Secondary complications of spinal cord injury: risk, inter-relationships, and effects on neurological outcomes

by

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**ABSTRACT**

**Background:** Although there have been major advances in acute care following spinal cord injury (SCI), individuals surviving the acute period experience a reduced life expectancy. Historically, acute respiratory and renal dysfunction were the most prevalent complications, and remain important contributors to mortality. However, all-cause cardiovascular disease (CVD) has now emerged as the leading cause of mortality in chronic SCI. Although it has been long speculated that individuals with SCI may be at a higher risk of complications such as CVD, quantitative data are currently limited. Furthermore, the inter-relationships among secondary complications are currently unknown, as is the relationship with changes in neurological function.

**Objectives:** to examine the risk of secondary complications among individuals with SCI; to examine the relationships among secondary complications in individuals with SCI; to examine the relationship among secondary complications and neurological outcomes.

**Methods:** Data were compiled from the Canadian Community Health Survey, the SCI Community Health Survey, the European Multi-Centre Study on Spinal Cord Injury dataset, and the Simon Fraser University SCI dataset. Several methods were employed for analysis of these data, including: multivariable logistic and linear regression, mixed effects models, and unbiased recursive partitioning.

**Results:** Findings identified elevated odds of heart disease, stroke, Type 2 diabetes, chronic respiratory conditions, and chronic pain among individuals with SCI when compared with non-SCI individuals. Complex correlations were also identified among secondary complications following SCI. These include positive associations between neuropathic pain and CVD, and between blood pressure fluctuations and CVD. Lastly, secondary complications (specifically neuropathic pain) following SCI were positively correlated with neurological decline in chronic phases of injury, and neurological motor recovery in acute phases. These relationships may be partly related through treatments for the secondary complications rather than the secondary complications themselves.

**Implications:** These novel findings update current knowledge of secondary complications among individuals with SCI. These data are useful in guiding the prospective collection of data elements within SCI-specific registries, as well as the
design/analysis of studies (i.e., issues of confounding in multivariable analyses). These epidemiological data will also be useful for refined, hypothesis-driven physiological studies exploring precise biological mechanisms.
PREFACE

Portions of Chapter 2 have been published in the Journal of Neurotrauma. The full citation for this manuscript is:


For this review, I was responsible for the study conception, literature searches, data extraction, quality scoring, literature synthesis, and drafting the manuscripts. Dr. Krassioukov and Dr. Stone contributed to study conception and revising the manuscript for intellectual content.

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LIST OF ABBREVIATIONS

AD Autonomic dysreflexia
AHA American Heart Association
AIC Akaike Information Criterion
AIS American Spinal Injury Association Impairment Scale
ANOVA Analysis of Variance
AOR Adjusted odds ratio
Apo Apolipoprotein
ASIA American Spinal Injury Association
BMI Body mass index
CCHS Canadian Community Health Survey (CCHS)
CI Confidence Interval
CNS Central Nervous System
COPD Chronic obstructive pulmonary disease
CRP C-reactive Protein
CVD Cardiovascular disease
d Day
DEXA Dual Energy X-ray Absorptiometry
EM-SCI European Multi-Centre Study about Spinal Cord Injury
FES Functional electrical stimulation
HDL-C High density lipoprotein cholesterol
Ht Height
HsCRP High-sensitivity CRP
IL Interleukin
ISNCSCI International standards for neurological and functional classifications of SCI
ISCIP International Classification of SCI Pain
kg Kilograms
LDL-C Low density lipoprotein cholesterol
LEMS Lower Extremity Motor Score
MI Myocardial infarction
N. Pain Neuropathic Pain
NSAID Non-steroidal anti-inflammatory drug
OGTT Oral glucose tolerance test
OH Orthostatic hypotension
OR Odds ratio
RAAS Renin-angiotensin-aldosterone system
SAP Systolic arterial pressure
SCI Spinal cord injury
SCI-CS Spinal Cord Injury Community Survey
SCIRE Spinal Cord Injury Rehabilitation Evidence
SD Standard Deviation
SE Standard Error
SFU Simon Fraser University
TC Total Cholesterol
TNF Tumor necrosis factor
<table>
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<tr>
<th>Acronym</th>
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<tr>
<td>UEMS</td>
<td>Upper extremity motor score</td>
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<tr>
<td>URP</td>
<td>Unbiased Recursive Partitioning</td>
</tr>
<tr>
<td>VLDL-C</td>
<td>Very low density lipoprotein cholesterol</td>
</tr>
<tr>
<td>WC</td>
<td>Waist Circumference</td>
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<tr>
<td>WHtR</td>
<td>Waist-to-height ratio</td>
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<tr>
<td>Wk</td>
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DEDICATION

To my father, who lived by these words:

I would rather be ashes than dust! I would rather that my spark should burn out in a brilliant blaze than it should be stifled by dry-rot. I would rather be a superb meteor, every atom of me in magnificent glow, than a sleepy and permanent planet. The function of man is to live, not to exist. I shall not waste my days trying to prolong them. I shall use my time.

~Jack London

And to Robert Frost (not for the inspiration, but for the ambiguity of his words):

Two roads diverged in a yellow wood,
And sorry I could not travel both
And be one traveler, long I stood
And looked down one as far as I could
To where it bent in the undergrowth;

Then took the other, as just as fair,
And having perhaps the better claim,
Because it was grassy and wanted wear;
Though as for that the passing there
Had worn them really about the same,

And both that morning equally lay
In leaves no step had trodden black.
Oh, I kept the first for another day!
Yet knowing how way leads on to way,
I doubted if I should ever come back.

I shall be telling this with a sigh
Somewhere ages and ages hence:
Two roads diverged in a wood, and I—
I took the one less traveled by,
And that has made all the difference
CHAPTER 1: INTRODUCTION

1.1 Rationale
We describe a program of research aimed at better understanding risk factors for CVD and other secondary complications in people with SCI, as well as their inter-relationships and effects on neurological outcomes.

Spinal Cord Injury Rehabilitation Evidence (“SCIRE”) is the largest comprehensive systematic review relating to secondary complications of SCI. Upon reviewing the comprehensive evidence presented in SCIRE, several limitations were noted based on the existing evidence with respect to secondary complications. Firstly, there is extremely limited evidence on the risk of secondary complications relative to non-disabled individuals. While evidence points towards elevated risk factors for some conditions (e.g., CVD based on abnormal glycemic control and dyslipidemia, described in Tables in Chapter 2), the excess risk of ‘real’ outcomes (i.e., clinically relevant endpoints) has never been quantified with respect to a representative control group in a relatively large, representative sample while adjusting for confounding factors. Secondly, SCIRE provides limited information on mechanisms of the potential excess risk for secondary complications (e.g. CVD) beyond traditional risk factors such as physical inactivity. It is likely that a condition as encompassing as SCI has its own independent factors that elevate risk. The contribution of factors such as orthostatic hypotension, autonomic dysreflexia, and neuropathic pain to CVD risk remains unknown, as are the inter-relationships among these secondary complications.

This has left a lack of understanding of mechanisms underlying these complications, which may contribute to the lack of treatment options for individuals with SCI. Thirdly, as causal inference (discussed in more detail below) is contingent upon producing unbiased estimates for measures of effect size (e.g., odds ratios), there is a need for multivariable analyses (i.e., adjustment for confounding). Likely due to a combination of factors (e.g. smaller sample sizes, lack of accessible and comprehensive SCI data registries), our review of SCIRE also indicated a major lack of multivariable analyses.
Lastly, there is also very limited evidence on the relationship between neurological outcomes and secondary complications. To our knowledge, only one study has examined a relationship of this kind. This study examined the relationship between infections and neurological recovery during acute stages of SCI. The contribution of other secondary complications to neurological outcomes thus remains unknown (in acute and chronic stages).

This lack of evidence has left a knowledge gap with respect to secondary complications seen in individuals with SCI. Thus, clinical practice guidelines for the global management of secondary complications among individuals with SCI are underdeveloped. But before clinical practice guidelines can be created, large prospective multicentre studies are needed. And even before such studies can be performed, several questions must be answered using existing data: is there a heightened risk of secondary complications following SCI? And, what (if any) SCI-specific factors contribute to these complications, to what extent do they contribute, and to what extent do they independently contribute?

To summarize, the following are major issues with respect to secondary complications following SCI:

- SCI research focuses more on motor-related secondary complications than sensory or autonomic
- There is extremely limited evidence on risk of secondary complications (eg. stroke) relative to control groups (e.g. able-bodied)
- There is extremely limited evidence on mechanisms to excess risk (contribute factors such as orthostatic hypotension, autonomic dysreflexia, respiratory infections, neuropathic pain) and inter-relationships between these conditions
- There is extremely limited methodology within the field (i.e., multivariable approaches to assess confounding)
- There is very limited evidence on the relationship between neurological outcomes and secondary complications
1.2 Issues Specific to SCI Studies

While SCI is a devastating neurological disorder with high public awareness, the prevalence of traumatic SCI is relatively low, which strongly affects recruitment rates and study sample sizes. In 2001, the National Center for Injury Prevention and Control estimated a prevalence of approximately 200,000 for traumatic SCI in the United States.\(^5\)

More recently, the National Spinal Cord Injury Statistical Centre estimated a prevalence of approximately 273,000 [range: 238,000 to 332,000] persons with traumatic SCI in 2013 in the United States.\(^5\) A commonly accepted definition of *rare disorders*, according to the Rare Disease Act of 2002, are “those [diseases/disorders] which affect small patient populations, typically populations smaller than 200,000 individuals in the United States.”\(^6\) Moreover, registries specific to SCI are relatively new and generally do not include individuals with non-traumatic SCI. The first Canada-wide registry (Rick Hansen SCI Registry) was launched in 2004,\(^7\) the first European registry (EM-SCI) in 2001, and the first US national database (US Model Systems) in 1970, but did not include detailed information on secondary complications until the late 1990’s. Given these limitations (i.e., a relatively small patient population and the lack of large-scale longitudinal epidemiological data), cross-sectional studies are a valid starting point within the field.

1.3 Objectives

The following are the primary research questions of this thesis (hypotheses are in the following section):

1. Is there an elevated risk of secondary complications among individuals with chronic SCI?
   
   1A. Is there an elevated risk of cardiovascular complications (heart disease and stroke) among individuals with chronic SCI?
   
   1B. Is there an elevated risk of metabolic complications (Type 2 diabetes) among individuals with chronic SCI?
   
   1C. Is there an elevated risk of respiratory complications among individuals with chronic SCI?
1D. Is there an elevated risk of chronic pain among individuals with chronic SCI?

2. What are the relationships among secondary complications following SCI?
   2A. How do secondary complications (cardiovascular, metabolic, respiratory, pain) inter-relate?
   2B. How do these secondary complications inter-relate after adjustment for injury characteristics?
   2C. Do any of these inter-relationships explain the excess risk of the above secondary complications?

3. How do secondary complications relate to neurological outcomes?
   3A. In chronic stages?
   3B. In acute stages?

1.4 Hypotheses and Conceptual Model

A conceptual model of these research questions is presented in Figure 1.1. We hypothesize that SCI results (in addition to neurological changes) in a direct increased risk of secondary complications. We further hypothesize that positive correlations exist among secondary complications, some of which might contribute to excess risk of the secondary complications themselves. Last, based on results from the first two sets of studies, we hypothesize that secondary complications are associated with neurological outcomes in acute stage and chronic stages.
Figure 1.1. Hypothetical conceptual Model for this thesis.
1.5 Thesis Organization

This thesis consists of 8 chapters. Background material, along with a critical review of the literature, is presented in Chapter 2. Chapters 4 to 7 each consist of manuscripts published in, or submitted to scientific peer-reviewed journals. Chapter 3 describes an overview of the data and methodology used. Chapter 4 contains a methodological study on using BMI in SCI studies (as BMI was used as a covariate in the following chapter). The risk of cardiovascular, metabolic, respiratory, and pain conditions is presented in Chapter 5. Chapter 6 examines the inter-relationships between secondary complications, as well as their relationship with neurological deterioration. Chapter 7 is a longitudinal study examining the relationship between the secondary complication of neuropathic pain and neurological outcomes in the acute stage of injury. Chapter 8, the concluding chapter, synthesizes the findings from each of the studies and discusses the strengths, limitations, and implications of the collective work.
CHAPTER 2: BACKGROUND

KEY DEFINITIONS
Before discussing specific secondary complications of SCI, we have first provided an overview of some key definitions regarding SCI that are relevant to this thesis.

SCI Etiology: Definitions, Epidemiology and Economic Burden

Traumatic SCI occurs as a result of external physical impact. Leading causes of traumatic SCI include motor vehicle accidents, violence, falls, and sport/recreational activities.\(^8\),\(^9\)

Non-traumatic SCI occurs as a result of disease, infection, or tumour of the spinal cord, when damage is done to the spinal cord by means other than an external physical force.\(^10\),\(^11\)

Generally accepted definitions include motor neuron diseases, infectious and inflammatory diseases, neoplastic diseases, vascular diseases, toxic and metabolic conditions, and congenital and developmental disorders.\(^11\),\(^12\)

The reported prevalence for traumatic SCI in Canada is approximately 40,000, with about 1785 new cases reported every year.\(^13\) The prevalence of non-traumatic SCI in Canada is not known because of inconsistent definitions and lack of inclusion into SCI registries. However, estimates suggest that total SCI figures would more than double if non-traumatic SCI cases were included.\(^13\)

Although SCI is a comparatively rare condition, SCI is extremely costly to the health care system. The estimated lifetime economic burden per individual with traumatic SCI in Canada ranges from $1.5 million for incomplete paraplegia to $3.0 million for complete tetraplegia.\(^14\) Further, the annual economic burden associated with incident cases in Canada is estimated to be $2.67 billion.\(^14\)

For the purpose of this thesis, when we refer to SCI, we are referring to both traumatic and non-traumatic SCI, unless otherwise stated. We have assumed for our specific research questions that mechanisms relating excess risk and/or relating secondary complications do not differ between individuals with traumatic versus non-traumatic SCI.
However, where available, the SCI etiology was included as a potential covariate in multivariable analyses.

**SCI Severity: Definitions of Complete vs. Incomplete**

Outcomes from SCI differ widely; individuals exhibit remarkable differences in injury severity, which is predictive of neurological and functional deficits. Accordingly, SCI is classified by both the *neurological level* and *completeness of injury*. Completeness of injury is measured by the five-point (A–E) American Spinal Injury Association (ASIA) Impairment Scale (AIS) according to the International standards for Neurological and Functional Classifications of SCI (ISNCSCI). This standard assesses motor function in ten muscle groups (arms, C5–T1; legs, L2–S1) and sensation (light touch and pinprick) in 28 dermatomes (C2–S4/5) on both sides of the body. Thus, the AIS is a multi-dimensional approach to capture sensory and motor impairment. The following are the five AIS classifications:

A: *complete*. No sensory or motor function is preserved in the sacral segments S4-S5.

B: *sensory incomplete*. Sensory but not motor function is preserved below the neurological level and includes the sacral segments S4-S5 (light touch, pin prick at S4-S5 or deep anal pressure), AND no motor function is preserved more than three levels below the motor level on either side of the body.

C: *motor incomplete*. Motor function is preserved below the neurological level and more than half of key muscle functions below the single neurological level of injury have a muscle grade less than 3.

D: *motor incomplete*. Motor function is preserved below the neurological level and at least half of key muscle functions below the neurological level of injury have a muscle grade of 3 or greater.

E: *normal*. If sensation and motor function as tested with the ISNCSCI are graded as normal in all segments, and the patient had prior deficits, then the AIS grade is E. Someone without an initial SCI does not receive an AIS grade.
**Injury Classification: Definition of Neurological Level of Injury**

Individuals with SCI are further classified into categories according to the neurological level of injury (paraplegia and tetraplegia). Persons with paraplegia have damage to their thoracic, lumbar or sacral spinal cord and tetraplegia occurs with damage to the cervical spinal cord. More precisely, individuals with SCI are also referred to with respect to the exact neurological level of injury. The spinal cord has segmental levels defined by the spinal roots which exit the spinal column between each of the spinal vertebrae. The standards define *neurological level* as the lowest spinal cord level that has normal motor and sensory function.¹⁶

**Definition of Secondary Complications**

In general, individuals with physical disabilities are at risk for a number of acute and/or chronic health conditions that may develop or be influenced by the presence of impairment. Within the field of SCI, a necessary step has been to propose a clear definition of health conditions related to (or occurring along with) the injury. Terms that have been used to label such health conditions in individuals with SCI include *comorbid conditions* or *comorbidities, medical complications, secondary complications, secondary conditions*, and *associated conditions.*¹⁷ While the literature often uses such terms interchangeably, researchers have sought to clarify this terminology. For example, Jensen *et al.* recently defined *secondary health conditions* as ‘physical or psychological health conditions that are influenced directly or indirectly by the presence of a disability or underlying physical impairment.’¹⁷ This definition acknowledges that these conditions can arise secondary to a disability via at least two pathways. Firstly, having a disability may increase the risk of developing a health condition that (1) directly results from the impairment (e.g., neuropathic pain, spasticity) or (2) indirectly results because of the impairment (for example, physical inactivity that contributes to the development of conditions such as Type 2 diabetes).¹⁷ Within this definition, Jensen included CVD, chronic pain, constipation, depression, urinary tract infection, and several others.¹⁷

A secondary health condition is distinct from a *comorbidity* which is generally defined as “a pre-existing secondary diagnosis of the admitted patient” and/or co-occurring injury
(e.g., brain injury with traumatic SCI). Because of the difficulty in distinguishing pre-existing conditions from indirect results of impairment (i.e., abnormal glycemic control could develop prior to SCI, but could also be exacerbated by SCI), and since timing of onset is not always available, for the purpose of this thesis the term secondary complication was used to reflect both terms (comorbidity and secondary health condition).

**Acute versus chronic SCI**

While there is some controversy in defining acute versus chronic stages of SCI, the following phases, proposed by Rowland et al., of SCI are generally accepted:

1. Immediate Phase (0-2 hours): dominated by the immediate results of the injury event.
2. Acute Phase, subdivided into two stages:
   - *Early Acute Phase (2-48 hours):* characterized by continuing hemorrhage, increasing edema and inflammation, and marks the onset of additional secondary injury processes.
   - *Subacute Phase (2 days to 2 weeks):* onset of repair mechanisms.
3. Intermediate Phase (2 weeks to 6 months): characterized by the continued maturation of the glial scar and by regenerative axonal sprouting.
4. Chronic Phase (more than 6 months): begins at 6 months following injury and continues throughout the lifetime of the patient. It is characterized by the maturation/stabilization of the lesion including continued scar formation and the development of cysts and/or syrinxes.

**SYSTEMATIC REVIEW**

**Secondary Complications: overview**

In addition to paralysis, all bodily systems are affected by SCI, including the genitourinary, cardiovascular, endocrine, respiratory, immune, musculoskeletal, and digestive systems. Not surprisingly, SCI is accompanied by a host of secondary complications, including neuropathic pain, CVD, autonomic dysreflexia, orthostatic hypotension, respiratory and urinary tract infections, and many others. Because all-cause CVD has emerged as the leading cause of death among individuals with SCI, we first
examined CVD risk factors among individuals with SCI in a systematic review.

**Methods of Systematic Review**

**Literature Searches:** We began the search using a MEDLINE electronic search strategy. Our strategy included MeSH headings and keyword searches incorporating variations of the following principal terms: *cardiovascular disease, risk factor, physical inactivity, dyslipidemia, blood pressure, glycemic control, inflammation,* and *spinal cord injury.*

Our MEDLINE search was complemented by systematically searching other general medical electronic databases (EMBASE), more specific (i.e., pharmacological) electronic databases, and the Cochrane Library; by performing hand-searches of neurological and cardiovascular journals, and by scanning reference lists of publications found through our electronic data base search. Our searches were documented as they developed, so that our search was replicable and transparent. All electronic references were documented using a bibliographic software package (Refworks).

**Inclusion Criteria:** We included any peer-reviewed human studies, examining traditional CVD risk factors specific to the traumatic SCI population. Non-traumatic individuals were excluded at this point due to the lack of consensus of the definition of non-traumatic SCI. We included studies with or without treatments, since studies examining treatment effects specifically in individuals with SCI are relatively rare. We included studies published in foreign languages when an English translation was available.

**Secondary Complications: Cardiovascular**

The World Health Organization defines *CVD* as a class of disorders of the heart and/or blood vessels. CVDs encompass a range of disorders, which include coronary artery disease, cerebrovascular disease, peripheral arterial disease, rheumatic heart disease, congenital heart disease, deep vein thrombosis, and many others. Worldwide, CVDs remain the number one cause of death in the general population. In general, the term technically refers to any disease that affects the cardiovascular system, though it usually is used to refer to those related to atherosclerosis (arterial disease). Many of these conditions have similar underlying causes, mechanisms, and treatments.
Over the last decade, researchers and clinicians have become more aware of changing trends in morbidity and mortality among individuals with SCI. With our advances in management of neurogenic bladder and renal complications following SCI, cardiovascular complications are now the leading cause of death in those with SCI. Numerous investigators have documented that CVD risk factors are prominent among common chronic diseases, and that they tend to occur at an earlier age, though the exact timing of onset is not entirely understood due to lack of prospective data. Nearly all risk factors (discussed in more detail below) tend to be more prevalent in SCI subjects compared with ambulatory subjects. These risk factors include a greater prevalence of lipid disorders, chronic inflammation, and abnormal glycemic control. Daily energy expenditure is also significantly lower in SCI individuals, not only because of a lack of motor function and reduced physical activity, but also because of a lack of accessibility and fewer opportunities to engage in physical activity.

**Traditional Cardiovascular Disease Risk Factors: Physical Inactivity**
The reduced physical function associated with SCI underlies a greater sedentary lifestyle and lower energy expenditure. Studies have shown that individuals with SCI have lower resting metabolic rates and expend significantly less daily energy than able-bodied individuals. This results in a higher proportion of fat mass and a greater prevalence of central obesity, contributing to a variety of related metabolic abnormalities associated with inactivity, including insulin resistance, dyslipidemia, and greater susceptibility to vascular inflammation (discussed in more detail below).

**Traditional Cardiovascular Disease Risk Factors: Dyslipidemia**
The link between dyslipidemia and CVD has been well established in able-bodied populations. Following SCI, there is consistent evidence of reduced high-density lipoprotein (HDL) cholesterol levels, relative to able-bodied controls (see Table 2.1 below, under “non-intervention studies”). Several studies have examined the effects of various forms of exercise (both active and passive) that improve lipid-profiles. Only a single RCT has examined any pharmacological treatment effect upon dyslipidemia in the
SCI population. This high quality RCT found that extended-release niacin is efficacious in improving lipid profiles and global risk in individuals with chronic tetraplegia.  

**Traditional CVD Risk Factors: Inflammation**

Chronic inflammation is being increasingly recognized for its link to CVD, as atherosclerosis is thought to be, in part, an inflammatory process. Measurement of systemic inflammation can be gauged using assays for C-reactive Protein (CRP). This measure is an independent risk factor for CVD; in a study of almost 30,000 healthy, able-bodied postmenopausal women, for example, CRP was found to be the strongest single predictor of cardiac events, with the caveat that high-sensitivity CRP (hsCRP) assays were used.

Table 2.2 below summarizes the evidence with respect to inflammation following SCI. As this table demonstrates, CRP and other inflammatory markers are elevated during the chronic stages of SCI, even in the absence of acute infection. In able-bodied populations, statins are known to lower CRP, as well as improve lipid profiles. Conversely, treatment paradigms targeting inflammation have not yet been established for the SCI population.

Little is known about the contribution of inflammation to CVD after SCI. However, given the link between inflammation and CVD in the able-bodied population, and given that individuals with SCI experience inflammation as a result of both chronic infection and that relating to atherogenesis, it may play a role in CVD pathophysiology following SCI. It may also play a role to a greater extent compared with able-bodied individuals.

**Traditional CVD Risk Factors: Abnormal Glycemic Control**

Following SCI, there is consistent evidence of a greater prevalence of abnormal glycemic control relative to able-bodied controls (see Table 2.3, “Non-Intervention Studies”).
Several studies have examined the effects of various forms of exercise that appear to favourably influence glycemic control (see Table 2.3 “Intervention Studies”), most being pre-post studies. To our knowledge, no RCTs exist that examine any pharmacological treatment effects on glycemic control in the SCI population.

Abnormalities in glycemic control, most notably hyperglycemia, often leading to diabetes and/or metabolic syndrome (the co-occurrence of central adiposity, hypertension, abnormal glycemic control, and dyslipidemia), are well recognized for their link to CVD in the able-bodied. Abnormalities in glycemic control can be identified with an oral glucose tolerance test (OGTT), where glucose is ingested and blood glucose levels are analyzed serially.

Non-traditional risk factors: Overview

Beyond traditional risk factors for CVD discussed above, it is likely that a condition as encompassing as SCI has its own independent factors that elevate CVD risk. In other pathologies such as rheumatoid arthritis and kidney disease, ‘non-traditional’ risk factors (i.e., distinct from Framingham risk factors) ‘overtake’ traditional risk factors and or/compound risks for CVD.

A Potential Non-traditional Risk Factor for CVD: Autonomic Dysreflexia

Autonomic dysfunction caused by SCI is associated with several conditions that may contribute to heightened cardiovascular risk, including abnormalities in blood pressure. One such abnormality in blood pressure is autonomic dysreflexia (AD). AD is defined as acute episodic hypertension resulting from sympathetic hyperreactivity after SCI, and occurs in up to 90% of people with injuries above T6. AD also occurs, though less frequently, in individuals with non-traumatic SCI. Although it can be asymptomatic, the signs and symptoms of AD generally include a sudden increase in blood pressure, altered heart rate (reflex bradycardia), anxiety, blurred vision, headache, flushing and sweating (above the level of injury). Because individuals with upper thoracic and cervical injuries often have a low resting blood pressure (90–100 mm Hg), elevated blood pressure from AD may not always be obvious.
AD can be a daily event and is triggered by stimuli from below the level of injury. Such stimuli may include: bladder distention (most common), bladder or kidney stones, kinked catheter, urinary tract infection, fecal impaction, pressure sores, ingrown toenails, fractures, menstruation, sunburns, hemorrhoids, invasive testing, and sexual intercourse. Even seemingly benign stimuli, such as a tightly tied shoelace can trigger AD. In most instances, AD is resolved as soon as the precipitating stimuli is eliminated (eg. bladder voided).

Why does AD occur? AD occurs because an afferent stimulus (eg. distended bladder) triggers a peripheral sympathetic response, which results in vasoconstriction and hypertension. Descending inhibitory signals, which would normally counteract the rise in blood pressure, are blocked at the level of the SCI.

While AD is generally resolved as soon as the precipitating stimulus is removed, in some cases, malignant episodes can occur. Moreover, AD has been linked with cardiovascular events such as myocardial ischemia and fatal cerebral haemorrhage in case studies, though no epidemiological studies have examined this association. While AD is not a documented risk factor for CVD, there is evidence from animal models to suggest that repeated episodes of hypertension may result in endothelial damage, and place individuals at a heightened risk of CVD. For these reasons, AD was one specific secondary complication of interest in the present thesis.

**A Potential Non-traditional Risk Factor: Orthostatic Hypotension**

While AD results in episodic hypertension, orthostatic hypotension (OH) is related to significant decline in blood pressure. More specifically, OH is defined as a drop in systolic blood pressure of 20 mmHg or more, or in diastolic blood pressure of 10 mmHg or more, following a change in body position from supine to upright. Symptoms such as light-headedness, dizziness, blurred vision, fatigue, muscle weakness and syncope may or may not be present. Symptoms of OH may be so severe as to prevent participation in rehabilitation programs. From a study of 28 subjects, it was estimated that 57% of
individuals with SCI experience OH.\textsuperscript{45} OH occurs for a myriad of reasons, including loss of sympathetic control, changes in baroreceptor sensitivity, lack of skeletal muscle pumps, cardiovascular de-conditioning, and abnormalities in salt and water metabolism.\textsuperscript{46-56}

In terms of treatments for OH, the best available evidence is from a small cross-over RCT (n=4) which demonstrated that 10mg midodrine (an oral alpha-sympathomimetic agent) enhanced exercise performance through elevated systolic blood pressure in 3 out of 4 individuals with SCI.\textsuperscript{57} There is limited evidence on the effects of fludrocortisone, ergotamine, and ephedrine.\textsuperscript{58} Moreover, Wecht et al. found that infusion with 1 mg/kg L-NAME (inhibitor of nitric oxide synthase) increased mean arterial pressure following head tilt compared to placebo controls, though the mean arterial pressure in the SCI group did not significantly differ with respect to able-bodied controls.\textsuperscript{59} In terms of non-pharmacological management of OH, Krassioukov et al. concluded that functional electrical stimulation (FES), which triggers intermittent muscular contractions that facilitate venous blood return, and increasing sodium intake, are non-pharmacologic interventions that have some benefit to support their utility.\textsuperscript{58}

The link between OH and CVD has been documented in large cohort studies in elderly, able-bodied populations that demonstrate that OH significantly and independently increases the risk of CVD, potentially via reduced blood flow to the myocardium and brain.\textsuperscript{60} The link between OH and CVD has not been established in individuals with SCI, although they are typically a younger patient population. Indeed, mechanisms relating OH and CVD may differ between individuals with SCI and able-bodied individuals, given the plethora of changes to the cardiovascular system that occur following SCI, and thus is a focus of this thesis.

