Cardiovascular autonomic consequences of spinal cord injury, cardiovascular disease risk, and exercise adjuncts

by

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Abstract

Spinal cord injury (SCI) is a devastating, life-changing event that impacts motor, sensory, and autonomic function. Cardiovascular disease (CVD), a secondary complication of SCI, has an earlier onset and faster progression following SCI and is the leading cause of morbidity and mortality. Traditional CVD risk factors (obesity, blood pressure, cholesterol etc.) are negatively impacted following SCI. Additionally, injury characteristics (level, severity, and duration of injury) and other secondary complications of SCI (neuropathic pain, poor mental health, and exercise intolerance) may contribute to the increased CVD burden after SCI. In this thesis I examined the impact of SCI characteristics and secondary complications on CVD risk and investigated the efficacy of exercise adjuncts following SCI. In Chapter 2, I aimed to identify key markers of obesity, injury characteristics, and autonomic function relating to CVD risk and establish population-specific cut-points for detection and risk management. I confirmed waist circumference as a practical, effective measure of CVD risk, and suggested a lower cut-point relative to the general population. Additional cut-points are suggested for injury characteristics and autonomic function. I expanded this work in Chapter 3 by examining the relationships between two non-traditional CVD risk factors – neuropathic pain and mental health – with cardiovascular autonomic function and CVD risk following SCI. Poor mental health was associated with increased CVD risk, while neuropathic pain was more prevalent in those with more intact cardiovascular function. In Chapter 4, I conducted a systematic review of two exercise adjuncts, passive lower limb movement and passive heat therapy, and found they were safe and efficacious in producing an exercise-like cardiovascular response. Finally, in Chapter 5, I conducted an experiment to test the safety of a prototype passive cycling wheelchair attachment and its efficacy to produce an exercise response and acutely improve cardiovascular function. While safety ratings were high and stroke volume and heart rate were increased, accessibility and usability need to be improved. The research conducted in this thesis helps to further our understanding of CVD risk following SCI, provides standards to increase detection of individuals at-risk for CVD, and offers evidence and options for mitigating CVD progression through exercise adjuncts.

Keywords: spinal cord injury; autonomic function; cardiovascular disease; secondary health conditions; exercise adjuncts; physical activity

“I think people who go through this are better for it, they are not made of better stock than other people, but they are better for what they have asked of themselves”

Lazarus Lake

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Lastly, to the trails.

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List of Acronyms

Term	Definition
AB	Able-bodied
AD	Autonomic dysreflexia
AIS	ASIA Impairment Scale
ASIA	American Spinal Injury Association
BMI	Body mass index
BWSTT	Body weight supported treadmill training
CBFv	Cerebral blood flow velocity
CI	Chronotropic incompetence
CO	Cardiac output
CRS	Comfort rating scale
CVD	Cardiovascular disease
DAP	Diastolic arterial pressure
DN4	Douleur Neuropathique 4 exam
DOI	Duration of spinal cord injury
FRS	Framingham risk score
HR	Heart rate
HR_{peak}	Peak heart rate
LOI	Spinal level of injury
MAP	Mean arterial pressure
MCAv	Middle cerebral artery blood flow velocity
MH-	Poor mental health
MHI-5	Five-item mental health inventory questionnaire
NP	Neuropathic pain
OH	Orthostatic hypotension
PC	Passive cycling
PHT	Passive heat therapy
PLLM	Passive lower limb movement

QUEST	Quebec User Evaluation of Satisfaction with Assistive Technology
ROC	Receiver operator curve
SAP	Systolic arterial pressure
SCI	Spinal cord injury
SV	Stroke volume
T_{core}	Core temperature
VO_{2peak}	Peak oxygen uptake
WC	Waist circumference
WHO	World Health Organization
WHtR	Waist-to-height ratio

Chapter 1.

Introduction

1.1. Spinal cord injury

Spinal cord injury (SCI) is defined as damage that temporarily or permanently changes spinal cord function and is known to have devastating physical and social implications. SCI can result from a variety of causes, including traumatic accidents, infections, tumors, and degenerative diseases. As there are distinct pathophysiological differences between the different aetiologies of SCI, this thesis will focus mainly on individuals living with injuries resulting from trauma.

There are currently an estimated 4 million individuals living with the devastating consequences of traumatic SCI worldwide, with approximately 500,000 new cases each year[1]. In Canada there are approximately 86,000 individuals with SCI, with 1,800 new cases annually[2]. Young adult males are most likely to sustain a traumatic SCI, however the age distribution is becoming increasingly bimodal, reflecting fall-related injuries in older populations. SCI presents a significant lifetime economic burden on the individual, ranging from $1.5 to 3 million (CAD), and the health care system as a whole. (**Fig 1.1**)

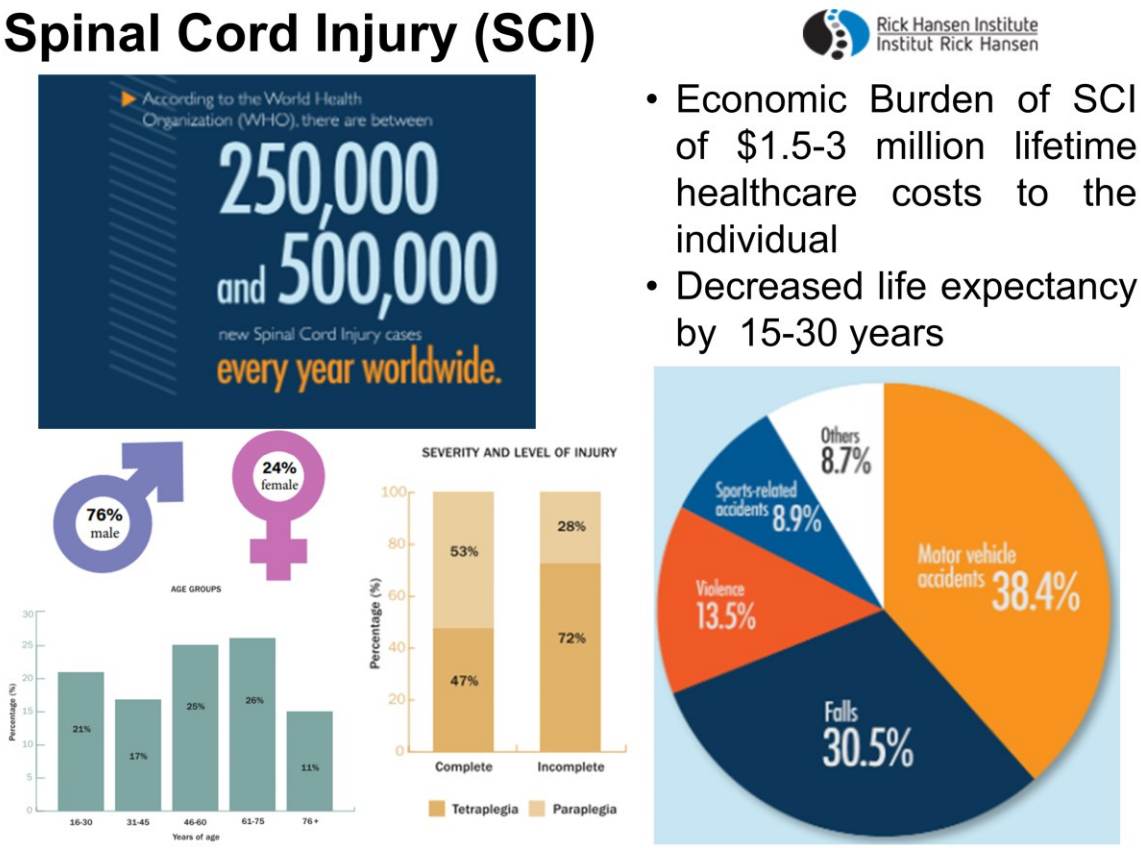

Figure 1.1. SCI demographics
The prevalence of SCI is increasing each year and is associated with a significantly reduced life expectancy and a large financial burden. The leading mechanisms are motor vehicle accidents and falls, disproportionately impacting males, with the average age increasing over the past 50 years. Adapted from Rick Hansen Institute[2].

One of the most challenging aspects of SCI is the heterogeneity of complications that accompany injury. SCI is primarily described based on the spinal level of injury (LOI), using the International Standards for Neurological Classification of Spinal Cord Injury examination to document remaining motor and sensory function, and the severity or completeness of the injury, using the American Spinal Injury Association (ASIA) Impairment Scale (AIS)[3]. Traumatic SCI most commonly involves the cervical spinal region (C1-C8) and most are motor and sensory incomplete (AIS B-D)[4]. Depending on the LOI and AIS, individuals with SCI may experience varying degrees of paralysis, loss of sensation, and autonomic dysfunctions (bladder and bowel, sexual, cardiovascular), all of which can significantly impact their health and quality of life. In general, higher-level, more complete injuries result in greater impairment and dysfunction[5].

Despite advances in medical and rehabilitation interventions, there remains a pressing need for further research to better understand the mechanisms underlying secondary complications resulting from SCI, develop effective treatments, and improve the lives of those living with SCI.

1.2. Secondary health complications of SCI

With improvements in acute care management, early death from complications following traumatic SCI (respiratory and renal failure, septicemia) have greatly decreased, and coupled with advances in chronic care management, life expectancy and quality of life after SCI are increasing[6]. As such, the impact and management of secondary health complications following SCI have become critical research priorities.

Cardiovascular disease (CVD), one secondary health complication, is the leading cause of morbidity and mortality following SCI[7] and is known to present earlier and progress more rapidly compared to able-bodied (AB), age-matched individuals[8]. Motor and sensory impairments from SCI may result in decreased physical activity, increased sedentary time, and dietary considerations known to impact susceptibility to CVD[9]. In addition to the profound SCI-related impairment to motor and sensory function, there are numerous secondary complications of SCI linked to impaired autonomic function that can also have profound, long-term, life-altering effects[10], as well as direct, but less well known links to CVD risk factors. These may include impaired respiratory function[11], bowel, bladder and sexual dysfunction[12], dyslipidemia[13], impaired thermoregulatory function[14], impaired blood pressure control[15], impaired cardiac and cardiovascular function and regulation[16], chronic pain (musculoskeletal and neuropathic)[17], and depression[18].

1.3. Effects of SCI on cardiovascular autonomic function

The autonomic nervous system consists of two major divisions, sympathetic and parasympathetic, with widespread innervation of almost all organs and systems capable of maintaining and responding to deviations from homeostasis[19] (**Fig 1.2**). The sympathetic and parasympathetic divisions commonly produce antagonistic responses. The parasympathetic system is most active under restful conditions and works to restore the body to resting homeostasis, while the sympathetic nervous system initiates

responses to stress (“fight-or-flight” response) such as increasing heart rate (HR) and blood pressure.

To better grasp the full impact of SCI on cardiovascular autonomic function, it is prudent to overview the autonomic nervous system in a normal, healthy state.

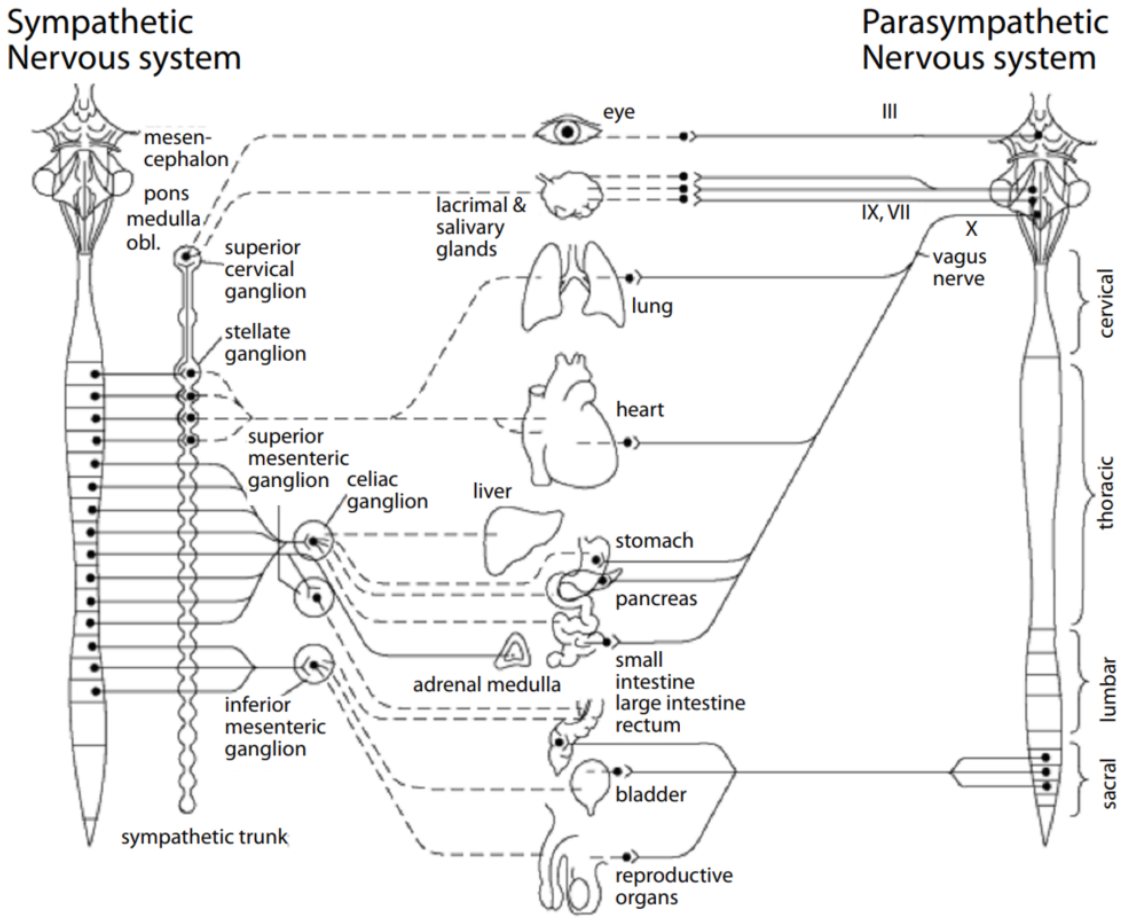

Figure 1.2. Overview of the autonomic nervous system
The autonomic nervous system is comprised of the sympathetic and parasympathetic divisions. SCI primarily impacts preganglionic (solid lines) and postganglionic (dotted lines) neurons of the sympathetic nervous system exiting the spinal cord, while supraspinal parasympathetic function remains intact. The sympathetic innervation of the skin and vasculature are not shown. III, oculomotor nerve; VII, facial nerve; IX, glossopharyngeal nerve; X, vagus nerve. Adapted with permission from Janig[19].

1.3.1. Cardiovascular autonomic function

The cardiovascular system is an intricate network of organs and blood vessels that work together to ensure adequate oxygen and nutrient delivery to all tissues and organs

in the body. Comprised mainly of the heart and the blood vessels, this system is under the control of the sympathetic and parasympathetic nervous systems[19].

While the heart receives innervation from both systems, the vasculature is primarily innervated by the sympathetic nervous system. The cell bodies of sympathetic preganglionic neurons responsible for cardiovascular control are located in the intermediolateral column of the thoracic and upper lumbar spinal cord (T1-L2) while their axons exit through the ventral root at various spinal levels and synapse onto postganglionic neurons in the paravertebral and prevertebral ganglia[20]. All sympathetic ganglia lie remotely to their target organs. The sympathetic preganglionic neurons that innervate the heart exit the spinal cord between the first and fifth thoracic vertebrae (T1-T5). Blood vessels are innervated by sympathetic fibres exiting the spinal cord from spinal levels T1-L2, depending on their location. The splanchnic vascular bed plays a key role in cardiovascular control due to its capacitance and resistance functions. The sympathetic preganglionic neurons that innervate this key vascular bed originate between the sixth and tenth vertebrae (T6-T10)[20]. Sympathetic innervation of the respiratory system (trachea, bronchi, lungs, and respiratory muscles) also exit the spinal cord between T1-T5, and facilitates bronchial vasodilatation and secretion from submucosal glands[21]. Sympathetic thermoregulatory control begins in the hypothalamus, with descending efferent nerves synapsing on sympathetic ganglia in the thoracolumbar section of the spinal cord, resulting in the release of acetylcholine triggering the sweat response[22].

In contrast, parasympathetic fibres that influence cardiovascular function originate from cranial nerves, exiting the central nervous system above the spinal cord. Parasympathetic preganglionic neurons that innervate the heart exit the central nervous system via the vagus nerve and thus are not affected by SCI[23]. Parasympathetic control of the pelvic viscera and genitals travel through the spinal cord to the sacral levels with significant functional impairment following SCI. Parasympathetic ganglia are located close to their target organs[24].

Cardiac function

Parasympathetic stimulation of the heart results in decreasing HR through a negative chronotropic effect via the sinoatrial node and decreasing conduction velocity through a negative dromotropic effect inhibiting the atrioventricular node[23]. On the other hand, the sympathetic system has a positive chronotropic effect (increasing HR), a

positive dromotropic effect (increasing conduction velocity), and a positive inotropic effect (increasing myocardial contractility)[23].

Blood pressure control

The key blood vessels (arteries and veins) involved in blood pressure regulation only receive sympathetic innervation. The release of norepinephrine and adrenaline from sympathetic nerve fibres activate α_1-adrenergic (vasoconstriction) and β_2-adrenergic (vasodilation) receptors providing basal vascular tone. As there is a greater distribution of α_1-adrenergic receptors in the arteries, sympathetic activation results in vasoconstriction, increasing systemic vascular resistance and blood pressure[23]. Vascular resistance is the opposition to blood flow as it passes through the vessels, primarily determined by the diameter of the vessels. Arteries, specifically arterioles, play a significant role in vascular resistance regulation as constriction and dilation alter blood distribution to different tissues and organs, consequently regulating blood pressure. When blood pressure is decreased, sympathetically induced vasoconstriction of the arteries of the splanchnic bed causes a significant reduction in blood flow decreasing the blood volume in the region. This leads to an increase in circulating blood volume, quickly increasing total peripheral resistance, improving venous return and cardiac preload, ultimately increasing blood pressure to meet the new demand. It is important to note that vessels at different locations may react differently to sympathetic stimulation, cooperatively working to redirect blood flow to where it is needed[23].

Vascular capacitance is the ability of blood vessels to store and release blood volume. Veins have greater capacitance relative to arteries due to a larger luminal diameter and thinner, more distensible walls, allowing them to accommodate a larger blood volume with less effect on pressure. The splanchnic bed is a highly compliant vascular bed containing around 20-25% of the total circulating blood volume at rest, making it the most important capacitance bed in the body[23].

Arterial baroreflex

The arterial baroreceptor reflex, or baroreflex, is a negative feedback system involved in the maintenance of blood pressure within a narrow range, ensuring blood flow to vital organs[24]. The baroreflex involves stretch-sensitive mechanoreceptors, called baroreceptors, located in the walls of the aortic arch, coronary arteries, and carotid sinus.

An increase in blood pressure distends arterial walls and activates the baroreceptors, increasing the firing rate of action potentials projected onto the nucleus of the solitary tract within the medulla via cranial nerves IX and X[23,24]. Signals are integrated in the rostral and caudal ventrolateral medulla and projections descend to sympathetic preganglionic neurons in the thoracic region of the spinal cord[25] (**Fig 1.3**). Sympathetic inhibition and parasympathetic activation result in vasodilatation and reduced cardiac output (CO) through negative chronotropic and inotropic regulation, ultimately reducing blood pressure. A decrease in blood pressure reduces the firing rate of the baroreceptor, increasing sympathetic activity and inhibiting parasympathetic activity, resulting in an increase in blood pressure[23].

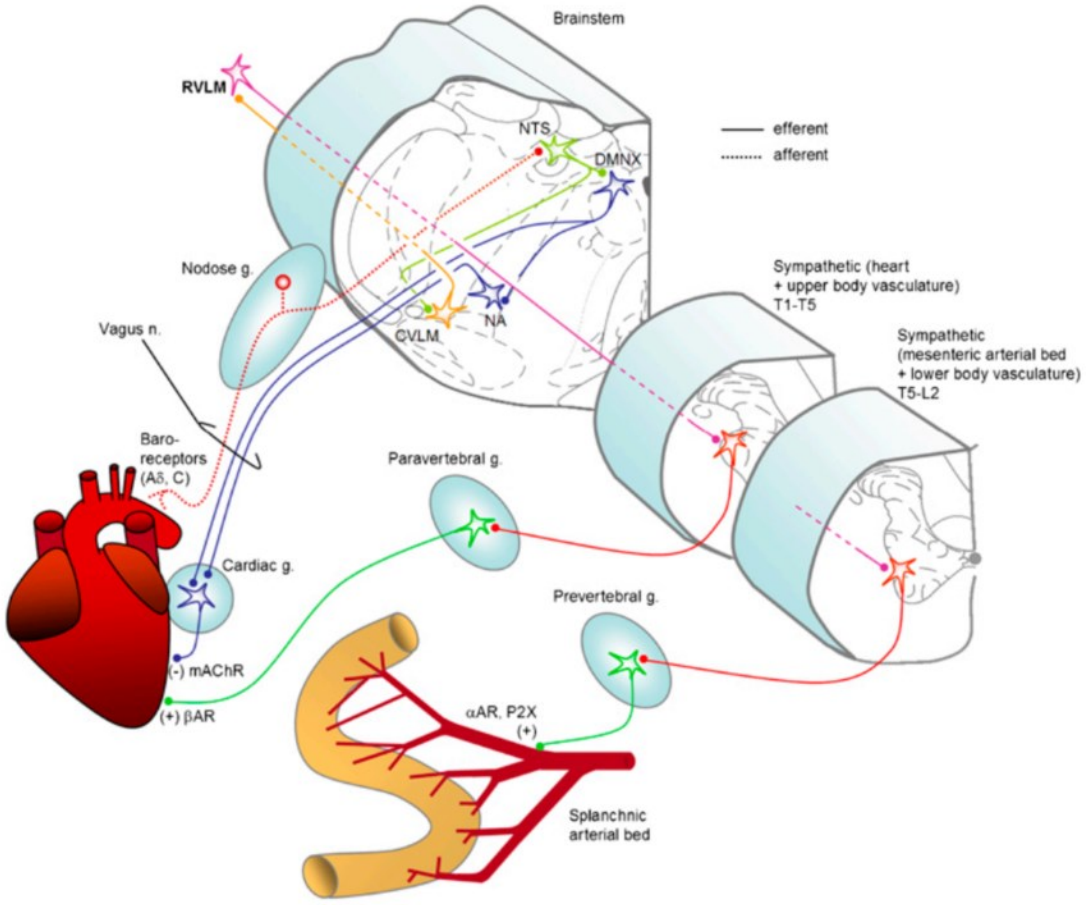

Figure 1.3. Cardiovascular autonomic innervation and the baroreflex
Parasympathetic innervation of the heart via the vagus nerve exiting from the medulla. Baroreceptor afferents also travel through the vagus nerve to the nucleus tractus solitarius. Sympathetic innervation of the heart exits the spinal cord at levels T1-T5, while sympathetic innervation of the splanchnic vasculature exits from T5-L2. Adapted with permission from Inskip[25].

1.3.2. Cardiovascular autonomic dysfunction following SCI

As descending spinal sympathetic pathways are a primary component of the sympathetic division of the autonomic nervous system, any damage to the spinal cord may result in disruption to the neuronal pathways controlling cardiovascular function and lead to autonomic impairment. The amount of disruption is dependent on the level and severity of the SCI, with higher, more complete injuries impacting a greater proportion of the neuronal pathways[5]. Since sympathetic innervation of the heart and key vasculature for blood pressure regulation exits the spinal cord between T1-T6, injuries at T6 and above commonly result in altered cardiac function[16] and structure[26] and impaired blood pressure control, including resting and orthostatic hypotension (OH)[15] along with periods of marked hypertension known as autonomic dysreflexia (AD)[27]. Although there are implications to the heart and vasculature following injuries below T6, they are primarily driven by impaired motor function and reduced physical activity resulting in detraining effects, as opposed to impaired autonomic function[28]. The numerous cardiovascular autonomic impairments have a devastating impact on quality of life, are consistently rated as a priority for improvement by individuals living with SCI[29], and are associated with an increased risk of CVD[30].

Furthermore, convergence and divergence within the spinal circuitry add to the complexity of secondary complications[31]. Convergent pathways allow for a single neuron (up to a whole organ) to receive input from several neurons that may leave the spinal cord at various levels. This can result in preserved organ function within different spinal levels of injury. Divergence is seen when a single neuron creates connections with multiple cells, establishing pathways to affect several organs[31]. The complexity and intricacy of the spinal circuitries contribute to the heterogeneity of injury and increase the difficulty of managing secondary health complexities following SCI.

Altered cardiac function and structure

As discussed above, the heart is innervated by both the sympathetic (spinal nerves from T1-T5) and parasympathetic (vagus nerve) nervous systems. SCI has a direct impact on the autonomic control of the heart and cardiovascular system and, as a result, significant alterations have been reported in cardiac function and structure following injury. It is generally accepted that functional changes drive structural changes after SCI[32–36]. Immediately after SCI there is a short period (3-5 minutes) of massive sympathetic

stimulation often resulting in bradycardia or tachyarrhythmias[37]. Following this, a condition known as neurogenic shock can occur, characterized by a loss of sympathetic tone and the resulting unopposed parasympathetic tone, leading to bradycardia, decreased CO, and possible cardiac arrhythmias[38]. These conditions continue to manifest through the acute phase (<1 year after SCI), with a decreasing risk of arrhythmias[39]. Although most prominent in the acute stage of SCI, arrhythmias also occur during episodes of AD as unregulated sympathetic discharge increases the transmural dispersion of ventricular repolarization[40]. In chronic SCI (>1 year), there are reported impairments in left ventricular function at rest including lower degrees of twist with slower twist and untwisting velocities, and a lower end-diastolic volume[41]. These changes result in a decreased SV, reducing circulating blood volume, leading to diminished venous return and cardiac preload[33,42,43]. Impaired sympathetic innervation restricts increases in HR to be achieved primarily through withdrawal of vagal tone. It has been shown that the peak heart rate (HR_{peak}) in the absence of significant sympathetic activity and solely mediated by withdrawal of vagal tone is between 100 and 120 beats per minute[44]. Decreases in both resting HR, HR_{peak}, and stroke volume (SV) result in a lower CO impacting the response to blood flow perturbations imposed by gravitational or vasodilatory changes.

Altered cardiovascular function following SCI results in a remodeling of structures of the heart. A recent study reported decreases in left ventricular internal diameter and mass occurring as early as 3 months post SCI, suggesting cardiac remodeling occurs relatively quickly. They also reported no plateau of remodeling changes up to 24 months, implying this remodeling likely continues for several years after SCI[43].

While reported to be worse following high-level injuries[33], these functional impairments and structural reductions of the heart were reported in individuals with injuries spanning all spinal levels[43]. These changes reflect both impaired autonomic function (especially in those with higher level injuries) along with several broader mechanistic and physiological consequences concurrently manifesting following SCI including: reduced physical activity and increased sedentary time[45], resting hypotension[46], loss of the skeletal muscle pump[47], and reduced total and circulating blood volume[26].

Impaired blood pressure control

As the vasculature is primarily innervated by sympathetic nerve fibres, loss or disruption of sympathetic control has a profound effect on blood pressure regulation after

SCI with consequences that negatively impact quality of life and increase morbidity and mortality. SCI at and above T10 have the potential to cause significant blood pressure dysregulation with impairments to efferent baroreflex function[48], splanchnic vascular resistance and capacitance responses[49], and impaired control of the general vasculature[50]. The afferent arm of baroreflex function is spared as baroreceptors remain functional due to their mechanical nature, and their afferent nerve fibres do not pass through the spinal cord; however, the damage to descending sympathetic pathways from the medulla oblongata inhibit efferent response below the LOI. Adaptations of the baroreflex are seen following SCI with acute reductions in baroreflex sensitivity and a longer reflex delay[51], with evidence of improvement over time[48]. Interference of signaling to the splanchnic vasculature severely impacts the ability to manipulate blood flow in response to acute changes in blood pressure due to postural or environmental stimuli. Impaired blood pressure control leads to resting hypotension, OH, and AD.

In the acute phase of SCI, neurogenic shock induces profound vasodilation resulting in severe hypotension[37]. As neurogenic shock is relieved, diminished sympathetic tone along with unopposed vagal activity maintains vasodilation[38]. Loss of the skeletal muscle pump and sympathetically-mediated vasoconstriction lead to blood pooling in the splanchnic bed and paralyzed lower limbs, decreasing circulating blood volume and minimizing venous return resulting in persisting hypotension, especially following cervical and high thoracic SCI. While a modest decrease in resting blood pressure is typically considered cardioprotective[52], caution should be taken when it results from the disruption of sympathetic pathways.

OH is defined as a decrease in blood pressure (>20/10 mmHg) when moving from supine to the upright position. As a result of this positional change, gravitational fluid shifts lead to a redistribution of blood volume away from the head and brain[53]. Following SCI, interruptions to motor and sympathetic autonomic pathways eliminate alternative ways of counteracting this cascade, such as activating muscle pumps (via skeletal muscle contractions), vasoconstriction of the splanchnic and peripheral vasculature, and sympathetically mediated increases in HR. OH may present with light-headedness, dizziness, nausea, sweating, presyncope, and syncope[54]. With chronic and persistent hypotension there is a risk of cognitive impairment, cerebral white matter lesions, morbidity, and mortality. OH is associated with reduced physical activity levels and decreased quality of life which are correlated with increased CVD risk[55].

In addition to resting hypotension, AD presents both an acute and chronic risk of CVD. AD consists of bouts of acute hypertension, caused by vasoconstriction of the vasculature below the LOI via sympathetic reflex to an afferent stimulus (pressure sores, infections, distended bladder or bowel, care routines, and external stimuli), which persists until the stimulus is removed[56]. Acutely, AD can result in stroke[57], arrhythmia[58], and myocardial infarction[59], while over time it decreases cardiac contractility[60].

In a cruel irony, those most prone to OH are also most prone to AD and this episodic shifting from low to high blood pressure may be putting excess strain on the cardiovascular system by increasing arterial stress and decreasing contractility, potentially furthering the risk of a cardiovascular event[61].

Cerebrovascular dysfunction

The regulation of blood flow to the brain is a crucial physiological process which ensures adequate oxygen and nutrient supply amidst perturbations due to physiological and environmental conditions. Cerebrovascular regulation maintains consistent cerebral perfusion over a wide range of systemic blood pressures (60-150mmHg)[62]. However, acute bouts of severe hypotension or hypertension can impair autoregulation and result in debilitating and life-threatening emergencies[61]. Chronic hypotension and hypertension have been shown to shift the set-point of cerebral blood flow velocity (CBFv), respectively[63]. Following SCI, both OH and AD present major challenges to cerebrovascular regulation, with reports of hypotensive and hypertensive episodes occurring as many as 28 and 41 times per day[64]. Symptoms of cerebrovascular dysfunction include headache, dizziness, nausea, and fatigue, with severe cases resulting in syncope, stroke, and aneursim[65]. While the cerebral vasculature is innervated by sympathetic neurons, it is unclear if they provide a functional contribution to the regulation of CBFv[66,67]. Following SCI, physical activity and exercise have been shown to ameliorate the systemic effects of OH and resting hypotension, however the effect of exercise, acute or chronic, on CBFv in individuals with SCI has been scarcely investigated[68].

1.4. Exercise intolerance and blunted cardiovascular autonomic responses

Much of the cardiovascular responses during and after exercise is mounted by autonomic responses. Typically, at the onset of exercise or physical activity, an initial rise

in HR is seen with the withdrawal of vagal tone, with any further increase resulting from the chronotropic effect (direct stimulation of the myocardium or circulating catecholamines) via sympathetic pathways[23]. Blood flow to working muscles is increased and redirected to increase oxygen and nutrient delivery through vasoconstriction, vasodilation, and activation of the skeletal muscle pump. Skin blood flow is increased to aid in thermoregulation. Ventilation and respiration are increased to meet the increased demand for oxygen. After exercise cessation, peripheral vasoconstriction preserves central blood volume maintaining cerebral perfusion.[69,70] Following SCI these responses are impaired, predisposing to exercise intolerance.

Cardiovascular impairments secondary to SCI seen at rest are often further exacerbated during exercise. LOI and AIS continue to be important considerations to exercise response[70]. With sympathetic innervation of the heart exiting from the upper thoracic spinal region (T1-T5), SCI within or above this region will significantly impact cardiovascular responses to exercise. The degree of exercise intolerance is seemingly associated with the level and completeness of injury, with higher, more complete injuries exhibiting greater detriments.

Following SCI, the initial rise in HR is present due to vagal withdrawal, however individuals with high level SCI have a significant lower HR_{peak} during high intensity exercise, chronotropic stimulation is blunted, and HR_{peak} is decreased[71]. Chronotropic incompetence (CI) refers to the inability to increase HR with increased activity or demand, with the interruption of descending sympathetic pathways due to SCI resulting in a HR_{peak} of about 125 beats per minute[72]. Therefore, HR_{peak} may provide a convenient metric of the severity of injury to cardiovascular autonomic pathways (with a lower HR_{peak} reflecting greater impairment), as well as the extent of impairment of exercise responses. After cervical SCI, maximal exercise results in a 2-fold increase in CO, compared to the 7-fold increase seen in the AB[73]. Disrupted sympathetic innervation removes the ability to redistribute blood flow via vasoconstriction from inactive muscles, the splanchnic bed, and organs not needed during exercise, thus limiting central blood volume and venous return.

SCI above T6 disrupts the function of respiratory muscles, decreasing lung volume and spirometric parameters of both inspiration and expiration. Oxygen consumption and minute ventilation are lower in individuals with high-thoracic and cervical SCI during exercise compared to AB controls, with decreased maximal ventilation being the most

limiting factor[74]. Respiratory muscle paralysis may hamper recovery from exercise and may increase post-exercise hypotension as the respiratory muscle pump is less effective[11]. Respiratory impairments, such as increased bronchoconstriction and excessive mucous production resulting from parasympathetic predominance, further hamper recovery from exercise. Peak oxygen uptake (VO_{2peak}) is regarded as the gold standard in determining cardiovascular fitness and an important index for predicting cardiovascular mortality[75]. Following SCI however, VO_{2peak} may be less reflective of cardiovascular fitness as it is limited by the inability to increase HR or ventilation during exercise, changes in body composition that alter the ratio of muscle and fat mass, and paralysis that impacts the active muscle mass. Furthermore, individuals with high-level lesions, who would be expected to have the lowest aerobic capacity and highest CVD risk, are les likely to be able to complete a maximal exercise test.

