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Carbohydrate and Lipid Disorders and Relevant Considerations in Persons with Spinal Cord Injury

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The information in this report is intended to help clinicians, employers, policymakers, and others make informed decisions about the provision of health care services. This report is intended as a reference and not as a substitute for clinical judgment.

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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-Based Practice Centers (EPCs), sponsors the development of evidence reports and technology assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. This report was requested and funded by the Spinal Cord Medicine Consortium, Paralyzed Veterans of America. The reports and assessments provide organizations with comprehensive, science-based information on common, costly medical conditions, and new health care technologies. The EPCs systematically review the relevant scientific literature on topics assigned to them by AHRQ and conduct additional analyses when appropriate prior to developing their reports and assessments.

To bring the broadest range of experts into the development of evidence reports and health technology assessments, AHRQ encourages the EPCs to form partnerships and enter into collaborations with other medical and research organizations. The EPCs work with these partner organizations to ensure that the evidence reports and technology assessments they produce will become building blocks for health care quality improvement projects throughout the Nation. The reports undergo peer review prior to their release.

AHRQ expects that the EPC evidence reports and technology assessments will inform individual health plans, providers, and purchasers as well as the health care system as a whole by providing important information to help improve health care quality.

We welcome written comments on this evidence report. They may be sent to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by email to **epc@ahrq.gov.**

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Structured Abstract

Objectives: To assess the prevalence of carbohydrate and lipid disorders in adults with chronic spinal cord injury and evaluate their risk contribution to cardiovascular diseases and the potential impact of exercise and pharmacologic and dietary therapies to alter these disorders and reduce cardiovascular disease risk.

Data Sources: MEDLINE® (PubMed®), Cochrane Database and websites of the American Spinal Injury Association, American Paraplegia Society, Paralyzed Veterans of America, Consortium of Spinal Cord Medicine, and WorldCat through August 2007.

Review Methods: English language observational studies addressing prevalence of carbohydrate and lipid disorders were included if they evaluated at least 100 adults with chronic spinal cord injury or a total of 100 subjects if using a control group. Epidemiologic investigations of more than 50 adults with spinal cord injury that were published in English after 1990 and reported cardiovascular morbidity and mortality were abstracted. Intervention studies from 1996-2007 were included regardless of design or size if they assessed exercise, diet, or pharmacologic therapies and reported carbohydrate, lipid, or cardiovascular outcomes.

Results: The quality of evidence regarding the prevalence, impact, and outcomes of carbohydrate and lipid disorders in adults with chronic spinal cord injuries is weak. Evidence is limited by relatively few studies, small sample size, lack of appropriate control groups, failure to adjust for known confounding variables, and variation in reported outcomes. However, the existing evidence does not indicate that adults with spinal cord injuries are at markedly greater risk for carbohydrate and lipid disorders or subsequent cardiovascular morbidity and mortality than able-bodied adults. Body mass index is not reliable for assessing body composition, especially percent body fat, in adults with spinal cord injury. There are no high quality studies evaluating the impact of exercise, diet, or pharmacologic therapies on these disorders.

Conclusions: Evidence does not support using different thresholds to define or treat abnormal lipid and carbohydrate measures or to incorporate other markers to assess risk (e.g., insulin resistance, impaired fasting glucose, or impaired glucose tolerance) for individuals with spinal cord injuries compared to able-bodied adults. Due to physiologic differences between adults with spinal cord injuries and able-bodied individuals, caution may be required when extrapolating findings from studies conducted in able-bodied adults. The role of exercise in individuals with spinal cord injuries represents a unique challenge and requires further exploration into the benefits, harms, and resource implications of broad-based spinal cord injury exercise programs.

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Appendixes cited in this report are available at http://www.ahrq.gov/clinic/tp/carbliptp.htm.

Executive Summary

Introduction

Spinal cord injuries (SCI) result in 11,000 hospitalizations of new cases annually in the United States.[5,6] More than 240,000 Americans live with a disability related to SCI and the estimated annual cost averages $9.7 billion.[5,7,8] Improved quality of care over the last several decades has resulted in a 40 percent decline in mortality during the two years following the injury.[9] However, improvement in long-term survival has been smaller. Cardiovascular diseases (CVD) have been reported as the most common cause of death in adults with chronic SCI.[2,10-12] CVD risk factors associated with SCI include behavior (smoking, limited exercise) and metabolic abnormalities (obesity, metabolic syndrome,[13-15] and diabetes[11]). The prevalence of dyslipidemia[16,17] and coronary heart disease has been reported to be higher in adults with SCI compared to the general population.[10,18] The Institute of Medicine recently released two reports that emphasized the role of cardiovascular risk assessment and management in adults with chronic SCI.[6,11] Some evidence suggests that exercise,[19] diet,[20,21] and pharmacological therapy[22] may reduce diabetes and CVD risk in these individuals. Furthermore, markers or thresholds of carbohydrate and lipid disorders commonly used in adults without SCI may not apply to the population that has sustained SCI. In particular, because adults with SCI lose muscle mass that is replaced with fat mass, traditional measures of obesity (weight or body mass index [BMI]) may not be appropriate.

Accurate estimates of diabetes prevalence and severity in adults with SCI may: 1) be underestimated relative to able-bodied controls because individuals with SCI may not undergo regular testing, 2) have lower levels of high-density lipoprotein (HDL) cholesterol that go unrecognized if providers only assess total cholesterol (TC) levels or base treatment solely on low-density lipoprotein (LDL) cholesterol, or 3) they have earlier evidence of impaired glucose tolerance or altered insulin sensitivity. Existing guidelines do not include routine evaluation of glucose and lipid abnormalities nor do they provide recommendations for threshold definitions of abnormality or target levels for interventions to achieve it.[23-25] Furthermore, the prevalence, morbidity, and mortality associated with carbohydrate and lipid disorders may differ in adults with SCI compared to able-bodied individuals.

Effective interventions to treat carbohydrate and lipid disorders and reduce cardiovascular complications in able-bodied individuals include dietary, pharmacologic, and exercise therapies. However, adults with SCI have unique physiologic characteristics that may preclude generalization of evidence from able-bodied individuals to those with SCI. Total daily energy expenditure for adults with SCI is difficult to calculate but likely much lower than for able-bodied individuals, especially among individuals requiring motorized wheelchairs for mobility. Treatment of obesity in SCI remains largely empiric, including guidelines developed for dietary intervention in SCI. Pharmacologic therapies to alter carbohydrate and lipid disorders may have different effectiveness and adverse effects in individuals with SCI compared to able-bodied patients. For example, assessment of hepatic or muscle toxicity in SCI individuals may be difficult using traditional serologic measures developed in able-bodied adults because SCI individuals have reduced muscle mass and potentially altered hepatic metabolism.

Despite the expected benefits of exercise for individuals with SCI, this group also faces unique challenges and risks from exercise that are not experienced by the able-bodied population.[8,26] For one, lack of access to and choices in exercise modes, depending on the

neurological impact and level of the injury, form physical barriers to obtaining exercise. Physiological risks of exercise are also a barrier to improved fitness among those with SCI. Depending on the level and completeness of the spinal injury, motor, sensory, and autonomic reflexes may still be intact but no longer under control of the brain. Individuals with SCI also experience various types of autonomic and circulatory dysregulation.[26] Risk of stress-related musculoskeletal injury is of concern, given the reliance on a small group of muscles for activities of daily living as well as for any physical conditioning. Fractures, joint dislocation, and overuse injuries are common for individuals with SCI.[27]

We conducted a systematic review of published evidence to address the following questions:

Question 1a: What proportion of adult patients with chronic posttraumatic spinal cord injuries have been diagnosed with:

a. Insulin resistance syndrome, metabolic syndrome
b. Diabetes mellitus Type 2, impaired glucose tolerance
c. Dyslipidemia
d. Obesity

Question 1b: Is the prevalence of carbohydrate and lipid disorders higher in the subgroups of patients by age, race, and gender compared to the general population? Does the prevalence of carbohydrate and lipid disorders differ by the time after trauma, the level of trauma, and functional impairment?

Question 2: For people with SCI, what is the evidence on contribution to risk of cardiovascular disease of:

a. Hyperinsulinemia
b. Abnormalities in carbohydrate metabolism
c. Abnormalities in lipid metabolism?
d. Obesity

This question was refined as:

Question 2: Regarding risk of cardiovascular disease for people with SCI:

a. What is cardiovascular prevalence and mortality in adults with chronic posttraumatic spinal cord injuries?
b. Does cardiovascular incidence and mortality in adults with chronic posttraumatic spinal cord injuries differ compared to the general population based on age, race, and gender categories?
c. What is the strength of the association between cardiovascular incidence and mortality and abnormalities in lipid and glucose metabolism including Type 2 diabetes mellitus after adjustment for possible confounding factors?
d. Does association vary depending on age, gender, race, the duration after SCI, the level of SCI, and functional impairment?

Question 3: What are the effects on carbohydrate or lipid-related outcomes in adults with SCI of:

a. Exercise
b. Dietary and pharmacologic interventions

Methods

Studies addressing prevalence of obesity, diabetes, impaired glucose tolerance, insulin resistance, and lipid disorders through August 2007 were included if:

1. adults had chronic SCI;
2. the total number of spinal cord subjects was at least 100, or totaling at least 100 subjects if a control group was included (SCI + controls ≥100);
3. reported prevalence of obesity, diabetes, impaired glucose tolerance, metabolic syndrome or insulin resistance, or lipid disorders *or* reported mean BMI or lipid levels,
4. were published in the English language. Abstracts of articles excluded due to small sample size were reviewed to assess for study quality and potential impact.

For Question 2, original epidemiologic investigations of more than 50 adults with chronic SCI and published in English after 1990 were identified in MEDLINE® via PubMed® and the Cochrane library. Websites of the American Spinal Injury Association, American Paraplegia Society, Paralyzed Veterans of America, Consortium of Spinal Cord Medicine, and the catalog WorldCat identified reviews.

For exercise interventions, the Endnote library containing original and review articles (n=2,212) was searched for abstracts that included the words *fitness, physical activity*, or *exercise*, resulting in a subset of 303 citations. A MEDLINE® search was conducted of articles written in English and published between 1996 and August 2007. Any identified study was included regardless of design, sample size, or duration if it reported carbohydrate, lipid, or cardiovascular results in adults with chronic SCI.

To assess dietary or pharmacologic interventions for treatment of carbohydrate and lipid metabolism disorders in the SCI population, studies were identified by searching in MEDLINE® through October 2007. Reference lists of included studies or reviews were also searched. Since no randomized trials were identified, nonrandomized studies were eligible. To be included, studies had to:
1. evaluate adults who had chronic SCI, defined as one year or more since sustaining the injury;
2. evaluate pharmacologic or dietary interventions;
3. report carbohydrate and/or lipid-related outcome measures; and 4) be published in the English language.

Reviewers extracted study and patient characteristics and outcomes onto standardized forms. A second reviewer assessed the findings and disagreements, while rare, were resolved by discussion. Prevalence estimates of obesity, diabetes, lipid disorders, and cardiovascular morbidity and mortality among adults with SCI and, where possible, able-bodied controls, are presented. Findings are reported separately where possible according to age, gender, race, and level/severity of SCI. For Question 3, carbohydrate and lipid outcomes are described according to the exercise, diet, or pharmacologic intervention studied. Due to heterogeneity in populations, interventions, comparator groups, and/or reported outcomes, pooled analyses was generally not conducted.

Results

For Question 1, 23 studies met the inclusion criteria, two studies for insulin resistance/ metabolic syndrome,[15,28] 12 studies for diabetes mellitus,[3,15,28-37] three studies for impaired glucose tolerance,[28,29,31] seven studies for lipid disorders,[16,17,21,31,38-40] and ten studies for obesity and body composition.[28,31,36,38,40-45] Potentially eligible studies excluded due to small sample size that limited generalizability (n=45, number of SCI individuals in each study ranged from 1-77) were also of low quality and relevance because they were from a single center, not from the

United States, lacked controls, and/or did not assess clinically relevant carbohydrate and lipid disorders.

For Question 2, 20 articles of 19 studies met inclusion criteria; most were conducted in the United States.[1-3,30,32,34,36,37,39,46-56] Studies included more than 50,000 patients with SCI. Males (pooled prevalence 86 percent) and Caucasians comprised the majority of individuals. Most used general population controls, were uncontrolled, or did not adjust for known confounding variables including: age, race, gender, smoking status, exercise, or duration of followup. Wide variation existed in the definitions of reported CVD outcomes.

For Question 3a, studies evaluating the following types of exercise were identified: Active Exercise (AE) (seven studies),[57-63] Functional Electrical Stimulation exercise (FES) (five studies),[64-68] Passive Exercise (PE) (no studies, Self-Reported Physical Activity (six studies),[13,14,54,69-71] and Other (one study).[72]

For Question 3b, only two prospective studies (neither randomized) evaluating dietary and/or lifestyle interventions to reduce lipid levels met inclusion criteria.[20,72]

Prevalence of Carbohydrate and Lipid Disorders

The prevalence of insulin resistance, metabolic syndrome, diabetes mellitus, impaired glucose tolerance, dyslipidemia, and obesity in a population are all highly dependent upon demographics of the population including age, socioeconomic status, and race/ethnicity. The dependence of these conditions on population characteristics makes it difficult to conduct between-study comparisons since population characteristics varied greatly, both between and within studies.