\textbf{OTHER SECONDARY COMPLICATIONS}

\textit{Respiratory Diseases and Infection}

In addition to cardiovascular dysfunction, individuals with SCI exhibit severe dysfunction of the respiratory system. Importantly, respiratory complications are the main cause of morbidity and mortality in the acute phase of SCI.\textsuperscript{61} Approximately two-thirds
of patients with acute SCI experience complications such as atelectasis, pneumonia, and respiratory failure.\textsuperscript{62} The degree of respiratory dysfunction is generally related to the extent and neurological level of injury: the higher level lesions result in decentralization of progressively more of the expiratory and inspiratory muscles.\textsuperscript{61} Complete paralysis of all muscles involved with respiration occurs when the lesion is above C3; this type of injury requires permanent ventilatory support. When the injury is between C3 to C5 respiratory insufficiency occurs via respiratory muscle dysfunction. The extent of respiratory dysfunction (with the exception of mortality) in the chronic stages of SCI has not been as widely studied as in acute stages, and is thus examined in the present thesis.

\textit{Neuropathic Pain}

In addition to respiratory and cardiovascular complications, direct damage to the nervous system as well as other complications result in several pain conditions after injury. Reported estimates of the prevalence of pain (nociceptive or neuropathic) following SCI range anywhere up to 60%, with a large majority of these individuals experiencing severe disabling pain.\textsuperscript{13} The lack of consensus over a classification system for SCI pain has led to considerable variation in incidence and prevalence rates for SCI-related pain. Most recently, however, an international group of clinicians and researchers developed a consensus for SCI pain classification: the International Spinal Cord Injury Pain Classification (ISCIP Classification).\textsuperscript{63} In terms of timing of development of pain, one of the largest studies to date indicated that pain started immediately after SCI in 34%, within the first year in 58%, and that pain increased over time in 47% and decreased over time in 7%.\textsuperscript{64}

Neuropathic pain is a particularly debilitating form of pain as it is generally described as severe and has few satisfying treatment options. Neuropathic pain is defined as “pain arising as a direct consequence of a lesion or disease affecting the central somatosensory system,” and is distinct from nociceptive pain (somatic pain). Neuropathic pain may be spontaneous, either ongoing or intermittent, or stimulus-evoked. This type of pain is divided into at-level and below-level pain, where “level” refers to the injured (neurological) level of the spinal cord. At-level pain is a central or peripheral pain caused
by the spinal cord or root lesion/disease located anywhere within the neurological level and three dermatomes below this level.\textsuperscript{66} Below-level pain is a central neuropathic pain arising as a direct consequence of damage to the spinal cord.\textsuperscript{66}

From experimental studies, we have gained increasing knowledge of the cellular and molecular changes underlying the development of neuropathic pain that occur following SCI. One of the primary physiological mechanisms underlying its development is central sensitization. Central sensitization refers to an enhancement in the function of circuits in nociceptive pathways caused by overlapping processes: increases in membrane excitability, reduced inhibition (from descending control and intraspinally), intraspinal sprouting, microglial activation, and the recruitment of previously subthreshold synaptic inputs to nociceptive neurons.\textsuperscript{67} Treating neuropathic pain is thus a challenging task, and has posed more of a challenge than treating other secondary complications (i.e., respiratory and cardiovascular). To date, in terms of pharmacological treatments, only gabapentin, pregabalin, and amitriptyline have shown some efficacy in treating SCI neuropathic pain in randomized trials.\textsuperscript{66}

Other types of pain are common among individuals with SCI, including musculoskeletal pain (eg. shoulder pain from overuse injuries), and “other” types of pain according to ISCIP, including migraine headaches and AD-induced headaches.\textsuperscript{63} However, the contribution of any of these types of pain to other secondary complications remains unknown.

Relationships Between Secondary Complications

Thus far, we have discussed various secondary complications of SCI in reference to distinct conditions (i.e., respiratory complications, pain), and have introduced the idea of inter-relationships among secondary complications (i.e., AD/OH with CVD). Indeed, the vast majority of secondary complications following SCI have been studied separately, whereas most individuals with SCI experience two or more conditions.\textsuperscript{2, 3, 68-70} Overlap in complications has been shown in patients with COPD and other chronic conditions, but has been yet to be examined among individuals with SCI.\textsuperscript{71} Prior studies have generally
focused on the number of co-occurring conditions that individuals with SCI experience versus the nature of the conditions which overlap, or the extent to which conditions correlate.\textsuperscript{68}

Although associations among some secondary complications, such as diabetes or OH with CVD, have been previously examined in able-bodied populations,\textsuperscript{72} it is currently unknown whether and to what extent secondary complications among individuals with SCI are interrelated. SCI represents a unique and valid condition to examine such relationships given the multitude of bodily systems disrupted by the injury. Knowledge of relationships between secondary complications will yield a better understanding of mechanisms underlying these conditions. This is also important from a methodological standpoint. Namely, if there is high correlation among conditions, this needs to be taken into consideration in the design and analysis of future studies (i.e., to adequately address confounding).

\textit{Neurological Recovery and Deterioration Following SCI}

Although not generally considered a secondary complication, neurological decline may represent a secondary complication of SCI, and fits within the broader definition of secondary complication used here. Before discussing neurological deterioration, it is first important to define and distinguish deterioration from neurological recovery, both of which represent (and define in fact) stages of SCI.

With respect to neurological recovery, studies report a considerable degree of conversion in AIS grade over the first year after SCI (transition from acute to chronic stages).\textsuperscript{73} The conversion rates vary greatly depending on the baseline AIS grade of the individual, as well as the neurological level of the injury. For example, recent studies demonstrate that 80\% of the initial AIS A patients remain as AIS A, with about 10\% converting to AIS B (i.e., some sensory function) and about 10\% of the initial AIS A patients regaining some motor function (i.e., convert to AIS C).

In individuals initially assessed as AIS B or AIS C (i.e., incomplete SCI) the extent of
spontaneous recovery is significantly greater compared to AIS A. The spontaneous one-year neurologic recovery rate varies slightly between studies, but AIS B conversion to AIS C was between 15 and 40% and AIS B conversion to AIS D was as much as 40%. AIS C conversion to AIS D was between 60 and 80% of all the patients examined.

Motor recovery over the first year after SCI has also been examined in the control groups of randomized studies.\textsuperscript{73} Some of these studies utilized motor scores (scores derived from 10 muscles on each side of the body for a maximum total score 100, which forms part of the AIS grade). From a landmark study, the observed motor recovery after one year was 4.6 points for AIS A subjects, 31.3 points for AIS B subjects, and 12.9 motor points for AIS C and D subjects combined.\textsuperscript{73}

While recovery during the acute stages of SCI has been well documented, the presence of motor, sensory, and autonomic neurological decline remains understudied among individuals with chronic SCI. An estimated 21% of individuals with SCI develop syrinxes (a fluid-filled cavity within the spinal cord) in the chronic stages of SCI, though this finding was derived from a relatively small sample size (n=153).\textsuperscript{74} From the same study, an estimated 62% of individuals with chronic SCI experienced cord atrophy.\textsuperscript{74} However, less than 10% of subjects with syrinx formation and with atrophy exhibited neurological decline (as measured in ‘decrease in motor power’ in this study). Large-scale epidemiological studies of deterioration (sensory or motor or autonomic) in chronic stages of SCI is lacking within the SCI literature.

Thus, as previously mentioned, neurological decline may represent a secondary complication of SCI, and fits within the broader definition of secondary complication used here. Lastly, although the terms neurological recovery and neurological deterioration can refer to sensory, autonomic, and/or motor function, in this thesis, we have generally focused on sensory and motor neurological outcomes.
<table>
<thead>
<tr>
<th>Study Title (Author, Year)</th>
<th>Main Findings Pertaining to Dyslipidemia</th>
<th>Study Design</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>INTERVENTION STUDIES- PHARMACOLOGICAL</strong></td>
<td></td>
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<tr>
<td>Safety, tolerance, and efficacy of extended release niacin monotherapy for treating dyslipidemia risks in persons with chronic tetraplegia: a randomized multicenter controlled trial <em>(Nash et al., 2011)</em></td>
<td>*SCI patients on niacin had significant increases in HDL-C levels and decreases in TC/HDL-C and LDL-C/HDL-C ratios, LDL-C levels, and TC levels</td>
<td>*intervention: niacin</td>
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<tr>
<td></td>
<td>*extended-release niacin monotherapy is safe and effective for treatment of dyslipidemia</td>
<td>*high quality RCT</td>
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<td></td>
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<td>*54 subjects (31 treatment arm; 23 placebo arm)</td>
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<tr>
<td><strong>INTERVENTION STUDIES- NON-PHARMACOLOGICAL</strong></td>
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<tr>
<td>Lipid profiles are influenced by arm cranking exercise and training in individuals with spinal cord injury <em>(El-Sayed et al., 2005)</em></td>
<td>*improved HDL levels but no difference in TC or triglyceride levels</td>
<td>*intervention: arm ergometry</td>
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<td></td>
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<td>*pre-post test</td>
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<td>*12 subjects</td>
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<tr>
<td>Treadmill training-induced adaptations in muscle phenotype in persons with incomplete spinal cord injury <em>(Stewart et al., 2004)</em></td>
<td>*significant reductions in TC, LDL, TC/HDL</td>
<td>*intervention: body-weight supported treadmill training</td>
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<td>*pre-post test</td>
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<td></td>
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<td>*9 subjects</td>
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<tr>
<td>Effect of training intensity on physical capacity, lipid profile and insulin sensitivity in early rehabilitation of spinal cord injured individuals <em>(de Groot et al., 2003)</em></td>
<td>*TC/HDL and triglycerides decreased significantly more in high intensity group</td>
<td>*intervention: low or high intensity arm ergometry</td>
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<td></td>
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<td>*RCT</td>
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<td></td>
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<td>*6 subjects</td>
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<tr>
<td>Circuit resistance training improves the atherogenic lipid profiles of persons with chronic paraplegia <em>(Nash et al., 2001)</em></td>
<td>*significant decreases in LDL, LDL/HDL, TC/HDL</td>
<td>*intervention: circuit resistance training</td>
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<td></td>
<td></td>
<td>*pre-post test</td>
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<td></td>
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<td>*5 subjects</td>
</tr>
<tr>
<td>Reciprocating gait orthosis powered with electrical muscle stimulation (RGO II). Part II: Medical evaluation of 70 paraplegic patients <em>(Solomonow et al., 1997)</em></td>
<td>*significant reductions in total cholesterol, LDL, LDL/HDL, and TC/HDL in 8 patients with initially high total cholesterol levels</td>
<td>*intervention: reciprocating gait orthosis with electrical muscle stimulation</td>
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<td></td>
<td></td>
<td>*pre-post test</td>
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<td>*70 subjects</td>
</tr>
<tr>
<td>Effects of low- and moderate-intensity training in spinal cord-injured persons <em>(Hooker &amp; Wells, 1989)</em></td>
<td>*significant increases in HDL and decreases in triglycerides, LDL, and TC/HDL in moderate intensity group</td>
<td>*intervention: low or moderate intensity wheelchair ergometry</td>
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<tr>
<td></td>
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<td>*prospective controlled trial</td>
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<td>*8 subjects</td>
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<tr>
<td><strong>NON-INTERVENTION STUDIES</strong></td>
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<tr>
<td>Adherence with the National Cholesterol Education Program guidelines in men with chronic spinal cord injury <em>(Liebermen et al., 2011)</em></td>
<td>*15/38 SCI patients had dyslipidemia</td>
<td>*no intervention</td>
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<tr>
<td></td>
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<td>*38 subjects with chronic SCI</td>
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<tr>
<td>Serum lipids and lipoprotein concentrations in young quadriplegic patients <em>(Heldenberg et al., 1981)</em></td>
<td>*SCI patients had significantly lower serum HDL-C</td>
<td>*no intervention</td>
</tr>
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<td></td>
<td></td>
<td>*10 subjects with chronic SCI and 10 healthy control subjects</td>
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<tr>
<td>High density lipoprotein cholesterol concentrations in physically active and sedentary spinal cord injured patients <em>(Brenes et al., 1986)</em></td>
<td>*SCI patients had significantly lower serum HDL-C</td>
<td>*no intervention</td>
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<tr>
<td></td>
<td></td>
<td>*66 subjects with chronic SCI and 126 healthy control subjects</td>
</tr>
</tbody>
</table>

Table Continued on Following Page
<table>
<thead>
<tr>
<th>Study Title (Author, Year)</th>
<th>Main Findings Pertaining to Dyslipidemia</th>
<th>Study Design</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk factors for cardiovascular disease in chronic spinal cord injury patients (<em>Krum et al., 1992</em>)</td>
<td>*SCI patients had significantly lower serum HDL-C</td>
<td>*no intervention *327 subjects with chronic SCI and 327 healthy control subjects</td>
</tr>
<tr>
<td>The serum lipoprotein profile in veterans with paraplegia: the relationship to nutritional factors and body mass index (<em>Zlotolow et al., 1992</em>)</td>
<td>*SCI patients had significantly lower serum HDL-C *no significance in LDL-C</td>
<td>*no intervention *28 subjects with chronic SCI and 52 healthy control subjects</td>
</tr>
<tr>
<td>Do spinal cord injuries adversely affect serum lipoprotein profiles (<em>Ozgurtas et al., 2003</em>)</td>
<td>*SCI patients had significantly lower serum HDL-C and ApoA *SCI patients had significantly higher serum HDL-C and ApoB</td>
<td>*no intervention *28 subjects with chronic SCI and 60 healthy control subjects</td>
</tr>
<tr>
<td>Lipoproteins and free plasma catecholamines in spinal cord injured men with different injury levels (<em>Schmid et al., 2008</em>)</td>
<td>* SCI tetraplegics had elevated VLDL-C and triglyceride levels and reduced HDL levels *SCI paraplegics had significantly higher LDL and total cholesterol levels</td>
<td>*no intervention * 80 subjects with chronic SCI and 16 healthy control subjects</td>
</tr>
</tbody>
</table>

**Table 2.1.** Studies of dyslipidemia in individuals with SCI. Abbreviations: SCI= spinal cord injury; HDL-C= high density lipoprotein cholesterol; LDL-C= low density lipoprotein cholesterol; TC= total cholesterol; VLDL-C= very low density lipoprotein cholesterol; Apo= apolipoprotein.
<table>
<thead>
<tr>
<th>Study Title (Author, Year)</th>
<th>Main Findings Pertaining to Inflammation</th>
<th>Study Design</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inflammation and insulin sensitivity in spinal cord injured subjects (Hollis et al., 2009)</td>
<td>*SCI patients had significantly higher serum CRP levels compared to healthy controls</td>
<td>*no intervention</td>
</tr>
<tr>
<td>*14 subjects with chronic SCI and 13 healthy control subjects</td>
<td></td>
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<tr>
<td>C-reactive protein in adults with chronic spinal cord injury: increased chronic inflammation in tetraplegia vs paraplegia (Gibson et al., 2008)</td>
<td>*Mean serum CRP levels were consistent with the AHA classification of high CVD risk</td>
<td>*no intervention</td>
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<tr>
<td>*75 subjects with chronic SCI (no controls)</td>
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<tr>
<td>Elevated C-reactive protein associated with decreased high-density lipoprotein cholesterol in men with spinal cord injury (Liang et al., 2008)</td>
<td>*odds of high serum CRP levels were higher in SCI group compared to healthy controls</td>
<td>*no intervention</td>
</tr>
<tr>
<td>*129 subjects with chronic SCI and 129 healthy control subjects</td>
<td></td>
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<tr>
<td>Circulating levels of markers of inflammation and endothelial activation are increased in men with chronic spinal cord injury (Wang et al., 2007)</td>
<td>*SCI patients had significantly higher serum CRP and IL-6 levels compared to healthy controls</td>
<td>*no intervention</td>
</tr>
<tr>
<td>*89 subjects with chronic SCI and 29 healthy control subjects</td>
<td></td>
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<tr>
<td>Clinical correlates of elevated serum concentrations of cytokines and autoantibodies in patients with spinal cord injury (Davies et al., 2007)</td>
<td>*SCI patients had significantly higher serum IL-6, TNF-alpha, IL-1RA, and anti-GM(1) (IgG) levels compared to healthy controls</td>
<td></td>
</tr>
<tr>
<td>*56 subjects with chronic SCI and 35 healthy control subjects</td>
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<tr>
<td>Inflammatory C-reactive protein and cytokine levels in asymptomatic people with chronic spinal cord injury (Frost et al., 2005)</td>
<td>*SCI patients had significantly higher serum CRP levels compared to healthy controls</td>
<td>*no intervention</td>
</tr>
<tr>
<td>*SCI patients did not differ with respect to pro-inflammatory cytokines (IL-6 or TNF-alpha) compared to healthy controls</td>
<td></td>
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<tr>
<td>*37 subjects with chronic SCI and 10 healthy control subjects</td>
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</tbody>
</table>

**Table 2.2.** Studies of chronic inflammation in individuals with SCI. Abbreviations: SCI= spinal cord injury; CRP= C-reactive protein; AHA=American Heart Association; IL= interleukin; TNF= tumor necrosis factor.
### Table 2.3. Studies of glycemic control in individuals with SCI.

<table>
<thead>
<tr>
<th>Study Title (Author, Year)</th>
<th>Main Findings Pertaining to Glycemic Control</th>
<th>Study Design</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>INTERVENTION STUDIES (ALL NON-PHARMACOLOGICAL)</strong></td>
<td></td>
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<tr>
<td>Changes in skeletal muscle size and glucose tolerance with electrically stimulated resistance training in subjects with chronic spinal cord injury (Mahoney et al., 2005)</td>
<td>*no significant changes in blood glucose or insulin after training</td>
<td>*intervention: 12 week residence-based, resistance exercise training *pre-post test *5 subjects</td>
</tr>
<tr>
<td>Body-weight-support treadmill training improves blood glucose regulation in persons with incomplete spinal cord injury (Phillips et al., 2004)</td>
<td>*improved glycemic regulation: greater fraction of glucose that was ingested was oxidized *capacity for nonoxidative disposal of glucose (i.e., storage) was enhanced</td>
<td>*intervention: weight supported treadmill training *pre-post test *9 subjects</td>
</tr>
<tr>
<td>Improved glucose tolerance and insulin sensitivity after electrical stimulation-assisted cycling in people with spinal cord injury (Jeon et al., 2002)</td>
<td>*significantly lower 2-hr OGTT glucose levels after 8 weeks of training</td>
<td>*intervention: FES cycling *pre-post test *7 subjects</td>
</tr>
<tr>
<td>Insulin action and long-term electrically induced training in individuals with spinal cord injuries (Mohr et al., 2001)</td>
<td>*Insulin-stimulated glucose uptake rates increased after intensive training</td>
<td>*intervention: FES leg-cycle training *pre-post test *10 subjects</td>
</tr>
<tr>
<td>Functional electrical stimulation exercise increases GLUT-1 and GLUT-4 in paralyzed skeletal muscle (Chilibeck et al., 1999)</td>
<td>*significant increase in expression of key genes involved in regulation of glucose metabolism</td>
<td>*intervention: FES leg-cycle ergometry training *pre-post test *5 subjects</td>
</tr>
<tr>
<td>Exercise-induced overexpression of key regulatory proteins involved in glucose uptake and metabolism in tetraplegic persons: molecular mechanism for improved glucose homeostasis (Hjeltnes et al., 1998)</td>
<td>*improved insulin action on whole body *improved glucose uptake in through significant increase in expression of key genes involved in regulation of glucose metabolism</td>
<td>*intervention: electrically stimulated leg cycling exercise *pre-post test *5 subjects</td>
</tr>
<tr>
<td><strong>NON-INTERVENTION STUDIES</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C-reactive protein, metabolic syndrome, and insulin resistance in individuals with spinal cord injury (Lee et al., 2005)</td>
<td>*metabolic syndrome and insulin resistance were present in 22.6% SCI subjects</td>
<td>*no intervention *93 subjects with chronic SCI *no controls</td>
</tr>
<tr>
<td>Influence of the sympathetic nervous system on insulin sensitivity and adipose tissue metabolism: a study in spinal cord-injured subjects (Karlsson et al., 1995)</td>
<td>*blood glucose and insulin after oral glucose were significantly increased in SCI subjects compared to controls</td>
<td>*no intervention *7 subjects with chronic SCI and 7 healthy control subjects</td>
</tr>
<tr>
<td>Disorders of carbohydrate and lipid metabolism in veterans with paraplegia or quadriplegia: a model of premature aging (Bauman et al., 1994)</td>
<td>*prevalence of diabetes 22% in individuals with SCI compared to 6% in control group *82% of controls had normal oral glucose tolerance vs. 38% with quadriplegia and 50% with tetraplegia *SCI subjects had significantly higher mean glucose and insulin values at several points during OGTT compared to controls</td>
<td>*no intervention *100 subjects with chronic SCI and 50 healthy control subjects</td>
</tr>
</tbody>
</table>
CHAPTER 3: METHODOLOGICAL OVERVIEW

3.1 Study Design Overview

The research questions being addressed in this thesis are in the realm of causal inference—a central aim of epidemiological investigations. The gold standard approach to answering questions related to causality involves conducting a controlled experiment in which treatments/exposures (independent variables) are allocated at random. However, when secondary complications are exposures themselves, such exposures cannot be randomized. For example, if we ask the question: does neuropathic pain (exposure or independent variable) cause CVD (dependent variable or outcome)?, both the exposure and outcomes are conditions. In these situations, causal inference must be based on observational data.\(^7\)

The standard approach to quantifying causal and associative relationships is a regression model, with an appropriate set of potential confounders (identified using a causal diagram,\(^7\) measured and included as covariates). Notably, regression techniques cannot distinguish associative relationships with causal relationships (the latter being assessed with a combination of subject matter knowledge, and general criteria for causality (eg. Bradford Hill criteria). Associative relationships are however a starting point to assess causal relationships. Indeed, this approach has been used in the present thesis, with more detailed methodology described below.

Within observational study designs, if using the risk of bias as an organizing principle in a hierarchy of evidence that contributes to causal inference, several study designs are available, including cohort (longitudinal), case-control (longitudinal), and cross-sectional studies (in order of highest to lowest strength of evidence).\(^7\) In cases where longitudinal data are not available, cross-sectional study designs represent starting points for causal inference, and also have the advantage of being able to assess a large number of confounding factors. For the purpose of this thesis, longitudinal data have been utilized where possible (Chapter 6), and cross-sectional data used elsewhere (Chapters 4, 5). Limitations of the use of cross-sectional data with respect to causal inference are
discussed within the limitations section of each section.

3.2 Data Sets

Four different data sets were analyzed to fulfill the objectives of this study. These are: 1) the 2010 cycle of the Canadian Community Health Survey; 2) the SCI-Community Survey; 3) the European Multi-Centre Study on SCI (EM-SCI) database; 4) the Simon Fraser University (SFU) Body Mass Index (BMI) dataset. Different data sources were required as each dataset had unique data elements, and each with their respective strengths and limitations (discussed in more detail in data chapters). The following is a brief overview of each database used (specific elements from each dataset are also discussed in more detailed in data chapters).

Canadian Community Health Survey

The Canadian Community Health Survey (CCHS) is a national, cross-sectional survey conducted by Statistics Canada.\textsuperscript{78} The CCHS gathers data by trained interviewers at a sub-provincial level on health-related topics including health status, health care utilization and health determinants. The target population of this survey includes individuals aged 12 years and older who reside in every province and territory within Canada. Excluded from this sample are persons living on reserves and Crown Lands, institutionalized individuals, full-time members of the Canadian Forces and certain remote populations. Using complex survey methods, the CCHS covers approximately 98\% of their target population with a combine household- and individual-level response rate of 71.5\% in 2010. Data is collected using a multistage, stratified cluster sampling technique. The 2010 Cycle contains information on neurological conditions, including SCI (note: neurological conditions are not available in other cycles).

SCI Community Survey

This national self-report cross-sectional survey sponsored by the Rick Hansen Institute, involved Canadians living in the community for at least 1 year after being discharged from a hospital or rehabilitation facility because of SCI (i.e., chronic SCI). Individuals
were eligible if they had a SCI caused by trauma or disease, were ≥18 years of age, and could speak English or French. All data were collected using measures developed for the Rick Hansen Spinal Cord Injury Registry Community Follow-up Version 2.0\textsuperscript{79} as well as other standardized surveys.\textsuperscript{80–87}

Individuals with SCI living in all provinces and territories across Canada were invited to participate in an online or telephone survey through a national consumer awareness campaign that included national and local media advertisements and a survey-specific website. Information packages were also distributed with the assistance of Rick Hansen Institute partners (Rick Hansen Foundation, SCI-Canada, Wheelchair Sports). Overall, 90\% of participants completed the survey online, whereas 10\% completed the survey over the phone. There were no responses from individuals living in Yukon, Northwest Territories, or Nunavut. According to Statistics Canada, these territories represent approximately 0.3\% of the Canadian population. The survey was provided in both official languages of Canada (English, French).

The Community Follow-up Questionnaire Version 2.0 is a comprehensive follow-up questionnaire designed specifically for individuals with chronic SCI.\textsuperscript{79} A subset of information collected in the Community Follow-up Questionnaire Version 2.0 was used to develop this comprehensive national survey including demographics, secondary complications, community participation, activities and employment, health care utilization measure, and overall quality of life rating. Other recent publications have arisen from this national survey.\textsuperscript{80–87}

\textit{European Multi-Centre Study on Spinal Cord Injury}

The European Multi-center Study about SCI (EM-SCI) is a longitudinal prospective cohort study of individuals with traumatic SCI (started in 2001). The EM-SCI is an internationally recognized clinical SCI network, with data management centralized at the University Hospital Balgrist in Zurich, Switzerland. Comprised of 19 participating trauma and rehabilitation centers from across Europe, neurological, neurophysiological, and functional outcomes are comprehensively tracked in individuals with SCI at four fixed time-points over the first year of injury. For this thesis, clinical data from a subset of these centres was linked with the EM-SCI registry data.
SFU BMI Dataset

This is cross-sectional clinical dataset from Simon Fraser University which includes adult individuals with traumatic SCI. Measurements were taken on individuals with chronic SCI (>1 year post injury), who had no known pre-existing (prior to injury) CVD, and were not taking any cardiovascular-related medications. This dataset includes neurological assessments, body composition measures (obtained through DEXA scans), anthropomorphic measures, and several biomarkers (eg. lipid plasma levels). This dataset was used for a methodology study (described in more detail below).

3.3 Overview of Analytical Techniques

The following is an overview of specific analytical techniques used, in relation to the study design. Each analytical technique is described in more detail within the methods section of each chapter.
<table>
<thead>
<tr>
<th>Data Source</th>
<th>Study Design</th>
<th>Exposures</th>
<th>Outcomes</th>
<th>Potential Confounders</th>
<th>Analytical Methods</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCHS 2010</td>
<td>Cross-sectional</td>
<td>Self-report SCI</td>
<td>Self report CVD (stroke, heart disease), Type 2 diabetes, chronic respiratory diseases (asthma, COPD), chronic pain (migraine)</td>
<td>Age, sex, BMI**, physical activity, diet, alcohol consumption, smoking, socioeconomic status</td>
<td>Multivariable logistic regression (with sampling weights)</td>
</tr>
<tr>
<td>SCI-CS (2011-2012)</td>
<td>Cross-sectional</td>
<td>Self-report Pain, respiratory infection, CVD, AD, OH</td>
<td>Age, sex, time post injury, Type 2 diabetes, BMI, hypertension, smoking</td>
<td>Multivariable logistic regression</td>
<td></td>
</tr>
<tr>
<td>BMI Study (2013)</td>
<td>Cross-sectional</td>
<td>Body Mass Index, Waist Circumference</td>
<td>Framingham Risk Score, DEXA-measured body fat</td>
<td>Age, sex, neurological level, completeness of injury</td>
<td>Correlation/linear regression</td>
</tr>
</tbody>
</table>

Table 3.1 Overview of analytical techniques used.
CHAPTER 4: METHODOLOGICAL STUDY

4.1 Methodological Study: Body Mass Index Calculations for SCI

In subsequent chapters and as mentioned in the above Table (Table 3.1), BMI will be used as a potential confounder in examining the relationship between SCI and CVD/diabetes. This methods-based study deals with the issue of BMI measurements in the context of SCI, using the Simon Fraser University BMI dataset.

Introduction

Obesity is a well-known risk factor for CVD, and is particularly important to examine following SCI as adverse changes in body composition, metabolic rate, and autonomic function are known consequences of injury.88, 89 These adaptations, in combination with reduced activity levels as a result of physical disability, may lead to a higher prevalence of obesity and greater CVD risk in this population.90 Thus, accurate and practical measures of obesity, coupled with better understanding of their relationships with CVD risk, are essential for this population.