Additionally, the impairments in resting autonomic function discussed previously (bradycardia, resting hypotension, OH, and AD) are often exacerbated during and after exercise, with others, such as impaired lung function[74], playing significant roles in limiting exercise and its beneficial effects post SCI.

1.5. Impaired thermoregulation

Thermal control is jeopardized following SCI and is significantly influenced by the LOI and AIS. Individuals with SCI have decreased skin temperatures (specifically below the LOI) which affects heat balance by altering the thermal gradient[76]. There is an absence or severe reduction in the sweat response below the LOI, particularly in those with high-level injuries[77]. Coupled with cardiovascular dysfunction (impaired vasoconstriction, decreased blood flow, etc.), thermoregulation presents a significant challenge for those with high-level SCI, while individuals with lower-level injuries show similar thermoregulatory control to that of AB[14,78].

Sweat responses in those with high-level SCI are diminished as a result of reduced afferent information from insensate skin, as well as impaired efferent vasomotor and sudomotor responses. Losses in evaporative cooling increase the rate of heat gain during exercise and/or heat exposure, while also increasing heat retention afterwards[78]. Controlled heat stress can improve thermoregulation and provide exercise-like adaptations and health benefits[79], which could offset some of the barriers to exercise

previously discussed. However, extreme or prolonged hyperthermia can result in severe hypotension leading to syncope, as well as increased risk of stroke, arrhythmias, and myocardial infarction[80].

1.6. Assessment of CVD risk

The Framingham risk score (FRS) is a sex-specific multivariable risk factor algorithm used to assess general CVD risk within the next 10[52] or 30[81] years. The FRS calculates a percentage risk for the occurrence of a cardiovascular event, such as myocardial infarction or stroke, based on several "traditional" risk factors including age, sex, total cholesterol, HDL cholesterol, systolic blood pressure, blood pressure treatment, smoking status, and the presence or treatment of diabetes. The FRS indicates a risk of 10% or higher as intermediate and suggests treatment considerations; however, the FRS is not population specific (i.e. race, ethnicity, clinical comorbidities).

Given the known association between obesity and CVD risk, the World Health Organization (WHO) has established cut-points for several different measures of adiposity used to classify obesity, indicating an increased risk of CVD[82–84]. Some of these include body mass index (BMI), waist circumference (WC), waist-to-height ratio (WHtR), and blood pressure. These cut-points are used when considering management and treatment options in different healthcare settings. Where data are available, these cut-points are adjusted for specific populations. However, in the absence of population specific cut-points, general cut-points are used, introducing the possibility of misdiagnosis and ineffective treatment.

1.6.1. Impact of SCI on traditional CVD risk factors

CVD is the leading cause of morbidity and mortality among individuals living with SCI, identified as a relevant factor in 40% of deaths compared to 30% in the general population[7]. CVD mortality rates are at least 3 times higher for individuals under 45 years of age living with an SCI, relative to age-matched, uninjured controls showing CVD to have an earlier onset and faster progression in this population[8,85]. Additionally, there is a higher prevalence of CVD among individuals with SCI[8,86]. Given the high CVD burden after SCI, there is considerable interest in understanding what may be driving its onset and progression and how this burden can be accurately assessed within this population.

Age

An article discussing aging used the term “accelerating aging” when describing the aging pattern following SCI, based on an increased risk of experiencing age-related health conditions (hypertension, arthritis, and CVD) at a younger age and with greater severity[87]. There is a higher frequency of secondary health complications and an increased risk of hospitalization due to chronic pain, osteoporosis, and kidney stones compared to aged-matched, AB individuals. Similar to aging, following SCI there is a significant reduction in autonomy, reduced ability to independently complete activities of daily living, and lower general participation within the community[87]. It is unresolved how age, age at the time of injury, and time since injury impact the progression of CVD.

Dislipidemia

Dislipidemia is more prevalent following SCI[88]. A recent review examining available literature on CVD risk factors in chronic SCI highlighted several studies showing significantly lower HDL cholesterol levels and increased ratios of total cholesterol to HDL cholesterol compared to healthy controls[89]. In general, the primary cause of dyslipidemia is attributed to decreased physical activity and an unhealthy, imbalanced diet, and these factors are prevalent barriers faced following SCI.

Blood pressure

As discussed in detail above, SCI severely impacts blood pressure control in individuals with chronic SCI, with a high prevalence of resting hypotension and OH, and yet bouts of sudden and profound hypertension associated with AD. In the general population, a lower blood pressure is generally considered cardioprotective and this is reflected in the determination and management of CVD risk[52]. Given that the severity of hypotension after SCI is related to the severity of injury, it may be that the protective associations between hypotension and CVD risk are lost after SCI.

Smoking

Smoking on its own increases risk of a cardiovascular event 1-2% when determining the 10-year risk using the FRS[52]. There is a higher prevalence of smoking among individuals living with SCI than the general population (19-48% vs. 13-15%, respectively)[90]. SCI can be accompanied by ventilatory complications including impaired function of the diaphragm, intercostal, abdominal, accessory respiratory muscles, and the

presence of baseline bronchoconstriction has been attributed to the disturbance of sympathetic innervation to the lungs[11]. Smoking can exacerbate these ventilatory complications, and coupled with ineffective cough and mucous retention, there is an increase in pulmonary infections and atelectasis following SCI[7]. Smoking is also associated with health disparities outside of respiration including increased risk of urinary tract infections[91] and pressure sores[92]. There is a strong association between current smokers and poor mental health (MH-)[93]. Chronic smoking is associated with increased neuropathic pain (NP) prevalence and severity, along with diminished treatment efficacy[94].

Diabetes

Diabetes is more prevalent following SCI and suggested to have an earlier onset relative to the general population[95]. Clinical conditions including high blood pressure, high cholesterol, stroke, myocardial infarction, and coronary heart disease were two times more likely when diabetes was present[96]. Additionally, MH- and pain were more likely to be reported by individuals with diabetes[95].

Obesity

SCI is associated with several changes in body composition resulting from the combination of motor, sensory, and autonomic impairments post injury. Obesity, and increased adiposity, are more prevalent following SCI[97], and are thought to be underreported as a result of measurement techniques and body composition changes. Several factors impact accuracy including reduced physical activity[98], increased sedentary time[99], decreased lean muscle mass[100], changes in metabolism[101], and gastrointestinal function[102]. In those with SCI, visceral adipose tissue surrounding internal organs is increased relative to subcutaneous adipose tissue[103]. Visceral adipose tissue is highly associated with hypertension, dislipidemia, and diabetes leading to a particularly poor prognosis in terms of CVD risk[104].

BMI ($weight \cdot height^{-1}$) is promoted by WHO as a simple indicator of obesity[82] and is the primary screening tool for obesity in the general population[105]. However, use of BMI as a risk stratification tool may not be ideal for the SCI population. From a practical standpoint, WC and WHtR eliminate the need for specialized wheelchair scales to determine weight. Height can be inferred from length, but contractures and spasticity can increase the difficulty of lying supine with flexed feet and straight legs. WC and WHtR

have been shown to be more valid measures of obesity in this population as BMI underestimates obesity following SCI[105], WC is more strongly correlated with visceral adiposity tissue[103], and WC and WHtR are correlated with a greater number of CVD risk factors after SCI[106]. Lowering the WC cut-point criteria for increased CVD risk following SCI has been suggested[103,106] due to the increased visceral adipose tissue for a given WC in this population.

1.6.2. Consideration of injury characteristics

Level and severity of SCI

As previously discussed, SCI has significant, broad, and diverse impacts on secondary health complications and associated morbidity and mortality that are inherently related to LOI and AIS. Although there are common delineations when considering level and severity of injury (tetraplegia vs paraplegia, complete vs. incomplete), there is a lack of discernment when attempting to tease out subtle differences on CVD risk factors. For example, there is an increased risk of CVD with higher (tetraplegia vs. paraplegia), more severe (AIS A-C vs. D) injuries[107], however similar differences have been shown for injuries above T6[86] and when considering AIS A vs. B-D[108]. These conflicting results highlight the need of specific, classified cut-points to help identify individuals at increased CVD risk.

Age at and time living with SCI

Time matters. Increases in age and duration of injury (DOI) for those living with SCI elevates CVD risk[108]. As stated previously, CVD presents earlier and progresses faster following SCI[8]; however, the timeline is not well understood and raises some general questions. Does the increased CVD risk reflect an immediate and direct result of SCI, or is it a consequence of accelerated CVD risk from the time of injury resulting from motor, sensory, and autonomic dysfunction? What role does age at time of injury play? These questions are difficult to answer, especially considering the heterogeneity of individuals experiencing SCI as well as the complications experienced after injury. Addressing these questions will allow for earlier, more accurate identification of at-risk individuals and improved management approaches.

1.6.3. Neuropathic pain

Defined as “pain arising as a direct consequence of a lesion or disease affecting the somatosensory system”[109], NP is prevalent in nearly 50% of individuals living with an SCI[110]. Following SCI, aberrant sprouting of sensory axons induces alterations to sympathetic pathways contributing to increased sensitivity of sympathetic reflexes through morphological changes[111], enhanced input from primary sensory neurons[112], central sensitization of nociceptive inputs[113], and hypersensitive postganglionic sympathetic responses[114], providing possible mechanistic links between NP and autonomic impairment. Furthermore, NP may intersect with AD, a cardiovascular condition unique to high-level SCI due to injury to descending autonomic (sympathetic) pathways, manifesting as paroxysmal hypertension in response to sensory stimuli below the LOI[114]. It may be that the presence of NP as a pervasive sensory stimulus, coupled with central sensitization of nociceptive input and excessive sympathetic responses link NP and AD, with adverse CVD consequences[112].

The presence of NP is associated with a two-fold increase in CVD risk following SCI[86]; however the causal pathway underlying this relationship remains unclear. There are conflicting results regarding the relationship between injury characteristics and the presentation of NP, with reports of NP being more common in people with tetraplegia[115]I, paraplegia[116,117], or no difference[110,118] based on the LOI. Shared mechanistic links between NP and AD suggest that impaired autonomic function may play a role in NP. A limitation that may be playing a role in these differences is how the data has been reported[86,110,115,119]. Research investigating relationships regarding NP have generally used measures of NP derived from self-report questionnaires. Questions asking about NP are broad (“Do you have neuropathic pain”, “Have you experienced neuropathic pain”), with differing timeframes (“in the last four weeks”, “in the last 12 months”), and differ between research studies. Validated, clinical measures, such as the Douleur Neuropathique 4 exam (DN4)[120], have not been employed when exploring the relationships and impact NP has with injury characteristics and secondary health complications of SCI.

1.6.4. Mental health

The prevalence of MH- following SCI is substantially greater than the general population (even when considering populations with other health conditions), with estimates that between 10-40% of the SCI population experience depressive symptoms[121,122]. A more severe injury is associated with a higher risk of MH-[123], while results for the effects of age[123,124] and DOI[125] on MH- are conflicting. It is known that in the AB, MH- symptoms or major depression are associated with increased CVD morbidity and mortality, and MH- is considered as an independent risk factor in the progression of CVD[126]. MH- induces dysregulation of the sympathoadrenal system, with increases in inflammation-related interleukins (IL-6, IL-1B), C-reactive protein, and triglycerides that promote systemic inflammation and dyslipidemia, predisposing to cardiovascular events[127]. Dyslipidemia and systemic inflammation are also increased following SCI, possibly creating an additive effect that further increases CVD risk in this population[8]. In addition, individuals with SCI experience unique barriers that may decrease the effectiveness of traditional treatment options (i.e. increased medication use, altered social involvement, decreased physical activity). The five-item mental health inventory (MHI-5) is a validated, clinical measure used to assess mental health in individuals with SCI[128]. However, previous research studies investigating the associations between MH-and CVD have altered the questionnaire, not using all of the questions or using differing timeframes.

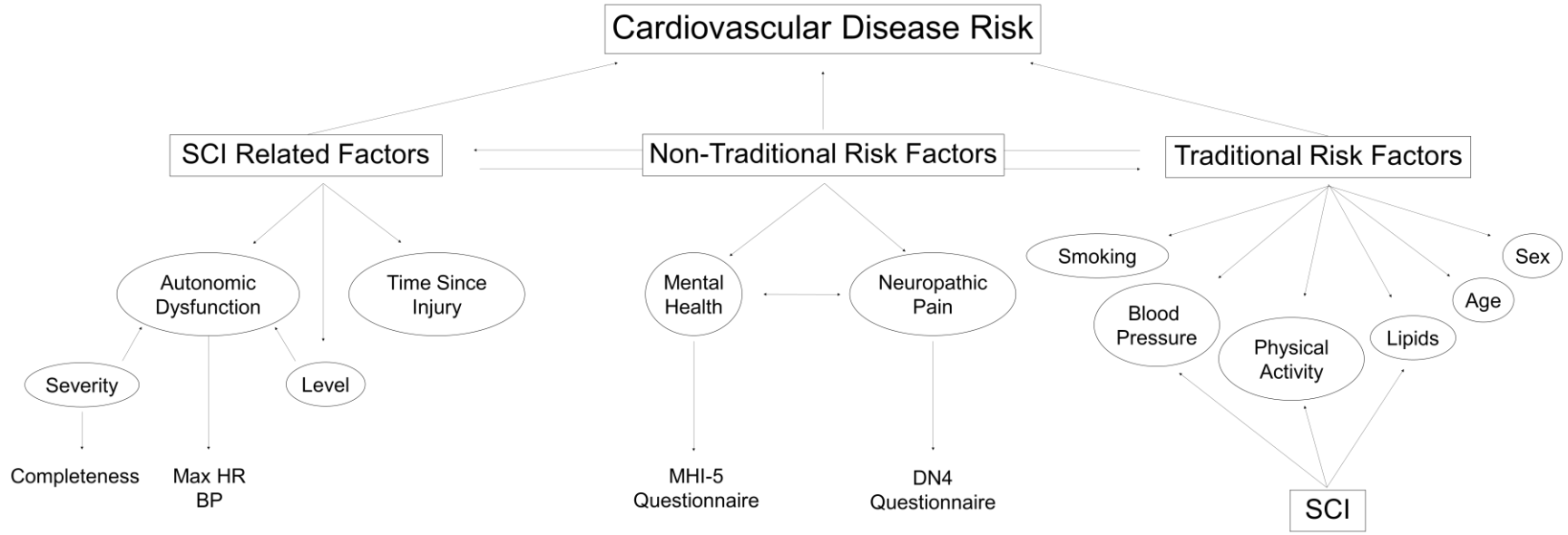

Figure 1.4. Theoretical model highlighting the interactions between traditional CVD risk factors, SCI related risk factors, and non-traditional risk factors

1.7. Exercise as medicine

Exercise is Medicine® is a health initiative created with the vision "to make physical activity assessment and promotion a standard in clinical care, connecting health care with evidence-based physical activity resources for people everywhere of all abilities"[129]. The concept is based on substantial evidence that exercise and physical activity reduce the risk of chronic disease and that most individuals can find simple ways to increase daily physical activity. WHO guidelines for the improvement of cardiorespiratory fitness, bone health, and to reduce the risk of non-communicable disease advocate at least 150 minutes of moderate-intensity aerobic or 75 minutes of vigorous-intensity aerobic activity throughout the week. Muscle strengthening activities involving major muscle groups should be performed 2 or more days a week[130]. Participation in regular physical activity significantly reduces the risk of CVD, diabetes, and dyslipidemia, it improves cardiovascular function and blood pressure control, and is a key determinant in energy balance and body composition[130]. Recent reports have also focused on the impact of increased sedentary time and suggest that the cardiovascular benefits of a daily bout of exercise are undone by being sedentary throughout the rest of the day[131,132].

Physical inactivity following SCI

For any given population, physical activity is often the first management intervention discussed to mitigate CVD progression and its associated risk factors with benefits encompassing physical[133], social[134], and mental[18] health domains. SCI introduces additional barriers to attaining guideline levels of physical activity. SCI results in motor impairment and muscle paralysis which can make voluntary physical activity impossible or ineffective. Physical activity participation is significantly reduced following SCI with up to 50% of individuals reporting 0 minutes of physical activity of any kind, with higher, more complete injuries associated with lower levels of physical activity[45,133,135]. This is accompanied with an increase in sedentary time associated with significant increases in CVD and diabetes risk[136]. A more sedentary lifestyle, whether imposed upon or adopted by individuals with SCI, results in decreased fitness and physical deconditioning, negative changes to cardiac and peripheral vasculature structure and function, blood pressure dysregulation, muscle atrophy, bone loss, fat gain, and dyslipidemia[137]. Of note, this list is similar to that of cardiovascular autonomic dysfunction discussed above, adding to the complexity of CVD progression after SCI.

The WHO physical activity guidelines come with the caveat that although they can be applied to individuals with disabilities, adjustments may be needed to compensate for exercise capacity and specific health risks and limitations[130]. Accordingly, specific guidelines were recently developed that specify the type and dose of exercise needed to elicit improvements in general fitness and cardiometabolic health for individuals living with SCI[138]. Aiming to identify the lowest effective dose, the guidelines recommend 20 minutes of moderate to vigorous-intensity aerobic exercise 2 times per week and 3 sets of strength exercises for each major functioning muscle group 2 times per week for general fitness, and 30 minutes of moderate to vigorous-intensity aerobic exercise 3 times per week for cardiometabolic health[138]. These guidelines are significantly less than those recommended by WHO for the general population, raising concerns that the associated health benefits may also be lower.

Several studies have been conducted to identify barriers and facilitators of physical activity following SCI[135,139,140]. A common barrier in all studies was related to the environment, specifically citing lack of accessible facilities, unaffordable equipment, and no available personal assistance.[140] Additional barriers directly relevant to this thesis include physical body, low return on physical investment, and fear of injury.

1.7.2. Exercise adjuncts for individuals living with SCI

Exercise and physical activity are key factors in mitigating the progression of CVD in the AB. SCI presents several barriers to achieving current exercise guidelines for decreasing CVD risk. Motor impairments preclude participation in many activities, while availability and access to accessible/adaptive equipment is a recognised barrier. Considering the barriers that exist for individuals living with SCI to meet current exercise and physical activity guidelines to improve cardiometabolic health, auxiliary means of improvement may be advantageous. Two avenues that could be particularly efficacious are passive heat therapy (PHT) and passive lower limb movement (PLLM).

Passive heat therapy

Passive heat exposure (i.e. sauna or hot bath use) resulting in core temperature (T_{core}) increase around 1°C have beneficial acute and chronic cardiovascular effects.[141] Although slight differences are reported between heating techniques, cardiovascular adaptations are reliant upon elevations in T_{core}. Like exercise, PHT has both acute and

chronic benefits on several markers of cardiovascular function. Acutely there is an increase in CO, driven by an increased HR while SV is maintained. We see an overall decrease in blood pressure with cutaneous vasodilation to increase skin blood flow and a simultaneous vasoconstriction of the splanchnic vascular bed, while CBF is maintained.[141] These are bolstered by an increase in total blood plasma volume. The magnitude of these responses are similar to those seen during moderate intensity exercise bouts of equal length, with similar recovery trajectories[142]. A recent review highlighted the considerable overlap between cardiovascular outcomes achieved through chronic PHT and those of exercise[143]. These findings are highlighted in (**Fig 1.5**) and encompass cardiorespiratory fitness, cardiometabolic health, and vascular health. A large (n = 2315) prospective cohort study showed a 50% decrease in the risk of CVD-related mortality in daily sauna use compared to weekly exposure, with frequency and exposure of sauna bathing predicting sudden cardiac death, fatal CVD, and all-cause mortality over a 30-year follow-up period[144].

Relatively few studies have looked at cardiovascular outcomes during acute heat therapy following SCI, with only one doing daily repeat exposures for 7 days[145]. Acute bouts of PHT have shown increases in HR[79,145–150] and CO[148] similar to the AB, however blood pressure reportedly increased[151]. Impaired sympathetic control of the vasculature may dampen the efficacy of passive heat stress as it was shown to be reliant on increased vasodilation and vasoconstriction, however there was reduced arterial stiffness, enhanced endothelial-dependent dilatation, and changes in arterial shear stress following a single bout of heat therapy[79].

Safety is a primary concern for heat therapy as SCI can impair sweating responses below the LOI and injuries above T6 may significantly reduce the ability to increase skin blood flow, impacting evaporative and conductive heat loss mechanisms. Individuals with SCI require less time to achieve a 1°C rise in T_{core} compare to AB individuals, while those with cervical injuries have the fastest rise [148,150]. Recovery from heat stress is also impaired in relation to LOI, with a slower decrease in T_{core} for higher-level injuries after heat stress is removed[150,152]. While it is evident that PHT holds promise for improving cardiometabolic health and may indeed be most beneficial for those with higher, more complete injuries, these individuals are also those for whom it poses the greatest risk of heat-related injury. A better understanding of the current state of the literature regarding PHT is needed to safely inform future research in this area.

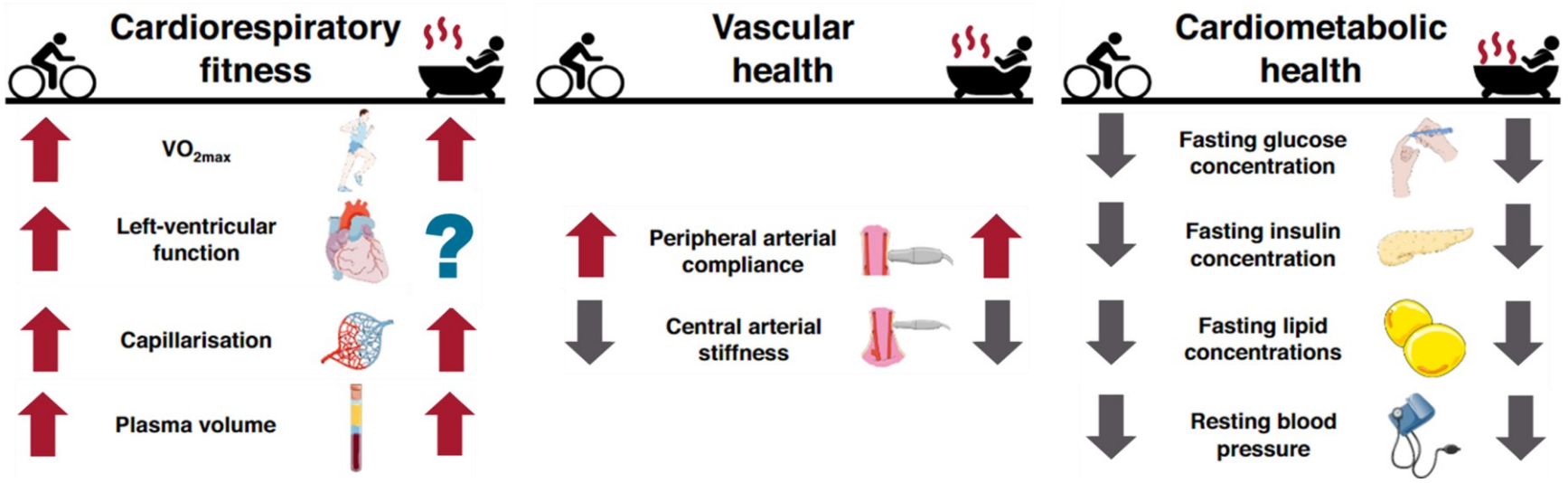

Figure 1.5. Chronic adaptations to exercise and passive heating
In the general population, PHT is effective at improving several indices of cardiorespiratory fitness, vascular health, and cardiometabolic health with responses that are similar to those seen during exercise. Adapted with permission from Cullen[143].

Passive lower limb movement

PLLM, including passive cycling (PC) and body weight supported treadmill training (BWSTT), has emerged as a potential therapeutic approach to counteract cardiovascular impairments and deconditioning known to lead to increased CVD risk following SCI. In healthy controls PLLM has been shown to improve CO, driven by an increase in SV, and mean arterial pressure (MAP), although not to the extent seen during active movement[153]. Even following a single bout, PLLM improves lipid profiles and cardiometabolic risk factors[154]. The increase in SV during PLLM is attributed to an increase in venous return resulting from passive mechanical activation of the skeletal muscle pump, along with muscle mechanoreceptor-evoked increases in myocardial contractility[153]. For individuals living with SCI, PLLM is efficacious at acutely improving cardiovascular outcomes, however results vary with differences attributed to protocol design and equipment used[155]. Several studies have reported increased peripheral blood flow[156,157], blood pressure[158], HR[158,159], SV[158–162], and CO[158–162] following acute sessions of PC with mixed results following multiple bouts of exercise[159,163]. With a greater amount of blood pooling in the lower limbs due to paralysis, the benefits of PLLM may be greater than for the AB at increasing circulating blood flow and reducing the likelihood of OH. In addition to cardiovascular effects, PC has also been shown to improve neurological (decreased spasticity), ventilatory[155] ,and musculoskeletal outcomes (increased range of motion, decreased muscle atrophy)[164]. Although efficacious, accessibility continues to be a barrier. Availability of adaptable equipment is limited to specialized centres and research institutions and can require great time and effort to access, and it remains necessary to devote specific time to exercise as there is not an option to integrate PLLM into activities of daily living or leisure time.

1.8. Thesis outline and project aims

This thesis aims to identify key characteristics of SCI that are contributing to the increased CVD burden following SCI and explore the safety and efficacy of exercise adjuncts to mitigate CVD burden and promote cardiometabolic health. This thesis is composed primarily of independent, yet complimentary manuscripts.

In *Chapter 2*, I aimed to evaluate which markers of obesity, injury characteristics, and autonomic function variables are related to CVD risk in chronic SCI and establish cut-

points for detection and risk management. This manuscript has been peer-reviewed and published:

M.C. Dorton, V-E.M. Lucci, S. de Groot, T.M. Loughlin, J.J. Cragg, J.K. Kramer, M.W.M. Post, V.E. Claydon. (2021). Evaluation of cardiovascular disease risk in individuals with chronic spinal cord injury. *Spinal Cord*; 59:716-729.

In *Chapter 3*, I aimed to determine if clinical measures of NP and MH- are related to CVD risk in chronic SCI, and further elucidate the relationships between CVD risk, autonomic function, NP, and MH-. This manuscript has been peer-reviewed and accepted for publication in *Spinal Cord*:

M.C. Dorton, J.K. Kramer, S. de Groot, M.W.M. Post, V.E. Claydon. (2023). Relationships between cardiovascular disease risk, neuropathic pain, mental health, and autonomic function in chronic spinal cord injury.

Next, in *Chapter 4*, I performed a systematic review to summarize the literature exploring the impact of two exercise adjuncts, PLLM and PHT, on cardiovascular outcomes following SCI. This manuscript is in preparation:

M.C. Dorton, C.B. Heavenor, V.E. Claydon. Exercise adjuncts in spinal cord injury: A systematic review and meta-analysis.

Chapter 5 aimed to establish the safety of a PC device and evaluate its efficacy to acutely improve cardiovascular outcomes following SCI. This manuscript is in preparation:

M.C. Dorton, M. Ruiz-Peters, R.H.Y. Lee, V.E. Claydon. Safety and efficacy of a novel passive cycling device on cardiovascular control in individuals living with spinal cord injury.

Lastly, Chapter 6 features a general discussion covering the overall implications of the results of these experiments from a clinical, patient, and research perspective, thesis limitations and future directions.

Chapter 2.

Evaluation of cardiovascular disease risk in individuals with chronic spinal cord injury

2.1. Abstract

Study design: Multicentre, cross-sectional study.

Objectives: To identify which markers of obesity, injury characteristics, and autonomic function variables are related to CVD risk after SCI and establish cut-points for detection and risk management.

Setting: Eight SCI rehabilitation centres in the Netherlands.

Methods: Individuals (n=257) with a traumatic, chronic (≥ 10yrs) SCI, with age at injury between 18-35 years, completed a self-report questionnaire and a one-day visit to a rehabilitation centre for testing. Three anthropometric measures were tested: BMI; WC; and WHtR. Injury characteristics included: AIS; DOI; and LOI. Autonomic function was assessed from HR_{peak} during maximal exercise. Systolic arterial pressure (SAP) and aerobic capacity (VO_{2peak}) were also determined. CVD risk was calculated using the FRS.

Results: All anthropometric variables were associated with FRS, with WC showing the strongest correlation ($r=0.41$, $p<0.001$) and greatest area under the curve (0.73) for 10-year CVD risk (%). Furthermore, WC was the only measure of obesity that was correlated with autonomic function. WC, DOI, SAP, HR_{peak}, LOI, and VO_{2peak} (variable importance: 0.81, 1.0, 0.98, 0.98, 0.66, 0.68, respectively) were important predictive variables for 10-year CVD risk in individuals with SCI.

Conclusions: We confirm that WC is a simple, practical measure of CVD risk and is associated with injury characteristics thought to play a role in the increased CVD risk following SCI.

2.2. Introduction

There are currently an estimated 4 million individuals living with the devastating consequences of SCI worldwide, with an average of 750,000 new cases each year[1]. SCI is more common in males (~76% of the SCI population), with falls representing the leading mechanism of SCI[2]. Due to advances in acute care and chronic management, the average

age of individuals living with SCI (51 years) is increasing[2]. With these advances, CVD, a secondary complication of SCI, is now the leading cause of morbidity and mortality among individuals with SCI[7], similar to the AB population[165]. However, CVD is reported to occur earlier and progress more rapidly in individuals with SCI than in the AB[166].

SCI disrupts sensory, motor, and autonomic pathways, with higher, more complete injuries resulting in greater loss of sensorimotor function[3] and increasing autonomic impairment[56]. The impairments in autonomic function are particularly pertinent in terms of CVD risk, as disruption to descending cardiovascular autonomic pathways impairs cardiovascular control of blood pressure and HR, particularly in those with injuries at or above the sixth thoracic vertebra (T6)[15,72]. These high-level autonomically-complete lesions are characterised by resting supine[10] and further OH[15]. This is accompanied by decreases in CO[15] and an inability to increase HR appropriately during exercise, contributing to the profound exercise intolerance seen after high-level SCI[70]. In addition, this day-to-day hypotension is often interrupted by AD, acute and severe hypertensive episodes with SAP increasing to levels in excess of 200 mmHg[167]. These life-threatening surges in blood pressure are a reflex response to sensory stimuli arising from below the level of the lesion[38] and are attenuated only with the removal of the stimulus[72]. AD can be proarrhythmogenic[59,168,169,9] and these intense hypertensive crises may increase the risk of stroke[170] and myocardial infarction[59,171], and may augment CVD progression in this population[60,166]. Furthermore, blood pressure instability and associated cardiac arrhythmia may contribute to the more than 2-fold increased risk of both heart disease and stroke after SCI[8]. These numerous cardiovascular autonomic impairments have a devastating impact on quality of life, are consistently rated as a priority for improvement by individuals living with SCI[29,172], and are associated with an increased risk of CVD[9,173]. However, assessing and categorizing autonomic function following SCI remains problematic, and quantitative tools for the assessment of autonomic function are not yet incorporated in the classification of SCI[174].

The repercussions of impaired autonomic function in this population are profound and affect multiple systems, negatively impacting traditional CVD risk factors, while possibly introducing new ones. Following SCI the prevalence of obesity is increased, likely from reduced physical activity[98], increased sedentary time[175], and decreased lean muscle mass[100], although alterations in metabolism[101] and gastrointestinal function[102] may also contribute to increased adiposity after SCI. There is also a high prevalence of metabolic

syndrome in individuals with SCI[176]. In those with autonomic impairment, increases in adiposity are commonly located around the viscera[103], which has a particularly poor prognosis in terms of CVD risk[104].

Given the high CVD burden after SCI, there is considerable interest in optimising assessment tools for the evaluation of CVD risk in individuals with SCI, to ensure they are appropriate for the unique needs and physiology of this population. Given the known association between obesity and CVD risk, metrics related to adiposity are often used as screening tools. While BMI remains the 'gold standard' measurement for the general population, it is reported to underestimate obesity in those with SCI[105]. From a practical standpoint, WC provides several measurement advantages in an SCI population eliminating the need for specialized wheelchair scales to determine weight, and avoiding the difficulties, brought by spasticity and contractures, of recording height or length. There are promising preliminary data supporting the use of WC, and perhaps WHtR, as valid measures of obesity-related CVD risk in individuals with SCI[106,177]. However, these need to be confirmed in larger cohorts. In addition, the impact of sex and injury characteristics on obesity-related CVD and the development of SCI-specific cut-point values for obesity-related CVD are lacking.

Accordingly, we aimed to identify which metrics of obesity, injury characteristics, and autonomic function variables are related to CVD risk (determined using the FRS in individuals with chronic traumatic SCI. We also aimed to establish SCI-specific cut-point values for increased CVD risk based on individual and injury characteristics, in order to help identify those individuals at high-risk for CVD and assist health care providers when considering risk management.

2.3. Methods

This study is part of the Dutch multicentre research programme "Active LifestyLe Rehabilitation Interventions in aging Spinal Cord injury (ALLRISC)", a cross-sectional study among individuals with long-term SCI living in the Netherlands[178]. This study was approved by the Medical Ethics Committee of the University Medical Center Utrecht and the Department of Research Ethics at Simon Fraser University. Investigations were performed in accordance with the Declaration of Helsinki of the World Medical Association[179]. All participants gave written informed consent prior to participation.

2.3.1. Participants

Individuals using a wheelchair (hand-rim or electric) with a traumatic, chronic (≥ 10yrs) SCI with age at injury between 18-35 years were included in the study. These criteria were applied to limit the confounding effects of age-related co-morbidities and reduce the impact of CVD risk factors present prior to injury.

2.3.2. Procedures

The study consisted of a one-day visit to a rehabilitation centre that included an extensive medical assessment, physical examination, oral interview, and several physical tests. Two weeks prior to the visit, participants were asked to complete a self-report questionnaire. On the day of the visit, participants were asked to fast (except for water) for 12 hours prior to testing. They were asked to refrain from vigorous exercise on the day of testing, and to ensure appropriate bladder and bowel care was performed prior to testing to minimise the likelihood of AD during testing in susceptible individuals.

Personal characteristics

Age, sex, and smoking status were extracted from the self-report questionnaire. Participant weight was determined by weighing participants in their wheelchair on a weigh bridge, and then subtracting the weight of the wheelchair. Participants reported their own height. BMI was calculated as weight divided by height squared ($kg \bullet m^{-2}$). WC was measured in cm in the supine position, at the narrowest part of the waist after a normal expiration, using a stretch resistant measuring tape. WHtR was determined by dividing the measured WC by the self-reported height. Medication use was noted.

