number of total current cases, Noonan and colleagues (2012) estimate that as of 2010 there are an estimated 85,556 cases of SCI in Canada.

**Traumatic versus non-traumatic SCI**

In Canada, it is estimated that roughly 51% of spinal cord injuries are traumatic in origin, with an approximate median age of 35 years at time of injury (Noonan et al., 2012). However, the bimodal distribution of age-related cases varies slightly with a peak incidence of traumatic SCI highest in the 15-29-year-old age range, and a slight second increase at 45-49 years old before tapering off. Non-traumatic causes of SCI far outweigh the incidence of traumatic SCI in groups over the age of 65 (Noonan et al., 2012). As the average age of Canada's population is steadily increasing, this rise may have an effect on the overall causes of SCI. For example, falls as a cause of SCI vary across Canada from 16.5% in Manitoba (McCammon & Ethans, 2011) to 43.2% in Ontario (Pickett et al., 2006), but are expected to increase in parallel with a steadily increasing average population age (Singh et al., 2014). This trend is supported by data showing that in provinces with a higher age of SCI incidence, such as British Columbia (females, 85 y/o peak incidence) and Ontario (male & female, 70 y/o peak incidence), falls are a more common cause of injury (28.5 & 43.2%, respectively) than any other means (Lenehan et al., 2012; Pickett et al., 2006). Comparatively, in provinces where the peak age of incidence is lower such as in Manitoba (male and
female, 16-24 y/o peak incidence) and Alberta (male 20-29, female 15-19 y/o peak incidence), falls were less often the cause of injury (16.5 & 19.1%, respectively) (Dryden et al., 2003; McCammon & Ethans, 2011).

**Level of Injury & Male:Female Ratio**

In a systematic review of 44 studies, 19 studies assessed the most common level of SCI and found that globally, in all regions and cities except two (Aragon, Spain, and Stockholm, Sweden) cervical spinal cord injury, or an injury to the cervical region of the spine, was the most prevalent (Singh et al., 2014). In Canada, cervical spinal cord injury is the most common although it ranges province to province from 42% in Manitoba (McCammon & Ethans, 2011) to 61.5% in Alberta (Dryden et al., 2003). The same trend holds for British Columbia, where from 1995 to 2005, cervical SCI was most common (49.7%) followed by thoracic (27.4%) and lumbar/sacral (22.9%) injuries (Lenehan et al., 2012).

A systematic review including 23 studies assessed the male to female ratio of SCI and found that the ratio of incidence consistently favoured males (Singh et al., 2014). As noted by Singh and colleagues, this trend seems to remain true for Canada although it may vary from province to province, ranging from 1.5:1 in Ontario to 4.4:1 in and Manitoba and British Columbia.

**1.3 Spinal Cord Injury, Secondary Consequences of Injury**

An incident resulting in a SCI can be further categorized into primary and secondary injuries. The primary injury will consist of an initial impact with either transient or persistent compression to the spinal cord from surrounding structures as well as
distraction, laceration or transection to the spinal cord (Dumont et al., 2001). Although
the severity of the primary injury may determine a patient’s neurological level and
therefore be most indicative of their prognosis, it is becoming more understood how
complications associated with secondary injuries may worsen prognosis and
contribute to long term morbidity and mortality (Dumont et al., 2001).

Following the acute and subacute phase of traumatic SCI, both physiological and
psychological health complications can continue on into the chronic phase. In a study
examining Canadian healthcare utilization in a 6-year post-SCI period, both
physiological and psychological healthcare resources were utilized more often by
those with a SCI when compared to their non-spinal cord injured counterparts (Dryden
et al., 2004). The most prevalent secondary complications in this 6-year period were
urinary tract infections (47.6%), pneumonia (33.9%), and depression (27.5%) (Dryden
et al., 2004). These findings are supported by a 15-year multicentre longitudinal study
indicating that as well as physiological complaints (i.e., pain, spasticity), psychological
issues (i.e., stress, financial worry) are among the most concerning long-term worries
for individuals with a SCI (Charlfue, 2007). These issues do not seem to correlate
with age (Charlfue, 2007; Kennedy et al., 2016; Krause, 2007), indicating that
although these concerns may not get significantly worse over time, they are also
unlikely to spontaneously improve. Considering stress is one of the most common
psychological secondary complications associated with a SCI, understanding what
stress is, and how a spinal cord injury may impact stress, is an important
consideration.
1.4 Stress

1.41 What is stress?

Stress can be broadly defined as the response to a threat, either real, perceived, or expected that might alter the homeostasis of an organism. The study of physiological stress dates back to the 1930’s when Hans Selye, an endocrinologist, first noted that following exposure to adverse conditions (i.e., surgical injury, cold exposure, spinal shock), rats would develop physiological complications. Selye coined the term ‘general adaptation syndrome’, to refer to the stress response that followed, which seemed to be independent of the nature of the damaging agent (Selye, 1936).

Selye later went on to elaborate on the general adaptation syndrome theory and noted that it seemed to be comprised of three distinct phases (Selye, 1936, 1946). The first phase, named the ‘alarm’ phase, is an initial response to the stressor lasting up until about 48 hours post-stressor and characterized by a decrease in the size of immune bodies (e.g., lymph nodes, spleen, thymus), edema of the thymus, erosion of the digestive tract, and in some severe cases, necrosis of the liver. Following the initial alarm phase, a secondary phase termed the ‘resistance’ phase initiates and is characterized by a general reduction in growth hormone activity in favour of an increase in adrenal gland activity, likely due to an increased need for vigilance and arousal to combat the stressor. Finally, following anywhere between one and three months of exposure, the third phase or the ‘exhaustion phase’ occurs. This phase appears to be dependent on the severity of the insult and can be characterized by a loss of ability to resist the stressor leading to eventual illness, disease, and in some cases death (Selye, 1946). In more recent years, Selye’s original concept of stress
and the general adaptation syndrome theory have been expanded to offer a clearer picture of humans’ response to stress.

The term stress is unique in that it can refer to both the stimulus and response, the antecedent or consequence of a physiological, psychological, or environmental stressor (Gerhart et al., 1999). The lack of a clear, singular, and cohesive definition for the term stress is echoed in the way the concept of stress is researched. In the field of health research the terms ‘stress’, ‘strain’, ‘distress’, and ‘psychological distress’ have at times been used synonymously to refer to a person’s (or patient’s) state of anxiety, irritability, discomfort, or mental anguish (Ridner, 2004). Further, the term stress, as it was first used in health research, was used specifically to describe physiological processes, rather than psychological ones (Selye, 1936).

Throughout this thesis, stress will either be referred to as physiological stress or perceived stress. Perceived stress will be defined as the interaction between an individual and their environment which they appraise as threatening or overwhelming their resources in a way which will affect their wellbeing (Lazarus & Folkman, 1984). More specifically, perceived stress can be thought of as an individual’s perception that they are unable to control their lives, cope with difficulties, feel overwhelmed, taxed, nervous, and stressed (Lorenzo-Blanco & Unger, 2015). In this thesis project, we will be measuring the extent to which people with a SCI appraise situations in their life as stressful (i.e. the extent to which they perceive that the demands of life exceed their ability to cope). Physiological stress will be operationalized as the level of circulating cortisol found in participants’ plasma. Cortisol, a glucocorticoid and hormone released from the adrenal cortex, is shown to be elevated in individuals with higher levels of
perceived stress when compared to 'low-stress' individuals (Hansen et al., 2010; van Eck et al., 1996). The use of cortisol as an indicator of perceived stress, although not without its limitations, has proven to be a useful biomarker in psychobiological stress research (Hellhammer et al., 2009; Kudielka et al., 2012).

It is important to distinguish between these two definitions of stress as the oversimplification of ‘stress’ as a finite and therefore easily measurable concept may lead to research and interventions that are specific to one type of stress and not another (Kasl, 1984). For example, the nuanced definition of stress may lead to an intervention designed to reduce perceived stress being inappropriately applied to individuals experiencing post-traumatic stress disorder or psychological distress in the context of physical discomfort.

1.42 The stress response pathways (SAM and HPA axis)

It has been shown that both cerebral and peripheral mechanisms coordinate the stress response (Sapolsky, 2003). When a stressor, either real, perceived, or anticipated enters the conscious awareness of an individual, a cascade of cortical and subcortical pathways are stimulated. These pathways commence locally within the brain and continue throughout the body using metabolic, immune, neuroendocrine, and autonomic systems to signal that a stressor is present. The coordination of this response is, in part, a function of the hypothalamic-pituitary-adrenocortical (HPA) and the sympathetic adrenal medullary (SAM) axis.

When a stressor is first perceived, the amygdala, an area of the brain involved in emotional responses such as fear and stress, is stimulated by the cortex (LeDoux,
Following stimulation, the amygdala may engage one of two regions of the hypothalamus: the lateral hypothalamus, and the paraventricular nucleus of the hypothalamus. The lateral hypothalamus and associated SAM axis activate sympathetic nervous system (SNS) neurons which innervate the adrenal medulla to secrete the catecholamines epinephrine and norepinephrine. Alternatively, the parvocellular region and associated paraventricular nucleus of the hypothalamus coordinate via the HPA axis to stimulate the eventual release of glucocorticoids (i.e. cortisol) from the adrenal cortex. For this to happen, the parvocellular region of the hypothalamus is stimulated to secrete corticotropin-releasing hormone (CRH), which then stimulates the release of adrenocorticotropic-releasing hormone (ACTH) from the pituitary gland. During the stress response, both cortisol and catecholamines function to facilitate the “fight-or-flight” response for the purpose of dealing with a stressor (Lupien et al., 2009; Sapolsky, 2003).

1.43 The nervous system and stress

The human nervous system can be grossly subdivided into two main divisions, the central and peripheral nervous systems. The central nervous system, as described earlier, refers to all the tracts and nuclei of the brain and spinal cord, whereas the peripheral nervous system refers to the nerves and ganglia outside of the central nervous system and can be further broken down into the somatic and autonomic divisions of the peripheral nervous system (Vilensky et al., 2015). The somatic nervous system is responsible for the voluntary control of movement through its innervation of skeletal muscle. The autonomic nervous system, however, is responsible for the innervation of non-skeletal muscle structures (e.g., smooth muscle,
glands, effector organs). The autonomic nervous system plays an important role in the maintenance of homeostasis and the ability to respond to threats through its sympathetic and parasympathetic divisions. The parasympathetic branch of the autonomic nervous system is often referred to as the “rest and digest” branch for its ability to decrease heart rate and increase gastric motility. The sympathetic branch, colloquially termed the “fight-or-flight” division, is named such for its ability increase vigilance and prepare an individual against a threat. Some of the mechanisms by which the sympathetic nervous system might accomplish this are to increase heart rate, stimulate the secretion of glucocorticoids and catecholamines from the adrenal glands, and dilate the pupils, all responses that might aid in an individual’s ability to combat a stressor (Rea, 2015).

Following a spinal cord injury, the autonomic nervous system and its sympathetic and parasympathetic branches may be dysregulated. The autonomic nervous system receives supraspinal input from cortical centres in the brain and although the autonomic nervous system is intact following a SCI, the disconnect between these supraspinal cortical centers and autonomic nerves can lead to dysregulated autonomic nervous system activity (Garstang & Miller-Smith, 2007). This dysregulation may be evidenced by the exercise-induced catecholamine response shown in those with an autonomically complete SCI. The adrenal medulla receives sympathetic innervation from the T5-T9 spinal segments and, in those with a higher level tetraplegic injury, demonstrates a reduced (Schmid et al., 1998) or completely absent (Kouda et al., 2012) catecholamine response to volitional exercise. Of note, the reduced catecholamine response to exercise is partially mitigated when
individuals receive functional electrical stimulation to paralyzed muscles during cycle ergometry (Bloomfield et al., 1994). Taken together, these results suggest that although volitional signals may not cross the lesion and facilitate the release of catecholamines from the adrenal medulla, sympathetic fibers of the autonomic nervous system are intact and functional despite a loss of supraspinal input.

1.44 Spinal Cord Injury and Stress

Given that perceived stress is one of the most common psychological health concerns for people with a SCI, it is important to understand the potential antecedents of perceived stress following a SCI for the purpose of designing interventions aimed at alleviating stress. Early work exploring the psychosocial consequences of a SCI has postulated that increases in stress may be the result of a loss of independence (Craig et al., 1990). However, more recent work exploring the correlates of stress in long-term SCI suggest that feelings of depression, poor life satisfaction, a lack of coping skills, and poor perceived well-being were associated with stress, while feeling a lack of independence was not (Gerhart et al., 1999). Of note, much of the work assessing perceived stress following SCI has found perceived stress to be correlated with pain (Gerhart et al., 1999; Martin Ginis et al., 2003; Rintala et al., 1998). Interestingly, self-reported stress is not correlated with injury severity, but may be closely related to coping and with multiple measures of adjustment (Gerhart et al., 1999).

Once an individual with a SCI has been discharged from the hospital, they may face myriad psychosocial challenges that may increase their levels of perceived stress. The feeling of general isolation is one of these challenges (North, 1999), which may at least be partly attributable to divorce rates being significantly higher in those with a
SCI compared to age and gender-matched controls (DeVivo et al., 1995). Further, it is suggested that 12-months post-discharge, only 40% of people with a SCI are employed (Young & Murphy, 2009), and once gainful employment is secured, individuals with a SCI are significantly more likely to experience discrimination in the workplace (McMahon et al., 2005). In sum, isolation, divorce, and unemployment are just few of the reasons perceived stress may be higher in those with a SCI for reasons beyond those related to the primary injury.

In addition to both general and injury-specific stressors faced by people with a SCI, the injury itself may also influence the way in which the stress response is activated. Following a SCI, reduced sympathetic nervous system innervation has been shown to alter the function of some sympathetically innervated structures. As the HPA axis is a neuroendocrine-associated pathway and is sympathetically innervated, nervous system dysregulation such as that associated with a SCI may alter this pathway as well. In the acute phase following a SCI, cortisol has been shown to be elevated and remain so for up to 3 months post-injury. This process is thought to be mediated by pro-inflammatory cytokines which are increased following SCI and play a role in HPA axis activation (Campagnolo et al., 1999; Cruse et al., 1996). In contrast, it has been shown that in men with chronic SCI (>1-year post-injury), basal cortisol levels were significantly lower than age-matched controls without SCI (Huang et al., 1998). Further, when compared to non-injured individuals, following the administration of exogenous corticotropin-releasing hormone (CRH), there was a significantly reduced cortisol response. This reduced response, however, disappeared when the values were corrected for the initial reduced baseline values (Huang et al., 1998). These
findings suggest that although individuals with a SCI may not exhibit a ‘normal’ cortisol response to CRH in magnitude, when the reduced baseline values are taken into account, a dampened albeit accurate response is observed. Taken together, these studies demonstrate a somewhat intact ability to increase cortisol when presented with a stressor, signifying that although altered, the sympathetic nervous system may remain functional. Given the potentially preserved ability of the SNS to alter cortisol, it is important to understand how the effects of common stressors (e.g., physical activity, exercise) might differ between individuals with and without a SCI.