Body mass index (BMI), measured as a ratio of weight to the square of height \( \frac{Wt}{Ht^2} \), has been used worldwide, and is espoused by the World Health Organization, as a simple proxy for obesity in the general population.91 Although BMI does not specifically measure fat mass, population studies have shown that it correlates well with measures of body fat.91 However, we often take for granted that BMI is measured as the ratio of weight to the square of height; other scaling powers for height are reported to be more strongly correlated with measures of obesity in the able-bodied.92

Other measures that have been used as surrogate markers for obesity in the able-bodied population are waist circumference (WC), waist-to-hip ratio, waist-to-height ratio (WHtR), and neck circumference.93 BMI is often considered to be a “gold standard” measure, but it underestimates obesity in those with SCI, probably due to decreases in muscle mass below the injury level.94 Moreover, clinicians and researchers are particularly interested in measures that incorporate WC, because they are well correlated with visceral fat, which is thought to be a key player in determining CVD risk.95
We recently showed that WC was the best measure of obesity-related CVD risk after SCI. In this study, BMI was strongly correlated with adiposity, but not with CVD risk. However, the impact of different scaling factors for height correction in individuals with SCI is unknown, and may improve the relationships between these measures, as has been shown in the able-bodied. We, therefore, aimed to determine the power of the scaling factors ‘x’ of Wt and WC with respect to height (Wt/Ht^x and WC/Ht^x) that are maximally associated with total body fat, abdominal body fat, and Framingham CVD Risk scores. In examining relationships between BMI/WC with both obesity and CVD risk, these measures can be properly incorporated into multivariable models which utilize either cardiovascular or metabolic outcomes (as potential confounders).

**Methods**

**Participants**
This study represents a retrospective analysis of data previously collected using the Simon Fraser University BMI dataset. The study received ethical approval from the Research Ethics Committee at Simon Fraser University, and the Vancouver Coastal Health Research Institute. Measurements were taken on individuals with chronic traumatic SCI (>1 year), who gave written informed consent, had no known pre-existing CVD, and were not taking any cardiovascular-related medications.

**Motor and sensory assessment**
Neurological classification was conducted according to the International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI) to determine American Spinal Injury Association (ASIA) Impairment Scale (AIS) severity and neurological level of injury (the last spinal cord segment with fully preserved sensory and motor function).

**Weight, Height, Waist Circumference, and Body Composition Measurements**
Weight (Wt) in kilograms was determined using a Dual Energy X-ray Absorptiometry (DEXA) whole body scan (QDR 4500, Hologic Inc., Bedford, MA, USA). Height (Ht) in metres was determined using an electronic ruler (Matlab 2012b, Math Works, MA, USA) on the DEXA images, as previously described. In cases where participants could not fully straighten their legs due to contractures or spasticity, self-reported height was used
(n=4). Waist circumference (WC) was measured in centimeters, using a stretch-resistant tensiometer measuring tape, at the narrowest part of the waist after a normal expiration, while lying supine on the DEXA scanner bed. Total body fat mass in kilograms and total body fat percentage, the latter computed as (total body fat mass / total mass) x 100, were determined using the whole body DEXA scan. Abdominal fat mass in kilograms was determined using standardized landmarks to distinguish the trunk region, and abdominal fat percentage was computed as (abdominal fat mass / total mass in the defined region) x 100.

**Fasting lipid plasma levels**

High-density lipoprotein cholesterol (HDL-C) and total cholesterol (TC) levels were assayed to compute Framingham Cardiovascular Disease Risk Scores (described below). Venous blood samples were collected following a 12-hour overnight fast (excluding water). Samples were centrifuged immediately at 3°C and 3,000 rpm for 10 minutes, and the plasma component was withdrawn for subsequent analysis. The plasma samples were sent to the clinical laboratory at Vancouver General Hospital where HDL-C and TC levels were determined by enzymatic assays (Dimension Vista system, Siemens Healthcare Diagnostics Inc., USA).

**Framingham 30-year risk for cardiovascular disease score**

We used the Framingham 30-year risk for CVD score as a measure of overall risk of CVD. This risk score incorporates the following risk factors: HDL-C; TC; age; gender; systolic arterial pressure (SAP) at rest; smoking status; diabetes; and antihypertensive treatments. However, instead of including the measured SAP, we entered a SAP value of 120 mmHg into the risk score formula for all participants. This decision was based on the fact that SCI can impair normal blood pressure control with lesions at or above the 5th thoracic level, leading to lower resting blood pressure. The known relationship between SAP and CVD risk, might, therefore, not exist in the same way in this population. Entering a value of 120mmHg is neutral to the score, and therefore excludes any effect of SAP on the generated risk score. As a sensitivity analysis, we re-ran the same analyses using the original Framingham scores, which included the measured SAP.
Statistics
R Statistical Software Version 2.15.3 was used for all analyses and creation of plots. For each value of ‘x’ ranging from 0.0–4.0, in increments of 0.1, the correlations between Wt/Ht\(^x\) and WC/Ht\(^x\) with total body fat percentage, absolute total body fat, abdominal fat percentage, absolute abdominal fat, and Framingham Risk Scores were computed and plotted, using Pearson’s correlation coefficient (r). We defined a ‘meaningful change’ with respect to the strength of a correlation as plus or minus 0.05 from the maximum correlation coefficient. Since there are already generally accepted standards in place for scaling of Wt/Ht\(^x\) and WC/Ht\(^x\), we wanted to only consider further evaluation of a new standard of measurement if there was a meaningful change.

Results
Participant Characteristics
A total of 27 subjects with traumatic SCI (mean age ± standard deviation: 40 ± 11 years; mean time since injury: 14 ± 10 years; 70% male) participated in this study. According to neurological levels, 59% had cervical injuries and 41% had thoracic injuries. The breakdown according to AIS severity was: 52% AIS A; 22% AIS B; 19% AIS C; and 7% AIS D.

Summary Statistics and Bivariable Relationships
Summary statistics (means, ranges, and measures of variability) for all study measures are provided in Table 4.1. Figure 4.1 shows the correlation between BMI (Wt/Ht\(^2\)) with each of: Framingham Risk Scores (A); absolute abdominal fat (B); and absolute total fat (C). Figure 4.2 shows the correlation between WC with each of: Framingham Risk Scores (A); absolute abdominal fat (B); and absolute total fat (C). Figure 4.1, Figure 4.2, and Table 4.2 reflect the ranges of BMI, WC, DEXA, and Framingham risk measurements captured in the sample, as well as the varying correlations between the standard measures (BMI and WC) with Framingham scores and fat measures (abdominal and total), discussed in more detail below.
Comparisons between $Wt/Ht^x$ and $WC/Ht^x$ for CVD Risk

Figure 4.3 shows correlations of $Wt/Ht^x$ at different scaling powers of ‘x’ ranging from 0 to 4, with each of: Framingham Risk Scores (A); absolute abdominal fat (B); and absolute total fat (C). Figure 4.4 shows correlations of $WC/Ht^x$ with these same measures. In Figure 3.3, when $x=2$, this is a typical BMI measurement; when $x=0$, this is the unscaled value for weight. With respect to $Wt/Ht^x$ and CVD risk, $Wt/Ht^x$ appears to be a poor predictor of CVD risk, regardless of the scaling power: the maximum correlation coefficient is $r=0.29$, and correlation coefficients are not statistically significant at all scaling powers (Figure 3.3A). In contrast, WC is more strongly and significantly correlated with CVD risk than $Wt/Ht^x$ (Figure 4.4A). More specifically, WC is most strongly correlated with CVD risk when uncorrected for height, i.e., when $x=0$, which is a commonly used standard; the maximum correlation coefficient is $r=0.66$ ($P<0.05$; Figure 4.4A). Moreover, the correlation coefficient is not “meaningfully different” when $x=1$, another standard scaling power.

Comparisons between $Wt/Ht^x$ and $WC/Ht^x$ for Obesity Measures

Both $Wt/Ht^x$ and $WC/Ht^x$ generally showed strong and statistically significant correlations with absolute measures of obesity (Figure 4.3B/C and Figure 4.4B/C, respectively). The maximum correlations with $Wt/Ht^x$ for absolute abdominal fat and absolute total fat mass occurred at $r=0.92$ and $r=0.91$, at values of $x=1.3$ and $x=1.5$, respectively (Figure 4.3B/C). However, these maximum correlations were not meaningfully different than those obtained using the standard value of $x=2$. Thus, a typical BMI measurement remains a strong predictor of obesity.

The maximum correlations with $WC/Ht^x$ for absolute abdominal fat and absolute total fat mass occurred at $r=0.82$ and $r=0.73$, at values of $x=0.60$ and $x=0.80$, respectively (Figure 4.4B/C). However, these maximum correlations were not significantly different compared to those at a value of $x=0$ or $x=1$ (standard scaling powers). Thus, typical WC and WHtR measurements remain strong predictors of obesity.

Table 4.2 summarizes the maximum correlations for the absolute obesity measures, and
also shows the maximum correlations for abdominal fat and total body fat percentages. As seen in the table, scaling of WC and Wt yielded stronger correlations with absolute body fat measures versus percentages. There was no meaningful benefit to the optimized scaling power for any of the variables tested (Table 4.2).

**Multivariable Analyses**

As a follow-up analysis, we also performed multivariable regression with both WC and BMI as explanatory variables (covariates). These results were consistent with the bivariable results in that only WC/Ht\(^2\) measures were significant components of the model in relation to CVD risk, but both measures of WC/Ht\(^2\) and Wt/Ht\(^2\) were important in models for obesity. However, due to the limited sample size, the confidence intervals for the effect sizes were wide (results not shown).

**Sensitivity Analyses**

We used a neutral value for SAP when calculating the Framingham risk score because of the known impact of high level SCI upon blood pressure control, whereby those with the most severe cardiovascular dysfunction tend to have lower resting blood pressure, contrary to the case in the able-bodied. As a sensitivity analysis, we re-ran our analyses using the original Framingham scores, which included the measured SAP; the overall findings were the same as reported here (results not shown). Further, the majority of our participants were male; therefore, we performed an additional sensitivity analysis excluding females from the analytic sample. This also did not affect our findings (results not shown).
Figure 4.1. Bivariable relationships for BMI. Correlation between BMI (Wt/Ht^2) with each of: Framingham Risk Scores (A); absolute abdominal fat (B); and absolute total fat (C).
Figure 4.2. Bivariable relationships for WC. Correlation between WC with each of: Framingham Risk Scores (A); absolute abdominal fat (B); and absolute total fat (C).
Figure 4.3. Correlations of Wt/Ht\(^x\). Correlations at different scaling powers of x ranging from 0 to 4, with each of: Framingham Risk Scores (A), absolute abdominal fat (B), and absolute total fat (C). The correlation coefficient at each value of x is indicated with overlapping open circles. The maximum correlation is indicated with a black line; dashed lines indicate the maximum correlation plus or minus 0.05, the limits of “meaningful change”. The red line indicates the point above which the correlation coefficient is statistically significant (P<0.05).
Figure 4.4. Correlations of WC/ht$^x$. Correlations at different scaling powers of x ranging from 0 to 4, with each of: Framingham Risk Scores (A), absolute abdominal fat (B), and absolute total fat (C). The correlation coefficient at each value of x is indicated with overlapping open circles. The maximum correlation is indicated with a black line; dashed lines indicate the maximum correlation plus or minus 0.05, the limits of “meaningful change”. The red line indicates the point above which the correlation coefficient is statistically significant (P<0.05).
<table>
<thead>
<tr>
<th>Variable</th>
<th>Range [maximum, minimum]</th>
<th>Mean</th>
<th>Standard Deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI (Wt/Ht²; kg/m²)</td>
<td>[15.6, 34.8]</td>
<td>23.4</td>
<td>4.4</td>
</tr>
<tr>
<td>WC (cm)</td>
<td>[68, 111]</td>
<td>87.4</td>
<td>11.7</td>
</tr>
<tr>
<td>Framingham Risk Score</td>
<td>[2, 29]</td>
<td>15.0</td>
<td>8.3</td>
</tr>
<tr>
<td>Abdominal Body Fat (kg)</td>
<td>[2.93, 18.23]</td>
<td>9.93</td>
<td>4.54</td>
</tr>
<tr>
<td>Total Body Fat (kg)</td>
<td>[7.14, 38.71]</td>
<td>20.32</td>
<td>8.16</td>
</tr>
</tbody>
</table>

Table 4.1. Summary Statistics for Study Measures.
Table 4.2. Correlations at optimal scaling powers. Correlations at optimal scaling powers are shown, for different combinations of dependent and independent variables. There was no meaningful benefit to the optimized scaling power for any of the variables tested.

<table>
<thead>
<tr>
<th>Independent Variable</th>
<th>Dependent Variable</th>
<th>Correlation at Optimal Scaling Power</th>
<th>Meaningful Benefit to Optimized Scaling</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Wt/Ht</strong></td>
<td>Abdominal Body Fat (kg)</td>
<td>0.92</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Total Body Fat (kg)</td>
<td>0.91</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Abdominal Body Fat (%)</td>
<td>0.80</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Total Body Fat (%)</td>
<td>0.77</td>
<td>No</td>
</tr>
<tr>
<td><strong>WC/Ht</strong></td>
<td>Abdominal Body Fat (kg)</td>
<td>0.82</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Total Body Fat (kg)</td>
<td>0.73</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Abdominal Body Fat (%)</td>
<td>0.76</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Total Body Fat (%)</td>
<td>0.70</td>
<td>No</td>
</tr>
</tbody>
</table>
**Discussion**

In this study, we aimed to evaluate whether alternate scaling powers for height might improve the relationships between WC/Ht and Wt/Ht with indices of obesity or CVD risk in individuals with SCI. Overall, we conclude that these standard measures were not improved by employing alternate scaling factors, and we reaffirm WC as a more valid and practical measure for obesity-related CVD risk in the SCI population. More specifically, our findings indicate that BMI is a poor predictor of CVD risk, regardless of the scaling factor. However, BMI is a useful measure of obesity. Conversely, we showed that WC and WHtR are strong predictors of both CVD risk and obesity.

Given the strong relationships between BMI and adiposity measures (abdominal and total body fat) after SCI, it is perhaps surprising that BMI is not a strong predictor of obesity-related CVD risk in this population. This may be because, despite being correlated with abdominal fat, BMI does not have the ability to differentiate between subcutaneous and visceral fat, the latter of which is thought to be the main contributor to CVD risk. Indeed, the Framingham risk score incorporates measures of dyslipidemia, diabetes and blood pressure, all of which are influenced more by visceral adiposity than abdominal or total body fat. As WC is reported to better reflect visceral adiposity than BMI, perhaps this explains why the risk score was better correlated with WC than with BMI. After SCI there is increased visceral fat for a given weight compared to the able-bodied. In addition, SCI-specific changes below the lesion level, such as a reduced muscle mass, differentially affect BMI and WC, and thus the corresponding relationships with adiposity and CVD risk.

In the general population, Heo *et al.* found the optimal scaling (for BMI) was x=1.0 in men and x=0.8 in women for maximal correlation with absolute total body fat. They also found the optimal scaling for WC was zero i.e., no scaling for height. Their findings with respect to BMI are quite different to the results of the present study, in which we found no meaningful benefit to scaling BMI from the standard x=2; this may reflect the unique anthropometric alterations that occur after SCI. In addition, the alternate scaling powers suggested by Heo *et al.* may not reflect a ‘meaningful change’
from standard measures as we have described here.

Unfortunately, no prior studies have examined the differences in able-bodied populations with respect to absolute versus body fat percentages in relation to scaling powers for Wt and WC. This might be of interest given our results in which stronger correlations were obtained with absolute than percentage fat data.

Given that obesity is associated with increased morbidity and mortality, the present findings may reinforce the need for accurate proxy anthropometric measures for adiposity and CVD risk. The development of obesity and CVD risk classification criteria based on optimal Wt/Ht indices and WC/Ht indices stratified for subgroups, such as individuals with SCI, will provide a more accurate assessment of the true burden of obesity. As such, we will be able to better understand the implications for obesity-related morbidity and mortality among these individuals. Furthermore, having accurate estimates for obesity and obesity-related CVD risk is an important consideration for statistical regression models where BMI and WC might be used to control for confounding, as in the CCHS studies below.

Study Limitations
The main limitation of this study is the relatively small sample size in this population, which limits the generalizability of these findings. With this limitation in mind, we were not able to differentiate optimal scaling powers for specific age categories, sexes, neurological levels of SCI, and completeness of injury. We did, however, perform a sensitivity analysis excluding females from the analytic sample; this did not affect the overall results of the study. We also interpret the results of our multivariable models cautiously in light of the limited sample size. In addition, due to the limited power, we were not able to statistically compare correlation coefficients at different values of ‘x’, and instead used a criterion of 0.05 for a “meaningful change”. These issues will be important to address in larger studies in the future.

Finally, the Framingham 30-year risk for CVD risk score was not designed or validated
for use in an SCI population, but rather for the population as a whole, which may include individuals with many comorbidities. It is possible that some aspects of the risk score, most notably the resting blood pressure, should be modified for use in SCI where those with the most severe cardiovascular dysfunction tend to have lower resting blood pressure,\textsuperscript{98} in contrast to the norm. Accordingly, we conducted our analyses using both a neutral blood pressure, and the participant’s actual blood pressure; our findings were unchanged. Therefore, regardless of how the risk score is utilized, we are confident that at least in this small cohort there was no benefit to CVD risk prediction with the use of alternate scaling measures for obesity. Ideally, a larger prospective study could assess these correlations with ‘actual’ outcomes (eg. clinical diagnosis of heart disease, stroke, MI) in this population.
CHAPTER 5: ASSOCIATION BETWEEN SCI AND SECONDARY COMPLICATIONS

5.1 Introduction and Background
To begin testing our conceptual model (Figure 1.1 above), we first examined the risk of several secondary complications following SCI: CVD (Objective 1A), Type 2 diabetes (Objective 1B), respiratory conditions (Objective 1C), and chronic pain (Objective 1D). These specific conditions were chosen as they also occur in able-bodied individuals (thus their prevalence can be compared with a control group), and also based on biological plausibility for an increased risk as discussed in the introduction section and in more detail below. We hypothesized that SCI results in a direct increased risk of secondary complications, i.e., SCI is an independent risk factor for these conditions.

Cardiovascular Complications
Over the last decade, there have been marked changes in the trends of morbidity and mortality among individuals with SCI. With advances in acute care and in the management of septicaemia and renal failure, cardiovascular complications are now the leading cause of death in those with SCI.\textsuperscript{20, 21} Moreover, we have previously discussed several risk factors for these conditions that are amplified in individuals with SCI compared with able-bodied individuals, including physical inactivity, dyslipidemia, blood pressure irregularities, chronic inflammation, and abnormal glycemic control.\textsuperscript{35, 58, 102-120}

While most of the literature with respect to CVD and SCI has shown a higher prevalence of risk factors for CVD,\textsuperscript{35, 58, 102-120} relatively few studies have examined the prevalence of CVD itself and corresponding risk estimates.\textsuperscript{121-124} None of these studies have provided direct comparisons of risk estimates for CVD outcomes in the SCI population compared to a non-SCI population, with appropriate adjustment for confounding.

Further, there has been controversy over whether or not individuals with SCI are actually at an increased risk of CVD as some consequences of SCI, such as resting hypotension, are at odds with an increased risk of CVD. Hypertension is a well-known risk factor for CVD, yet individuals with SCI, particularly higher lesions (eg. cervical injuries), tend to
have lower resting blood pressure. As an example of this controversy, a 2008 report issued by the federal Agency for Healthcare Research and Quality concluded that “existing evidence does not indicate that adults with SCIs are at markedly greater risk for carbohydrate and lipid disorders or subsequent cardiovascular morbidity and mortality than able-bodied adults.”

**Metabolic Complications**

With respect to metabolic complications, a few studies have also shown or suggested an increased prevalence of Type 2 diabetes among individuals with both traumatic and non-traumatic SCI. However, these studies are generally based on small, underpowered, and/or non-generalizable convenience samples; they lack appropriate controls and proper adjustment for confounding. It thus remains uncertain if there is excess risk of diabetes after appropriate adjustment for potential confounders in individuals with SCI. An excess risk of diabetes may contribute, at least in part, to the increased risk of stroke, heart disease, and kidney disease seen following SCI.

**Respiratory Complications**

In addition to Type 2 diabetes and CVD, individuals with SCI may be at an increased risk of chronic respiratory conditions. Paresis or paralysis of the respiratory muscles can lead to respiratory insufficiency, which has a major impact on cough effectiveness and susceptibility to infection. Prior studies have typically focused on breathing mechanics as well as pneumonia in the acute stages of SCI, but there is a dearth of evidence with regards to secondary chronic conditions, such as asthma and COPD among SCI populations.

In the general population, risk factors for the development of asthma and COPD include genetic, sociodemographic (sex, age), and environmental components (including smoking), as well as gene-by-environment interactions. In addition, exposure to air pollutants such as traffic pollution, occupational exposures, and indoor exposure to pollutants such as mold, increase susceptibility to both diseases. Lastly, asthma itself is a risk factor for the development of COPD. However, that SCI may be an independent risk
factor for COPD and asthma has not been previously examined. It thus remains unknown if there is excess risk of chronic respiratory diseases (after adjustment for potential confounders) in individuals with SCI.

*Chronic Pain Conditions*

An important step towards improving treatment outcomes, the International Classification of SCI pain (ICSCIP) was recently developed, principally differentiating neuropathic and nociceptive pain. Among nociceptive pain, an “other” category specifically includes migraine headaches, which are considered “unrelated to SCI” according to ICSCIP.

With an estimated prevalence of 11% among the general population in Western countries, migraines are characterized by nausea, sensitivity to light and noise, and visual auras, in addition to intensely painful headaches. Previously well-established risk factors for migraine headaches include family history, sex, and age. Somewhat more controversial, social and psychological (e.g., anxiety and mood disorders) variables have also been implicated as potential risk factors. That SCI may be an independent risk factor for migraine has not been previously studied. Indeed, supraspinal changes in addition to changes in cerebrovasculature as a result of injury could potentially result in an excess risk. Moreover, increasing evidence suggests that migraine may be a form of neuropathic pain.

*Study Objectives*

Overall, we hypothesized that there is an excess risk of heart disease, stroke, Type 2 diabetes, chronic pain (migraine) and chronic respiratory disease (after adjustment for potential confounders) in individuals with chronic SCI. The current study addresses this hypothesis by utilizing the national Canadian Community Health Survey, which is comprised of comprehensive, up-to-date cross-sectional data. Our aim was to estimate the prevalence of these outcomes in the SCI population, to compare their risk with a non-SCI population, and to investigate this relationship after controlling for confounders.
5.2 Methods

Data Source

This study utilized data from the Canadian Community Health Survey (CCHS) 2010 Annual Component. The CCHS is a comprehensive national cross-sectional survey conducted by Statistics Canada. It provides data obtained by trained interviewers on individuals aged 12 and over, residing in households in all the provinces and territories. Those living on reserves or Crown lands, full-time members of the Canadian armed forces, and those living in institutions (prisons, hospitals, universities) are excluded from the survey. The CCHS includes data on a range of topics, including access to health care services, health care utilization, lifestyle behaviours, socio-demographic information, and health status. Statistics Canada utilizes a multistage, stratified cluster sampling design, more details of which are provided elsewhere. Ethical approval for the use of the data was obtained via the publicly available data clause from the University of British Columbia, in accordance with the Tri-Council Policy Statement.

Exposure and Outcomes

The primary explanatory (exposure) variable in this analysis was self-reported SCI. SCI status was obtained with the following question: “Do you have a neurological condition caused by a spinal cord injury?” There were six outcome variables of interest: stroke, heart disease, Type 2 diabetes, COPD, asthma, and migraine.

Stroke status was obtained with the following question: “Do you suffer from the effects of a stroke?” Heart disease status was obtained with the following question: “Do you have heart disease?” An individual could respond “yes” to both questions asking about heart disease and stroke. Diabetes status was obtained with the following question: “Do you have diabetes?” If the respondent answered “yes” to this question, they were asked the following: “How old were you when this was first diagnosed?”, “Were you pregnant when you were first diagnosed with diabetes?”, “Other than during pregnancy, has a health professional ever told you that you have diabetes?”, “When you were first diagnosed with diabetes, how long was it before you were started on insulin?”, “Do you currently take insulin for your diabetes?”, and “In the past month, did you take pills to control your blood sugar?” Based on the response to these diabetes-related questions,
using the Ng-Dasgupta-Johnson algorithm, Statistics Canada provides a derived variable for diabetes type: Type 1 diabetes, Type 2 diabetes, and gestational diabetes, based on the following sequential steps:

**STEP 1**
Target population: Respondents who replied “yes” to having diabetes. These respondents constitute the diabetes cohort. Those who did not know, refused to answer or did not respond were excluded.

**STEP 2**
Gestational diabetes: If the respondents were women who said that they had not been diagnosed with diabetes at any time other than when they were pregnant and the age of diagnosis was 15 to 49 (childbearing age range), they were considered to be cases of gestational diabetes. Screening forward: Respondents in the diabetes cohort not asked this question (males; females younger than 15), women who reported being diagnosed with diabetes during pregnancy and at another time, and those who did not answer were moved forward.

**STEP 3**
If respondents reported taking an oral medication, they were assigned type 2 diabetes. Screening forward: If the response was “no,” “not applicable,” “don’t know” or “not stated,” they were moved forward.

**STEP 4**
If the respondents were not currently taking insulin, they were assigned type 2 diabetes. Screening forward: If the response was “yes,” “not applicable” or “don’t know,” they were moved forward.

**STEP 5**
If the respondents were younger than 30 and began taking insulin within 6 months of being diagnosed, they were assigned type 1 diabetes. Screening forward: If the respondents were 30 or older or began taking insulin 6 or more months after being diagnosed, they were moved forward.

**STEP 6**
If the respondents’ age of diagnosis was younger than 30 and they began taking insulin within 6 months of being diagnosed, they were assigned type 1 diabetes. Screening forward: If the respondents’ age of diagnosis was 30 or older or if they did not know or refused to answer this question, or if they had started taking insulin more than 6 months after being diagnosed, they were moved forward.

**STEP 7**
All the remaining respondents were assigned type 2 diabetes, regardless of when they started taking insulin.

Since Type 2 diabetes was the outcome variable of interest, those with Type 1 diabetes and gestational diabetes were excluded from the analysis.

Asthma status was obtained with the following questions: “Do you have asthma?”; “Have
you had any asthma symptoms or asthma attacks in the past 12 months?”; “In the past 12 months, have you taken any medicine for asthma such as inhalers, nebulizers, pills, liquids, or injections?” COPD status was obtained with the following question: do you have chronic bronchitis, emphysema, or chronic obstructive pulmonary disease (or COPD)?” Questions regarding medication use were not available for the COPD variable. Migraine headache status (as a measure of chronic pain) was determined using the question: “Do you have migraine headaches?”

During the survey, individuals were given the following reminder: “Remember, we’re interested in conditions diagnosed by a health professional.” Only those with valid responses for the primary explanatory variable and outcome variables were included in the analysis. Non-respondents (those in the categories of “don’t know”, “refusal”, and “not stated”) were excluded.

**Confounding and Interaction: Definitions and Variable Selection**

Confounding was assessed both from a theoretical (i.e., causal) perspective based on previous studies as well as a statistical perspective (i.e., in examining changes in effect sizes in the presence/absence of possible confounders). We used the commonly accepted definition of confounding: a factor ‘x’ is a confounder if factor x is a known risk factor for the outcome/disease (in this case, heart disease, stroke, Type 2 diabetes, asthma/COPD, or migraine), and factor x is associated with the primary explanatory variable (in this case, SCI), but is not a result of the primary explanatory variable. Thus, factors which are associated only with the outcomes but not SCI, factors which are associated only with SCI but not the outcomes of interest, or factors which are the result of SCI that might lead to the outcomes, did not meet the criteria for confounding, and are not adjusted for in the final analysis. However, since some variables are debatable as to whether they meet all of the criteria for confounding, sensitivity analyses were performed where possible to examine the effect of additional self-report covariates on the reported effect sizes.

Risk factors for traumatic SCI include younger age and male sex. Risk factors for non-
traumatic SCI are more difficult to examine, as non-traumatic SCI includes tumours, congenital/developmental (e.g. spina bifida), infectious (viral, bacterial, fungal, parasitic), inflammatory (e.g. multiple sclerosis), and ischaemic causes, as well as several others. However, sex and age are well-known risk factors for the majority of non-traumatic SCIs. Risk factors for CVD have been well documented in the Framingham study, which identified the following risk factors and used these to calculate a 10-year absolute risk of sex-specific general CVD: age, diabetes, total cholesterol, high-density lipoprotein cholesterol, systolic blood pressure, and smoking status. The recent Canadian global INTERHEART study identified similar risk factors for myocardial infarction, including dyslipidemia, smoking status, diabetes, hypertension, abdominal obesity, stress, lack of daily consumption of fruits and vegetables, and lack of daily exercise, in more than 37,000 individuals from 55 different countries and cultural environments. Similar risk factors have been documented for Type 2 diabetes. In the general population, risk factors for the development of asthma and COPD include genetic, sociodemographic (sex, age), and environmental components (including smoking), as well as gene-by-environment interactions. In addition, exposure to air pollutants such as traffic pollution, occupational exposures, and indoor exposure to pollutants such as mold, increase susceptibility to both diseases. Sex and age were thus selected a priori as possible confounders for all analyses, with additional variables selected for sensitivity analyses (described in more detail below).