Injury characteristics

DOI was extracted from the self-report questionnaire. A physiatrist determined the LOI and AIS according to the International Standards for Neurological Classification of Spinal Cord Injury[3]. A complete lesion was defined as the absence of motor and sensory function in the sacral segments and classified as AIS grade A. AIS grades B, C, and D were classified as incomplete lesions. In addition to using LOI linearly (C1=1, C2=2, etc.), LOI was categorised according to three groups based on the known impact of LOI on cardiovascular autonomic pathways: C1–C8 levels were defined as “high” injuries (potential loss of autonomic control of cardiac function and key vascular beds for blood

pressure control); T1–T6 levels as “mid” injuries (potential loss of autonomic control of key vascular beds for blood pressure control, but minimal impairment to cardiac function); and SCI levels below T6 as “low” injuries (largely intact cardiovascular autonomic function).

Lipoprotein and metabolic measures

Fasting blood samples were taken to determine the lipoprotein profile (high-density lipoprotein cholesterol [HDL-C], low-density lipoprotein cholesterol [LDL-C] and total cholesterol [TC]), as well as the fasting blood glucose and glycated haemoglobin levels (HbA1c), used to determine the presence of diabetes mellitus. Participants were considered to have diabetes mellitus if their HbA1c levels were ≥48 $mmol•mol^{-1}$ or they were taking a medication associated with the treatment of diabetes (metformin or insulin). Standardized laboratory techniques were used.

Cardiovascular autonomic function

We evaluated the integrity of cardiovascular autonomic function from the HR_{peak} during graded maximal exercise testing[46]. We also determined resting SAP, which is heavily influenced by the integrity of cardiovascular autonomic pathways after SCI. Systolic (SAP) and diastolic arterial blood pressure (DAP) were recorded using a digital sphygmomanometer while participants were seated in their wheelchair. We determined the prevalence of hypotension using WHO criteria: for men, SAP <110 mmHg; for women, SAP<100 mmHg. HR_{peak} (Polar Electro, Kempele, Finland) and VO_{2peak} (Oxycon Delta) responses to exercise were determined while participants performed a standardised graded peak wheelchair exercise test on a treadmill[178,180]. The test was preceded by 5 minutes of seated rest. Participants then began manually wheeling at a speed of 2km/h for those with tetraplegia and 4 km/h for those with paraplegia (3km/h was used in cases where the other options were too slow or too fast for the individual). The treadmill incline was increased by 0.36° every minute until the test was terminated because of exhaustion or inability to keep pace with the speed. The HR_{peak} was determined as the highest 5s average HR during the entire test. CI was defined as a HR_{peak} <125 beats per minute and a normal HR_{peak} as ≥125 beats per minute (based on peak responses observed previously in those with high-level SCI and associated CI)[72].

CVD risk

We used the FRS to calculate both the 10-year[52] and 30-year[81] CVD risk. This score utilizes the following risk factors: sex; age; smoking status; diabetes; SAP; antihypertensive treatment; HDL-C; and TC. However, because SCI can impair blood pressure regulation (particularly with lesions above T6) such that a lower SAP in a SCI population may not be associated with a reduced overall CVD risk in the same way as seen in AB individuals, a neutral SAP of 120mmHg was used when calculating the risk score. A risk score of 10% is considered "intermediate risk" and this was the cut-point used for classifying "at-risk" individuals[52].

2.3.3. Statistical analyses

Statistical analyses were performed using SigmaPlot statistical software (version 13; Systat Software Inc., San Jose, CA) and R (version 3.5.1, 2015). Continuous data were tested for normality using the Shapiro-Wilk test and parametric or nonparametric statistics were used as appropriate. Correlations were performed using Spearman's rank-order tests (nonparametric data) or Pearson's product moment analyses (parametric data) to examine the relationships between anthropometric measures, individual risk factors and 10-year and 30-year FRS. Numeric variables included: age (years); DOI (months); WC (cm); BMI ($kg \bullet m^{-2}$); WHtR ($cm \bullet m^{-1}$); HbA1C ($mmol \bullet mol^{-1}$); HDL-C ($mmol \bullet L^{-1}$); TC ($mmol \bullet L^{-1}$) and VO_{2peak} ($mL \bullet kg^{-1} \bullet min^{-1}$). Categorical variables included: sex (1=male, 2=female); presence of diabetes (0=non-diabetic, 1=diabetic); smoking status (0=non-smoker, 1=smoker; defined as currently smoking, having smoked within the last 5 years, or having smoked >20 pack years in the last 15 years[181–183]).

Several variables were incorporated in the analyses as both numeric and categorical parameters: FRS (categorical: defined as at-risk FRS≥10%=1; not at-risk FRS<10%=0; numeric: risk score %); LOI (categorical: classified as "high"=1, "mid"=2, or "low"=3; ordinal, to be handled as numeric : C1=1, C2=2 etc.); AIS (categorical: categorised as complete (A)=1, incomplete (B-D)=2; ordinal, to be handled as numeric: A=1, B=2, C=3, D=4); HR_{peak} (categorical: classified as CI present (HR_{peak}<125bpm)=1, CI absent (HR_{peak}≥125bpm)=0; numeric: HR_{peak} bpm); SAP (categorical: normal (110-140mmHg)=0, abnormal (<110mmHg or >140mmHg)=1; numeric: SAP mmHg). This approach was taken because we felt it might be preferable clinically to use categorical

values for risk assessment, but we wanted to validate that information contained in the linear analyses was not being lost with this approach. Linear regression and Akaike information criterion (AIC) model-averaging were used to assess the impact of each variable on the FRS. We did not include potential predictors in the model that were incorporated in the generation of the FRS score. Receiver operator characteristic (ROC) curves were produced, and the area under the curve (AUC) calculated. Cut-point values were determined using the Euclidean, Youden, and Product indices, derived from the sensitivity and specificity values generated from ROC analysis[184,185]. Agreement between at least two indices was necessary for a cut-point value recommendation[184]. Unbiased recursive partitioning (URP) was employed as an additional method to confirm variables of interest and their cut-point values. URP identifies homogenous subgroups from an initial heterogeneous population, creating conditional inference trees.[186] Note that a given variable can appear in more than one location in a conditional inference tree. In some cases, where sample sizes permitted, separate analyses were conducted for male and female participants. Sex differences were determined using unpaired student t-tests (parametric data) or Mann-Whitney t tests (nonparametric data) and chi-squared analyses for proportions. The level of significance was set at $p < 0.05$. Continuous data are reported as mean ± standard error unless stated otherwise; categorical variables are reported as percentages.

2.4. Results

2.4.1. Participants

A total of 282 individuals participated in the study. We were specifically interested in the effects of traumatic SCI, so data from 257 individuals (61 females) aged 47±8 (SD) years with chronic (24±9 (SD) years) traumatic SCI were included in the analyses. Participant characteristics are shown in **Table 2.1**. For various reasons not all data were collected in all participants; sample sizes for each measure are provided in **Table 2.1**. Most lesions were cervical (45%) or thoracic (50%); 71% were motor/sensory complete and 79% had lesions that could affect cardiovascular autonomic control. For the cohort as a whole, 87 individuals (38%: 82 male and 5 female) were considered at risk of CVD using the 10-year FRS, and 176 individuals (77%: 149 male and 27 female) were at risk of CVD using the 30-year FRS. As in the AB, males were at greater risk for CVD based on both

the 10-year and 30-year FRS, compared to females. Male sex was associated with higher 10-year and 30-year FRS, and a higher prevalence of resting hypotension (p=0.01) and diabetes (p=0.01). Males also had significantly higher WC, HbA1C and lower HDL-C. Males had higher VO_{2peak}, but not higher $HR_{peak,}$ than females (**Table 2.1**). Older individuals had higher 10-year (r=0.70; p<0.001; n=228) and 30-year (r=0.64; p<0.001; n=228) FRS.

Table 2.1. Participant characteristics

Characteristic	All	n	Male	n	Female	n	p value
Age (years)	47±8	257	47±9	196	47±9	61	0.98
Duration of injury (years)	24±9	257	24±9	196	23±9	61	0.86
Level of injury (%)							
Cervical	45	114	47	93	34	21	0.07
Thoracic	50	128	47	92	59	36	0.10
Lumbar	5	14	6	11	5	3	0.77
Sacral	0	0					
Motor/sensory completeness of injury (%)							
Complete	71	183	70	138	75	45	0.45
Incomplete	29	73	30	58	25	15	0.45
Stratification by autonomic impairment (%)							
High (C1-C8)	45	114	47	93	34	21	0.07
Mid (T1-T6)	34	88	32	63	41	25	0.20
Low (Below T6)	21	54	20	40	23	14	0.61
BMI ($kg \cdot m^{-2}$)	25±5	254	26±5	193	25±5	61	0.21
WC (cm)	97±15	239	**100±14**	**184**	**89±14**	**55**	**<0.001**
WHtR ($cm \cdot m^{-1}$)	0.54±0.08	238	0.55±0.08	183	0.53±0.09	55	0.14
HbA1C ($mmol \cdot mol^{-1}$)	36±7	209	**37±8**	**160**	**35±4**	**49**	**0.04**
Diabetes (%)	12	25	**15**	**24**	**2**	**1**	**0.01**
Smoking (%)	35	89	35	69	33	20	0.77
HDL-C ($mmol \cdot L^{-1}$)	1.2±0.36	228	**1.1±0.28**	**172**	**1.5±0.45**	**56**	**<0.001**
TC ($mmol \cdot L^{-1}$)	4.9±1	228	4.8±1	172	5.1±1	56	0.06
SAP (mmHg)	126±26	253	125±26	192	126±325	61	0.78
HR_{peak} (bpm)	147±29	156	145±30	118	152±26	38	0.24
VO_{2peak} ($ml \cdot min^{-1} \cdot kg^{-1}$)	17.1±6.1	160	**17.8±6.2**	**118**	**15.2±5.4**	**42**	**0.017**
Hypotension (%)	26	69	**30**	**57**	**13**	**8**	**0.01**
CI (%)	23	36	25	29	47	7	0.43
10-year FRS (%)	10±8	227	**12±8**	**172**	**5±4**	**55**	**<0.001**
10-year increased FRS (%)	38	87	**48**	**82**	**9**	**5**	**<0.001**
30-year FRS (%)	23±16	228	**27±16**	**172**	**14±10**	**56**	**<0.001**
30-year increased FRS (%)	77	176	**87**	**149**	**50**	**27**	**<0.001**

Data are presented as mean ± standard deviation or percentages. Note that not all measures were obtained in all participants. Bold text denotes significant differences ($p<0.05$) between males and females, with significance indicated in the last column (p value). Abbreviations: BMI, body mass index; WC, waist circumference; WHtR, waist-height ratio; HbA1C, glycated haemoglobin; HDL-C, high-density lipoprotein cholesterol; TC, total cholesterol; SAP, systolic arterial pressure; HR_{peak}, maximum heart rate at peak aerobic capacity; VO_{2peak}, peak oxygen uptake during maximal exercise; CI, chronotropic incompetence; FRS, Framingham risk score; n, sample size.

2.4.2. Anthropometric measures and FRS

All three anthropometric measures (WC, WHtR, and BMI) were positively correlated with both the 10-year and 30-year FRS for all participants combined ($p<0.001$), as well as for the male cohort ($p<0.001$) (**Table 2.2**). Correlations were not statistically

significant in females, in whom the sample size was much smaller. For the group as a whole, WC had the numerically highest correlation with both 10-year and 30-year CVD risk.

Table 2.2. Correlations between markers of obesity and 10-year and 30-year FRS

	10-year FRS (%)			30-year FRS (%)		
	All	**Male**	**Female**	**All**	**Male**	**Female**
WC (cm)	**r=0.406** **p<0.001** **n=210**	**r=0.328** **p<0.001** **n=160**	r=0.247 p=0.084 n=50	**r=0.415** **p<0.001** **n=210**	**r=0.355** **p<0.001** **n=160**	r=0.245 p=0.087 n=50
BMI ($kg•m^{-2}$)	**r=0.340** **p<0.001** **n=226**	**r=0.398** **p<0.001** **n=170**	r=0.077 p=0.569 n=56	**r=0.367** **p<0.001** **n=226**	**r=0.436** **p<0.001** **n=170**	r=0.105 p=0.439 n=56
WHtR ($cm•m^{-1}$)	**r=0.351** **p<0.001** **n=209**	**r=0.356** **p=<0.001** **n=159**	r=0.234 p=0.102 n=50	**r=0.368** **p<0.001** **n=209**	**r=0.380** **p<0.001** **n=159**	r=0.246 p=0.085 n=50

Bold text indicates correlations that achieved statistical significance ($p<0.05$). Correlation coefficients (r), significance levels (p), and sample sizes (n) are shown. Abbreviations: WC, waist circumference; BMI, body mass index; WHtR, waist-height ratio; FRS, numeric Framingham risk score.

ROC curves were generated for all three anthropometric measures and both the 10-year and 30-year FRS (**Fig 2.1**). The AUC for WC was significantly greater than both BMI (p=0.002) and WHtR (p=0.04) for the 30-year FRS, and greater than WHtR (p=0.02) for the 10-year FRS. Using the sensitivity and specificity values derived from the ROC analysis, optimal WC cut-point values for the identification of at-risk individuals were determined to be 97 cm and 94 cm for males, for the 10-year and 30-year FRS scores respectively (**Table 2.3**). Note that there were only 5 women who were considered at-risk for the 10-year FRS, and only 27 women at-risk for the 30-year FRS, and accordingly the determination of the cut-point criteria, particularly for 10-year risk, in females is not considered reliable. The cut-point value for the 30-year risk was 80 cm for females but should be considered with caution due to the low sample size.

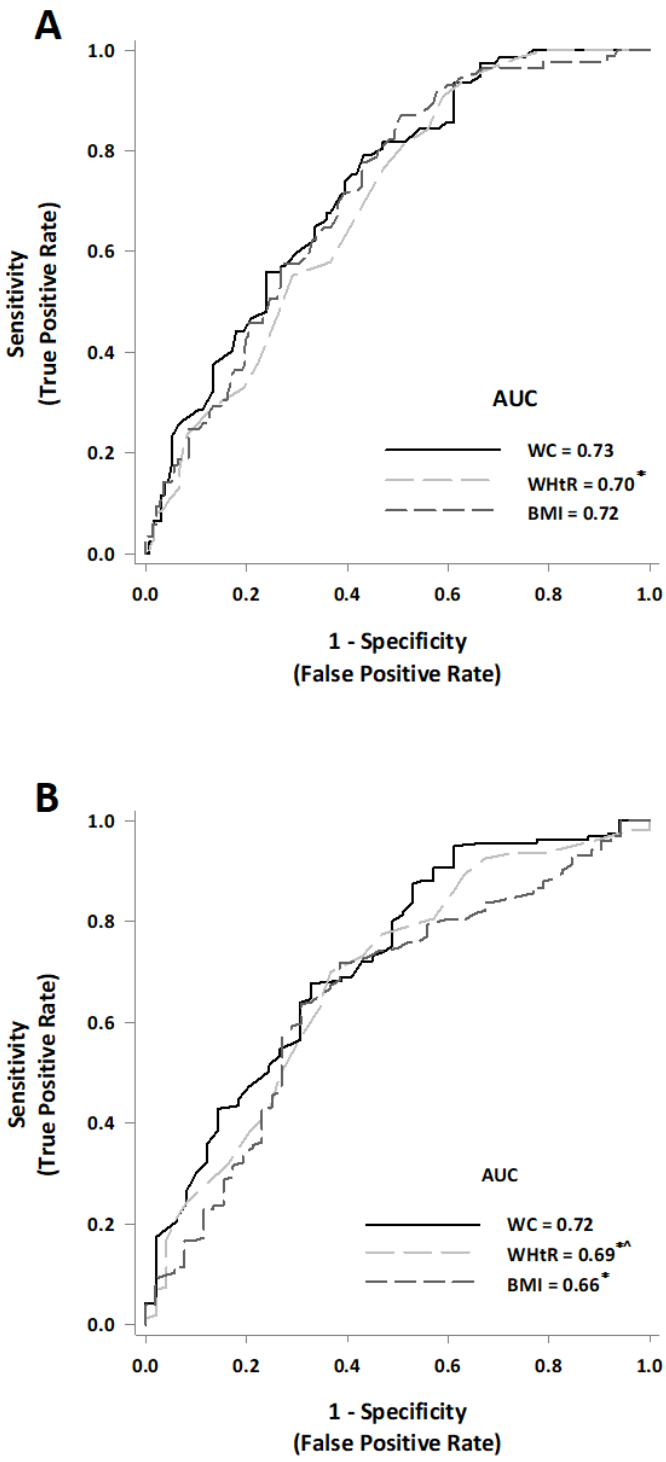

Figure 2.1. Receiver operator characteristic curves showing the ability of markers of obesity to predict an adverse 10-year (A) and 30-year (B) Framingham Risk Score

The area under the curve (AUC) for each metric is provided; a higher AUC signifies a greater ability to correctly classify at-risk individuals. * $p<0.05$ compared to WC, ^ $p<0.05$ compared to BMI. Abbreviations: WC, waist circumference; BMI, body mass index; WHtR, waist-to-height ratio.

Table 2.3. Cut-point values for 10-year and 30-year FRS indicating "at risk" status for CVD

	WC cut-points for increased 10-year FRS (cm)			WC cut-points for increased 30-year FRS (cm)		
	All	Male	Female	All	Male	Female
Euclidean Index	97	97	*	94	94	92
Product Index	95	97	*	94	94	80
Youden Index	95	95	*	94	94	80
WHO Guideline	-	102	88	-	102	88

Data are shown for all participants combined (n=257), and for male (n=196) and female (n=61) subgroups. Abbreviations: FRS, categorical Framingham risk score; CVD, cardiovascular disease; WC, waist circumference; WHO, World Health Organisation. * indicates the inability to determine a 10-year FRS cut-point in females, because of the low number of women (n=5) that were identified as having a high 10-year FRS score.

2.4.3. Anthropometric measures and CVD risk factors

Correlations between anthropometric measures and traditional CVD risk factors are shown in **Table 2.4**. All three anthropometric measures were positively correlated with age, and the presence of diabetes, and negatively correlated with HDL-C. WC was the only anthropometric measure significantly correlated with sex, with males having a larger WC. BMI was also positively correlated with SAP, HbA1C, and TC.

Table 2.4. Correlations between markers of obesity and traditional CVD factors

	Sex	Age (years)	Smoking	Diabetes	SAP (mmHg)	HbA1C ($mmol \cdot mol^{-1}$)	HDL-C ($mmol \cdot L^{-1}$)	TC ($mmol \cdot L^{-1}$)
WC (cm)	**r=-0.283** **p<0.001** **n=239**	**r=0.194** **p=0.003** **n=239**	r=-0.018 p=0.778 n=238	**r=0.281** **p<0.001** **n=211**	r=0.091 p=0.163 n=236	r=0.136 p=0.061 n=192	**r=-0.428** **p<0.001** **n=210**	r=0.037 p=0.591 n=210
BMI ($kg \cdot m^2$)	r=-0.086 p=0.169 n=254	**r=0.128** **p=0.042** **n=254**	r=0.060 p=0.345 n=253	**r=0.223** **p<0.001** **n=227**	**r=0.133** **p=0.036** **n=250**	**r=0.165** **p=0.018** **n=207**	**r=-0.370** **p<0.001** **n=226**	**r=0.160** **p=0.017** **n=226**
WHtR ($cm \cdot m^{-1}$)	r=-0.092 p=0.159 n=238	**r=0.219** **p<0.001** **n=238**	r=-0.001 p=0.985 n=237	**r=0.240** **p<0.001** **n=210**	r=0.071 p=0.279 n=235	r=0.103 p=0.155 n=191	**r=-0.407** **p<0.001** **n=209**	r=0.067 p=0.335 n=209

Bold text indicates correlations that achieved statistical significance ($p<0.05$). Correlation coefficients (r), significance levels (p) and sample sizes (n) are shown. Abbreviations: CVD, cardiovascular disease; WC, waist circumference; BMI, body mass index; WHtR, waist-to-height ratio; SAP, systolic arterial pressure; HbA1C, glycated haemoglobin; HDL-C, high density lipoprotein cholesterol; TC, total cholesterol. Categorical data: sex (1=male, 2=female); presence of diabetes (0=non-diabetic, 1=diabetic); smoking status (0=non-smoker, 1=smoker).

2.4.4. Impact of injury characteristics on CVD risk factors and FRS

Correlations between injury characteristics, traditional CVD risk factors, and FRS scores are shown in **Table 5**. Longer duration injuries were associated with higher blood pressure, greater adiposity (WC, WHtR), and an increased 10-year and 30-year FRS. Interestingly, when we regressed only DOI and age as determinants of 10-year and 30-year FRS, age alone was significantly associated with FRS, suggesting that the relationship between DOI and FRS reflects that DOI is a corollary for age. Higher level injuries were associated with greater impairments in cardiovascular autonomic function (reflected in lower HR_{peak} and lower SAP), as well as a lower HDL-C. Those with higher LOI were also less likely to smoke and tended to have a higher WC, although this did not achieve statistical significance (p=0.056). LOI was not significantly correlated with the 10-year or 30-year FRS.

Higher AIS scores (more complete lesions) were associated with higher HR_{peak}, SAP, and prevalence of diabetes, and a lower LOI (r=-0.25; p<0.001; n=256). The AIS score was not significantly correlated with the 10-year or 30-year FRS.

Markers of impaired autonomic function (lower SAP and lower HR_{peak}) were correlated with each other. Higher SAP and impaired HR_{peak} were associated with increased 10-year and 30-year FRS. Impaired HR_{peak} was associated with higher LOI and greater WC. Higher SAP was associated with lower LOI, longer DOI, higher TC and HDL-C, higher HbA1C, and higher BMI (**Table 2.5**).

Table 2.5. Correlations between injury characteristics, traditional CVD risk factors, and 10-year and 30-year FRS

	Smoking	Diabetes	HR_{peak} (bpm)	SAP (mmHg)	HbA1C ($mmol \cdot mol^{-1}$)	HDL-C ($mmol \cdot L^{-1}$)	TC ($mmol \cdot L^{-1}$)	WC (cm)	BMI ($kg \cdot m^{2}$)	WHtR ($cm \cdot m^{-1}$)	10-year FRS (%)	30-year FRS (%)
DOI (months)	r=-0.083 p=0.183 n=256	r=0.068 p=0.304 n=229	r=-0.142 p=0.077 n=156	**r=0.244** **p<0.001** **n=253**	r=0.124 p=0.075 n=209	r=0.037 p=0.580 n=228	r=0.070 p=0.290 n=228	**r=0.195** **p=0.002** **n=239**	r=0.099 p=0.116 n=254	**r=0.221** **p<0.001** **n=238**	**r=0.548** **p<0.001** **n=228**	**r=0.493** **p<0.001** **n=228**
LOI (…)	**r=0.126** **p=0.044** **n=255**	r=-0.015 p=0.820 n=229	**r=0.619** **p<0.001** **n=156**	**r=0.443** **p<0.001** **n=253**	r=0.116 p=0.094 n=209	**r=0.144** **p=0.029** **n=228**	r=0.075 p=0.257 n=228	r=-0.12 p=0.056 n=238	r=0.024 p=0.701 n=253	r=-0.099 p=0.128 n=237	r=0.023 p=0.735 n=227	r=0.027 p=0.691 n=228
AIS (…)	r=-0.112 p=0.074 n=255	**r=-0.135** **p=0.042** **n=229**	**r=-0.252** **p<0.001** **n=156**	**r=-0.150** **p=0.017** **n=252**	r=-0.069 p=0.324 n=209	r=0.030 p=0.652 n=228	r=0.113 p=0.089 n=228	r=-0.01 p=0.859 n=238	r=-0.0 p=0.887 n=253	r=-0.041 p=0.528 n=237	r=0.035 p=0.597 n=228	r=0.026 p=0.697 n=228
HR_{peak} (bpm)	r=-0.004 p=0.966 n=155	r=-0.099 p=0.247 n=138	-	**r=0.358** **p<0.001** **n=155**	r=-0.014 p=0.884 n=124	r=0.090 p=0.295 n=138	r=-0.025 p=0.768 n=138	**r=-0.17** **p=0.042** **n=147**	r=-0.03 p=0.707 n=155	r=-0.121 p=0.144 n=146	**r=-0.201** **p=0.018** **n=138**	**r=-0.186** **p=0.029** **n=138**
SAP (mmHg)	r=0.081 p=0.202 n=252	r=0.086 p=0.198 n=225	**r=0.358** **p<0.001** **n=155**	-	**r=0.279** **p<0.001** **n=206**	**r=0.162** **p=0.015** **n=224**	**r=0.160** **p=0.016** **n=224**	r=0.091 p=0.163 n=236	**r=0.133** **p=0.036** **n=250**	r=0.071 p=0.279 n=235	**r=0.293** **p<0.001** **n=224**	**r=0.282** **p<0.001** **n=224**

Bold text indicates correlations that achieved statistical significance ($p<0.05$). Correlation coefficients (r), significance levels (p) and sample sizes (n) are shown. Abbreviations: CVD, cardiovascular disease; DOI, duration of injury; LOI, numeric level of injury; AIS, ordinal (considered as numeric) ASIA impairment scale (A=1, B=2, C=3, D=4); HR_{peak}, maximum heart rate at peak aerobic capacity; SAP, systolic arterial pressure; HbA1C, glycated haemoglobin; HDL-C, high density lipoprotein cholesterol; TC, total cholesterol; WC, waist circumference; BMI, body mass index; WHtR, waist-height ratio; FRS, numeric Framingham risk score. Categorical data: presence of diabetes (0=non-diabetic, 1=diabetic); smoking status (0=non-smoker, 1=smoker).

We also examined whether fitness, inferred by VO_{2peak}, was associated with FRS scores. There were no statistically significant correlations between VO_{2peak} ($mL \cdot kg^{-1} \cdot min^{-1}$) and either 10-year (r=-0.21, p=0.80; n=141) or 30-year (r=-0.034, p=0.693; n=141) FRS.

ROC analyses were performed for each injury characteristic and cut-point values were determined for an increased risk of CVD using the derived sensitivity and specificity values (**Table 2.6**). Individuals with a WC in excess of 95 cm, DOI >23 years, HR_{peak} <145 bpm, or SAP >128 mmHg had a higher 10-year FRS. Cut-point criteria for AIS and LOI indicate a threshold level for increased CVD risk at C8-T2, with AIS A completeness, but these were not statistically significant for either 10-year or 30-year FRS. The 30-year FRS was greater in those with a WC in excess of 94 cm, DOI >20 years, HR_{peak} <154 bpm, and SAP >113 mmHg.

Table 2.6. Proposed cut-point values for SCI related variables to identify increased CVD risk using ROC analyses

	WC (cm)	DOI (yrs)	AIS	LOI	HR_{peak} (bpm)	SAP (mmHg)
10-year FRS						
Cut-point	95	23	A	C8	145	128
AUC	0.73	0.76	0.51	0.50	0.60	0.62
Sensitivity	79	70	71	60	62	55
Specificity	57	72	28	41	63	63
p value	<0.001	<0.001	0.86	0.99	0.049	0.003
30-year FRS						
Cut-point	94	20	A	T2	154	113
AUC	0.72	0.76	0.51	0.54	0.64	0.64
Sensitivity	68	65	71	65	67	73
Specificity	67	77	27	48	61	50
p value	<0.001	<0.001	0.80	0.36	0.018	0.002

Individuals with a longer duration injury, higher waist circumference, evidence of cardiovascular autonomic impairment, or higher SAP had a higher CVD risk. Our sample of predominantly male individuals with SCI have an increased risk of CVD for a given WC compared to the able-bodied (in whom the recommended cut-point value for identifying individuals at risk of CVD is WC > 102cm for males). The HR_{peak} cut-point value is higher than the threshold for CI (defined as HR_{peak} <125bpm). Abbreviations: FRS, categorical Framingham risk score (0=not at risk, 1=at risk); AUC, area under the curve; WC, waist circumference; DOI, duration of injury; AIS, ordinal (considered as numeric) ASIA impairment scale (A=1, B=2, C=3, D=4); LOI, numeric level of injury; HR_{peak}, maximum heart rate at peak aerobic capacity; SAP, systolic arterial pressure.

2.4.5. Associations between CVD risk factors, FRS and obesity in SCI

We constructed a multiple linear regression model to determine the key predictors of the 10-year and 30-year FRS (**Table 2.7**). We did not include parameters in the model

that were already incorporated in the generation of the FRS score. Based on these analyses, the significant predictors of an adverse 10-year and 30-year FRS were a longer DOI, impaired autonomic function (lower HR_{peak}) and higher SAP. There was a trend for a higher WC to be associated with adverse 10-year (p=0.058) and 30-year (p=0.054) FRS, but this did not quite achieve statistical significance. LOI also tended to be associated with the 10-year FRS (p=0.056) and was significantly associated with the 30-year FRS (p=0.031). Aerobic capacity tended to be associated with the 10-year FRS (p=0.068) but not with the 30-year FRS (p=0.141).

Table 2.7. Regression model outcomes for multivariate regression between injury characteristics, anthropometric variables and aerobic capacity and 10-year and 30-year FRS

	10-year FRS (n=119) r=0.604, p<0.001			**30-year FRS (n=119) r=0.599, p<0.001**		
	β (SE)	95% confidence interval	p	β (SE)	95% confidence interval	p
Constant	-10.7 (7.6)	4.35 to -25.8	0.161	-16.3 (15.8)	14.9 to -47.5	0.303
WC (cm)	0.21 (0.11)	0.43 to -0.01	0.058	0.45 (0.23)	0.91 to -0.01	0.054
BMI ($kg•m^2$)	0.25 (0.30)	0.85 to -0.35	0.410	0.63 (0.63)	1.88 to -0.62	0.321
WHtR ($cm•m^{-1}$)	-27.6 (25.1)	22.1 to -77.3	0.274	-54.5 (52)	48.5 to -158	0.297
DOI (months)	**0.26 (0.07)**	**0.40 to 0.12**	**<0.001**	**0.40 (0.15)**	**0.70 to 0.10**	**0.010**
AIS	0.50 (0.62)	1.73 to -0.73	0.425	0.62 (1.28)	3.16 to -1.92	0.631
LOI	1.89 (0.98)	3.83 to -0.05	0.056	**4.42 (2.02)**	**8.42 to 0.42**	**0.031**
HR_{peak} (bpm)	**-0.10 (0.04)**	**-0.02 to -0.18**	**0.006**	**-0.24 (0.08)**	**-0.08 to -0.40**	**0.002**
CI	-1.23 (2.12)	2.97 to -5.43	0.561	-3.84 (4.38)	4.84 to -12.5	0.383
SAP (mmHg)	**0.07 (0.03)**	**0.13 to 0.01**	**0.025**	**0.16 (0.06)**	**0.29 to 0.04**	**0.016**
VO_{2peak} (ml.min.kg)	0.21 (0.11)	0.43 to -0.01	0.068	0.35 (0.23)	0.81 to -0.11	0.141

Bold text indicates variables that were statistically significant contributors to the FRS. Sample sizes (n), beta coefficients (β), standard errors (SE), and significance levels (p) are shown. Abbreviations: WC, waist circumference; BMI, body mass index; WHtR, waist-to-height ratio; DOI, duration of injury; AIS, ordinal (considered as numeric) ASIA impairment scale (A=1, B=2, C=3, D=4); LOI, level of injury categorised as high (1, C1-C8), mid (2, T1-T6), low (3, below T6); HR_{peak}, maximum heart rate at peak aerobic capacity; CI, chronotropic incompetence categorised as present (1) or absent (0); SAP, systolic arterial pressure incorporated as a linear variable; VO_{2peak}, peak oxygen uptake during maximal exercise; FRS, numeric Framingham risk score.

We employed AIC model-averaging to determine variable importance in estimating 10-year and 30-year CVD risk. After running 271 models for 10-year FRS, and 296 models for 30-year FRS, a larger WC, a longer DOI, and a higher SAP had high variable importance (appearing in more than 80% of all models), while a lower HR_{peak}, higher VO_{2peak} and low LOI (cat) had moderate variable importance (appearing in 60-80% of all models) for estimating the 10-year FRS. All of these variables had high variable importance for estimating the 30-year FRS (**Fig 2.2**) with the exception of VO_{2peak}, which was no longer an important predictor.

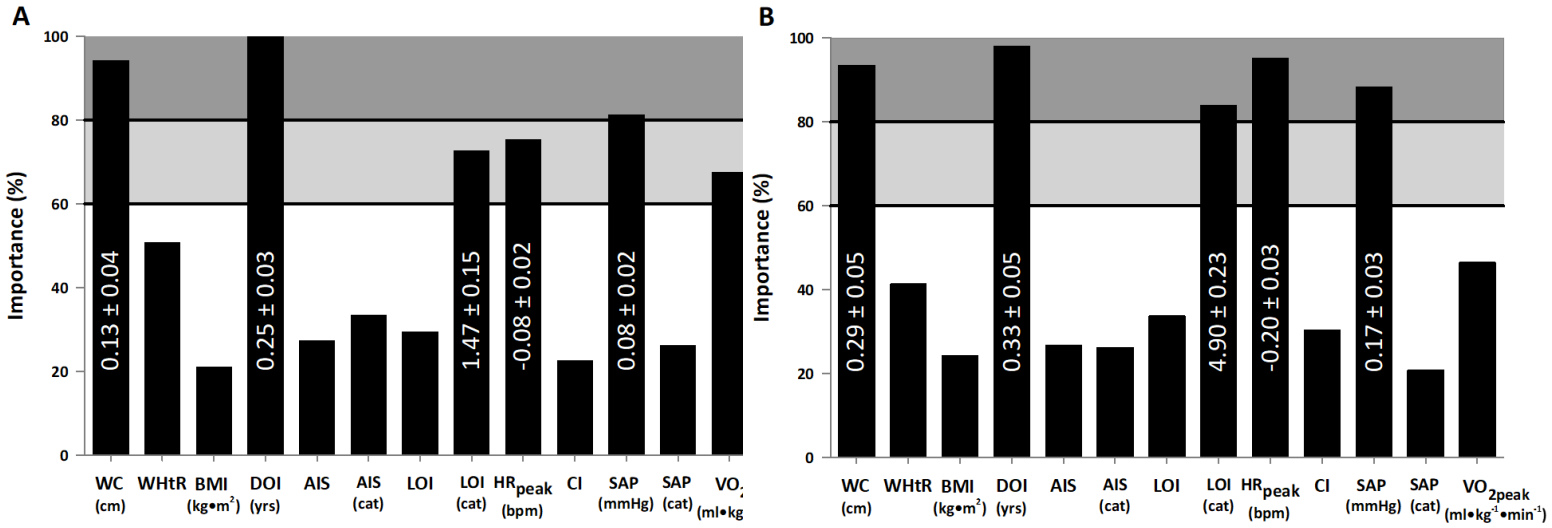

Figure 2.2. Akaike Information Criterion model-averaged importance of predictors of CVD risk

WC, DOI, and SAP were highly important predictors, with HR_{peak}, LOI (cat) and VO_{2peak} being moderately important predictors of increased CVD risk for the 10-year FRS (A). WC, DOI, SAP, HR_{peak}, and LOI (cat) were highly important predictors for the 30-year FRS (B). The horizontal bars represent high (appears in >80% of models) and moderate (appears in 60-80% of models) variable importance. Beta coefficients ± standard errors are provided for parameters with moderate-high variable importance. Abbreviations: WC, waist circumference; WHtR, waist-to-height ratio; BMI, body mass index; DOI, duration of injury; AIS, ordinal (considered as numeric) ASIA impairment scale (A=1, B=2, C=3, D=4); AIS (cat), ASIA impairment scale categorized as complete (1, AIS A) or incomplete injury (0, AIS B-D); LOI, numeric level of injury; LOI (cat), level of injury categorised as a high (1, C1-C8), mid (2, T1-T6), or low (3, below T6) injury; HR_{peak}, maximum heart rate at peak aerobic capacity; CI, chronotropic incompetence categorised as present (1) or absent (0); SAP, numeric systolic arterial pressure; SAP (cat), categorized as normal (0, 110-140mmHg) or abnormal (1, <110mmHg or >140mmHg); VO_{2peak}, peak oxygen uptake during maximal exercise.