Insulin resistance/metabolic syndrome. There was little data on the prevalence of insulin resistance/metabolic syndrome in adults with SCI. There are no high-quality data to determine if insulin resistance or metabolic syndrome are elevated in adults with SCI compared to similar individuals without SCI because no studies included a non-SCI control or comparison group. Only two studies assessed the prevalence of insulin resistance. The one study that provided results by severity of injury showed increased hyperinsulemia in persons with tetraplegia compared to paraplegia following a glucose challenge.[28] The only study assessing metabolic syndrome was small, uncontrolled, and used definitions for specific metabolic disorders likely to increase the estimated prevalence of the disorders and therefore their estimated prevalence of metabolic syndrome. Their definitions are not widely recommended.[15,73]

Diabetes mellitus or impaired glucose tolerance (IGT). The prevalence of diabetes appeared higher on average in SCI populations studied compared to the general population. However, there is credible scientific reason to believe that the general population groups selected were not appropriate controls for the studied SCI individuals. For example, lifestyle and comorbidities, irrespective of SCI, could be quite different. Therefore, the extent to which the observed increased prevalence of diabetes is due to a causal relationship between the SCI and the development of subsequent diabetes is not known. Overall, control groups comprised of veterans using Veterans Affairs (VA) medical centers for health care tended to be similar to VA SCI populations in their rate of diabetes. Only when the rate of diabetes in the VA SCI group was compared to the general public did the SCI individuals appear to be at higher risk. Users of the VA health care system have greater comorbidities than either veterans not using the VA health care system or non-VA populations. Therefore, current evidence is insufficient to determine to what extent the higher rate of diabetes is independently attributable to SCI or to other factors that

might be higher in adults who subsequently have a SCI than in the general public. There was little evidence suggesting that fasting plasma glucose was elevated in adults with SCI. There was some evidence that adults with SCI may be more likely to meet IGT or diabetes diagnostic criteria following oral glucose tolerance tests (OGTT). However, no studies reported repeated OGTT.

Lipid disorders. There is some evidence that individuals with SCI compared to controls may possess favorably lower average TC (three studies n = 1,427; weighted mean difference (WMD) = -14.3 mg/dL [95 percent CI = -22.2, 6.4]),[38-40] LDL cholesterol (two studies, n = 773 WMD = -10.77 [95 percent CI = -16.0, -5.6]),[38,40] and triglyceride levels (two studies n = 773; WMD = -10.0 mg/dL [95 percent CI = -18.3, 1.6]).[38,40] HDL cholesterol was lower in SCI individuals compared to controls (three studies n = 1,427; WMD = -7.6 mg/dL [95 percent CI = -10.6, 4.6]), though confidence intervals were wide and results not statistically significant.[38-40]

Obesity and body composition. While BMI is unlikely to be an accurate measure of obesity in the SCI population, it is by far the predominant measure reported in research studies of the prevalence of obesity. There is no high quality evidence that obesity defined by BMI is elevated in individuals with SCI compared to appropriately matched controls. There is some evidence that when obesity is measured as percent body fat, individuals with SCI may be at elevated risk. However, the absence of validated measures of body composition in SCI individuals or large studies that include accurate measurements of body fat precludes stronger conclusions regarding the prevalence of obesity and the impact of injury type and duration on obesity.

Cardiovascular Prevalence and Mortality in Adults with SCI

CVD prevalence among SCI individuals ranged from 1-3 percent in the majority of studies,[32,50,52,53,55] with an increase to 19 percent in older patients and to 14 percent in those 30 or more years after injury.[52] The prevalence of cerebrovascular diseases was 1-2 percent[3,39,53] and coronary heart disease ≤2 percent,[32,39,53] being increased to 12 percent among members of Paralyzed Veterans of America.[37] SCI veterans using VA health care had a higher prevalence of myocardial infarction (14 percent[37]to 25 percent)[48] than SCI civilians (<5 percent in three studies.[3,39,53] The highest prevalence of 33 percent was reported among veterans who were older than 50 years at the time of injury.[48]

Mortality from CVDs was more consistent than prevalence across five studies that reported this outcome;[1-3,49,52] 0.8[49] to 1.5[2] per 1,000 injured died from diseases of the arteries; 1[49] -6 percent[1] to 10 percent[52] died from cardiovascular disease. Mortality was higher in men (5.3 percent) compared to women (1 percent)[1] and in older patients, being the highest after 75 years (10 percent).[52] Less than 1 percent of SCI patients died from cerebrovascular diseases and stroke,[1,2,49] with higher mortality in men (0.7 percent) than women (0.2 percent).[1] Mortality from ischemic heart disease was <1 percent in two studies[2,3] and 2.5 percent (including 2 percent men) in one European study.[1] One long-term followup study of VA users reported a two-fold increase in mortality from 5 years (0.4 percent) to 20 years (0.9 percent) after injury.[3] Lung embolus caused death in 0.7 percent of patients with chronic SCI.[1]

Three studies reported that coronary heart diseases constitute approximately 9 percent among primary causes of death in SCI patients.[1-3] The proportion of deaths attributable to all CVDs varied from 18.8 percent for diseases of the heart[49] to 24 percent for circulatory system disorders.[1] Cardiovascular diseases are among the leading causes of death in patients with chronic SCI[1,49,52] however, the contribution of age cannot be estimated analyzing crude

proportion of aging SCI patients who died from heart diseases. One study of 402 veterans with chronic SCI followed for 55.6 months[36] showed that diabetes (relative risk 2.62, 95 percent CI 1.19; 5.77) and heart diseases (relative risk 3.66, 95 percent CI 1.77; 7.78) were significant risk factors for death after adjustment for age.

When compared to able-bodied adults, cardiovascular morbidity in SCI patients did not show significant differences.[34,39] Inconsistent and limited evidence suggested that patients with chronic SCI had lower prevalence of congestive heart failure[34] but no differences in the odds of diabetes, myocardial infraction, angina pectoris, or cerebrovascular diseases.[34,39,55]

Diabetes contributed to a higher risk of CVD in veterans with SCI compared to SCI veterans without diabetes. One large study of veterans with SCI, able-bodied veterans, and the general population reported a three times higher rate of diabetes in injured veterans compared to the general population (20 percent vs. 6.7 percent, odds ratio 3.32, 95 percent CI 1.34; 8.26) but similar odds compared to other veterans (21 percent, odds ratio 0.94, 95 percent CI 0.47; 1.87).[37] Injured veterans with diabetes had higher adjusted rates of coronary heart disease by 280 percent, myocardial infarction by 270 percent, arterial hypertension by 250 percent, and stroke by 230 percent compared to SCI patients without diabetes.[37] Age may modify the association with injury and diabetes. For example, odds of diabetes were higher in injured veterans compared to the general population in all age groups but higher compared to able-bodied veterans in those ages 45-59, 55-59, and older than 70 years.[37]

Some evidence suggested that neurological functional status may be associated with cardiovascular morbidity.[53] Patients with tetraplegia and no functional motor preservation had higher age adjusted odds ratio of cerebrovascular diseases, dysrhythmia, and valvular diseases and lower odds ratio of coronary heart disease compared to paraplegic patients.[53] Injured patients with functional motor preservation had higher age adjusted odds of all CVDs, coronary atherosclerosis, dysrhythmia, and valvular disease.[53] Some electrocardiogram abnormalities including left bundle branch block, left ventricular hypertrophy with strain, and atrial fibrillation accompanied the higher hazard ratio of death in patients with SCI.[34] Furthermore, these abnormalities were associated with a greater risk of dying in injured compared to able-bodied patients.[34]

Cardiovascular mortality in injured patients was compared to a standardized by age mortality in the general population in three studies.[1,2,36] Mortality from nonischemic heart diseases (standardized mortality ratio 5.6, 95 percent CI 4.4; 6.8), artery diseases (standardized mortality ratio 4.5 95 percent CI 2.1; 6.9), and lung emboli (standardized mortality ratio 11.4, 95 percent CI 4.2; 24.8) was higher in all injured adults compared to the general population.[1] Cardiovascular mortality was lower in those injured after 1972 (standardized mortality ratio 2.4 95 percent CI 1.95; 3.01) compared to those injured from 1953-1971 (7.1, 95 percent CI 2.31; 9.32).[1] Patients with complete tetraplegia died from ischemic heart disease (standardized mortality ratio 2.6, 95 percent CI 1.3; 3.9), nonischemic heart diseases (standardized mortality ratio 23.4, 95 percent CI 16.5; 30.3), and cerebrovascular diseases (standardized mortality ratio 5.4, 95 percent CI 1.8; 9) more often than would be expected from the same age able-bodied adults.[1,2,36]

The role of lipid disorders to alter the risk of cardiovascular morbidity and mortality in SCI adults has not been adequately addressed in the published articles. One study concluded that increased blood pressure, elevated blood cholesterol, or smoking could not explain the increased cardiovascular prevalence in SCI patients.[39] One study showed that diabetes in SCI patients was associated with an increased risk of coronary heart disease, myocardial infarction, arterial

hypertension, high cholesterol, and stroke.[37] The relative risk contribution to adults with SCI compared to able-bodied individuals was not reported.

Diabetes mellitus contributed to an increased risk of cardiovascular diseases compared to individuals with SCI but not having a diagnosis of diabetes.[37] The relative contribution versus able-bodied individuals is not known. The role of metabolic syndrome had not yet been investigated. Cardiovascular morbidity varied substantially among studies and was highest in injured veterans. Many important confounders might explain such differences beyond the veteran status and many veterans do not receive health care from the VA.[74] Indirect comparisons of cardiovascular morbidity in adults with SCI with the general population were inadequate to estimate the relative contribution of metabolic disorders in patients with SCI.

Exercise to Alter Carbohydrate and Lipid Disorders in Adults with SCI

Of the 19 peer reviewed original articles, none were randomized controlled trials (RCTs).[13,14,54,57-72] The majority consisted of small case series or uncontrolled cross-sectional surveys using measures of self-reported physical activity. Six studies (n=57) involved active exercise, five (n=32) assessed functional electrical stimulation, and six studies (n=219) evaluated self-reported physical activity. No studies evaluated passive exercise. Carbohydrate related outcomes were reported in ten studies (n=101) and lipid related measures were reported in 13 studies of 292 individuals. Variation in study design, intervention, and reported outcomes precluded quantitative pooling of results or accurate assessment of efficacy. Evidence on effects of exercise on lipid and carbohydrate metabolism disorders is of poor quality and inconclusive in findings. Studies to date have been short in duration, have involved few subjects, and have relied on study designs highly susceptible to error. None assessed glycosylated hemoglobin.

Dietary and Pharmacologic Intervention for Carbohydrate or Lipid Outcomes in Adults with SCI

There were no prospective studies that evaluated dietary and/or lifestyle interventions on carbohydrate related outcomes.

Only two poor quality prospective studies evaluated dietary and/or lifestyle interventions to alter lipid levels.[20,72] No studies assessing pharmacologic interventions were identified. The two dietary/lifestyle case-series studies included 238 subjects, overwhelmingly male (87 percent).

One controlled trial compared the effect of a dietary intervention referral compared to no dietary referral[20] over a mean of 16 months. Group 1 subjects were older (mean 42.8 versus 35.7, $p<0.0001$) and had a longer post-injury duration (15.6 versus 11.1 years, $p<0.0001$) compared to Group 2 subjects. There were reductions in total and LDL cholesterol levels from baseline in Group 1, 234 to 224 ($p<0.001$) and 159 to 151 ($p=0.004$), respectively. Levels increased slightly but not significantly in Group 2. There were no significant effects on HDL cholesterol or triglyceride (TG) levels. An uncontrolled study evaluated a weight management program consisting of 12 classes for 12 weeks, primarily led by a registered dietician.[72] There were no significant changes in total and LDL cholesterol levels from baseline at weeks 12 and 24. HDL cholesterol was not different at week 24 compared to baseline value.

Discussion

The present report systematically evaluated published evidence regarding the prevalence of lipid and carbohydrate disorders, CVD, and mortality in adults with chronic posttraumatic SCI. The overall quality of evidence is low. Most studies were retrospective, small, lacked adequate controls, and did not assess or adjust for confounding factors. Outcome measure definitions varied widely. However, limited low quality data suggest that adults with SCI are not at markedly higher risk of carbohydrate and lipid disorders or CVD than age and gender matched able-bodied individuals. Assessment of obesity using BMI is likely to be inaccurate and underestimates body fat in adults with SCI.

The prevalence of insulin resistance, metabolic syndrome, diabetes mellitus, impaired glucose tolerance, dyslipidemia, obesity, and CVD in a population are all highly dependent upon the demographics of the population, including, most importantly, the age distribution, but also socioeconomic status and race/ethnicity. The dependence of these conditions on population characteristics makes it difficult to make between-study comparisons, since the population characteristics range greatly both between and within studies. These factors may explain the wide variation in study prevalence estimates as well as the relative risk compared to different able-bodied control populations.