In addition to assessing confounding, interaction terms were also assessed in the multivariable models. Interaction terms were initially formed based on biological plausibility and were also assessed for their statistical significance in sensitivity analyses (using AIC criterion), using the primary exposures along with the other covariates (discussed above) to form interaction terms added to the multivariable models.

Statistical Analyses
Logistic regression models were obtained separately for the binary outcomes (yes/no) with SCI as the main explanatory variable. Both bivariable and multivariable logistic regression models were developed. Multivariable logistic models also included age and
sex. Logistic models were evaluated with empirical probability plots, partial residual plots, and local mean deviance plots. Using the results from the logistic models, both unadjusted and adjusted odds ratios (ORs), with corresponding 95% confidence intervals, are presented. The CCHS sampling design (clustering and stratification) was accounted for in the analyses using probability weighting. Probability weights were obtained by dividing the frequency weights provided by Statistics Canada (these correspond to the number of persons represented by the individual) by the average frequency weight for the given sample. Reported percentages and ORs are weighted. SAS statistical software (SAS Institute, Cary, NC, USA, Version 9.3) was used for all analyses.

5.3 Results

SCI and Cardiovascular Disease

Study Sample

After excluding those with invalid responses for the primary explanatory and outcome variables, the final study sample included 60,959 individuals for the SCI/heart disease analysis and 61,031 individuals with a valid response for the SCI/stroke analysis (Table 4.1). There was a similar proportion of males and females (Table 5.1) in both analytic samples. The median age category for both analytic samples is also shown in Table 5.1.

There were a total of 354 unique individuals with SCI who had a valid response to the heart disease question and 356 unique individuals with SCI who had a valid response to the stroke question (Table 5.1). This yielded a prevalence of 0.49% for SCI in both analytic samples (Table 5.1). Among the individuals with SCI, there was a higher proportion of males versus females (Table 5.2). The age distribution for those with SCI is also shown in Table 5.2, with the highest prevalence among the 50-54 year age group.

Among the entire samples, the prevalence of stroke and heart disease was 1.1% and 5.0%, respectively. The prevalence of individuals with both stroke and heart disease was 0.38%. The proportion of males with stroke was higher than that of females with stroke (Table 5.1). Similarly, the proportion of males with heart disease was higher than that of females with heart disease (Table 5.1). The median age category for individuals with stroke and
heart disease was higher than those without (Table 5.1). The proportion of individuals with stroke and heart disease steadily increased with age, with 75% of strokes and 72% of heart disease cases accounted for by individuals greater than 60 years of age.

**SCI and Cardiovascular Disease**

Among individuals with SCI, the prevalence of self-reported stroke was 5.7% compared to 1.1% in individuals without SCI. Similarly, among those with SCI, the prevalence of heart disease was 17.1%, compared to 4.9% in individuals without SCI. Thus, the prevalence of stroke and heart disease was higher amongst individuals with SCI compared to those without.

**Odds ratios: SCI and Heart Disease**

Table 5.3 provides unadjusted and adjusted ORs for heart disease. The odds of heart disease was 4.01 times greater in individuals with SCI versus individuals without SCI (95% CI 2.96, 5.44). After adjusting for sex and age, the heightened odds persisted but was reduced; the fully adjusted OR for heart disease was 2.72 (95% CI 1.94, 3.82), suggesting confounding by sex and age. In examining the adjusted ORs from the model adjusted for sex only, and the model adjusted for age only, it appears that both age and sex were important confounders (results not shown).

**Odds ratios: SCI and Stroke**

Table 5.3 also provides unadjusted and adjusted ORs for stroke. The odds of stroke was 5.68 times greater in individuals with SCI versus individuals without SCI (95% CI 3.46, 9.32). After adjusting for sex and age, the OR for stroke was 3.72 (95% CI 2.22, 6.23), suggesting confounding by sex and age. In comparing the adjusted ORs from the model adjusted for sex only, versus the model adjusted for age only, it appears that age was a more important confounder (results not shown).
**Non-respondents**

For the SCI/heart disease analysis, 1950 individuals were excluded based on non-response; for the SCI/stroke analysis, 1878 individuals were excluded based on non-response. Since sex and age were collected on all participants regardless of their response to the SCI/CVD questions, both sex and age of the non-responders were examined. The sex distribution of non-responders (52.0% male; 48.0% female) showed a slightly higher proportion of males than in the responders. The median age category for non-responders was the same for responders (40-44 years). Moreover, when using non-response as a separate response category (for exposures) in the multivariable analysis, the reported effects sizes for the primary exposure (SCI) did not differ significantly.

**Sensitivity Analyses**

Variables such as smoking, obesity, hypertension, physical inactivity, lack of consumption of fruits and vegetables, alcohol consumption, and diabetes status were examined in the multivariable models. Although it is debatable if these variables meet the criteria for confounding, due to the nature of these composite variables, we wanted to examine the robustness of our results to their inclusion in the models. The inclusion of each of these variables did not significantly change the estimated ORs adjusted for sex and age only (for either stroke or heart disease). With stepwise-inclusion of these additional variables into the regression models, the adjusted ORs for heart disease ranged from 2.63 to 3.10, all remaining statistically significant. Likewise, the ORs for stroke ranged from 3.35 to 3.82, all remaining statistically significant. Thus, these covariates were likely not confounding factors. With respect to interaction terms, none significantly improved the multivariable models, and thus were not included in the final reported models.
SCI and Type 2 Diabetes

Study Sample
After excluding those with invalid responses for the primary explanatory and outcome variables, and those with gestational diabetes (n=9) and Type 1 diabetes (n=145), the final study sample included 60,678 individuals for the SCI/diabetes analysis. There was a similar proportion of males and females in the total sample; the median age category for the entire sample is also shown (Table 5.4). Among the entire sample, the prevalence of Type 2 diabetes was 5.94%. The proportion of males with Type 2 diabetes was higher than that of females; the median age category for individuals with Type 2 diabetes was higher than those without (Table 5.4).

SCI and Type 2 Diabetes
There were a total of 353 individuals with SCI; this yielded a prevalence of 0.49% for SCI in the overall sample. Among individuals with SCI, the prevalence of Type 2 diabetes was 13.66% compared to 5.91% in individuals without SCI. Type 2 diabetes tended to occur at younger ages among those with SCI versus those without (Figure 4.1). Table 5.5 provides unadjusted and adjusted ORs for Type 2 diabetes. The odds of Type 2 diabetes was 2.52 times greater in individuals with SCI versus individuals without SCI (95% CI 1.81, 3.52). After adjusting for sex and age, the heightened odds persisted but was reduced; the age/sex adjusted OR for Type 2 diabetes was 1.66 (95% CI 1.16, 2.36), suggesting confounding by sex and age.

Sensitivity Analyses
We also examined the effect of additional risk factors for Type 2 diabetes on the previously reported effect sizes. Table 5.5 provides ORs which are adjusted for age, sex, and BMI (AOR2), as well as an OR adjusted for age, sex, smoking status, hypertension status, body mass index, daily physical activity, daily alcohol intake, and daily consumption of fruits and vegetables (AOR3). The OR adjusted for BMI in addition to sex and age (AOR2) did not differ significantly from the OR adjusted for sex and age only (AOR1), which confirmed our findings related to BMI from our methods chapter.
(Chapter 3 above). The OR adjusted for all potential confounders (AOR3) was similar in magnitude to the unadjusted OR. In sum, regardless of the variables included in the models, all ORs indicated an approximately 2-fold increased odds.

Non-respondents
A total of 2080 individuals were excluded based on non-response. Since sex and age were collected on all participants regardless of their response to the SCI/diabetes questions, both sex and age of the non-responders were examined. The sex distribution of non-responders (50.62% male; 49.38% female) showed a similar sex distribution as in the responders (49.29% male; 50.71% female). The median age category for non-responders was the same for responders (40-44 years).

SCI and Respiratory Diseases
Study Sample
After excluding those with invalid responses for the primary explanatory and outcome variables, the final study sample included 61,049 individuals for the SCI/asthma analysis and 61,010 individuals with a valid response for the SCI/COPD analysis (Table 5.6). There was a similar proportion of males and females (Table 5.6) in both analytic samples. The median age category for both analytic samples is also shown in Table 5.6. There were a total of 356 unique individuals with SCI who had a valid response to the asthma question and 354 unique individuals with SCI who had a valid response to the COPD question (Table 5.6). Among the entire samples, the (weighted) prevalence of asthma and COPD were 8.46% and 2.77%, respectively (and 0.95% for both asthma and COPD). Among individuals with SCI, the prevalence of COPD was 7.84% compared to 2.74% in individuals without SCI. Similarly, among those with SCI, the prevalence of asthma was 12.02% compared to 8.44% in individuals without SCI. Thus, the prevalence of both COPD and asthma was higher amongst individuals with SCI compared to those without.

Odds ratios: SCI and COPD
Table 5.7 provides unadjusted and adjusted ORs for COPD. The odds of COPD was 3.02
times greater in individuals with SCI versus individuals without SCI (95% CI 1.97, 4.62). After adjusting for sex, and age, and smoking status, the heightened odds persisted but was reduced; the fully adjusted OR for COPD was 1.88 (95% CI 1.20, 2.92).

**Odds ratios: SCI and Asthma**

Table 5.8 provides unadjusted and adjusted ORs for asthma. The odds of asthma was 1.48 times greater in individuals with SCI versus individuals without SCI (95% CI 1.05, 2.11). After adjusting for sex, age and smoking status, the OR for asthma was 1.59 (95% CI 1.12, 2.27).

**Odds ratios: SCI and Recent Asthma**

Since we saw an increased odds of asthma among individuals with SCI, we also wanted to examine if there was an increased odds of recent asthma among individuals with SCI. To this end, we examined 1) whether or not individuals had shown symptoms of asthma in the last year, and 2) whether or not individuals had taken medications for asthma in the last year. Table 5.9 provides unadjusted and adjusted ORs for recent asthma (based on symptoms). The odds of recent asthma was 1.88 times greater in individuals with SCI versus individuals without SCI (95% CI 1.24, 2.85). After adjusting for sex, age and smoking status, the OR for recent asthma was 2.03 (95% CI 1.34, 3.08). Table 5.9 also provides unadjusted and adjusted ORs for recent asthma (based on medications). The odds of recent asthma was 1.69 times greater in individuals with SCI versus individuals without SCI (95% CI 1.16, 2.47). After adjusting for sex, age and smoking status, the OR for recent asthma was 1.76 (95% CI 1.21, 2.57).

**Non-respondents**

Since sex and age were collected on all participants regardless of their response to the SCI/respiratory questions, both sex and age of the non-responders were examined. The sex distribution of non-responders (45.5% male; 56.5% female) showed a slightly higher proportion of females than in the responders. The median age category for non-responders was also slightly higher than the responders (50-54 years).
SCI and Chronic pain (migraine)

Study Sample
The total study sample (n=61,047) for the SCI/migraine analysis was equally distributed across males (49.3%) and females (50.8%). It was approximately equally divided across age groupings, with a lower number of respondents in the younger (below 19 years of age) and older (above 60 years of age) categories.

The prevalence of migraine headache in the final study sample was 10.0%. As predicted, migraine headache prevalence was unequally distributed among sexes, with a higher prevalence in females. Migraine headache prevalence also increased in the categories between 30-49 years of age. The prevalence of SCI was 0.49%.

SCI and Migraine
The prevalence of migraine was higher in the population with SCI (28.9%) than in those without SCI (9.9%). Correspondingly, the unadjusted logistic regression model revealed that the odds of migraine headache was 3.69 (2.40, 5.68) times higher in those with SCI than in those without (Table 5.10). In the multivariable model, the adjustment for age and sex strengthened the results (Table 5.10): the adjusted odds ratio for migraine headache was 4.82 (3.02, 7.67) among those with SCI.

SCI, Migraine, and Perceived General Health
As an indicator of quality of life, we next examined whether individuals with migraine and SCI experienced differences in self-perception of general health versus individuals with migraine only, individuals with SCI only, and individuals who suffer from neither condition. The results in Table 5.11 demonstrate that individuals who reported SCI and migraine tended to report poorer perceived health compared with the other groups.

Sensitivity Analysis
Prior to the statistical analyses, variables including smoking, high blood pressure, heart disease, stroke, smoking and SES were excluded from the main model as it was not clear whether or not they satisfied the criteria of a confounder. A sensitivity analysis was
conducted in order to investigate the potential effects of these variables on the relationship between migraine headache and SCI and to test the robustness of our results. The addition of these variables in the multivariable model did not significantly affect the adjusted OR for migraine headache, as it went from 4.82 (3.02, 7.67) to 4.43 (2.77, 7.10).

Non-respondents
A total of 1,862 individuals were excluded from the main analysis due to invalid answers (don’t know, refusal, or not stated) to the questions regarding SCI and migraine headache status. The sex of the non-respondents (52.12% male, 47.88% female) was similar to that of the study sample (49.25% male, 50.75% female). Both the study sample and the non-respondent group had the same median age of 40-49 years old.
<table>
<thead>
<tr>
<th>Variable</th>
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<th>Stroke (%)</th>
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<th>No Heart</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>(%)</td>
<td>n (%)</td>
<td>(%)</td>
<td>Disease (%)</td>
<td>(%)</td>
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<tr>
<td></td>
<td>N=61,031</td>
<td>N=60,959</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spinal Cord Injury</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
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<td>99.5</td>
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<td>98.3</td>
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<td>Sex</td>
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<td></td>
<td></td>
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</tr>
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<td>Male</td>
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<td>49.2</td>
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<td>48.7</td>
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<td>Female</td>
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<td>50.8</td>
<td>33345 (50.8)</td>
<td>40.9</td>
<td>51.3</td>
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<tr>
<td>Median Age Category (years)</td>
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<td>65-69</td>
<td>40-44</td>
<td>65-69</td>
<td>40-44</td>
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</tr>
</tbody>
</table>

**Table 5.1. Characteristics of the two analytic samples:** sample sizes and percentages. All percentages are probability weighted to account for the Canadian Community Health Survey sampling design. Column percentages are shown.
<table>
<thead>
<tr>
<th>Variable</th>
<th>Total N (%)</th>
<th>SCI (%)</th>
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<tr>
<td>12-14</td>
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<td>15-17</td>
<td>2624 (4.2)</td>
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<td>18-19</td>
<td>1733 (3.0)</td>
<td>1.1</td>
<td>3.0</td>
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<tr>
<td>20-24</td>
<td>3495 (8.2)</td>
<td>4.3</td>
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<td>25-29</td>
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<td>7.3</td>
</tr>
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<td>4.2</td>
<td>7.7</td>
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<td>5380 (6.6)</td>
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<td>65-69</td>
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<td>6.3</td>
<td>5.2</td>
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<td>80+</td>
<td>3961 (3.6)</td>
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<td>3.6</td>
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<td><strong>Sex</strong></td>
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<tr>
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<td>27649 (49.3)</td>
<td>59.6</td>
<td>49.2</td>
</tr>
<tr>
<td>Female</td>
<td>33382 (50.8)</td>
<td>40.5</td>
<td>50.8</td>
</tr>
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</table>

Table 5.2. Sample sizes and probability weighted estimates by SCI status. SCI= spinal cord injury. Column percentages are shown.
Odds ratios derived from logistic regression models. Both unadjusted and adjusted odds ratios (adjusted for both sex and age) are reported.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Unadjusted OR Heart Disease (95% CI)</th>
<th>Adjusted OR Heart Disease (95% CI)</th>
<th>Unadjusted OR Stroke (95% CI)</th>
<th>Adjusted OR Stroke (95% CI)</th>
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<td>Spinal Cord Injury</td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Yes</td>
<td>4.01 (2.96, 5.44)</td>
<td>2.72 (1.94, 3.82)</td>
<td>5.68 (3.46, 9.32)</td>
<td>3.72 (2.22, 6.23)</td>
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<td>No‡</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1.52 (1.41, 1.64)</td>
<td>1.86 (1.72, 2.01)</td>
<td>1.11 (0.95, 1.30)</td>
<td>1.29 (1.10, 1.50)</td>
</tr>
<tr>
<td>Female§</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Age*</td>
<td>1.49 (1.47, 1.51)</td>
<td>1.51 (1.48, 1.53)</td>
<td>1.49 (1.45, 1.53)</td>
<td>1.49 (1.45, 1.54)</td>
</tr>
</tbody>
</table>

Table 5.3. Odds Ratios (95% Confidence Intervals) for heart disease and stroke (probability weighted). Odds ratios derived from logistic regression models. Both unadjusted and adjusted odds ratios (adjusted for both sex and age) are reported. ‡ Reference Category; CI=confidence interval. *ORs shown are the effect for one category increase (5 year groupings).
<table>
<thead>
<tr>
<th>Variable</th>
<th>Total</th>
<th>Type 2 Diabetes</th>
<th>No Type 2 Diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>%</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>N=60,678</td>
<td>N=4629</td>
<td>N=56,049</td>
<td></td>
</tr>
<tr>
<td>[Median age 40-44 yrs]</td>
<td>[Median age 60-64 yrs]</td>
<td>[Median age 40-44 yrs]</td>
<td></td>
</tr>
</tbody>
</table>

**Spinal Cord Injury**

- Yes: 0.49%
- No: 99.51%

**Sex**

- Male: 49.29%
- Female: 50.71%

**Table 5.4. Characteristics of the study sample.** Percentages are probability weighted to account for the CCHS sampling method. Column percentages are shown.
### Table 5.5. ORs and corresponding 95% Confidence Intervals for Type 2 diabetes (probability weighted).

Both unadjusted and adjusted odds ratios (AORs) are reported. AOR1 is adjusted for age and sex only; AOR2 is adjusted for age, sex, and body mass index; AOR3 is adjusted for age, sex, smoking status, hypertension status, body mass index, daily physical activity, alcohol intake, and daily consumption of fruits and vegetables. †Reference Category. *ORs shown are the effect for one category increase (5 year groupings).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Unadjusted OR</th>
<th>AOR1</th>
<th>AOR2</th>
<th>AOR3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Spinal Cord Injury</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>2.52 (1.81, 3.52)</td>
<td>1.66 (1.16, 2.36)</td>
<td>1.65 (1.13, 2.42)</td>
<td>2.45 (1.34, 4.47)</td>
</tr>
<tr>
<td>No†</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1.46 (1.36, 1.56)</td>
<td>1.68 (1.57, 1.81)</td>
<td>1.62 (1.50, 1.75)</td>
<td>2.20 (1.91, 2.55)</td>
</tr>
<tr>
<td>Female†</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.37 (1.35, 1.38)</td>
<td>1.37 (1.36, 1.39)</td>
<td>1.40 (1.39, 1.42)</td>
<td>1.25 (1.22, 1.29)</td>
</tr>
<tr>
<td>Variable</td>
<td>Total</td>
<td>With COPD</td>
<td>No COPD</td>
<td>Total</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>---------</td>
<td>-----------</td>
<td>---------</td>
<td>---------</td>
</tr>
<tr>
<td></td>
<td>N=61,010</td>
<td></td>
<td></td>
<td>N=61,049</td>
</tr>
<tr>
<td>Spinal Cord Injury</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>354</td>
<td>42</td>
<td>312</td>
<td>356</td>
</tr>
<tr>
<td>No</td>
<td>60,656</td>
<td>2384</td>
<td>58,272</td>
<td>60,693</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>33,369</td>
<td>950</td>
<td>26,691</td>
<td>27,659</td>
</tr>
<tr>
<td>Female</td>
<td>27,641</td>
<td>1476</td>
<td>31,893</td>
<td>33,390</td>
</tr>
<tr>
<td>Median Age Category (years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>40-44</td>
<td>40-44</td>
<td>40-44</td>
<td>40-44</td>
<td>40-44</td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daily</td>
<td>8780</td>
<td>744</td>
<td>9371</td>
<td>10,123</td>
</tr>
<tr>
<td>Occasional</td>
<td>18,350</td>
<td>1121</td>
<td>17,229</td>
<td>18,375</td>
</tr>
<tr>
<td>Former Daily</td>
<td>10,115</td>
<td>171</td>
<td>8609</td>
<td>8783</td>
</tr>
<tr>
<td>Never</td>
<td>23,615</td>
<td>383</td>
<td>23,232</td>
<td>23,619</td>
</tr>
</tbody>
</table>

Table 5.6. Characteristics of the two analytic samples: sample sizes.
<table>
<thead>
<tr>
<th>Variable</th>
<th>Raw OR COPD (95% CI)</th>
<th>AOR1 COPD (95% CI)</th>
<th>AOR2 COPD (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spinal Cord Injury</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>3.02 (1.97, 4.62)</td>
<td>2.18 (1.41, 3.37)</td>
<td>1.88 (1.20, 2.92)</td>
</tr>
<tr>
<td>No‡</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>0.79 (0.72, 0.87)</td>
<td>0.86 (0.78, 0.95)</td>
<td>0.69 (0.62, 0.76)</td>
</tr>
<tr>
<td>Female§</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Age*</td>
<td>1.32 (1.30, 1.34)</td>
<td>1.32 (1.30, 1.34)</td>
<td>1.35 (1.33, 1.37)</td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daily</td>
<td>6.31 (5.45, 7.31)</td>
<td>-</td>
<td>7.45 (6.42, 8.71)</td>
</tr>
<tr>
<td>Occasional</td>
<td>4.28 (3.71, 4.93)</td>
<td>-</td>
<td>2.99 (2.58, 3.45)</td>
</tr>
<tr>
<td>Former Daily</td>
<td>1.38 (1.12, 1.71)</td>
<td>-</td>
<td>1.25 (1.01, 1.55)</td>
</tr>
<tr>
<td>Never§</td>
<td>1.00</td>
<td>-</td>
<td>1.00</td>
</tr>
</tbody>
</table>

Table 5.7. Odds Ratios (95% Confidence Intervals) for COPD (probability weighted). Odds ratios derived from logistic regression models. Both unadjusted and adjusted odds ratios (AORS) are reported: AOR1 is adjusted for age and sex; AOR2 is adjusted for age, sex, and smoking status. ‡ Reference Category; CI=confidence interval. *ORs shown are the effect for one category increase (5 year groupings).
### Table 5.8. Odds Ratios (95% Confidence Intervals) for asthma (probability weighted)

Odds ratios derived from logistic regression models. Both unadjusted and adjusted odds ratios (AORS) are reported: AOR1 is adjusted for age and sex; AOR2 is adjusted for age, sex, and smoking status. Reference Category; CI=confidence interval. *ORs shown are the effect for one category increase (5 year groupings).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Raw OR Asthma (95% CI)</th>
<th>AOR1 Asthma (95% CI)</th>
<th>AOR2 Asthma (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spinal Cord Injury</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1.48 (1.05, 2.11)</td>
<td>1.68 (1.18, 2.39)</td>
<td>1.59 (1.12, 2.27)</td>
</tr>
<tr>
<td>No‡</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>0.69 (0.66, 0.74)</td>
<td>0.69 (0.65, 0.73)</td>
<td>0.67 (0.63, 0.71)</td>
</tr>
<tr>
<td>Female§</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Age*</td>
<td>0.96 (0.95, 0.97)</td>
<td>0.96 (0.95, 0.97)</td>
<td>0.95 (0.94, 0.96)</td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daily</td>
<td>1.30 (1.20, 1.41)</td>
<td>-</td>
<td>1.44 (1.33, 1.57)</td>
</tr>
<tr>
<td>Occasional</td>
<td>1.09 (1.01, 1.17)</td>
<td>-</td>
<td>1.28 (1.19, 1.38)</td>
</tr>
<tr>
<td>Former Daily</td>
<td>1.02 (0.92, 1.11)</td>
<td>-</td>
<td>1.11 (1.01, 1.21)</td>
</tr>
<tr>
<td>Never§</td>
<td>1.00</td>
<td>-</td>
<td>1.00</td>
</tr>
<tr>
<td>Variable</td>
<td>Raw OR Recent Asthma (95% CI)</td>
<td>AOR1 Recent Asthma (95% CI)</td>
<td>AOR2 Recent Asthma (95% CI)</td>
</tr>
<tr>
<td>-----------------------------</td>
<td>-------------------------------</td>
<td>-----------------------------</td>
<td>----------------------------</td>
</tr>
<tr>
<td><strong>Spinal Cord Injury</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1.88 (1.24, 2.85)</td>
<td>2.12 (1.40, 3.22)</td>
<td>2.03 (1.34, 3.08)</td>
</tr>
<tr>
<td>No‡</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>0.60 (0.55, 0.65)</td>
<td>0.59 (0.55, 0.64)</td>
<td>0.57 (0.52, 0.61)</td>
</tr>
<tr>
<td>Female‡</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.97 (0.96, 0.98)</td>
<td>0.97 (0.96, 0.98)</td>
<td>0.96 (0.95, 0.97)</td>
</tr>
<tr>
<td><strong>Smoking</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daily</td>
<td>1.40 (1.26, 1.56)</td>
<td>-</td>
<td>1.57 (1.41, 1.75)</td>
</tr>
<tr>
<td>Occasional</td>
<td>1.21 (1.10, 1.33)</td>
<td>-</td>
<td>1.42 (1.29, 1.56)</td>
</tr>
<tr>
<td>Former Daily</td>
<td>1.05 (0.93, 1.18)</td>
<td>-</td>
<td>1.15 (1.02, 1.30)</td>
</tr>
<tr>
<td>Never‡</td>
<td>1.00</td>
<td>-</td>
<td>1.00</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Variable</th>
<th>Raw OR Asthma (95% CI)</th>
<th>AOR1 Asthma (95% CI)</th>
<th>AOR2 Asthma (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Spinal Cord Injury</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1.69 (1.16, 2.47)</td>
<td>1.83 (1.25, 2.67)</td>
<td>1.76 (1.21, 2.57)</td>
</tr>
<tr>
<td>No‡</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>0.64 (0.60, 0.69)</td>
<td>0.64 (0.60, 0.68)</td>
<td>0.61 (0.57, 0.66)</td>
</tr>
<tr>
<td>Female‡</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.99 (0.98,1.00)</td>
<td>0.99 (0.98, 1.00)</td>
<td>0.98 (0.97, 0.99)</td>
</tr>
<tr>
<td><strong>Smoking</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daily</td>
<td>1.33 (1.21, 1.46)</td>
<td>-</td>
<td>1.45 (1.32, 1.59)</td>
</tr>
<tr>
<td>Occasional</td>
<td>1.23 (1.14, 1.33)</td>
<td>-</td>
<td>1.37 (1.26, 1.50)</td>
</tr>
<tr>
<td>Former Daily</td>
<td>0.99 (0.89, 1.10)</td>
<td>-</td>
<td>1.05 (0.94, 1.17)</td>
</tr>
<tr>
<td>Never‡</td>
<td>1.00</td>
<td>-</td>
<td>1.00</td>
</tr>
</tbody>
</table>

Table 5.9. Odds Ratios (95% Confidence Intervals) for recent asthma (based on symptoms: shaded, based on medications: unshaded, probability weighted). Odds ratios derived from logistic regression models. Both unadjusted and adjusted odds ratios (AORS) are reported: AOR1 is adjusted for age and sex; AOR2 is adjusted for age, sex, and smoking status. ‡ Reference Category; CI=confidence interval. *ORs shown are the effect for one category increase (5 year groupings).
<table>
<thead>
<tr>
<th>Variable</th>
<th>Unadjusted OR (95% CI)</th>
<th>AOR1 (95% CI)</th>
<th>AOR2 (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>3.69 (2.40, 5.68)</td>
<td>4.82 (3.02, 7.67)</td>
<td>4.43 (2.77, 7.10)</td>
</tr>
<tr>
<td>No†</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12-19‡</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>20-29</td>
<td>1.07 (0.91, 1.27)</td>
<td>1.07 (0.90, 1.27)</td>
<td>1.08 (0.88, 1.32)</td>
</tr>
<tr>
<td>30-39</td>
<td>1.48 (1.25, 1.75)</td>
<td>1.47 (1.24, 1.73)</td>
<td>1.47 (1.20, 1.81)</td>
</tr>
<tr>
<td>40-49</td>
<td>1.50 (1.26, 1.80)</td>
<td>1.48 (1.23, 1.77)</td>
<td>1.41 (1.14, 1.75)</td>
</tr>
<tr>
<td>50-59</td>
<td>1.08 (0.90, 1.29)</td>
<td>1.05 (0.87, 1.25)</td>
<td>0.91 (0.73, 1.14)</td>
</tr>
<tr>
<td>60-69</td>
<td>0.74 (0.62, 0.88)</td>
<td>0.72 (0.60, 0.86)</td>
<td>0.57 (0.46 0.71)</td>
</tr>
<tr>
<td>70-79</td>
<td>0.44 (0.35, 0.55)</td>
<td>0.40 (0.32, 0.50)</td>
<td>0.29 (0.23, 0.38)</td>
</tr>
<tr>
<td>80+</td>
<td>0.35 (0.26, 0.47)</td>
<td>0.30 (0.23, 0.40)</td>
<td>0.20 (0.15, 0.28)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male†</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Female</td>
<td>2.57 (2.33, 2.85)</td>
<td>2.67 (2.41, 2.95)</td>
<td>2.87 (2.59, 3.19)</td>
</tr>
</tbody>
</table>

Table 5.10. Migraine and spinal cord injury. Unadjusted and Adjusted Odds Ratios from Logistic Regression Examining the Relationship Between Migraine Headache and Spinal Cord Injuries. AOR1 is adjusted for age and sex only. AOR2 is adjusted for age, sex, stroke, heart disease, hypertension, smoking status, and education level.
<table>
<thead>
<tr>
<th>Perceived health</th>
<th>SCI Migraine n=83 (%)</th>
<th>SCI No migraine n= 272 (%)</th>
<th>No SCI Migraine n= 5864 (%)</th>
<th>No SCI No migraine n= 54755 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poor</td>
<td>36.14</td>
<td>18.75</td>
<td>6.84</td>
<td>3.13</td>
</tr>
<tr>
<td>Fair</td>
<td>31.33</td>
<td>28.31</td>
<td>14.99</td>
<td>9.96</td>
</tr>
<tr>
<td>Good</td>
<td>16.87</td>
<td>28.31</td>
<td>31.77</td>
<td>29.44</td>
</tr>
<tr>
<td>Very Good</td>
<td>10.84</td>
<td>20.59</td>
<td>32.53</td>
<td>37.53</td>
</tr>
<tr>
<td>Excellent</td>
<td>4.82</td>
<td>4.04</td>
<td>13.64</td>
<td>19.93</td>
</tr>
</tbody>
</table>

**Table 5.11. General perceived health.** Self-reported perceived health among SCI and non-SCI populations with and without migraine.
Figure 5.1. Grouped bar plot of prevalence of Type 2 diabetes. The weighted prevalence (%) of Type 2 diabetes is shown separately for the SCI group (black bars) and non-SCI group (grey bars), for each age category.
5.4 Discussion

The present study utilized a comprehensive national survey with data collected from over 60,000 individuals to investigate the relationship between SCI and chronic conditions. Here, we demonstrate for the first time in a large, representative population that SCI is independently associated with a significant increased odds of self-reported heart disease, stroke, Type 2 diabetes, chronic respiratory diseases, and chronic pain (migraine) (Figure 4.2). To put these values into context, these heightened ORs reported here are similar in magnitude (or greater) to the estimated ORs in the general population for the relationship between smoking and myocardial infarction (MI), diabetes and MI, and are in fact higher than those for the relationship between hypertension and MI, and abdominal obesity and MI.28

**SCI and Cardiovascular Disease**

That individuals with SCI are at an increased risk of CVD is in line with previous evidence. Namely, risk factors for CVD are amplified in individuals with SCI, relative to able bodied individuals.35, 58, 102-120 In addition to the immobility caused by SCI, individuals with SCI have unique disadvantages that may further contribute to these risks relating to the disconnection between autonomic circuits and supraspinal control. As an example, significant lability in blood pressure, from extreme hypotension during episodes of orthostatic hypotension to extreme hypertension during episodes of autonomic dysreflexia—are typical post SCI and unique features of SCI.35, 58 Researchers have speculated that this blood pressure instability could result in vascular injury, and consequently results in a greater risk for arterial disease in individuals with SCI.144

In addition to these studies examining risk factors, others have reported a hazard ratio of 2.85 for stroke in individuals with SCI (using age, sex, and propensity-score matched controls) from a longitudinal sample of over 20,000 Taiwanese individuals, but this study did not examine other cardiovascular outcomes such as heart disease.123 Similarly, a longitudinal study among diabetic American veterans with SCI reported an increased risk of ‘macrovascular complications’ (including stroke and heart disease) compared to non-diabetic veterans with SCI, but this study did not include separate risk estimates for
stroke and heart disease, and did not include a control group.\textsuperscript{121} In addition, another group demonstrated an increased risk of ischaemic heart disease in a small convenience sample of males injured before 1974.\textsuperscript{122} Taken together, these biological and epidemiological results support the hypothesis that SCI is associated with an increased risk of CVD.