Figure 2.3 shows conditional inference trees for 10-year and 30-year CVD risk. URP was employed as a method to both determine and confirm cut-point values, and independently identify predictors of CVD risk. The identification of homogenous subgroups is based on DOI and WC (10-year), and DOI, WC, and SAP (30-year), confirming the predictive importance of these variables (variables that do not appear in the trees are not significant predictors). A multiple testing-adjusted p value is given, which gives a statistical description of the strength between these early predictors (WC, DOI, SAP) and the outcome measure (FRS). The final nodes at the bottom show the full distribution of CVD risk using box plots. The cut-point values for DOI were similar to those determined through ROC analyses. Cut-points values for WC based on URP depended on the DOI. For example, in individuals who had a longer DOI (>20 years) the 10-year FRS was reduced if WC was <94cm. However, in those who had a shorter DOI (≤20 years), and therefore an inherently lower CVD risk, further reduction was only seen where WC was <80cm.

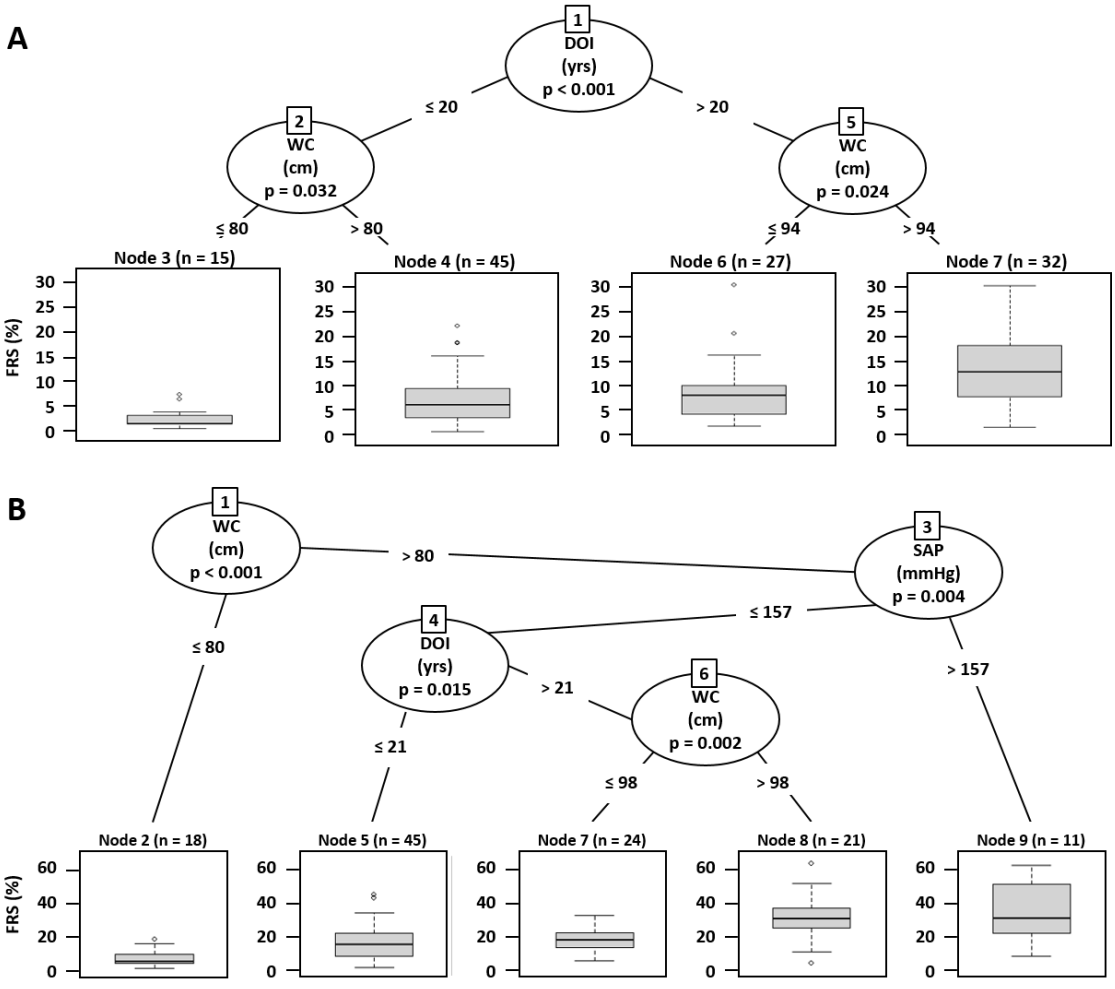

Figure 2.3. Unbiased recursive partitioning (URP) conditional inference tree for CVD risk after traumatic SCI

The upper part represents significant sequential splits based on early predictors, while the lower part represents the partition of the initial population as homogenous subgroups. Boxplots show the sample size and distribution of FRS within each subgroup. (A) 10-year FRS; (B) 30-year FRS. Abbreviations: DOI, duration of injury; WC, waist circumference; SAP, systolic arterial pressure; FRS, Framingham risk score; n, sample size.

2.5. Discussion

The main findings of this study are that measures of obesity can be used to infer CVD risk following SCI, with WC being the strongest obesity-related predicted for CVD risk. WC was significantly associated with DOI and impaired autonomic function (HR_{peak}). This suggests that WC may provide a proxy marker for other factors, beyond obesity and other traditional cardiovascular risk factors, that are thought to play a role in the earlier onset and faster progression of CVD following SCI[187], such as autonomic dysfunction and specific injury characteristics. This study suggests a WC cut-point value for males for an increased 10-year CVD risk following SCI of 97 cm, which is lower than the cut-point value for AB males (102 cm)[84] and reflects the higher CVD risk in this population[8]. These results are similar to those reported by Ravensbergen et al.[106] in a small North American cohort of individuals with SCI. Due to a low number of females, and in particular a low number of females at risk for CVD, a reliable cut-point value specific for 10-year CVD risk in females with SCI could not be determined. Accordingly, at the present time we recommend use of the AB cut-point value of 88 cm[84] to stratify CVD risk in women with SCI until risk profiles can be confirmed in a larger sample of women with SCI at risk for CVD. We note, however, that this may be an overestimate of the optimal cut-point for women with SCI in light of the reduced cut-point for males with SCI, and the lower cut-point for the 30-year risk for females in this study of 80 cm.

Given that WC performed as well as, or better than, BMI and WHtR in terms of its ability to predict CVD risk, from a practicality standpoint, we advocate for the routine use of WC as a screening tool for both individuals with SCI and their caregivers to consider when assessing CVD risk and guide healthy weight management. In practical terms, when determining WC in individuals with SCI, measurements should be conducted in the supine position, at the narrowest part of the waist, and at the end of a normal expiration, with a stretch-resistant measuring tape. This is important to ensure reliable estimates of WC, and to avoid the potential confound of flaccid paralysis of the abdominal muscles on measurements of WC when performed in the seated position. Males with a WC >97 cm, and females with a WC >88 cm, should be considered at higher risk for CVD and advised regarding risk management strategies accordingly. While these cut-point values are useful for identifying at risk individuals, WC is a modifiable factor that can be used to reduce CVD risk whether or not the cut-point value is attained. Based on this study, there is an

approximate reduction in CVD risk of ~1% for every 2-5 cm reduction in WC, with URP analyses showing up to 75% FRS reduction between subgroups. Previous studies have identified a 20-25% reduction in FRS as biologically meaningful[188–191]. Individuals with an adverse risk profile (considering both traditional and injury related risk factors) should be targeted for aggressive management of risk using lifestyle modification and/or pharmacologic therapy. Future research should consider how this suggested cut-point may change when factors such as ethnicity and sex are accounted for, as has been performed in the general population[84].

A secondary aim of this study was to better understand the CVD risk profile for individuals with SCI, including consideration of unique risk parameters such as injury characteristics and autonomic function and their relationship with CVD risk. Traditional CVD risk factors were also considered important variables, and known associations between traditional risk factors in the AB (smoking, presence of diabetes, adverse lipid profiles etc.) were also pertinent risk factors for individuals with SCI. Accordingly, smoking cessation and careful management of diabetes and lipid profiles, remain important considerations to reduce CVD risk following SCI, particularly because individuals with SCI are at higher risk for diabetes and metabolic syndrome[166,192,176]. In addition, the proportion of individuals with diabetes and who were smokers in this SCI cohort was considerably higher than in a matched AB cohort[193,194], highlighting the importance of risk reduction in these areas for those living with SCI. As in the AB[96], we found that males were at higher risk of CVD than females, and that the CVD risk was increased with advancing age following SCI.

We found that longer DOI (particularly if in excess of ~20 years), higher SAP, lower HR_{peak}, and a larger WC were all significantly associated with increasing CVD risk based on ROC analyses. DOI is likely a covariate with age, and the relationships between DOI and CVD risk seem to reflect an indirect effect of advancing age on CVD risk rather than a direct impact of a longer time living with SCI. However, we note that our inclusion criteria excluded individuals with recent injuries. The relationship between LOI and CVD risk is complex. There is no independent correlation between LOI and FRS. However, we identified a threshold for CVD risk whereby those with cervical and high-thoracic lesions tended to be at greater risk based on ROC analyses. When data were adjusted for other factors using regression and AIC analyses we found an increased risk of CVD in those with low-level lesions. Motor/sensory completeness of injury was not an important

independent predictor of CVD risk; however, using ROC analyses we identified a threshold for CVD risk for those with AIS A injuries. Higher level motor/sensory complete injuries are associated with greater decrements in mobility and increased sedentary time, which are known to increase CVD risk[107]. There are also reports that nutritional status is further impaired in those with high-level motor/sensory complete lesions[173], and this might also have a negative impact on CVD risk. Indeed, those with high-level lesions tended to have adverse HDL-C profiles. Conversely, those with low-level lesions were more likely to smoke and have high blood pressure, all factors that might adversely impact risk, despite their preserved cardiovascular autonomic function.

The severity of impairment to autonomic function (considered in this study from the ability to increase HR during exercise) was an important independent factor in predicting the increased CVD burden following SCI. This observation is particularly important given that there were missing data for the exercise HR response, where individuals theoretically most at risk of cardiovascular autonomic impairment are those in whom the type of exercise testing (manual wheeling) used to derive cardiovascular measures would be most difficult (i.e. high-level injuries resulting in tetraplegia). This might have introduced a selection bias, with the potential for underestimation of the importance of autonomic function in determining CVD risk, as those with the greatest impairments in autonomic function were most likely to have missing data. One benefit of using HR_{peak} as a measure of cardiovascular autonomic function is that it does not necessarily require a laboratory-based exercise test for evaluation. If an individual is able to undertake a bout of moderate-vigorous aerobic exercise as part of their activities of daily living, and HR increases to approximately 125-140 bpm, the assumption can be made that there is at least some residual sympathetic control of the cardiovascular system, and a decreased risk of CVD. For individuals who complete moderate-vigorous activity in whom HR does not exceed this threshold, the CVD risk can be presumed to be high, and aggressive management of risk factors should be considered. One question that remains unanswered is whether the increased CVD risk associated with impaired HR regulation is a direct effect of the loss of descending control of the cardiovascular system, or an indirect effect of other factors known to increase mortality that would present as a consequence of the cardiovascular autonomic impairment, such as OH[195,196], AD[170,197], arrhythmias[171], and other vascular abnormalities[60]. There are several methods that have been used to quantify remaining autonomic function following SCI including sympathetic skin response[167], muscle

sympathetic nerve activity[198], plasma norepinephrine[199], and heart rate and blood pressure variability[200]. While these methods provide specific measures of autonomic function, a primary limitation is accessibility and practicality. These methods require expensive equipment, invasive measurement techniques, and in-depth analysis to interpret the results. Additionally, guidelines for documenting autonomic function following SCI were introduced in 2012[174], however the Autonomic Function after Spinal Cord Injury document fails to specifically quantify remaining autonomic function.

The contribution of hypertension to CVD risk is typically incorporated within the FRS; however, it is unclear if the same association between hypertension and CVD risk is present following SCI, as SCI is associated with altered cardiovascular reflex control of blood pressure [192]. Resting hypotension may present following injury above T6, as descending sympathetic pathways are compromised, and blood pressure regulation is impaired. In the AB, lower SAP is considered to be protective against CVD risk[52]; however, in those living with SCI, hypotension is strongly associated with susceptibility to AD[196]. These large blood pressure swings may contribute to impairments in cerebrovascular health and increased CVD mortality[61] and as such, resting hypotension may not necessarily be protective of CVD risk after SCI. In addition, accurate representation of resting blood pressure is difficult in individuals with SCI. Although we took care to minimise the risk of concurrent AD during blood pressure measurements, it is likely that some participants were experiencing AD, as reflected by some significantly elevated SAP (>150 mmHg) recordings in individuals with lesions above T6 (n=33). Conversely, because we measured blood pressure in the seated position, and because of the high incidence of OH in individuals with SCI, we may also have exacerbated hypotensive recordings in susceptible individuals. These challenges with appropriate blood pressure determination in individuals with SCI may unpredictably influence risk calculations that utilise blood pressure metrics. Accordingly, we used a neutral blood pressure in the determination of the FRS. However, when we repeated our analyses using the recorded SAP rather than a neutral value, our results were essentially unchanged. While of course the absolute FRS value changed, the same parameters were identified as significant risk factors for CVD (WC, DOI, HR_{peak}, SAP, LOI). The only meaningful differences were that when the recorded SAP was incorporated within the FRS score the influence of VO_{2peak} was no longer significant and the WC cut-points tended to increase. The cut-points for the other variables were not affected.

Despite these nuances in the interpretation of blood pressure data in individuals with SCI, it is important to note that we did observe significant relationships between blood pressure abnormalities and FRS. When incorporated as a linear scale, there was an approximately 1% increase in FRS for every 10mmHg increase in SAP. Whether this represents the known association between hypertension and CVD risk seen in the AB[165], or reflects an association between AD and CVD risk[60,201], or a combination of the two, cannot be determined from this study.

It is often assumed that individuals with SCI have a high risk for CVD because of the tendency to a more sedentary lifestyle secondary to associated paralysis and use of a wheelchair for mobility[98,101]. While this may be at least partly true, in this study low VO_{2peak} was not independently correlated with increased 10-year or 30-year FRS, suggesting other factors play at least an equally important role in determining CVD risk profiles. In fact, there was a trend for *higher* VO_{2peak} to be associated with increased 10-year FRS (but not 30-year FRS) based on the regression data and AIC analyses. Why individuals with greater aerobic capacity would tend to be at higher risk is unclear, and challenges our assumptions about the relationships between physical fitness, VO_{2peak} and CVD risk after SCI. It may be that VO_{2peak} less strongly reflects physical activity/fitness after SCI where oxygen consumption is limited by other parameters such as the ability to increase HR or ventilation during exercise, and the active muscle mass. Of note, it was not possible to determine VO_{2peak} in many individuals with high-level lesions who could not complete the exercise test, and who would be expected to have the lowest aerobic capacity and highest CVD risk. It is likely that this bias would have influenced our analyses and might be one additional factor behind the lack of association between low VO_{2peak} and high CVD risk. Certainly there are current exercise guidelines[138] for the SCI population aimed at improving aerobic capacity with the goal of improving cardiometabolic risk. The recommended exercise target for individuals with SCI to achieve cardiometabolic health benefits is at least 30 minutes of vigorous aerobic activity 3 times per week[138], but depending on several social, mental and physical factors, these may or may not be feasible for many individuals with SCI. While there are a myriad of benefits to regular physical activity, the efficacy and practicality of the modification of CVD risk through increased physical activity is uncertain at the present time.

This study considered only traumatic SCI, because of the small numbers of individuals with non-traumatic SCI in the sample, and the possibility that risk factors may

not equate equally across injury subtypes because of pathological differences between traumatic and non-traumatic SCI that exert separate influences on CVD risk factors. In general, the demographic data from this cohort compared well with known SCI statistics[2]. However, there was a larger proportion of high LOI in this cohort compared to population averages. The females in this cohort tended to have a low cardiovascular risk profile, with only 9% considered at-risk for the 10-year FRS (compared to 48% for males). As a result, we were not able to reliably determine CVD risk cut-point values for females, and this limited our ability to evaluate sex differences regarding CVD risk following SCI. Women in general did seem to have a lower risk profile, as is the case in the AB, and until sex-specific data become available in a larger cohort of women that includes more women at-risk for CVD, we advocate that existing AB cut-point values be utilised for women living with a SCI.

With any analysis approach there are strengths and weaknesses regarding the way covariates or confounding variables are addressed, as well as with how missing values are handled. Some techniques are more suitable for particular data management approaches, and in terms of dissemination of information to different populations (clinicians, patients, etc.) some approaches will be more intuitive. Here we confirmed the rigor of our results by employing several different techniques to evaluate CVD risk factors, including more traditional correlations and regressions, to more novel AIC and URP analyses. We did not adjust our criteria for statistical significance for our correlations to account for multiple testing, because they were exploratory in nature, rather than hypothesis testing. Of note, when corrections were incorporated for multiple testing our key results were largely unchanged. With correction for multiple comparisons, some independent correlations between BMI, SAP, and HR_{peak} were no longer significantly correlated with some CVD risk factors, and HR_{peak} was no longer independently correlated with FRS. However, the importance of WC and HR_{peak} as predictors for FRS when other factors were considered was unchanged. This multipronged approach increases our confidence in our findings and recommendations. In particular, our analysis approaches consistently featured the importance of WC, DOI, and autonomic control of HR for the prediction of CVD in individuals with SCI.

It is recognised that there are several factors related to CVD risk that were not incorporated into this current risk profile. Family history of CVD was not investigated directly; however, we feel this may represented through some of the traditional risk factors

influenced by genetics (blood pressure, lipid profiles). While we suspect that the presence of a family history of CVD would be deleterious, the absence might not translate to reduced CVD risk. We considered a number of clinical metrics that influence CVD risk; however, we did not consider the impact of diet and nutrition on CVD risk. This is important because WC was one of the few modifiable risk factors for individuals with SCI to target improvements in CVD risk. Future studies should investigate the effects of dietary modification and increased physical activity for CVD risk reduction.

2.6. Conclusions

These data confirm WC as a simple, practical measure of CVD risk following SCI. WC is also associated with injury characteristics and impaired autonomic function. We provide cut-point values for WC, injury characteristics and autonomic measures for preliminary identification of those who may have an increased risk of an adverse cardiovascular event. This offers a simple tool that may be used to guide further evaluation and risk management. Furthermore, WC, DOI, HR_{peak}, and SAP were repeatedly identified as important variables in determining CVD risk. We propose that, whenever possible and in addition to traditional cardiovascular risk factors, measures of autonomic function and WC are determined and used to create a risk profile and guide management of CVD risk.

Chapter 3.

Relationships between cardiovascular disease risk, neuropathic pain, mental health, and autonomic function in chronic spinal cord injury

3.1. Abstract

Study design: Multicentre, cross-sectional study.

Objectives: To determine if clinical measures of MH- and NP are related to increased CVD risk in individuals with chronic SCI, and further elucidate the relationships between CVD risk, autonomic function, NP, and MH-.

Setting: Eight SCI rehabilitation centres in the Netherlands.

Methods: Individuals (n=257) with a traumatic, chronic (≥ 10yrs) SCI, with age at injury between 18-35 years, completed a self-report questionnaire and a one-day visit to a rehabilitation centre for testing. CVD risk was calculated using the FRS. NP was inferred using the DN4 clinical examination, and MH- was assessed using the MHI-5. Cardiovascular autonomic function was determined from HR_{peak}.

Results: There was a high prevalence of both NP (39%) and MH- (45%) following SCI. MH- was significantly correlated with an adverse CVD risk profile (r=0.174; p=0.01), increased the odds of adverse 30-year CVD risk by 2.2 (CI 0.92-2.81, p=0.02), and is an important variable in determining CVD risk (importance=0.74, p=0.05). Females (p=0.05) and those with a higher HR_{peak} (p=0.046) tended to be more likely to have NP.

Conclusions: Clinical measures of MH-, but not NP, are important factors for increased CVD risk following SCI. NP tended to be more prevalent in those with more preserved cardiovascular autonomic function. The interrelationships between secondary consequences of SCI are complex and need further exploration.

3.2. Introduction

SCI disrupts sensory, motor, and autonomic pathways, with higher, more severe injuries resulting in greater loss of sensorimotor function[3] and increasing autonomic impairment[56]. In particular, individuals with lesions above the 6th thoracic level (T6) may

experience loss of descending control of sympathetic pathways that regulate the heart and key vascular resistance and capacitance beds in the splanchnic circulation[202], leading to abnormal control of HR and blood pressure[15,72]. Accordingly CVD, the leading cause of morbidity and mortality among individuals with SCI[7], occurs earlier and progresses more rapidly following SCI[166]. In addition to traditional CVD risk factors, injury characteristics including the DOI and LOI, as well as autonomic function (using indices of SAP and HR_{peak}) have been identified as key predictors of an adverse CVD risk profile[108]. In order to build a comprehensive CVD risk profile for individuals living with SCI, potential risk factors that may have a compounding effect with the impacts of injury need to be further explored.

There is a high prevalence of NP[110] and MH-[121] in individuals with chronic SCI and these factors have been reported to be associated with increased CVD in this population [86]. However, in these and other studies NP and MH- have generally been derived from self-report questionnaires using broad questions with differing timeframes. Validated clinical measures, such as the DN4[120] for NP and the MHI-5[203] for MH-, have not been employed when exploring these variables in relation to CVD risk and other health outcomes following SCI.

Chronic pain is associated with CVD in the general population[204,205]. Pain, and in particular NP, is prevalent after SCI[110]. There are conflicting results regarding the relationships between injury characteristics and the presentation of NP, with reports of NP being more common in people with tetraplegia[115], paraplegia[116,117], or no difference with differing LOI[110,118]. Following SCI, aberrant sprouting of sensory axons induces alterations to sympathetic pathways contributing to increased sensitivity of sympathetic reflexes through morphological changes[111], enhanced input from primary sensory neurons[112], central sensitization of nociceptive inputs[113], and hypersensitive postganglionic sympathetic responses[114], providing possible mechanistic links between NP and autonomic impairment. Furthermore, NP may intersect with AD, a cardiovascular condition unique to high-level SCI due to injury to descending autonomic (sympathetic) pathways, manifesting as paroxysmal hypertension in response to sensory stimuli below the LOI[114]. It may be that the presence of NP as a pervasive sensory stimulus, coupled with central sensitization of nociceptive input and excessive sympathetic responses link NP and AD, with adverse CVD consequences[112].

MH- is more common in individuals living with SCI relative to the general population[121], particularly in those with high-level SCI[122]. In the general population, MH- is considered an independent risk factor for CVD as it induces dysregulation of the sympathoadrenal system, with increases in inflammation-related interleukins (IL-6, IL-1B), C-reactive protein, and triglycerides that promote systemic inflammation and dyslipidemia, predisposing to cardiovascular events[127]. Dyslipidemia and systemic inflammation are also increased following SCI, possibly creating an additive effect that further increases CVD risk in this population[8]. Coupling these effects with the sympathetic consequences of SCI, MH- could have a greater impact on CVD risk following SCI.

The primary purpose of this study was to confirm NP and MH-, using validated clinical measures, as key variables related to CVD risk following SCI. A secondary purpose was to elucidate the relationships between NP, MH-, autonomic function and injury characteristics, as well as the prevalence and efficacy of medicinal management for MH- and NP, to aid understanding of CVD risk profiles in individuals with chronic SCI.

3.3. Methods

This study is part of the Dutch multicentre research programme “Active LifestyLe Rehabilitation Interventions in aging Spinal Cord injury (ALLRISC)”, a cross-sectional study among individuals with long-term SCI living in the Netherlands[178]. This study was approved by the Medical Ethics Committee of the University Medical Center Utrecht and the Department of Research Ethics at Simon Fraser University. Investigations were performed in accordance with the Declaration of Helsinki of the World Medical Association[179]. All participants gave written informed consent prior to participation. As part of the wider ALLRISC study, aspects of the methodology are similar to those reported previously[108].

3.3.1. Participants

Individuals using a wheelchair (hand-rim or electric) with a traumatic, chronic (≥ 10yrs) SCI with age at injury between 18-35 years were included in the study. The younger age criterion was applied to limit the confounding effects of age-related co-morbidities and reduce the impact of CVD risk factors present prior to injury.

3.3.2. Procedures

The study consisted of a one-day visit to a rehabilitation centre that included an extensive medical assessment, physical examination, oral interview, and several physical tests. Two weeks prior to the visit, participants were asked to complete a self-report questionnaire. On the day of the visit, participants were asked to fast (except for water) for 12 hours prior to testing to ensure blood markers for the determination of CVD risk (e.g. lipid profiles) were collected in the fasted state. They were asked to refrain from vigorous exercise on the day of testing, and to ensure appropriate bladder and bowel care was performed prior to testing to minimise the likelihood of AD during testing in susceptible individuals.

Personal characteristics

Age, sex, and DOI, were extracted from the self-report questionnaire. WC was measured in the supine position, at the narrowest part of the waist after a normal expiration, using a stretch resistant measuring tape. A physiatrist determined the LOI and AIS according to the International Standards for Neurological Classification of Spinal Cord Injury[3]. LOI was considered both linearly (C1=1, C2=2, etc.), and categorically according to three groups based on the known impact of LOI on cardiovascular autonomic pathways: C1–C8 levels were defined as “high” injuries (potential loss of autonomic control of cardiac function and key vascular beds for blood pressure control); T1–T6 levels as “mid” injuries (potential loss of autonomic control of key vascular beds for blood pressure control, but minimal impairment to cardiac function); and SCI levels below T6 as “low” injuries (largely intact cardiovascular autonomic function). A complete lesion was defined as the absence of motor and sensory function in the sacral segments and classified as AIS grade A. AIS grades B, C, and D were classified as incomplete lesions[3].

Neuropathic pain

For participants who indicated that NP had been a concern for them at some point post-injury, NP was objectified using the DN4, administered by a physiatrist, which consists of 7 items related to symptoms of NP (burning, painful cold, electric shocks, tingling, pins and needles, numbness, and itching) and 3 related to a clinical examination (hypoesthesia to touch or pinprick and presence of allodynia) [120]. Individuals with SCI were included in the development of this assessment, and it is therefore validated for clinical

use in populations with SCI[120]. NP was considered both linearly (1-10), and categorically (present=1, absent=0). For categorical analyses, individuals were considered to have NP if they had a DN4 score ≥4 or were taking medications with a primary indication for NP. Those who had never experienced NP were considered to have a score of zero.

Mental health

Mental health was evaluated using the MHI-5[203], which consists of five questions on mood over the last 4 weeks. This clinical instrument has been validated for use in populations with SCI, with high internal consistency[128]. MH- was considered both linearly (0-100) and categorically (present=1, absent=0). For categorical analyses, individuals were considered to have MH- if they had an MHI-5 score ≤72 or were taking medications with a primary indication for depression.

Cardiovascular autonomic function

We inferred cardiovascular autonomic function from HR_{peak} during graded maximal exercise testing as a marker of injury severity to descending autonomic (sympathetic) pathways[46]. HR_{peak} was determined as the highest 5s average HR during the entire test. CI was defined as a HR_{peak} <125 beats per minute and a normal HR_{peak} as ≥125 beats per minute (based on peak responses observed previously in those with high-level SCI and associated CI)[72]. We recorded resting SAP, which is heavily influenced by the integrity of cardiovascular autonomic pathways after SCI, using a digital sphygmomanometer while participants were seated in their wheelchair.

CVD risk

We calculated the FRS for both 10-year[52] and 30-year[81] CVD risk. This score utilizes the following risk factors: sex; age; smoking status; diabetes; SAP; antihypertensive treatment; high-density lipoprotein cholesterol; and total cholesterol. Since SCI can impair blood pressure regulation (particularly with lesions above T6) such that a lower SAP in a SCI population may not be associated with a reduced overall CVD risk in the same way as seen in AB individuals, a neutral SAP of 120mmHg was used when calculating the risk score. A risk score of 10% is considered “intermediate risk” and this was the cut-point used for classifying “at-risk” individuals[52].

3.3.3. Statistical analyses

Statistical analyses were performed using SigmaPlot statistical software (version 14.5; Systat Software Inc., San Jose, CA) and R (version 4.1.3, 2015; Coding packages used are freely available while specific code is available upon reasonable request). Continuous data were tested for normality using the Shapiro-Wilk test and parametric or nonparametric statistics were used as appropriate. Correlations were performed using Spearman's rank-order tests (nonparametric data) or Pearson's product moment analyses (parametric data) to examine the relationships between NP, MH-, personal and injury characteristics, and 10-year and 30-year FRS. Linear variables included: age (years); DOI (months); WC (cm); HR_{peak} (bpm); SAP (mmHg). Categorical variables included: sex (0=male, 1=female); LOI ("high"=1, "mid"=2, or "low"=3); AIS (complete (A)=1, incomplete (B-D)=0). NP was considered as both a numeric (DN4 score 1-10) and categorical (no NP, DN4 score 0-3=0; NP present, DN4 score 4-10=1) variable. MH- was also considered as both a numeric (MHI-5 score 0-100) and categorical (normal MH, MHI-5 score 73-100=0; MH-, MHI-5 score 0-72=1) variable. This approach was taken because we felt it might be preferable clinically to use categorical values for risk assessment, but we wanted to validate that information contained in the linear analyses was not being lost with this approach. Linear regression and Akaike information criterion (AIC) model-averaging were used to assess the impact of each variable on the FRS. Where sample sizes permitted, separate analyses were conducted for male and female participants using unpaired student *t* tests (parametric data) or Mann-Whitney *t* tests (non-parametric data), and chi-squared analyses for proportions. The level of significance was set at $p<0.05$. Continuous data are reported as mean±standard error unless stated otherwise; categorical variables are reported as percentages.

3.4. Results

3.4.1. Participants

A total of 282 individuals participated in the study. We were specifically interested in the effects of traumatic SCI, so data from 257 individuals (61 females) aged 47±8 (SD) years with chronic (24±9 (SD) years) traumatic SCI were included in the analyses. Participant characteristics are shown in **Table 3.1**. For various reasons not all data were collected in all participants; sample sizes for each measure are provided.

Table 3.1. Participant characteristics

Characteristic	All	n	Male	n	Female	n	p value
Age (years)	47±8	257	47±9	196	47±9	61	0.98
Duration of injury (years)	24±9	257	24±9	196	23±9	61	0.86
Level of injury (%)							
Cervical	45	114	47	93	34	21	0.07
Thoracic	50	128	47	92	59	36	0.10
Lumbar	5	14	6	11	5	3	0.77
Sacral	0	0					
Motor/sensory completeness of injury (%)							
Complete	71	183	70	138	75	45	0.45
Incomplete	29	73	30	58	25	15	0.45
Stratification by autonomic impairment (%)							
High (C1-C8)	45	114	47	93	34	21	0.07
Mid (T1-T6)	34	88	32	63	41	25	0.20
Low (Below T6)	21	54	20	40	23	14	0.61
WC (cm)	97±15	239	**100±14**	**184**	**89±14**	**55**	**<0.001**
SAP (mmHg)	126±26	253	125±26	192	126±325	61	0.78
HR_{peak} (bpm)	147±29	156	145±30	118	152±26	38	0.24
VO_{2peak} ($ml \cdot min^{-1} \cdot kg^{-1}$)	17.1±6.1	160	**17.8±6.2**	**118**	**15.2±5.4**	**42**	**0.017**
Hypotension (%)	26	69	**30**	**57**	**13**	**8**	**0.01**
CI (%)	23	36	25	29	47	7	0.43
NP (%)	39	99	35	69	49	30	0.05
MH- (%)	45	116	46	91	41	25	0.46
NP and MH- (%)	19	49	18	36	21	13	0.61
10-year FRS (%)	10±8	227	**12±8**	**172**	**5±4**	**55**	**<0.001**
10-year increased FRS (%)	38	87	**48**	**82**	**9**	**5**	**<0.001**
30-year FRS (%)	23±16	228	**27±16**	**172**	**14±10**	**56**	**<0.001**
30-year increased FRS (%)	77	176	**87**	**149**	**50**	**27**	**<0.001**

Data are presented as mean ± standard deviation or percentages. Note that not all measures were obtained in all participants. Bold text denotes significant differences ($p<0.05$) between males and females, with significance indicated in the last column (p value). Abbreviations: BMI, body mass index; WC, waist circumference; WHtR, waist-height ratio; HbA1C, glycated haemoglobin; HDL-C, high-density lipoprotein cholesterol; TC, total cholesterol; SAP, systolic arterial pressure; HR_{peak}, peak heart rate during maximal exercise; VO_{2peak}, peak oxygen uptake during maximal exercise; CI, chronotropic incompetence; FRS, Framingham risk score; n, sample size. Some variables were previously published in Dorton et al. [8].