Some potentially eligible studies (n=45) were excluded due to small sample size (i.e., less than 100 SCI subjects if lacking controls or less than 100 total subjects if including controls). Based on review of published abstracts, the impact of these studies on our overall findings regarding carbohydrate, lipid and body composition disorder prevalence, and subsequent clinical decisionmaking is likely to be small. The number of SCI individuals in the excluded studies ranged from one to 77. Only 17 had control groups. The largest excluded study reporting impaired glucose tolerance and insulin resistance in the United States lacked controls, was comprised of 57 adults from a single center, and was published in 1983. The largest excluded controlled study of lipid disorders was a single center report comprised of 60 young SCI adults (mean age = 28 years) and 28 healthy able-bodied controls matched by age and gender. Serum LDL cholesterol was higher (109 mg/dL vs. 91 mg/dL; $p = 0.04$) and HDL cholesterol lower (33 mg/dL vs. 44 mg/dL; $p = 0.004$) in SCI adults versus controls. The authors concluded that "serum lipoprotein levels should not be ignored for the followup of patients with spinal cord injury."[75] We agree with their conclusion. Other excluded studies were of even lower quality and relevance to health care in the United States because they were smaller, from a single center, not from the United States, lacked controls, and/or did not assess clinically relevant carbohydrate and lipid disorders.

A previous review[76] suggested a high prevalence of CVD in individuals with SCI. However, this report included, but did not differentiate between, highly prevalent self-reported signs and symptoms, such as leg swelling or palpitations[56] and less common but more serious conditions or those documented in medical records, such as myocardial infarction (0.28 to 3 percent of SCI patients).[3,53] Several factors may contribute to the prevalence of undiagnosed CVD in SCI individuals, including access and quality of care, asymptomatic angina in patients with diabetes or upper level injury,[77,78] and metabolic syndrome, unstable blood pressure, and cardiac rhythm.[79,80] If screening intensity or criteria to detect/define asymptomatic heart diseases, including coronary heart disease, arrhythmias, and autonomic dysreflexia, differs in SCI compared to able-bodied adults this could bias comparative CVD prevalence estimates.

Prevalence of CVD in aging SCI individuals can be attributable to age rather than injury. Patients differed by the prevalence of risk factors prior to injury and by age at the time of injury. Both could modify the association between SCI and CVD. Indeed, a recently published

retrospective analysis found that the presence of cardiovascular disease prior to injury was associated with a 280 percent increase in risk of death.[81] For each additional year of age at injury, the relative risk of dying was increased by 8 percent (RR 1.08, 1.06; 1.09).[81] Whether the reported increased risk of all CVD in tetraplegic compared to paraplegic individuals can be interpreted as an evidence of higher morbidity[53,76] requires additional studies. Limited evidence suggests that cardiovascular mortality may contribute to approximately 20 percent of all deaths in SCI patients[1,36,49,52] and coronary heart disease to 9 percent of all deaths.[1-3] There is insufficient evidence to determine whether percentage of deaths due to CVD differs in SCI adults compared to appropriately matched able-bodied individuals. One study suggested that presence of heart diseases was associated with a 3.7 fold increased risk of death in SCI patients compared to SCI patients without CVD, independent of age and other risk factors.[52] Limited evidence suggests that the contribution of different forms of heart disease (e.g., ischemic vs. nonischemic coronary heart disease) to overall CVD mortality in SCI patients may differ from the general population. However, proportionate mortality in SCI patients cannot give a valid estimation of mortality rates in this population. Standardized mortality ratios from nonischemic heart diseases, artery diseases, and lung emboli were higher in all injured adults compared to the general population.[2] Mortality from lung emboli contributed the most to the overall differences within the total population. However, the inconsistency of results and the multiplicity of outcomes assessed makes it very plausible that these are chance findings.

Whether the independent contribution of diabetes and impaired glucose tolerance on CVD prevalence differs in adults with versus without SCI has not been reported. The association between metabolic control and CVD in adults with SCI remains unclear. Prevalence of retinopathy was not different in SCI users of the VA health care system who were diabetic compared to diabetic able-bodied veterans.[37] The impact of lipid disorders on CVD in SCI individuals is not well documented and needs future investigation.

There is no evidence that diagnostic and treatment threshold for carbohydrate and lipid disorders should differ in SCI vs. able-bodied individuals. Assessment of insulin resistance and impaired glucose tolerance are not routinely performed in able-bodied individuals. The effectiveness of screening to improve clinical outcomes by detection of pre-diabetes (impaired fasting glucose or impaired glucose tolerance), insulin resistance, and diabetes in asymptomatic adults has not been demonstrated.[73] Use of these tests is limited due to their inconvenience, complexity of testing requirements, costs, and current lack of accuracy. The OGTT is inconvenient and not ordered by most physicians to diagnose diabetes, even among those at risk. Additionally, about one-half with IGT or OGTT would have normal tests if repeated. Similar concerns exist with the criteria used to define impaired fasting glucose. Because the glucose concentration distribution is unimodal, the choice of cutpoints used to designate abnormalities of carbohydrate metabolism is arbitrary. A recent systematic review assessed the comparative effectiveness and safety of oral medications for Type 2 diabetes mellitus. The authors reported that there was no definitive evidence about the comparative effectiveness of oral diabetes agents on all-cause mortality, cardiovascular mortality, or morbidity, peripheral arterial disease, neuropathy, retinopathy, or nephropathy.[82] Two more recent meta-analyses of thiazolidinediones have been conducted. Among able-bodied patients with impaired glucose tolerance or Type 2 diabetes (n=14,291), rosiglitazone use for at least 12 months was associated with an increased risk of myocardial infarction and heart failure. There was no difference in increased risk in cardiovascular mortality.[83] A review of pioglitazone (n=16,390) showed a significantly lower risk of death, myocardial infarction, or stroke among patients with Type 2 diabetes and

inadequate glycemic control. Serious heart failure was increased.[84] Existing recommendations to assess cardiovascular risk for able-bodied individuals suggest that all adults should have a complete lipid profile, including HDL and LDL cholesterol levels, as well as family history, smoking status, and gender. The treatment recommendations should be based on that comprehensive risk assessment. Future studies are needed to determine if SCI should be included as an independent risk factor.

The evidence that exercise programs alter carbohydrate and lipid outcomes is of poor quality and inconclusive. Only one study examined the effects of exercise on coronary heart disease outcomes or survival, with no identified associations. There were relatively few consistent findings pertaining to plasma glucose, two-hour post-load glucose, fasting insulin, or two-hour post-load insulin. Similarly, little consistency was reported between studies for HDL cholesterol, TC/HDL, and TG. Results may have indicated some overall post-training benefits for outcomes of TC and LDL cholesterol. While many reported findings are suggested as beneficial in the primary papers as well as past reviews,[85] caution in warranted. There was a general lack of quantity, quality, and consistency in methods and outcomes across studies. Reports were based on short-term exercise protocols, often involved carefully recruited hospital- and/or clinic-based patients, and failed to consider implementation or sustainability of exercise interventions in community-based populations. The exercise described in these papers varied considerably from one study to the next. In the cross-sectional surveys, parameters of physical activity were rarely reported.

Exercise and dietary programs among able-bodied individuals have demonstrated a modest improvement in carbohydrate and lipid parameters among selected highly motivated individuals. Translation of these findings to community settings of SCI adults has not been demonstrated and even the effectiveness in the general able-bodied population is unclear. For example, a recent randomized trial evaluated the effects of 22 weeks of aerobic training, resistance training, or both (three times per week) on glycemic control in 251 able-bodied adults with Type 2 diabetes.[86] Combined training resulted in a 1 percent absolute reduction in glycated hemoglobin values versus sedentary controls. Reductions due to either resistance or aerobic training alone were about one-half that seen with combination therapy. There was no difference in lipid values, blood pressure, lean body mass, fat mass, or percent body fat of any of the exercise programs versus controls. Adverse events were more common in the exercise group, and 14 percent of those randomized to exercise dropped out.

Conclusions

The available evidence regarding the prevalence, impact, and outcomes of carbohydrate and lipid disorders in adults with chronic SCI is weak. Evidence is limited by relatively small sample size, lack of appropriate control groups, failure to adjust for known confounding variables, and variation in reported outcomes. However, the existing evidence does not indicate that adults with SCI are at markedly greater risk for carbohydrate and lipid disorders or subsequent cardiovascular sequelae than able-bodied adults. The available evidence does not support incorporating SCI status as an independent variable to assess risk of cardiovascular morbidity and mortality or to alter diagnostic/treatment thresholds compared to able-bodied adults. Individuals with SCI may have unique physiologic differences compared to able-bodied individuals. Therefore, caution is advised in attempting to extrapolate findings from studies conducted in able-bodied adults evaluating efficacy and harms of interventions to improve

carbohydrate, lipid disorders, and subsequent CVD. Assessment of obesity and body composition by BMI is likely inaccurate and underestimate risks. Alternative methods for assessment in SCI populations are needed. However, unless future high-quality studies suggest otherwise, current evidence supports the conclusion that detection and treatment of carbohydrate and lipid disorders in adults with SCI should be similar to able-bodied individuals.

Future Research

A major gap in the evidence is the lack of high-quality prospective epidemiologic studies assessing the prevalence and impact of lipid and carbohydrate abnormalities and corresponding CVD complications in SCI individuals, especially compared to appropriately matched able-bodied controls. Future research could include a large prospective multicenter cohort study of adults with SCI. Risk assessment should be started at the time of injury and continued during long-term followup. Prevalence and incidence assessment needs to be objective rather than self reported. Inclusion of baseline and followup physiologic and serologic values (e.g. body composition measures, actual lipid and carbohydrate laboratory values) and standardized outcomes should be made according to well-recognized diagnostic criteria of heart diseases. Expansion of existing cohort studies in the VA, a large non-VA cohort study, and future RCTs that aim to test whether more aggressive screening or treatment within SCI populations actually reduces disease prevalence, morbidity, and mortality could be initiated. Additional information on women is needed.

If prospective cohort studies identify an increased risk in adults with SCI, RCTs will be needed to further extend the information. Techniques for identifying and treating these carbohydrate and lipid disorders and CVDs may need to be modified to meet the specific needs of those with SCI.

The level of injury, neurological impairment, and other known or potential confounders including smoking status, hypertension, family history, race, age, diabetes, infections, socioeconomic status, and quality of health care should be analyzed as possible effect modifiers of the association between well known risk factors and cardiovascular morbidity and mortality.

Consistent, higher quality research on exercise and metabolic and cardiovascular health in SCI patients is needed. Studies examining effectiveness as well as efficacy of exercise interventions are needed. Continued research should be conducted to gain a better idea of the important barriers to exercise experienced by individuals with SCI and to develop novel methods to overcome these barriers. Preliminary studies may also assess which patients are most in need of intervention, the best types of exercise programs and equipment, and how to modify them based on characteristics of the injury. Whether qualitative or quantitative, this preliminary work would not only inform the development of exercise programs but also the research used to evaluate efficacy and effectiveness.

Short-term, intermediate outcomes of exercise, as were typically reported in the current studies, may not be ideal or definitive measurements for this type of research. Studies ideally would focus on long-term clinically relevant outcomes such as prevention of or improvement in diabetes mellitus, coronary heart disease, and mortality. Long-term harms and adherence also need to be assessed. Key variables to be included in future studies are age, race, and gender; comorbid conditions; baseline lipid and carbohydrate related measures; duration, level, and completeness of SCI; functional status; baseline physical activity; exercise program type,

frequency, intensity, and duration; and life satisfaction and other important psychosocial variables.

An RCT would provide the best evidence for or against the use of exercise to prevent or control carbohydrate and lipid disorders among those with SCI, though conducting adequately sized studies would be difficult and require cooperative group participation. Further research will be needed to translate any findings of exercise efficacy into effective community-based interventions. Even if efficacy is promising, it will remain to be seen if these interventions are feasible in a community setting and if the interventions, as well as health outcomes, are sustainable over time. Further evidence on how best to motivate individuals to sustain exercise, while preventing and identifying potential harms, will be needed.

RCTs evaluating the potential effectiveness and harms of pharmacologic and dietary interventions to alter CVD risk factors (diabetes, lipid abnormalities and/or obesity) and reduce CVD incidence, morbidity, and mortality may be needed if there is continued concern that results may differ in SCI populations compared to able-bodied adults.

Evidence Report

Chapter 1. Introduction

Overview

Spinal cord injuries (SCI) result in 11,000 hospitalizations of new cases annually in the United States.[5,6] More than 240,000 Americans live with a disability related to SCI and the estimated annual cost averages $9.7 billion.[5,7,8] Improved quality of care over the last several decades has resulted in a 40 percent decline in mortality during the two years following the injury.[9] However, improvement in long-term survival has been smaller. Cardiovascular diseases (CVD) have been reported as the most common cause of death in adults with chronic SCI.[2,10-12] CVD risk factors associated with SCI include behavior (smoking, limited exercise) and metabolic abnormalities (obesity, metabolic syndrome,[13-15] and diabetes[11]). The prevalence of dyslipidemia[16,17] and coronary heart disease has been reported to be higher in adults with SCI compared to the general population.[10,18] The Institute of Medicine recently released two reports that emphasized the role of cardiovascular risk assessment and management in adults with chronic SCI.[6,11] Some evidence suggests that exercise,[19] diet,[20,21] and pharmacological therapy[22] may reduce diabetes and cardiovascular disease risk in these individuals. Furthermore, markers or thresholds of carbohydrate and lipid disorders commonly used in adults without SCI may not apply to the population that has sustained SCI. In particular, because adults with SCI lose muscle mass that is replaced with fat mass, traditional measure of obesity (weight or body mass index [BMI]) may not be appropriate.