\textit{SCI and Type 2 diabetes}

We next demonstrated for the first time in a large, representative population that SCI is independently associated with a two-fold increased odds of Type 2 diabetes. These heightened odds of Type 2 diabetes are consistent with previous evidence. Several prior studies have shown or suggested an increased prevalence of diabetes among individuals with SCI.\textsuperscript{88, 111, 122, 126-128} One possible mechanism may be due to the association between immobility, muscle wasting, and insulin sensitivity.\textsuperscript{145} However, there has not been epidemiological data until now to support this hypothesis.

\textit{SCI and Respiratory Conditions}

In addition to cardiometabolic conditions, there are several reasons why individuals with SCI may also be at a greater risk of developing chronic respiratory conditions.\textsuperscript{61, 62, 130} First, injury to the spinal cord can cause ventilatory impairment via paralysis of inspiratory and expiratory respiratory muscles; such impairments are most severe among individuals with high thoracic and cervical level injuries. Second, ineffective cough and the inability to breathe deeply may lead to general respiratory problems, such as atelectasis and pneumonia.\textsuperscript{61, 62} Additional factors may include reduced lung and chest wall compliance, airway hyper-responsiveness, and paradoxical inward movement of the chest wall during inspiration – all of which lead to less efficient breathing.\textsuperscript{130, 146-151} Moreover, disturbances in the equilibrium of microbes in the gut (both directly as a result of SCI and/or medications used to treat SCI), may also contribute.\textsuperscript{152, 153} Overall, these pathological physiological changes associated with SCI may contribute to an increased risk of chronic conditions such as asthma and COPD.
SCI and Chronic Pain (migraine)
Also in agreement with a previous report, migraines were associated with a 4-fold increased odds in individuals with neurological disorders. In the present study, after adjusting for major confounding variables (e.g., age and sex), this association increased to nearly 5-fold. Highlighting functional significance, individuals who experienced SCI and migraines also tended to report poorer self-perceived health compared to those with SCI and no migraine.

While the causal pathway remains largely unknown, a number of studies have reported a strong association between stroke and migraines. Putative mechanisms linking migraine with stroke include impaired vascular function, prominently evidenced by reduced number and function of endothelial progenitor cells, as well as chronic inflammation. In line with stroke findings, migraines could increase the risk of non-traumatic forms of SCI (e.g., spinal cord infarctions). However, the relative incidence of spinal cord infarctions is low compared to traumatic and other forms of non-traumatic SCI (e.g., tumors), thus we would not favor such an explanation to account for dramatically increased odds reported here.

From a pragmatic perspective, migraines could be linked to SCI through head injuries sustained in the course of traumatic injury. Reported in approximately one third of individuals sustaining traumatic cervical SCI, the association we are observing would represent a form of ‘posttraumatic headache,’ potentially misclassified as migraine.

Also a potential source of misclassification, autonomic dysreflexia (AD) is characterized by a dramatic increase in blood pressure, sweating, and, occasionally, intense (non-migraine) headaches in response to afferent stimulation below the level of injury. Potentially more difficult to differentially diagnosis from migraines after SCI, AD however, is known to occur in only a subpopulation of individuals with high thoracic and cervical traumatic injuries, and is very rare in non-traumatic injuries. Moreover, not all individuals with this condition report headaches associated with their AD. Further, the distinction between self-report non-migraine headaches with migraine headaches has shown high sensitivity and specificity (with respect to clinical diagnosis) in other studies.
To our knowledge, no study has examined the ability to distinguish self-report migraine headache from migraine without headache (eg. acephalalgic migraine) is a rarer form of migraine. In addition, although validation studies of self-report migraine headache have not been carried out specifically among individuals with SCI, AD-associated headaches are generally associated with afferent below-level stimulation (eg. full bladder) and do not share common features of migraine (eg. aura and nausea), and thus would be less likely misclassified with migraines headaches. Although we cannot rule out these potential sources of misclassification, the sheer magnitude of the association between migraine and SCI (~5-fold after correcting for age and sex) is striking, suggestive of other contributing factors.

Related to a variety of pathophysiological mechanisms, an alternative relationship to consider is that migraine headaches are acquired more directly in response to SCI. Indeed, a number of factors could exacerbate or trigger migraines, contributing to their increased prevalence after SCI. For example, migraines are associated with an increased risk of other chronic pain conditions (approximately 5-fold), including “spinal pain” from back and neck injuries. A substantial proportion of individuals with SCI report other types of nociceptive and neuropathic pain, which in turn could significantly increase the odds of migraine. The overlap between neuropathic pain and migraines could be a function of similar underlying mechanisms, such as central sensitization. From the perspective that migraine headaches are associated with vascular impairments, disruption of autonomic pathways in the spinal cord may also play a pivotal role. Along these same lines, an association between SCI and migraine headaches could be secondary to poor cardiovascular health.

In addition to the recent report, to our knowledge, two other studies have considered the prevalence of headaches after SCI. Spierings and colleagues (1992) surveyed 20 individuals with tetraplegia (18 with complete injuries), identifying common sources of headaches (e.g., bowl and bladder stimulation causing AD), but finding no evidence of migraines. In a larger sample (n=114), 15% of individuals with SCI reported migraines. Due to the low number of subjects and lack of comprehensive data, these
previous studies did not control for known confounding factors that influence the prevalence of migraine (e.g., sex and age), nor was there a comparison to a representative control group. The important contribution of our work relative to these prior studies is two-fold. First, potential confounding variables (i.e., associated with both the outcome and the explanatory variable) were considered. Importantly, when controlling for these variables, the odds of migraines in individuals with SCI markedly increased, further highlighting the strength of this association. Second, we have demonstrated that migraines potentially compound the impact of SCI on perceived general health.

According to the ICSCIP, nociceptive pain is principally differentiated into musculoskeletal and visceral categories pain.\(^{133}\) A third category of nociceptive pain captures SCI related and unrelated conditions, including headaches caused by AD (“related”) and migraines (“unrelated”).\(^{133}\) The increased odds of migraine headache relative to a healthy population suggest that migraine headaches may, in fact, be related to SCI. Future studies should confirm this finding using standard definitions of migraine (i.e., International Classification of Headache Disorders\(^ {136}\)) and detailed clinical examinations, examine the association with AD and posttraumatic headaches, as well as establish the temporality of events (i.e., migraines developing after SCI).

**Study Limitations and Future Directions**

There are possible limitations to the current study. Firstly, the data are derived from a cross-sectional study design; therefore, it is impossible to determine if SCI preceded the outcomes of interest. However, we did perform a sensitivity analysis, restricting the study sample to a group of younger individuals, to reduce the likelihood that the outcomes preceded SCI. The increased odds persisted, but had very wide confidence intervals due to the reduced power (results not shown). Another limitation of this study is the lack of detailed neurological and cardiovascular examination records. The CCHS provides no information on neurological level, completeness of injury, etiology of SCI, other proxies for obesity (e.g. WC), or information on other respiratory/cardiovascular/pain conditions. However, with respect to SCI etiology, recent studies from Canada estimate that approximately 51% of prevalent SCI cases are traumatic, versus 49% non-traumatic.\(^ {13}\)

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Non-traumatic SCIs are less likely to be neurologically complete, i.e., have preserved movement or sensation below the injury level\(^\text{10}\); as completeness of injury is associated with more adverse effects,\(^\text{175}\) the inclusion of non-traumatic individuals would likely dilute the observed effects seen here. Thus, while our estimates may represent an overall approximation of risk, ORs for sub-populations of individuals with SCI (e.g., paraplegia versus tetraplegia or traumatic versus non-traumatic) may vary substantially.

In addition, although the data are from self-report, self-reported heart disease, stroke, Type 2 diabetes, asthma, COPD, and migraine have been validated against clinical records in other (non-SCI) studies, demonstrating a relatively high accuracy of self-report,\(^\text{176-178}\) generally with higher specificity than sensitivity.\(^\text{179, 180}\) Any misclassification of these outcomes would likely be non-differential by SCI status, which tends to bias effect sizes toward the null. With respect to SCI status, the high prevalence rate reported here was surprisingly high. While there are no studies to our knowledge which examine the validity of self-reported SCI status, accurate reporting is more likely to occur for diseases with a well-defined and easily communicated diagnosis, as well as for diseases requiring hospitalization.\(^\text{181}\) Arguably, SCI, a condition characterized by unique and distinct losses of movement and sensation, requiring hospitalization during the acute stages of injury and often in chronic stages, would satisfy these criteria. However, if misclassification of SCI status occurred, it would likely occur for less severe ‘injuries’ (e.g., protruding discs). Given that completeness and severity (neurological level) are correlated with cardiovascular risk,\(^\text{175}\) the inclusion of these individuals with less severe injuries would likely dilute the reported effect size, and would also likely be non-differential by outcome status. In general, validation of this self-report data was internally confirmed, for example, with the unadjusted (raw) odds ratios observed for the relationship between smoking status and COPD, and between smoking status and asthma; that is, this relationship and dose-response relationship confirmed results seen in prior studies.\(^\text{131, 132}\)

Furthermore, as with all observational studies, there may be residual confounding. We were not able to adjust the models for measures of dyslipidemia, for example. Moreover, BMI does not perfectly capture adiposity, particularly in individuals with SCI (discussed
in more detail in Chapter 3). However, we were able to adjust the models for a substantial number of potential confounders which are generally not all available in clinical studies. These limitations withstanding, the drastic increased odds of secondary complications among individuals with SCI is an impetus for future investigations. Although there is physiological plausibility for a causal relationship between SCI and these conditions, future research is needed to better understand this and whether interventions can modify risk. For example, it will be important for future research to examine timing of onset of conditions, how patients with SCI are managed acutely (or in early stages in the case of non-traumatic SCI), if treatments can be adjusted to reduce the list of long-term secondary complications, and interactions between exposures (i.e., additive/multiplicative) before versus after the injury. Additional cohort studies with the use of SCI-specific registries, such as the Rick Hansen Spinal Cord Injury Registry, are needed to build on this evidence. Indeed, results from this study may also inform the data collected prospectively in such registries (e.g., the type and severity of stroke/heart disease, age of onset, etiology of SCI, neurological level and completeness), which will be necessary for prospective analyses.

Moreover, current clinical practice guidelines for the management of chronic conditions following SCI are by and large based on short-term ‘efficacy’ outcomes; thus these future studies may better inform clinical practice guidelines for individuals with SCI. In addition, findings from this research will be important from a health care planning perspective since there is a change in the epidemiology of SCI—an increase in the average age for traumatic SCI and a rise in non-traumatic SCI. In sum, research of this kind will ultimately lead to interventions and targeted prevention strategies addressing modifiable risk factors for chronic conditions in individuals with SCI.
Figure 5.2. Summary of CCHS findings. Point estimates for age- and sex-adjusted odds ratios. Dashed line indicates reference value of 1.00 (i.e., values that cross 1.00 are not statistically significant).
CHAPTER 6
RELATIONSHIPS BETWEEN SECONDARY COMPLICATIONS FOLLOWING SCI

6.1 Introduction and Background
After establishing excess risk for several major secondary complications (Chapter 5), we next wanted to examine how these and other secondary conditions correlate. An important component here was examining these inter-relationships while adjusting for important confounding factors (Objectives 2A, 2B, 2C; Figure 1.1). This area of study is important because it recognizes that biological systems do not function independently in healthy individuals, and that failure or impairments in one system may lead to failures and impairments in another. Importantly here, we intended to go beyond conventional relationships between biological systems (e.g., depression and pain), seeking novel evidence of inter-relatedness between more distinct systems (e.g., cardiovascular and pain). We hypothesized that inter-relationships (correlations) between secondary complications exist following SCI, that these relationships may explain excess risk (e.g. excess risk of heart disease), and further hypothesized that inter-relationships would exist among secondary conditions after adjustment for confounding factors such as injury characteristics. In Chapter 5, we examined the risk of heart disease, stroke, Type 2 diabetes, chronic respiratory disease (asthma/COPD) and migraine (as an indicator of chronic pain). Since our next set of questions was more refined with respect to wanting to take into consideration injury characteristics and to examine factors that are specific to SCI populations (e.g. AD), we sought an additional dataset to answer these questions. Namely, the survey data used in this chapter contained information on injury severity and injury etiology (not available in the CCHS data), and also contained information on injury-related conditions (e.g. AD and neuropathic pain, also not available in the CCHS data).

General Inter-relationships
SCI is a complex and heterogeneous neuropathology, with the injury disrupting multiple body systems. Such secondary conditions, in addition to the injury, affect symptom burden, functional abilities, and quality of life in individuals with SCI.
The vast majority of secondary complications following SCI have been studied separately, whereas most individuals with SCI have two or more chronic conditions.\textsuperscript{68} Overlap in self-reported complications has been shown in patients with COPD and other chronic conditions, but has been yet to be examined among individuals with SCI.\textsuperscript{71} Prior studies have generally focused on the number of co-occurring conditions that individuals with SCI experience\textsuperscript{68} (versus the nature of the conditions which overlap and the extent to which they correlate). Although associations among some secondary complications, such as diabetes or OH with cardiovascular disease,\textsuperscript{72} have been previously examined in able-bodied populations, it is currently unknown whether and to what extent secondary complications cluster among individuals with SCI. SCI represents a unique and fascinating condition to examine such relationships given the multitude of bodily systems disrupted by the injury. Understanding these relationships will shed light on biological mechanisms underlying the development of these complications, and may yield insight into prevention strategies.

**Specific Inter-relationships: Pain and Cardiovascular Disease**

Furthermore, the association between seemingly unrelated secondary complications (eg. neuropathic pain and CVD), has not been previously examined. Some of these associations may explain the increased risk of chronic conditions noted in previous chapters and other studies. For example, individuals with SCI have a more than two-fold increased risk of CVD compared with able-bodied individuals.\textsuperscript{123, 183-187} We have shown in Chapter 4 that the increased risk appears to be in excess of the risk conferred by several well-established risk factors, including diabetes and hypertension.\textsuperscript{123, 183} This raises the question whether other factors, secondary to SCI, are contributing to the increased risk.

Potential factors linking SCI and CVD are pain and depression. Both are frequently reported among individuals with SCI, develop in the acute stage of injury, and are commonly described as severe.\textsuperscript{66, 188} In able-bodied individuals, depression and pain confer an excess risk of CVD, though through mechanisms that are not entirely
understood. However, previous studies have not considered the high degree of correlation between depression and pain, which may confound the relationship with CVD. One possibility is that pain causes depression which in turn causes CVD (i.e., depression is on the causal pathway). Another possibility is that depression amplifies so-called dysphoric physical sensations (including pain).

Two different types of pain are common after SCI: 1) nociceptive (eg. shoulder pain resulting from overuse injuries), and 2) neuropathic pain (eg. spontaneous below level burning sensation resulting from damage to the spinal cord). Since neuropathic pain can occur independently of nociceptive pain, SCI serves as a model to investigate the unique effects of these types of pain on the risk of developing CVD. No previous study, in any neurological condition or a “healthy” population, has distinguished the effects of different types of pain on cardiovascular outcomes.

Specific Inter-relationships: Blood pressure control and Cardiovascular Disease

In addition to suffering from neuropathic pain and depression, individuals with SCI tend to exhibit lower resting blood pressure, as well as repetitive and significant blood pressure instability—from extremely low during episodes of orthostatic hypotension (OH) to extremely high due to episodes of autonomic dysreflexia (AD). Such lability in blood pressure is unique to SCI, though the long-term effects of blood pressure fluctuations are unknown. Some have speculated that blood pressure instability could contribute to vascular injury, and consequently results in a greater risk for arterial disease in individuals with SCI. In addition, several case reports have implied a causal relationship between AD and acute myocardial infarction and between AD and stroke. However, these studies are anecdotal and did not consider other potential factors that may contribute to CVD risk. A mechanistic hypothesis relating AD and OH with CVD has never been formally tested.

Specific Inter-relationships: Neurological Deterioration

The presence of neurological deterioration following SCI is an understudied phenomenon. Indeed, we have introduced the concept in Chapter 2 that neurological deterioration may itself be considered a secondary complication of SCI. Moreover, the relationship between
neurological deterioration with other secondary complications has never been previously examined, but may reveal novel insight into the mechanisms underlying deterioration.

Why examine the relationship between neurological outcomes and other secondary complications? A recent study demonstrated that hyperlipidemia adversely affected neurological outcomes in individuals with SCI, and that statins partially reverse this risk of disability. Another recent study in humans have demonstrated that acute upper respiratory and postoperative infections may limit the capacity for neurological recovery after SCI. Although infections persist into chronic stages of injury (e.g., urinary and respiratory tract), their effect on neurological status at later time-points is unknown, as is the effect of other secondary complications such as neuropathic pain. That secondary complications may be related to neurological outcomes is a relatively novel concept within the field of SCI research, and reveals exciting avenues to explore which may directly benefit individuals with SCI.

**Objectives**

Therefore, the present chapter investigated relationships between secondary complications (including neurological deterioration) in a well-characterized sample of individuals with chronic SCI (Objective 3A). Results of this type of analysis will be important for identifying individuals with SCI at a high risk of developing certain conditions, and for other neurological conditions (e.g., multiple sclerosis).

**6.2 Methods**

**Study Population**

Individuals with SCI were surveyed as part of the cross-sectional SCI Community Survey. The survey covers a wide range of topics, including demographic information, accessible housing, attendant care, income support, equipment, medical supplies, secondary complications, work-related activities, communication devices, emotional counseling, peer support, job training, transportation, and healthy living programs. It is the largest Canadian survey of its kind. Canadians who have a SCI caused by a trauma or disease, and have been living in a community setting for at least one year after discharge from a hospital or rehabilitation facility, and are at least 18 years of age are eligible for the study.
Individuals were recruited by SCI community organizations such as SCI Canada, from databases of the Rick Hansen SCI Registry, and rehabilitation facilities. The survey was administered online and via telephone. Subjects received a stipend ($25.00 CAD gift certificate) for study participation. Informed consent was obtained from each subject; ethical approval was obtained via the Rick Hansen Institute and the Université Laval.

Those who responded to the SCI Community Survey who reported traumatic SCI (due to transport, fall, assault, and sports) and with non-traumatic SCI (due to tumour, infection, congenital abnormalities, degenerative spine, stroke within the spinal cord [and not within the brain], degenerative spine, neurological syndromes such as transverse myelitis, and other non-traumatic SCIs) were included. Those with invalid responses (eg. “don’t know”) were also excluded from the primary analyses, but were included in sensitivity analyses (described in more detail below).

Validated questionnaires and a subset of information collected in the Community Follow-up Questionnaire Version 2.0 were used to develop this comprehensive national survey including. In addition, all questions were pilot tested in a consumer review.

**Outcome and Explanatory Variables**

Primary variables of interest included AD, OH, CVD, neuropathic pain, and neurological deterioration (Conceptual Model, Figure 1.1). Secondary variables of interest (hypertension, diabetes, infection, and depression) were also examined in the first exploratory analysis, and used to address confounding in multivariable analyses (discussed in more detail below).

Cerebrovascular disease status was obtained with the following question: “In the past 12 months, have you experienced cerebrovascular disease, stroke, or transient ischemic attack?” Heart disease status was obtained with the following question: “In the past 12 months, have you experienced heart disease?” Because we were examining recent events/conditions (which may affect power), we *a priori* combined recent cerebrovascular disease and recent heart disease into one category, from hereon referred to as the “CVD” category, as has been done previously.

Recent depression/mood problems were assessed with the following question: “In the
past 12 months, have you experienced depression/mood problems (a state of intense sadness that lasts for more than two weeks, and has advanced to the point of interfering with daily life- feeling “down”, being tired, or feeling irritable for no apparent reason)?”.

Neuropathic pain was captured by the question: “In the past 12 months, have you experienced pain that is often ongoing and intense, caused by damage to nerves that occurs spontaneously or by light touching and is characterized by feelings of burning, shooting, tingling, etc.” Non-neuropathic pain (shoulder pain) was captured by the question: “In the past 12 months, have you experienced shoulder problems (this includes pain in the shoulder joints and/or muscles. People who must overuse a particular muscle group, such as shoulder muscles, or who put too much strain on their joints are at risk of developing pain)?”. Response categories for neuropathic pain and shoulder pain frequency were determined a priori, and included the following categories: “frequent” (everyday or a few times a week), “infrequent” (few times a month) and “rare-never” (never or once a year or a few times a year). Response categories for depression included “most/all the time”, “little/some of the time”, and “none of the time.” Multiple categories were chosen (versus a binary variable) as to be able to investigate a dose-response relationship. As a measure of interference with activities of daily living, the following self-report questions were also asked of individuals reporting pain and depression: “You mentioned that you experienced [condition] in the past 12 months. When you had this condition, to what extent did it limit your activities?”. AD status was obtained with the question: “In the past 12 months, have you experienced autonomic dysreflexia?” OH status was obtained with the following question: “In the past 12 months, have you experienced orthostatic hypotension?” In each case, brief descriptions of the conditions were described in lay terms in case the medical term was not familiar to the individual (eg. light headedness for OH). For AD and OH, 3 groupings were made a priori: “frequent” (everyday or a few times a week), “infrequent” (few times a month), and “rare-never” (never, once a year, or few times a year). The “rare-never” group was used as the reference category. As before, groupings were made as to be able to investigate a dose-response relationship (versus using a binary variable).

Recent (within the past 12 months) self-reported neurological deterioration was assessed
with the following question: “in the past year have you experienced loss of muscle
strength and/or skin sensation, such as having less strength or losing all strength in an
area, or having less feeling or losing all feeling in an area?”

Infections were a composite variable of urinary tract infection and respiratory infection,
captured with the questions “In the past 12 months, have you experienced urinary tract
infection (this includes infections such as cystitis and pseudomonas. Symptoms include
pain when urinating, a burning sensation throughout the body, blood in the urine, and
cloudy urine.”), and “respiratory infections (also called pneumonia- short term lung
disease caused by infection that includes inflammation and congestion, followed by
clearing. It includes increased secretions, fever, chills, coughing, and difficulty
breathing”).

Statistics
Logistic regression models were created using the binary outcomes (yes/no). Bivariable
logistic models were first developed to assess the unadjusted (raw) relationship between
the covariates (described in more detail below). In order to develop the multivariable
models, confounding was assessed from both a statistical (i.e., by examining changes in
effect sizes and using bivariable analyses) and theoretical (i.e., from a putative causal
framework based on literature and subject matter knowledge) perspective. We used the
commonly accepted definition of confounding: a factor ‘x’ is a confounder if factor x is a
known risk factor for the outcome/ and factor x is associated with the primary
explanatory variable, but is not a result of the primary explanatory variable.\textsuperscript{140} Covariates
initially included all available factors possibly associated with the outcome (‘full model’),
and were then excluded stepwise if they did not change the estimate for the primary
explanatory variable (AD or OH) by more than 10%; this reduced multivariable model
was termed the ‘final model’.\textsuperscript{203} Logistic models were evaluated with empirical
probability plots, partial residual plots, and local mean deviance plots.

For examining all relationships, the following potential confounders were considered (all
derived from self-report): age, sex, time since injury, diabetes status, hypertension status,
whether or not they were taking medications for hypertension, level of injury (tetraplegia
or paraplegia)- defined as the most caudal level at which both motor and sensory levels
are intact, and completeness of injury (motor complete [AIS A/B] versus incomplete [AIS C/D/E]) according to the American Spinal Injury Association (ASIA) Impairment Scale (AIS) - where a ‘complete’ injury refers to an injury in which all function below the injury level is lost. Both AIS grade and injury level were derived from questions worded in lay-terms, for example: “my injury is in my upper neck” or “I have full feeling throughout my body.”

Interaction terms in the regression models were initially formed based on biological plausibility and were also assessed for their statistical significance (using AIC criteria) in sensitivity analyses, using the primary exposures along with the other covariates (discussed above) to form interaction terms added to the previously described multivariable models. In addition, because the association between these variables may be mediated through other factors (eg. diabetes), we repeated the analyses without adjustment for such factors.

Using the results from the logistic models, both unadjusted and adjusted odds ratios (ORs), with corresponding 95% confidence intervals, were calculated. Significance levels were set at P<0.05 (where ORs were significantly greater or less than one); significant values are bolded throughout. For summary statistics of continuous variables, means ± standard deviations and medians with ranges are presented. R statistical software (Version 2.15.3) was used for all analyses.

6.3 Results

Study Sample- General Characteristics
A total of 1549 individuals responded to the survey (67% male, 33% female). The mean age ± standard deviation was 49.6 ± 13.9 years (median: 51.0 years, range 18-90 years) with a mean time since injury ± standard deviation of 18.5 ± 14.3 years (median: 15.1 years, range 1-81 years).