1.5 Physical Activity and Fitness: Defining Key Concepts

Although sometimes used synonymously, the concepts of physical activity, exercise, and leisure time physical activity refer to distinct forms of movement with their own unique psychological and physiological benefits. Quite broadly, physical activity refers to any bodily movement produced by skeletal muscle that results in energy expenditure (Caspersen et al., 1985). Physical activity can refer to activities completed in any number of an individual’s life domains such as occupational, sport, and household domains (Caspersen et al., 1985; WHO, 2020). One of the life domains in which physical activity can occur is during an individual’s leisure time. As such, this form of physical activity is termed leisure time physical activity (LTPA) and is, by definition, completed in an individual’s discretionary or free time (Bouchard et al., 2012; Physical Activity Guidelines Advisory Committee, 2008). LTPAs can vary in their intensity and setting, ranging anywhere from going for a walk to playing sports (Moore et al., 2012). Considering the potential need for adaptable physical activities for those
with a SCI, LTPAs amongst this population can include going for a wheel and gardening, to swimming or playing sports (Martin Ginis et al., 2010).

Whereas physical activity refers to any bodily movement, planned or unplanned, exercise is a subcategory of physical activity that refers specifically to bodily movement that is planned, structured, repetitive and done for the purpose of improving or maintaining components of physical fitness (Caspersen et al., 1985). Although the distinction between exercise and physical activity is subtle, understanding the difference between these forms of movement is paramount in health-related fields such as rehabilitation sciences and nursing. If one method of activity is prescribed interchangeably with another, (e.g., exercise instead of physical activity), this can lead to a behaviour change prescription that lacks detail and reproducibility and may deter from a patient’s or participant’s long-term adherence and outcomes (Dasso, 2019).

One potential outcome of exercise or physical activity is improved physical fitness, which refers to an individual’s ability to perform muscular work satisfactorily (Bouchard et al., 2012). In contrast to physical activity, however, which is related to the movements performed by individuals, physical fitness is suggested to be a set of achievable physical attributes divided into health-related and performance/skill-related components (Caspersen et al., 1985). The five health-related components of physical fitness are cardiorespiratory/cardiovascular fitness, muscular endurance, muscular strength, body composition, and flexibility, all of which are closely related to health status (Bouchard et al., 1994). Performance or skill-related components of physical fitness are less specifically defined but may be thought of as particular aspects of fitness that aid in an individual’s ability to compete in their respective sport.
Aspects of skill-related physical fitness include, but are not limited to agility, balance, coordination, speed, power, and reaction time (Bouchard et al., 2012; Caspersen et al., 1985; Pate, 1988).

One health-related aspect of physical fitness pertinent to this thesis is that of cardiovascular fitness. Cardiovascular fitness refers to the collective ability of the circulatory and respiratory systems to both supply oxygen during sustained physical activity, and to remove waste from the body once oxygen has been supplied (Farnsworth & Cannon, 2008). Cardiovascular fitness can be measured through the use of a maximal oxygen uptake, or \( \text{VO}_2\text{max} \) test. A \( \text{VO}_2\text{max} \) test measures the amount of oxygen that an individual can use in a given amount of time and can be measured in L/min as an absolute value, or in mL/kg/min taking into account an individual’s body weight. One of the defining features of a \( \text{VO}_2\text{max} \) test is that an individual achieves a plateau in oxygen consumption, indicating that an individual is circulating oxygenated blood as efficiently as possible. This limit in oxygen uptake is called a ‘plateau’, as no further increases in oxygen consumption are seen despite continual work. A similar measure of cardiovascular fitness is the \( \text{VO}_2\text{peak} \) test, or the peak oxygen consumption achieved by an individual during an exercise test. The difference between these two tests is that during the \( \text{VO}_2\text{peak} \) test, an individual will stop volitionally prior to achieving a plateau in oxygen consumption, theoretically limiting the certainty that they did in fact achieve their full \( \text{VO}_2\text{max} \). Interestingly, when comparing an individual’s \( \text{VO}_2\text{peak} \) to their \( \text{VO}_2\text{max} \) (confirmed with the presence of a plateau), research has found that values do not differ significantly between the two tests, indicating the \( \text{VO}_2\text{peak} \) test is a valid index of cardiovascular fitness (Deuster &
Heled, 2008). Given \( \dot{VO}_2 \text{peak} \) is a valid index of cardiorespiratory fitness, for the present thesis project, the measurement of \( \dot{VO}_2 \text{peak} \) will be used in place of \( \dot{VO}_2 \text{max} \). Further, current reference fitness value for individuals with a SCI utilize \( \dot{VO}_2 \text{peak} \) rather than \( \dot{VO}_2 \text{max} \) as an indication for cardiorespiratory fitness (Simmons et al., 2014).

Additionally, the use of \( \dot{VO}_2 \text{peak} \) is appropriate for use in those with a SCI as, depending on injury level and severity, upper body exercise is likely to be the method of physical activity during an exercise test. This is a consideration as oxygen uptake during a cardiopulmonary exercise test is shown to be significantly less during arm crank ergometry when compared to cycle ergometry (Orr et al., 2013), likely due to smaller muscle mass and reduced oxidative capacity of arm muscles (Muraki et al., 2004). Without use of the lower body during an arm ergometry exercise test, a \( \dot{VO}_2 \text{max} \) test would not account for lower body oxygen uptake and would therefore be misrepresentational of an individual’s true \( \dot{VO}_2 \text{max} \). Furthermore, not only is the measurement of \( \dot{VO}_2 \text{peak} \) in line with current conventions, the use of \( \dot{VO}_2 \text{peak} \) will allow the results of the present study to be easily comparable and relatable to separate studies investigating cardiorespiratory fitness in adults with a SCI.

1.51 The Effects of PA, Exercise, and Fitness on Cortisol and Perceived Stress

Cortisol

One distinction to be aware of when examining the physiological effects of exercise on cortisol is the distinction between physical activity, and physical fitness. The distinction between these two concepts may be most obvious in the time frame they
refer to. While physical activity refers to a behaviour, physical fitness refers more to a chronic or adaptive state of physical ability. This difference is important, as the cortisol response to acute physical activity behaviour can be different than the cortisol response to chronic physical activity training and adaptation.

For example, while cortisol levels have been shown to increase significantly immediately during and after a single exercise session of adequate intensity, cortisol is shown to reduce back to baseline within approximately 24 hours of the session (Rahman et al., 2010). In contrast to cortisol’s return to baseline levels following acute exercise sessions, a 12-week exercise training study of 142 healthy male adults found that basal cortisol levels were significantly increased at 6 and 12 weeks compared to baseline (Klaperski et al., 2014). In addition to the increase in basal cortisol levels, participants’ anaerobic thresholds, an indicator of endurance fitness (Ghosh, 2004), were significantly elevated at 6 and 12 weeks. A similar study was conducted comparing competitive and non-competitive able-bodied athletes’ serum and salivary cortisol responses to a maximal exercise session (Paccotti et al., 2005). Although the competitive and non-competitive athletes were similar in terms of height, weight, and training history, the competitive athletes engaged in approximately 10 more hours a week of exercise training. This study found that competitive athletes displayed significantly elevated cortisol levels both 30- and 120-minutes following exercise when compared with the non-athletes. It is not clear, however, whether the competitive athletes had elevated cortisol levels because they were more fit, or because they engaged in more exercise training which may have led to inadequate recovery and/or the accumulation of acute increases in cortisol. Nonetheless, these studies suggest
that improved fitness and/or increased exercise training may elevate both basal cortisol levels and post-exercise cortisol levels.

Not only does the cortisol response vary between acute and chronic physical activity, the effects of physical activity on cortisol vary between able-bodied individuals and those with a SCI as well (Leicht & Bishop, 2016). Studies conducted by Yamanaka et al (2010) and Kouda et al (2012) compared the cortisol responses of individuals with a cervical SCI (cSCI) to able-bodied controls following a 20-minute arm-crank ergometry test at 60% VO$_2$max. Both studies exhibited comparable baseline cortisol values between groups and a similar elevation in cortisol immediately following exercise. The similarity ended here, however, as for those with a cSCI, cortisol remained significantly elevated for up to 2-hours post-test when compared to controls.

The cortisol response to exercise has also been shown to be intensity dependent, as demonstrated in a study examining the serum cortisol levels of 389 able-bodied participants in response to moderate and vigorous intensity exercise (Hansen et al., 2010). The study found that following moderate intensity physical activity (30 minutes of cycling three times per week at 50% VO$_2$peak, no increase in serum cortisol was found, whereas following vigorous physical activity, cortisol was shown to increase. Earlier research examining the cortisol response to 30 minutes of exercise at 40, 60, and 80% VO$_2$max has also indicated that following each increase in intensity, circulating cortisol increased significantly when compared to the previous intensities (Hill et al., 2008), indicating a dose-response effect.
The exercise intensity dependent rise in cortisol has also been shown in those with a SCI. A full marathon was shown to increase basal cortisol in those with paraplegia (Furusawa et al., 1998), whereas a half marathon did not significantly increase levels of cortisol (Furusawa et al., 2003). As noted in a review by Leicht et al (2013), these findings contest work conducted by Kouda (2012), which demonstrated an increase in cortisol with as little as 20-minutes of arm crank cycle ergometry. Whereas Kouda (2012) and Yamanaka (2010) found cortisol levels to reduce to baseline 1 hour following 20-minutes of cycle ergometry at 60% \( \dot{V}O_2 \)peak, Rahman and colleagues (2010) found that following a maximal exercise test, cortisol levels were still elevated 1-hour post-test in able bodied individuals. In contrast to the elevations observed in cortisol acutely following exercise or physical activity, more prolonged exposure to physical activity may induce the opposite response. Research conducted by Wood and colleagues found that able-bodied individuals who engaged in more physical activity and who were more fit had reduced cortisol secretion in response to stressors, a phenomenon attributed to the cross-stressor adaptation hypothesis (Wood et al., 2017). Taken together, these results suggest that the cortisol response to exercise is both duration and intensity dependent and exhibits varying responses between acute and chronic physical activity stimuli.

Notwithstanding previously mentioned research exploring the relationship between acute exercise and cortisol levels in adults with SCI, there does not appear to be any work investigating the effects of overall fitness level on cortisol in those with a SCI. Although earlier work, such as that conducted by Furusawa and colleagues (1998, 2003), has explored the cortisol response in recreational athletes with SCI, without
having a control ‘untrained’ group with which to compare, it is not possible to determine the effects of physical fitness on basal cortisol levels and the cortisol response in adults with SCI.

**Perceived Stress**

Numerous psychological health benefits of physical activity have been demonstrated in both the general population and those living with a SCI. The effects of exercise on psychological stress in particular, have been demonstrated in both acute and chronic exercise studies. A single bout of exercise has been shown to improve mood, reduce sensitivity to stress, and act as a short-term antidepressant and anxiolytic in able-bodied individuals (Basso & Suzuki, 2017; Salmon, 2001). The relationship between leisure time physical activity and perceived stress has also been demonstrated, such as in work conducted by Aldana, Sutton, and Jacobson (1996) which investigated the relationship between physical activity and perceived stress in 32,229 participants. The study found that those who had more self-reported major life changes or problems, displayed certain Type A personality traits, and were less physically active reported a higher level of perceived stress than individuals who were more physically active. Although the acute beneficial effects of exercise have been shown to be short-lived, it has been suggested that these acute effects may in fact accumulate over repeated bouts and create long-term antidepressant, anxiolytic, and stress-reduction effects (Salmon, 2001). The accumulated benefit of acute exercise sessions leading to a positive adaptation is supported by research focusing on neurologically intact individuals. It has been shown that men who are more physically trained display a
significantly reduced acute cortisol response to the Trier Social Stress Test (TSST) (Kirschbaum et al., 1993)

Whereas the cortisol response to exercise appears to be intensity dependent, research indicates that even low-intensity physical activity can be beneficial for alleviating perceived stress. Rödjer and colleagues (2012) found that individuals who engage in even light leisure time physical activity, such as biking or walking, have lower levels of perceived stress when compared to inactive individuals.

To date, there are no studies exploring the relationship between acute exercise and perceived stress in people with a SCI, however one study has examined the effect of an acute exercise session on affect in those with a SCI. Work conducted by Martin Ginis and Latimer (2007) has shown that a single bout of body-weight supported treadmill training can improve feeling states in those with SCI. These findings, however, suggested that improvements in subjective well-being (SWB) were at least in part mediated by exercise-associated reductions in pain. One RCT with multiple secondary analyses explored the relationship between changes physical activity and perceived stress in those with a SCI. The RCT (Hicks et al., 2003) demonstrated that following 3 months of exercising twice per week, individuals with a SCI reported less stress, pain, and depression while also reporting improved overall quality of life and physical self-concept when compared to a control group. Secondary analyses of this RCT indicated that changes in quality of life and psychological well-being were mediated by changes in perceived stress and pain (Martin Ginis et al., 2003; Latimer et al., 2004). Three months following completion of the RCT, individuals that maintained adherence to exercise reported significantly lower levels of stress and pain.
compared with those with poorer adherence rates (Ditor et al., 2003). This
aforementioned body of evidence suggests that physical activity can improve
numerous aspects of subjective well-being, including perceived stress, among people
with a SCI. It is not clear, however, how these variables are related.

1.52 Potential explanations for relationships between Perceived Stress,
Cortisol, and Physical Activity/Physical Fitness

Seemingly contradictory evidence exists pertaining to the relationships between
cortisol, perceived stress, and physical activity/physical fitness. Whereas individuals
with elevated levels of perceived stress appear to have elevated levels of circulating
cortisol (Hansen et al., 2010; van Eck et al., 1996), individuals with increased physical
fitness appear to also have elevated basal cortisol (Ghosh, 2004), but demonstrate
reduced levels of perceived stress (Stults-Kolehmainen & Sinha, 2014). Some
researchers have attempted to explain the complicated relationship between stress,
cortisol, and PA/physical fitness. Explanations have ranged from purely physiological
explanations to more psychological-focused reasons.