Accurate estimates of diabetes prevalence and severity in adults with SCI may:
1. be underestimated relative to able-bodied controls because individuals with SCI may not undergo regular testing,
2. have lower levels of high-density lipoprotein (HDL) cholesterol that go unrecognized if providers only assess total cholesterol (TC) levels or base treatment solely on low-density lipoprotein (LDL) cholesterol, or
3. they have earlier evidence of impaired glucose tolerance or altered insulin sensitivity.

Existing guidelines do not include routine evaluation of glucose and lipid abnormalities nor do they provide recommendations for threshold definitions of abnormality or target levels for interventions to achieve.[23-25] Furthermore, the prevalence, morbidity, and mortality associated with carbohydrate and lipid disorders may differ in adults with SCI compared to able-bodied individuals.

Effective interventions to treat carbohydrate and lipid disorders and reduce cardiovascular complications in able-bodied individuals include dietary, pharmacologic, and exercise therapies. However, adults with SCI have unique physiologic characteristics that may preclude generalization of evidence from able-bodied individuals to those with SCI. Total daily energy expenditure for adults with SCI is difficult to calculate but likely much lower than for able-bodied individuals, especially among individuals requiring motorized wheelchairs for mobility. Treatment of obesity in SCI remains largely empiric, including guidelines developed for dietary intervention in SCI. Pharmacologic therapies to alter carbohydrate and lipid disorders may have different effectiveness and adverse effects in individuals with SCI compared to able-bodied patients. For example, assessment of hepatic or muscle toxicity in SCI individuals may be difficult using traditional serologic measures developed in able-bodied adults because SCI individuals have reduced muscle mass and potentially altered hepatic metabolism.

Despite the expected benefits of exercise for individuals with SCI, this group also faces unique challenges and risks from exercise that are not experienced by the able-bodied population.[8,26] For one, lack of access to and choices in exercise modes, depending on the neurological impact and level of the injury, form physical barriers to obtaining exercise. Physiological risks of exercise are also a barrier to improved fitness among those with SCI. Depending on the level and completeness of the spinal injury, motor, sensory, and autonomic reflexes may still be intact but no longer under control of the brain. Individuals with SCI also experience various types of autonomic and circulatory dysregulation.[26] Risk of stress-related musculoskeletal injury is of concern, given the reliance on a small group of muscles for activities of daily living as well as for any physical conditioning. Fractures, joint dislocation, and overuse injuries are common for individuals with SCI.[27]

In selected highly motivated able-bodied population, exercise, and its resulting improvements in aerobic capacity, appear to modestly improve carbohydrate metabolism, lipid profiles, and general cardiovascular health.[7,87-90] For example, even moderate levels of physical activity, defined as three to six metabolic equivalents (METs) sustained for 30 minutes five to six times per week, may reduce the risk of cardiovascular disease and all-cause mortality.[91] Current Centers for Disease Control and Prevention (CDC) and American College of Sports Medicine recommendations for exercise in the able-bodied population include 30 minutes of moderate physical activity, five to six times per week, or 20 minutes of vigorous (greater than six METs) physical activity, three or more times per week.[92]

However, translation of these findings to community settings of SCI adults has not been demonstrated, and even the effectiveness in the general able-bodied population is unclear. For example, a recent randomized trial evaluated the effects of 22 weeks of aerobic training, resistance training, or both (three times per week) on glycemic control in 251 able-bodied adults with Type 2 diabetes.[86] Combined training resulted in a 1 percent absolute reduction in glycated hemoglobin values vs. sedentary controls. Reductions due to either resistance or aerobic training alone were about one-half that seen with combination therapy. There was no difference in lipid values, blood pressure, lean body mass, fat mass, or percent body fat of any of the exercise programs vs. controls. Adverse events were more common in the exercise group and 14 percent of those randomized to exercise dropped out.

Whether this amount of physical activity would produce the same benefits in patients with SCI is unknown. However, it is reasonable to assume that similar metabolic responses to exercise would occur for these individuals. No evidence-based guidelines for exercise in this population currently exist.[93] At present, the American College of Sports Medicine's endurance training recommendations for those with SCI are relatively similar to advice directed toward the general population. Generally, the recommended exercise prescription, at least for those with paraplegia, is three to five weekly sessions of 20 to 60 minutes in duration and at an intensity of 50 to 80 percent of the individual's peak heart rate.[94] Suggested modes of exercise include arm cranking, wheelchair propulsion, swimming, wheelchair sports, circuit resistance training, electrically-stimulated cycling, and electrically-stimulated walking.

Based on a topic and key questions nominated by the *Consortium for Spinal Cord Medicine,* we conducted a systematic review of published evidence to address the following questions:

Question 1a: What proportion of adult patients with chronic posttraumatic spinal cord injuries have been diagnosed with:

a. Insulin resistance syndrome, metabolic syndrome
b. Diabetes mellitus Type 2, impaired glucose tolerance

c. Dyslipidemia
d. Obesity

Question 1b: Is the prevalence of carbohydrate and lipid disorders higher in the subgroups of patients by age, race, and gender compared to the general population? Does the prevalence of carbohydrate and lipid disorders differ by the time after trauma, the level of trauma, and functional impairment?

Question 2: For people with SCI, what is the evidence on contribution to risk of cardiovascular disease of:

a. Hyperinsulinemia
b. Abnormalities in carbohydrate metabolism
c. Abnormalities in lipid metabolism?
d. Obesity

This question was refined as:

Question 2: Regarding risk of cardiovascular disease for people with SCI:

a. What is cardiovascular prevalence and mortality in adults with chronic posttraumatic spinal cord injuries?
b. Does cardiovascular incidence and mortality in adults with chronic posttraumatic spinal cord injuries differ compared to the general population based on age, race, and gender categories?
c. What is the strength of the association between cardiovascular incidence and mortality and abnormalities in lipid and glucose metabolism including Type 2 diabetes mellitus after adjustment for possible confounding factors?
d. Does association vary depending on age, gender, race, the duration after SCI, the level of SCI, and functional impairment?

Question 3: What are the effects on carbohydrate or lipid-related outcomes in adults with SCI of:

a. Exercise
b. Dietary and pharmacologic interventions

Chapter 2. Methods

Topic Assessment and Refinement and Literature Review

A Technical Expert Panel (TEP) was convened, comprised of individuals with expertise in rehabilitation/physical therapy/neuromuscular aspects of chronic SCI, primary care relevant to patients with chronic SCI, lipid and carbohydrate disorders, dietary intervention, exercise, and pharmacotherapy in patients with chronic SCI. Names of individuals who agreed to participate, their CVs, and disclosure statements were sent to the Agency for Healthcare Research and Quality (AHRQ) for review and approval by the end of January 2007. Those members are identified in Appendix A.

Based on discussions with our partner and TEP members, we developed inclusion and exclusion criteria for study design and size, population, intervention, comparator groups, and outcomes. Question 2 was refined to read:

- What is cardiovascular prevalence and mortality in adults with chronic posttraumatic spinal cord injuries?
- Does cardiovascular prevalence and mortality in adults with chronic posttraumatic spinal cord injuries differ compared to the general population based on age, race, and gender categories?
- What is the strength of the association between cardiovascular prevalence and mortality and abnormalities in lipid and glucose metabolism including Type 2 diabetes mellitus, after adjustment for possible confounding factors?
- Does association vary depending on age, gender, race, the duration after SCI, the level of SCI, and functional impairment?

We evaluated, but ultimately did not include, findings from systematic reviews of randomized controlled trials (RCTs) related to behavioral, dietary or pharmacologic interventions as primary prevention of CVD and carbohydrate and lipid disorders in able-bodied adults. The rationale was that little RCT evidence regarding the efficacy and harms of these interventions in SCI individuals existed. It was unlikely that outcomes from these interventions would markedly differ between SCI and able-bodied individuals. Therefore, findings from these intervention studies in able-bodied controls were used to assess baseline lipid and carbohydrate characteristics as well as effectiveness and harms in able-bodied individuals. We also sought to determine whether evidence from these RCTs or current practice guidelines suggested that thresholds for diagnosis or intervention in SCI individuals currently recommended for able-bodied adults should be altered for SCI individuals.

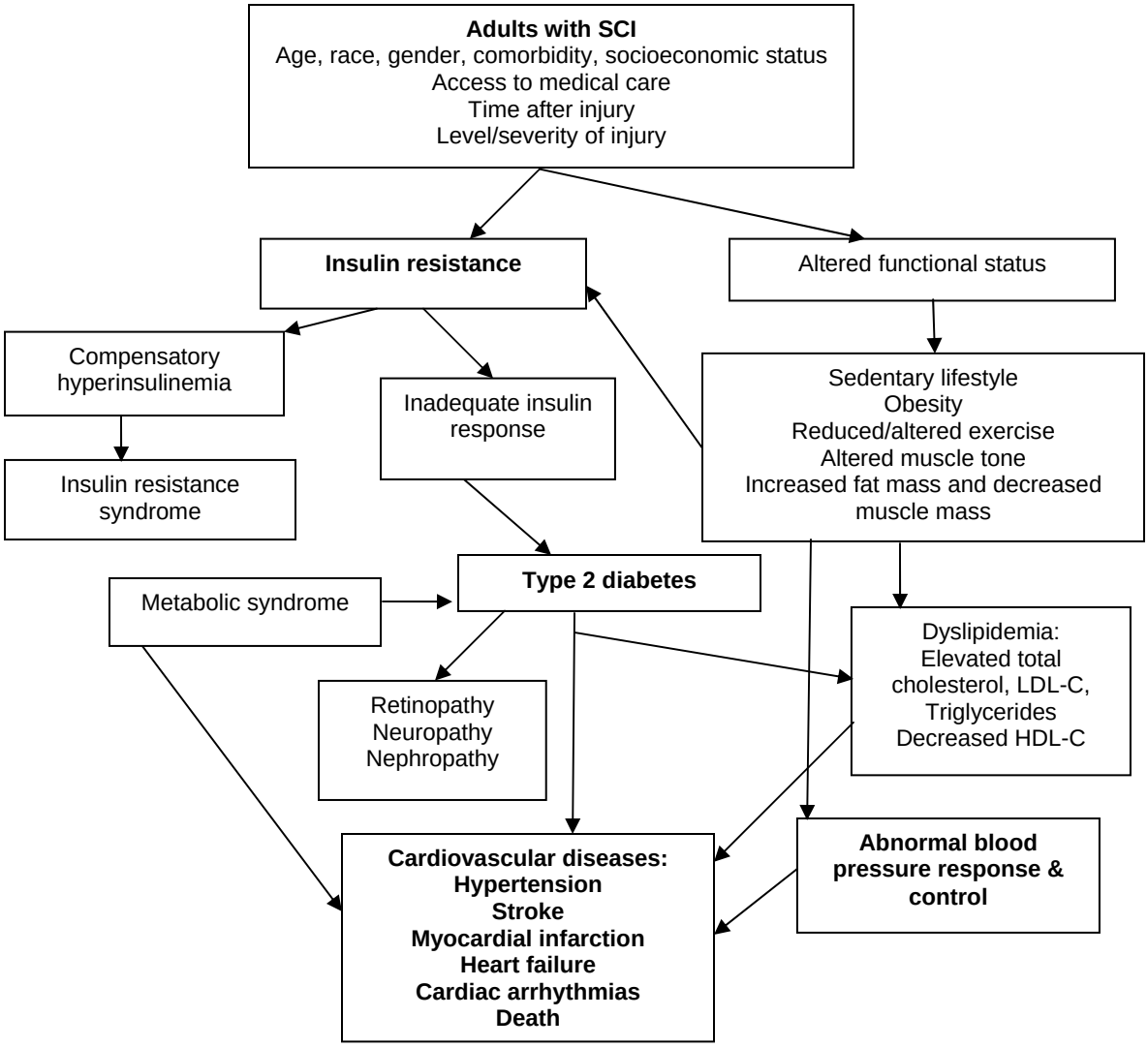
Following the initial conference calls, the Minnesota Evidence-based Practice Center (EPC) conducted a systematic review and meta-analysis (where feasible) of published evidence of the association between lipid and carbohydrate disorders and risk of cardiovascular diseases in adults with chronic SCI. The prevalence of insulin resistance, metabolic syndrome, diabetes mellitus, impaired glucose tolerance, obesity, and abnormalities in lipid metabolism in patients with chronic SCI was estimated from cross-sectional studies that attempted to capture a nationally representative sample of adults with SCI. Observational cohort and case-control studies that tested the hypothesis of the association between carbohydrate and lipid disorders and risk of CVDs in adults with chronic SCI were reviewed. The risk of CVDs among patients with chronic

SCI was analyzed. We examined case control and cohort studies to determine if risks of carbohydrate and lipid disorders and CVDs are greater in adults with SCI than in age/gender matched controls without SCI.