General Relationships
Table 6.1 below illustrates the relationship between various (bivariable) combinations of secondary complications. For simplicity, and because this was an exploratory analysis,
we first treated each secondary complication as a dichotomous outcome. The strength of each relationship is colour-coded, with red indicating the strongest relationship (for point estimates of odds ratios). From Table 6.1, there are a few major conclusions:

1) there are several significant associations between secondary complications following SCI
2) there are associations between conditions thought to be derived from similar pathology (eg. AD and OH are both significantly correlated and both related to autonomic cardiovascular dysfunction)
3) there are associations between conditions thought to be derived from dissimilar pathology (eg. neuropathic pain and CVD)
4) neurological deterioration (which may be considered a secondary condition in itself), was significantly associated with several other secondary complications (See Figure 6.1).

We next examined specific relationships in more detail (i.e., using all the response categories, as well as examining relationships after adjusting for confounding).

**Specified Relationships: Pain and Cardiovascular Disease**

**Study sample**

A total of 74 individuals had reported heart disease within the last year; a total of 19 individuals had experienced cerebrovascular disease within the last year; therefore, a total of 93 individuals experienced CVD (composite outcome).

**Pain and Cardiovascular Disease: results from bivariable analysis**

The odds of CVD among individuals with frequent neuropathic pain was 1.76 times greater than those without frequent neuropathic pain (95% CI: 1.04-3.14, p=0.042; Table 6.1). In contrast, non-neuropathic pain (shoulder pain) was not significantly associated with CVD (P=0.13 for frequent vs. rare-never; Table 6.2).

**Pain and Cardiovascular Disease: results from multivariable analysis**

After adjustment for confounding variables in the multivariable model (Table 6.3),
neuropathic pain was significantly and independently associated with CVD. The odds of CVD among individuals who reported frequent neuropathic pain was 2.27 times those who reported rare-never neuropathic pain, after adjustment for age, sex, injury characteristics, and depression (95% CI [1.21, 4.60]; P=0.02; AOR1 in Table 5.3). Additional adjustment for non-neuropathic pain (shoulder pain) did not significantly alter these ORs (AOR2 in Table 6.3). Hypertension status and diabetes status also did not significantly affect the reported OR estimates for neuropathic pain, shoulder pain, and depression (AOR3 in Table 6.3). While neuropathic pain and depression were significantly correlated (P<0.001), these multivariable models allow one to partition their independent effects. Thus, neuropathic pain and depression were significantly and independently associated with CVD.

Pain Interference
Based on interference with activities of daily living, Table 6.4 shows odds ratios for CVD among those individuals reporting neuropathic pain, shoulder pain, and depression. For these conditions, interference with activities of daily living was not significantly associated with CVD (p>0.05).

Specified Relationships: AD/OH with Cardiovascular Disease
Sample Characteristics
In addition to examining the relationship between neuropathic pain with CVD, we next examined the relationship between AD and OH with CVD. Approximately 15% of individuals experienced frequent AD; 13.0% experienced frequent OH (Table 6.5).

Relationship between AD with Cardiovascular Disease
The results of the bivariable and multivariable logistic regression models for CVD are presented in Table 6.5. Infrequent AD was significantly associated with CVD (AOR1-AD=2.73, 95% CI [1.22, 5.64]; AOR2-AD=2.51 [1.13, 5.13]; P<0.05). However, frequent AD was not significantly associated with CVD, though the point estimates were in the positive direction (Table 6.5).
**Relationship between OH with Cardiovascular Disease**

There was a significant relationship between OH and CVD: the odds of CVD was 3.68 times (95% CI: 1.86-7.06) in individuals with frequent OH versus individuals with “rare-never” OH, after adjustment for age, sex, time since injury, level of injury, AIS grade (completeness), and diabetes status (P<0.05; Table 5.5, AOR1-OH). The adjusted odds of CVD was 1.96 times in individuals with infrequent OH versus individuals with “rare-never” OH, suggesting a dose-response relationship, though the OR was not statistically significant (P>0.05). Similar results were found in terms of a heightened odds of CVD among individuals with frequent OH when adjusting for only AIS grade, injury level, and diabetes status (AOR2-OH in Table 6.5). When both AD and OH were included in the multivariable model (Table 6.5: AOR-AD&OH), the heightened odds of CVD persisted for frequent OH but was reduced slightly.

**Sensitivity Analyses**

As sensitivity analyses, we examined the effects of additional variables that may confer increased or decreased risk for CVD but which are questionable as true confounders. To this end, we ran the same multivariable models as presented in Table 6.5 with hypertension status, medication status (for hypertension), and SCI etiology (traumatic vs. non-traumatic). The addition of these variables did not significantly alter the overall results of the study (the heightened odds of CVD among individuals with frequent OH persisted; results not shown). Thus, these variables were likely not confounders as hypothesized.

**Specified Relationships: Neurological Deterioration**

**Study Sample**

Having examined the relationships between pain, AD, and OH with CVD, we next decided to explore the relationship between these secondary complications with neurological decline. Based on previous findings in addition to the exploratory analysis above, there was the strongest preliminary evidence (and biological plausibility) to suggest that neuropathic pain may play a role in neurological deterioration.
Furthermore, because neuropathic pain and infection are correlated, we analyzed these two complications in relationship to neurological deterioration. A total of 584 individuals experienced neurological deterioration; a total of 262 individuals experienced infections, a total of 1086 experienced neuropathic pain, and a total of 676 individuals were receiving treatment for neuropathic pain (Table 5.6).

**Relationship between infection and neurological deterioration**

Infection and neurological deterioration were significantly associated (raw OR), and this relationship persisted after adjustment for neuropathic pain (AOR2), treatment for neuropathic pain (AOR1), and after adjustment for both neuropathic pain and treatment (AOR3; P<0.05 for all; Table 6.7). Furthermore, after adjustment for injury characteristics and demographic factors, a significant association between infection and neurological deterioration remained (AOR4-AOR7). Namely, individuals who reported infections were twice as likely to exhibit neurological deterioration.

**Relationship between neuropathic pain and neurological deterioration**

Table 6.7 also shows odds ratios for neurological deterioration among individuals who reported neuropathic pain and who reported treatment for neuropathic pain. These were both significantly associated with neurological deterioration, and this relationship persisted after adjustment for infection and injury characteristics/demographics (Table 6.7; P<0.05 for all). Specifically, individuals who reported neuropathic pain or were receiving treatments for neuropathic pain exhibited a two-fold increased odds of neurological deterioration.

**Post-Hoc Analyses**

We next wanted to examine the strata-specific ORs for individuals with complete SCI (versus incomplete), as well as individuals with traumatic SCI (versus non-traumatic SCI). The rationale for this analysis was two-fold: firstly, individuals with complete injuries tend to be more neurologically stable, and individuals with non-traumatic SCI tend to have incomplete injuries;\(^1\) secondly, non-traumatic SCI can arise from infection itself (eg. spinal cord abscess) and tumours, which would be directly associated with deterioration. For individuals with traumatic SCI, the odds of deterioration among those with neuropathic pain was 2.22 [1.62, 3.05] and with infection was 1.50 [1.07, 2.10]. For
individuals with non-traumatic SCI, the odds of deterioration among those with neuropathic pain was 3.41 [2.19, 5.37] and with infection was 1.88 [1.09, 3.32]. For individuals with a complete injury, the odds of deterioration among those with neuropathic pain was 1.99 [1.34, 3.02] and with infection was 1.85 [1.29 2.83]. For individuals with an incomplete injury, the odds of deterioration among those with neuropathic pain was 2.47 [1.76, 3.49] and with infection was 1.60 [1.06, 2.44]. Thus, regardless of injury etiology or completeness of injury, the heightened odds persisted. Lastly, with respect to interaction terms in the multivariable models above, none of the interaction terms examined were statistically significant and thus were not included in the final model (according to AIC criteria).

**Missing Data**

To account for potential bias due to those reporting “don’t know” to any of the primary explanatory variables and the outcome variable, we examined the demographics of these individuals in comparison to those with valid responses (sex, age, and time since injury were collected on all participants regardless of their responses to the other questions). These demographic characteristics did not differ significantly between those with valid and those with invalid responses. Moreover, when using non-response as a separate response category (for exposures) in the multivariable analysis, the reported effects sizes for the primary exposures did not significantly change.
<table>
<thead>
<tr>
<th>AD</th>
<th>OH</th>
<th>CVD</th>
<th>Hypertension</th>
<th>Diabetes</th>
<th>Infection</th>
<th>N.Pain</th>
<th>Depression</th>
<th>Deterioration</th>
</tr>
</thead>
<tbody>
<tr>
<td>AD</td>
<td>-</td>
<td>4.78 [3.70, 6.19]</td>
<td>1.39 [0.83, 2.24]</td>
<td>1.38 [1.02, 1.86]</td>
<td>0.59 [0.36, 0.93]</td>
<td>2.87 [2.15, 3.83]</td>
<td>3.39 [2.46, 4.78]</td>
<td>2.02 [1.58, 2.58]</td>
</tr>
<tr>
<td>OH</td>
<td>4.78 [3.70, 6.19]</td>
<td>-</td>
<td>1.91 [1.19, 3.01]</td>
<td>1.35 [1.01, 1.78]</td>
<td>0.83 [0.55, 1.24]</td>
<td>2.75 [2.07, 3.64]</td>
<td>2.79 [2.08, 3.79]</td>
<td>2.71 [2.14, 3.43]</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.38 [1.02, 1.86]</td>
<td>1.35 [1.01, 1.78]</td>
<td>2.42 [1.49, 3.87]</td>
<td>-</td>
<td>3.44 [2.38, 4.95]</td>
<td>1.36 [0.96, 1.88]</td>
<td>1.23 [0.92, 1.66]</td>
<td>1.34 [1.03, 1.75]</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0.59 [0.36, 0.93]</td>
<td>0.83 [0.55, 1.24]</td>
<td>3.59 [2.07, 6.00]</td>
<td>3.44 [2.38, 4.95]</td>
<td>-</td>
<td>1.22 [0.77, 1.87]</td>
<td>0.91 [0.63, 1.35]</td>
<td>1.11 [0.77, 1.59]</td>
</tr>
<tr>
<td>Infection</td>
<td>2.87 [2.15, 3.83]</td>
<td>2.75 [2.07, 3.64]</td>
<td>1.86 [1.10, 3.04]</td>
<td>1.36 [0.96, 1.88]</td>
<td>1.22 [0.77, 1.87]</td>
<td>-</td>
<td>2.60 [1.82, 3.79]</td>
<td>2.11 [1.61, 2.77]</td>
</tr>
<tr>
<td>N. Pain</td>
<td>3.39 [2.46, 4.78]</td>
<td>2.79 [2.08, 3.79]</td>
<td>1.68 [1.00, 2.98]</td>
<td>1.23 [0.92, 1.66]</td>
<td>0.91 [0.63, 1.35]</td>
<td>2.60 [1.82, 3.79]</td>
<td>-</td>
<td>2.29 [1.78, 2.98]</td>
</tr>
<tr>
<td>Depression</td>
<td>2.02 [1.58, 2.58]</td>
<td>2.71 [2.14, 3.43]</td>
<td>1.82 [1.17, 2.81]</td>
<td>1.34 [1.03, 1.75]</td>
<td>1.11 [0.77, 1.59]</td>
<td>2.11 [1.61, 2.77]</td>
<td>2.29 [1.78, 2.98]</td>
<td>-</td>
</tr>
</tbody>
</table>

Table 6.1. Secondary Complications Matrix. Bivariable relationships between secondary complications following SCI. Colours relate to the strength of the relationship (point estimates for odds ratios): <1.00; 1.00-2.00; 2.01-3.00; 3.01-4.00; 4.01-5.00. Non-significant relationships are indicated in black. 95% Confidence intervals are in brackets. Abbreviations: AD=autonomic dysreflexia; OH=orthostatic hypotension; CVD=cardiovascular disease; N.Pain=neuropathic pain.
<table>
<thead>
<tr>
<th></th>
<th>Total N</th>
<th>N with CVD</th>
<th>N without CVD</th>
<th>Unadjusted OR for CVD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Neuropathic Pain</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frequent</td>
<td>937</td>
<td>64</td>
<td>873</td>
<td>1.76 (1.04, 3.14)</td>
</tr>
<tr>
<td>Infrequent</td>
<td>105</td>
<td>4</td>
<td>101</td>
<td>0.95 (0.27, 2.64)</td>
</tr>
<tr>
<td>Rare-Never†</td>
<td>426</td>
<td>17</td>
<td>409</td>
<td>1.00</td>
</tr>
<tr>
<td><strong>Shoulder Pain</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frequent</td>
<td>590</td>
<td>42</td>
<td>548</td>
<td>1.43 (0.91, 2.28)</td>
</tr>
<tr>
<td>Infrequent</td>
<td>181</td>
<td>7</td>
<td>174</td>
<td>0.75 (0.30, 1.62)</td>
</tr>
<tr>
<td>Rare-Never†</td>
<td>709</td>
<td>36</td>
<td>673</td>
<td>1.00</td>
</tr>
<tr>
<td><strong>Depression</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Most/all time</td>
<td>165</td>
<td>22</td>
<td>143</td>
<td>3.40 (1.88, 6.06)</td>
</tr>
<tr>
<td>Little/Some time</td>
<td>653</td>
<td>35</td>
<td>618</td>
<td>1.25 (0.76, 2.08)</td>
</tr>
<tr>
<td>None of the time †</td>
<td>669</td>
<td>29</td>
<td>640</td>
<td>1.00</td>
</tr>
</tbody>
</table>

Table 6.2. Raw (unadjusted) odds ratios for CVD. 95% confidence intervals are in brackets. N=sample size in given category. †Reference Category. Significant values (P<0.05) are bolded.
<table>
<thead>
<tr>
<th>Variable</th>
<th>AOR1 for CVD</th>
<th>AOR2 for CVD</th>
<th>AOR3 for CVD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuropathic Pain</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frequent</td>
<td>2.27 (1.21, 4.60)</td>
<td>2.09 (1.09, 4.29)</td>
<td>2.00 (1.04, 4.16)</td>
</tr>
<tr>
<td>Infrequent</td>
<td>1.65 (0.44, 5.04)</td>
<td>1.66 (0.44, 5.10)</td>
<td>1.74 (0.46, 5.43)</td>
</tr>
<tr>
<td>Rare-Never†</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Shoulder Pain</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frequent</td>
<td>-</td>
<td>1.28 (0.74, 2.22)</td>
<td>1.14 (0.65, 2.01)</td>
</tr>
<tr>
<td>Infrequent</td>
<td>-</td>
<td>0.69 (0.25, 1.63)</td>
<td>0.62 (0.22, 1.47)</td>
</tr>
<tr>
<td>Rare-Never†</td>
<td>-</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Depression</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Most/all time</td>
<td>4.07 (2.10, 7.87)</td>
<td>4.09 (2.10, 7.98)</td>
<td>4.18 (2.09, 8.35)</td>
</tr>
<tr>
<td>Little/Some time</td>
<td>1.33 (0.75, 2.38)</td>
<td>1.31 (0.74, 2.36)</td>
<td>1.33 (0.74, 2.45)</td>
</tr>
<tr>
<td>None of the time†</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
</tbody>
</table>

Table 6.3. Adjusted odds ratios (AORs) for cardiovascular CVD. 95% confidence intervals are in brackets. AOR1 is derived from a multivariable model including both neuropathic pain and depression as explanatory variables, and adjusting for injury etiology (traumatic vs. non-traumatic), current age, years since injury, sex, injury level (tetraplegia or paraplegia), and completeness of injury (motor complete [AIS A/B] versus incomplete [AIS C/D]). AOR2 was adjusted for the same variables as AOR1, with shoulder pain being an additional explanatory variable. AOR3 was adjusted for the same variables as AOR1, with shoulder pain, hypertension and diabetes as additional explanatory variables. Significant values (P<0.05) are bolded. Abbreviations: CVD=cardiovascular disease. †Reference Category.
<table>
<thead>
<tr>
<th>Variable</th>
<th>Unadjusted OR for CVD</th>
<th>AOR CVD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuropathic Pain Interferes with Daily Activities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Completely/Great Extent</td>
<td>1.49 (0.90, 2.45)</td>
<td>1.30 (0.66, 2.53)</td>
</tr>
<tr>
<td>Some/Very Little/Not at All†</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Depression Interferes with Daily Activities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Completely/Great Extent</td>
<td>1.19 (0.55, 2.36)</td>
<td>1.12 (0.48, 2.40)</td>
</tr>
<tr>
<td>Some/Very Little/Not at All†</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Shoulder Pain Interferes with Daily Activities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Completely/Great Extent</td>
<td>1.65 (0.91, 2.90)</td>
<td>1.38 (0.68, 2.72)</td>
</tr>
<tr>
<td>Some/Very Little/Not at All†</td>
<td>1.00</td>
<td>1.00</td>
</tr>
</tbody>
</table>

Table 6.4. Odds ratios for CVD. Unadjusted (raw) odds ratios (ORs) and adjusted ORs (AORs) for cardiovascular disease (CVD) among only those individuals with frequent and infrequent pain or depression. 95% confidence intervals are in brackets. †Reference Category.
**Table 6.5. Odds ratios for CVD.** 95% confidence intervals are in brackets. Abbreviations: AD=autonomic dysreflexia; OH=orthostatic hypotension; CVD=cardiovascular disease. N=sample size. Unadjusted OR is the raw OR for the bivariable effect of each variable on the outcome variable (CVD). AOR1-AD is the model where AD is the primary explanatory variable, and all other variables are included in this ‘full model.’ AOR2-AD is the model where AD is the primary explanatory variable, and other variables are only included in the model if they had a significant effect on the primary explanatory variable. AOR1-OH is the model where OH is the primary explanatory variable, and all other variables are included in this ‘full model.’ AOR2-OH is the model where OH is the primary explanatory variable, and other variables are only included in the model if they had a significant effect on the primary explanatory variable. The last column shows results of the model which included both AD and OH as primary explanatory variables. Dashes indicate instances where the given variable was not included in the model.

<table>
<thead>
<tr>
<th>Variable</th>
<th>N (%) or mean ± sd</th>
<th>Unadjusted OR</th>
<th>AOR1-AD Full Model</th>
<th>AOR2-AD Final Model</th>
<th>AOR1-OH Full Model</th>
<th>AOR2-OH Final Model</th>
<th>AOR-AD&amp;OH Final Model</th>
</tr>
</thead>
<tbody>
<tr>
<td>AD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frequent</td>
<td>221 (15.1)</td>
<td>1.34 (0.71, 2.39)</td>
<td>2.04 (0.95, 4.07)</td>
<td>1.93 (0.90, 3.81)</td>
<td>-</td>
<td>-</td>
<td>1.34 (0.58, 2.36)</td>
</tr>
<tr>
<td>Infrequent</td>
<td>140 (9.5)</td>
<td>1.45 (0.68, 2.80)</td>
<td>2.73 (1.22, 5.64)</td>
<td>2.51 (1.13, 5.13)</td>
<td>-</td>
<td>-</td>
<td>2.46 (1.09, 5.18)</td>
</tr>
<tr>
<td>Rare-Never†</td>
<td>1106 (75.4)</td>
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<td>1.00</td>
<td>1.00</td>
<td>-</td>
<td>-</td>
<td>1.00</td>
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<tr>
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<td></td>
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</tr>
<tr>
<td>Frequent</td>
<td>196 (13.0)</td>
<td>3.68 (1.48, 4.42)</td>
<td>-</td>
<td>-</td>
<td>3.68 (1.86, 7.06)</td>
<td>3.38 (1.73, 6.39)</td>
<td>2.91 (1.38, 5.90)</td>
</tr>
<tr>
<td>Infrequent</td>
<td>216 (14.3)</td>
<td>1.32 (0.66, 2.44)</td>
<td>-</td>
<td>-</td>
<td>1.96 (0.95, 3.80)</td>
<td>1.72 (0.84, 3.28)</td>
<td>1.78 (0.84, 3.56)</td>
</tr>
<tr>
<td>Rare-Never†</td>
<td>1101 (72.8)</td>
<td>1.00</td>
<td>-</td>
<td>-</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Age (years)</td>
<td>49.6 ± 13.9</td>
<td>1.04 (1.03, 1.06)</td>
<td>1.04 (1.02, 1.06)</td>
<td>1.04 (1.02, 1.06)</td>
<td>1.04 (1.02, 1.06)</td>
<td>1.04 (1.02, 1.06)</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
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<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Female†</td>
<td>1041 (67.2)</td>
<td>1.36 (0.85, 2.26)</td>
<td>1.39 (0.80, 2.51)</td>
<td>-</td>
<td>1.46 (0.84, 2.62)</td>
<td>-</td>
<td>1.52 (0.86, 2.81)</td>
</tr>
<tr>
<td>Time since injury (years)</td>
<td>18.5 ±14.3</td>
<td>1.00 (0.99, 1.02)</td>
<td>1.00 (0.98, 1.01)</td>
<td>-</td>
<td>1.00</td>
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<td>1.00</td>
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<tr>
<td>AIS</td>
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</tr>
<tr>
<td>A/B</td>
<td>685 (47.1)</td>
<td>1.48 (0.93, 2.41)</td>
<td>1.64 (0.95, 2.87)</td>
<td>1.64 (0.97, 2.84)</td>
<td>1.74 (1.01, 3.04)</td>
<td>1.99 (1.18, 3.42)</td>
<td>1.78 (1.02, 3.16)</td>
</tr>
<tr>
<td>C/D/E†</td>
<td>769 (52.9)</td>
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<td>1.00</td>
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<td>1.00</td>
<td>1.00</td>
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<tr>
<td>Injury Level</td>
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<tr>
<td>Cervical</td>
<td>656 (42.4)</td>
<td>0.80 (0.43, 1.50)</td>
<td>0.93 (0.45, 2.02)</td>
<td>0.98 (0.48, 2.11)</td>
<td>0.80 (0.39, 1.71)</td>
<td>0.78 (0.38, 1.63)</td>
<td>0.83 (0.40, 1.81)</td>
</tr>
<tr>
<td>Upper thoracic</td>
<td>253 (16.3)</td>
<td>1.00 (0.48, 2.07)</td>
<td>1.10 (0.44, 2.71)</td>
<td>1.12 (0.44, 2.76)</td>
<td>1.43 (0.61, 3.35)</td>
<td>1.46 (0.62, 3.42)</td>
<td>1.21 (0.48, 3.06)</td>
</tr>
<tr>
<td>Lower thoracic</td>
<td>323 (20.9)</td>
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<td>2.38 (1.14, 5.22)</td>
<td>2.34 (1.12, 5.08)</td>
<td>2.22 (1.07, 4.79)</td>
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<td>Lumbar†</td>
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<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
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<td>Diabetes</td>
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<tr>
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<td>143 (9.5)</td>
<td>3.59 (2.07, 6.00)</td>
<td>3.35 (1.80, 5.99)</td>
<td>3.33 (1.79, 5.95)</td>
<td>3.18 (1.72, 5.68)</td>
<td>3.74 (2.04, 6.59)</td>
<td>3.53 (1.89, 6.38)</td>
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<td>No†</td>
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<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Variable</td>
<td>Total</td>
<td>N or mean +/- SD with Neurological Deterioration</td>
<td>N or mean +/- SD with no Neurological Deterioration</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>------------------------------</td>
<td>---------</td>
<td>-----------------------------------------------</td>
<td>--------------------------------------------------</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>49.6 ± 13.9</td>
<td>52.2 ± 13.5</td>
<td>47.9 ± 14.0</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Sex</td>
<td>Male</td>
<td>960</td>
<td>387</td>
<td>573</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>461</td>
<td>197</td>
<td>264</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time Since Injury</td>
<td>18.4 ± 14.2</td>
<td>18.3 ± 14.9</td>
<td>18.5 ± 13.7</td>
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<td>Injury Etiology</td>
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Table 6.6. Study Group Characteristics.
Table 6.7. Odds ratios and adjusted odds ratios (AORs) for neurological deterioration. 95% confidence intervals are in brackets. The raw OR is the unadjusted OR. AOR4, AOR5, AOR6, and AOR7 (shaded) are adjusted for (in addition to the indicated variables) injury characteristics and demographics, including: injury etiology (traumatic vs. non-traumatic), current age, years since injury, sex, injury level (tetraplegia or paraplegia), and completeness of injury (motor complete [AIS A/B] versus incomplete [AIS C/D]). Significant values (P<0.05) are bolded. †Reference Category.

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<th>AOR2</th>
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<th>AOR5</th>
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<td>1.42 [1.06, 1.89]</td>
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<td>2.33 [1.81, 2.99]</td>
<td>-</td>
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<tr>
<td>Yes</td>
<td>873</td>
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<td>1.00</td>
<td>-</td>
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Figure 6.1. Odds ratios for neurological deterioration. Bars are 95% confidence intervals.
6.4 Discussion

General Relationships
Here, the relationship between several clinically relevant and well-known secondary complications were characterized in a sample of individuals with chronic SCI. From these bivariant relationships using binary response categories, we show that the majority of these secondary conditions are correlated.

Pain and Cardiovascular Disease
In examining some of these general relationships in a more in-depth fashion, we also showed that among a large sample of individuals with SCI, neuropathic pain and depression are significantly and independently associated with CVD. Conversely, non-neuropathic pain in the shoulder was not significantly associated with increased odds of CVD after SCI. This raises the interesting possibility that neuropathic pain may convey unique effects on cardiac functioning, resulting in an increased risk of disease. To our knowledge, this is the first study to link pain with CVD while controlling for depression, and the first to demonstrate differences in CVD risk based on the type of chronic pain (i.e., nociceptive versus neuropathic).

Unconventional risk factors for developing CVD after SCI: Inter-relationship between secondary complications
In Chapter 4, the increased risk of CVD after SCI was found to be in excess of the risk conferred by several well-known risk factors (e.g., smoking, hypertension, physical inactivity, diabetes, diet, alcohol, and obesity). Established risk factors in the general population, such as hypertension, may not apply after SCI due to the nature of the injury, including that damage in the spinal cord disrupts sympathetic flow to the heart, rendering the majority of individuals with injuries T6 or above with low resting blood pressure. To account for this discrepancy, other factors need to be considered.

While the incidence of secondary complications after SCI has been extensively studied, there is currently limited knowledge regarding if the occurrence of one condition (e.g., neuropathic pain/depression) affects the likelihood of developing another, seemingly unrelated condition (e.g., CVD). In principle, an understanding of the inter-
relationship between secondary conditions after SCI could lead to the identification of high-risk groups requiring targeted treatment and prevention strategies. For the first time, we have identified an association between previously unrelated secondary conditions after SCI, establishing a greater than 2-fold increased odds of CVD among individuals with neuropathic pain and 4-fold increase associated with depression. Our findings build on previous studies in the general population, which did not account for the inter-relationship between depression and pain, nor the impact of different types of pain on CVD. Furthermore, while we have demonstrated associations between pain, depression, and CVD in individuals with SCI, the implications of our study have much broader clinical implications. Indeed, other neurological conditions, accompanied by neuropathic pain and depression in the early stages of disease, and high incidence of CVD at later time-points (e.g., MS), may be subject to similar increased risk.

Potential mechanisms: physical inactivity, medications, and stress

There are several putative mechanisms linking neuropathic pain and depression with CVD. To address one potential candidate, we examined if interference with daily activity influenced the relationship with CVD. We hypothesized that individuals with neuropathic pain and depression may experience more interference with daily activities, which in turn may lead to higher risk of CVD, though we found no significant relationship.

Moreover, a number of other factors common to SCI, including medications, inflammation, and stress, should also be considered. Indeed, almost all classes of drugs commonly used to manage neuropathic pain and depression have been associated with deleterious cardiovascular effects, including anti-convulsants (e.g., congestive heart failure), anti-depressants (e.g., heart disease), and non-steroidal anti-inflammatories (e.g., stroke). Non-traditional medications commonly used to treat pain (e.g., cannabis) may also increase the risk of CVD. In the case of SCI, a variety of medications are often used to simultaneously manage pain symptoms, particularly neuropathic pain, as well as depression, and other secondary conditions (e.g., spasticity). Moreover, coronary heart disease is more common in the general population subjected to chronic stress and inflammation, a process thought to be mediated by the over activation of several neuroendocrine systems, including the hypothalamic–pituitary axis (HPA).
In terms of explaining why neuropathic but not nociceptive pain increased the odds of CVD, we had hypothesized that neuropathic pain may be more severe, and thus have a greater impact on cardiovascular health. While there appeared to be no major differences with respect to interference with activities of daily living on CVD between those individuals reporting neuropathic versus non-neuropathic pain, this may not perfectly capture physical activity levels. For example, neuropathic pain may lead to greater reductions in physical activity than non-neuropathic pain, be accompanied by more frequent use and higher dosages of pain medications, and lead to higher levels of discomfort and stress. Indeed, neuropathic pain is often reported as severe among individuals with SCI, and refractory to most treatment options. Shoulder pain may also take a longer time to develop compared to neuropathic pain, which, in turn, has a lesser impact on cardiovascular health.