The physiological explanation put forth by Nieman (Nieman, 1991), is that enhanced
cardiovascular fitness reduces circulating catecholamines and other hormones
associated with stress. Although interesting, this explanation will not be used as a
basis for formulating the thesis hypothesis for two reasons: 1) Conflicting literature
has shown basal cortisol to both increase and decrease with chronic exercise training,
offering only partial support for Nieman’s explanation, and 2) given the significance of
perceived stress in the present thesis and the lack of psychologically-relevant
variables in this purely physiological explanation, Nieman’s explanation offers little
insight into the nature of the often bidirectional and mutually dependent physiological and psychological outcomes.

One explanation with potential relevance to this thesis is Hansen et al’s (2010) psycho-physiological framework used to explore the relationship between LTPA, perceived stress, and salivary cortisol. Although Hansen’s psycho-physiological model suggests that physical activity influences perceived stress, it fails to include the reciprocal ways in which these variables may influence each other. For example, a literature review of 55 studies investigating the effects of stress on physical activity found that in addition to physical activity mitigating stress, increased stress can reduce one’s ability to become physically active (Stults-Kolehmainen & Sinha, 2014).

Alternatively, the Chronic Pain Processing Model (Gatchel, 1996) (Figure 1), proposes that a cyclical relationship exists between physical changes, emotional changes, and changes in stress and tension. Understanding exercise as a means to initiate ‘physical changes’, the Chronic Pain Processing Models suggest that reduced levels of LTPA negatively affect physical functioning, which in turn affect stress. As applied to the SCI context, the model suggests that physical changes associated with a SCI may result in increased levels of pain. As a result of increased pain, psychophysiological stress and tension increase, resulting in heightened states of emotional distress. These emotional changes, having altered one’s ability to engage in their activities of daily living (ADL), are suggested to ultimately be responsible for further reductions in activity and physical functioning, continuing the cycle of pain.
Latimer and colleagues (2004) explored whether this cycle could be reversed in people with a SCI, using exercise to reduce one aspect of the triad (i.e., perceptions of pain), which in turn might affect an individual’s emotion. Consistent with the Chronic Pain Process Model, Latimer et al (2004) found that following a 9-month exercise intervention, changes in perceived pain mediated changes in perceived stress which in turn mediated changes in emotional outcomes (e.g., depression). In agreement with these findings, additional work conducted by Martin Ginis et al (Ginis et al., 2003) found that decreased pain as a result of exercise training can decrease stress.

**Figure 1.** The Chronic Pain Processing Model (Gatchel, 1996). Adapted from (Hoffman & Hoffman, 2007).

Given its interpretation of psychological and physiological variables, and demonstrated applicability in the SCI context, the Chronic Pain Processing Model will be used to formulate the thesis hypotheses.
2.0 Summary and Significance

2.1 Addressing the Gap

Although research involving able-bodied individuals has explored the relationship between cardiorespiratory fitness, cortisol, perceived stress, and physical activity, limited research has investigated these relationships in those with a SCI. Studies have explored the relationship between two of these variables (e.g. perceived stress and physical activity, or physical activity and cortisol), however there is currently no research exploring the relationship between perceived stress, cortisol, physical activity and cardiorespiratory fitness in individuals with a SCI.

Further, given the anatomical and psychosocial differences between these two populations, we cannot assume that the pattern of findings in able-bodied individuals will hold true for those with a SCI. One reason for this is that individuals with a SCI are known to have altered SNS innervation, including altered HPA-associated afferents which may blunt an appropriate exercise-induced cortisol response (Allison & Ditor, 2015). Due to SNS disruption following SCI, it is not known whether people with SCI show the same correlations between fitness, perceived stress, and circulating levels of cortisol that have been shown in people without SCI. Understanding these relationships is important for determining if exercise can be an effective stress-reduction strategy in people with SCI.

This study will bridge a gap in knowledge regarding relationships between perceived stress, fitness, physical activity and cortisol in people with a SCI. The results of this work could have clinical implications by identifying the potential for non-
pharmaceutical methods (i.e., physical activity) to reduce stress in adults with SCI. A stress reducing intervention could be hugely beneficial given people with a SCI experience significant psychological stress and prolonged exposure to stress is known to be immunosuppressive (Khansari et al., 1990). Such effects may compound in a population that already deals with injury-related immunosuppression and immune dysregulation (Allison & Ditor, 2015).

2.2 Purpose
The purpose of this study is to determine if physical activity levels and cardiorespiratory fitness are related to psychological (i.e., perceived) and physiological (i.e., circulating cortisol) stress in adults with chronic SCI.

2.3 Hypothesis
It is hypothesized that congruent with current literature examining physical activity, fitness, and perceived stress and predictions described in the Chronic Pain Processing Model, that 1) physical activity levels and cardiorespiratory fitness will negatively correlate with levels of perceived stress, 2) and LTPA and cardiorespiratory fitness will negatively correlate with levels of circulating cortisol, such that individuals who have higher cardiorespiratory fitness and engage in more LTPA will experience lower perceived stress and lower levels of circulating cortisol. Given the known mediators between physical activity and perceived stress, it is expected that upon further analysis additional factors not explored in the present thesis will explain a significant amount of variation in perceived stress or circulating cortisol.
3.0 Methods

3.1 Participants

Participants were 9 individuals (M=18.4 years post-injury, M=46.4 years old, 9 male) with chronic SCI. Individual demographics can be found in Table 1. Participants were recruited using a combination of word-of-mouth as well as reaching out to participants who, in the past, had agreed to be contacted in the future should any research opportunities arise.

To be included in this study, participants had to: 1) have been diagnosed with a spinal cord injury more than 1 year ago, 2) have an injury level at C3 or below, 3) have an arm vein that could accommodate multiple venipunctures, 4) experience chronic pain, 5) experience neuropathic or musculoskeletal pain, and 6) have no medical contraindications to performing a maximal exercise test. Further, as this study was part of a larger randomized controlled trial testing the effects of exercise on pain (NCT04160858), all individuals had to participate in less than 40 min/week of structured, moderate intensity, aerobic exercise and less than 2 bouts/week of strength training, (i.e. less than the minimum recommended by the SCI Exercise Guidelines (Martin Ginis et al., 2018).

Participants were excluded if they 1) had chronic pain with exclusively non-musculoskeletal or non-neurological origins, 2) could not perform upper-body exercise due to limited diaphragmatic control and/or reduced arm functioning, 3) lived beyond driving distance of the research site (Vancouver or Okanagan centres), 4) could not read, write, or orally communicate in English, 5) had been previously told they have
had a cognitive or memory impairment, 6) were pregnant, or 7) were an in-patient at a hospital at the time of enrollment. Further enrollment criteria can be found in appendix 1. For transparency and reproducibility, further information pertaining to the larger randomized controlled trial can be retrieved through Open Science Framework (EPIC-SCI Trial. Retrieved from osf.io/m5xtu).

Table 1. Participant characteristics

<table>
<thead>
<tr>
<th>Baseline Characteristic</th>
<th>Paraplegia (n = 5; 5 male)</th>
<th>Tetraplegia (n = 4; 4 male)</th>
<th>Total (n = 9; 9 male)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>44 ± 10.2</td>
<td>49.5 ± 12.9</td>
<td>46.4 ± 11.1</td>
</tr>
<tr>
<td>Time Since Injury (years)</td>
<td>13.8 ± 2.3</td>
<td>24.1 ± 8.4</td>
<td>18.4 ± 7.6</td>
</tr>
<tr>
<td>Cause of Injury (number)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vehicle Related</td>
<td>5</td>
<td></td>
<td>5</td>
</tr>
<tr>
<td>Sport</td>
<td>3</td>
<td></td>
<td>3</td>
</tr>
<tr>
<td>Disease</td>
<td>1</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Participant</td>
<td>Neurological Level of Injury</td>
<td>AIS</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>T7</td>
<td>A</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>T4</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>C5</td>
<td>A</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>C5-6</td>
<td>D*</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>T6-7</td>
<td>A*</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>T4</td>
<td>A*</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>C6-7</td>
<td>A*</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>T12-L1</td>
<td>B*</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>C6-7</td>
<td>B*</td>
<td></td>
</tr>
</tbody>
</table>

Values as mean ± SD
n – number
AIS – ASIA Impairment Scale (AIS-A=motor/sensory complete, AIS-B=motor complete/sensory incomplete, AIS-C=motor incomplete (<half of muscles function below NLI), AIS-D=motor incomplete (>half of muscles function below NLI, AIS=normal sensory and motor score)
* – The participant was unaware of their official ISNCSCLI-AIS grade and a proxy measure was used. The specifics of this protocol are described in detail below.

3.2 Protocol Overview

Prior to enrollment in the study, participants were first invited to engage in an initial screening and familiarization session. This session occurred over the phone or
through videoconferencing software for the purpose of explaining and discussing the informed consent and study procedures. If the participant agreed that they had read and understood the informed consent form, provided consent, and they met study inclusion/exclusion criteria, they were officially enrolled as participants. Once participants were enrolled, they were invited to UBC Okanagan for a single visit to complete a baseline testing session. Prior to the in-person visit, participants were asked to not consume any anti-inflammatory medicine, and not to consume any food or drink (with the exception of water) for 12 hours so that a fasted blood sample could be taken. At the in-person session participants completed the demographics questionnaire (e.g., age, ethnicity, AIS classification, proxy AIS classification, time since injury, mechanism of injury, health complications experienced, etc.).

If participants were not aware of their clinically-determined AIS classification, they were asked which of the following definitions best describes them: 1) No feeling or movement below the level of injury, 2) feeling all the way down to your rectum/bum but no use of muscles, 3) Limited movement or muscle contractions below level of injury but these serve no useful function, 4) Functional, but not necessarily full use of at least half of the muscle groups below the level of the injury, or 5) Feeling and movement is normal below the level of injury. These responses are meant to correspond with AIS grades such that 1=A, 2=B, 3=C, 4=D, and 5=E. These proxy scores are recorded in the participant demographics table (Table 1) with an asterisk next to the grade to denote the use of a proxy measure rather than the official AIS grading system.
An additional battery of questionnaires was administered on a tablet, through REDCap as part of the larger RCT (NCT04160858), however they are beyond the scope of this thesis and will not be discussed further, except for the measure of perceived stress (see 3.23). If participants had difficulty completing these questionnaires for any reason (e.g., lack of sufficient hand dexterity), a team member present would aid participants in completing the questionnaire(s).

As part of the larger RCT, and following the completion of the questionnaires, an additional interview was conducted that aimed to further probe the specific type(s) of pain the participant experienced. This was done through use of the International Spinal Cord Injury Pain Basic Data Set (v2.0) which asks about the interreference of different pain types (i.e., musculoskeletal, neuropathic pain), as well as their relative intensities and location. Upon completing the questionnaires and interviews, the physiological and biometric testing began. This testing was composed of a single blood draw, body weight measurements, pressure response test, maximal strength tests, and a peak aerobic exercise test. The pressure response test and maximal strength tests were conducted for the larger RCT and will not be described further.

3.21 Blood Collection

Blood samples were taken by a trained phlebotomist from participants’ antecubital vein into an Ethylenediaminetetraacetic acid (EDTA) coated vacutainer. Two EDTA lined tubes were collected and immediately following collection, blood samples were moved to an adjacent wet lab on the same campus. The samples were then centrifuged at 2000g and 5°C for 5 minutes before plasma was aliquoted into four 200
μL tubules and stored in a -80°C freezer until the cortisol assay was ready to be completed.

3.22 Cortisol Assay Protocol

Plasma samples were removed from the -80°C freezer and levels of total circulating cortisol were assessed in triplicate using an enzyme-linked immunosorbent assay (ELISA) kit (ab108665, Lot:GR3340194-2) from Abcam (Cambridge, United Kingdom). The complete Abcam cortisol ELISA protocol can be found in Appendix 2.

An important consideration to make when measuring serum cortisol is that of the diurnal variation seen to occur in cortisol levels. As per clinical guidelines (Pagana & Pagana, 2014), as well as guidelines set forth by the SOP that accompanied our cortisol assay (Abcam, 2018), typical values for total cortisol in adults range diurnally from a peaking at 60-230 ng/ml at 8-10am, to a low point of approximately 30-150 ng/ml at around 4 pm. An important consideration when analyzing cortisol is that samples taken around 4pm will typically be one to two thirds of the morning level and levels typically considered ‘normal’ in the morning can actually be clinically significant if they are observed in the afternoon.

Interestingly, in a study examining daily stressors and salivary cortisol in adults with SCI, no significant differences were seen in cortisol levels with respect to diurnal variation between those with SCI and controls, indicating that diurnal variation is similar between groups (Kalpakjian et al., 2009). That study, however, pooled people with paraplegia (n=12) and tetraplegia (n=13) together, not accounting for injury level or completeness. A more recent study conducted by Fatima and colleagues (2016)
examined the circadian variations in cortisol between those with a cervical SCI (cSCI; i.e., tetraplegia) compared to able-bodied controls. When comparing these groups, it was found that individuals with a cSCI had significantly higher evening and nighttime cortisol levels when compared to controls, indicating that diurnal variation of cortisol may in fact be injury-level dependent. Given the heterogeneity, lack of clinically determined AIS classification, and size of our sample, it was not feasible to separate participants based on injury completeness. In an attempt to mitigate the diurnal variation seen in circulating cortisol, all participants had blood samples taken in the late morning.

### 3.23 Perceived Stress Scale
Perceived stress was measured using the Perceived Stress Scale (PSS) (Cohen et al., 1983). The PSS (attached in appendix 1) consists of 10 questions designed to measure the level of stress an individual perceives they have experienced over the last month. Once asked a question, the respondent provides an answer between 0 and 4, 0 being ‘never’ and 4 being ‘very often’, indicating how often they have felt a certain way. For example, question 3 asks “In the last month, how often have you felt nervous and stressed?”. If the respondent answered ‘0’, it would indicate that in the last month they never felt nervous and stressed. Other response options are 1=almost never, 2=sometimes, and 3=fairly often. Of note, items 4, 5, 7, and 8 are positively worded questions and therefore needed to be reverse scored before the final score is added up. To reverse the score, the respondent’s score is replaced with the number at the opposite end of the scale such that 0=4, 1=3, and 2=2. Once these 4 positively worded items have been reversed, item responses are summed up to produce a total
score. A higher score on the perceived stress scale indicates greater stress. Perceived stress scale normative values for a sample of 2,387 respondents in the United States indicates that on average, males have a mean and standard deviation perceived stress scale score of 12.1 ± 5.9 (Cohen et al., 1994).