The role of different forms of exercise (passive and active, person initiated, and due to electrical stimulation) and diet in the prevention and treatment of carbohydrate and lipid disorders and corresponding sequelae in adults with chronic SCI was evaluated from observational studies and clinical trials. Controlled and randomized trials that examined the effects of exercise, diet, and pharmacological intervention on cardiovascular risk and outcomes in adults with chronic SCI were analyzed. Our preliminary search found few controlled trials of these interventions and only one survey report that assessed their impact on major cardiovascular endpoints, such as morbidity and mortality. Therefore, we estimated the potential impact of early detection and treatment of adults with SCI by evaluating large RCT and systematic reviews of treatments for lipid and carbohydrate disorders in adults without SCI. Our comprehensive work plan covered the assessment and refinement of study questions, proposed literature search and review, inclusion/exclusion criteria, and methods for evaluating the quality of studies and rating the strength of evidence.

The following conceptual model (Figure 1) was created:

Figure 1. Conceptual model. Contribution of carbohydrate and lipid disorders to risk of cardiovascular disease in adults with chronic posttraumatic SCI



Adapted from American College of Endocrinology statement on insulin resistance[4]
Bold - eligible outcomes

Literature Search Strategy and Eligibility Criteria

The search strategy is presented in Appendix B. The general approach is described below. Specific items for each question are based on conference calls with our TEP members.

Question 1. A literature search was conducted on Ovid MEDLINE®, using the search term *spinal cord injury* combined with the following terms: *hyperinsulinemia* or *hyperinsulinism* or *insulin resistance* or *Metabolic Syndrome X* or *metabolic syndrome*; *diabetes mellitus* or *glucose intolerance* or *impaired glucose tolerance*; *hyperlipidemias* or *HDL cholesterol* or *low HDL cholesterol*; and *obesity*. The search was limited to articles published from 1990 to May 2007 or to articles recommended by peer reviewers through October 2007.

Studies were included if:

1. Adults had chronic SCI, defined as 1 year or more since sustaining the injury;
2. The total number of spinal cord subjects was at least 100, or totaled at least 100 subjects if a control group was included;
3. Reported outcomes such as the prevalence of obesity, diabetes, impaired glucose tolerance, metabolic syndrome or insulin resistance, or lipid disorders *or* reported mean BMI or lipid levels (total cholesterol, HDL cholesterol, LDL cholesterol, or triglycerides);
4. Were published in the English language. For able-bodied individuals we used nationally representative samples from NHANES that reported on obesity, diabetes and glucose intolerance, and lipid disorders. In particular, we were interested in results provided according to age categories and male gender because nearly 90 percent of reported SCI individuals were male. We also included a single uncontrolled study of 93 SCI adults that assessed insulin resistance and metabolic syndrome because only one other report for insulin resistance and no studies for metabolic syndrome met our predefined eligibility criteria.

Question 2. Original epidemiologic investigations of more than 50 patients with traumatic chronic (>1 year after injury) SCI published in English after 1990 were identified in MEDLINE® via PubMed®. The search of the Cochrane library and the websites including the American Spinal Injury Association, American Paraplegia Society, Paralyzed Veterans of America, Consortium of Spinal Cord Medicine, and the catalog WorldCat identified reviews but not additional original studies.

Question 3a (exercise). The Endnote library containing original and review articles (n=2,212) was searched for abstracts that included the words *fitness*, *physical activity*, or *exercise*, resulting in a subset of 304 citations. In addition, a University of Minnesota medical reference librarian assisted in a MEDLINE® search in response to the question, "*What is the role of exercise in the prevention/treatment of carbohydrate and lipid metabolism disorders in people with spinal cord injury or disease?*" This search, limited to human studies written in English and published between 1996 and 2007, resulted in 13 original articles as well as one review article. Of these, one relevant original article[65] and the review article[85] were not previously identified in the Endnote library. The original article was added to the database, for a total of 305 citations.

Question 3b. To identify and evaluate evidence whether pharmacologic or dietary interventions play a role in the prevention and/or treatment of carbohydrate and lipid metabolism disorders in the SCI population, studies were identified by searching in MEDLINE® through May 2007 or by recommendations of peer reviewers through October 2007. Our initial literature search used the same search string utilized for Question 1. In addition, reference lists of relevant studies or reviews were also searched. Since no randomized trials were identified, nonrandomized (controlled or uncontrolled) studies were eligible. To be included, studies had to:

1. Evaluate adults who had chronic SCI, defined as one year or more since sustaining the injury;
2. Evaluate pharmacologic or dietary interventions;
3. Report carbohydrate and/or lipid related outcome measures;
4. Be published in the English language.

To address question 3b regarding the effectiveness of interventions on carbohydrate and lipid disorders to prevent CVD outcomes and mortality and diabetes in able-bodied adults, we relied on RCTs or systematic reviews of RCTs. Studies were identified using the Cochrane Library and searching MEDLINE® through September 2007. The search was limited to the English language. Included studies must have enrolled or evaluated separately able-bodied adult subjects without pre-existing CVD or Type 2 diabetes and reported clinical outcomes such as mortality, myocardial infarction, stroke, or prevalence of Type 2 diabetes. Studies reporting only improvements in lipid or glucose values were excluded. To limit the scope of the therapeutic interventions, we evaluated primarily clinically proven pharmacologic interventions, with the exception of omega-III fatty acids. Results were assessed and summarized but not formally included in the final report (they are available from the authors upon request).

Data Synthesis

For Questions 1 and 2 related to prevalence, we extracted the percentage of individuals with a diagnosis of diabetes, impaired glucose tolerance, insulin resistance, lipid abnormality, obesity (including BMI categories), CVD, and mortality according to the definitions provided to the authors. Additionally, we extracted mean carbohydrate, lipid, or BMI values. We pooled values to estimate the mean total, LDL, HDL cholesterol, and triglyceride (TG) values as well as BMI for adults with SCI and displayed these in comparison to a representative sample of U.S. adults from NHANES. Where data were available we used age stratified NHANES values for U.S. males because nearly 90 percent of SCI subjects were male with mean ages between approximately 30 and 60. We used a random-effects model to estimate the weighted mean difference with 95 percent confidence intervals (CI) in lipid values between SCI adults and able-bodied controls.

For Question 2, the results of individual studies were abstracted (see Appendix C for abstraction form) and summarized in evidence tables to analyze the level of evidence, differences in populations and definitions of the outcomes, and the association between risk factors with cardiovascular prevalence and mortality by age and injury status. We analyzed outcomes using the exact definitions from the individual studies. Any combinations were possible only for the same International Classification of Diseases (ICD) codes. Prevalence was calculated as the number of CVD events among the total number of SCI patients in the study; standard error and CI for population prevalence were calculated with Wilson estimate.[95] We calculated mortality as a proportion of the patients who died from CVDs during the time of the data collection among the total sample of SCI patients. We could not analyze annual mortality rates because the authors did not report this outcome. We calculated crude odds ratios (OR) of the outcomes when the author reported rates in SCI patients and able-bodied controls.[96] Meta-analysis was used to assess the pooled prevalence of CVD with random effects models.[97] Assumptions underlying meta-analysis included valid measurements of the outcomes and similarity in study and target populations. Chi squared tests and I squared tests were used to assess heterogeneity in study results.[98-100] Calculations were performed using STATA software.[101]

For Question 3, we extracted and reported the individual study outcome results with tests of significance for SCI patients as reported by authors. Variation in study design, population, intervention, and outcome did not permit pooling.

Strength of Evidence

The strength of the available evidence was rated according to methods of the U.S. Preventive Services Task Force via a three-point scale (high, medium, and low). Confidence in the level of evidence from the review of assessing interventions in able-bodied adults is considered high based on the consistent results from at least two high-quality studies with long-term followup. For all other questions strength is considered low due to serious flaws in study design, inconsistency in findings, and subsequent risk of bias in outcome assessment.

Chapter 3. Results

Study Identification

Figures 2-4 trace the flow of our literature search. Excluded studies are listed in Appendix D.