3.4.2. Prevalence of CVD risk and cardiovascular autonomic dysfunction

There were 87 individuals (38%: 5 females) considered to be at risk of CVD utilizing the 10-year FRS, and 176 individuals (77%: 27 females) at risk utilizing the 30-year FRS. Most lesions were cervical (45%) or thoracic (50%), with 79% (n=202: 46 females) having mid- or high-level injuries that could affect cardiovascular autonomic control. HR_{peak} was collected in 156 individuals (61%: 38 females). There were 36 individuals (23%: 7 females)

who presented with CI, implying cardiovascular autonomic dysfunction. Some of these data were previously published and further discussed by Dorton et al.[108].

3.4.3. Prevalence of NP and MH-

The prevalence of NP and MH- was 39% and 45% respectively, with 19% of individuals experiencing both conditions. MH- and NP were not correlated with one another (r=0.022, p=0.74). NP tended to be more prevalent in females, although this did not quite achieve criteria for statistical significance (p=0.05). Using Chi-squared analyses, we found that there tended to be a higher prevalence of NP in those with more intact autonomic function (p=0.051), and a lower prevalence in those with higher level injuries (p=0.065), but again, these did not quite reach criteria for statistical significance. There were no significant associations with the prevalence of NP or MH- when considering DOI or AIS.

3.4.4. Relationships between NP, cardiovascular autonomic function and CVD risk

We first examined the characteristics of NP in this cohort (n=257). Of those with NP the most common descriptors for their pain were tingling (77%), burning (63%), pins/needles (57%), numbness (50%), followed by electric shock (42%), painful cold (28%), and rarely, itching (8%). Hypoesthesia to touch (73%) and pin prick (75%) were common, but allodynia was not (24%).

Correlations revealed a tendency for NP to be associated with female sex (r=0.122, p=0.05) and more intact cardiovascular autonomic function (r=-0.156, p=0.052), although criteria for statistical significance were not quite met. Individuals with low- and mid-level injuries tended to present with NP more often than those with high-level injuries (p=0.065) although this did not meet statistical criteria. Multiple linear regression (**Table 3.2**) and AIC analyses (**Fig 3.1**) showed that NP was not a key predictor of 10-year or 30-year FRS. The presence of NP did not impact the odds of an adverse 10-year (0.73, p=0.27) or 30-year (0.78, p=0.42) CVD risk profile.

Table 3.2. Regression model outcomes for multivariate regression between personal and injury characteristics, NP, MH-, and 10-year and 30-year CVD risk

	10-year CVD Risk (n=122) r=0.610, p<0.001			**30-year CVD Risk (n=122) r=0.604, p<0.001**		
	β (SE)	95% CI	p	β (SE)	95% CI	p
Constant	-16.1 (5.78)	-4.77 to -27.4	0.006	-30.8 (12.1)	-7.08 to -54.5	0.012
WC (cm)	**0.14 (0.04)**	**0.21 to 0.06**	**<0.001**	**0.34 (0.08)**	**0.50 to 0.18**	**<0.001**
DOI (months)	**0.21 (0.06)**	**0.33 to 0.08**	**0.002**	**0.30 (0.13)**	**0.55 to 0.05**	**0.027**
AIS Cat	-1.79 (1.29)	0.74 to -4.32	0.168	-2.50 (2.70)	2.79 to -7.79	0.357
LOI Cat	**2.29 (0.89)**	**4.05 to 0.55**	**0.011**	**5.14 (1.87)**	**8.81 to 1.48**	**0.007**
HR_{peak} (bpm)	**-0.05 (0.02)**	**-0.01 to -0.10**	**0.036**	**-0.13 (0.05)**	**-0.03 to -0.23**	**0.009**
SAP (mmHg)	0.05 (0.03)	0.10 to -0.01	0.096	0.12 (0.06)	0.24 to 0.01	0.052
NP Cat	0.47 (1.05)	21.2 to -20.2	0.656	1.99 (2.21)	6.32 to -2.34	0.371
MH- Cat	**3.30 (1.02)**	**5.30 to 1.29**	**0.002**	**6.08 (2.14)**	**10.3 to 1.89**	**0.005**

Bold text indicates variables that were statistically significant contributors to CVD risk. Sample sizes (n), beta coefficients (β), standard errors (SE), confidence intervals (CI) and significance levels (p) are shown. Abbreviations: WC, waist circumference; DOI, duration of injury; AIS (cat), ASIA impairment scale categorised as complete (1, AIS A) or incomplete injury (0, AIS B-D); LOI (cat), level of injury categorised as a high (1, C1-C8), mid (2, T1-T6), or low (3, below T6) injury; HR_{peak}, maximum exercise heart rate; SAP, numeric systolic arterial pressure; NP (cat), neuropathic pain categorised as present (1) or absent (0); MH- (cat), decreased mental health categorised as present (1) or absent (0); CVD, cardiovascular disease.

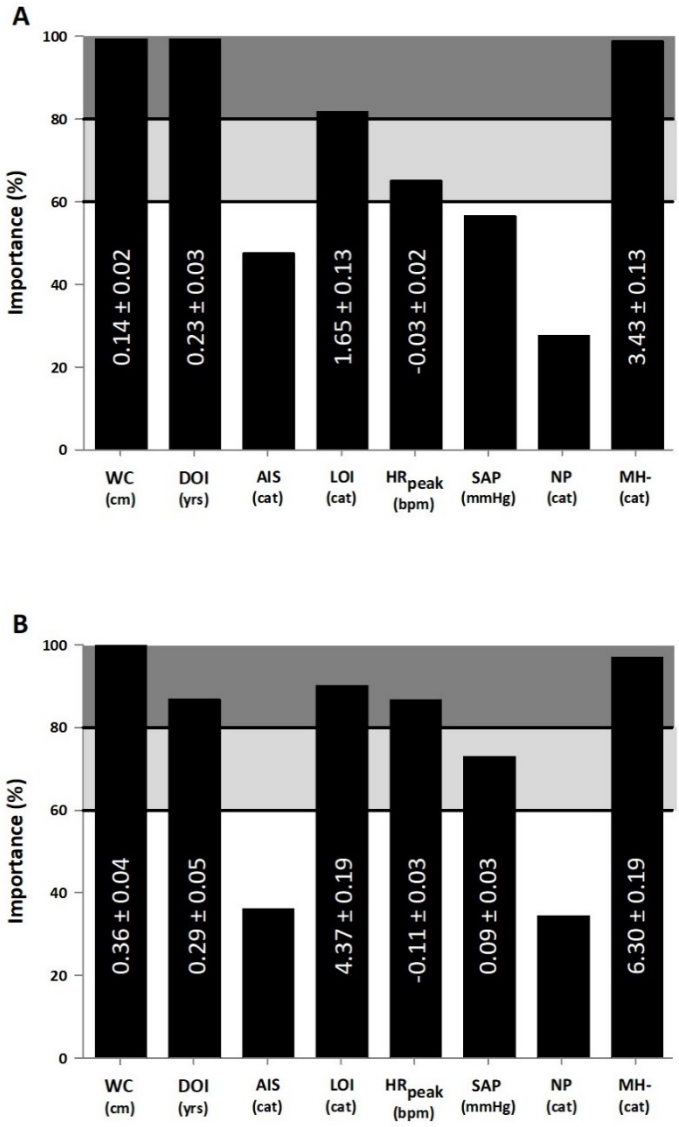

Figure 3.1. Akaike Information Criterion model-averaged importance of predictors of CVD risk

WC, DOI, LOI (cat), and MH- (cat) were highly important predictors, with HR_{peak}, being a moderately important predictor of increased CVD risk for the 10-year FRS (A). WC, DOI, LOI (cat), HR_{peak}, and MH- (cat) were highly important predictors, with SAP being a moderately important predictor for the 30-year FRS (B). The horizontal bars represent high (appears in >80% of models) and moderate (appears in 60-80% of models) variable importance. Beta coefficients ± standard errors are provided for parameters with moderate-high variable importance. Abbreviations: CVD, cardiovascular disease; WC, waist circumference; DOI, duration of injury; AIS (cat), ASIA impairment scale categorised as complete (1, AIS A) or incomplete injury (0, AIS B-D); LOI (cat), level of injury categorised as a high (1, C1-C8), mid (2, T1-T6), or low (3, below T6) injury; HR_{peak}, peak heart rate during maximal exercise; SAP, numeric systolic arterial pressure; NP (cat), neuropathic pain categorised as present (1) or absent (0); MH- (cat), decreased mental health categorised as present (1) or absent (0); FRS, Framingham risk score.

We considered whether the type of pain experienced was influenced by autonomic severity of injury (inferred from the presence or absence of CI) (n=156). Overall, a DN4 score indicating the presence of NP was less likely in those with autonomically severe injuries (22% vs 40%, p=0.047). Those with autonomically severe lesions were less likely to report sensations of painful cold (0% vs 14%, p=0.0063) or electric shock (3% vs21%, p=0.013).

3.4.5. Relationships between MH-, cardiovascular autonomic function and CVD risk

There tended to be a higher prevalence of CVD risk in those with MH- (55%) than those without MH- (43%, p=0.09), although this did not reach criteria for statistical significance. MH- was significantly correlated with an adverse 10-year (r=0.174, p=0.01) and 30-year (r=0.141, p=0.038) CVD risk profile. Older individuals were more likely to experience MH-, although this did not quite meet criteria for statistical significance (r=0.124, p=0.055). MH- was identified as an important predictor using AIC analyses for both the 10-year and 30-year CVD risk (**Fig 3.1**), with similar results using multiple linear regression (**Table 3.2**). Additionally, individuals with MH- were 1.6 (10-year FRS; p=0.09) and 2.2 (30-year FRS; p=0.02) times more likely to present with an adverse CVD risk profile, although the MH- data did not achieve criteria for statistical significance.

3.4.6. Prevalence and efficacy of medications primarily for NP and MH-

There were 136 individuals that completed the DN4 (suggesting concern for, or had experienced NP), with 99 individuals identified as presenting with NP at the time of evaluation (87 with DN4 score ≥ 4, 12 based on medication use). Of these 99 individuals, 37 indicated medication use directly targeting NP; of these, 12 individuals (32%) presented with a DN4 score < 4, indicating efficacious pain management. Regarding MH-, 116 individuals presented with MH- (102 with MHI-5 score ≤ 72, 14 based on medication use). Of these 116 individuals, 32 indicated pharmacological treatment of MH- with 14 individuals (44%) having an MHI-5 score ≥ 75, indicating efficacious medicinal management. In total, 64% of individuals classified as having NP and 72% as having MH- were not taking a primary use medication for these conditions (**Table 3.3**).

Table 3.3. Description, prevalence, and efficacy of pharmacological treatments used primarily for managing NP and MH-

Primary Use	Class/Name	n	Treatment Efficacy (%)
NP		99	
	Untreated	62	
	Treated	37	
	Gabapentin	8	13
	Pregabalin	10	50
	Carbamazepine	3	33
	Amitriptyline	14	36
	Opioid	12	33
MH-		116	
	Untreated	84	
	Treated	32	
	SSRI	5	40
	Venlafaxine	1	0
	TCA	10	60
	Benzodiazepine	16	38
	Lithium	2	100

Medications with more than one primary use were only considered if primary use was specified. Note that one individual could be concurrently taking multiple medications. Treatment efficacy is the percentage of managed cases relative to total cases. Abbreviations: MH-, decreased mental health; n, sample size; NP, neuropathic pain; SSRI, selective serotonin reuptake inhibitors; TCA, tricyclic antidepressants.

3.5. Discussion

The main findings of this study are that when using validated, clinical measures, MH- was confirmed to be significantly and independently associated with CVD risk following SCI, while NP was not.

3.5.1. MH- and CVD risk

MH- is a known CVD risk factor for the general population through increases in inflammatory substrates and triglycerides[127]. MH- is more prevalent in those living with an SCI relative to the general population[86], and was present in 45% of individuals within our cohort. MH- can impact CVD risk from a physiological (e.g. impaired autonomic function, increased inflammatory responses, dyslipidemia and endothelial dysfunction) and

behavioural (e.g. decreased physical activity, increased smoking, and disrupted sleep patterns) perspective[206]. Individuals presenting with MH- had a two-fold greater likelihood of an adverse CVD risk profile. Considering that SCI independently impacts each of these variables, mental health should be a primary consideration in risk evaluation and management after injury. While others have shown causality for MH- to negatively impact CVD risk after SCI[86], it may also be that some part of this association relates to the devastating impact of cardiovascular dysfunction after SCI and its possible association with MH-[207] and poorer quality of life[208]. The possibility of this bidirectional component to the relationship should be considered in future studies.

3.5.2. NP and CVD risk

NP was present in 39% of participants, consistent with previous reports[110,115]. However, NP was not significantly associated with CVD risk, contrary to previous literature[86]. There are several factors that could explain these conflicting results. First, we used a clinical measure to assess the presence of NP at the time of the examination. This clinically relevant snapshot could have underestimated the prevalence of NP in the long term and impacted the association with CVD risk. Indeed, previous studies showing associations between NP and CVD used questionnaires regarding the presence of pain spanning back 12 months[86,115,209]. Second, we used a calculated CVD risk with an “at-risk” threshold, while previous studies used the presence of CVD events (e.g. heart disease or stroke)[8,86,166]. We calculated 38% of individuals with chronic SCI to be “at-risk” of CVD compared to estimates of 5-10% using the presence of CVD[8]. This may suggest that NP and CVD have a common cause such that they occur together, as opposed to one condition leading to another.

Relationships between lesion characteristics and NP are unclear, with previous literature reporting an increased risk for NP in those with high-level lesions[115], those with paraplegia[116,117] or no differences based on LOI[110,118]. Our data suggest that those with mid- and low-level lesions are at a greater risk for NP. These discrepancies suggest further investigation of the relationships between NP and highlight that it should be considered in all individuals with SCI, regardless of lesion characteristics.

3.5.3. MH-, NP, and autonomic function

A secondary aim of this study was to further explore the relationships between MH- and NP and remaining cardiovascular autonomic function, inferred from HR responses to exercise, to better understand and establish a CVD risk profile in chronic SCI. Impaired autonomic function was previously shown to be an important independent factor in predicting increased CVD burden following SCI[108], however it is unclear whether this association is a direct effect of the loss of descending control of autonomic pathways, or an indirect effect of other factors presenting as a consequence of autonomic impairment. This is the first study to investigate the relationship between NP, MH-, and remaining autonomic function following SCI. As outlined above, there are several physiological and behavioural mechanisms that may link NP and MH- with autonomic function[113,114,206] and help elucidate their relationships with CVD risk. Our findings suggest that females and those with low-level injuries with more intact cardiovascular autonomic function might be more likely to experience NP. Given the relationships between impaired autonomic function and CVD risk, and lower likelihood of NP in those with impaired autonomic function, it is not surprising that pain was not a predictor of CVD risk. While there were no strong associations between MH- and autonomic function, shared mechanisms should be investigated further as they are both associated with increased CVD risk. Of note, preserved autonomic function was associated with a higher prevalence of painful cold and electric shock pain. It may be that those with preserved autonomic (sympathetic) function have a stronger substrate for aberrant sprouting within and between sensory and autonomic pathways, providing a mechanistic association between NP and cardiovascular autonomic function. Future research should emphasize more direct measures of remaining autonomic function to robustly explore these relationships. The observation that females tended to experience more severe NP has been reported before both in humans[210] and in animal models[211] but the mechanism underlying this observation remains unclear.

3.5.4. Consideration of medicinal management for NP and MH-

Individuals living with SCI commonly use a variety of medications to manage secondary health conditions related to their injury, including MH-, NP, and CVD. Primary use medications for a specific condition often impact another condition, positively or negatively, and these effects are not always known or possible to account for. We looked

at the efficacy of primary use medications for MH- and NP and found that relatively few individuals were well managed, with 56% and 68% still meeting clinical thresholds for the disorder, despite taking medications with a primary indication for the condition. It is likely, however, that although symptoms were not reduced below the clinical thresholds, symptom severity with medication use may have decreased. Interestingly, a high number of individuals presenting with MH- and NP did not report taking any primary use medications for these conditions (64% and 72%), with ongoing symptomology beyond clinical thresholds, highlighting the importance of considering medicinal management for NP and MH- in individuals with chronic SCI. This may reflect the principle of hierarchy of care, where individuals and clinicians choose to prioritize conditions that are most detrimental at the present time. Additionally, while medications may be beneficial for improving specific conditions, these benefits may not outweigh the risk or presence of side effects and, depending on medications, primary use medications may not be able to be taken concurrently. Alternative medications and practices (i.e. cannabis, acupuncture) were not accounted for when determining use and efficacy of pharmacological treatments, as they are not considered primary indicated medications for NP or MH-. Due to the nature of the questionnaire, we were unable to interpret the specific purpose for use of alternative medications. Particular consideration should be given to those at higher risk for MH- and NP; MH- tended to be more present in older individuals and NP tended to be more prevalent in females. Of note, LOI and AIS were not associated with MH-, suggesting it be considered in all individuals with SCI, regardless of lesion characteristics.

3.5.5. Analytical considerations

The FRS incorporates resting blood pressure as a positive correlate of CVD risk, however, it is unclear if resting hypotension, prevalent in high-level SCI and strongly associated with severe autonomic impairment, provides the same cardio-protective benefit seen in the AB[192]. Accordingly, we used a neutral SAP (120 mmHg) in the determination of the FRS. When we repeated our analysis using the recorded SAP, our results were essentially unchanged.

We assumed that individuals taking a primary use medication for MH- or NP at the time of testing had either experienced or been diagnosed with that condition. We did not change the respective raw scores of the DN4 or MHI-5, however, in the categorical analysis, they were classified as presenting with that condition. When we repeated our

analyses using the recorded DN4 or MHI-5 scores, without accounting for medication use, our results were essentially unchanged.

While the DN4 and MHI-5 are validated clinical measures, they do not offer a longitudinal perspective and so do not permit the evaluation of the duration of each respective condition on CVD risk.

Another consideration is the use of HR_{peak} to evaluate autonomic impairment in this study. The strengths of this approach are the ability to effectively and simply discriminate autonomic severity of injury, with clear translation and accessibility to the lived experience – clinicians and individuals with SCI can readily monitor HR_{peak} using simple wearable devices during a bout of moderate-severe exercise to evaluate whether CI is present. The challenge with this approach is that some individuals with high-level SCI were not able to complete the exercise testing protocol, representing a selection bias, with loss of those individuals likely to have the most severe autonomic impairment based on their high-level of injury. Additionally, there may be a selection bias directly related to NP and MH-, where those experiencing these conditions may be less likely to enroll in an intensive research study, thereby underrepresenting the prevalence of these conditions within this population.

For statistical rigour, we employed two-tailed testing in our analyses, when, given our unidirectional hypotheses, we could have performed one-tailed testing. This would render several of our results that did not quite reach criteria for statistical significance clearly within the statistical significance threshold.

3.6. Conclusions

These data confirm that a validated, clinical measure of MH-, but not NP, is an important predictor of increased CVD risk in individuals with chronic SCI. MH- is associated with a two-fold increased likelihood of an adverse CVD risk profile, likely impacted by both physiological and behavioral factors. NP tended to be more present in those with more preserved cardiovascular autonomic function, suggesting a link between the preservation of spinal autonomic pathways and NP. In general, many individuals had clinically relevant NP and MH-, but were not taking medication for these conditions, or their medication use did not improve symptoms below clinical thresholds. Medication use

for MH- and NP needs to be carefully considered, including evaluation of individual treatment efficacy, adherence, and side-effects. The onset and progression of CVD following SCI is complex, combining traditional, SCI specific, and non-traditional risk factors that need to be considered when creating a risk profile and determining appropriate management.

Chapter 4.

Exercise adjuncts in spinal cord injury: A systematic review and meta-analysis

4.1. Abstract

Background and Aims: While meeting exercise guidelines for maintaining or improving cardiovascular health is difficult for many, individuals living with SCI face unique exercise challenges. PLLM and PHT are promising exercise adjuncts that may offer cardiovascular benefits while mitigating exercise challenges following SCI. We aimed to evaluate current evidence for the effectiveness of these exercise adjuncts on cardiovascular outcomes following SCI.

Methods: PRISMA guided rapid review of literature based on searches in the PubMed/MEDLINE and Web of Science databases (20/01/2023). Peer-reviewed publications were included if they described cardiovascular outcomes (blood pressure, HR, SV, CO) of single or multiple sessions of PLLM or PHT. Studies were reviewed, and data extracted independently in duplicate. Where possible, meta-analyses were performed.

Results: Our search identified 2,785 unique records, of which twenty-one papers met inclusion criteria. Of these, 12 examined PLLM and 9 examined PHT. 17 were single session studies and 4 were multiple session studies, with 3 multiple session studies reporting results of single session interventions. The total number of participants was 199. There were 7 single session studies that reported a significant change in at least one cardiovascular outcome following PLLM. Of the 2 multiple session interventions, 1 reported a significant decrease in resting HR (-6±3 mmHg) while the other reported no significant changes. All 9 of the single session PHT interventions reported a significant increase in HR, with several others reporting increases in CO, SV, and blood pressure. PLLM had no overall effect on HR, SV, CO, or SAP, while PHT significantly increased HR (+26.9±12 bpm) and T_{core} (+1.1±0.5 °C).

Conclusion: Both acute and chronic passive PLLM and PHT show promise as effective exercise adjuncts in producing cardiovascular responses to help maintain or improve cardiovascular health and overall quality of life.

4.2. Introduction

The consequences of SCI impact motor, sensory, and autonomic function as a result of the disruption of communication between the brain and body, with the extent of the impairment associated with the LOI and AIS[3]. Secondary complications of SCI are a primary concern for individuals with chronic SCI, as advancements in acute care have increased life expectancy following injury[2]. CVD is the leading cause of morbidity and mortality in all populations worldwide[165], however it is known to present earlier and progress faster following SCI[8]. Physical activity and exercise are known to decrease the risk of CVD[130], but individuals living with SCI have unique challenges to increasing physical activity and the efficacy of exercise may be mitigated due to motor, sensory, and autonomic impairments. Common barriers included environment and physical body[139,140]. Environmental barriers included lack of access to equipment, increased time to access equipment, and unaffordable equipment[140]. Barriers related to physical body included low return on physical investment, loss of body control (paralysis, spasticity, range of motion), and post-exercise consequences (fatigue, hypotension, musculoskeletal pain)[139,140]. Importantly, many of these physical impairments have been shown to be improved through regular physical activity, highlighting the need for accessible alternatives to specialized equipment with limited availability.

Recent guidelines for the improvement of cardiorespiratory fitness and cardiometabolic health after SCI suggest moderate to vigorous aerobic and/or strength training 2-3 times per week[138]. Within any given population, for many complex reasons, approximately 50% of individuals will fail to meet recommended physical activity guidelines, for those not meeting the guidelines the consensus opinion is that more is better and any exercise is preferable to sedentary behaviours. Exercise is medicine® promotes leisure time activity (walking, gardening, etc.) and using activities of daily living (taking the stairs, parking further away to promote walking) to increase overall physical activity. But what do these strategies look like for individuals living with SCI?

PLLM and PHT are two adjuncts, or auxiliary means, of exercise that could be beneficial to increase physical activity and provide benefits difficult to attain due to cardiovascular impairments and exercise intolerance after SCI. These represent two relatively low-cost, accessible options available for this population. Different variations of PLLM include PC, BWSTT, and elliptical training. A previous systematic review[155]

highlighted the beneficial cardiovascular, musculoskeletal, and neurological impacts of PC in chronic SCI. However, this review only included PC and other forms of PLLM need to be reviewed in a like manner to further our understanding of their impact after SCI. PHT, including hot water immersion, sauna use, general skin heating, or any combination of these approaches, has been shown to have benefits for general overall health and for exercise and sport performance in AB[143]. There are few studies that have investigated cardiovascular responses during PHT following SCI or examined whether benefits noted in the AB extend to individuals with SCI in whom there may be impairments to cardiovascular autonomic function and thermoregulation. To-date there has not been a review of the literature including PHT following SCI.

The aim of this review is to describe PLLM and PHT interventions used in chronic SCI and to assess the effectiveness of these interventions on improving cardiovascular outcomes associated with cardiorespiratory fitness and cardiometabolic health.

4.3. Methods

A systematic review was conducted using PubMed and Web of Science databases on January 20, 2023. In the PubMed database the following search strategy was used: ((((spinal cord injuries[MeSH Major Topic] OR paraplegia[MeSH Major Topic] OR quadriplegia[MeSH Major Topic]) AND (motion therapy, continuous passive[MeSH Major Topic] OR Lower Extremity[Mesh Major Topic] OR Transcutaneous Electric Nerve Stimulation[Mesh] OR "passive cycl*" OR "passive movement" OR "cycle ergometer" OR lower limb movement OR heat therap* OR thermoregulation OR hyperthermia OR exercise response)))) AND (alladult[Filter]). The search strategy was adapted appropriately for use in the Web of Science database.

Study selection

Database search results were uploaded and organized using Covidence, a reference management software. In the first phase, two reviewers (M.D. and C.H.) independently screened titles and abstracts for compliance with pre-set inclusion and exclusion criteria. Abstracts (n=2) and full text articles (n=1) were translated to English using Google Translate as needed to promote equity and to avoid deprioritisation of research published in languages other than English. Upon completion of independent

review, any conflicts were discussed together with a third reviewer (V.C.) to reach a common consensus. Full text screening was conducted in a similar manner.

Peer-reviewed articles with a PLLM or PHT intervention that included adult humans (>18 years old) living with chronic (>6 months since injury) SCI with data involving cardiovascular outcomes (HR, CO, SV, blood pressure, cerebrovascular blood flow; CBF, or increases in T_{core}) were included in this review. Studies were excluded if they were case reports (less than 4 participants), examined responses in those with acute SCI (within 6 months of injury), involved exoskeletons, overground ambulation, or orthostatic maneuvers, or used only localized heating.

Upon discussion with SCI community stakeholders including individuals with lived experience, clinicians, and individuals within Spinal Cord Injury-British Columbia, it was decided to focus on passive exercise adjuncts that did not require electrical stimulation. Functional electronic stimulation can be painful for those with sensory incomplete lesions, carries a theoretical risk of AD, and does not address the accessibility barrier. Accordingly, articles using FES as the stimulus were not considered at the present time. (**Fig 4.1**). Inherent within any systematic review, the authors recognise the probability of publication bias (failure to publish insignificant or negative results). A funnel plot allows for the identification of publication bias or systematic heterogenicity of studies included for analysis, using Egger's regression as a statistical measure[212]. These statistical measures will be included as this manuscript is prepared for submission.

Data extraction

Data were extracted by the two reviewers into an excel spreadsheet. The following data were extracted: publication year, lead author, title, abstract, country of study, study design, exercise type and duration, sample and control size, sample and control age, DOI, LOI, AIS, type, duration, and resistance or degree of heating of the intervention, measurement tools for outcome measures, statistical analysis used, specific outcome measures for HR, SV, CO, blood pressure, CBFv or T_{core}, and details of outcomes. The study outcomes were categorized into groups based on intervention type. Where possible, meta-analyses were performed. Aggregate metrics of individual cardiovascular outcomes were combined and reported as weighted averages. Greater weight was given to trials with a larger sample size. Studies were included in the meta-analysis for a given cardiovascular outcome if data were available for both baseline and intervention values.

A summary estimate of effect along with confidence intervals was calculated and visualized using forest plots.

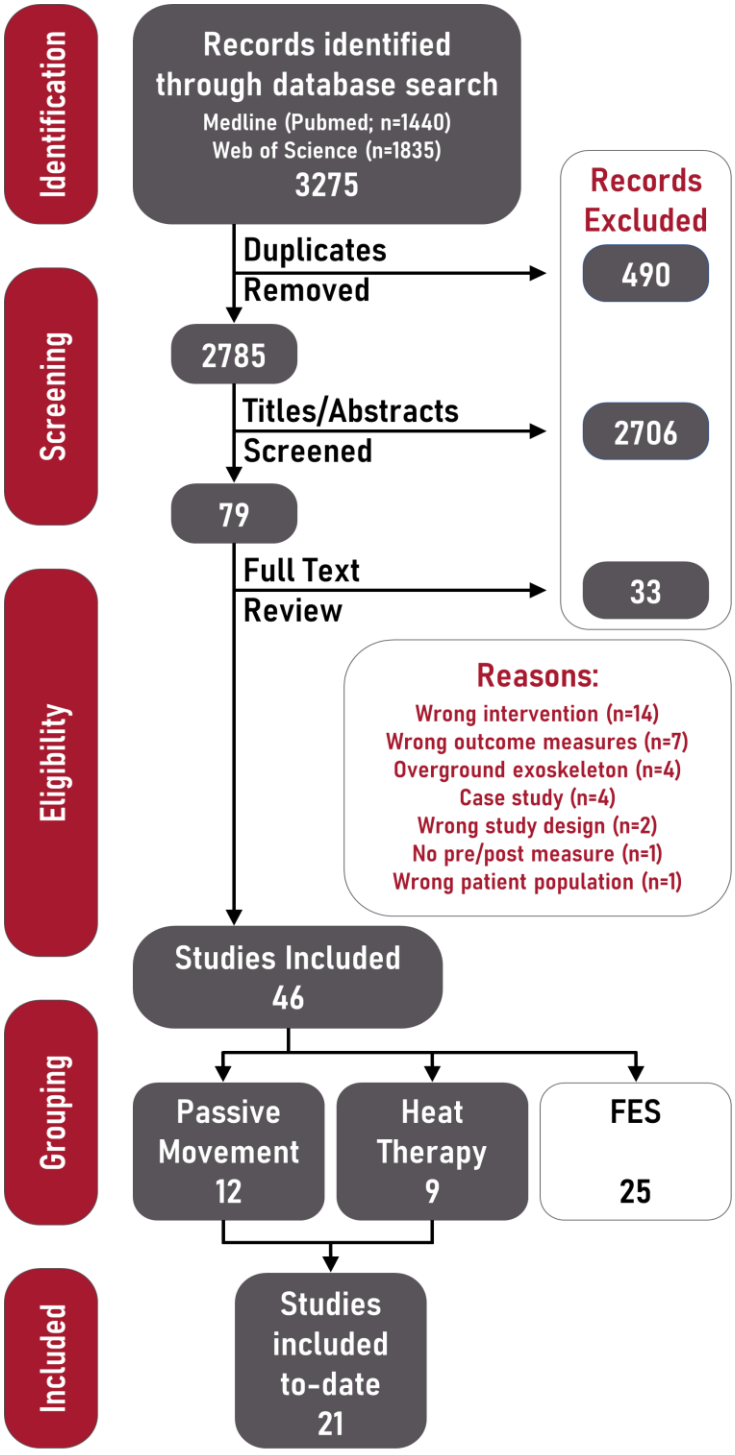

Figure 4.1. PRISMA flow diagram of systematic search

Studies evaluated at this time included only passive interventions. As such, studies utilizing FES interventions are not included in the current results. FES, functional electronic stimulation.

4.4. Results

A summary of the studies is presented in **Tables 4.1** and **4.2**, addressing PLLM and PHT, respectively. Of the 21 studies that met inclusion criteria (12 examined PLLM[157–163,213–217] and 9 examined PHT[79,145–149,151,218,219]), 17 were single session studies and 4 were multiple session studies (training/acclimation studies), with 3 multiple session studies reporting results of single session interventions. There were 16 pre-post single-group designs and 5 crossover trials (with multiple cadences or heat settings)) The total number of individual participants in the included studies was 199 (117 in PLLM, 82 in PHT, 176 in single session studies, 29 in multiple session studies). The average age of participants was 34±20 years, with an average DOI of 24±7 years. The LOI ranged from C3-L1, with AIS ranging from A-D.

Study characteristics

A summary of PLLM study protocols is given in **Table 4.1**. Single session therapies ranged from 5-30 minutes of passive movements, with interventions including BWSTT at 2.4km/hr, leg swinging at 30 swings per minute, and PC ranging from 15-50 rpm. Multiple session therapies included BWSTT protocols of 16 and 24 weeks, respectively, with 3 training sessions per week lasting up to 60 minutes each. One of the multiple session studies[214] included data from single session therapies before and after training, therefore we will include each of these measures in their respective categories.

A summary of PHT study protocols is given in **Table 4.2**. Study characteristics for two of the studies[79,151] have been combined as they utilized the same participants and protocol but focused on different cardiovascular outcomes. Single session therapies included 30-60 minutes of heat exposure via full body and lower limb water immersion, heated ambient air in climatic chambers, water-perfused suits, and warming blankets. Multiple session therapies included 7 days of 60 minutes, full body immersion in 39°C water, and 14 days of 30 minutes in ambient air of 40°C. Most studies reported a maximum T_{core} cut-off including a 1°C T_{core} increase or absolute T_{core} and skin temperatures from 38-40°C.

Cardiovascular outcome measures extracted from the studies included: 1) HR, 2) blood pressure (SAP, DAP, MAP), 3) CO, 4) SV, 5) CBFv, and 6) T_{core} (rectal, esophageal, and aural/tympanic probes, telemetric pill).