A systematic literature search of 19 articles related to evaluating psychometric properties of the PSS found it to have well reported reliability, factorial validity, and hypothesis validity in numerous fields and subfields of health sciences (Lee, 2012). In the present study, Cronbach’s alpha for the 10 item Perceived Stress Scale was .763, constituting acceptable internal consistency within the questionnaire (Field, 2013; Tavakol & Dennick, 2011). A Cronbach’s alpha value of below .6 is suggested to display poor internal consistency whereas a Cronbach’s alpha value of greater than .9 may suggest redundancy in some of the items on a scale (Streiner, 2003).

**3.24 Leisure time Physical Activity Questionnaire**

Participants reported their physical activity levels using the validated leisure time physical activity questionnaire for individuals with a SCI (LTPAQ-SCI) (Martin Ginis et al., 2012). The LTPAQ-SCI assesses the duration (minutes) and frequency (times/week) of participants’ mild, moderate, and heavy intensity leisure time physical activity over the past week. Prior to completing the questionnaire participants were given SCI-specific definitions and examples of mild, moderate, and heavy intensity leisure time physical activity.

Mild intensity LTPA was defined as requiring very light physical effort and includes activities that make the participant feel like they are working a little bit but can keep
doing the activity for a long time without getting tired. Moderate intensity exercise was described as requiring some physical effort that make the participant feel they are working somewhat hard but can keep doing the activity for a while without getting tired. Lastly, heavy intensity exercise was defined as exercise that requires a lot of physical effort. This type of exercise should make participants feel like they are working really hard, almost at their maximum, and cannot do these activities for very long without getting tired as they are exhausting (Martin Ginis & Latimer, 2007).

Total minutes of mild, moderate, and heavy LTPA were calculated by multiplying the frequency of physical activity (sessions/week) by the duration (minutes/session) for each intensity. For example, if a participant engaged in 30 minutes of moderate LTPA three times per week they would accrue 90 minutes of moderate LTPA per week. The sum of the mild, moderate, and heavy minutes of physical activity for each participant was used for the purpose of this study to derive a ‘total LTPA’ value for each participant (minutes/week). Total LTPA was calculated as, given the relatively small sample size, it was anticipated that the variety of physical activity intensities the participants engaged in (e.g., significant amounts of heavy but no mild intensity LTPA) might create bi-, or even trimodal distributions, rendering the data nearly uninterpretable. Therefore, to maximize statistical power physical activity, total LTPA was calculated, however, individual minutes a week of all LTPA intensities were recorded and can be found in Table 2.

3.25 Cardiorespiratory fitness testing
Cardiorespiratory fitness was measured using a graded \( \dot{V}O_{2\text{peak}} \) test on a wall-mounted LODE Angio CPET arm crank ergometer (LODE, Groningen, the
Netherlands). The graded VO$_2$peak test began with a load of 10 watts for those with paraplegia and 2 watts for people with tetraplegia and increased 10 and 2 watts every minute, respectively. Inspired and expired gases as well as oxygen consumption in L/min and ml/kg/min as well as the respiratory exchange ratio (RER) were calculated using a metabolic cart (TrueOne 2400, Parvo Medics Salt Lake City, Utah, USA). Heart rate was recorded using a Polar FT1 watch and accompanying Polar H10 heart rate sensor (Polar, Kempele, Finland).

Data recorded from 12 studies has proposed reference fitness values for individuals with a SCI (Simmons et al., 2014). These values include VO$_2$peak (L/min) and suggests that for those with tetraplegia a value of 0.39-0.64 L/min is ‘fair’, 0.65-0.81 L/min is ‘average’ 0.82-1.02 L/min is ‘good’, and >1.02 L/min is ‘excellent’. These reference values also suggest that for those with paraplegia a value of 1.06-1.27 L/min is ‘fair’, 1.28-1.41 L/min is ‘average’, 1.42-1.69 L/min is ‘good’, and a value above 1.68 L/min is ‘excellent’.

3.3 Statistical Analysis

3.3.1 Data Cleaning and Treatment

All data cleaning, treatment, and statistical analysis were run using IBM SPSS version 27 (SPSS Inc., Chicago, IL.). One participant (P3) was missing data for VO$_2$peak and cortisol concentration. These data points were not replaced, and the participant’s data were removed from further analysis as the participant’s completeness of injury, a variable that might influence VO$_2$peak and cortisol, was unknown and therefore the missing value cannot be accurately predicted. Participant 3 did, however, complete the perceived stress scale and LTPAQ-SCI so these measures were included in
further analysis. The time since injury for participant 7 was a potential outlier (35.92 years, $z=2.30$), so in line with current outlier management methods (Field, 2013), this value was replaced with a value of 1 year below the next highest value (24 years post-injury). Participants’ $\dot{V}O_2$peak values were standardized for injury level (para/tetra) by transforming to standardized $z$-scores. $\dot{V}O_2$peak values are known to be significantly higher for those with paraplegia versus those with tetraplegia (Simmons et al., 2014). Transforming the data to standardized $z$-scores allows us to better normalize the distribution rather than having bimodal distribution for $\dot{V}O_2$peak.

3.32 Descriptive Statistics, Assumption Testing

Descriptive statistics for all variables were calculated including the mean, standard deviation, minimum and maximum values, skewness and kurtosis, and range. For bivariate Pearson correlations, the assumptions of continuous variables, normal distribution, no outliers, and a linear relationship were tested before running the analyses. Concerning the standard linear regressions, the assumptions of linearity, independent errors, homoscedasticity, and normally distributed errors were all tested after computing the models. The assumptions concerning linear regressions were tested following model computations as in order to test the residuals, the residuals must first be identified by the model.

3.33 Statistical Significance and effect sizes

For all analyses, the alpha was set for $p<0.05$. Alpha was not adjusted for multiple correlations as a priori hypotheses were used for all correlations. Given the small $n$, and low power, we also interpreted correlations in terms of effect size. The magnitude
of the correlations were interpreted in accordance with Cohen’s conventions for small (≥.1), medium (≥.3), and large (≥.5) correlations (Cohen, 1992).

3.34 Testing covariates

Previous research has shown that aging is commonly associated with declines in leisure time physical activity and measures of fitness, such as \( \dot{V}O_2 \text{peak} \), which is estimated to reduce approximately 10% per decade (Hagberg, 1987; Ogawa et al., 1992). Whether regular aerobic activity can mitigate the age-related decline in \( \dot{V}O_2 \text{peak} \) remains unclear. Some cross-sectional (Ogawa et al., 1992) and longitudinal studies (Katzel et al., 2001) demonstrate an attenuated loss of peak \( \dot{V}O_2 \text{max} \) in older adults who regularly exercise versus their sedentary counterparts. Conversely, a meta-analysis of 242 studies exploring the relationship between the age-associated decline in \( \dot{V}O_2 \text{max} \) and training status found that there were no statistical differences in age-associated reductions in aerobic capacity for sedentary, active, and endurance trained individuals (Wilson & Tanaka, 2000). Given that the effect of aging on \( \dot{V}O_2 \text{peak} \) and physical activity is currently unknown, prior to running linear regression models, an exploratory bivariate correlation was run to determine if either age or time since injury were significantly correlated with \( \dot{V}O_2 \text{peak} \) or leisure time physical activity (LTPA) minutes.

3.35 Regression analysis

Standard linear regressions were conducted to determine whether total minutes of leisure time physical activity and \( \dot{V}O_2 \text{peak} \) predicted levels of perceived stress and total circulating cortisol.
4.0 Results

Individual participant values and descriptive statistics for each variable can be found in Table 2. Participants with tetraplegia had a mean \( \dot{V}O_2 \text{peak} \) of \( 0.93 \pm 0.22 \) L/min, indicating they had a ‘good’ \( \dot{V}O_2 \text{peak} \) (Simmons et al., 2014). Participants with paraplegia had a mean \( \dot{V}O_2 \text{peak} \) of \( 1.4 \pm 0.25 \) L/min, indicating they had a ‘average’ \( \dot{V}O_2 \text{peak} \).

In regard to cortisol levels, participants had an average total cortisol level of \( 141.48 \pm 57.06 \) ng/ml, which coincides with current clinical guidelines for ‘normal’ total cortisol values in adults (Pagana & Pagana, 2014). Further, given that all the blood samples were collected around noon, none of our participants appear to have cortisol levels outside of what is to be expected at that time (Fatima et al., 2016). Additionally, the average coefficient of variability (CV) for the present cortisol ELISA was 4.3%, well below the manufacturers limit of 9% (Abcam, 2018).

Based on normative values of perceived stress in males (12.1 ± 5.9), as suggested by Cohen et al (1994), participants do not have an elevated level of perceived stress (11.22 ± 3.83).

Concerning LTPA, participants engaged in an average of 59.38 ± 82.57 minutes of mild, 40 ± 57.66 minutes of moderate, and 26.67 ± 52.92 minutes of heavy leisure time physical activity a week. In regard to total minutes of LTPA, participants engaged in 119.44 ± 110.81 minutes LTPA. Currently, no published reference values exist suggesting what duration and intensity of LTPA is ‘average’ for people with a SCI.
Table 2. Participants’ VO₂peak, circulating cortisol, perceived stress, and activity levels.

<table>
<thead>
<tr>
<th>Participant</th>
<th>VO₂peak (L/min)</th>
<th>Circulating Cortisol (ng/ml)</th>
<th>Perceived Stress (PSS)</th>
<th>LTPAQ-SCI PA (minutes/week)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Mild</td>
</tr>
<tr>
<td>1</td>
<td>1.08</td>
<td>130.233</td>
<td>10</td>
<td>180</td>
</tr>
<tr>
<td>2</td>
<td>1.68</td>
<td>145.896</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>-</td>
<td>-</td>
<td>16</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>1.08</td>
<td>63.522</td>
<td>7</td>
<td>180</td>
</tr>
<tr>
<td>5</td>
<td>1.88</td>
<td>123.104</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>1.54</td>
<td>193.337</td>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>0.68</td>
<td>230.48</td>
<td>9</td>
<td>10</td>
</tr>
<tr>
<td>8</td>
<td>1.53</td>
<td>73.088</td>
<td>18</td>
<td>105</td>
</tr>
<tr>
<td>9</td>
<td>1.03</td>
<td>172.201</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>1.22 ± 0.33</td>
<td>141.48 ± 57.06</td>
<td>11.22 ± 3.83</td>
<td>59.38 ± 82.57</td>
</tr>
</tbody>
</table>

L/min – Litres of oxygen per minute
ng/ml – nanogram of cortisol per millilitre of sample
PSS – Perceived Stress Scale

4.1 Correlations

Correlation matrices for all variables can be found in Table 3. Concerning the assumptions of bivariate correlations, all the variables were measured on interval or ratio scale, so the assumption of continuous variables was met. For all variables except for time since injury and LTPA, which displayed a significant Shapiro-Wilk test of normality (p=0.043 and p=0.012, respectively), the assumption of normal distribution appears to have been met. A Log10 transformation was computed on time since injury and LTPA to improve normality, however no improvement was made. A histogram plot of the bimodal distribution of total LTPA can been seen in appendix 1.

4.11 Correlations between cortisol and perceived stress, total LTPA and VO₂peak

Perceived stress, total minutes of LTPA, and VO₂peak were all negatively correlated with cortisol concentration. The correlations between perceived stress and cortisol (r
= -.407), as well as total minutes of LTPA and cortisol (r = -.475) were medium-large. A medium-sized negative correlation was observed between \( \dot{V}O_{2\text{peak}} \) and cortisol (-.306). Small negative correlations were observed between perceived stress and \( \dot{V}O_{2\text{peak}} \) (r = -.076), and perceived stress and total LTPA (r = -.187).

4.12 Hypothesis 1: physical activity levels and cardiorespiratory fitness will negatively correlate with levels of perceived stress

This hypothesis received partial support. \( \dot{V}O_{2\text{peak}} \), an index of cardiorespiratory fitness, was only trivially negatively correlated with perceived stress (r = -.076). However, a small negative correlation was observed between total LTPA, and perceived stress (r = -.187), indicating that individuals who reported more LTPA also reported lower levels of perceived stress.

4.13 Hypothesis 2: physical activity levels and cardiorespiratory fitness will negatively correlate with levels of circulating cortisol

This hypothesis was supported. Both \( \dot{V}O_{2\text{peak}} \) (r = -.306) and total LTPA (r = -.475) demonstrated a medium-large negative correlation with levels of cortisol, suggesting that individuals with higher fitness and more minutes of total LTPA exhibited lower levels of circulating cortisol.

4.2 Results of covariate testing

Results of covariate tests are in Table 3. The only variable positively correlated with cortisol was time since injury, which displayed a medium-sized positive correlation (r = .377). Additionally, there was a large negative correlation between age and cortisol (r = -502). The correlations between perceived stress and age (r = -.076), and time
since injury and age \((r = 0.040)\) were trivial-small. Time since injury displayed a negligible negative correlation with \(\dot{V}O_2\text{peak} \quad (r = -0.003)\) and age \((r = -0.020)\). A large, negative correlation was observed between age and \(\dot{V}O_2\text{peak} \quad (r = -0.534)\). A positive medium-large correlation was observed between total LTPA and \(\dot{V}O_2\text{peak} \quad (r = 0.498)\), whereas a small negative correlation was observed between total LTPA and time since injury \((r = -0.103)\). An inconsequential positive correlation was observed between total LTPA and age \((r = 0.087)\). Despite some medium-large effect sizes between variables, no correlations exhibited statistical significance of \(p<0.05\), therefore no variables were entered as covariates in the following linear regressions.

### Table 3

<table>
<thead>
<tr>
<th>Measure</th>
<th>Cortisol concentration</th>
<th>Perceived Stress</th>
<th>Total LTPA</th>
<th>Time since injury</th>
<th>Age</th>
<th>(\dot{V}O_2\text{peak} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cortisol Concentration</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Perceived Stress</td>
<td>-0.407</td>
<td>-0.187</td>
<td>-</td>
<td>-</td>
<td>-020</td>
<td>-0.534</td>
</tr>
<tr>
<td>Total LTPA</td>
<td>-0.475</td>
<td>-0.076</td>
<td>0.087</td>
<td>-0.103</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Time since injury</td>
<td>0.377</td>
<td>0.040</td>
<td>-0.103</td>
<td>-</td>
<td>-</td>
<td>-0.020</td>
</tr>
<tr>
<td>Age</td>
<td>-0.502</td>
<td>-0.076</td>
<td>0.498</td>
<td>-0.03</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>(\dot{V}O_2\text{peak} )</td>
<td>-0.306</td>
<td>-0.076</td>
<td>0.498</td>
<td>-0.534</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>

\(\dot{V}O_2\text{peak}\) is a measure of aerobic fitness and refers to the peak amount of oxygen an individual can uptake in a minute (L/min), LTPAQ-SCI is the Leisure time physical activity Questionnaire for Spinal cord Injury. All correlations exhibited an alpha of \(p>0.05\).