Figure 2. Flow chart for Question 1 references

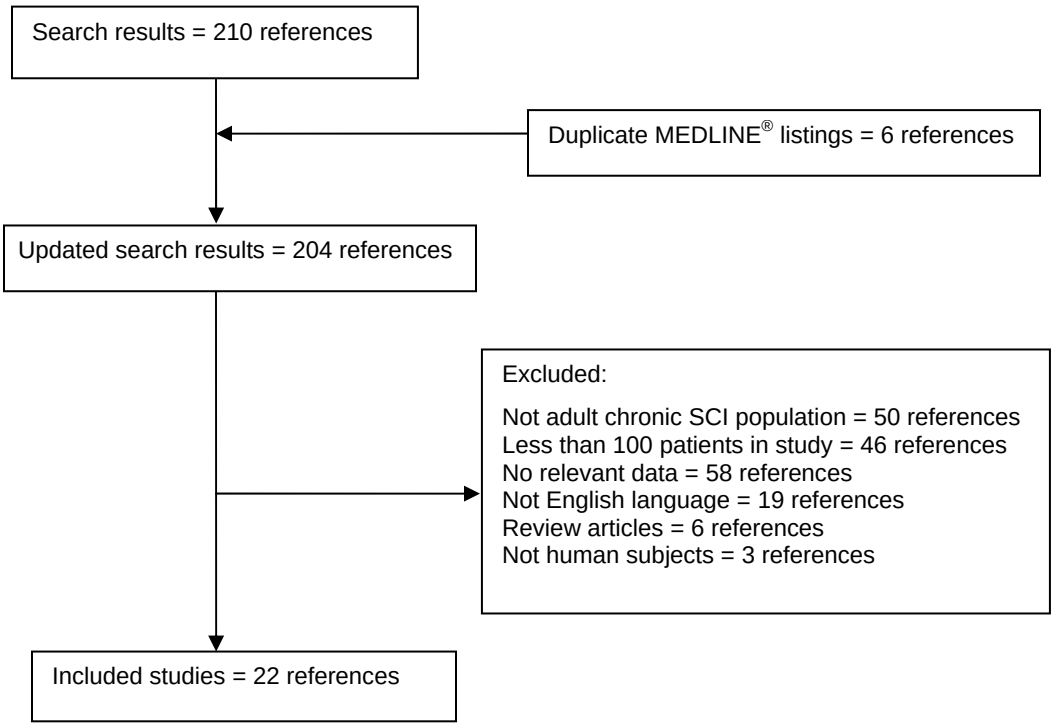


Figure 3. Flow chart for Question 2 references

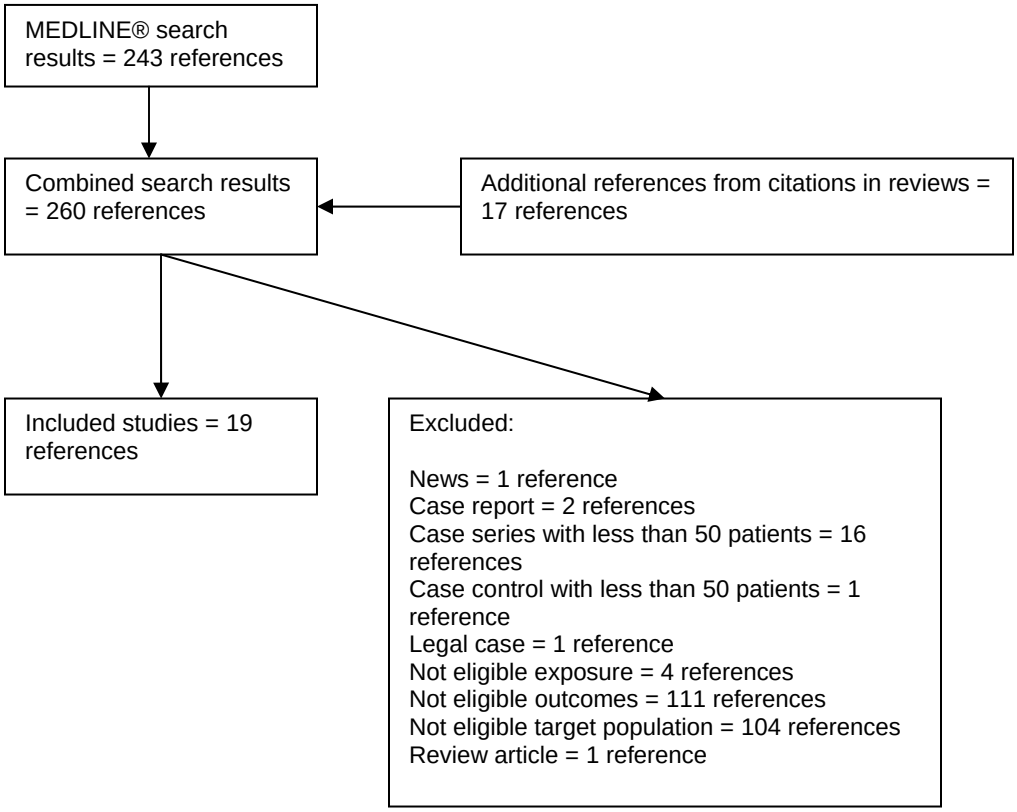
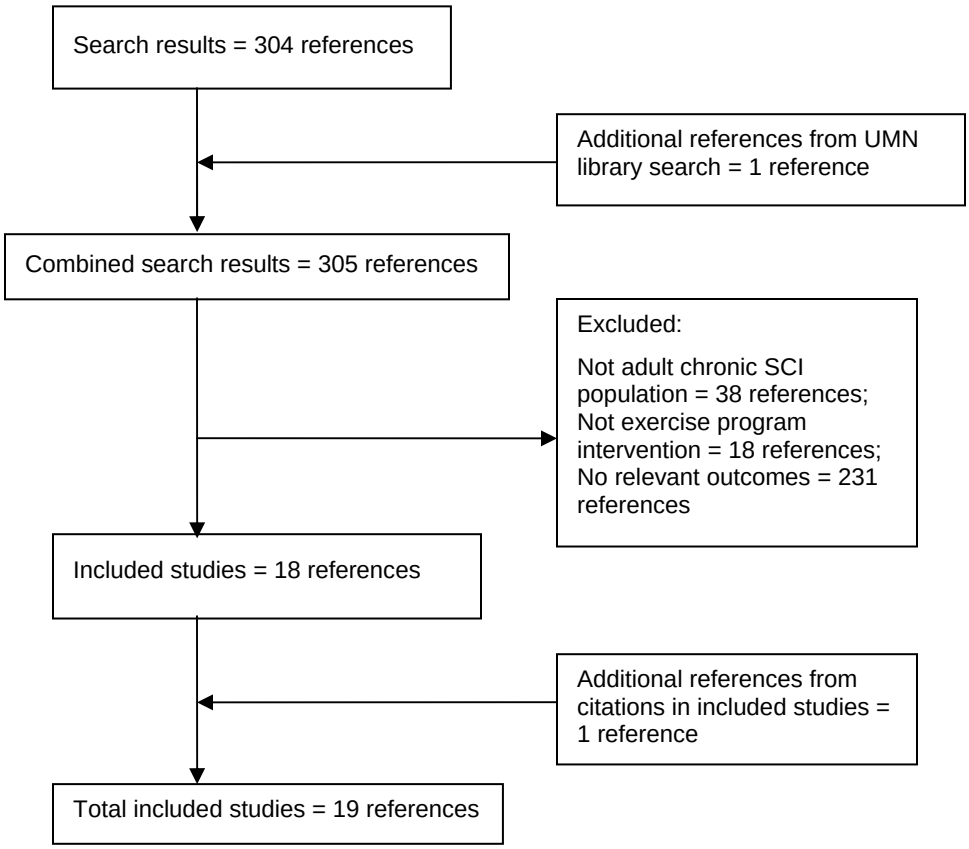


Figure 4. Flow chart for Question 3a references (exercise/physical activity interventions)



For Question 1, the 210 citations identified through the search were screened for inclusion. Exclusions were based on the following reasons: not human subjects (three articles), duplicate citation listings (six articles), review articles with no data of interest (six articles), not English language (19 articles), studies with less than 100 subjects (45 articles), not adult chronic SCI patients (50 articles), and no relevant data (58 articles). The remaining 22 articles meeting the inclusion criteria contained data for one or more of the following: metabolic syndrome or insulin resistance (one article), glucose intolerance or Type 2 diabetes (12 articles), lipid values (six articles), or obesity (nine articles) (Appendix E Table 1). Abstracts of the 45 identified studies that were excluded primarily for small sample size (i.e. they contained less than 100 SCI subjects if lacking controls or less than 100 total subjects if including controls) were further reviewed to determine the potential impact on our results and conclusions. The impact of these studies on our overall findings regarding carbohydrate, lipid and body composition disorder prevalence, and subsequent clinical decisionmaking is likely to be small. The number of SCI individuals in the excluded studies ranged from one to 77. Only 17 had control groups. The largest study reporting glucose intolerance and insulin resistance in the United States lacked controls, was comprised of 57 adults from a single center, and was published in 1983. The largest excluded *controlled* study of lipid disorders was a single center report comprised of 60 young SCI adults (mean age = 28 years) and 28 healthy able-bodied controls matched by age and gender. Serum LD cholesterol was higher (109 mg/dL vs. 91 mg/dL; p = 0.04) and HDL cholesterol lower (33 mg/dL vs. 44 mg/dL; p = 0.004) in SCI adults versus controls. The authors concluded that "serum lipoprotein levels should not be ignored for the followup of the patients with spinal cord injury."[75] We agree with their conclusion. Other excluded studies were of even lower quality and relevance to health care in the United States because they were smaller, from a single center, not from the United States, lacked controls, and/or did not assess clinically relevant carbohydrate and lipid disorders.

For Question 2, the library included 260 references after the deletion of duplicates; 18 references were found with a manual search of the citation lists; 243 were identified in MEDLINE®. We excluded 241 references for the following reasons: one review, one legal case, one news, two case reports, one case control study with <50 SCI patients, 16 case series with <50 patients, four evaluated events after diet, acupuncture, surgery, or drug therapy, 111 (46 percent) did not report cardiovascular events, and 104 (43 percent) examined patients with acute traumatic or not traumatic injuries. We reviewed 20 articles of the 19 studies that reported cardiovascular events in adults more than 1 year after traumatic SCI (Appendix E Table 2). Observational studies were conducted in the United States,[2,3,34,36,37,46-51] United Kingdom,[52,53] Canada,[54] Denmark,[1] Sweden,[55,56] Australia,[39] and Japan.[30,32] Two publications reported different outcomes from the same Stockholm Spinal Cord Injury Study.[55,56] The results from the Japanese National Livelihood Basic Survey were published twice and were considered as one study.[30,32] Several American studies were conducted in the Veteran Affairs Spinal Cord Injury Services but differed by location, time, and outcome.[3,34,37,48,51] One prospective cohort examined incidence of CVD in people with long-term SCI.[53] Another prospective study evaluated mortality in patients with chronic SCI.[36] One case control study compared probability of CVDs in patients with SCI compared to age-matched able-bodied persons.[46] Retrospective cohorts evaluated prevalence of electrocardiogram (ECG) abnormalities,[34] cardiovascular morbidity, and mortality in patients with chronic SCI[1-3,47,49,52] compared to the general population[1,2,52] and after adjustment for age, gender, level of injury, time after injury,[52] race, etiology of injury, neurologic level of injury, American Spinal Injury Association Impairment Scale, ventilator dependency, sponsor of care, and autopsy.[49] Cross-sectional surveys reported prevalence of diabetes after adjustment for age,

race, marital status, duration of injury, employment and education,[37] and prevalence of cardiovascular diseases after adjustment for age,[30,32] gender, education, ethnicity, marital and vocational status,[50] duration of cigarette use,[54] duration of injury and functional status,[56] and socioeconomic status of the patients.[55]

For Question 3, based on the criteria identified above, 304 citations identified through the keyword search were reduced to 19 for use as evidence. Exclusions were based on the following: 38 due to lack of adult, chronic SCI patient population; 18 due to lack of exercise program or measure of self-reported physical activity; 231 due to lack of relevant carbohydrate or lipid related outcome measures. Upon review of citations from the 18 eligible references and one previous review paper, one additional reference was identified and added to the evidence base.[69] Thus, results of 19 original studies were synthesized to address this question.

For Question 3b, only two prospective studies in adults with SCI evaluated dietary and/or lifestyle interventions to reduce lipid levels and met inclusion criteria.[20,72]

Outcomes

Question 1

Overall Description. The prevalence of insulin resistance syndrome, metabolic syndrome, diabetes mellitus Type 2, impaired glucose tolerance, dyslipidemia, and obesity in a population are all highly dependent upon demographics of the population, including most importantly the age distribution, but also factors such as socioeconomic status and race/ethnicity. The dependence of these conditions on population characteristics makes it difficult to conduct between-study comparisons, since the population characteristics range greatly both between and within studies. For example, one study might include men and women between the ages of 18 and 70, and within such a study one would expect age and gender stratified proportions of Type 2 diabetes to vary several fold; however, studies of this sort might only present an overall percent that are diabetic. Such an overall value is difficult to interpret and nearly meaningless unless the study has an appropriate control group. In the included evidence tables and figures, results have been presented stratified by age and other key factors (including severity or duration of injury) when such information was reported, but the paucity of consistently stratified results makes pooled estimates nearly impossible. Therefore, we have chosen to focus primarily on the higher quality studies (largest observational reports with control groups).

Hyperinsulinemia (insulin resistance/metabolic syndrome). Little is known regarding the extent to which hyperinsulinemia is related to SCI. Only one relatively small observational study reported results for metabolic syndrome and insulin resistance syndrome (Appendix E Table 1).[15] This study included a convenience sample of 93 SCI subjects (mean age = 50 years) recruited from a single VA and local community clinics (86 percent male). Of these 93 subjects, 11 percent were insulin resistant when relying entirely on mean fasting glucose and insulin values; however, when glucose-regulating medications were taken into account, 22 percent of the subjects were insulin resistant.[15] Metabolic syndrome was defined as the presence of three or more metabolic disorders, including hypertension (systolic blood pressure ≥130 mmg/Hg, diastolic pressure ≥85 mmg/Hg, or the use of antihypertensive medications), obesity (defined by waist circumference), hyperglycemia (fasting glucose ≥110 mg/Dl or presence of glucose-lowering medications), hypertriglyceridemia (fasting serum triglycerides ≥150 mg/dL or taking

cholesterol-lowering medications), and low HDL cholesterol (<40 mg/dL). Using this definition, metabolic syndrome was noted in 22 percent. This study did not include a control group or attempt to present results stratified by age and gender or level and duration of injury. The authors definitions for specific metabolic disorders are not widely accepted and are likely to increase the estimated prevalence of a given disorder.[73] A second study of 201 SCI patients included results from an oral glucose challenge and reported rates of hyperinsulinemia by type of SCI injury.[28] This study found hyperinsulinemia in 53 percent of people with tetraplegia and 37 percent of paraplegics.

Summary. Currently, there are no high quality studies adequately assessing the prevalence of metabolic syndrome and insulin resistance syndrome in a large population of adults with SCI. There are also no data to assess if the prevalence of either metabolic syndrome or insulin resistance are elevated in adults with SCI compared to similar individuals without SCI. Since metabolic and insulin resistance rates are dependent on age, gender, and race/ethnicity, future studies are needed that are large enough to report rates stratified by these key factors.

Abnormalities in carbohydrate metabolism (diabetes mellitus and impaired glucose tolerance). The prevalence of diabetes in SCI subjects has been reported in multiple studies (Appendix E Table 1).[3,15,28-37] Several of these studies have also reported a comparison between SCI individuals and non-SCI subjects (Figure 5).[29,32,34,37]

A total of 6,832 persons with SCI and 254,847 controls were included in the reviewed studies, of which the vast majority of all of SCI individuals came from two large Veterans Health Administration (VHA) studies.[34,37] The largest of these studies included a national cross-sectional survey of 3,737 SCI adults who were users of the VA health care system, along with a control group of 6,413 non-SCI VA health-care user control subjects and data from the CDC Behavioral Risk Factor Surveillance System 2003 survey of 221,650 community-dwelling adults.[37] This large study found a substantially greater portion of VA SCI individuals self reported that they had diabetes compared to the general population surveyed by the CDC (20 percent versus 7.6 percent, $p<0.001$). However, overall self-reported prevalence of diabetes in VA users with SCI was similar to the prevalence of diabetes in the non-SCI VA user population (20 percent vs. 21 percent). Another large study also from a VA population found similar rates of diabetes in SCI and non-SCI subjects (11 percent vs. 10 percent, respectively).[34] Differences in the overall prevalence of diabetes between these two studies are likely due in part to differences in ascertainment of diabetes status (self-report versus diagnosis in administrative dataset) and differences in the ages of the subjects, with the study reporting higher veteran prevalence of diabetes including older subjects and self-reported surveys. Results from national representative able-bodied populations clearly show that the prevalence of diabetes is highly dependent on method of ascertainment or definition (diagnosed vs. undiagnosed diabetes vs. impaired fasting glucose (Figure 6). The two other studies that included non-SCI control groups reported increased diabetes prevalence among SCI individuals.[29,32] Both of these studies found several-fold higher rates of diabetes among the SCI subjects but were published more than a decade earlier and had smaller sample sizes. The first of these studies also involved veterans with and without SCI from a single institution. This study had a small number of controls (n=50) and only three controls had diabetes.[29] For this study diabetes was diagnosed using a one-time oral glucose tolerance test. There was some evidence that persons with SCI had higher scores on their oral glucose tolerance tests than would be expected based on their fasting plasma glucose levels compared to non-SCI controls. In the non-SCI control group, people who were categorized as diabetics had an average mean fast plasma glucose level of 115 mg/dl while mean levels for

paraplegic and tetraplegic diabetics were 99 mg/dl and 102 mg/dl, respectively. The other study presented results from a survey of Japanese subjects with overall diabetes rates much lower than those observed in the U.S. population (the control group had a 1.2 percent prevalence of diabetes).[32]

The relationship between increased age and increased diabetes prevalence in both able-bodied individuals and those with SCI is strong and clearly demonstrated in the large survey of SCI individuals by Lavela and colleagues[37] and results from the nationally representative NHANES III study (Figure 6).[102] However, we found no evidence to suggest that the association between age and diabetes was substantially different in SCI compared to non-SCI groups.