Table 4.1. Passive Lower Limb Movement Study Characteristics

Study 1. Author, year 2. Study design	*n* (male)	Age years	Injury level	AIS	DOI (years)	Measurement time-points	Outcome measures	Modality and protocol
Characteristics of single session therapy								
1. Figoni, 1990[160] 2. Pre/Post Experimental	30(26)	TP 28±7 PP 32±8	*	A-D	6±4	Rest, minute 5	HR, CO, SV, SAP, DAP	ERGYS 1 Ergometer; 5 min rest, 5 min PC at 50 rpm
1. Fornusek, 2008[163] 2. Pre/Post Crossover	9(7)	37±11	T4-T10	A	*	Rest, minute 10	HR, CO, SV, SAP, DAP	Isokinetic Cycle Ergometer; 5 min rest, 10 min PC at 15, 30, and 50 rpm
1. Jeffries, 2015[215] 2. Pre/Post Crossover	8(7)	32±12	T5-T12	*	5±4	Rest, minute 5 of each position	HR	BSWTT; 5 minutes at each: seated rest, standing rest, stepping at 2.4km/h
1. Muraki, 2000[162] 2. Pre/Post Experimental	6(6)	49±5	T8-L1	*	21±8	Rest, minute 5	HR, CO, SV	Modified Cateye Ergociser EC-3500; 10 min rest, 6 min PC at 40 rpm
1. Muraki, 1996[161] 2. Pre/Post Crossover	8(1)	42±11	T8-L1	*	15±9	Rest, minute 5	HR, CO, SV, SAP, DAP	Modified Cateye Ergociser EC-3500; 10 min rest, 7 min at 20 and 40 rpm
1. Nash, 1995[159] 2. Pre/Post Experimental	6(6)	26±7	C5-C6	A-B	7±4	Rest, minutes 15 & 30	HR, CO, SV, SAP, DAP, MAP	Cycle ergometer; 15 min rest, 30 min at 50 rpm
1. Ogata, 2009[216] 2. Pre/Post Crossover	12(12)	HSCI 31±11 LSCI 31±9	C6-T6 T10-T12	A-B	7±8	Seated rest, standing rest, minutes 6 & 12 of PLLM	HR, SAP, DAP, MAP	Easy Stand Glider 6000; 6 minutes of seated and standing rest, 12 minutes of PLLM
1. Raymond, 2000[217] 2. Pre/Post Experimental	7(7)	37±6	T5-T11	*	11±7	Rest, minute 5	HR, MAP	ERGYS 2; 5 min rest, 5 min PC at 50 rpm
1. Soriano, 2022[158] 2. Pre/Post Experimental	11(7)	40±10	C3-C7	A-C	18±9	Rest, minute 10	HR, CO, SV, SAP, DAP, MAP, MCAv	Modini Z-40; 15 min rest, 10 min PC at 30 rpm

1. Ter Woerds, 2006[157] 2. Pre/Post Experimental	8(8)	35±8	T2-L1	A-B	8±6	Rest, every 2.5 mins	CO, MAP	Cycle ergometer; 20 min rest, 20 min PC at 35 rpm
Characteristics of multiple session therapy								
1. Ditor, 2005a[213] 2. Pre/Post Experimental	8(6)	28±5	C4-C5	B-C	10±8	Baseline; pre/post training	HR, SAP, DAP, MAP	BWSTT; Supine rest, 3 times per week, up to 60 min session, 24 weeks
1. Ditor, 2005b[214]€ 2. Pre/Post Experimental	4(2)	38±15	C4-T12	A-B	8±9	Baseline, supine and standing pre/post training	HR, SAP, DAP, MAP	BWSTT; Supine rest, 3 times per week, up to 60 min session, 16 weeks

DOI, duration of injury; AIS, American spinal injury association impairment scale; BWSTT, body weight supported treadmill training; PC, passive cycling; PLLM, passive lower limb movement; HSCI, high spinal cord injury; LSCI, low spinal cord injury; Rest, values measured just prior to intervention; RPM, revolutions per minute; HR, heart rate; CO, cardiac output; SV, stroke volume; SAP, systolic blood pressure; DAP, diastolic blood pressure; MAP, mean arterial pressure; MCAv, middle cerebral artery blood flow velocity; Km/h, kilometers per hour; Baseline, resting values pre/post training; €, study included in both single and multiple session results; *Information not provided.

Table 4.2. Passive Heat Therapy Study Characteristics

Study 1. Author, year 2. Study design	*n* (male)	Age years	Injury Level	AIS	DOI (years)	Protocol and Measurement time-points	Outcome measures	Heating Method
Characteristics of single session therapy								
1. Coombs, 2018[79] 2. Pre/Post Experimental	15(10)	43±12	C3-C7	A-C	21±13	60 min; rest, after 5 min in 33°C water, every 15 min in 40°C water to end	HR, SAP, DAP, MAP, T_{core}	Lower leg water bath (40°C), Upper body heat blanket
1. Coombs, 2019[151]§ 2. Pre/Post Experimental	15(10)	43±12	C3-C7	A-C	21±13	60 min; rest, after 5 min in 33°C water, every 15 min in 40°C water to end	MCAv, PCAv	Lower leg water bath (40°C), Upper body heat blanket
1. Freund, 1985[146] 2. Pre/Post Experimental	5(5)	34±8	T1-T10	*	8±5	Skin Temp = 38-39°C, at least 30 min; rest, end	HR, T_{core}	Water-perfused suit
1. Gass, 2002[147] 2. Pre/Post Experimental	4(4)	38±5	C5-C7	A	16±4	60 min or T_{core} = 38.5°C; rest, every 30 sec to end	HR, T_{core}	Immersion to nipple (39°C)
1. Hashizaki, 2018[148] 2. Pre/Post Experimental	19(19)	38±3	C5-L1	A	16±3	1°C rise in T_{core}; rest, end	HR, CO, SV, MAP, T_{core}	Water-perfused suit (50°C)
1. Leicht, 2015[149] 2. Pre/Post Experimental	7(7)	39±12	C5-C8	A-B	9±7	60 min or T_{core} = 39°C; rest, end	HR, SAP, DAP, T_{core}	Immersion to neck in water 2°C above T_{core}
1. Yamasaki, 2000[218] 2. Pre/Post Experimental	7(7) 4 HSCI 3 LSCI	41±10	T6-T12 T6-T10 T11-T12	B-C	13±11	up to 60 min; rest, every 5-10 min to end	HR, T_{core}	Air Temp 33°C, RH 50-55%
Characteristics of multiple session therapy								
1. Gass 2001[145]€ 2. Pre/Post Experimental	5(5)	37±9	T5-T12	*	14±13	7 Sessions; 60 min or T_{core} = 39°C; baseline, rest, every 5 minutes to end	HR, T_{core}	Immersion to nipple (39°C)
1. Petrofsky, 1992[219] 2. Pre/Post Crossover	12(12) 6 TP 6 PP	23	C6-T12 C6-C8 T3-T12	A	*	14 sessions, 30 min at 40°C; 30 min at each temp, end	HR, T_{core}	Air temps of 30°C, 35°C, 40°C; RH 50%

DOI, duration of injury; AIS, American spinal injury association impairment scale; C, cervical; T, thoracic; L, lumbar; TP, tetraplegia; PP, paraplegia; HR, heart rate; SAP, systolic blood pressure; DAP, diastolic blood pressure; MAP, mean arterial pressure; T_{core}, core body temperature; MCAv, middle cerebral artery blood flow velocity; PCAv, posterior cerebral artery blood flow velocity; CO, cardiac output; SV, stroke volume; RH, relative humidity; Rest, values measured just prior to intervention; Baseline, resting values pre/post training; *Information not provided; €, study included in both single and multiple session results; §, this study incorporated the same participants and protocol as Coombs 2018 with reported outcome measures focusing on cerebral responses. Accordingly, duplicate variables are not provided.

Cardiovascular responses to exercise adjuncts

The impact of PLLM on cardiovascular outcomes is summarized in **Table 4.3**. Of the 11 single therapy interventions, 7 reported a significant change in at least one cardiovascular outcome following PLLM. Of these, 4 therapies resulted in an increased HR[158,214–216], while 1 reported a decrease in HR[217]. There were 3 therapies which reported significant increases in CO, attributable to significant increases in SV[158,161,162], with another reporting moderate, although non-significant increases in CO and SV[160]. Only 1 study measured CBFv and reported a reduction in cerebrovascular conductance, but no change in velocity during PLLM[158]. Significant increases in SAP and MAP were reported in 2 studies[158,216], with 1 study showing this effect only in individuals with a high-level SCI[216]. Of the 2 multiple session interventions, 1 reported a significant decrease in resting HR[213] while the other reported no significant changes[214]. Additionally, 3 studies reported higher HR values at rest in individuals with SCI relative to AB[161,215,216], with 2 of those reporting higher HR values during PLLM[215,216]. Lower resting SV was reported in individuals with SCI compared to the AB in 1 study[161], while another reported lower resting blood pressure at rest and during PLLM in those with high-level SCI[216].

The impact of PHT on cardiovascular outcomes is summarized in **Table 4.4**. All of the interventions were successful at increasing T_{core}, with 2 studies reporting a faster increase in individuals with high-level SCI relative to individuals with lower-level SCI[148,219]. All 8 of the single session PHT interventions reported a significant increase in HR. Of the 2 studies that reported CO, 1 study reported a significant increase[148], driven by the increased HR, while the other reported no significant difference[218]. Of the 3 studies that reported blood pressure responses, 1 noted an increase in blood pressure[149], while 2 found no significant difference[79,148]. Only 1 study measured CBFv during PHT with no significant changes reported[151]. The 2 multiple session PHT interventions only reported measures of HR and T_{core} with no significant changes to resting measures or responses to PHT following acclimation[145,219].

Several studies reported reduced T_{core}, HR, CO, and SV at rest[79,148,218] and during PHT[148,218] in individuals with SCI relative to the AB. In addition, 2 studies reported a blood pressure increase in individuals with SCI, while blood pressure decreased in the AB[79,149]. Several studies reported faster rates of rise in T_{core}[79,148,218,219], along with slower recovery following PHT[149] for individuals with SCI compared to the AB. Increases in HR were slightly

lower, with a greater increase in T_{core} during PHT compared to moderate intensity exercise in individuals with SCI[147]. In 1 multiple session study it was reported that following acclimation, AB had a reduced T_{core} elevation during PHT which was not seen in individuals with SCI[145].

Meta-analyses were performed on HR (n=119), SV (n=88), CO (n=88), and SAP (n=94), during PLLM (**Fig 4.2**) and HR (n=84), T_{core} (n=84), and MAP (n=41) during PHT (**Fig 4.3**). PLLM did not significantly alter any of the measured variables (weighted averages: HR, +7.6±9.5 bpm; SV, +6.0±9.9 mL; CO, 0.4±0.7 L/min; SAP, +4.4±11.5 mmHg). PHT significantly increased HR (+26.9±12 bpm) and T_{core} (+1.1±0.5 °C), with no significant change in MAP (+6.5±9.0 mmHg).

Table 4.3. Summary of Outcomes of Passive Lower Limb Movement

Study	Pre-intervention values	Intervention values	Conclusion
		Outcomes of single session therapy	
1990 Figoni[160]	**Rest** HR (bpm):65±12 CO (L/min): 3.9±0.8 SV (mL): 62±18 SAP (mmHg): 98±12 DAP (mmHg): 67±8 MAP (mmHg): 78±9	**50 RPM** HR (bpm):63±13 CO (L/min): 4.5±0.8 SV (mL): 73±19 SAP (mmHg): 104±13 DAP (mmHg): 73±11 MAP (mmHg): 83±12	PC did not result in a significant increase in any of the measured cardiovascular outcomes. Moderate increases in CO, driven by changes in SV, are attributed to reduced venous pooling in the lower limbs thereby enhancing venous return.
2008 Fornusek[163]	**Rest prior to 15 RPM** HR (bpm):64 ±3 CO (L/min): 4.8±0.2 SV (mL): 74±5 SAP (mmHg): 121±6 DAP (mmHg): 84±4 **Rest prior to 30 RPM** HR (bpm):64±3 CO (L/min): 4.6±0.4 SV (mL): 71±5 SAP (mmHg): 117±6 DAP (mmHg): 82±4 **Rest prior to 50 RPM** HR (bpm):64±3 CO (L/min): 4.7±0.5 SV (mL):73±5 SAP (mmHg): 123±6 DAP (mmHg): 80±4	**15 RPM** HR (bpm):61±3 CO (L/min): 4.6±0.2 SV (mL):75±5 SAP (mmHg): 124±6 DAP (mmHg): 86±4 **30 RPM** HR (bpm):63±3 CO (L/min): 4.7±0.4 SV (mL): 75±5 SAP (mmHg): 121±6 DAP (mmHg): 85±5 **50 RPM** HR (bpm): 63±3 CO (L/min): 4.8±0.4 SV (mL):79±5 SAP (mmHg): 129±6 DAP (mmHg): 88±4	PC did not result in a significant increase in any of the measured cardiovascular outcomes.
2015 Jeffries[215]	**Seated** HR (bpm): 87±5 **Stand HWS** HR (bpm): 104±6* **Stand LWS**	**Step HWS** HR (bpm): 118±10*,† **Step LWS**	There was a significant main effect of phase on HR levels for SCI. Post hoc analyses showed a significant increase in HR with stepping when compared to seated and standing and a significant increase from seated to standing. **Additional Findings**

	HR (bpm): 102±6*	HR (bpm): 128±15*,†	HR was higher in SCI compared to AB at all time-points and increased from seated to stepping in AB.
2000 Muraki[162]	**Rest** HR (bpm): 63±7 CO (L/min): 3.4±1.0 SV (mL):54±19	**40 RPM** HR (bpm): 64±8 CO (L/min): 3.7±1.1* SV (mL): 58±20*	There was a significant increase in CO, driven by a significant increase in SV, compared to resting values. **Additional Findings** CO was significantly increased in AB during PC, resultant from mild, non-significant increases in both SV and HR.
1996 Muraki[161]	**Rest** HR (bpm) 69±5 CO (L/min): 4.1±0.6 SV (mL): 59±6 SAP (mmHg): 137±24 DAP (mmHg): 77±16	**20 RPM** HR (bpm): 66±5 CO (L/min): 4.9±0.9* SV (mL): 72±11* SAP (mmHg): 137±21 DAP (mmHg): 82±12 **40 RPM** HR (bpm): 67±3 CO (L/min): 5.1±0.8* SV (mL): 76±12* SAP (mmHg): 139±28 DAP (mmHg): 83±18	There was a significant increase in CO, driven by a significant increase in SV, during both PC speeds compared to resting values. **Additional Findings** At rest, individuals with SCI had lower SV and higher HR compared to AB. During the 40 rpm phase, CO was significantly increased in AB.
1995 Nash[159]	**Rest** HR (bpm): 82±22 CO (L/min): 3.6±1.4 SV (mL): 44±6 SAP (mmHg): 96±13 DAP (mmHg): 64±7 MAP (mmHg): 78±14	**50 RPM** HR (bpm): 70±19 CO (L/min): 3.3±1.0 SV (mL): 46±6 SAP (mmHg): 102±14 DAP (mmHg):73±14 MAP (mmHg): 79±11	PC did not result in a significant increase in any of the measured cardiovascular outcomes.
2009 Ogata[216]	**Seated** **HSCI** HR (bpm):76±3 SAP (mmHg): 97±4 DAP (mmHg):66±2 MAP mmHg):77±3Ŧ **LSCI** HR (bpm):75±3 SAP (mmHg):110±4 DAP (mmHg):76±4	**PLLM 6th minute** **HSCI** HR (bpm):76±2 SAP (mmHg):108±5* DAP (mmHg):78±4* MAP (mmHg):88±4* **LSCI** HR:78±5* SAP (mmHg):109±7 DAP (mmHg):77±5	Seated MAP was significantly lower in HSCI compared to LSCI. During stand phase, HR increased in HSCI group. All measures of blood pressure were lower in HSCI compared to LSCI during stand phase. PLLM significantly increased SAP and MAP in the HSCI group, with a decrease in HR to near seated value. PLLM significantly increased HR in the LSCI group. **Additional Findings** While seated, HR in both SCI groups was significantly higher than AB. During both the seated and stand phases, all blood pressure values in HSCI were significantly lower than those in

	MAP (mmHg):87±4 **Standing** **HSCI** HR (bpm):87±3 SAP (mmHg): 86±7 DAP (mmHg):60±4 MAP (mmHg):69±5 **LSCI** HR (bpm):80±4 SAP (mmHg):106±4 DAP (mmHg):72±4 MAP (mmHg):83±4	MAP (mmHg):88±5 **PLLM 12th minute** **HSCI** HR (bpm):76±1 SAP (mmHg):105±5* DAP (mmHg):75±4* MAP (mmHg):85±4* **LSCI** HR (bpm):81±6 SAP (mmHg):110±7 DAP (mmHg):76±4 MAP (mmHg):87±5	AB. HR for both SCI groups was significantly higher compared to AB during PLLM phase.
2000 Raymond[217]	**Rest** HR (bpm): 69±11 MAP (mmHg): 92±6.	**50 RPM** HR (bpm): 63±10* MAP (mmHg): 93±7	PC significantly decreased HR relative to rest.
2022 Soriano[158] ¥	**Rest** HR (bpm): 63±8 CO (L/min): 5.4±1.1 SV (mL): 87±13 SAP (mmHg): 114±10 DAP (mmHg): 64±9 MAP (mmHg): 82±8	**30 RPM** HR (bpm): 64±9* CO (L/min): 5.7±1.2* SV (mL): 90±14* SAP (mmHg): 119±9* DAP (mmHg): 68±7 MAP (mmHg): 86±8*	All cardiovascular measurements increased significantly during PC, however, clinical relevance is questionable. Cerebrovascular conductance was reduced during PC.
2006 Ter Woerds[157]	CO (L/min): 6.6±2.0 MAP (mmHg): 93±3	Data not provided	PC did not result in a significant increase in any of the measured cardiovascular outcomes.
Outcomes of multiple session therapy			
2005a Ditor[213]	**Baseline** HR (bpm): 62±7 SAP (mmHg): 117±20 DAP (mmHg): 73±11 MAP (mmHg): 88±14	**Baseline** HR (bpm): 56±8* SAP (mmHg): 115±15 DAP (mmHg): 72±9 MAP (mmHg): 86±11	Resting HR decreased after 6 months of BWSTT. No significant changes in any resting blood pressure value.
2005b Ditor[214]	**Baseline** **Supine** HR (bpm): 62±9 SAP (mmHg): 114±19 DAP (mmHg):66±11 MAP (mmHg):82±13	**Baseline** **Supine** HR (bpm): 67±6 SAP (mmHg): 113±10 DAP (mmHg):64±7 MAP (mmHg): 80±7	During passive exercise HR increased significantly (p=0.09). HR during stand and PLLM phases was significantly higher compared to supine phase. PLLM phase had an average HR increase of 67±39% for individuals with TP, while individuals with PP experienced a 37±10% increase.

	Standing HR (bpm): 80±12 * **PLLM** HR (bpm): 98±22*	4 months of BWSTT did not result in a significant change in any of the measured cardiovascular outcomes.

AIS, American spinal injury association impairment scale; SCI, spinal cord injury; BWSTT, body weight supported treadmill training; PC, passive cycling; PLLM, passive lower limb movement; HR, heart rate; CO, cardiac output; SV, stroke volume; SAP, systolic blood pressure; DAP, diastolic blood pressure; MAP, mean arterial pressure; AB, able-bodied; HSCI, high spinal cord injury; LSCI, low spinal cord injury; Baseline, resting values pre training; *, statistically different from pre-intervention phase; †, statistically different from stand phase; ₸, statistically different from LSCI group; ¥, data extracted from figure using WebPlotDigitizer.

Table 4.4. Summary of Outcomes of Passive Heat Therapy

Study	Pre-intervention values	Intervention values	Conclusion
		Outcomes of single session therapy	
2018 Coombs 2019 Coombs§	**Rest** HR (bpm): 55±10 SAP (mmHg): 120±18 DAP (mmHg): 68±16 MAP (mmHg): 81±10 T_{core} (°C): 36.4±0.6 MCAv (sec·cm^{-1}): 61±13 PCAv (sec·cm^{-1}): 42±12	**60 min immersion** HR (bpm): 58±9* SAP (mmHg): 118±24 DAP (mmHg): 66±17 MAP (mmHg): 84±15 T_{core} (°C): 37.1±0.6* MCAv (sec·cm^{-1}): 58±13 PCAv (sec·cm^{-1}): 41±12	HR and T_{core} significantly increased during PHT **Additional Findings** T_{core} was significantly lower in individuals with SCI before PHT and increased to a greater extent compared to AB. MAP changed differently between individuals with SCI (+6±14) and AB (-8±12) in response to PHT.
1985 Freund	**Rest** HR (bpm): 63±12 T_{core} (°C): 36.4±0.5	**T_{core} = 38°C, perfusion** HR (bpm): 104±6* T_{core} (°C): 38.3±0.9*	PHT significantly increased both HR and T_{core}.
2002 Gass	**Rest** HR (bpm): 67±4 T_{core} (°C): 36.0±0.3	**60 min immersion** HR (bpm): 87±3* T_{core} (°C): 37.3±0.5*	PHT significantly increased both HR and T_{core}. **Additional Findings** Increases in HR during PHT were slightly lower compared to HR during moderate exercise. T_{core} increased more during PHT compared to exercise.
2018 Hashizaki	**Rest** **HSCI** HR (bpm): 59±2 CO (L/min): 4.7±0.1 SV (mL): 78±5 MAP (mmHg): 79±5 T_{core} (°C): 36.5±0.2 **LSCI** HR (bpm): 62±3 CO (L/min): 5.3±0.2 SV (mL): 89±5 MAP (mmHg): 92±4 T_{core} (°C): 36.6±0.1	**1°C rise in T_{core}, perfusion** **HSCI** HR (bpm): 69±3* CO (L/min): 6.0±0.2* SV (mL): 84±34 MAP (mmHg): 83±5 T_{core} (°C): 37.6±0.2* Time to 1°C increase (min): 41±4$^{\text{Ŧ}}$ **LSCI** HR (bpm): 84±4* CO (L/min): 6.9±0.3* SV (mL): 90±5 MAP (mmHg): 86±5 T_{core} (°C): 37.6±0.1*	PHT significantly increased CO, driven by a significant increase in HR for both SCI groups. T_{core} was significantly increased for both groups, however a faster rate of increase was seen in HSCI. **Additional Findings** CO and HR values at rest and at the end of PHT, and time to 1°C increase were significantly lower in individuals with HSCI compared to AB. There were no differences between individuals with LSCI and AB.

		Time to 1°C increase (min): 65±5	
2015 Leicht	**Rest** HR (bpm): 76±13 SAP (mmHg): 89±24 DAP (mmHg): 55±15 T_{core} (°C): 37.7±0.5	**60 min immersion** HR (bpm): 85±14* SAP (mmHg): 104±16* DAP (mmHg): 66±8* T_{core} increase (°C): 2.2±0.4*	PHT significantly increased all cardiovascular outcomes. **Additional Findings** HR increased to a larger extent in AB compared to individuals with SCI. DAP increased in individuals with SCI and decreased in AB. There was a slower recovery of T_{core} for individuals with SCI following PHT.
2000 Yamasaki	**Rest** **T6-T10** HR (bpm): 67 CO (L/min): 4.7±0.4 SV (mL): constant at about 70 T_{core} (°C): 36.4 **T11-T12** HR (bpm): 66 CO (L/min): 4.81±0.17 SV (mL): constant at about 70 T_{core} (°C): 36.6	**60 min ambient** **T6-T10** HR (bpm): 73* CO (L/min): 4.9±0.3 SV (mL): constant at about 70 T_{core} (°C): 37.8* **T11-T12** HR (bpm): 72* CO (L/min): 5.16±0.2 SV (mL): constant at about 70 T_{core} (°C): 37.9*	PHT significantly increased HR and T_{core} in individuals with SCI. **Additional Findings** HR, SV, and CO were significantly lower in individuals with SCI compared to the AB, both at rest and during PHT.
		Outcomes of multiple session therapy	
2001 Gass	**Rest** **Pre-Acclimation** HR (bpm): 64±4 T_{core} (°C): 36.7±0.1 **Post-Acclimation** HR (bpm): 74±5 T_{core} (°C): 36.8±0.37	**60 min immersion** **Pre-Acclimation** HR (bpm): 99±6* T_{core} (°C): 38.1±0.1* **Post-Acclimation** HR (bpm): 99±5* T_{core} (°C): 38.1±0.17*	PHT significantly increased HR and T_{core} in individuals with SCI to the same extent both before and after acclimation. PHT acclimation did not result in changes to resting values or responses of HR and T_{core} to PHT. **Additional Findings** PHT acclimation resulted in a reduced T_{core} elevation during PHT in the AB not seen in individuals with SCI.
1992 Petrofsky	**Rest** **Pre-Acclimation** Data not provided	**35 min ambient** **30°C** **TP** HR (bpm): 82±18 T_{core} (°C): 37.3±0.44 **PP** HR (bpm): 76±21 T_{core} (°C): 37.1±0.45 **35°C**	PHT at 35°C and 40°C significantly increased HR and T_{core} compared to 30°C condition in both groups of individuals with SCI. Both HR and T_{core} exhibited faster rates of rise in TP compared to PP. **Additional Findings** There was no difference in HR or T_{core} values during the 30°C condition between TP, PP, or AB group. TP and PP groups exhibited faster rates of rise in both HR and T_{core} compared to AB in the 35°C and 40°C conditions.

	TP HR (bpm): 118±14*,Ŧ T_{core} (°C): 37.8±0.24*,Ŧ **PP** HR (bpm): 99±12* T_{core} (°C): 37.4±0.5* **40°C** **TP** HR (bpm): 140±8*,Ŧ T_{core} (°C): 38.0±0.5*,Ŧ **PP** HR (bpm): 107±10* T_{core} (°C): 37.8±0.42*	Both TP and PP groups have poorer heat tolerance compared to AB.

AIS, American spinal injury association impairment scale; SCI, spinal cord injury; HR, heart rate; CO, cardiac output; SV, stroke volume; SAP, systolic blood pressure; DAP, diastolic blood pressure; MAP, mean arterial pressure; MCAv, middle cerebral artery blood flow velocity; PCAv, posterior cerebral artery blood flow velocity; AB, able-bodied; PP, paraplegic; TP, tetraplegic; HSCI, high spinal cord injury; LSCI, low spinal cord injury; Baseline, resting values pre-training; *, statistically different from pre-intervention phase; Ŧ, statistically different from LSCI/PP group; §, this study incorporated the same participants and protocol as Coombs 2018 with reported outcome measures focusing on cerebral responses. Accordingly, cardiovascular outcomes have been reported together.

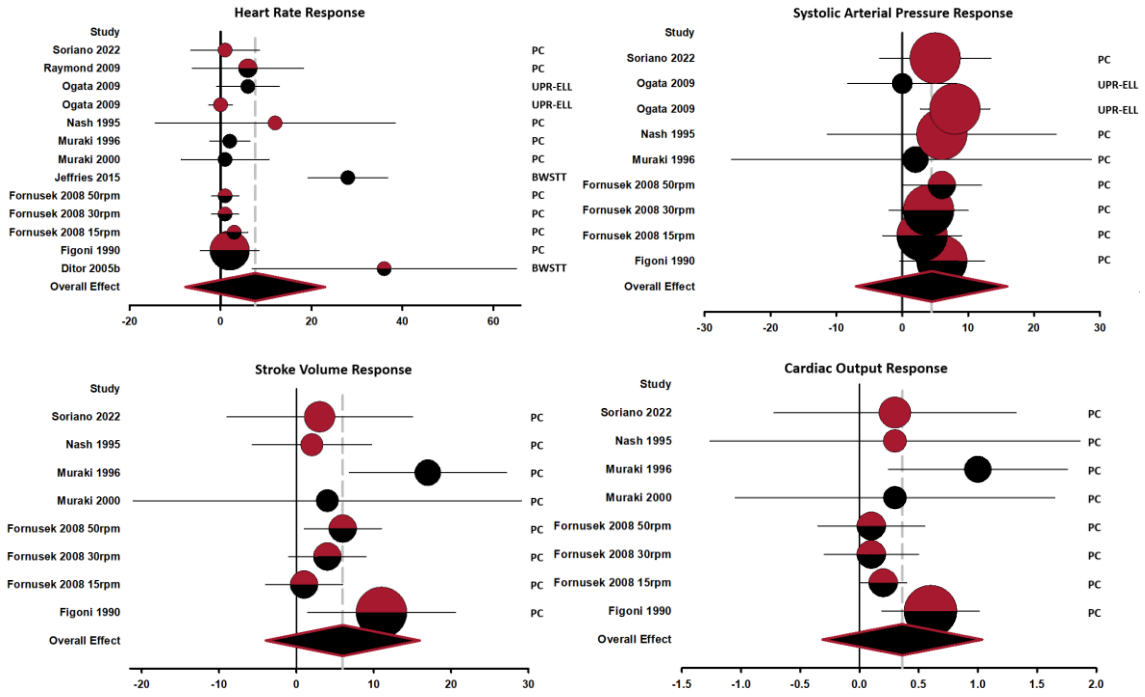

Figure 4.2. Meta-analyses of cardiovascular responses during acute PLLM interventions

Acute PLLM did not significantly increase cardiovascular responses in individuals living with chronic SCI. Alternatively, PLLM did not result in exercise induced hypotension or cardiovascular decompensation. PLLM, passive lower limb movement; PC, passive cycling; UPR-ELL, upright elliptical; BWSTT, body weight supported treadmill training; SCI, spinal cord injury; red circles, high-level SCI; black circles, low-level SCI; split circles, both high and low-level SCI.

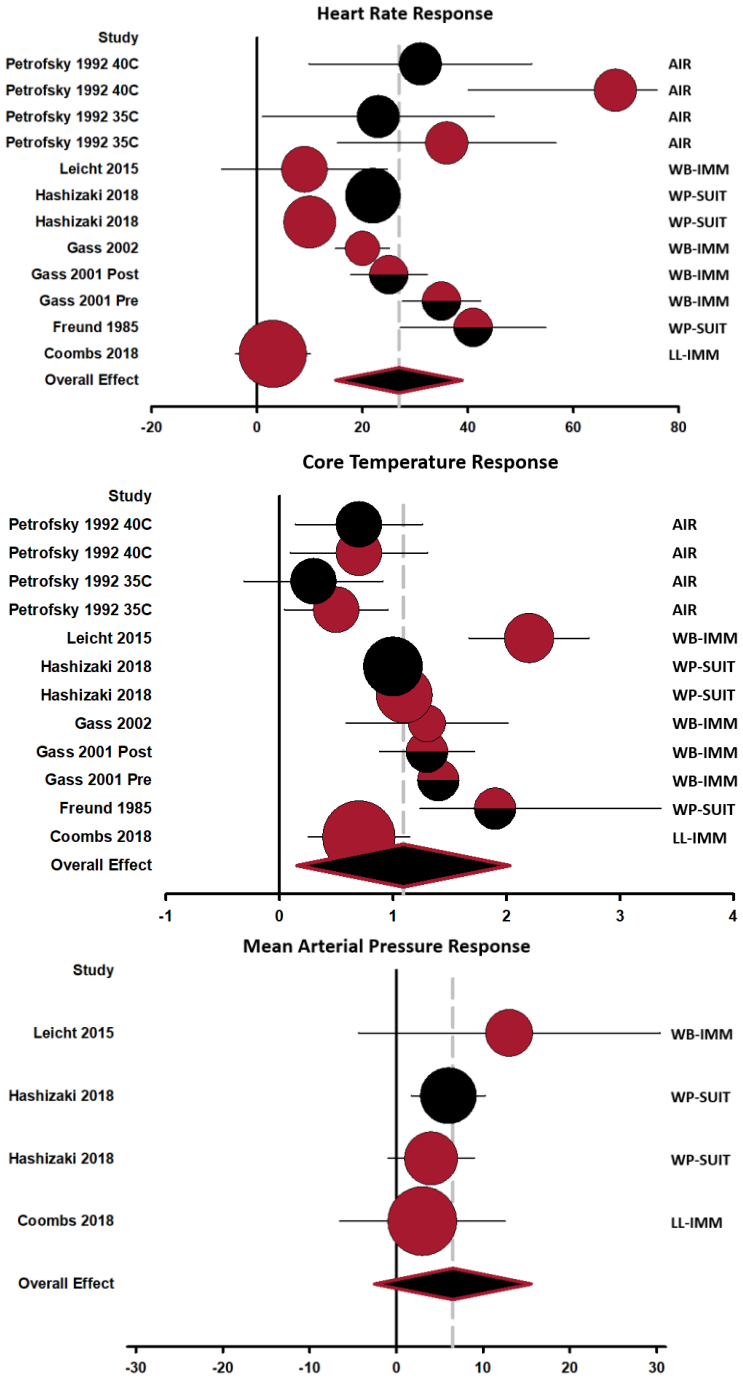

Figure 4.3. Meta-analyses of cardiovascular responses during acute PHT interventions

Acute PHT significantly increased heart rate and core temperature responses in individuals living with chronic SCI. Additionally, PHT tended to increase mean arterial pressure with no studies reporting exercise induced hypotension or cardiovascular decompensation. PHT, passive heat therapy; AIR, increased ambient air; WB-IMM, whole body immersion in hot water; LL-IMM, lower limb immersion in hot water; WP-SUIT; hot water perfused suit; SCI, spinal cord injury; red circles, high-level SCI; black circles, low-level SCI; split circles, both high and low-level SCI.

4.5. Discussion

Increasing physical activity has been shown to decrease CVD risk, augment cardiovascular control, and improve overall quality of life[130]. However, individuals living with SCI are presented with unique challenges to increasing physical activity[139,140] and the efficacy of exercise is often mitigated as a result of injury. In this systematic review we aimed to describe two exercise adjuncts accessible to individuals with chronic SCI, PLLM and PHT, and assess the effectiveness of these interventions for improving cardiovascular outcomes. These exercise adjuncts are not meant to replace exercise, but rather to highlight alternative means to increasing motion and physical activity (PLLM) or introducing a modality that is known to result in exercise-like responses (PHT), while limiting known barriers for individuals living with SCI. We reviewed the protocols and efficacy of both single and multiple session therapies. This study builds on a previous review outlining cardiovascular, musculoskeletal, and neurological outcomes during PC[155] by reviewing other forms of PLLM, including BWSTT and elliptical motion, along with the addition of PHT.

There were a wide range of modalities used within PLLM and PHT, however 75% of reviewed single session studies reported a statistically significant increase in at least one cardiovascular outcome, providing confidence in these exercise adjuncts to promote cardiovascular health. The cardiovascular response to chronic PLLM or PHT were unclear, and more research is needed in this domain to fully grasp the efficacy for health benefits.

Cardiovascular outcomes

The cardiovascular variables selected as primary outcomes for this review included measures of blood pressure, HR, CO, SV, CBFv, and T_{core}. These were selected as they are primary determinants of exercise intensity, they have direct correlations with CVD risk, and most of them are common, simple measurements which could increase inclusion and strengthen our results. The relatively low number of studies included in this review highlight the necessity for more research into exercise adjuncts following SCI. Of note, several studies had to be excluded because although they stated they recorded one of our primary outcome measures, they failed to report results or provide the relevant data.

Blood pressure

Blood pressure is a key marker of cardiovascular health and is used to initiate and assess risk management interventions. Just over half of the studies included in this review reported on blood pressure responses to PLLM or PHT (n=13). Of these, 4 reported increases in blood pressure, with the remaining studies reporting no difference. Both of these findings have important implications. Blood pressure control is often impaired following SCI as descending control of sympathetic innervation of the heart and vasculature may be interrupted, especially in high-level SCI. Additionally there can be a reduction in circulating blood volume as gravitational effects and the loss of the skeletal muscle pump result in blood pooling in the lower limbs. The consequence is resting hypotension, with associated OH and exercise-induced hypotension. The ability to maintain, and improve, blood pressure during conditions that challenge blood pressure regulation could be very beneficial to those living with SCI.