### 4.3 Regressions

#### 4.3.1 Predicting Levels of Perceived Stress

A standard linear regression was conducted to determine whether a participant’s \(\dot{V}O_2\text{peak} \) predicted levels of perceived stress. The results suggest a negligible, non-significant negative relationship between the two variables \((\beta = -0.076, t = -0.186, p =\)
A standard linear regression was conducted to determine whether a participant’s minutes of LTPA predicted levels of perceived stress. The results suggest a small, nonsignificant negative relationship between the two variables ($\beta = -0.187$, $t = -0.502$, $p = 0.631$), and 10.3% ($R^2 = .103$) of the variance in perceived stress was explained by LTPA ($F(1,7) = 0.252$, $p = 0.631$).

A forced entry multiple linear regression was conducted to determine whether a participant’s minutes of LTPA in combination with $\dot{V}O_2$peak predicted levels of perceived stress. The results suggest a small, nonsignificant negative relationship between LTPA and perceived stress ($\beta = -0.198$, $t = -0.391$, $p = 0.712$), and a nonsignificant trivial relationship between $\dot{V}O_2$peak and perceived stress ($\beta = 0.023$, $t = 0.045$, $p = 0.966$), and 3.5% ($R^2 = .035$) of the variance in perceived stress is explained by LTPA and $\dot{V}O_2$peak ($F(2,5) = 0.091$, $p = .914$).

### 4.32 Predicting Levels of Cortisol

A standard linear regression was conducted to determine whether a participant’s $\dot{V}O_2$peak predicted levels of circulating cortisol. The results suggest a medium-sized, nonsignificant negative correlation between the two variables ($\beta = -0.306$, $t = -0.787$, $p = .461$) and 5.7% ($R^2 = -0.057$) of the variance in circulating cortisol was explained by $\dot{V}O_2$peak ($F(1,6) = 0.620$, $p = 0.461$).

A standard linear regression was conducted to determine whether a participant’s minutes of leisure time physical activity (LTPA) predicted levels of circulating cortisol.
The results suggest a medium-large, nonsignificant negative correlation between the two variables ($\beta = -0.475$, $t=-1.322$, $p = 0.234$) and 9.6% ($R^2=.096$) of the variance in cortisol was explained by LTPA ($F(1,6) = 1.747$, $p = 0.234$).

A forced entry multiple linear regression was conducted to determine whether a participant’s minutes of LTPA in combination with $\dot{V}O_2$ peak predicted levels of circulating cortisol. The results suggest a medium-large, nonsignificant negative relationship between LTPA and cortisol ($\beta = -0.429$, $t=-.949$, $p = 0.386$), and a small nonsignificant relationship between $\dot{V}O_2$ peak and cortisol ($\beta = -0.092$, $t=-.204$, $p = 0.846$), and 23.2 % ($R^2=.232$) of the variance in cortisol was explained by LTPA and $\dot{V}O_2$ peak ($F(2,5) = .755$, $p = .517$).

**4.33 Regression Assumption Testing**

The four assumptions of standard linear regressions (linearity, independent errors, homoscedasticity, and normally distributed errors) were all tested. When plotted on a probability-probability (P-P) regression standardized graph, all residuals appeared to be linearly distributed thereby meeting the first assumption. A Durbin-Watson value of between 0-4 was achieved for linear regression between perceived stress and LTPA (3.0), perceived stress and $\dot{V}O_2$ peak (2.81), cortisol and LTPA (2.27), and cortisol and $\dot{V}O_2$ peak (2.29), suggesting the assumption of independent errors has been met. A line of best fit with a near zero slope on the standardized residuals graph indicate that the data appear to be homoscedastic, meeting this assumption. Concerning the final assumption of standard linear regressions, normality, cortisol, perceived stress, and $\dot{V}O_2$ peak appear to be normally distributed whereas LTPA exhibits a bimodal, non-
normal distribution. As described earlier, no transformations were able to rectify this and a histogram plot of LTPA can be seen in appendix 1.

In addition to the assumptions of standard linear regressions (i.e., linearity, independent errors, homoscedasticity, and normally distributed errors), multiple linear regressions must also meet the assumptions of multicollinearity, or assessing whether the predictor variables share a strong correlation with each other. The assumption of multicollinearity appears to have been met as a variance inflation factor (VIF) value of .752 and a tolerance statistic of 1.33 are within acceptable ranges (Bowerman & O’connell, 1990; Menard, 1995).
5.0 Discussion

The purpose of this study was to determine if physical activity levels and cardiorespiratory fitness were related to psychological (i.e., perceived) and physiological (i.e., circulating cortisol) stress in adults with a chronic SCI. Data from nine participants, recruited for the EPIC-SCI trial, were used to test these relationships. Perceived stress and minutes of leisure time physical activity (LTPA) were measured using validated questionnaires, cardiorespiratory fitness was measured using a \( \dot{V}O_2 \) peak test, and levels of circulating cortisol were measured via a venous blood sample. In general, it was found that LTPA and cardiorespiratory (CR) fitness were negatively correlated with both perceived stress and circulating cortisol. Further, LTPA showed a stronger negative correlation with both perceived stress and cortisol than did CR fitness. Although exercise training and perceived stress, and acute exercise and subjective well-being have been explored in individuals with a SCI, to the best of my knowledge this is the first study to explore the relationship between CR fitness and self-reported LTPA with perceived stress and cortisol in individuals with a SCI. This study helps elucidate the often complex relationships that exist between physical activity and fitness, and psychophysiological indices of stress.

5.1 Perceived Stress, LTPA and CR Fitness

Hypothesis 1, stating that LTPA and CR fitness would negatively correlate with perceived stress was supported, as both variables demonstrated a negative correlation with perceived stress. These negative correlations are partially consistent with, and may act as an extension to, literature showing reduced levels of stress following 3 months of exercise training twice per week in individuals with a SCI (Hicks
Further regression analysis indicated that LTPA and CR fitness explained 10.3% and .6% of the variance in perceived stress, respectively. These findings indicate that the behavioural aspects of physical activity may play a more important role in perceived stress than the physiological adaptations to physical activity. Although this is the first study to suggest that short-term physical activity is related to perceived stress in those with a SCI, these findings are consistent with what is observed in non-SCI samples. For example, current research suggests that even one 30-minutes bout of hand-cycle exercise can reduce stress in neurologically intact individuals (Basso & Suzuki, 2017).

The notion that the behavioural rather than adaptive aspects of physical activity may play a more important role in perceived stress receives support from Gatchel's Chronic Pain Processing Model. In addition to suggesting a multidirectional relationship between adverse physical changes, emotional dysfunction, and stress, the Model also suggests that reduced activity levels may be one of the factors that moderates these relationships. More specifically, Gatchel's model suggests that altered physical activity levels and not altered fitness may moderate changes in perceived stress, supporting our findings that behaviour of engaging in physical activity and not strictly increasing fitness may play an important role in perceived stress.

The Chronic Pain Processing Model, as depicted in Figure 1, also indicated that pain plays a role in perceived stress. This is notable, as not only has pain been shown to fluctuate throughout the day in adults with a SCI, case series data also suggest that even a single bout of physical activity can significantly reduce pain in adults with a
SCI (Todd, 2017). This relationship has been further explored and supported by Martin Ginis (2003) and Latimer (2004), who found that changes in perceived stress following exercise training were mediated by changes in pain. Taken together, these findings lend credence to the idea that physical activity behaviours, and not strictly adaptive outcomes, play an important role in perceived stress. In other words, physical activity can reduce stress through its impact on pain, not necessarily through its impact on physical fitness.

Another possible explanation as to why physical activity behaviours may play an important role in perceived stress comes from Bahrke and Morgan’s distraction hypothesis (1978), which suggests that physical activity may distract individuals from certain negative states. The distraction hypothesis has been further tested in terms of physical activity distracting from pain and stress in non-SCI samples (Paluska & Schwenk, 2000); however the distraction hypothesis has not been explored in adults with a SCI as an explanation for the effects of physical activity on stress. That being said, it stands to reason that given the distraction hypothesis appears to rely upon appraisal and not sub-cortical processes, a spinal cord injury shouldn’t impact the ways in which physical activity might distract from pain and/or stress.

Another way in which physical activity may influence the level of perceived stress experienced by an individual is through developed resilience. Resilience has been described as a set of attributes, dispositions, or personal characteristics on which an individual can rely on to cope in difficult situations (Kaplan, 1999). This definition has been expanded upon to include not only the absence of psychopathologies, but the presence of healthy psychological functioning (Bonanno, 2004). Research indicates
that individuals who acquire a spinal cord demonstrate a considerable degree of psychological resilience (Bonanno et al., 2012). In addition to potentially delaying the depressive and anxiety symptoms associated with a SCI (Bonanno et al., 2012), research on the general population has demonstrated that personal resilience can affect the level of perceived stress an individual experiences (Tung et al., 2014).

Research has explored how individuals with a SCI may develop resilience and what role sport may play (Machida et al., 2013). Machida and colleagues conducted phenomenological interviews with 12 male quadriplegic athletes and found that among other factors, the development of resilience required various behavioural and cognitive coping strategies. These findings align with the Chronic Pain Processing Model as acute behavioural coping strategies (e.g., physical activity) and not necessarily chronic adaptations (e.g., fitness) develop resilience. Machida and colleagues found that sport fostered resiliency through enhancing social support (i.e., teammates, peers, mentors) and providing unique opportunities (e.g., achievement experiences, opportunity to practice coping skills, sense of normality). Given sport is a type of LTPA, the explanation of sport-fostered resilience through enhanced social support and unique opportunities may at least partly explain the negative correlation between LTPA and perceived stress. Although the relationship between resilience, perceived stress, and physical activity behaviours is yet to be explored in people with a SCI, future research exploring this topic could further our understanding of the ways in which these variables relate to each other and further mechanisms by which we may mitigate perceived stress.
One of the complexities involved in studying perceived stress is the high degree of variability in stress experienced between individuals. While one person may experience a situation to be highly stressful, another individual may appraise the same situation as inert. Given the variability in appraising stress, as well as the breadth of what factors might be perceived as stress-inducing, the finding of even a small correlation between LTPA and perceived stress speaks to the robustness of this relationship.

Although small, a negative correlation was also observed between CR fitness and perceived stress such that as CR fitness increased, levels of perceived stress decreased. One potential explanation as to why CR fitness may negatively correlate with perceived stress involves the release of catecholamines, hormones released during a stress response. Nieman and colleagues (1991) suggested that improved cardiovascular fitness in able-bodied individuals can reduce the amount of circulating catecholamines, insinuating that a reduction in catecholamines might lead to a reduced stress response and lower levels of perceived stress.

Gatchel’s Chronic Pain Processing Model may partially support the catecholamine reduction hypothesis, as reduced levels of circulating catecholamines may be seen as a ‘physical change’, one of the factors Gatchel’s model suggests mediates changes in stress. As previously noted however, Gatchel’s Model appears to place more weight on more acutely modifiable factors such as changes in pain, physical activity, and emotional states, indicating that longer term adaptations, such as CR fitness induced catecholamine alterations, may be less likely to influence perceived stress.
Further, although non-SCI literature may indicate a relationship between catecholamine concentration and perceived stress, spinal cord injury level and severity have been shown to impair sympathetic nervous system activity and result in lower catecholamine concentrations both at rest and following exercise (Leicht et al., 2013). Given the CR fitness-catecholamine hypothesis would state a reduction in catecholamines would result in lower perceived stress for people with a SCI, it is difficult to explain how despite potentially lower circulating catecholamines, perceived stress is still one of the most common psychological health concerns among those with a SCI (Richardson et al., 2019). Without studying this relationship more extensively, it cannot be determined whether the relationship between perceived stress and CR fitness is mediated by reductions in circulating catecholamines or other variables in adults with a SCI, how these results compare to the general population, or how injury level and severity may further moderate this relationship.

The present thesis has added to the body of literature on the relationship between LTPA, fitness and perceived stress. In alignment with current research, and supported by the Chronic Pain Processing model, the results of this study suggest that the behavioural aspects of engaging in physical activity play a more significant role in perceived stress than the physiological adaptations associated with physical activity. Further, current literature may suggest that specific factors such as reductions in pain, increased distraction, or increased resilience, may mediate the relationship between physical activity and perceived stress.
5.2 Cortisol, LTPA and CR Fitness

Hypothesis 2 was supported as both LTPA and CR fitness were negatively correlated with circulating cortisol. Additionally, further analysis indicated that LTPA and CR fitness explained 9.6% and 5.7% of the variance in cortisol, respectively. Interestingly, when taken together, LTPA and CR fitness explained 23.2% of the variance in cortisol, suggesting that a combination of both the behavioral and physiological adaptation aspects of physical activity may explain more of the variance in cortisol than either LTPA or CR fitness alone.

Our findings that both physical activity and fitness demonstrate a medium-large negative correlation with cortisol find partial support in current literature. Whereas we observed a negative correlation between LTPA and cortisol, such that as LTPA increased cortisol decreased, the acute exercise literature may tell another story. In the acute exercise setting, research in both SCI (Kouda et al., 2012; Yamanaka et al., 2010) and non-SCI (Hill et al., 2008) populations demonstrates an intensity-dependent increase in cortisol concentrations with reductions to baseline shortly following completion of the bout. Moving into the adaptive responses to physical activity, non-SCI literature has shown that following a 12-week exercise training study, participants who became more fit (i.e., increased anaerobic threshold), exhibited a reduced cortisol secretion during psychosocial stress, indicating an attenuated stress response in fitter individuals (Klaperski et al., 2014). The negative correlations observed in the present study, in concert with the blunted cortisol response reported by Klaperski (2014), has also been observed in work by Rimmele and colleagues (2007, 2009) and may be explained, in part, by the cross stressor adaptation
hypothesis. This hypothesis suggests that physical activity is a stressor, and repeated exposure to this stressor may alter biological processes and attenuate the HPA response to stress (Sothmann et al., 1996). In line with the cross-stressor hypothesis, the present study observed medium-large negative correlations between LTPA, CR Fitness, and cortisol, such that as LTPA and CR fitness increased (i.e., increase exposure to physical activity), cortisol levels decreased (i.e., a potentially attenuated HPA axis response).