The prevalence of impaired glucose intolerance (IGT) has been studied less frequently. In the three studies that met our inclusion criteria,[28,29,31] only one study included a non-SCI control group (n=50) (Appendix E Table 1).[29] All three studies were of veterans receiving care at a VA hospital, and all reported approximately 30 percent SCI patients with IGT, while only 12 percent of controls had IGT. The fact that only six control individuals with IGT were included in the one study with a non-SCI control group makes it impossible to determine from these data whether IGT is increased or not.

*Summary***.** The prevalence of diabetes appeared higher on average in SCI populations studied as compared to the general population. However, there is considerable reason to believe that the general population groups used were not appropriate controls for SCI patients. For example, lifestyle and comorbidities, irrespective of SCI, could be quite different. Therefore, the extent to which this increased the prevalence of diabetes is due to a causal relationship between the SCI and the development of subsequent diabetes is not well known. Overall, the VA patient control groups tended to be similar to the VA SCI patient populations in their rate of diabetes, and it was only when the rate of diabetes in the VA SCI patients was compared to the general public that the SCI individuals appeared to be at higher risk. Users of the VA health care system have greater comorbidities than either veterans not actively using the VA health care system or non-VA populations. Therefore, current evidence is insufficient to determine to what extent the higher rate of diabetes is independently attributable to SCI or to other factors that might be higher in adults who subsequently have a SCI than in the general public. While there was not consistent evidence that fasting plasma glucose was substantially different in SCI patients, some evidence suggests that these individuals may be more likely to meet IGT or diabetes mellitus diagnostic criteria following oral glucose tolerance tests. More research is needed to determine whether using the oral glucose tolerance test (OGTT) is more likely to diagnose diabetes in SCI compared to non-SCI patients, and whether individuals diagnosed with diabetes by OGTT benefit from treatment.

Abnormalities in lipid metabolism (hyperlipidemia and/or low HDL cholesterol). Lipid disorders among SCI populations have been reported in seven included articles,[16,17,21,31,38,39,103] of which three appear to have included SCI individuals from the same study.[16,17,40] There appear to be a total of 1,413 SCI individuals in all of these studies. Three studies (n=747 SCI adults) included some form of a non-SCI control group (n=680 for controls assuming the Krum et al. 1992 study included a 1:1 match, even though the number of controls was not reported) (Appendix E Table 1 and Figure 7).[38,39,103] The pooled results of the three studies with control groups (one study only reported total cholesterol) showed that on average individuals with SCI had lower TC, LDL cholesterol, HDL cholesterol, and TG. While these differences were statistically significant, none were likely to result in differences in clinical decisionmaking. All

mean values were within less than a half a standard deviation. Furthermore, the mean 7.5 mg/dL lower (worse) value of HDL cholesterol among SCI individuals was counterbalanced by 11 mg/dL lower (better) LDL cholesterol and 10 mg/dL lower TG levels. When the mean lipid values from SCI individuals were compared to those of the able-bodied national male age norms for the NHANES study, the similarities between SCI and able-bodied lipid values were also observed (Figures 8-13). None of the mean lipid values were outside of the threshold established for primary prevention among able-bodied adults. Mean lipid values for SCI individuals were: total cholesterol (six studies) 194 mg/dL (range 188-205); LDL cholesterol (five studies) 125 mg/dL (range 120-126); HDL cholesterol (five studies) 42 mg/dL (range 39-46), and triglycerides (five studies) 122 mg/dL (range 108-148). Therefore in the absence of evidence that SCI status conveys an independent risk for coronary vascular events, detection and treatment strategies would be similar compared to able-bodied individuals.

The small number of SCI adults with reported lipid values makes it difficult to draw conclusions regarding subcategories of SCI adults with respect to age, sex, race/ethnicity, severity of SCI injury, and duration of SCI injury. The largest study of ethnicity and lipid levels in an SCI population included a total of 600 adults (percentage of whom were male was not reported) of whom 27 percent were White, 47 percent were Hispanic, and 27 percent were African American.[17] While this study reported some racial/ethnic differences in lipid levels, there exists almost no evidence regarding whether these possible ethnic differences are unique to SCI individuals. Additionally, this study did not report whether the percentage of individuals who were male differed by ethnicity. The majority of SCI individuals in the studies were men, and even in studies that appeared to contain both men and women, the lipid values were not always reported by sex. In the few studies that did report female-specific lipid values,[21,39,40] only two reported control groups (n=139 SCI women in controlled studies). Therefore, little evidence exists for whether women with SCI have different lipid levels than able-bodied women. With respect to the type of SCI injury (tetraplegia versus paraplegia, complete versus incomplete), the studies did not report a substantial difference in lipid levels.[16,31,38,40]

Summary. There is some evidence that on average SCI individuals may possess slightly, but likely not clinically meaningfully, reduced total cholesterol, LDL cholesterol, triglycerides (beneficial) and HDL cholesterol (detrimental). The evidence does not support a policy that lipid screening should differ in SCI adults compared to able-bodied adults.

Obesity. Reports in the general population have consistently shown that the level of obesity is increasing in the United States[104] and that this increase in obesity is contributing to an excess in mortality.[105] BMI is the primary method used for assessing obesity in population-based studies. However, several alternative methods for assessing obesity exist, including waist circumference, waist-to-hip ratio, percent body fat measured through multiple different techniques, percentage of ideal weight, and others. The use of general population cutpoints for obesity from BMI (>30 kg/m^2) have been called into question by the finding that SCI individuals tend to have lower body fat at a given BMI as compared to non-SCI individuals.[42] BMI has been and remains the predominant measure of obesity reported in SCI studies.

The prevalence of obesity among SCI populations has been reported in multiple studies,[28,31,36,38,40-45] most of which have included some form of a non-SCI control group.[38,40,42,43,45]

A total of 10,226 persons with SCI (7,959 from one large VA clinical and administrative database study)[45] and 246,478 control subjects (246,025 from one national population-based survey)[43] contributed data to this section. Across these studies, mean BMI between SCI and non-

SCI populations were relatively similar with non-SCI populations consistently having slightly elevated mean BMI (Figures 14 and 15). However, differences in mean BMI are difficult to interpret, not only because BMI might underestimate obesity in SCI individuals, but also because the relationship between BMI and disease is typically U- or J-shaped with those in the middle categories of BMI having the lowest risk compared to the lowest extreme and upper levels of BMI. Separating out the studies by category of BMI is therefore important. However, whether the category cutpoints for underweight, normal, overweight, and obese used in able-bodied populations can be applied to adults with SCI, is worthy of greater discussion and cannot be addressed based upon the available research. To date, many of the studies have either only reported mean BMI or merged underweight and normal weight categories together. Also, the extent to which the lower mean BMI findings in SCI populations compared to controls are due to an underestimate of obesity by BMI in individuals with SCI is difficult to address.

Only one of the included studies directly assessed obesity by means other than algorithms based on weight and/or height, primarily recorded as BMI.[42] This study of 133 SCI individuals and 100 age-, height-, and ethnicity-matched able-bodied male controls measured percent fat mass using dual energy x-ray absorptiometry (DXA). This study found that total percent lean mass was lower and total percent fat mass higher in SCI individuals for a given level of BMI. The findings from this study combined with the prior studies showing no striking difference in BMI between SCI and able-bodied populations would suggest that future studies should focus less on comparing BMI and should investigate whether other indicators of obesity are more relevant for this population and correspondingly more predictive of future adverse health events. However, it should be noted that while DXA is a reliable measure of body composition, it is also much more difficult and expensive to obtain than BMI.

Several studies have attempted to explore whether differences in injury type (paraplegia versus tetraplegia or complete versus incomplete) or injury duration are correlated with obesity, but as with the overall studies of obesity and SCI, these studies are mostly conducted only with BMI measurements of obesity. Studies that have looked at injury type have tended to find a slightly higher average BMI in adults with paraplegia versus tetraplegia.[28,38,42-45] However, it is not clear from these studies the extent to which mean BMI is driven by more underweight individuals with tetraplegia or possibly a greater tendency for BMI to underreport obesity in people with tetraplegia compared to people with paraplegia.

Several clinical and research questions remain to be answered, including what is an appropriate definition for obesity in an SCI population? For example, can BMI be used to define obesity? If not, what should be used in its place? If so, can current general population cutpoints for BMI be used or does the cutpoint need to be different (i.e., either specific for SCI in general or even more specific for type of SCI injury)?

*Summary***.** There is no high-quality evidence that obesity defined by BMI is elevated in SCI individuals compared to appropriately matched controls. While several authors have reported that BMI might not be an accurate measure of obesity in the SCI population, it is by far the predominant measure used in research studies of the prevalence of obesity. There is some evidence that when obesity is measured as percent body fat, SCI individuals may be at elevated risk; however, the absence of large studies that include accurate measurements of body fat preclude stronger conclusions from being made about the burden of obesity on individuals with SCI and the impact of injury type and duration on the extent of obesity.

Figure 5. Diabetes prevalence, SCI vs. control

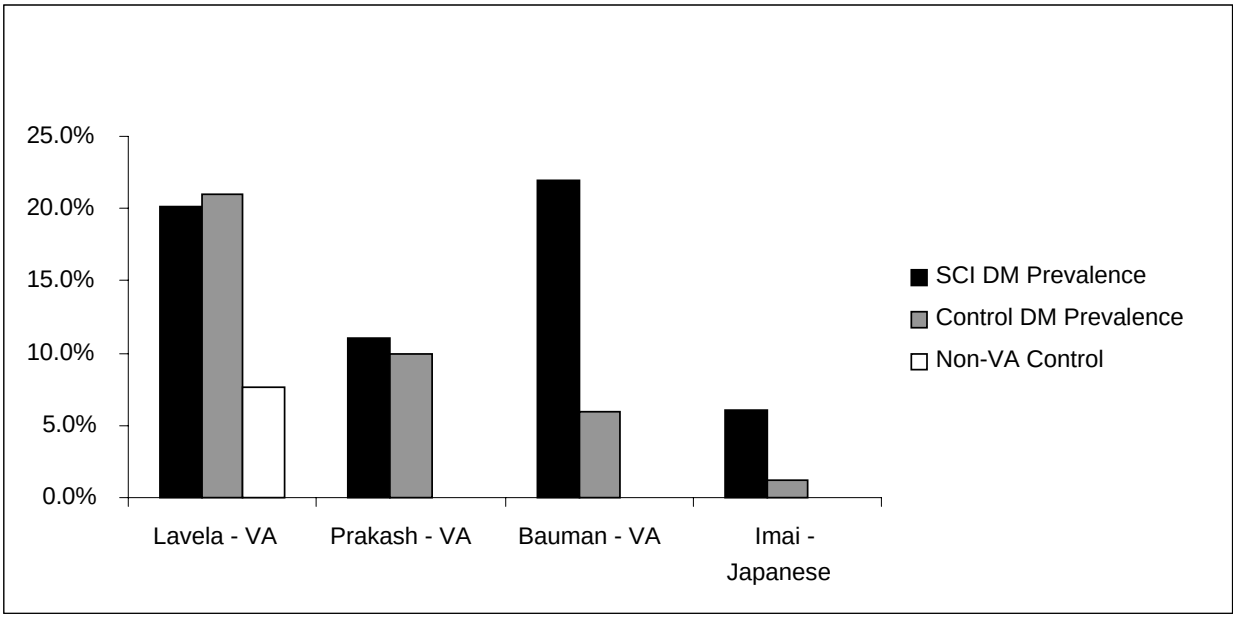


Figure 6. Prevalence of diagnosed diabetes, undiagnosed diabetes, and impaired fasting glucose in men (NHANES 1999-2002)[102]