**AD and OH with Cardiovascular Disease**

*Orthostatic Hypotension*

Our findings are in agreement with other studies from able-bodied elderly populations which have shown an increased risk of stroke, acute myocardial infarction, congestive heart failure, and death among individuals with orthostatic hypotension. In these studies, OH conferred an approximate 1.3- and 2.0- fold increased risk of coronary heart disease and stroke, respectively (based on adjusted hazards ratios). Here, we report an almost 3-fold increased adjusted odds of recent CVD among SCI individuals with frequent OH.

It has been previously shown that individuals with SCI have an increased odds of stroke and heart disease compared with individuals without SCI. These prior studies did not, however, take into account either the AD or OH status of the study subjects with SCI. Given the significant association we show here between OH with CVD, it is tempting to speculate that the heightened odds of CVD among individuals with SCI (relative to able bodied individuals) is at least in part due to OH, in addition to neuropathic pain and depression.
The pathophysiological mechanisms for OH causing CVD are currently unknown. Others have speculated from studies in hypertensive individuals in the general population that the association is due to reduction in coronary and cerebral blood flow resulting in ischaemia. Given that individuals with SCI, particularly those with higher lesions, tend to experience chronic hypotension in addition to OH, there may be unique CVD pathophysiology specific to individuals with SCI. We were not able to capture the effects of chronic hypotension in this study, though it will be of interest to investigate in future studies.

Other mechanisms relating OH with CVD among individuals with SCI may be related to the renin-angiotensin-aldosterone system (RAAS), the hormonal system responsible for blood pressure control, which has been implicated in the progression of vascular degeneration in able-bodied individuals, and which is significantly altered post-SCI. Due to the loss of descending supraspinal control on sympathetic cardiovascular circuitry, persons with higher injuries tend to rely more heavily on the RAAS for orthostatic blood pressure maintenance: the dependency on the RAAS for blood pressure maintenance during an orthostatic challenge is approximately 130% increased in persons with tetraplegia compared with able-bodied controls. This RAAS-mediated sequelae leading to vascular dysfunction may be another mechanism relating OH and CVD.

With respect to OH, it was interesting to note that the prevalence was relatively high in our SCI cohort. In the able bodied population, studies of the Honolulu Heart Program cohort (n=3,522) reported a prevalence of OH (using clinical measurements) in 71-74 year olds, 75-79 year olds, 80-84 year olds, and 85+ as 5.1%, 6.3%, 9.2%, and 10.9%, respectively. Interestingly, the prevalence of OH in our study with an average age of only 48.3 years was 27.6% (those who experienced frequent or infrequent OH), significantly higher than the 85+ group from the Honolulu study.
**Autonomic Dysreflexia**

With respect to AD, several case reports have implied a causal relationship between AD and acute myocardial infarction and between AD and stroke.\(^{40,198}\) To our surprise, infrequent AD was associated with a significantly increased odds of CVD, though frequent AD was not. However, a post hoc analysis indicated that when we combine both categories for AD (infrequent and frequent), the fully adjusted odds of CVD is $1.39 \, [0.83, 2.24]$, i.e., there is no significant association. This may reflect the true association, or may have been a result of the limited sample size with respect to the outcomes. As we were only able to capture recent outcomes, this may have underestimated the number of cases, particularly of stroke. As AD may have differential effects on stroke versus heart disease, which we could not tease out in this study with our composite outcome, this ought to be the subject of future investigation. Further, we were not able to capture asymptomatic AD ("silent AD"), which is known to occur in some individuals.\(^{235}\) Conversely, the anecdotal case reports implying a causal relationship between AD and CVD did not take into consideration other factors that may contribute to CVD risk. These studies also did not take into consideration that AD is not a sporadic event, but rather is a frequently occurring event (i.e., the co-occurrence of AD with CVD may have been coincidental).

**Neurological Deterioration**

Adjusting for subject demographics and injury characteristics, the results of the present study demonstrate a significant association between pain (and pain medications) and infections with neurological deterioration in a large cohort of individuals with chronic SCI, as well as significant associations between infections and pain themselves. While we cannot determine the direction of this relationship, that is, whether infections are causing neurological deterioration or vice versa, this is the first study in humans to support the idea that secondary complications may influence neurological function in chronic stages of injury, and is consistent with clinical observation.

The presence of neurological deterioration remains understudied among individuals with chronic SCI. Indeed, in other conditions where neurological deterioration is better studied (eg. multiple sclerosis), deterioration significantly affects activities of daily living and
quality of life, particularly due to the unpredictable nature of the onset/duration of impairment. Very little is known about what initiates deterioration in chronic stages, but immunological mechanisms seem to play a major role. Among individuals with MS, there is good evidence that clinical manifestations of exacerbations are the result of focal areas of inflammation that block impulse conduction. The central role of the immune system in the pathogenesis of exacerbations is further supported by the observed influence of clinically manifest infections: these situations of increased release of inflammatory mediators increase the exacerbation rate.

However, deterioration in the chronic stages of SCI is a major knowledge gap within the field. Only one other study, to our knowledge, has identified the presence of deterioration in the chronic stages of SCI. In this study, an estimated 2% of individuals (n=153) with SCI developed neurological deterioration (measured in this study by ‘decreases in motor power’). In this case, neurological deterioration was attributed primarily to syrinx formation and atrophy of the spinal cord, although syrinx formation and atrophy were reported in a small fraction of these subjects. Indeed, the presence of neurological deterioration was much higher in the present study, likely due to the broader definition of deterioration used here.

Lastly, while the relationship between infections and neurological outcomes has been recently examined in the acute stages, the relationship between pain and neurological outcomes in the acute stages of injury has not been studied in the field of SCI, and is therefore an important future direction (studied in more detail in following chapter).

Study Limitations and Future Directions
There are some limitations of the current study. Firstly, the data are derived from a cross-sectional design, which does not allow us to determine the temporality in the exposure-outcome relationship. However, AD and OH are both conditions that tend to develop shorting following SCI: the vast majority of individuals develop AD and OH within the first year post-injury. Since we were examining only individuals at least one-year post injury, it is highly likely that the AD and OH conditions preceded CVD. It is also certain that SCI preceded CVD since we asked only about CVD that occurred within the past year, and our cohort was relatively young compared with CVD occurrences in the
general population. Moreover, because we were only examining recent events, this put limitations on our sample size, and required the use of composite outcome and exposures. Future studies should examine stroke and heart disease outcomes separately, ideally with subclassifications for these as well, such as ischaemic vs. hemorrhagic stroke, myocardial infarction vs. heart disease (e.g. coronary artery disease), and separate classifications for infection.

Moreover, neuropathic pain is also present in the acute stages of injury (i.e., at time-points before CVD will have developed)\(^{188}\) and typically persists into the chronic stages of injury (i.e., when CVD is observed). Regardless, we cannot exclude the possibility that CVD has an effect on both neuropathic pain and depression (i.e., bidirectional), as well as the bi-directional relationship between pain/infection and neurological deterioration.

Secondly, although the data here are from self-report, any misclassification of outcome status or other measures would likely be non-differential by exposure status (and vice-versa). Moreover, self-report heart disease, stroke, depression, neuropathic pain, infection, OH, and neurological level/completeness have been validated against clinical records and tests in other (non-SCI) studies, demonstrating a relatively high accuracy of self-report, generally with higher specificity than sensitivity.\(^{179, 180, 239-243}\) Self-report AD has also shown to be valid among individuals with SCI, using 24-hour ambulatory blood pressure monitoring (Hubli et al., in press). Also, we performed internal validation analyses, such as examining self-report AD against neurological level (since AD tends to occur in higher thoracic and cervical injuries).\(^{35}\)

With regards to reporting neuropathic pain, compared to an earlier survey study, our findings indicate a similar prevalence (~65%).\(^{244}\) In terms of the wording of the question used to capture neuropathic pain, *tingling, burning and shooting*, are among the most common (and validated) descriptions of neuropathic pain after SCI.\(^{244}\) Furthermore, descriptions of spontaneous and allodynic pain (brushing) should have provided clarity to distinguish neuropathic from other types of pain (i.e., musculoskeletal). While we believe we were able to sensitively determine those individuals with SCI and neuropathic pain, this questionnaire did not include a measure of pain intensity; future studies should
consider incorporating a numeric rating scale of pain intensity in addition to frequency. Regarding the question used to capture non-neuropathic pain, other shoulder problems unrelated to pain may have been reported – pain was provided as only one common example of a shoulder problem. Indeed, some individuals may have interpreted their lack of movement or sensation in the shoulder, potentially unrelated to pain (e.g., heterotopic ossification), and were therefore not actually been experiencing chronic shoulder pain. Furthermore, other types of nociceptive pain were not considered (e.g., knee pain due to locomotor training or post-operative pain). However, given the difficulty of distinguishing below-level neuropathic and nociceptive pain also incurred below level, particularly based on self-report, shoulder pain may represent the most sensitive and specific surrogate measure of non-neuropathic pain. With regards to self-report neurological deterioration, there may have been some misclassification of deterioration based on pain status (i.e., individuals may have reported ‘deterioration’ as a result of changes in pain).

Lastly, we were not able to capture variables (unmeasured confounders) such as smoking status as well as obesity/BMI, though these effects were likely captured through adjustment for hypertension and diabetes status. In addition, we show in Chapter 4 that BMI is a poor predictor of CVD risk in individuals with SCI.

These limitations aside, these correlations between secondary complications are an impetus for future investigations. Although there is physiological plausibility for a causal relationship between these complications, future research is needed to better understand this. Additional cohort studies, with the use of SCI-specific registries linked with other health data, and which have records of timing of onset of conditions, medication information, and physiological data (eg. imaging and electrophysiology), are needed to build on this evidence and to provide evidence-based guidelines. Indeed, based on all the results presented, it is not advantageous to look at these relationships independently. Future clinical practice guidelines may, instead of focusing on a secondary complication in isolation, focus on chronic health management in general. It will also be important to examine whether interventions for mitigating secondary complications among individuals with SCI, modify this suggested heightened risk.
CHAPTER 7
RELATIONSHIPS BETWEEN SECONDARY COMPLICATIONS AND NEUROLOGICAL OUTCOMES FOLLOWING SCI:
Focus on neuropathic pain in acute stages

Having examined the relationship between secondary complications and neurological deterioration in the previous chapter, and having noted a significant relationship between pain (and pain medications) and neurological deterioration in the chronic stages of SCI, we next examined the relationship between pain and neurological motor recovery during acute stages (the last step of our Conceptual Model, Figure 1.1; Objective 3B). This area of study is important because there is considerable variability in how people recover during the transition from acute to chronic SCI. Our primary research interest was to determine if an acute secondary complication and the management of secondary complications had the potential to contribute to variability in neurological recovery after SCI. The potential impact of acute secondary complications on neurological outcomes is a relatively novel area of investigation (only one previous study examining the impact of infections on neurological outcomes has been previously published), and places additional emphasis on implementing adequate management early after injury. Because EM-SCI contains a rich pain data subset that we linked with the large-scale EM-SCI database containing neurological outcomes, we were also able to examine how pain-related factors (eg. medications and classifications) impact neurological recovery. The focus on pain at this point was because the EM-SCI does not capture other secondary complications (eg. cardiovascular or respiratory). As mentioned in the introductory chapters, it is important to distinguish deterioration (discussed in Chapter 5) from neurological recovery (discussed here), as both represent (and define in fact) distinct stages (physiological and functional) of the SCI continuum.

7.1 Introduction
Approximately 60% of patients suffering from acute SCI develop nociceptive or neuropathic pain within days to weeks after injury, which ultimately persists into chronic stages.66, 188, 247, 248 To date, the deleterious consequences of pain after SCI, as well as the effectiveness of pain management, have been largely examined in terms of interfering
with quality of life and functional independence.\textsuperscript{194, 249} However, preclinical studies indicate that neuropathic pain and treatment of pain with different classes of medications may also impact neurological outcomes. Indeed, the neuromodulatory properties of pain and almost every major class of pain medication, including antidepressants, anticonvulsants, non-steroidal anti-inflammatories (NSAIDs), and opioids, has been demonstrated in animal models mimicking damage in the central nervous system (CNS).\textsuperscript{205-211} Furthermore, acute nociceptive and neuropathic pain often necessitates treatment during the early stages of injury, during a window of opportunity to ameliorate secondary injury mechanisms (i.e., neuroprotection).\textsuperscript{205}

The primary aim of this study was to examine the hypothesis that pain outcomes (i.e., classification and intensity), as well as pain management (i.e., medications) may impact the course of neurological recovery in humans after SCI. The effects of two different drug classes were specifically examined: medications typically administered to manage neuropathic pain (i.e., anticonvulsants), and medications more generally administered for the management of nociceptive (i.e. musculoskeletal) pain symptoms (i.e., NSAIDS).

\textbf{7.2 Methods}

\textit{Data Source and Study Design: European Multi-center Study about Spinal Cord Injury}

This was a cohort (longitudinal) study of individuals in the European Multi-center Study about Spinal Cord Injury (EM-SCI). The EM-SCI is an internationally recognized clinical SCI network, with data management centralized at the University Hospital Balgrist in Zurich, Switzerland. Comprised of 19 participating trauma and rehabilitation centers from across Europe, neurological, neurophysiological, and functional outcomes are comprehensively tracked in individuals with SCI at fixed time-points over the first year of injury. Several publications have arisen from the EM-SCI database (www.emsci.org).\textsuperscript{250, 251} All patients gave their written informed consent before being included in the database. The study is in accordance with the Declaration of Helsinki and was approved by all responsible institutional review boards.
Inclusion and Exclusion Criteria

To be included in EM-SCI, individuals must have met the following criteria: the patient was capable and willing to give written informed consent, the first EM-SCI assessment was possible within the first 6 weeks following injury, and the injury was a single event (traumatic or ischemic paraplegia or tetraplegia). Exclusion criteria were: non-traumatic paraplegia or tetraplegia (i.e., disc protrusion, tumour, AV-malformation, myelitis), previously known dementia or severe reduction of intelligence leading to reduced capabilities of cooperation or giving consent, previously known polyneuropathy, and relevant brain injury.

Pain questionnaire

Initiated in 2007, seven member centers of the EM-SCI participated in the collection of pain questionnaire data (which was linked to the core EM-SCI data). Briefly, the structured interview is comprised of the assessment of pain related features, including the intensity, location, time to onset, frequency, as well as alleviating and aggravating factors. Pain was classified as nociceptive or neuropathic by trained examiners according to international standards. Neuropathic pain comprised at- and below-level symptoms, described as burning, stabbing, electric, or shooting. According to established definitions, symptoms located diffusely three levels or more caudal to the neurological level of the SCI was defined as “below-level” neuropathic pain. Major pain medications prescribed, including the use of antidepressants, anticonvulsants, NSAIDS, and opioids, were recorded. Pain intensity was determined for the maximum over a 2-week period.

Neurological outcomes: International Standards for the Neurological Classification of Spinal Cord Injury

Neurological function was examined according to established international standards (i.e., International Standards for the Neurological Classification of Spinal Cord Injury [ISNSCI]). In brief, muscle strength is evaluated on a 5-point scale (0 to 5, complete paralysis to normal strength, against resistance) in 5 key myotomes in the upper and lower extremities. Pinprick and light touch sensation is examined in 28 dermatomes (C2-
C8, T1-T12, L1-L5, S1-S4/S5). Based on patient report, sensation is rated as abolished, impaired, or normal. From the motor and sensory scores, the American Spinal Injury Association Impairment Scale Grade (AIS-grade) is determined as a measure of injury severity (A, B, C or D). To ensure the quality of ISNCSCI, examiners at EM-SCI centers annually participate in training. All scores from the motor and sensory exam are imputed into a computer algorithm for accurate determination of sub-scores (e.g., AIS-grade).253

*Outcome and Exposure Assessments*

Individuals were followed at four fixed time points following injury: 1, 3, 6, and 12 months post injury. Total motor score (maximum value = 100) was the primary outcome variable, assessed at each of the four time points. Upper extremity motor score (UEMS) and lower extremity motor score (LEMS), both of which combine to form the total motor score (each with a maximum value of 50), were also examined in a posthoc analysis (see Unbiased Recursive Partitioning). Three pain-related variables collected at one month were used as primary explanatory variables: 1) pain classification (none, neuropathic, or nociceptive), 2) pain intensity (maximum over past two weeks, scale from 0-10), and 3) pain drug classification: NSAID and anticonvulsant use. A secondary analysis was performed on pain intensity (i.e., where intensity was the outcome), modelling the effects of one-month anticonvulsant use on pain intensity (i.e., drug efficacy).

*Statistics*

To take into account the longitudinal nature of the data (e.g., individual trajectories over the four time points), we analyzed the data using mixed effects models. Mixed effects models are advantageous over traditional methods (e.g., repeated-measures ANOVA) for several reasons: 1) they allow for non-linear trends in data (e.g., through the use of polynomial terms), 2) random effects can be included to capture and quantify patient-level variability, and 3) unbalanced data as well as unevenly spaced time points (eg. data at 1, 3, 6, and 12 months post injury) can be appropriately handled. To build the statistical models, the individual trajectories over the four time points were visually examined using ‘spaghetti’ plots. Akaike Information Criterion (AIC) was used to statistically compare non-nested models – that is, to determine if additional terms such as polynomial or
interaction terms statistically improved models. The Likelihood Ratio Test was used to compare nested models. As our primary interest was in rates of motor recovery, we examined if covariates (e.g., explanatory variables described above) affected these rates using formal testing of interaction terms (covariate-time interactions). R Statistical Software Version 2.15.3 was used for all analyses. The R package lme was used for the mixed models.

**Unbiased recursive partitioning**

In addition to utilizing mixed effects models to examine changes over time in the recovery of motor function, we were also interested in addressing if pain factors (i.e., classification and medications) had specific effects within different cohorts. To this end, we employed ‘unbiased recursive partitioning’ – a technique utilizing conditional inference trees (URP-CTREE). URP is a tree-structured regression model based on sequential tests of independence between predictors and a specified clinical endpoint (i.e., future outcome). More detailed information can be found elsewhere. In brief, URP-CTREE divides an initial heterogeneous population into successively disjoint and more homogeneous pairs of subgroups with regard to the clinical endpoint of interest, and thus creates an algorithm for predicting future outcomes within more homogeneous subgroups. The R package rpart was used for the URP.

**Step 1:** Association of early predictors (subject’s characteristics) with the clinical endpoint (outcome). The algorithm assesses whether any early predictor is statistically associated with the selected clinical endpoint. This is performed by individually calculating the statistical association of each possible predictor–endpoint pair (no data are presumed to be normally distributed). To each association, a multiple-testing corrected P-value is assigned (i.e, Bonferroni correction). If the initial null hypothesis of total independence between predictors and outcome cannot be rejected (no statistically significant association between any early predictor and the endpoint), the algorithm stops without producing any split of the initial population. On the contrary, if the null hypothesis of independence can be rejected, meaning that at least one early predictor is
significantly associated with the subsequent clinical endpoint, then the algorithm selects the predictor with the strongest statistical association (smallest $P$-value) and passes it to step 2.

**Step 2**: Splitting procedure for defining more homogeneous pairs of subgroups. Once the most significant predictor has been selected (as expressed in step 1), the algorithm evaluates all possible dichotomous splits on this variable, each one inevitably producing 2 subgroups. The goodness of each split is evaluated by a two-sample $t$-statistic (eg, $\chi^2$ statistic for a binary outcome), to maximize the discrepancy between the newly formed subgroups. This partitions the initial population into 2 subgroups that are as distinct as possible.

**Iterative steps**: Recursively proceed to identify any additional early characteristics (predictors) that significantly predict the selected clinical endpoint. The recursive part of the algorithm starts over and the 2 fundamental steps (steps 1 and 2 listed above) are repeated separately for 2 newly formed subgroups. The URP-CTREE calculations proceed until no more statistically significant predictors are associated with the selected endpoint (null hypothesis cannot be rejected).

### 7.3 Results

*Study cohort description*

Table 7.1 shows basic demographics and other characteristics of the study sample at all time-points after injury. One-month baseline subject and injury characteristics based on medication classification are shown in Table 7.2.

*Pain and neurological recovery*

Table 7.3 and 7.4 shows the output from mixed effects analysis: AIS-adjusted and unadjusted models. In each of these models (and subsequent tables), we were interested in comparing the rates of recovery between each group (i.e., the interaction term indicated in the table). We found that regardless of how pain classification was modelled (i.e., pain versus no pain, neuropathic pain versus no neuropathic pain), there was no significant effect on the rate of neurological recovery (Table 7.3 and Table 7.4)
respectively; \(P>0.05\) for interaction terms). As expected, AIS grade had a significant effect on total motor score recovery: individuals with motor incomplete injuries (AIS-C and D) recovered more than individuals with complete injuries (AIS-A).

*Pain medications and neurological recovery*

Table 7.5 shows the relationship between anticonvulsant use at one month and total motor score recovery. In an unadjusted model, the use of anticonvulsants at one-month post injury significantly improved neurological recovery (drug \(X\) time interaction: \(p=0.031\)). According to the mixed effects model, individuals who were treated at this early time point with anticonvulsant drugs recovered an average of 7.3 motor points greater over the first year compared to those untreated with anticonvulsants (Figure 7.1A, Table 7.5). Importantly, the effect of anticonvulsants persisted after adjusting for initial AIS-grade \((p=0.039)\).

We also examined whether the effect of anticonvulsants on neurological recovery was confounded by initial pain intensity (i.e., two week maximum), initial pain classification (i.e., neuropathic versus non-neuropathic), other pain-related medications administered at the first time point (i.e., opioids [\(n=63\) at one month] and antidepressants [\(n=46\) at one month]), as well as injury level (i.e., tetraplegia vs. paraplegia). After adjusting the model for each of these factors, the effect of anticonvulsants on neurological recovery remained relatively unchanged (i.e., approximately 7 points over one year, \(P<0.05\) for interaction term).

By contrast, NSAID use at one month post injury had no significant affect on neurological recovery (drug \(X\) time interaction: \(P=0.586\) and \(P=0.593\), unadjusted and adjusted for AIS-grade, respectively; Figure 7.1B and Table 7.6).

*Effect of anticonvulsants on pain intensity*

In addition to influencing neurological recovery, the use of anticonvulsants significantly reduced maximum pain intensity in individuals initially classified with nociceptive and neuropathic pain \((P=0.04\) for time \(X\) drug interaction; Figure 7.2). The effect of
anticonvulsants on pain intensity persisted after adjusting for initial pain classification (nociceptive versus neuropathic, \( P=0.03 \) for interaction term).

**Clinical Prediction Trees: Unbiased recursive partitioning (URP)**

To include the greatest number of subjects, URP focused on changes in motor scores between 1 and 6 months. Initial motor scores at one-month and whether they were administered anticonvulsants and NSAIDs were included as explanatory variables. Only those explanatory variables that are significant predictors of outcome (i.e., motor recovery between 1 and 6 months) are present in the trees. Figure 6.3 shows that anticonvulsants are indeed significant predictors of changes in UEMS, notably among those with a baseline UEMS of <40. Conversely, in the lower extremities, there was a significant effect of anticonvulsants on changes in LEMS, but this did not depend on initial LEMS (results not shown). NSAIDs, by contrast, were not significant predictors of changes in upper or lower extremities.
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>1 month</th>
<th>3 months</th>
<th>6 months</th>
<th>12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>225</td>
<td>204</td>
<td>165</td>
<td>136</td>
</tr>
<tr>
<td>Male Female</td>
<td>180, 45</td>
<td>163, 41</td>
<td>132, 33</td>
<td>109, 27</td>
</tr>
<tr>
<td>Total Motor Score</td>
<td>53·15 ± 25·89</td>
<td>59·33 ± 26·33</td>
<td>62·36 ± 28·51</td>
<td>65·93 ± 26·98</td>
</tr>
<tr>
<td>Pain Intensity</td>
<td>6·8 ± 2·2</td>
<td>6·4 ± 2·3</td>
<td>6·8 ± 2·2</td>
<td>6·1 ± 2·2</td>
</tr>
</tbody>
</table>

Table 7.1 Cohort description. Results are expressed as N or mean ± standard deviation.
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Anticonvulsant</th>
<th>NSAID</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>YES (N=40)</td>
<td>NO (N=185)</td>
</tr>
<tr>
<td>Male</td>
<td>27 (67·5)</td>
<td>153 (82·7)</td>
</tr>
<tr>
<td>Female</td>
<td>13 (32·5)</td>
<td>32 (17·3)</td>
</tr>
<tr>
<td>Age at Injury (years)</td>
<td>47·8 ± 13·6</td>
<td>47·9 ± 18·6</td>
</tr>
<tr>
<td>AIS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>12 (30·0)</td>
<td>70 (37·8)</td>
</tr>
<tr>
<td>B</td>
<td>3 (7·5)</td>
<td>20 (10·8)</td>
</tr>
<tr>
<td>C</td>
<td>8 (20·0)</td>
<td>31 (16·8)</td>
</tr>
<tr>
<td>D</td>
<td>17 (42·5)</td>
<td>64 (34·6)</td>
</tr>
<tr>
<td>Paraplegia</td>
<td>16 (40·0)</td>
<td>86 (46·5)</td>
</tr>
<tr>
<td>Tetraplegia</td>
<td>24 (60·0)</td>
<td>96 (51·9)</td>
</tr>
<tr>
<td>Total Motor Score</td>
<td>55·6 ± 27·3</td>
<td>52·6 ± 25·6</td>
</tr>
<tr>
<td>Intensity</td>
<td>7·3 ± 2·1</td>
<td>6·7 ± 2·3</td>
</tr>
<tr>
<td>Pain Classification</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>5 (12·5)</td>
<td>59 (31·9)</td>
</tr>
<tr>
<td>Nociceptive</td>
<td>19 (47·5)</td>
<td>79 (42·7)</td>
</tr>
<tr>
<td>Neuropathic</td>
<td>16 (40·0)</td>
<td>47 (25·4)</td>
</tr>
</tbody>
</table>

Table 7.2 Cohort description by drug status at first time-point. Results are expressed as N (%) or mean ± standard deviation. Abbreviations: AIS= American Spinal Injury Association (ASIA) Impairment Scale.
<table>
<thead>
<tr>
<th>Variable</th>
<th>Coefficient</th>
<th>SE</th>
<th>P-Value</th>
<th>Coefficient</th>
<th>SE</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Unadjusted Effects</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intercept</td>
<td>45·98</td>
<td>3·27</td>
<td>P&lt;0·001</td>
<td>31·20</td>
<td>2·73</td>
<td>P&lt;0·001</td>
</tr>
<tr>
<td>Time Post Injury</td>
<td>0·11</td>
<td>0·01</td>
<td>P&lt;0·001</td>
<td>0·11</td>
<td>0·01</td>
<td>P&lt;0·001</td>
</tr>
<tr>
<td>Time Post Injury²</td>
<td>-0·0002</td>
<td>0·0002</td>
<td>P&lt;0·001</td>
<td>-0·0002</td>
<td>0·0002</td>
<td>P&lt;0·001</td>
</tr>
<tr>
<td>Any Pain</td>
<td>7·49</td>
<td>3·82</td>
<td>0·051</td>
<td>3·23</td>
<td>2·78</td>
<td>0·247</td>
</tr>
<tr>
<td>Time Post Injury * Any Pain</td>
<td>0·003</td>
<td>0·007</td>
<td>0·681</td>
<td>0·002</td>
<td>0·007</td>
<td>0·818</td>
</tr>
<tr>
<td><strong>Adjusted Effects</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AIS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B vs. A</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>3·06</td>
<td>4·17</td>
<td>0·464</td>
</tr>
<tr>
<td>C vs. A</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>13·14</td>
<td>3·44</td>
<td>P&lt;0·001</td>
</tr>
<tr>
<td>D vs. A</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>42·81</td>
<td>2·79</td>
<td>P&lt;0·001</td>
</tr>
</tbody>
</table>

Table 7.3. Effect of early pain classification (nociceptive or neuropathic versus no pain) on neurological recovery (total motor score). Results from mixed effects regression models. Note: units of time are in days post-injury. Any pain= nociceptive or neuropathic AIS= ASIA Impairment Scale; SE=Standard Error. Shaded portion: model adjusted for AIS; un-shaded portion: model not adjusted for AIS.
<table>
<thead>
<tr>
<th>Variable</th>
<th>Unadjusted Effects</th>
<th>Adjusted Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Coefficient</td>
<td>SE</td>
</tr>
<tr>
<td>Intercept</td>
<td>48·61</td>
<td>2·07</td>
</tr>
<tr>
<td>Time Post Injury</td>
<td>0·11</td>
<td>0·009</td>
</tr>
<tr>
<td>Time Post Injury²</td>
<td>-0·0002</td>
<td>0·00002</td>
</tr>
<tr>
<td>Neuropathic Pain</td>
<td>9·77</td>
<td>3·80</td>
</tr>
<tr>
<td>Time Post * N· Pain</td>
<td>0·009</td>
<td>0·007</td>
</tr>
<tr>
<td>AIS</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>B vs. A</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>C vs. A</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>D vs. A</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Table 7.4. Effect of neuropathic pain on neurological recovery (total motor score). Results from mixed effects regression models. Note: units of time are in days post-injury. AIS= ASIA Impairment Scale; SE=standard error. Shaded portion: model adjusted for AIS; un-shaded portion: model not adjusted for AIS.
<table>
<thead>
<tr>
<th>Variable</th>
<th>Unadjusted Effects</th>
<th>Adjusted Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Coefficient</td>
<td>SE</td>
</tr>
<tr>
<td>Intercept</td>
<td>50.72</td>
<td>1.97</td>
</tr>
<tr>
<td>Time Post Injury</td>
<td>0.11</td>
<td>0.009</td>
</tr>
<tr>
<td>$Time Post Injury^2$</td>
<td>-0.0002</td>
<td>0.0002</td>
</tr>
<tr>
<td>Drug (Anticonvulsant)</td>
<td>3.67</td>
<td>4.52</td>
</tr>
<tr>
<td>$Time Post Injury \ast Drug$</td>
<td>0.02</td>
<td>0.008</td>
</tr>
<tr>
<td>AIS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B vs. A</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>C vs. A</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>D vs. A</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Table 7.5. Results from mixed effects regression models of anticonvulsant drugs on neurological recovery (total motor score). Note: units of time are in days post-injury. AIS= ASIA Impairment Scale; SE=Standard Error. Shaded portion: model adjusted for AIS; un-shaded portion: model not adjusted for AIS.
<table>
<thead>
<tr>
<th>Variable</th>
<th>Coefficient</th>
<th>SE</th>
<th>P-Value</th>
<th>Coefficient</th>
<th>SE</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>48·13</td>
<td>2·79</td>
<td>P&lt;0·001</td>
<td>31·12</td>
<td>2·54</td>
<td>P&lt;0·001</td>
</tr>
<tr>
<td>Time Post</td>
<td>0·11</td>
<td>0·01</td>
<td>P&lt;0·001</td>
<td>0·11</td>
<td>0·01</td>
<td>P&lt;0·001</td>
</tr>
<tr>
<td>Time Post²</td>
<td>-0·0002</td>
<td>0·0002</td>
<td>P&lt;0·001</td>
<td>-0·0002</td>
<td>0·0002</td>
<td>P&lt;0·001</td>
</tr>
<tr>
<td>NSAID</td>
<td>5·34</td>
<td>3·53</td>
<td>0·132</td>
<td>3·62</td>
<td>2·55</td>
<td>0·157</td>
</tr>
<tr>
<td>Time Post *NSAID</td>
<td>-0·004</td>
<td>0·007</td>
<td>0·586</td>
<td>-0·003</td>
<td>0·007</td>
<td>0·593</td>
</tr>
</tbody>
</table>

**Table 7.6. Effect of NSAIDS on neurological recovery (total motor score).** Results from mixed effects regression models. Note: units of time are in days post-injury. AIS= ASIA Impairment Scale; SE=Standard Error. Shaded portion: model adjusted for AIS; un-shaded portion: model not adjusted for AIS.
Figure 7.1. Effect of pain medications on motor recovery following spinal cord injury. A. Effect of anticonvulsants on motor recovery following spinal cord injury. Fitted curves derived from mixed-effects models. Red: Anticonvulsant-users; Blue: Non-anticonvulsant users. *P=0.031 for interaction effect. B. Effect of NSAID use on motor recovery following spinal cord injury. Fitted curves derived from mixed-effects models. Red: NSAID-users; Blue: Non-NSAID users. C. Difference between motor scores (fitted values) at each time point between anticonvulsant users and non-users (blue) and between NSAID users and non-users (green).
Figure 7.2. Effect of anticonvulsant use on pain intensity following SCI. Fitted curves derived from linear mixed-effects models. Red: Anticonvulsant-users; Blue: No-anticonvulsant.
Figure 7.3. Result tree of unbiased recursive partitioning. Outcome: change in upper extremity motor score (UEMS) from 1 to 6 months post injury. Each box contains a box plot (dark horizontal line is the median value) for UEMS in each group. The analysis was run on all study subjects.
7.4 Discussion
In the present observational study, we have provided empirical preliminary evidence, through a secondary analysis of data, that medications for the management of pain administered at 1-month following SCI have a significant impact on motor outcomes. Specifically, individuals treated with anticonvulsants demonstrated greater recovery of muscle function over the first year post injury compared to individuals not treated with anticonvulsants. In contrast, acute treatment with NSAIDs had no significant effect on neurological recovery. In accordance with previous clinical studies in chronic SCI, anticonvulsants significantly reduced maximum pain intensity during the transition from acute to chronic injury. Collectively, these findings support the use of anticonvulsants to relieve neuropathic pain, as well as highlight potential beneficial effects on motor outcomes.