In addition to use as a biomarker of stress, cortisol may also be implicated in cardiovascular disease (CVD), another secondary health outcome often associated with spinal cord injury. In fact, CVD is suggested to be the primary cause of mortality in those with a chronic spinal cord injury (Garshick et al., 2005). Although the link between cortisol and CVD is yet to be explored in those with a SCI, excess cortisol is known to be associated with CVD risk factors such as hypertension, obesity, hyperglycemia, and insulin resistance (Whitworth et al., 2005). Interestingly, following blockade of the autonomic nervous system, cortisol-induced hypertension is shown to increase (Tam et al., 1997), suggesting that autonomic nervous system impairments, such as those associated with a SCI, may contribute to hypertension and the increased risk of CVD seen in those with a SCI.

One interesting finding from the present thesis is that when assessed in combination, LTPA and CR fitness explained more variance in cortisol than either variable alone. This suggests that the means in which LTPA and CR fitness may influence cortisol are more similar than distinct. Whereas the behavioural aspects of physical activity seem to play a more important role in perceived stress than the adaptive aspects and may
influence perceived stress through different mechanisms (e.g., Chronic Pain Processing Model versus CR fitness-induced catecholamine changes), a common explanation, such as the cross-stressor adaptation hypothesis, might suffice in explaining how cortisol responds to LTPA and CR fitness.

Whereas previous research has examined the response of cortisol to either acute physical activity or fitness separately, the present thesis has explored the role of both the behavioural and adaptive aspects of physical activity and their relationship with cortisol together. In doing so, the findings of this thesis indicate for the first time, that both behavioural and adaptive aspects of physical activity may play similarly important roles in circulating cortisol levels, and further, that this relationship might occur through similar mechanisms.

5.3 Strengths of the Study

5.3.1 Measures

One of the strengths of the present study was that the measures were appropriate, valid, and reliable. The assessment of cardiorespiratory fitness through the use of a \( \dot{V}O_2 \)peak test is a strength for two reasons. First, although the assessment of \( \dot{V}O_2 \)max is typically considered the gold standard for assessing cardiorespiratory fitness, research has shown that the values obtained through \( \dot{V}O_2 \)peak and \( \dot{V}O_2 \)max do not differ significantly, indicating \( \dot{V}O_2 \)peak is a valid index of CR fitness (Deuster & Heled, 2008). Second, current reference fitness values for CR fitness in adults with SCI are based on \( \dot{V}O_2 \)peak and not \( \dot{V}O_2 \)max, leading the results of this study to be more comparable to both reference values and other studies using the same measure (Simmons et al., 2014).
Leisure time physical activity was measured using the LTPAQ-SCI. In addition to the LTPAQ-SCI being created specifically for individuals with a SCI, the questionnaire has demonstrated reliability and validity as a measure of LTPA (Martin Ginis et al., 2012). This ensures that although highly variable, individuals’ LTPA behaviours were recorded using the best available assessment tool. Similar in terms of its demonstrated validity, using Cohen’s Perceived Stress Scale (PSS) (1983) to measure psychological stress allow the results of this study to be widely comparable as the PSS is considered to be one of the best measures of perceived stress (Crosswell & Lockwood, 2020). Finally, the measurement of circulating cortisol using a standardized ELISA kit allowed for the precise and repeatable measurement of this psychobiological biomarker of stress. Additionally, the average coefficient of variability achieved for the ELISA assay during the present study was 4.3%, well below the manufacturer’s suggested CV of 9-9.8%, and an indicator of the precision of the analysis and low intra-assay variability.

5.32 Community Engagement

As this study was part of a larger randomized controlled trial (RCT) (NCT04160858), there were ample resources available to ensure the rigor of the study design. Utilizing integrated knowledge translation (IKT) methods, the RCT was co-created with over 150 individuals living with a SCI and over 50 SCI-specific clinicians. Engaging with knowledge users such as individuals with lived experiences or SCI clinicians throughout the inception, design, and implementation of this project helped to ensure acceptability of the protocol to participants. For example, before beginning the official data collection, we conducted pilot testing with a few community partners with a SCI
and, upon their recommendation, made alterations to the protocol to enhance future participant experiences. Further, engaging with research partners from multidisciplinary backgrounds facilitated a biopsychosocial approach to this thesis. This biopsychosocial approach is necessary to fully understand concepts like perceived stress, physical activity, fitness, and cortisol, as these variables contain biological, psychological, and social components.

5.4 Limitations

5.41 Study Design

Although the larger RCT, of which this project is a sub study, utilized a longitudinal design, the present thesis used a cross-sectional study design. There are drawbacks associated with cross-sectional designs such as the inability to measure changes and relationships over time, as well as the inability to infer causality (Caruana et al., 2015). In addition to the inability to measure changes over time, a cross-sectional study prevents us from assessing the directionality of relationships. This is particularly relevant to the present thesis as research has shown that in addition to physical activity influencing stress, stress has also been shown to influence physical activity participation (Stults-Kolehmainen & Sinha, 2014). Despite the drawbacks associated with a cross-sectional study design, this design is not without utility. In addition to being time and cost effective, cross-sectional research may have lower participant burden as only a single visit/timepoint is required. Further, cross-sectional designs may preliminarily identify the existence of a relationship, justifying further exploration with more resource intensive designs (e.g., longitudinal).
5.42 Sample Size

Small sample sizes, although not uncommon in SCI-related research, may pose limitations to the statistical analyses that can be conducted as well as the generalizability of the results. In a recent systematic review examining sample sizes and statistical methods in interventional studies on individuals with a SCI, 167 of 207 studies had ‘small’ samples (i.e., n<20), with a median sample size of 18 (ranging from 4-582) (Zimmermann et al., 2019). The present study included 9 participants; half of the median sample size typically found in interventional SCI research. Although our small sample size may have reduced the power of our statistics, we still reported medium-large correlations between some variables, indicating that despite a small sample size, the hypothesized relationships between our variables were present.

5.43 Injury Characteristics

In light of the impact altered sympathetic innervation may have on the cortisol response, and the effect cortisol may have on perceived stress, examining participants’ autonomic completeness is important to fully understand how participant injury variability may impact the stress response. The present study did not evaluate the autonomic completeness of participants' injuries and therefore we cannot determine what influence this injury characteristic may have played on the cortisol response to LTPA or CR fitness, or how autonomic dysregulation may impact perceived stress. When possible, this injury characteristic should be evaluated during future research to better understand the relationship between autonomic function and the cortisol and perceived stress responses to physical activity stimuli.
5.44 Unexplained Variance

Given the variability of perceived stress experienced by individuals, it is not surprising that after entering LTPA and CR fitness in the regression models, there was still much unexplained variance in perceived stress. Research examining perceived stress in both able-bodied and SCI participants has found that a wide array of factors can contribute to perceived stress including unemployment and discrimination in the workplace (Feizi et al., 2012; McMahon et al., 2005; Young & Murphy, 2009), isolation (North, 1999) and sexual dissatisfaction (van Koppenhagen et al., 2008). Further inter-individual characteristics such as lifestyle and personal characteristics as well as traits like resilience may result in the same or similar stressors to be mediated or moderated, and therefore perceived as more or less stressful between individuals (Bonanno et al., 2012; Feizi et al., 2012; Tung et al., 2014).

5.45 Cortisol and Diurnal Variation

Regarding inter-individual variability, using a single time-point measurement of cortisol may be a limitation as cortisol is shown to have significant diurnal variations such that ‘normal’ morning values may be considered clinically elevated if observed in the afternoon (Pagana & Pagana, 2014). Further, factors such as lifestyle, caffeine, recent infection, steroid medications, and antibiotic intake have been shown to impact the measurement of cortisol (Pagana & Pagana, 2014; Pritchard et al., 2017). Although we attempted to control for these factors by asking participants to arrive fasted, to not consume any caffeine or anti-inflammatory medications 12-hours prior to the blood sample, and samples were collected around noon to account for diurnal variation, we cannot guarantee that participants adhered to these guidelines.
Additionally, a single timepoint measurement of cortisol may not accurately represent an individual’s daily cortisol pattern.

5.5 Implications

To the best of my knowledge, this thesis is the first to examine the relationship between LTPA and CR fitness on perceived stress and cortisol in adults with a chronic SCI. As such, we have gleaned insights and understanding that add a unique and interesting contribution to the field in terms of theoretical, practical, and methodological implications. These implications are listed below.

Theoretically, this thesis may uphold and support models that examine physical activity, fitness, and measures of stress through a multidirectional lens. One example of this model is Gatchel’s Chronic Pain Procession Model (1996). While there may be merit in models that propose physical activity influences stress through a single pathway, such as the psycho-physiological model proposed by Hansen (2010), it appears there are multiple pathways by which physical activity influences stress in people with a SCI. In addition to physical activity influencing stress, it seems that these factors may reciprocally influence each other, refuting the idea that these relationships are unidirectional (Stults-Kolehmainen & Sinha, 2014). Further, although the present study did not examine mediating (e.g., pain) (Martin Ginis et al., 2003; Latimer et al., 2004) or moderating factors (e.g., resilience) (Machida et al., 2013) by which physical activity may influence perceived stress or cortisol, it still may uphold certain multidirectional or multifactorial theoretical viewpoints by which we can explore the effects of physical activity on stress. Given the limited variance explained in perceived stress and cortisol by LTPA and CR fitness, in concert with research indicating a
reciprocal, moderated, and mediated relationship may exist between these variables, it stands to reason that multidirectional models such as the Chronic Pain Processing Model are most appropriate when trying to understand how stress is affected in adults with chronic SCI.

The most pertinent practical implication from this thesis is the understanding that both behavioural and physiological adaptation aspects of physical activity may uniquely, and in the case of cortisol, synergistically, contribute to levels of perceived stress and cortisol. Further, the findings of this thesis suggest that engaging in physical activity behaviours, even below a level that might initiate adaptive changes, may be sufficient to influence perceived stress.

From a methodological standpoint, this thesis promotes the idea that it may sometimes be helpful to examine variables in their constituent parts. During the present thesis, either CR fitness or LTPA could have been used alone as an index of physical activity/exercise behaviours, yet in measuring and analyzing both of these variables we were able to observe that these perhaps similar concepts were not in fact the same and yielded separate but interesting results. Further, if we were to only have collected CR fitness or LTPA as a measure of physical activity/exercise behaviours we would not have been able to show that both the behavioural and adaptive aspects of physical activity related to cortisol and stress in unique ways.

5.6 Future Directions
The most germane future directions for research suggested by this thesis fall under controlling for potentially mediating, moderating or confounding variables, and
expanding the collection of data relating to physical activity and cortisol. With respect to controlling for potentially mediating, moderating, or confounding variables, it would be helpful for future researchers to measure and attempt to control for certain personality traits or characteristics that might influence the level of perceived stress an individual might experience. For example, resilience has been mentioned as one factor that might mitigate the degree of stress an individual perceives. Furthering our understanding of how personality traits and characteristics such as resilience can be measured and controlled for might aid in finding ways to enhance resilience in people with a SCI, further reducing how much stress an individual might experience. Another example of a variable that could be measured and controlled for is pain. Pain seems to be a significant factor in the perception and experience of stress by people with a SCI, and future researchers should explore how physical activity-induced reductions or alterations in pain might impact stress in adults with a SCI. Additionally, controlling for other injury- (e.g., injury-related secondary health complications) and non-injury-specific factors (e.g., financial worry) that might influence stress will aid in our understanding of which factors might be implicated in physical activity-associated alterations in stress.

Regarding expanding the measures used in this thesis, future research might also consider collecting salivary or plasma cortisol at multiple timepoints to better assess how diurnal variations in cortisol may relate to physical activity and fitness in those with a SCI. Although controlled for as best as possible with overnight fasting and time of sampling, collecting cortisol at only a single timepoint may limit our understanding of an individual's cortisol pattern. This becomes increasingly important in those with a
SCI as diurnal rhythms, such as those that govern cortisol, are effected by circadian rhythms and are shown to be altered in those with a SCI (Kostovski et al., 2018). In addition to the broad assessment of life stressors and the careful control of cortisol-influencing factors, future research could benefit from stratifying LTPA based on the intensity at which the physical activity was completed. Because of our small sample size and limited variability in the amount of time spent on the different intensities of LTPA, ‘Total LTPA’, or the sum of mild, moderate, and heavy minutes of LTPA was the measure used in this study. However, understanding how varying intensities of LTPA are related to perceived stress and/or cortisol in those with a SCI is important for understanding how best to prescribe exercise to reduce stress.
6.0 Conclusion

The findings of this thesis suggest that both leisure time physical activity and cardiorespiratory fitness negatively correlate with both cortisol and perceived stress, such that as physical activity and fitness increase, levels of perceived stress and cortisol decrease. Further, when physical activity and fitness are entered in a model together, they may explain more of the variance in cortisol than either variable alone. These results suggest that a combination of both LTPA behaviours and chronic adaptations to physical activity (i.e., fitness) may influence levels of perceived stress and cortisol. When measuring levels of perceived stress and cortisol in adults with SCI, it is vital to explore and understand the myriad factors that can influence these variables, so that future research can account for additional factors that might influence an individual’s level of perceived stress or circulating cortisol. In doing so, research will be able to paint a clearer picture of the ways in which we can accurately and reliably understand cortisol and mitigate perceived stress in adults with a spinal cord injury.
References

https://www.abcam.com/cortisol-elisa-kit-ab108665.html?productWallTab=ShowAll


https://doi.org/10.1038/sc.2014.184

https://doi.org/10.1007/BF01172650


https://doi.org/10.1249/00005768-199410000-00006


https://doi.org/10.14288/1.0357431


Appendices
Appendix A

PERCEIVED STRESS SCALE

The questions in this scale ask you about your feelings and thoughts during the last month. In each case, you will be asked to indicate by circling how often you felt or thought a certain way.