Heart rate

HR was a primary outcome variable in every study included in this review., and in one study was the only outcome reported. From the PLLM studies, only 1 PC protocol reported an increase in HR, while all BWSTT and elliptical motion studies reported increased HR during the standing phase of their protocol and mixed results during the PLLM phase. PLLM in the AB typically results in a decrease or no change in HR, as there is little to no metabolic increase and postural changes are responded to by changes in peripheral resistance mediated through an intact baroreflex. Following SCI, the baroreflex vascular resistance responses may be impaired, increasing reliance on other avenues such as HR to increase CO and maintain blood pressure and oxygen delivery. This might explain the increased HR in response to the posture of the intervention that is not seen in AB controls. Whether this modest HR rise during some PLLM paradigms conveys cardiovascular benefit akin to exercise is not clear. However, individuals that increase participation in regular physical activity and moderate intensity exercise, typically identified by increases in HR, have a healthier cardiometabolic profile, regardless of whether the exercise undertaken reaches population specific exercise guidelines. Of note, all PHT protocols resulted in an increase in HR, and PHT in the AB has been shown to induce cardiometabolic benefits similar to those obtained from moderate intensity exercise[143]. The results presented in this review indicate that individuals living with SCI may likewise benefit from PHT.

Cardiac output and stroke volume

CO and SV were reported in 5 PLLM studies and 2 PHT studies. Significant increases were reported for CO in 3 and 1 of those studies, respectively. Interestingly, during the PLLM therapies increases in CO were driven by an increase in SV, while during the PHT therapies, it was driven by an increase in HR. The increased SV during PLLM protocols is consistent with responses seen during mild physical activities which don't significantly increase metabolic demand or increase T_{core}, while increased HR is more typical of moderate intensity exercise or instances of thermoregulatory stress. Increases in SV often reflect an increase in venous return resulting from augmented circulating blood volume. The mechanical activation of the skeletal muscle pump during PLLM is likely driving this cascade, improving blood pressure regulation and mitigating the effects and symptoms of resting and orthostatic hypotension.

Cerebral blood flow

Only 2 studies in this review measured CBFv, 1 PLLM therapy and 1 PHT therapy. There were no changes in middle or posterior cerebral artery blood flow velocity, however a reduction in cerebrovascular conductance, which would offset increases in CBFv was reported during PLLM therapy. Cerebral autoregulation is thought to be impaired in chronic SCI resultant from persistent, systemic hypotension[63] leading to cerebral hypoperfusion. Symptoms of cerebral hypoperfusion include lightheadedness, dizziness, fatigue, nausea, and syncope, with consequences thought to include cognitive impairment and increased risk of CVD[61]. Increasing circulating blood volume and improving blood pressure control may help mitigate changes in systemic blood pressure and help preserve cerebral autoregulation. The mechanisms underlying cerebral autoregulation during physical activity in chronic SCI are not well understood and future research should investigate this important marker of cardiovascular health.

Core temperature

For inclusion in this study, PHT studies needed to include a measure of T_{core}. Many of the cardiometabolic benefits of PHT in the AB are attributable to increases in T_{core} and the stress responses it provides[143]. All of the PHT protocols were successful in increasing T_{core}. Important considerations for PHT following SCI include increased susceptibility to heat stress or heat illness and heat induced hypotension. Of the 5 PHT studies that included AB participants as a control, 4 of them reported a faster rise or slower recovery

of T_{core} in response to PHT and concluded that individuals with SCI have poorer heat tolerance. Thermoregulatory eccrine sweat glands are innervated by descending sympathetic neurons that exit the spinal cord throughout the thoracic and lumbar levels, therefore the degree of impairment is associated with the LOI and AIS[77]. Heat stress presents a perturbation to the maintenance of blood pressure as blood is redirected to the periphery to aid in convective heat loss. Circulating blood flow is maintained as blood flow is shunted from the splanchnic vascular bed and inactive muscles, mediated by the baroreflex. Impairments to sympathetic efferent neurons due to SCI limit vasoconstriction and the baroreflex and may result in widespread vasodilation and heat induced hypotension. While there were no reported incidences of hypotension, none of the included studies indicated a quantitative evaluation of abnormal or adverse responses to the intervention (i.e. unexpected decreases in BP, AD indicated by BP increase of >20mmHg with concurrent decrease in HR). Daily, repetitive bouts of heat stress for 7 days did not alter the cardiovascular response in individuals with SCI, while AB had a reduced T_{core} elevation after 7 days. It is possible that due to impaired cardiovascular autonomic function, the benefits of heat stress and increased T_{core} are mitigated, with increasing safety concerns. The cardiovascular responses to heat stress in individuals with SCI likely differ based on LOI, AIS, and remaining autonomic function. Further research is needed to characterize the rate of rise and recovery of T_{core} to PHT specific to LOI and AIS considering both acute and chronic interventions, to allow for the safe utilization of this promising exercise adjunct.

It is recognised that these are not the only options available when considering exercise adjuncts accessible to individuals living with SCI. However, PLLM and PHT have been shown to be efficacious, in individuals living with SCI or the general population, at augmenting cardiovascular outcomes or improving cardiometabolic health. Additionally, these two interventions directly address identified barriers to participation in physical activity and exercise by individuals living with SCI[139,140].

4.6. Conclusion

Evidence from this systematic review indicates that two forms of exercise adjuncts, PLLM and PHT, showed some promise for improving cardiovascular outcomes and reducing CVD risk for individuals living with chronic SCI. Additionally, these exercise adjuncts did not induce episodes of orthostatic, exercise, or heat induced hypotension that

are a primary concern among individuals living with SCI, although as noted above, these were not explicitly monitored for in any of the included studies. More evidence is required to understand ideal parameters for PLLM and PHT. Future research should focus on long-term benefits of PLLM and PHT following SCI and mitigating safety concerns, specifically for PHT. These represent two avenues to reducing barriers and improving accessibility to increasing physical activity and exercise for the betterment of cardiometabolic health and overall quality of life for individuals living with SCI.

Chapter 5.

The effect of passive cycling on cardiovascular control in individuals living with spinal cord injury

5.1. Abstract

Aims: Individuals with SCI may have autonomic impairment adversely affecting cardiovascular control, resulting in resting and orthostatic hypotension with decreased SV and CO. PC may augment cardiovascular control; however, accessibility is a barrier. We aimed to establish the safety, efficacy, and acceptability of a PC wheelchair attachment on blood pressure, HR, SV, CO, CBFv, and user ratings of comfort and satisfaction (URCS).

Methods: In this analysis-blinded study, AB controls (AB) (n=16, 9 females, aged 27±6 years) and individuals with SCI (n=6, 2 females, aged 43±19 years) sat in a wheelchair while an attachment cycled their legs in 10-minute intervals at 3 randomized speeds (0.3, 0.6, and 0.9 $m \cdot sec^{-1}$), separated by a 5-minute rest period. Cardiovascular parameters were continuously measured using beat-to-beat finger plethysmography. CBF was derived via Doppler ultrasound. After cycling, two questionnaires were completed: Comfort Rating Scale (CRS) and Quebec User Evaluation of Satisfaction with Assistive Technology (QUEST).

Results: URCS were high, particularly for safety and tolerance in both AB and individuals with SCI. There were several suggestions to improve ease of use and accessibility of the device. In AB, systolic BP was increased at 0.6 $m.sec^{-1}$ (8±10 mmHg, p=0.038) and 0.9 $m.sec^{-1}$ (10±14 mmHg, p=0.003). CO was increased at these same speeds (0.5±0.5 $L \cdot min^{-1}$, p= 0.036; 0.6±0.4 $L \cdot min^{-1}$ p=0.004), driven by increased SV (p=0.013). In individuals with SCI, there were no significant differences in any cardiovascular outcomes during any pedal phase, or relative to AB.

Conclusion: These data establish the safety of a prototype, PC wheelchair attachment and its efficacy in improving cardiovascular outcomes in the AB and individuals living with SCI. Improvements in CO, driven by increases in SV, appear to be dependent on pedal speed, suggesting a minimum threshold to be efficacious. Individuals with SCI face unique challenges to meeting physical activity guidelines and a PC wheelchair attachment could

aid in overcoming some of those barriers and provide another avenue to enjoy the benefits of increased physical activity.

5.2. Introduction

In addition to motor and sensory deficits, individuals living with SCI may have autonomic impairment that adversely affects cardiovascular control, presenting as bradycardia and resting and orthostatic hypotension[15]. Reduced physical activity and increased sedentary time are known risk factors for CVD[130], the leading cause of morbidity and mortality in individuals living with SCI[7]. Physical activity can help regulate cardiovascular control by maintaining circulating blood volume, improving venous return and CO, and ensuring adequate perfusion of the cerebral vasculature and other key organs. However, adherence to physical activity guidelines is challenging with a significantly lower proportion of the SCI population meeting recommended amounts of physical activity compared to the general population[45].

PC has been shown to augment cardiovascular outcomes in chronic SCI and is an avenue to increase physical activity and mitigate CVD risk. Several studies have reported increased peripheral blood flow[156,157], blood pressure[158], HR[158,159], SV[158–162], and CO[158–162] following acute sessions of PC with mixed results following multiple bouts of exercise[159,163]. Importantly, no adverse events were reported such as AD or exercise induced hypotension. PC has also been shown to reduce spasticity[220]. Although efficacious, accessibility presents a significant challenge when considering this as an adjunct to exercise as availability to adaptable PC equipment is limited to research institutions or a small number of centres with specialized, adaptable equipment.

The aim of this study is to establish the safety and acceptability of a prototype, PC wheelchair attachment and its efficacy on improving cardiovascular outcomes including blood pressure, HR, SV, CO, and CBFv measured in the middle cerebral artery (MCAv) during an acute bout of PC.

5.3. Methods

This study was jointly approved by the Department of Research Ethics at Simon Fraser University and the Office of Research Ethics at the University of British Columbia.

Investigations were performed in accordance with the Declaration of Helsinki of the World Medical Association[179]. All participants gave written informed consent prior to participation. There is an NDA associated with the prototype device used in this study which precludes the inclusion of pictures and certain details regarding the device.

5.3.1. Participants

Eligible participants were individuals aged >18 years of age. Able-bodied participants were excluded if they had any known cardiovascular or neurological disorders or complications. Individuals with SCI were excluded if they had any known cardiovascular or neurological complications prior to injury, currently had a urinary tract infection, pressure sores, or skin breakdown, or were unable to communicate in English. Individuals were recruited from posters displayed at Simon Fraser University campus, community rehabilitation centres, research conferences, and through local SCI support groups.

5.3.2. Procedures

General health questionnaire

Study participants reported to the research laboratory at Simon Fraser University for a single testing session. All participants were asked to avoid caffeine, alcoholic beverages, and strenuous exercise for at least 12 hours prior to testing. A general medical history was taken with questions concerning overall health, CVD, hypertension, family history concerning CVD, medication use, smoking status, and alcohol consumption. Women were asked about menstrual cycle stage and hormone medication use. AB controls were measured for height, weight and body composition using a Tanita scale[221]. Individuals with SCI self-reported height and weight, provided injury details including date of injury, LOI, and AIS score, and responded to questions regarding any symptoms of OH and AD associated with SCI. For individuals that did not know their LOI or AIS score, a physician examined them according to the International Standards for Neurological Classification of Spinal Cord Injury[3] Participants were asked to complete bladder and bowel care prior to coming in and voided their bladder immediately before testing as necessary.

Spasticity measures

Participants with SCI transferred to a bed for a muscle spasticity examination. Using the Modified Ashworth Scale (MAS) for grading, joints of the upper and lower limbs were passively moved through their range of motion. The MAS grades muscle spasticity as follows: 0, no increase in muscle tone; 1, slight increase in muscle tone, with a catch and release or minimal resistance at the end of the range of motion when an affected part(s) is moved in flexion or extension; 1+, slight increase in muscle tone, manifested as a catch, followed by minimal resistance through the remainder (less than half) of the range of motion; 2, marked increase in muscle tone throughout most of the range of motion, but affected part(s) are still easily moved; 3, considerable increase in muscle tone, passive movement difficult; 4, affected part(s) rigid in flexion or extension[222]. Spasticity measures were taken before and after the PC intervention.

Passive cycling protocol

All participants were asked to independently transfer into the test wheelchair and strap themselves into the PC device. Assistance was provided as requested. Following instrumentation (described below), participants were asked to remain still for a 5-minute resting baseline followed by a 5-minute paced breathing period at a rate of 15 breaths per minute by keeping pace to a metronome. The PC protocol consisted of 3 x 10-minute randomized cycling sessions at 0.3, 0.6, and 0.9$m \cdot s^{-1}$, respectively, with a 5-minute rest period between each cycling session. These speeds correlate with the low-end, average, and high-end wheeling speeds of wheelchair users in a community setting[223]. To achieve the desired velocity the attached PC device and front caster wheels of the wheelchair were placed on an in-ground treadmill (FIT, Bertec Corporation, Columbus, OH, USA), while the back wheels remained off the treadmill in a locked position, allowing the PC device to pedal at the set treadmill speed. After the PC protocol and de-instrumentation, participants were asked to independently remove themselves from the PC device and transfer out of the wheelchair.

Instrumentation

Primary outcome variables included changes in blood pressure, HR, SV, CO, and MCAv. Beat-to-beat blood pressure and HR were recorded using finger plethysmography (Finometer Pro, Finapress Medical Systems, Amsterdam, The Netherlands) and an integrated 3-lead (lead II) electrocardiogram. SV and CO were calculated using the

Modelflow technique[224]. MCAv was measured through the temporal window using transcranial Doppler ultrasound with a 2MHz probe (Doppler Box, Compumedics DWL, Singen, Germany). A headband was used to maintain a constant angle of insonation throughout the test. Ventilation rate and breath-by-breath partial pressure of end tidal carbon dioxide were recorded through a nasal canula (O2Cap, Oxigraf Inc, Mountain View, CA). Recordings were sampled at a frequency of 1 KHz using an analog-to-digital converter (Powerlab 16/30, AD Instruments, Colorado Springs, CO) and stored for offline analysis through LabChart (LabChart 7, AD Instruments, Colorado Springs, CO).

Questionnaires

Lastly, participants were asked to fill out two questionnaires examining the safety, comfort and satisfaction of assistive devices, the QUEST[225] and CRS[226], respectively. Both questionnaires were modified to specifically reflect on the accessibility of this device and can be found in Appendix A. The QUEST questionnaire has the participant score each respective category by marking a number (1-5) that corresponds with their level of satisfaction. The CRS questionnaire has the participant mark on a 10cm line, with dashes every 0.5cm, indicating their level of satisfaction for each respective category. Each questionnaire provides an opportunity for narrative responses or feedback.

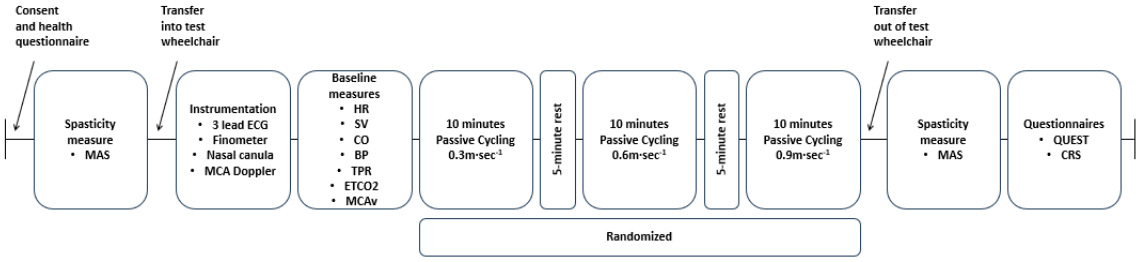

Figure 5.1. Protocol schematic

5.3.3. Statistical analyses

All data were cleaned and filtered in a blinded manner using LabChart (LabChart 7, AD Instruments, Colorado Springs, CO) and Microsoft Excel (Version 2305 Build 16.0.16501.20074). Artifact removal was done using Labchart peak detection settings and further filtering using known physiological ranges and changes. Data were averaged over 30-second periods and analyses were performed on data from the last 2-minutes of each respective phase. Statistical analyses were performed using SigmaPlot statistical software

(version 14.5; Systat Software Inc., San Jose, CA). Continuous data were tested for normality using Shapiro-Wilk test and parametric or non-parametric statistics were used as appropriate. Correlations were performed using Spearman's rank-order tests or Pearson's product moment analyses. Comparisons of cardiovascular outcomes and cycling conditions were performed using two-way repeated measures ANOVA. T-tests were performed to compare means of the QUEST and CRS data for each respective category. CRS scores were inverted to maintain a consistent direction of effect between questionnaires. Statistical significance was assumed at $p<0.05$. Data were reported as mean ± standard error, unless otherwise stated.

5.4. Results

5.4.1. Participants

A total of 18 individuals participated in the study, 6 (2 females) with SCI and 16 (9 females) AB controls. Participant characteristics ae shown in **Table 5.1**. Individuals with SCI were older compared to AB, with no differences in height or weight. LOI ranged from C5-T11, with varying levels of severity (AIS A-D).

Table 5.1. Participant characteristics

Category	SCI Group	AB Group	P Value
Sex (men/women)	4/2	7/9	
Age (years)	43±19	27±6	0.09
Height/Length (cm)	165±9	171±9	0.52
Weight (kg)	79±15	74±18	0.18
DOI (years)	19±17		
LOI/AIS	C5/A		
	C6/C		
	C7/B		
	T6/D		
	T8/D		
	T11/C		

Data are presented as mean ± standard deviation.

5.4.2. Safety and comfort ratings

There were no significant differences in safety, security, ease of use, or perception of harm found between individuals with SCI and AB using the QUEST and CRS questionnaires (**Fig 5.1A** and **B**). The question regarding “harm” received the highest comfort score with the narrowest range for individuals with SCI.

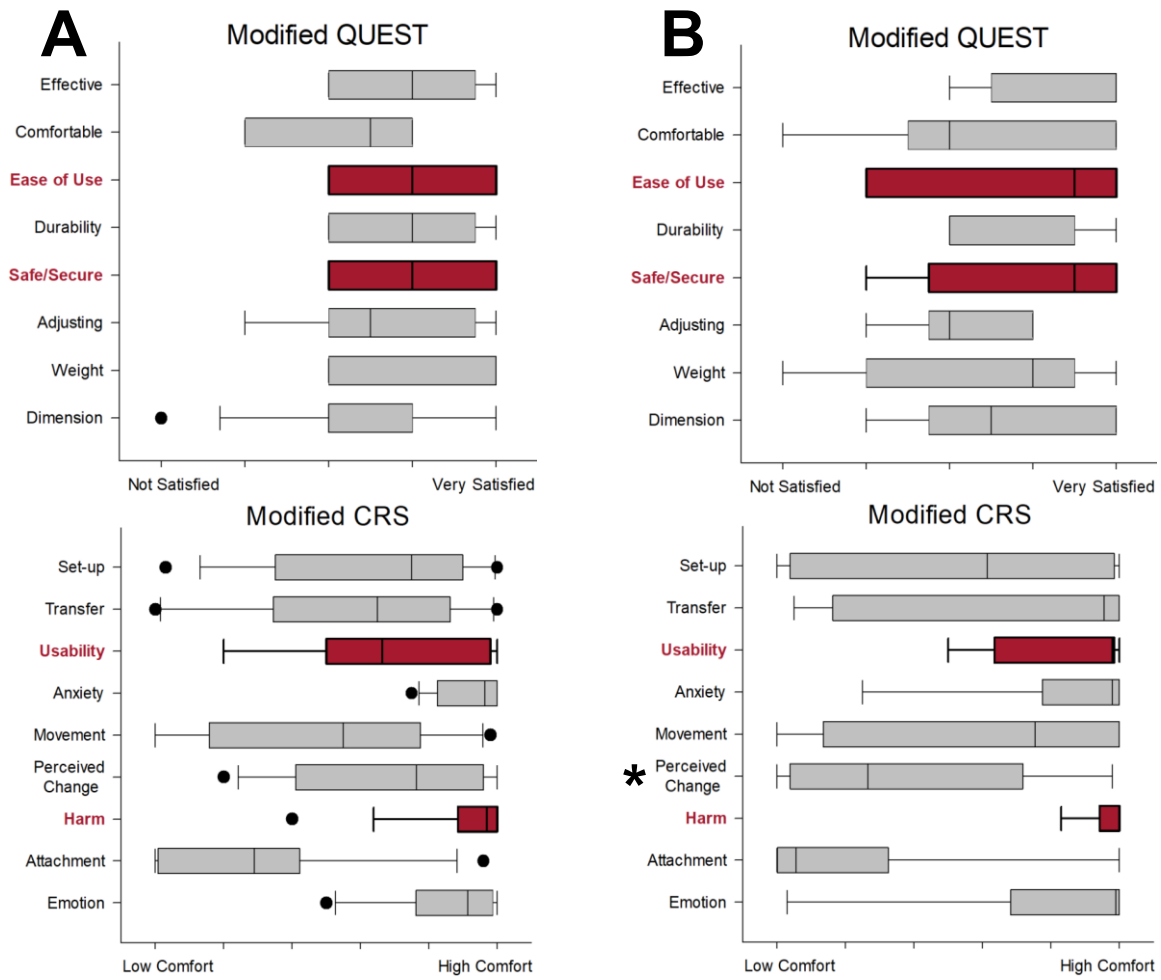

Figure 5.2. QUEST and CRS questionnaire responses
Primary markers of safety and usability were not different between AB (A) and individuals with SCI (B). * statistical difference between AB and individuals with SCI.

5.4.3. Cardiovascular outcomes during passive cycling

There were no significant differences between baseline resting values and any intermittent rest periods for AB or individuals with SCI, respectively. Unless noted, all comparisons are made using intermittent rest period values to account for postural changes and manipulations resultant from any pedal phase.

Responses in AB controls

PC significantly increased SAP during both the 0.6m·s^{-1} (+10±2 mmHg) and 0.9m·s^{-1} (+8±2 mmHg) pedal phases in AB participants (**Table 5.2**). CO was significantly higher during the 0.6m·s^{-1} (+0.51±0.36 L/min) and 0.9m·s^{-1} (+0.62±0.32 L/min) pedal

phases, primarily driven by an increase in SV (main effect, $p<0.05$; **Fig 5.3**). There were no sex differences shown in any of the cardiovascular outcomes.

Responses in individuals with SCI

There were no significant differences in any cardiovascular outcomes during any of the respective pedal phases (**Table 5.2**, **Table 5.3, Fig 5.3**). However, there was a trend for increases in SAP and MAP responses during the $0.3 m \cdot s^{-1}$ pedal phase. CO tended to be higher during the $0.6 m \cdot s^{-1}$ pedal phase, driven by an augmented SV, while during the $0.9 m \cdot s^{-1}$ pedal phase a higher HR was the primary effector for a higher CO. A trend for an augmented MCAv was also seen during the $0.6 m \cdot s^{-1}$ pedal phase.

Comparing cardiovascular responses between AB and individuals with SCI

Individuals with SCI had a significantly larger HR response during the $0.9 m \cdot s^{-1}$ pedal phase, relative to AB (**Fig 5.3**). SAP tended to increase more in individuals with SCI during the $0.3 m \cdot s^{-1}$ and $0.9 m \cdot s^{-1}$ pedal phases, although this did not reach statistical significance. Individuals with SCI tended to have a greater SV response to PC (main effect, $p=0.067$).

Table 5.2. Absolute cardiovascular responses of individuals with SCI and AB to PC at baseline and different pedaling speeds

Parameter	Group	Baseline	Pedal $0.3 m \cdot s^{-1}$	Pedal $0.6 m \cdot s^{-1}$	Pedal $0.9 m \cdot s^{-1}$
SAP (mmHg)	SCI	135±8	144±5	147±10	146±17
	AB	120±2	127±4	131±4*	129±4*
DAP (mmHg)	SCI	76±5	81±5	80±7	78±8
	AB	73±2	75±3	77±3	75±3
MAP (mmHg)	SCI	96±5	102±4	102±7	101±10
	AB	88±2	93±3	95±3*	93±3
TPR ($mmHg \cdot L \cdot min^{-1}$)	SCI	16±2	16±2	15±2	16±2
	AB	17±1	17±1	16±1	16±1
MCAv ($cm \cdot s^{-1}$)	SCI	57±7	59±7	63±7*	60±10
	AB	56±3	57±4	55±4	58±4

SCI, spinal cord injury; AB, able-bodied; PC, passive cycling; SAP, systolic arterial pressure; DAP, diastolic arterial pressure; MAP, mean arterial pressure; TPR, total peripheral resistance; MCAv, middle cerebral artery blood flow velocity;*, statistical difference from baseline phase.

Table 5.3. Change in cardiovascular responses of individuals with SCI and AB to PC at different speeds relative to the preceding rest period

Parameter	Group	Pedal $0.3 m \cdot s^{-1}$	Pedal $0.6 m \cdot s^{-1}$	Pedal $0.9 m \cdot s^{-1}$
SAP (mmHg)	SCI	+10±5	+8±7	+7±10
	AB	+5±3	+7±3*	+9±3*
DAP (mmHg)	SCI	+5±2	+3±3	-1±4
	AB	+1±2	+3±2	+3±2
MAP (mmHg)	SCI	+6±3	+4±4	+1±6
	AB	+3±2	+4±2	+5±2
TPR ($mmHg \cdot L \cdot min^{-1}$)	SCI	+0.1±0.5	-2.0±1.4	-0.9±0.8
	AB	-0.3±0.5	-0.8±0.6	-0.8±0.4
MCAv ($cm \cdot s^{-1}$)	SCI	+5±3	+6±2	+2±3
	AB	+2±3	-1±2	+0±2

SCI, spinal cord injury; AB, able-bodied; PC, passive cycling; SAP, systolic arterial pressure; DAP, diastolic arterial pressure; MAP, mean arterial pressure; TPR, total peripheral resistance; MCAv, middle cerebral artery blood flow velocity;*, statistically different from preceding rest period.

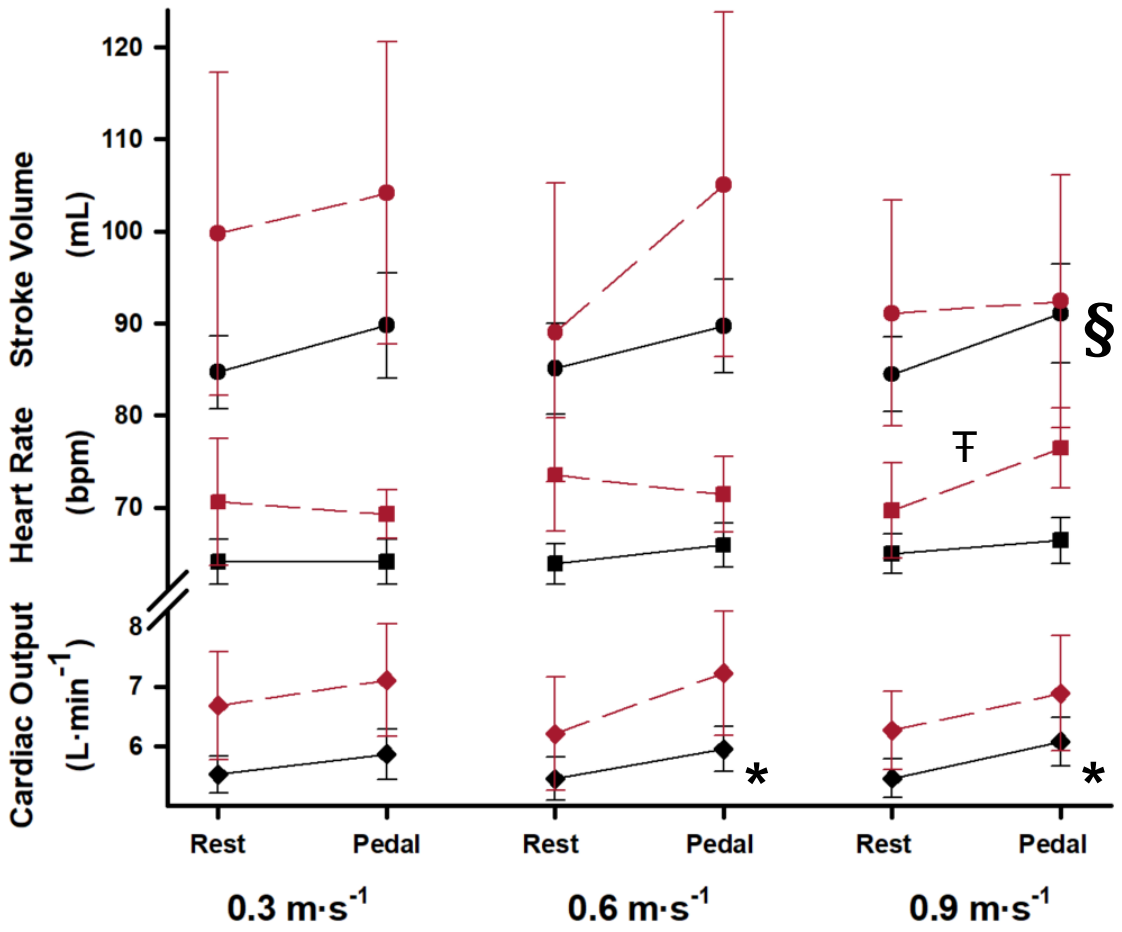

Figure 5.3. Central hemodynamic responses of individuals with SCI and AB to PC at different speeds

In AB individuals, PC increased CO, driven by an increase in SV, when moving at the average and high-end wheeling speeds of community-based wheelchair users. Individuals with SCI had a greater HR response to the 0.9m·s^{-1} pedal phase relative to AB.*, significantly different than preceding rest period; §, significant main effect of pedal intervention, Ŧ, significantly different than the AB response.

5.5. Discussion

Here we show that a novel, PC wheelchair attachment prototype can provide a safe and efficacious way for individuals with SCI to increase physical activity in a way that could improve cardiovascular health.

Safety, security, and comfort

Safety, security, and comfort of the device were measured using the QUEST and CRS questionnaires. All AB participants completed the test protocol prior to testing

individuals with SCI to evaluate the device for fit and function. A primary concern with the use of assistive devices following SCI is areas of friction and pressure that can result in soft tissue damage and degradation, while also provoking episodes of AD. Loss of sensation, coupled with decreased blood flow in the lower limbs, can make it difficult to identify, remedy, and recover from potential injury. Testing individuals with no lower limb sensory impairment allowed us to be confident that this device was safe to use for individuals living with SCI. As such, our primary interest from the AB responses to the questionnaires were focused on the safety, security, and harm categories, which received high satisfaction and comfort ratings, along with qualitative information on ways to improve comfort or eliminate potential areas of harm.

To-date, no experiment has been stopped as a result of discomfort or dissatisfaction with the prototype device, or due to signs or symptoms of AD or exercise-induced hypotension. Individuals with SCI have given high ratings of safety and security. Participants have provided insightful suggestions on how to improve the usability and set-up of this device to increase accessibility.

Cardiovascular responses to PC

PC, particularly at higher speeds, significantly increased cardiovascular outcomes in AB, with similar trends seen in individuals with SCI. These results are similar to other PC studies performed using cycle ergometers adapted for use by individuals with SCI[156–162]. The magnitude of cardiovascular responses seen with this device were similar to those seen during mild physical activity such as yoga in the AB[227] or slow walking in individuals with peripheral artery disease[228]. Consistent with previous studies[161,162], improvements in SAP, MAP, CO, and SV were seen at the two higher speeds for AB participants, suggesting a minimum threshold to achieve a cardiovascular response, although SAP and MAP showed mild improvement at the lowest speed for participants with SCI. For individuals with SCI, PC is theorized to engage the skeletal muscle pump in the lower limbs, reducing blood pooling and increasing venous return. Our results support this as CO was significantly increased, primarily driven by an increase in SV, presumably due to an increased circulating blood volume and venous return. Decreased HR during PC at lower cadences following SCI has been shown previously[163], and is thought to be induced by a mild increase in blood pressure at the onset of PC activating the baroreflex, promoting sympathetic activation and a concurrent withdrawal of vagal tone. Increased HR seen at

higher cadences resembles a more traditional response to moderate intensity exercise. The test wheelchair, attached with the prototype device, offered less support than typically found in most daily-use chairs. As a result, participants often had to engage muscles of the upper limbs and core to stabilize themselves, and this was more evident and necessary at the higher pedal speeds. Utilizing more muscle mass would increase the metabolic demand and could result in the increased HR seen.

Cerebral autoregulation helps maintain perfusion of the brain within a narrow range, regardless of moderate fluctuations in systemic pressure. While changes in cerebral autoregulation sensitivity and reactivity have been shown in cases of chronic hypotension and hypertension[63], moderate acute interventions have not shown to impact CBFv in individuals with SCI[158]. However, large and consistent swings in systemic blood pressure (such as those presented by AD and OH) are thought to play a role in cerebral and cognitive impairment[61]. Increasing circulating blood volume can help improve blood pressure control and may help mitigate large, dangerous fluctuations in systemic blood pressure and help preserve cerebral autoregulation.

A current limitation of this study is the small, underpowered number of participants with SCI who have completed the study. We performed sample size calculations for each of our primary outcome variables (BP, HR, SV, CO, and CBFv). The lowest calculated sample size to achieve a power of > 0.8 was 12 participants. While trends are typically not a primary focus, as recruitment and testing are ongoing, I consider these results to be preliminary and the results of statistical analyses to be somewhat unreliable.

5.6. Conclusions

These data establish the safety of a prototype, PC wheelchair attachment and its efficacy in improving cardiovascular outcomes in the AB and individuals living with SCI. Improvements in CO, driven by increases in SV, appear to be dependent on pedal speed, suggesting a minimum threshold to be efficacious. Individuals with SCI face unique challenges to meeting physical activity guidelines and a PC wheelchair attachment could aid in overcoming some of those barriers and provide another avenue to enjoy the benefits of increased physical activity.

Chapter 6.

Discussion

In this thesis, I examined the cardiovascular autonomic consequences of SCI and the implications on CVD risk. I explored the impact of SCI on traditional CVD risk factors, the contribution of injury characteristics to CVD risk, and how exercise adjuncts might mitigate the cardiovascular consequences of SCI. This chapter includes a general discussion of how the results of these investigations build upon previous literature, implications for individuals living with SCI and the clinical field, and directions for future research stemming from this thesis.