Recovery of motor outcomes after spinal cord injury
The transition to chronic injury is characterized by an inherent but limited capacity for neurological recovery. A central goal of rehabilitation is to capitalize on this recovery, translating neurological changes into functional improvements. Documented in several large-scale observational studies, significant recovery of muscle strength in upper and lower limbs is expected during the transition from acute to chronic injury.250, 255, 256 According to international standards, residual sensory and motor sparing below the neurological level of SCI, reflecting the initial severity or “completeness” of damage in the spinal cord, is the single most important predictor of the magnitude of recovery.257 However, a high degree of variability remains even after considering injury severity, and seemingly identical severities of injuries recover within a rather broad range.258 While a recent study has highlighted the deleterious effects of infection on neurological outcomes,200 the present findings are the first to demonstrate that acute management of neuropathic pain may have beneficial effects.
Motor recovery and clinical trials in spinal cord injury

To measure efficacy, changes in muscle strength greater than achieved due to spontaneous recovery have been examined in past clinical trials aimed at neuroprotection ¹⁹, ²⁵⁹, ²⁶⁰ and neuroregeneration.²⁶¹–²⁶⁴ Employing motor scores, recent studies have reported preliminary efficacy for minocycline ²⁶⁵, ²⁶⁶ and riluzole ²⁶⁷–²⁶⁹ – two drugs that have been repurposed as potential neuroprotective agents in SCI, based on several potential mechanisms of action including inhibition of microglial activation, attenuation of apoptosis, and antioxidant properties.²⁷⁰ Based on our findings, we have identified a significant effect (i.e., approximately 7 motor points) of acute anticonvulsant treatment on motor scores after SCI. To put this recovery into context, 7 motor points is comparable to that reported in landmark clinical trials examining the effects of acutely administered methylprednisolone (NASCIS Trial),²⁷¹ and a recent observational study demonstrating the efficacy of early surgical intervention.²⁷² Importantly, the effect of anticonvulsants was observed independently of injury related characteristics, such as the severity (AIS-grade) and level of injury (para- and tetraplegia), and other pain medications (e.g., antidepressants and opioids). Moreover, findings from the mixed effects modelling are supported by URP, which revealed that anticonvulsants had a beneficial effect in both the upper and lower extremities.

Anticonvulsants and SCI: Mechanisms of action

From a pragmatic perspective, greater neurological recovery in individuals administered anticonvulsants may be as a result of improved pain outcomes (i.e., reductions in pain), which in turn led to increased participation in rehabilitation. Rehabilitation during the transition from acute to chronic SCI serves an important role in the recovery of functional outcomes, which are, in part, related to neurological function.²⁷³ Although pragmatic, if participation in rehabilitation was the major contributing factor, individuals not reporting pain (i.e., nociceptive or neuropathic) at 1-month post injury should demonstrate significantly greater motor recovery than those with neuropathic pain. Our findings do not support such an explanation, as neither pain classification or pain rating at 1-month had a significant impact on neurological recovery.
Translating findings from preclinical studies to humans, the “therapeutic window” for neuroprotection purportedly ranges from hours to days after injury.\textsuperscript{205} In terms of preventing the deleterious secondary consequences of inflammation, a post-mortem study in humans suggests a time-line between 1 to 3 days.\textsuperscript{274} Depending on the anticonvulsant medication administered, neuroprotection could be mediated through blockade of calcium and/or sodium channels, which in turn reduces the deleterious consequences of several well-known secondary injury mechanisms (e.g., free radical generation, glutamate release, lipid peroxidation, lactate accumulation, and cell death).\textsuperscript{275} Although preclinical SCI studies have demonstrated the neuroprotective effects of anticonvulsants,\textsuperscript{276, 277} administration may be required in a very narrow time window (i.e., minutes to hours). Whereas medications for nociceptive pain (e.g., NSAIDs and opioids) would expectedly be administered in the initial hours after injury (e.g., as part of the peri-surgical pain management), the neuroprotective window may be closed by the time neuropathic pain develops\textsuperscript{278} and intervention with anticonvulsants are initiated.

An interesting alternative to consider is that anticonvulsants may affect endogenous neuroplasticity, such as sprouting. Proposed to mediate spontaneous repair in preclinical models of SCI,\textsuperscript{279} sprouting is considered a major therapeutic target for the recovery of neurological function after SCI. In terms of direct effects, anticonvulsants (i.e., carbamazepine) have been shown to promote liver regeneration through the activation of the mTOR-signalling pathway\textsuperscript{280} – a pathway that has been implicated in the enhancement of sprouting in the injured CNS. More in line with known mechanisms, anticonvulsants may attenuate aberrant plasticity through a reduction in hyperexcitability.\textsuperscript{281} While mechanisms of neuropathic pain after SCI are poorly understood, aberrant neuroplasticity and hyperexcitability in the spinal cord have been suggested as potential underlying substrates.\textsuperscript{282} Through the attenuation of aberrant plasticity and hyperexcitability, anticonvulsants administered early after SCI in individuals with neuropathic pain may “redirect” or unmask potential for neurological recovery.
To investigate if anticonvulsants are a viable candidate to enhance neurological and functional outcomes, further studies are obviously warranted. In particular, information regarding different types of anticonvulsants (e.g., gabapentin, pregabalin, carbamazepine, and valproic acid), as well as dosing and timing of administration are essential. Nonetheless, this study represents a pivotal first step, raising the possibility that an acute treatment, administered for purposes unrelated to improving neurological outcomes, impacts neurological recovery. In terms of next steps, there are several advantages to repurposing anticonvulsants to promote neurological recovery, including that the safety and tolerability profile in SCI is already well established. Additionally, a number of pain conditions (e.g., post surgical pain) have demonstrated efficacy in prophylactic treatment with anticonvulsants, begging the question as to whether neuropathic pain can be prevented after SCI. So far, one small study in SCI has addressed this question, administering carbamazepine before the onset of neuropathic pain until 1-mont post injury. Although reporting significant prevention at 1-month, differences in neuropathic pain between treated and untreated with prophylactic carbamazepine did not persist at 3 and 6 months post injury. A major limitation of this study is that neuropathic pain, in particular below-level neuropathic pain, is known to develop at later time-points after injury, thus potentially warranting longer duration of anticonvulsant usage.

Although NSAIDs have also been attributed neuroprotective properties in animal models of SCI, we could not discern beneficial effects in terms of neurological recovery in this study. Several factors may explain the lack of a statistical effect, including that dosing for pain-relief may have been suboptimal to achieve anti-inflammatory properties (i.e., mechanism of neuroprotection).

**Limitations and future directions**

The current study does not have information regarding the detailed type, dosing and timing of exposure to anticonvulsants. In terms of establishing biological activity and a window of therapeutic efficacy, such information is of vital importance. Outside the scope of this analysis, we did not examine the relationship between changes in pain intensity and the recovery of motor function. This requires that time-varying covariates
be included in longitudinal models (i.e., changes in pain occurring in conjunction with motor recovery), which adds considerable complexity to the interpretation of results. In principle, this represents an important future line of investigation, to determine if pain relief represents a mechanism of motor recovery. Patient dropout, inherent in all longitudinal studies, may present a problem. In an observational study, at 6 and 12 months after SCI (typically around the time patients are discharged from rehabilitation centres), this may be of particular concern, especially with relatively small exposure groups (i.e., the relatively small numbers administered anticonvulsants). Lastly, other factors related to the patient or their acute management, which are not captured in the EMSCI (e.g. non-traditional pain therapies), may explain our observations (i.e., unmeasured confounders). For example, early surgical intervention has been attributed beneficial neurological effects after SCI.\textsuperscript{272,291,292} However, in considering other confounders, there is similar probability that both groups (i.e., anticonvulsants and no anticonvulsants) would be equally affected, which would negate any meaningful change in interpretation.

\textit{Conclusion}

In addition to the management of neuropathic pain, the present study reveals for the first time that the administration of anticonvulsants has the potential to improve motor recovery after acute SCI. While additional studies are needed, including prospective cohort studies with more detailed medication information and physiological measures (e.g. imaging or electrophysiology) and followed-up with randomized clinical trials, these seminal findings suggest that acute standards of care (i.e., treatment with pain medications) beyond surgical intervention can impact neurological outcomes.\textsuperscript{293}
CHAPTER 8 CONCLUSION

The primary goal of this thesis was to examine the risk of secondary complications among individuals with SCI, to examine relationships among secondary complications, and to examine the relationships between secondary complications with neurological outcomes. Key findings of this thesis and the comparisons with published data were presented in Chapters 4-7. A brief discussion of the key findings is provided below.

8.1 Key Findings
The following are the key findings of this thesis:
1) There is an elevated odds of self-reported heart disease, stroke, Type 2 diabetes, chronic respiratory conditions, and chronic pain (migraine) among individuals with SCI (compared with non-SCI individuals)
2) There are complex inter-relationships between secondary complications following SCI. Namely, there are positive associations between neuropathic pain and CVD, and between blood pressure fluctuations and CVD. Some of these inter-relationships may explain the excess risk of CVD.
3) Secondary complications (specifically neuropathic pain) following SCI are positively correlated with neurological decline in chronic phases, and neurological motor recovery in acute phases. These relationships may be in part related through treatments for the secondary complications (versus the secondary complications themselves).

8.2 Strengths of the Study
The major strengths of this study design are the relatively large, representative study populations, with relatively comprehensive datasets. Indeed, prior studies of secondary complications following SCI have generally used small samples, have lacked control groups, have used surrogate markers (versus clinically relevant events) and have not adequately adjusted for confounding factors; the present thesis was able to address some of these major limitations.
8.3 Overall limitations of the Study

Although specific limitations of each specific component of this thesis were discussed in Chapters 4 to 7, several limitations of the overall study, as well as key limitations, are discussed here. Firstly, the CCHS and SCI-CS data are derived from a self-report cross-sectional study design, thereby limiting causal inference. However, as previously mentioned, cross-sectional analyses may represent a valid starting point within the field of SCI research. Moreover, the longitudinal EM-SCI data does not include information on timing/dosage of medications, which will be important before providing more definitive recommendations (i.e., differential effects on neurological outcomes may occur depending on when the medications are administered, and at which dosage).

Due to the limited nature of SCI datasets, multiple separate datasets were required for this thesis; ideally, we would have utilized a comprehensive unified dataset (i.e., for more consistent variable definitions and timing), and/or used external validation with overlapping data elements. Since we were using datasets that were not prospectively developed with these research questions in mind, the risk of unmeasured confounders is also a limitation.

8.4 Implications and Further Research

As previously mentioned, large-scale epidemiological studies within the SCI field are relatively rare, partially due to the relatively low prevalence of SCI, and also due to the fact that SCI-specific registries are relatively new. However, there are several major emerging SCI-specific registries, including the Rick Hansen Spinal Cord Injury Registry (pan-Canadian), the US Model Systems (pan-American), the Department of Veterans Affairs Database, and the European Multi-Centre Study about Spinal Cord Injury (used in the present thesis).

While we had originally set out with these research questions to be able to directly inform clinical practice guidelines and clinical practice for individuals with SCI, we found through our literature searches and available data that several steps were needed before such recommendations can be made. We have therefore made recommendations for future studies that, once completed, will directly influence clinical management
guidelines. Comprehensive clinical practice guidelines which factor in these associations between secondary complications and integration between biological systems are currently lacking, and must be addressed specifically among individuals with SCI. There are unique characteristics that occur as a result of the injury (i.e., multiple secondary complications, multitude of medications used in both acute and chronic stages, and practical limitations associated with physical disability), in addition to correlations among secondary complications. A more general clinical practice guideline on chronic health management may be needed (in addition to a personalized approach).

**Implications for SCI Core Datasets**

It is of course necessary to have comparable data elements across registries (or other data sources) so that outcomes can be properly assessed and compared. As data are used to guide clinical practice, for health care planning, and in earlier stages used to secure and/or maintain financial support for SCI research, data elements must be comprehensive, valid, and user friendly. Within the field of SCI research, calls have been made for international SCI data sets. Such a course of action was initiated subsequent to an international meeting of experts in the field of SCI. This was the first international meeting to discuss the steps required to select and recommend the variables that should be included in future SCI datasets. The participants at this meeting represented several countries, including Australia, Canada, Denmark, India, Israel, Italy, Japan, the Netherlands, Sweden, Switzerland, United Kingdom, and the United States. The meeting resulted in guidelines for the recommended number of data elements that could provide a ‘lowest common denominator’ and be the start of a common language among SCI datasets worldwide. This also subsequently resulted in a document entitled “Approved and finalized International SCI Data Sets,” and included distinct modules for each secondary complication (eg. the Cardiovascular Function International SCI Dataset and the Pain International SCI Dataset). However, as we have seen complex inter-relationships between secondary complications, we are making recommendations for including a variable regarding other secondary complications (in addition to the primary complication of interest) in each core data set (eg. the Pain SCI Dataset does not include other secondary complications besides pain itself). This will involve several knowledge
translation and dissemination strategies, including presentations at SCI-specific conferences where individuals involved in the international SCI datasets are present.

These common elements and development of SCI-specific registries will be necessary for prospective cohort studies to examine the timing of the onset of these risk factors and time-dependent relationships between secondary health complications themselves. Since there are limitations on the number of data elements which can be collected in a given registry, another realistic option will be for SCI registries to have linkages established with hospital databases and other data sources.

**Implications for Cohort Studies and Clinical Trials**

Prospective studies are necessary within the field of SCI research to ultimately determine causality and direct intervention strategies. A so-called ‘SCI Framingham Study’ within the field of SCI research has indeed been called upon by prominent SCI epidemiologists and SCI physicians. The results reported in the present thesis may impact the success of a ‘SCI Framingham Study’ by influencing its study design. Such a study would include detailed and frequent information on secondary complications (eg., date of diagnosis, frequency, specific medications/dosing) and neurological outcomes, information on pre-existing conditions and other secondary complications, as well as biomarkers, from very acute to chronic stages. In addition to accounting for the presence of these conditions, future studies should consider both the frequency and impact of these conditions (eg. a secondary health complication such as spasticity may be beneficial for motor function). This line of investigation would also include both individuals with traumatic and non-traumatic SCI, and would likely need to be an international effort due to the low prevalence of SCI.

This potential ‘SCI Framingham Study’ will better inform clinical practice and consumer guidelines which may ultimately improve the quality of life for individuals with SCI. This research may also guide basic science studies to tease apart mechanisms related to the secondary health conditions in animal models of SCI. These findings may also be important from a health care planning perspective since the secondary health complications of SCI are costly to the health care system.
With respect to the anticonvulsant findings (Chapter 6), to further investigate if anticonvulsants are a viable candidate to enhance neurological and functional outcomes, further studies are warranted. Before proceeding to clinical trials, the first important step will be to examine the findings with respect to specific anticonvulsants (e.g., gabapentin, pregabalin, carbamazepine, and valproic acid), as well as to determine the dosage and timing associated with the greatest neurological benefit. Once timing and dosage are determined in cohort studies, ideally this will be followed up in a randomized clinical trial. Indeed, there are several advantages to repurposing anticonvulsants to promote neurological recovery, including that the safety and tolerability profile in SCI is already well established. 283-286

Given that we noticed an effect of anticonvulsants used in the treatment of acute neuropathic pain, but there was no effect of neuropathic pain itself, this raises the possibility that medications used in the treatment of secondary complications may have effects (in addition to or solely) on neurological outcomes, and other secondary complications. While secondary complications themselves may affect other secondary complications, the prevention of one through medication management is likely more clinically feasible than the prevention of onset of the other secondary complications.

Relevance to Definition of Secondary Health Complications
As previously mentioned, Jensen et al. recently defined secondary health conditions as ‘physical or psychological health conditions that are influenced directly or indirectly by the presence of a disability or underlying physical impairment.’ 17 This is distinct from a comorbidity which is generally defined as “pre-existing secondary diagnoses.” 18 However, we have shown that the risk of some conditions such as Type 2 diabetes, migraine, and CVD, is elevated such that SCI itself may be a contributing factor. Although these conditions can occur prior to SCI and thus could be considered comorbidities, it is likely that these conditions also occur directly or indirectly as a result of SCI (i.e., are both secondary conditions and comorbidities).

Relevance to Methodology in SCI Studies
The work in this thesis will also be important from a methodological standpoint. As
causal inference is contingent upon producing unbiased estimates for measures of effect size (eg. odds ratios or relative risk), there is a need for multivariable analyses (i.e., adjustment for confounding) within the field of SCI. Likely due to a combination of factors (eg. smaller sample sizes, lack of accessible and comprehensive SCI data registries), our review of SCIRE indicated a major lack of multivariable analyses. Our work shows that there are significant correlations among secondary complications of SCI, which will be important to incorporate into study design of future studies, particularly in the assessment of confounding factors. Prior studies of the relationship between AD and cardiovascular events\textsuperscript{40, 41} for example, failed to take into consideration the strong relationship between AD and OH, the strong relationship between OH and CVD (both shown here), which may indicate OH as a confounder in the relationship between AD and CVD.

**SCI and Ageing**

Ageing is broadly defined as the “time-dependent functional decline that affects most living organisms” and is characterized by a progressive decline of physiological systems.\textsuperscript{295} Ageing itself is a primary risk factor for several diseases, including those affecting the cardiovascular and neurological systems. It has been hypothesized that SCI represents a model for premature or accelerated ageing,\textsuperscript{24, 296} particularly in specific physiological systems (i.e., cardiovascular, musculoskeletal and respiratory). Further, the standardized mortality ratio of total death in long-term SCI is approximately three times higher than in the general population.\textsuperscript{24} These observations would of course suggest that the decline associated with natural ageing is compounded by SCI. Therefore, one would expect that certain diseases are likely to occur earlier and more frequently among individuals with SCI. Our cross-sectional data are consistent with these observations, though this concept of accelerated ageing is indeed a broad concept which is perhaps best tested in animal models and physiological human studies (i.e., using biomarkers).

In line with the notion of ageing is the issue of *polypharmacy*: the prescription and use of multiple drugs to deal with concomitant multiple diseases. In the general ageing population, the high prevalence of polypharmacy has led to inappropriate drug use,
under-use of effective treatments, medication errors, poor adherence, drug–drug and drug–disease interactions and, adverse drug reactions. 297, 298 In the elderly, it has been proposed that these negative consequences are usually related to the fact that elderly people are often frail and highly sensitive to pharmacotherapy, because of changes in pharmacokinetic and pharmacodynamic parameters and impairment in many organ functions. 297, 298 This issue of polypharmacy has been also applied within the context of SCI. 299 One study noted that individuals with SCI were prescribed significantly more medications than their control counterparts. Moreover, they noted that there was a higher rate of individuals being prescribed medications from multiple high-risk classes (e.g. analgesic/narcotics, anticonvulsants, antidepressants, and muscle relaxants), as well as multiple medications within each class (e.g. multiple analgesic narcotics). Consequently, the SCI group had a higher incidence of ‘drug-related problems’. The authors of this study concluded that this higher rate of polypharmacy and drug-related adverse events can impact rehabilitation goals and community integration following injury. Based on this evidence, and in conjunction with our findings regarding inter-relationships between secondary complications and drug-related effects, we contend that the issue of polypharmacy also be dealt with in the International SCI datasets (i.e., to comprehensively record drug-use in addition to secondary complications).

Relevance to Non-traumatic SCI and other neuropathologies

As mentioned in the introductory section, for the present thesis we have included individuals with both traumatic and non-traumatic SCI. Though we included injury etiology as a covariate in the multivariable analyses where possible (and did not find any major differences with respect to the various associations examined, i.e., the relationship between pain and CVD did not differ with respect to traumatic versus non-traumatic injury), going forward, more work will be needed to see if mechanisms differ between types of SCI. Given that non-traumatic SCI includes a wide range of conditions, it seems likely that mechanisms underlying some of these relationships may differ. Moreover, it will be interesting to examine these relationships in other neuropathologies.

To further explore traumatic versus non-traumatic differences, consistent definitions for non-traumatic SCI are needed, and non-traumatic SCI will need to be included in current
SCI-specific registries. This is of course a non-trivial task given the greater difficulty in identifying individuals with non-traumatic SCI: unlike with traumatic SCI, where initial hospitalization defines the occurrence of SCI, this is not the case for non-traumatic SCI.

**Implications for Economic Costs of SCI**

As previously mentioned, the estimated lifetime economic burden per individual with traumatic SCI in Canada ranges from $1.5 million for incomplete paraplegia to $3.0 million for complete tetraplegia. Further, the annual economic burden associated with incident cases in Canada (~1500 new persons with traumatic SCI surviving their initial hospitalization) is estimated to be $2.67 billion. This figure includes direct costs (initial hospitalization, subsequent hospitalizations, physician visits, home modifications, prescription drug-use, adaptive equipment, vehicle modifications, attendant care) as well as indirect costs (morbidity and mortality). This figure, does not, however, take into consideration non-traumatic SCI, as well as indirect costs relating to loss of productivity, which may occur as a result of experiencing frequent and persistent secondary complications. Given the inter-relationships we have seen between secondary complications, reducing the burden of even one may have benefits beyond the targeted treatment, which may also factor in to reducing the economic burden of SCI.

**8.5 Conclusion**

These novel findings update current knowledge of secondary complications among individuals with SCI. Specifically, this thesis demonstrated that individuals with SCI are at an elevated risk of several secondary complications affecting the cardiovascular, respiratory, and sensory systems. Moreover, there are complex inter-relationships between several secondary complications among individuals with SCI, as well as significant relationships with neurological outcomes in both acute and chronic stages. To achieve these objectives, four secondary analyses of existing datasets were completed, including the Canadian Community Health Survey (CCHS), the SCI Community Health Survey, the European Multi-Centre Study on Spinal Cord Injury (EM-SCI) dataset, and the Simon Fraser University SCI dataset. Several methods were employed for analysis of
these data, including: multivariable logistic regression, multivariable linear regression, linear mixed effects models, and unbiased recursive partitioning. This thesis made several recommendations for future studies in SCI research (specific future directions related to the major findings are summarized below in Table 8.1 and Figure 8.1). Namely, these findings will guide the prospective collection of data elements within SCI-specific core data sets and registries, as well as the design and analysis of future cohort and clinical trial studies (i.e., issues of confounding in multivariable analyses). Furthermore, these findings may have broader implications for other neuropathologies which also exhibit multiple secondary complications (eg. multiple sclerosis). Our findings with respect to pain medications used during acute SCI may also have implications for the acute care of individuals with SCI. Overall, the concept that secondary complications exhibit significant ‘overlap’ and may influence one-another, and may also influence neurological changes, is a relatively new concept in the field, and warrants future investigation.
<table>
<thead>
<tr>
<th>Key Finding</th>
<th>Specific Future Direction</th>
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<tbody>
<tr>
<td>1) There is an elevated odds of heart disease, stroke, Type 2 diabetes,</td>
<td>*evaluate in large-scale prospective analysis with:</td>
</tr>
<tr>
<td>migraine, and chronic respiratory conditions among individuals with SCI</td>
<td>adequate adjustment for confounding, representative control group, biomarkers, frequent</td>
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<td></td>
<td>follow-up, accounting for pre-existing conditions</td>
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<tr>
<td>2) There are complex inter-relationships between secondary conditions</td>
<td>*evaluate in large-scale prospective analysis with</td>
</tr>
<tr>
<td>following SCI, namely relationships between neuropathic pain and</td>
<td>adequate adjustment for confounding, detailed</td>
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<tr>
<td>cardiovascular disease, and between blood pressure fluctuations and</td>
<td>information on secondary conditions (including biomarkers), frequent follow-up,</td>
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<tr>
<td>cardiovascular disease</td>
<td>accounting for pre-existing conditions</td>
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<td></td>
<td>*incorporate comprehensive information on secondary complications in SCI core</td>
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<td>datasets</td>
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<td>3) Secondary conditions following SCI are related to neurological</td>
<td>*evaluate in large-scale prospective analysis with</td>
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<tr>
<td>deterioration in chronic phases, and neurological recovery in acute</td>
<td>adequate adjustment for confounding, detailed</td>
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<td>phases</td>
<td>information on secondary conditions (including biomarkers) and neurological</td>
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<td></td>
<td>outcomes, frequent follow-up, accounting for pre-existing conditions</td>
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<tr>
<td></td>
<td>*for drug-related findings, possible follow-up in randomized controlled clinical trials</td>
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Table 8.1. Summary of Future Directions.
Figure 8.1. Conceptual Model: Future Directions.
1. SCIRE Team. SCIRE: Spinal Cord Injury Rehabilitation Evidence. Available at:


92. Heo M, Kabat GC, Gallagher D, Heymsfield SB, Rohan TE. Optimal scaling of weight and waist circumference to height for maximal association with DXA-measured total body fat mass by sex, age and race/ethnicity. *Int J Obes (Lond).* 2012.