Name ________________________________ Date ___________

Age ______ Gender (Circle): M F Other __________________________

0 = Never 1 = Almost Never 2 = Sometimes 3 = Fairly Often 4 = Very Often

1. In the last month, how often have you been upset because of something that happened unexpectedly? 0 1 2 3 4
2. In the last month, how often have you felt that you were unable to control the important things in your life? 0 1 2 3 4
3. In the last month, how often have you felt nervous and “stressed”? 0 1 2 3 4
4. In the last month, how often have you felt confident about your ability to handle your personal problems? 0 1 2 3 4
5. In the last month, how often have you felt that things were going your way? 0 1 2 3 4
6. In the last month, how often have you found that you could not cope with all the things that you had to do? 0 1 2 3 4
7. In the last month, how often have you been able to control irritations in your life? 0 1 2 3 4
8. In the last month, how often have you felt that you were on top of things? 0 1 2 3 4
9. In the last month, how often have you been angered because of things that were outside of your control? 0 1 2 3 4
10. In the last month, how often have you felt difficulties were piling up so high that you could not overcome them? 0 1 2 3 4

mind garden
info@mindgarden.com
www.mindgarden.com

References
Leisure Time Physical Activity Questionnaire-SCI
(modified by Rocchi et al. 2017 to measure compliance with the SCI Exercise Guidelines)
(This questionnaire is administered along with the PARA-SCI Physical Activity Intensity Classification Sheet, which has been validated to help participants accurately designate the intensity of their exercise)

A. Aerobic Exercise
I am going to ask you about the time you spent engaging in mild, moderate, and heavy intensity aerobic exercise in the last 7 days. Recall that aerobic exercise activities are planned activities that are done continuously and that likely increase your heart rate and breathing rate, such as wheeling, swimming, hand cycling and fitness classes.

1. Keep in mind that mild intensity exercise requires very light physical effort. Mild intensity activities make you feel like you are working a little bit, but you can keep doing them for a long time without getting tired.
   During the last 7 days, on how many days did you do mild intensity exercise? ______
   On those days, how many minutes did you usually spend doing mild intensity exercise? ______

2. Recalling that moderate intensity exercise requires some physical effort. Moderate intensity activities make you feel like you are working somewhat hard, but you can keep doing them for a while without getting tired.
   During the last 7 days, on how many days did you do moderate intensity exercise? ______
   On those days, how many minutes did you usually spend doing moderate intensity exercise? ______

3. As you know, heavy intensity exercise requires a lot of physical effort. Heavy intensity activities make you feel like you are working really hard, almost at your maximum. You cannot do these activities for very long without getting tired. These activities may be exhausting.
   During the last 7 days, on how many days did you do heavy intensity exercise? ______
   On those days, how many minutes did you usually spend doing heavy intensity exercise? ______

B. Strength Training
Strengthening exercises are planned exercises that increase muscle strength such as exercises using resistance bands, or weights, or wall pulleys.
During the last 7 days, on how many days did you do strengthening exercises? ______
On those days, how many different exercises did you do? ______
How many sets of the exercises did you do? ______

Was last week representative of your typical exercise routine? YES  NO
If NO, please describe your usual routine.
Page 1/2 of the American Spinal Injury Association (ASIA) work sheet.
Muscle Function Grading

- 0 = total paralysis
- 1 = palpable or visible contraction
- 2 = active movement; full range of motion (ROM) with gravity eliminated
- 3 = active movement; full ROM against gravity
- 4 = active movement; full ROM against gravity and moderate resistance in a muscle specific position
- 5 = normal; active movement; full ROM against gravity and full resistance in a functional muscle position expected from an otherwise unimpaired person

NT = not testable (i.e., due to immobilization, severe pain such that the patient cannot be graded, paralysis of limbs, or contracture of > 50% of the normal ROM)

Sensory Grading

- 0 = absent
- 1 = light touch, light pinprick, and light pinprick at pain threshold
- 2 = light pinprick at pain threshold

When to Test Non-Key Muscles:

In a patient with an acute ASIA classification, non-key muscle functions more than 3 levels below the motor level on each side should be tested to most accurately classify the injury (differently between ASIA B and C).

Movement

- Shoulder: Flexion, extension, abduction, adduction, internal and external rotation
- Elbow: Flexion, Supination, Pronation
- Wrist: Flexion, Extension, Abduction and Adduction, Opposition, Abduction and Adduction perpendicular to palm
- Finger: Abduction of the index finger
- Hip: Abduction
- Knee: Flexion
- Ankle: Flexion and Extension
- Toe: MP and P-Extensor
- pellet and toe: DIP and PIP flexion and abduction
- Hallux: Abduction

ASIA Impairment Scale (AIS)

A = Complete. No sensory or motor function is preserved in the sacral segments S4-5.
B = Sensory Incomplete. Sensory but not motor function is preserved below the neurological level and includes the sacral segments S4-5. Light touch or pinprick at SA-5 or deep pain or pressure at sacral segments S4-5 is preserved on one side of the body.
C = Motor Incomplete. Motor function is preserved at the most caudal sacral segments for voluntary and/ or contraction (VAC). On the patient meets the criteria for sensory incomplete status (sensory function preserved at the most caudal sacral segments S4-5 on one side or both) and has some sparing of motor function; more than three levels below the level of the highest motor level on either side of the body.
D = Motor Incomplete. Motor incomplete status as defined above, with at least half (2/3) or more of key muscle functions below the sacral level to have a motor grade = 3.
E = Normal. Full motor and function as tested with the ENGIN-3 are graded as normal in all segments, and the patient has no pain or sensory deficits, and in the ASIA grade is C. Individual with minimal sensory loss without pain should be graded as ASIA grade E.

Steps in Classification

1. Determine sensory levels for right and left sides.
2. Determine motor levels for right and left sides.
3. Determine the neurological level of injury (NL):
   - NL is the most caudal segment of the cord with intact sensation and voluntary and motor function.
   - NL is the most caudal of the sensory and motor levels determined in steps 1 and 2.
4. Determine whether the injury is Complete or Incomplete.
   - If sensory and motor complete, no need for AIS.
   - If sensory incomplete, AIS = C.
   - If motor complete, AIS = D.
5. Determine AIS Impairment Scale (AIS) Grade:
   - Injury Complete? If YES, AIS = A and can record.
   - Injury Motor Complete? If YES, AIS = B.
   - Injury Motor Incomplete? If NO, AIS = C.
6. If execution and motor function is normal in all segments, AIS = E.

Note: AIS is used to follow-up function of an individual with a documented SD has increased function. If initial testing no details are found, the individual is neurologically intact, the ASIA Impairment Scale does not apply.
Figure 1. A histogram plot of the bimodal distribution of total LTPA.
Participant Information and Consent Form

“Exercise guidelines Promotion and Implementation in Chronic Spinal Cord Injury (EPIC-SCI): A Randomized Controlled Trial”

Principal Investigator:
Kathleen Martin Ginis, Ph.D.
Professor
Department of Medicine
School of Health and Exercise Sciences
UBC, Okanagan Campus
Kathleen_martin.ginis@ubc.ca

Co-Investigator:
Joan Ubeda-Colomer, Ph.D.
Postdoctoral Fellow
School of Health and Exercise Sciences
UBC, Okanagan Campus
joan.ubedacolomer@ubc.ca

Co-Investigator:
Femke Hoekstra, Ph.D.
Postdoctoral Fellow
School of Health and Exercise Sciences
UBC, Okanagan Campus
Femke.hoekstra@ubc.ca

Co-Investigator:
Jennifer Davis, Ph.D.
Assistant Professor
Faculty of Management
UBC, Okanagan Campus
Jennifer.davis@ubc.ca

Co-Investigator:
Mohammad Ehsanul Karim, Ph.D.
Assistant Professor
School of Population & Public Health
UBC, Vancouver Campus
ehsan.karim@ubc.ca

Co-Investigator:
John (Kip) Kramer, Ph.D.
Assistant Professor
School of Kinesiology
UBC, Vancouver Campus
Kramer@icord.org
1. INVITATION

You are being invited to participate in this research study for the following reasons: 1) you are over the age of 18, 2) you have had a spinal cord injury for longer than 1 year, 3) you experience chronic pain and 4) you do some or no physical exercise.

2. YOUR PARTICIPATION IS VOLUNTARY

Your participation is voluntary. You have the right to refuse to participate in this study. If you decide to participate, you may still choose to withdraw from the study at any time. There will be no negative consequences to the medical care, education, or other services to which you are entitled to or are presently receiving.

Before you decide, it is important for you to understand what the research involves. This consent form will inform you about: 1) the research study, 2) why the research is being done, 3) what will happen to you during the study, and 4) the possible benefits, risks and discomforts. The researchers have a duty of care to all participants and will inform you of any information that may affect your willingness to remain in the study.
If you wish to participate in this study, you will be asked to sign this form.

Please take time to read the following information carefully and to discuss it with your family, friends, and doctor before you decide.

3. WHO IS CONDUCTING THE STUDY?

The study is being conducted by Dr. Kathleen Martin Ginis, who is the Director of the Chronic Disease Prevention Program within the Southern Medical Program at UBC, a Professor in the School of Health and Exercise Sciences at UBC Okanagan and a Principal Investigator for ICORD (International Collaboration on Repair Discoveries). This study is being funded by the Canadian Institutes of Health Research (CIHR).

4. BACKGROUND

Over 85,000 Canadians live with a spinal cord injury (SCI). The vast majority experience chronic pain from neuropathic or musculoskeletal origins, with many reporting the pain to be more physically, psychologically and socially debilitating than the injury itself. Neuropathic pain can be understood as pain being felt at, or below the level of SCI where sensation is typically absent or impaired. Musculoskeletal pain exists due to a specific, known injury (e.g., repetitive strain or overuse). Currently, pharmaceuticals are the most commonly prescribed treatment for SCI pain, despite having many side-effects and giving minimal relief. Alternatively, studies conducted in controlled lab and clinical settings suggest that exercise may be a safe, effective behavioural strategy for reducing SCI-related chronic pain.

To date, no study has tested the effects of exercise, performed in a home-/community-setting, on chronic pain in adults with SCI. Furthermore, information on the exercise dose required to alleviate chronic SCI pain is virtually non-existent, making it impossible for clinicians and fitness trainers to make evidence-informed recommendations regarding the types and amounts of exercise to perform in order to manage SCI pain. Recently (2018), an international team published two scientific SCI exercise guidelines: one to improve fitness and one to improve cardiometabolic health. Cardiometabolic health is related to measures of body composition (e.g., fat mass, muscle mass) and risk factors for cardiovascular disease (e.g., cholesterol levels). Participants in this study will be following these newly developed SCI exercise guidelines. We are aiming to recruit 88 participants in total (inclusive of both Vancouver and Okanagan testing sites).
5. WHAT IS THE PURPOSE OF THE STUDY?

This study seeks to identify how exercise may affect pain in people living with SCI. The purpose of this project is four-fold; (1) to determine whether a regular program of exercise, performed in a person's home or in a local fitness facility, can significantly reduce chronic pain in adults with SCI, (2) to test whether exercise has different effects on different types of pain, (3) to see if exercise reduces pain by reducing inflammation in the body and reducing a person's sensitivity to pain, and (4) to see if reductions in pain lead to changes in psychological outcomes and health care costs.

6. WHO CAN PARTICIPATE IN THIS STUDY?

You may be able to participate in this study if you:

1) are over the age of 18  
2) can read, speak and understand English  
3) have access to a phone  
4) have been diagnosed with a spinal cord injury more than 1 year ago  
5) have an injury level at C3 or below  
6) participate in less than 40 min/week of structured, moderate intensity, aerobic exercise and less than 2 bouts/week of strength training, i.e. less than the minimum recommended by the SCI Exercise Guidelines  
7) experience chronic pain  
8) experience neuropathic or musculoskeletal pain  
9) have no medical contra-indications to performing a maximal exercise test

7. WHO SHOULD NOT PARTICIPATE IN THE STUDY?

You cannot participate in this study if you:

1) have chronic pain with exclusively non-musculoskeletal or non-neurological origins  
2) cannot perform upper-body exercise due to limited diaphragmatic control and/or reduced arm functioning  
3) live beyond driving distance of the research site (Vancouver or Okanagan centres)  
4) cannot read, write, or orally communicate in English  
5) have been previously told you have had a cognitive or memory impairment,  
6) are pregnant  
7) are an in-patient at a hospital at the time of enrolment
8. WHAT DOES THE STUDY INVOLVE?

This study involves a total of 3 visits to the health and wellness laboratory at UBC Okanagan or ICORD Vancouver which are spread over a 6-month period. The procedures include an initial visit for familiarization with the testing procedures, screening for eligibility, and completing the first set of measures. This will be followed by a 3- and 6-month visit to test for any changes in these measures. If you are allocated to the Exercise Intervention Group (please see below), then there are also two follow-up phone calls involved (9 months and 12 months after starting the study) to see if there any changes in your physical activity and pain levels. You may also be invited to participate in one of two sub study’s that will involve either interview sessions or focus groups sessions. Participation in either sub study is optional. Please, check the following box if you agree to be invited to take part in one of the sub study’s related to this main study:

I agree to be invited to take part in future interview sessions or focus groups sessions related to this study.

A separate consent form will be provided for each sub-study.

If You Decide to Join This Study: Specific Procedures

If you agree to take part in this study, we will first invite you for an Initial Screening Visit and Familiarization. During this visit, a member of the study team will confirm you have read and understood the consent form and will answer any further questions you have. Should you remain interested in the study, we will complete a basic health screening test and record demographics. The remainder of this first visit will be the same as the second and third visit and will consist of the following:
1. **Blood sample.** A person highly experienced in blood testing will take a fasting blood sample (6.6 ml or about 1.5 teaspoons of blood) from your antecubital vein (located on the inner forearm) to measure immune system markers, glucose, insulin, triglycerides and cholesterol levels; for this we ask you to not eat or take any anti-inflammatory medication for 12 hours prior to the visit.

2. **Pressure response test.** This will help inform us how your body reacts to a mildly painful stimulus. Before starting, we ask a few questions about your neuropathic pain and check if/where you can feel this using a little pinprick, brief touch or light brush of the painful area. Then we start a test in which a small metal device (contact area 1 cm²) will be used to apply pressure on a place on your upper body where you still have sensory feelings. The pressure will slowly be increased until you tell us that you can feel the first hunch of pain. The pressure will then immediately be stopped. This will be done 3 times. After a 5-minute break, we will ask you to hold your opposite hand in cold-water for 1 min. Following a second 5-minute break, we will repeat this procedure to see if there are any changes in your body's response. As with all procedures, you can stop the test at any time you wish to.

3. **Maximal strength tests.** You will be asked to perform 4-12 repetition maximal bench press and 4-12 repetition maximal seated row tests using HUR strength equipment that is specifically designed for wheelchair users and others with a physical impairment.