6.1. Implications of SCI on CVD risk

SCI is associated with a decrease in life expectancy of 15-30 years[2], with CVD being the leading cause of morbidity and mortality[7]. CVD has been shown to present earlier and progress faster following SCI[8]. CVD risk is impacted by a multitude of factors, and with the importance of specific risk factors differing among populations, determining CVD risk is complex. However, the importance of understanding how these factors influence specific populations is paramount in the detection and management of CVD.

6.1.1. Measures of adiposity

Obesity is a well documented CVD risk factor in both the AB and in those with SCI. In Chapter 2, the primary aim was to explore the efficacy of different measures of adiposity on predicting CVD risk and suggest the use of population specific cut-points for individuals with SCI. We compared WC, WHtR, and BMI and while all measures were significantly correlated, WC was the strongest correlate of CVD risk. These results are similar to those from a previous report within a small cohort of individuals with SCI who found only WC and WHtR to be significantly correlated with CVD risk[106]. Of these measurements, WC is the most practical as it doesn't require specialized wheelchair scales and avoids difficulties associated with measuring height including spasticity and contractures. Given that WC performed as well as, or better than, WHtR and BMI in predicting CVD risk, its strong

correlation with visceral adiposity[103,104], and ease of use, we advocate for the routine use of WC as a screening tool to assess CVD risk.

I suggest a WC cut-point value for males for an increased CVD risk of 97 cm. This is lower than the cut-point value for AB males (102cm)[84] and reflects the higher CVD risk in this population. Due to the low number of females at risk for CVD, a reliable cut-point value was not determined, although long-term risk analysis provided a cut-point value of 80 cm. At this time I recommend the use of the AB cut-point value of 88 cm[84] until risk profiles can be confirmed for women with SCI, with the caveat that this may be an overestimation. The lower cut-point value for WC following SCI supports previous studies showing underestimations of general[105] and visceral adipose tissue[103] when AB BMI cut-points were used in individuals with SCI. Notably, there is an approximate reduction in CVD risk of ~ 1% for every 2-5 cm reduction in WC, highlighting that while these cut-point values are useful for identifying at risk individuals, WC is a modifiable factor that can be used to reduce CVD risk whether or not the cut-point value is attained.

Further research is needed to determine reliable cut-point values for females living with SCI. As SCI predominantly affects males, this can be challenging. We used a neutral blood pressure in the determination of CVD risk as individuals with SCI often experience resting hypotension. Future research could be done to clarify the impact of blood pressure lability has on CVD risk and how this can be incorporated into risk predictions.

6.1.2. Impact of SCI characteristics on CVD risk

A secondary aim of Chapter 2 was to evaluate the impact of injury characteristics and cardiovascular autonomic function on CVD risk and establish cut-points for individual and clinical use. Of the 3 primary injury characteristics (DOI, LOI, AIS), only DOI was determined to be a highly important predictor of increased CVD risk. LOI was a moderately important predictor of CVD risk when categorized as “high”, “mid”, and “low”. Although not all injury characteristics were deemed as highly important, cut-point values were determined for increased CVD risk; DOI longer than 23 years, LOI above T1, and AIS A categorized injuries. Using HR_{peak} as a marker, impaired cardiovascular autonomic function was an independent factor of CVD risk. The inability to increase HR above 112bpm indicates the absence of sympathetic control of the cardiovascular system and is associated with a high CVD risk profile.

While it has been shown that there is an earlier onset and faster progression of CVD following SCI[8], the direct impact of age and DOI is not well understood. DOI is a covariate with age, so at the present time it is unclear whether this relationship reflects an indirect effect of advancing age and/or a direct impact of a longer time living with SCI. Although theoretically the LOI[229] and AIS[16] of SCI have clear implications on CVD risk factors, the heterogeneity of SCI and disconnect between motor and sensory impairment and that of autonomic impairment[230] introduce complexity. There are several clinical autonomic function tests used to assess autonomic injury following SCI including sympathetic skin response, muscle sympathetic nerve activity, plasma norepinephrine, and HR and blood pressure variability. While informative, these tests can be cumbersome, invasive, costly, and difficult to access. Although less informative and specific, a major benefit of using HR_{peak} is that it does not necessarily require a laboratory-based test for evaluation. HR monitoring can be done using a multitude of accessible wearable technology, and if daily physical activity results in a HR above 125 bpm, some residual sympathetic control of the cardiovascular system remains and is associated with a reduced CVD risk. While additional studies are needed to confirm these cut-points, they provide a starting point for individuals with SCI and caregivers to better monitor CVD risk. Future research should focus on accounting for factors such as sex and ethnicity in regards to these cut-point values and the presented CVD risk profile.

Stratification of participants with SCI presents a unique research challenge. There are several injury characteristics that can be used to stratify risk, however stratification is not always the same between research studies and is often considered secondarily depending on sample size and participant characteristics. With any analysis approach there are strengths and weaknesses regarding the way covariates or confounding variables are addressed, as well as with how missing values are handled. Some techniques are more suitable for particular data management approaches, and in terms of dissemination of information to different populations (clinicians, patients, etc.) some approaches will be more intuitive. Longitudinal studies beginning in the acute phase of SCI are needed to truly understand how CVD risk factors develop and change over time following SCI to improve detection and management strategies.

6.1.3. Non-traditional CVD risk factors

To help establish a comprehensive CVD risk profile for individuals living with SCI, in Chapter 3, I explored whether clinical measures of MH- and NP are associated with increased CVD risk and elucidate the relationships between NP, MH-, cardiovascular autonomic function, and injury characteristics. Additionally, the efficacy of primary use medications for MH- and NP were investigated.

Mental health

Within our cohort there was a high prevalence of MH- (45%) following SCI. Meeting the clinical threshold for MH- was significantly correlated with being at-risk for a cardiovascular event, was identified as a highly important variable in determining CVD risk and increased the odds of an adverse 30-year CVD risk two-fold.

Previous investigations have similarly reported a higher prevalence and increased CVD risk associated with MH- or depression following SCI[86,231]. MH- is a known CVD risk factor for the general population[127] in whom it also increases the likelihood of an adverse CVD risk profile two-fold[206]. Shared mechanisms associated with both MH- and CVD risk include physiological (inflammation, dyslipidemia, and impaired endothelial function) and behavioural (decreased physical activity, increased smoking, and disrupted sleep patterns) factors[206]. The directionality of the association between MH- and CVD risk is unclear and arguably more complex following SCI considering SCI independently impacts each of these factors.

Unexpectedly, MH- was not associated with markers of impaired autonomic function. MH- is common in individuals living with SCI, particularly in those with high-level injuries[122], who are also predisposed to experience impaired cardiovascular autonomic function. This study utilized HR_{peak} measured during an optional exhaustive exercise test as a marker of cardiovascular autonomic function, a test that is problematic for those with greater degrees of motor impairment. Given this methodological consideration, it is possible that MH- and cardiovascular autonomic function are associated, however we were unable to detect it because of missing data. Future research should utilize different measures of autonomic function or provide more accessible exercise modalities to allow for participation.

Interestingly, only 64% of individuals meeting the clinical threshold for MH- reported taking a primary use medication for this condition. Of those taking a primary use medication, more than half still met the clinical threshold for MH-, suggesting the treatment was ineffective.

Individuals living with SCI commonly use a variety of medications to manage secondary health conditions related to their injury. Polypharmacy can complicate and impact the efficacy of treatments, and these effects are not always known or possible to account for. This may lead to the consideration of hierarchy of care, where individuals living with SCI may prioritize physical functioning over mental health. Future research should consider treatment prioritization and explore alternative ways of improving mental health.

Neuropathic pain

Our data showed a high prevalence of NP (39%) following SCI. NP was not associated with an increased CVD risk, however those with more preserved autonomic function and females were more likely to experience NP. Only 28% of individuals meeting the clinical threshold for NP reported taking a primary use medication, with 68% of those who were taking a primary use medication for NP still met the clinical threshold for NP, again highlighting suboptimal pain management.

The prevalence rates for NP using a clinical measure are similar to previous reports[86,110,118]. However our finding of no correlation between a clinical measure of NP and CVD risk is contradictory to published literature[86,115]. There are several factors that could explain these differences. Ours is the first to use a clinical measure to assess the presence of NP, instead of using self-report questionnaires. However, this clinical measure does not provide information relative to how often NP is experienced or how long it has been present, which limits the scope of its use. Previous studies used the presence of CVD, whereas we used a calculated CVD risk with an “at-risk” threshold, which assumes a directional relationship that NP is leading to CVD. Interestingly, NP was more prevalent in those with more preserved autonomic function, who also have lower CVD risk. It may be that those with preserved autonomic (sympathetic) function have a stronger substrate for aberrant sprouting within and between sensory and autonomic pathways, providing a mechanistic association between NP and cardiovascular autonomic function.

The observation that females tended to experience more severe NP has been reported before both in humans[210] and in animal models[211] but the mechanism underlying this observation remains unclear. As SCI disproportionately impacts males and considering the disparity of sex equality in research in general, sex-specific research questions and studies are limited. Future research needs to address this gap and prioritize sex difference following SCI. There is promising research that exercise can reduce the risk of developing NP and NP symptoms, however additional research is needed to understand mechanisms and the dose-response relationship.

The novel findings from Chapters 2 and 3 provide a foundation for a CVD risk profile for individuals living with SCI. This includes outlining the impact that SCI can have on traditional risk factors, followed by evaluating which measures of obesity and injury characteristics are important in predicting CVD risk and establishing cut-point values to help identify at-risk individuals, and lastly beginning to explore non-traditional CVD risk factors and how they are experienced and managed by individuals with SCI. With this foundation, I chose to explore avenues by which CVD risk might be mitigated.

6.2. Adjuncts to exercise following SCI

Increasing physical activity and reducing sedentary time is known to decrease CVD risk, improve health, and overall quality of life in the AB. While exercise is known to be beneficial following SCI, there are accessibility barriers to participation and has resulted in cardiovascular complications. For individuals that are meeting exercise guidelines, these adjuncts could provide an additional option for physical activity or an alternative way to improve cardiovascular function. For the majority of individuals with SCI, those that are not meeting exercise guidelines, these adjuncts could be used on their own or as part of an exercise program to increase participation in, efficacy of, and accessibility to physical activity. In Chapters 4 and 5, I explore the safety and efficacy of two practical passive adjuncts to exercise, PLLM and PHT, which are more accessible, have shown potential benefits for the improvement of cardiometabolic health, and could help manage CVD risk factors.

6.2.1. Systematic review of passive exercise adjuncts

In Chapter 4, I conducted a systematic review of the literature regarding the impact of PLLM and PHT on cardiovascular function in adults living with chronic SCI, that provided data involving at least one cardiovascular outcome (HR, CO, SV, blood pressure, or cerebrovascular blood flow velocity (CBFv)).

The reviewed studies utilized a wide range of modalities, with 75% of single session interventions reporting a significant improvement in at least one cardiovascular outcome. PLLM improved CO through increases in SV, while PHT had a more pronounced effect on HR. Although there were not any adverse responses to either exercise adjunct, several PHT studies highlighted that individuals with SCI have impaired heat tolerance. Only 2 studies measured CBFv with no significant changes.

These findings build on a previous review outlining cardiovascular outcomes during PC[155] by reviewing additional forms of PLLM, along with the inclusion of PHT. PLLM produced cardiovascular responses similar to those seen during mild physical activities[227,228], while PHT responses were more closely related to those seen during moderate intensity exercise[143]. Exercise intolerance, the failure to mount cardiovascular responses to increased activity, has been reported during bouts of active exercise, specifically in those with high-level injuries and during upright activity[37,232]. With significant increases in CO and SV, PLLM presents as a prime therapy to increase cardiovascular function while mitigating exercise intolerance. Although no evidence of hypotension was reported during PHT, given the impaired heat tolerance from several studies in our review[79,148,149,219], safety considerations need to be prioritized. CBFv represents a prime area for future research. Evidence from these reviews suggest that PLLM and PHT could be safe and efficacious avenues to promoting cardiovascular health and mitigating CVD risk following SCI.

The limited number of studies available highlight the need for further investigation into the safety and efficacy of passive exercise adjuncts in individuals living with SCI. Accessibility is a barrier for individuals with SCI to increase participation in physical activity and exercise and should be addressed in all exercise studies. Longitudinal experiments investigating the chronic impacts of passive exercise adjuncts on cardiovascular function and CVD risk factors are needed for informed management of a healthy lifestyle.

6.2.2. Safety and efficacy of a PC wheelchair attachment

As highlighted in the previous chapter, PC is efficacious in improving cardiovascular outcomes following SCI, however accessibility remains a barrier. In Chapter 5, I evaluated the safety and acceptability of a prototype PC wheelchair attachment and its efficacy for improving cardiovascular outcomes in both AB controls and individuals with SCI. User ratings of comfort and satisfaction were high, particularly for safety, security, and usability. In AB participants, SAP, CO, and SV were increased at the average and high-end wheeling speeds of community dwelling wheelchair users. In individuals with SCI, there were no significant differences in any cardiovascular outcomes although trends were evident for increases in CO and SV. While initially this could be interpreted as a negative result, the absence of exercise intolerance within this paradigm is noteworthy and may facilitate improved adherence to increasing physical activity. Furthermore, these results represent an interim report and should be treated as a pilot study, as statistical power has not been reached in individuals with SCI.

The potential cardiovascular benefits of PC in individuals with SCI have been highlighted in a recent review[155] and in Chapter 4 of this thesis. However, accessibility remains a significant challenge to PC with availability limited to centres with specialized equipment or research institutions. Exercise and assistive device use following SCI has resulted in cardiovascular complications including episodes of OH during and after exercise[37,232], AD[12,71], and arrhythmias[58]. While there were some challenges with comfort, transferring, and set-up, there were no cardiovascular contraindications to using the device over a range of pedaling speeds in individuals with SCI. This unique PC device represents a safe, accessible solution to improving cardiovascular health and potentially mitigating the risk of CVD following SCI.

This study includes participants with both traumatic and non-traumatic SCI. As these data have the potential to apply in a broader context to all wheelchair users who have difficulty meeting exercise guidelines, future studies should include evaluation of cardiovascular responses of a wide range of wheelchair users. Of note, this is one of the first studies to report ground speed of PC, opposed to cadence, providing more comparable results as it is not dependent on machine characteristics. Future directions of PC and other exercise adjuncts include the development of devices to be suitable for

community use, as well as assessing the impact of chronic use on cardiovascular control in individuals with SCI.

6.3. Limitations

Conducting research within a specific clinical population, such as individuals with SCI, presents unique challenges. Participants are commonly stratified according to physical and injury characteristics (age, sex, DOI, LOI, AIS), however these stratifications are not consistent across research studies and can impact statistical power. Unbiased participant recruitment can be difficult as individuals self-select for research studies, introducing the risk of exclusion based on physical capabilities. Experimental research in within clinical populations often results in smaller sample sizes which can limit statistical power; however, the results can provide rich physiological data giving insight into mechanistic details.

The selection of outcome variables and analyses can impact results and may be the cause of conflicting results. Throughout this thesis, the focus was directed at practical and clinically relevant outcomes with accessible, real-world measurement techniques. While this increases the practicality of the results and will hopefully improve knowledge translation and end-user uptake, this can limit the sensitivity and specificity of results.

Adopting existing framework for use in specific populations presents limitations. Analytical considerations, such as handling missing and confounding variables, removing and adding population specific variables, and decisions related to defining and implementing stratification can increase the risk of bias and challenge the validity of the results. Evidence based decisions were made whenever possible using available, peer-reviewed research, along with consultations with stakeholders and respective ‘experts in the field’. A primary limitation to each of these experiments was the lack of engagement of targeted end-users during the early stages of these research projects. The comments, suggestions, and feedback received during testing and while disseminating interim results to end-users has been invaluable, and if directly sought after earlier would have largely benefitted this research. Although we tried to account for confounding variables (i.e. comorbidities, medication use), these factors reflect the reality of daily life for individuals living with SCI, highlighting the importance of understanding the impacts of these variables.

6.4. Final thoughts

The cardiovascular autonomic consequences of SCI present daily challenges and have lifelong impacts for those living with SCI. This thesis explored the impact of SCI characteristics and cardiovascular function on CVD risk, along with investigating the safety and efficacy of exercise adjuncts following SCI. Utilizing widely available and easily accessible measures, these data provide a framework for establishing a CVD risk profile readily adoptable for clinicians, caretakers, and individuals with SCI to identify, evaluate, and mitigate CVD risk. Above all, it is imperative that we involve these stakeholders throughout the entire research process to ensure their needs are prioritized and met.

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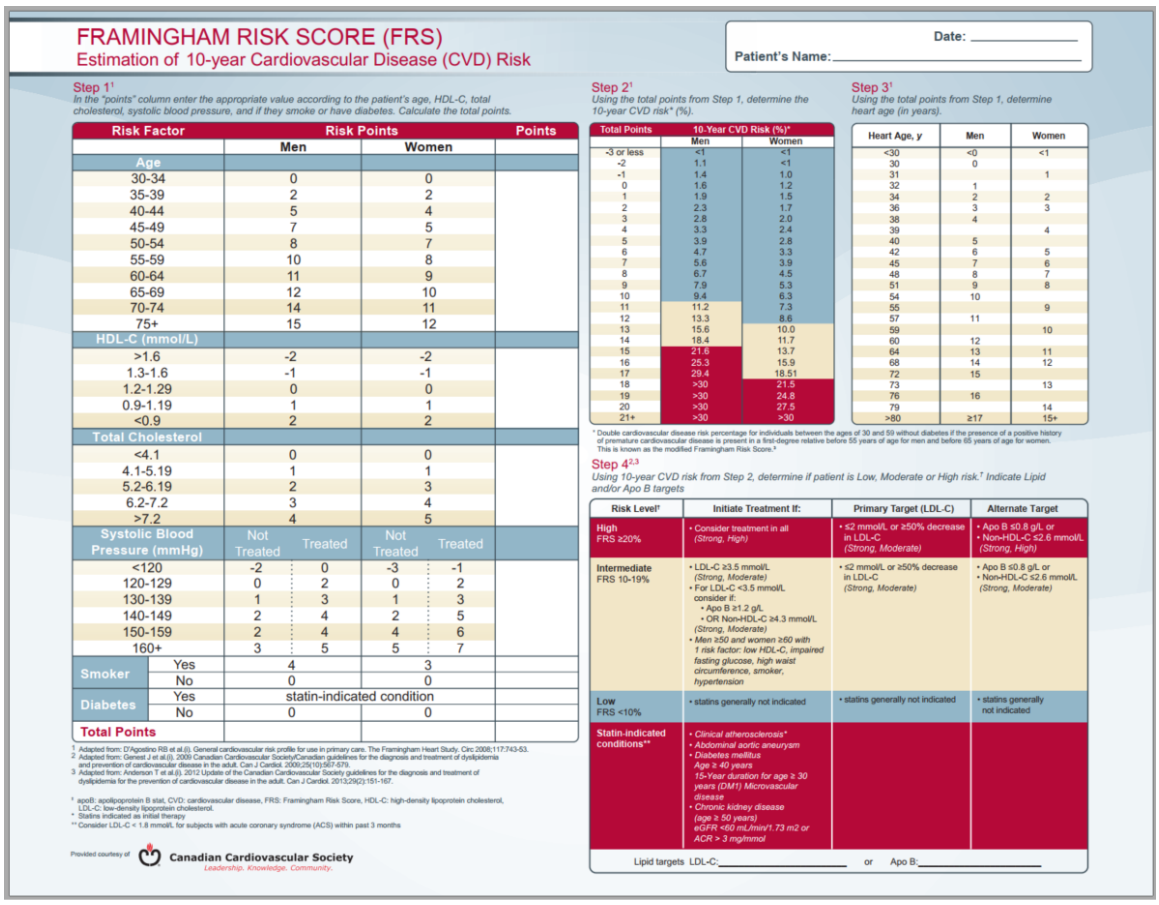
Appendix A.

Questionnaires

1. Framingham risk score questionnaire



FRAMINGHAM RISK SCORE (FRS)

Estimation of 10-year Cardiovascular Disease (CVD) Risk

Date: _____

Patient's Name: _____

Step 1[1]

In the "points" column enter the appropriate value according to the patient's age, HDL-C, total cholesterol, systolic blood pressure, and if they smoke or have diabetes. Calculate the total points.

Risk Factor	Risk Points				Points
	Men		Women		
Age					
30-34	0		0		
35-39	2		2		
40-44	5		4		
45-49	7		5		
50-54	8		7		
55-59	10		8		
60-64	11		9		
65-69	12		10		
70-74	14		11		
75+	15		12		
HDL-C (mmol/L)					
>1.6	-2		-2		
1.3-1.6	-1		-1		
1.2-1.29	0		0		
0.9-1.19	1		1		
<0.9	2		2		
Total Cholesterol					
<4.1	0		0		
4.1-5.19	1		1		
5.2-6.19	2		3		
6.2-7.2	3		4		
>7.2	4		5		
Systolic Blood Pressure (mmHg)	Not Treated	Treated	Not Treated	Treated	
<120	-2	0	-3	-1	
120-129	0	2	0	2	
130-139	1	3	1	3	
140-149	2	4	2	5	
150-159	2	4	4	6	
160+	3	5	5	7	
Smoker Yes	4		3		
Smoker No	0		0		
Diabetes Yes	statin-indicated condition				
Diabetes No	0		0		
Total Points					

1 Adapted from: D'Agostino RB et al.(i). General cardiovascular risk profile for use in primary care. The Framingham Heart Study. Circ 2008;117:743-53.
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* apoB: apolipoprotein B stat, CVD: cardiovascular disease, FRS: Framingham Risk Score, HDL-C: high-density lipoprotein cholesterol, LDL-C: low-density lipoprotein cholesterol.
* Statins indicated as initial therapy
** Consider LDL-C < 1.8 mmol/L for subjects with acute coronary syndrome (ACS) within past 3 months

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Step 2[1]

Using the total points from Step 1, determine the 10-year CVD risk (%).*

Total Points	10-Year CVD Risk (%)*	
	Men	Women
-3 or less	<1	<1
-2	1.1	<1
-1	1.4	1.0
0	1.6	1.2
1	1.9	1.5
2	2.3	1.7
3	2.8	2.0
4	3.3	2.4
5	3.9	2.8
6	4.7	3.3
7	5.6	3.9
8	6.7	4.5
9	7.9	5.3
10	9.4	6.3
11	11.2	7.3
12	13.3	8.6
13	15.6	10.0
14	18.4	11.7
15	21.6	13.7
16	25.3	15.9
17	29.4	18.51
18	>30	21.5
19	>30	24.8
20	>30	27.5
21+	>30	>30

* Double cardiovascular disease risk percentage for individuals between the ages of 30 and 59 without diabetes if the presence of a positive history of premature cardiovascular disease is present in a first-degree relative before 55 years of age for men and before 65 years of age for women. This is known as the modified Framingham Risk Score.[4]

Step 3[1]

Using the total points from Step 1, determine heart age (in years).

Heart Age, y	Men	Women
<30	<0	<1
30	0	
31		1
32	1	
34	2	2
36	3	3
38	4	
39		4
40	5	
42	6	5
45	7	6
48	8	7
51	9	8
54	10	
55		9
57	11	
59		10
60	12	
64	13	11
68	14	12
72	15	
73		13
76	16	
79		14
>80	≥17	15+

Step 4[2,3]

Using 10-year CVD risk from Step 2, determine if patient is Low, Moderate or High risk.[1] Indicate Lipid and/or Apo B targets

Risk Level[1]	Initiate Treatment If:	Primary Target (LDL-C)	Alternate Target
High FRS ≥20%	• Consider treatment in all *(Strong, High)*	• ≤2 mmol/L or ≥50% decrease in LDL-C *(Strong, Moderate)*	• Apo B ≤0.8 g/L or • Non-HDL-C ≤2.6 mmol/L *(Strong, High)*
Intermediate FRS 10-19%	• LDL-C ≥3.5 mmol/L *(Strong, Moderate)* • For LDL-C <3.5 mmol/L consider if: • Apo B ≥1.2 g/L • OR Non-HDL-C ≥4.3 mmol/L *(Strong, Moderate)* • *Men ≥50 and women ≥60 with 1 risk factor: low HDL-C, impaired fasting glucose, high waist circumference, smoker, hypertension*	• ≤2 mmol/L or ≥50% decrease in LDL-C *(Strong, Moderate)*	• Apo B ≤0.8 g/L or • Non-HDL-C ≤2.6 mmol/L *(Strong, Moderate)*
Low FRS <10%	• statins generally not indicated	• statins generally not indicated	• statins generally not indicated
Statin-indicated conditions**	• *Clinical atherosclerosis** • *Abdominal aortic aneuryam* • *Diabetes mellitus Age ≥ 40 years 15-Year duration for age ≥ 30 years (DM1) Microvascular disease* • *Chronic kidney disease (age ≥ 50 years) eGFR <60 mL/min/1.73 m2 or ACR > 3 mg/mmol*		

Lipid targets LDL-C: _____ or Apo B: _____

2. Mental health inventory 5 questionnaire

The Mental Health Inventory - 5 (MHI-5)

Instructions:

Please read each question and tick the box by the **ONE** statement that best describes how things have been FOR YOU during the past month.

There are no right or wrong answers.

1. **During the past month, how much of the time were you a happy person?**

All of the time	Some of the time
Most of the time	A little of the time
A good bit of the time	None of the time

2. **How much of the time, during the past month, have you felt calm and peaceful?**

All of the time	Some of the time
Most of the time	A little of the time
A good bit of the time	None of the time

3. **How much of the time, during the past month, have you been a very nervous person?**

All of the time	Some of the time
Most of the time	A little of the time
A good bit of the time	None of the time

4. **How much of the time, during the past month, have you felt downhearted and blue?**

All of the time	Some of the time
Most of the time	A little of the time
A good bit of the time	None of the time

5. **How much of the time, during the past month, have you felt so down in the dumps that nothing could cheer you up?**

All of the time	Some of the time
Most of the time	A little of the time
A good bit of the time	None of the time

3. Douleur neuropathique 4 questionnaire

DN4 – QUESTIONNAIRE

To estimate the probability of neuropathic pain, please answer yes or no for each item of the following four questions.

INTERVIEW OF THE PATIENT

QUESTION 1:

Does the pain have one or more of the following characteristics?	**YES**	**NO**
Burning	❑	❑
Painful cold	❑	❑
Electric shocks	❑	❑

QUESTION 2:

Is the pain associated with one or more of the following symptoms in the same area?	**YES**	**NO**
Tingling	❑	❑
Pins and needles	❑	❑
Numbness	❑	❑
Itching	❑	❑

EXAMINATION OF THE PATIENT

QUESTION 3:

Is the pain located in an area where the physical examination may reveal one or more of the following characteristics?	**YES**	**NO**
Hypoesthesia to touch	❑	❑
Hypoesthesia to pinprick	❑	❑

QUESTION 4:

In the painful area, can the pain be caused or increased by:	**YES**	**NO**
Brushing?	❑	❑

YES = 1 point
NO = 0 points

Patient's Score: /10

4. Medical history questionnaire

Participant ID _____ Date of Test DD/MM/YYYY

Date of Birth DD/MM/YYYY Date of Injury DD/MM/YYYY Age _____ Sex _____

Level of Injury _____ AIS Score_____ Height (cm) _____ Weight (kg)_____

Are you feeling well today?

Are there any medical problems you are currently seeing your doctor for?

Do you have cardiovascular disease? Hypertension?

Do you currently have a UTI?

Do you have any pressure sores or skin breakdown?

Are you currently on any medications? If yes, please list.

Do you have a family history of cardiovascular disease?

Lifestyle management:

Drinking status (units per week):

Smoking status (units per week):

Are you fully vaccinated?

Would you like to be contacted for participation in future studies?

Women:

LMP_____ OCP_____ Pregnancy_____

Participant ID: Date of Test:

ORTHOSTATIC HYPOTENSION QUESTIONS

42. Have you ever fainted prior to your injury?
- ☐ Yes
- ☐ No
- ☐ Don't know

43. If yes, how many times?
- ☐ Once only
- ☐ 1-3 times
- ☐ 4-7 times
- ☐ More than 8 times

44. Have you ever fainted since your injury?
- ☐ Yes
- ☐ No
- ☐ Don't know

45. If yes, how many times?
- ☐ Once only
- ☐ 1-3 times
- ☐ 4-7 times
- ☐ More than 8 times

46. How often do you experience the following symptoms WHEN UPRIGHT (and NOT while experiencing autonomic dysreflexia)?

	Daily	Weekly	Monthly	Rarely	Never
Dizziness	☐	☐	☐	☐	☐
Fainting/Blackouts	☐	☐	☐	☐	☐
Lightheadedness	☐	☐	☐	☐	☐
Blurred vision	☐	☐	☐	☐	☐
Visual tunneling	☐	☐	☐	☐	☐
Profuse sweating	☐	☐	☐	☐	☐
Profound tiredness/lethargy	☐	☐	☐	☐	☐
Spasticity	☐	☐	☐	☐	☐
Nausea	☐	☐	☐	☐	☐
Shortness of breath	☐	☐	☐	☐	☐
Palpitations	☐	☐	☐	☐	☐
Uncomfortable fast heart rate	☐	☐	☐	☐	☐
Uncomfortable slow heart rate	☐	☐	☐	☐	☐
Extreme pallor	☐	☐	☐	☐	☐
Seizure	☐	☐	☐	☐	☐
Other, please specify; _____	☐	☐	☐	☐	☐

Participant ID: Date of Test:

47. What sorts of things trigger these symptoms?

	Yes	No	Not applicable
Bladder trigger	☐	☐	☐
Postural change in the morning	☐	☐	☐
Sitting still in a wheelchair	☐	☐	☐
Being in a warm room	☐	☐	☐
Drinking alcohol	☐	☐	☐
Stopping exercise	☐	☐	☐
After meals	☐	☐	☐
After bathing	☐	☐	☐
Blood sampling/ sight of blood	☐	☐	☐
Physiotherapy	☐	☐	☐
Other, please specify; _____	☐	☐	☐

48. Has orthostatic hypotension interfered with your ability to participat in the following activities?

	Yes	No	Not applicable
Activities of daily living	☐	☐	☐
Work	☐	☐	☐
Exercise	☐	☐	☐
Sexual activity	☐	☐	☐
Rehabilitation	☐	☐	☐
Household chores	☐	☐	☐
Driving	☐	☐	☐
Social activities	☐	☐	☐
Sleep	☐	☐	☐
Other, please specify; _____	☐	☐	☐

Recording settings and standardizations

Finometer: Cuff size: XS/S/M/L Physiocal: ON/OFF

Transcranial Doppler: Depth _____ Gain _____ Ambient Temp (c) _____

Doppler-Heart Sensor Length _____

Comments:

Protocol: _____

Baseline recorded values

BP _____

HR _____

SV (Finometer)_____

CO _____

CBFV _____

5. Modified Ashworth scale grading scoresheet

MAS Grading Scoresheet
Participant ID:
Date of Testing:

Muscle group	Right	Left
Shoulder adductors		
Shoulder internal rotators		
Elbow flexors		
Elbow extensors		
Pronators		
Supinators		
Wrist flexors		
Wrist extensors		
FDS		
FDP		
FPL		
Lumbricals		
Hip flexors		
Hip Adductors		
Knee extensors		
Knee flexors		
Ankle plantar flexors (knee flexed)		
Ankle plantar flexors (knee extended)		
Inverters		
Evertors		
Great toe flexors		
Great toe extensors		
Toe flexors		

0 No increase in tone
1 slight increase in tone giving a catch then release when slight increase in muscle tone, manifested by the limb was moved in flexion or extension.
1+ slight increase in muscle tone, manifested by a catch followed by minimal resistance throughout (ROM)
2 more marked increase in tone but more marked increased in muscle tone through most limb easily flexed
3 considerable increase in tone, passive movement difficult
4 limb rigid in flexion or extension

6. Modified comfort rating scales questionnaire

Participant ID: Date of Test:

Modified Comfort Rating Questionnaire

Instructions: Please mark on the line your level of agreement from low to high to the following statements.

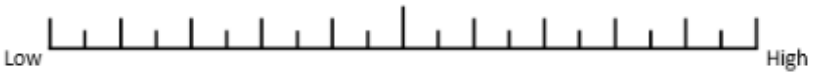
Emotion: I am worried about how I look when I use this device. I feel tense or on edge because I am using this device.

Attachment: I can feel the device on my body. I can feel the device moving.

Harm: The device is causing me some harm. The device is painful to use.

Perceived Change: Using the device makes me feel physically different. I feel strange using this device.

Movement: The device affects the way I move. The device inhibits or restricts my movement.



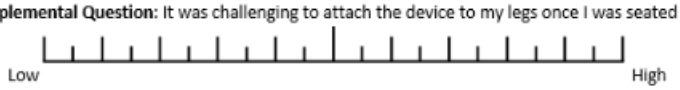
Anxiety: I do not feel secure using the device.

Usability: I would like to use this device frequently.

Participant ID: Date of Test:

Attachment Supplemental Question: The device inhibits my ability to transfer in and out of my chair.

Attachment Supplemental Question: It was challenging to attach the device to my legs once I was seated in my chair.



Other Comments: Please use the space below for any additional comments that you may have on the device, its application, function, comfort, or usability.

7. Modified Quebec User Evaluation of Satisfaction with Assistive Technology questionnaire

Participant ID: Date of Test:

Modified QUEST Questionnaire

The purpose of the QUEST questionnaire is to evaluate how satisfied you are with your assistive device. The questionnaire consists of 8 satisfaction items. For each of the items, rate your satisfaction with the assistive device by using the following scale of 1 to 5.

1	2	3	4	5
Not satisfied at all	Not very satisfied	More or less satisfied	Quite satisfied	Very satisfied

Please circle or mark the **one number** that best describes your degree of satisfaction with each of the items. Do not leave any questions unanswered.

ASSISTIVE DEVICE ***How satisfied are you with:***	
1. The **dimensions** (size, height, length, width) of the assistive device? *Comments:*	1 2 3 4 5
2. The **weight** of the assistive device? *Comments:*	1 2 3 4 5
3. The **ease in adjusting** (fixing, fastening) the parts of the assistive device? *Comments:*	1 2 3 4 5
4. How **safe and secure** the assistive device is? *Comments:*	1 2 3 4 5
5. The **durability** (endurance, resistance to wear) of the assistive device? *Comments:*	1 2 3 4 5
6. How **easy** it is to use the assistive device? *Comments:*	1 2 3 4 5
7. How **comfortable** the assistive device is? *Comments:*	1 2 3 4 5
8. How **effective** the assistive device is (the degree to which the device meets your needs)? *Comments:*	1 2 3 4 5