4. **Questionnaires.** You will be asked to fill out the following questionnaires using an electronic tablet or laptop (someone can help you with that if your hand function limits the use of a touch-screen tablet or keyboard):
   - **Pain.** The two-item SF-36 Bodily Pain (SF-36 Pain) subscale which measures overall pain severity and interference during the past 4 weeks. The *International Spinal Cord Injury Pain Basic Data Set v2.0* will be used to measure overall interference of musculoskeletal and neuropathic pain, as well as the intensity of each specific pain location and type (up to three pain problems). We will also ask a single question about your expectations of how the exercise program might influence your pain. The pain questionnaire will be assessed via an interview with a trained research assistant.
   - **Fatigue.** The four-item SF-36 Vitality scale as a general measure of energy/fatigue.
   - **Subjective well-being.** The *Perceived Stress Scale*, the SCI-QOL measurement system measures of *Positive Affect and Well-Being*, and *Satisfaction with Social Roles and Activities*, Diener’s *Satisfaction with Life Scale* and the Measure of Experiential Aspects of Participation.
   - **Economic evaluation.** The Health Resource Utilization questionnaire will be used to assess cost-utility and cost-mobility of this exercise program. In addition, health-related quality of life will be evaluated using the 5 level version of EuroQol-5D (EQ-5D), while capability wellbeing will be evaluated using an index of capability for adults (ICECAP-A).

5. **Peak aerobic exercise test.** Your *peak oxygen uptake* and *peak power output* will be assessed using a Lode arm crank ergometer and a special mask that cover your face to measure your
breathing during arm cranking. The intensity of aerobic exercise will increase until you feel that you are no longer able to continue arm cranking. The steps are tailored to your abilities such that the test is finished after about 6-12 minutes.

If you are allocated to the “**Exercise Group**”, the protocol will occur as follows: You will begin at the Starting Level SCI Exercise guideline and be instructed to complete 20 minutes of aerobic exercise, two times/week, at 70% of your max heart rate, plus three sets of 10 repetitions of strengthening exercises for each major functioning muscle group at 50-80% of 1-repetitions max, two times/week. Target heart rate, strengthening exercises and loads will be determined at baseline and 3-month fitness testing (Section 2.9). You may break up the 20-min bout as needed (e.g. two 10-min bouts) and work up to 20 min of continuous exercise. You will be encouraged to gradually increase the aerobic exercise to 30 min, three times/week, but can progress at your own rate.

You will be visited by a personal trainer in your preferred exercise location in weeks 1 and 13 (right after baseline and 3-mo. fitness tests) to show how to do the prescribed exercise, self-monitor exercise intensity, and check exercise progression (at 3 months). An exercise counsellor will call or meet you one time per week for 15-min to discuss your health and safety, and exercise progression. The audio of these sessions will be recorded and then stored in a confidential manner.

If you are allocated to the “**Control Group**”, you will not get an exercise prescription. You will be asked not to change your lifestyle for 6 months. After this 6-month period, you will receive the same resources as Exercisers.

You will be allocated to your Intervention Group randomly by a clinical trial support unit, through a computer-generated allocation sequence (like the flip of a coin). This support unit will be independent of the recruitment process.

**Please note:** Blood samples collected will only be used by the research team to determine your responses in inflammation and other cardiometabolic markers (e.g. glucose and cholesterol levels). There will be no blood banking or genetics research done using these samples. They will be identified by a number/code only with no personal identifiers. Before analyses they will be stored in a freezer in a locked laboratory on the Okanagan campus (supervised by Dr Jon Little) or ICORD Vancouver site (supervised by an ICORD investigator whose name we can confirm after the spring of 2020). Your blood samples will be transported from Vancouver to Okanagan campus using a safe method approved by UBC. Any leftover blood samples will be destroyed following the conclusion of this research study.

An overview of the time commitment for this study: For those randomized to the Exercise Group or the Control Group, we will ask you to attend the Kelowna or Vancouver testing site three times for outcome assessment testing (3 hours for 3 visits).

For those randomized to the Exercise Group, you are encouraged to do a total of 50-75 hours of exercise training time (2-3 hours per week, subject to ability and progression, across 6 months) in the

Version 5. Feb 19, 2020
settings of your choice (for example at home, in a community gym). To do this effectively, a personal trainer will spend a total of 2 hours with you to provide exercise training instructions (1 visit at start of exercise training program, one check-up visit after 3 months). In addition, an exercise counsellor will contact you weekly to discuss your progression and potential challenges so far (15 minutes per week across 6 months). After that, we ask you to participate in two 15-min phone calls (9 and 12 months after the study) to see if there are any changes in your physical activity and pain levels.

9. WHAT ARE MY RESPONSIBILITIES?

1) Please show up to your appointments fasted if required. You are required to be fasted (i.e., no food or drink except for water for 10 hours prior to the testing) before each of the three testing days.
2) Avoid anti-inflammatory medication (e.g., Ibuprofen, Naproxen, Tylenol) for 24 hours before the trial as to not interfere with the blood analysis.
3) Report any noticeable changes in your health status (e.g., sickness, cold) during the trial.
4) Ensure your physician has cleared you for doing maximal or moderate-to-vigorous intensity aerobic and strength exercise, and bring a list of your medication for the first visit.

10. WHAT ARE THE POSSIBLE HARMS AND DISCOMFORTS?

The insertion of a needle for blood sampling is a common medical practice and involves minimal risk provided proper precautions are taken. The needle is inserted under completely sterile conditions, however there is a risk of infection. There is also chance of bleeding if adequate pressure is not maintained upon removal of the needle. This may cause some minor discomfort and could result in bruising/skin discolouration that could last for up to a few weeks. There is also a risk that trauma to the vessel wall could result in the formation of a small blood clot, which could travel through the bloodstream and become lodged in a smaller vessel. However, we have never experienced such a complication in our laboratory after several hundred venous blood sampling procedures. Risks will be minimized by a trained researcher who will follow proper sterile techniques. Any complications beyond mild redness/inflammation or slight soreness should be reported to the researcher or a medical doctor. These risks are Extremely Rare (less than 1%).

In regards to the measurement of neuropathic pain sensations and musculoskeletal pain, frequent reminders of the presence of neuropathic pain and musculoskeletal pain may potentially exacerbate symptoms. However, every effort has been made to minimize these potential risks. The number of questionnaires was reduced to the lowest amount possible that still allows the student investigator to
capture the spontaneous, dynamic nature of neuropathic and musculoskeletal pain sensations experienced by persons with SCI.

Aerobic and strength exercise at moderate to vigorous intensities may cause some discomfort. These risks include fatigue, fainting, and or muscle soreness. These risks will be minimised by instructing participants about standardised warm-up and cool-down procedures as well as how to monitor exercise intensity and the prevention of overexertion. The weekly phone calls with the exercise counsellor will also be used to track and discuss any fatigue, fainting or other discomfort.

A more severe risk, although very uncommon at only 1 in 40,000, is the risk of heart attack. To further minimize these risks, you will be asked to obtain clearance from your family physician. When completing the maximal aerobic test there may be some discomfort when wearing the facemask. However, the exercise investigator will adjust the equipment to ensure this feels as comfortable as possible. The maximal aerobic and strength exercise tests are similar to what someone might be exposed to when a health care or sport professional would like to test exercise tolerance. We will make sure that each exercise test is overseen by at least two trained staff members and we have UBC-approved emergency procedures and equipment in place in the highly event that something unusual happens. Exercise training and progression are tailored to your needs and abilities and are closely monitored for any unusual discomfort.

11. WHAT ARE THE POTENTIAL BENEFITS OF PARTICIPATING?

You will learn the maximum amount of oxygen your body uses during exercise participation, in addition to your current levels of muscular strength for your individual, major muscle functioning groups (e.g., biceps, triceps). This information can be used to help you learn about your general health and fitness, therefore helping you develop targeted health and fitness goals.

There are no other guaranteed benefits of participation. It is possible that by following this study, you may experience fitness and cardiometabolic health benefits (e.g., improved heart function, decreased fat mass). Depending on your current activity level, these benefits may be critically important. Further, you may gain insight into how exercise participation impacts your levels of chronic pain and psychological state (e.g., depression, anxiety, satisfaction with life). Given the lack of knowledge, coupled with the incidence and burden of chronic pain experienced by persons with SCI, any relationships that become apparent may be useful for well-being and quality of life for study participants.
Our lab cannot diagnose any disease but if incidental findings of possible disease are discovered, the participant will be contacted by the PI and encouraged to see their doctor for further testing (please see below section 22).

12. WHAT HAPPENS IF I DECIDE TO WITHDRAW MY CONSENT TO PARTICIPATE?

You may withdraw from this study at any time without giving reasons. If you choose to enter the study and then decide to withdraw at a later time, you have the right to request the withdrawal of your information [and/ or samples] collected during the study. This request will be respected to the extent possible. Please note however that there may be exceptions where the data [and/ or samples] will not be able to be withdrawn for example where the data [and/or sample] is no longer identifiable (meaning it cannot be linked in any way back to your identity) or where the data has been merged with other data. If you would like to request the withdrawal of your data [and/ or samples], please let your study doctor know. If your participation in this study includes enrolling in any optional studies, or long-term follow-up, you will be asked whether you wish to withdraw from these as well.

13. CAN I BE ASKED TO LEAVE THE STUDY?

If you are not able to follow the requirements of the study or for any other reason, the researchers may withdraw you from the study.

14. WILL MY TAKING PART IN THIS STUDY BE KEPT CONFIDENTIAL?

Your confidentiality will be respected. However, research records and health or other source records identifying you may be inspected in the presence of the Investigator or his or her designate by representatives of UBC, and UBC Clinical Research Ethics Board for the purpose of monitoring the research. No information or records that disclose your identity will be published without your consent, nor will any information or records that disclose your identity be removed or released without your consent unless required by law.

You will be assigned a unique study number as a subject in this study. Only this number will be used on any research-related information collected about you during the course of this study, so that your identity [i.e. your name or any other information that could identify you] as a subject in this study will be kept confidential. Information that contains your identity will remain only with the Principal
Investigator and/or designate. The list that matches your name to the unique study number that is used on your research-related information will not be removed or released without your consent unless required by law.

Your rights to privacy are legally protected by federal and provincial laws that require safeguards to ensure that your privacy is respected and also give you the right of access to the information about you that has been provided to the sponsor and, if need be, an opportunity to correct any errors in this information. Further details about these laws are available on request to your study doctor.

15. AFTER THE STUDY IS FINISHED

Future Contact

___ Y: If future research opportunities present themselves, the researcher may contact me as a potential research subject (If yes, please place a checkmark, or “X”) in this box).

16. WHAT HAPPENS IF SOMETHING GOES WRONG?

Signing this consent form in no way limits your legal rights against the sponsor, investigators, or anyone else, and you do not release the study doctors or participating institutions from their legal and professional responsibilities. If you become ill or physically injured as a result of participation in this study, medical treatment will be provided at no additional cost to you. The costs of your medical treatment will be paid by your provincial medical plan.

17. WHAT WILL THE STUDY COST ME?

There are no financial costs to you for participating in this study beyond what someone might spend on exercise in regular daily life. If an individual agrees to participate in this study, all costs associated with transportation to the testing site (UBC Kelowna or ICORD Vancouver) will be reimbursed. In addition, parking will be provided free of charge for testing sessions. Finally, you will be compensated with a $50 gift card after participation in the 6-month study. For those deciding to withdraw their participation in the study before completing the 6-month trial, they will be compensated as follows: a) a $10 gift card
for participating in the baseline measurement only; b) a $25 gift card for participating in the baseline and 3-month measurements only.

18. WHO DO I CONTACT IF I HAVE QUESTIONS ABOUT THE STUDY DURING MY PARTICIPATION?

If you have any questions or desire further information either before or during this study with respect to this study, you may contact:
Kendra Todd, MSc: ktodd03@mail.ubc.ca
Dr. Joan Ubeda Colomer: joan.ubedacolomer@ubc.ca

19. WHO DO I CONTACT IF I HAVE ANY QUESTIONS OR CONCERNS ABOUT MY RIGHTS AS A PARTICIPANT?

If you have any concerns or complaints about your rights as a research participant and/or your experiences while participating in this study, contact the Research Participant Complaint Line in the University of British Columbia Office of Research Ethics by e-mail at RSIL@ors.ubc.ca or by phone at 604-822-8598 (Toll Free: 1-877-822-8598). Please reference the study number [H19-01650] when calling so the Complain Line staff can better assist you.

20. WHAT HAPPENS WITH THE COLLECTED DATA BESIDES THE USE FOR THIS STUDY?

Your de-identified research data may be published or deposited into a publicly accessible location at the time of publication. At no time will identifying information, such as your name, birth date or street address be included in such data. This means that other researchers may analyze the data for different reasons other than those described in this consent form. Once the data is made publicly available, you will not be able to withdraw your data. The extent of the risk of you being identified through public data is unknown, but currently appears to be low.
21. Primary Care Physician(s)/Specialist(s) Notification

Please indicate, by checking the applicable box, whether you want us to notify your primary care physician(s) or specialist(s) of your participation in this study. This is not a consent to release medical information.

☐ Yes, I want the study investigator to advise my primary care physician(s) or specialist(s) of my participation in this study. My primary care physician(s) and/or specialist(s) name(s) is/are: ____________

The name of the medical clinic I attend is: ____________________________

Participant Initials: _______

☐ No, I do not want the study investigator to advise my primary care physician(s) or specialist(s) of my participation in this study.

Participant Initials: _______

☐ I do not have a primary care physician or specialist.

Participant Initials: _______

☐ The study investigator is my primary care physician/specialist.

Participant Initials: _______
22. SIGNATURES

Subject Consent

My signature on this consent form means:

- I have read and understood the subject information and consent form.
- I have had sufficient time to consider the information provided and to ask for advice if necessary.
- I have had the opportunity to ask questions and have had satisfactory responses to my questions.
- I understand that all of the information collected will be kept confidential and that the results will only be used for scientific objectives.
- I understand that my participation in this study is voluntary and that I am completely free to refuse to participate or to withdraw from this study at any time.
- I understand that I am not waiving any of my legal rights as a result of signing this consent form.
- I understand that there is no guarantee that this study will provide any benefits to me.

I will receive a signed copy of this consent form for my own records.

I consent to participate in this study, titled: Exercise guidelines Promotion and Implementation in Chronic Spinal Cord Injury (EPIC-SCI): A Randomized Controlled Trial

____________________________  __________________________  _________________
Participant’s Signature       Printed name               Date

Signature of Person Obtaining Consent

____________________________  __________________________  __________________  _________________
Signature of Person Obtaining Consent       Printed name       Study Role               Date
Investigator Signature (Optional)

____________________________  ______________________  ______________
Investigator Signature  Printed name  Date

My signature above signifies that the study has been reviewed with the study subject by me and/or by my delegated staff. My signature may have been added at a later date, as I may not have been present at the time the subject’s signature was obtained.