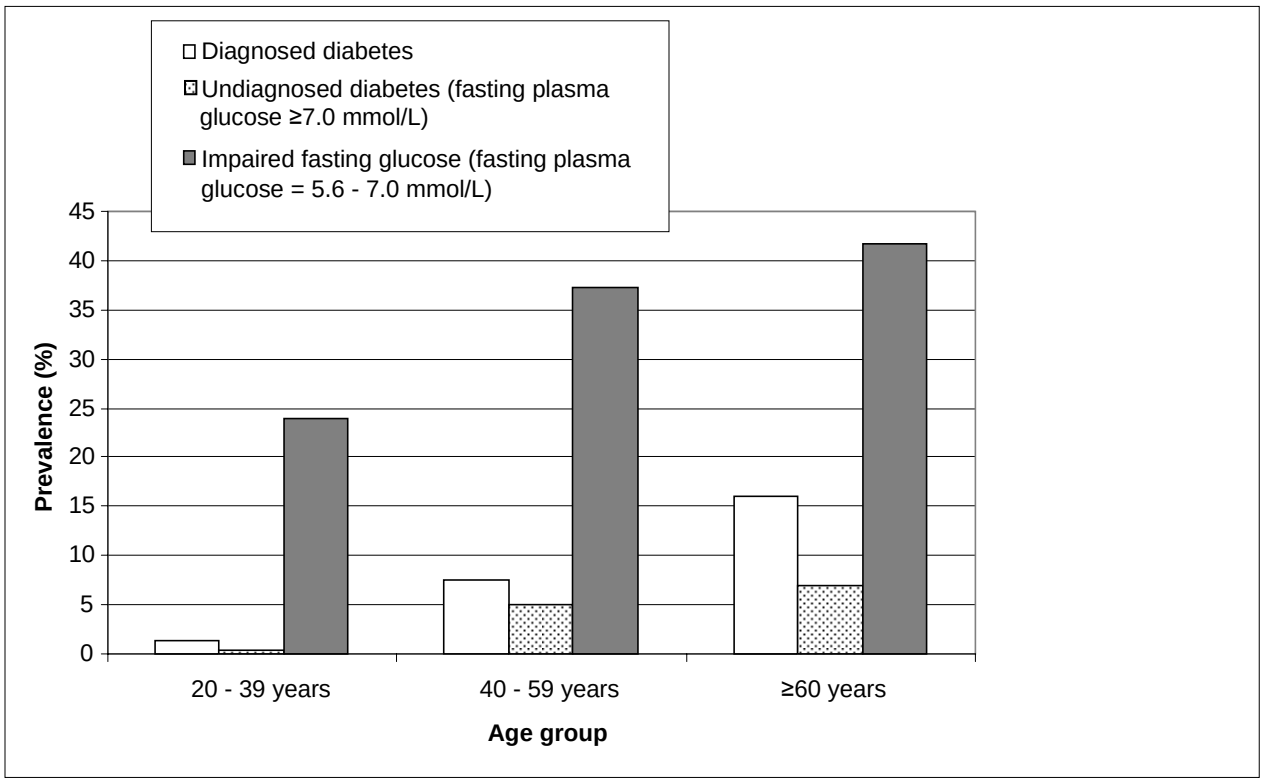
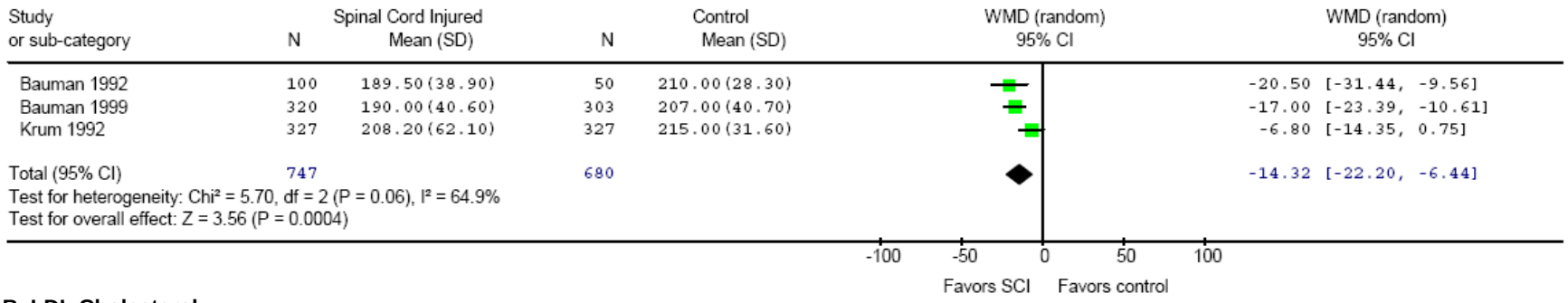
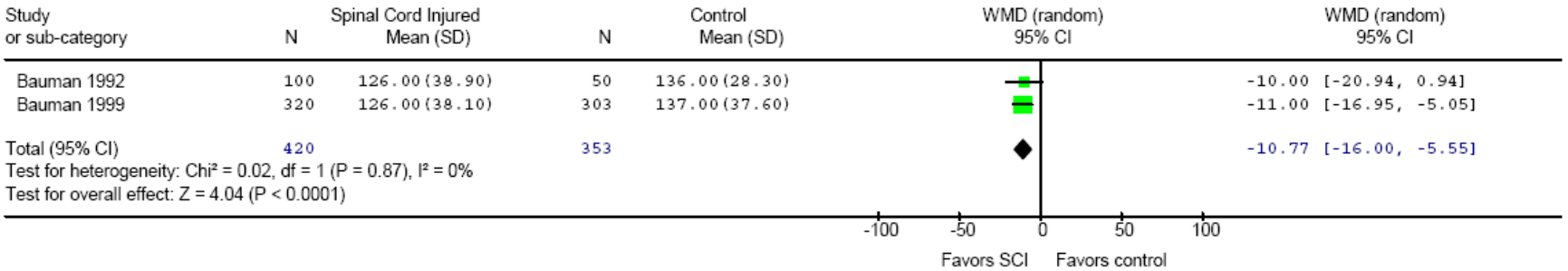


Figure 7. Weighted mean differences in lipid levels (mg/dL): Spinal cord injured subjects vs. controls

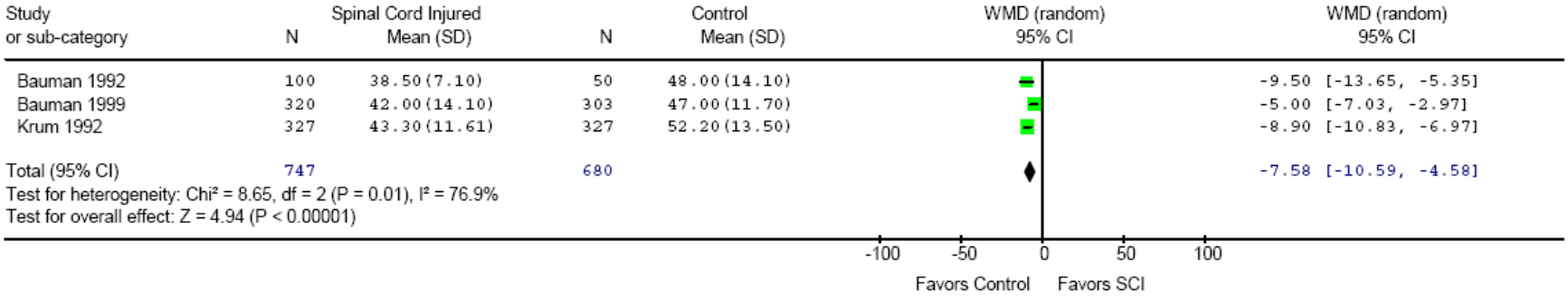
A. Total Cholesterol



B. LDL Cholesterol



C. HDL Cholesterol



D. Triglycerides

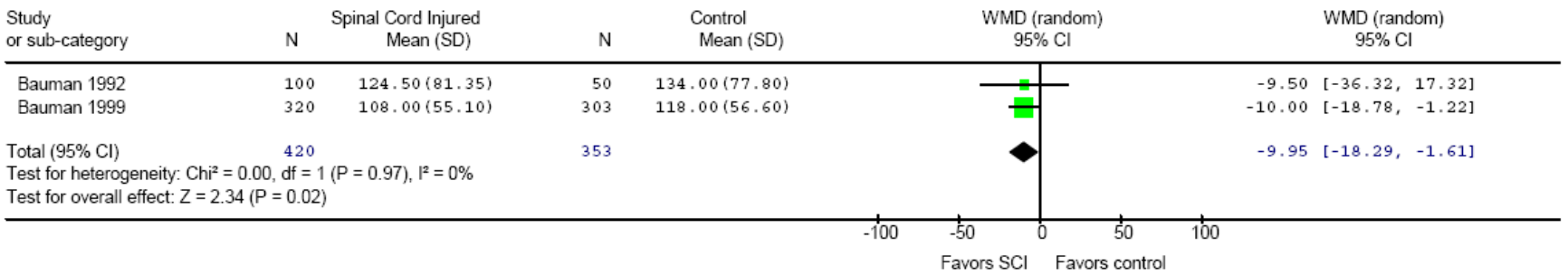


Figure 8. Mean levels of total cholesterol, SCI studies

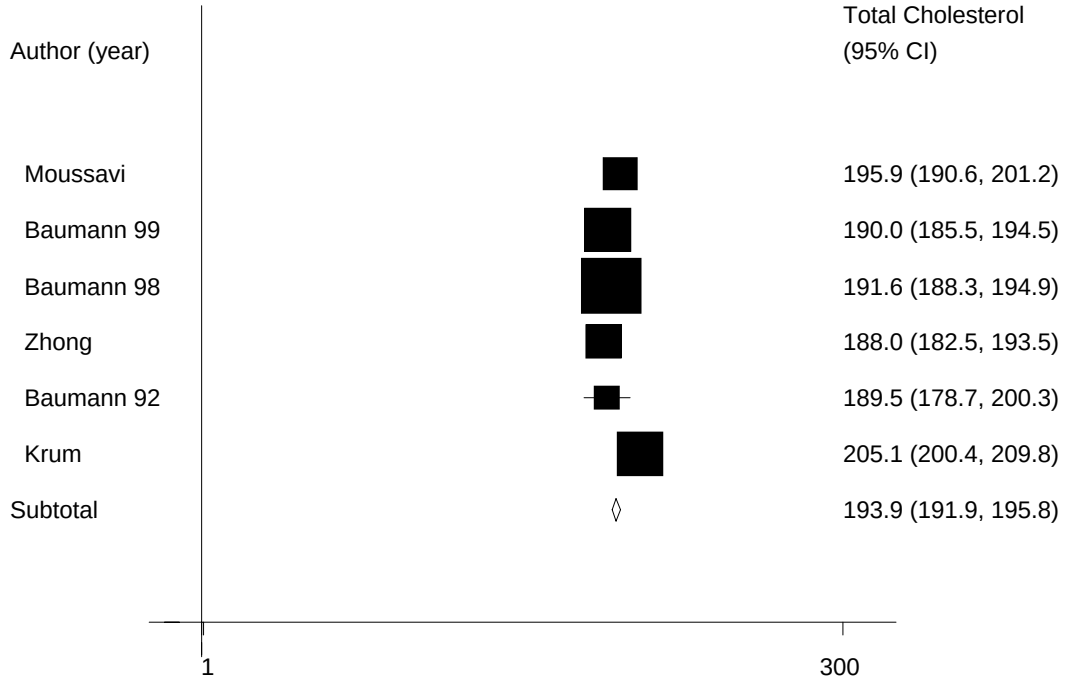


Figure 9. Mean levels of LDL cholesterol, SCI studies

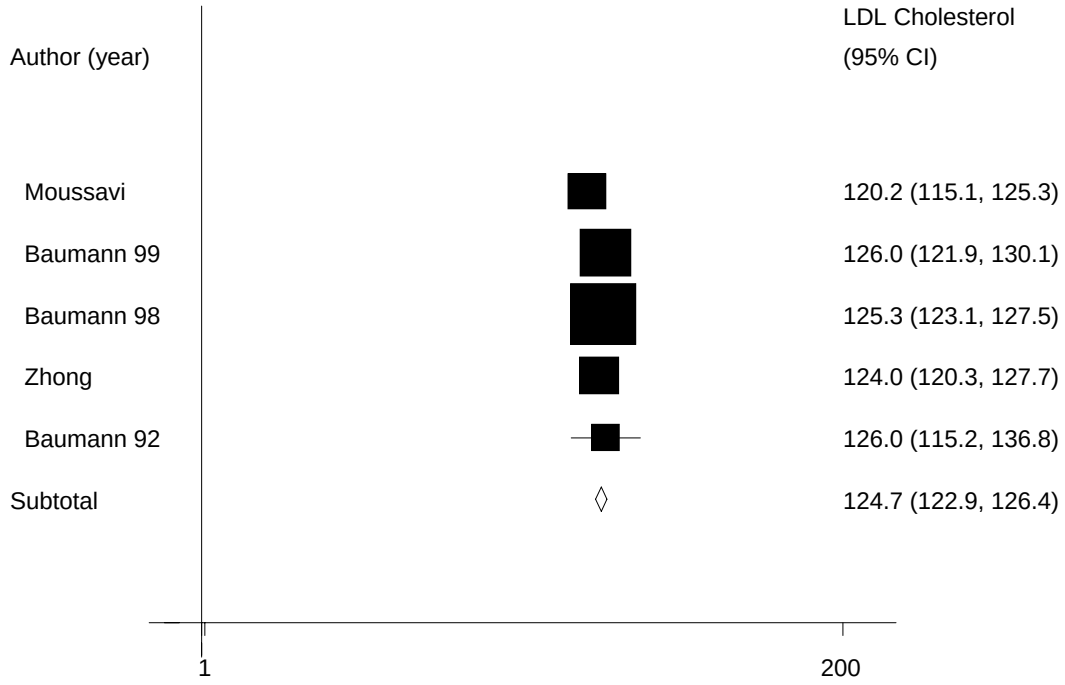


Figure 10. Mean levels of HDL cholesterol, SCI studies

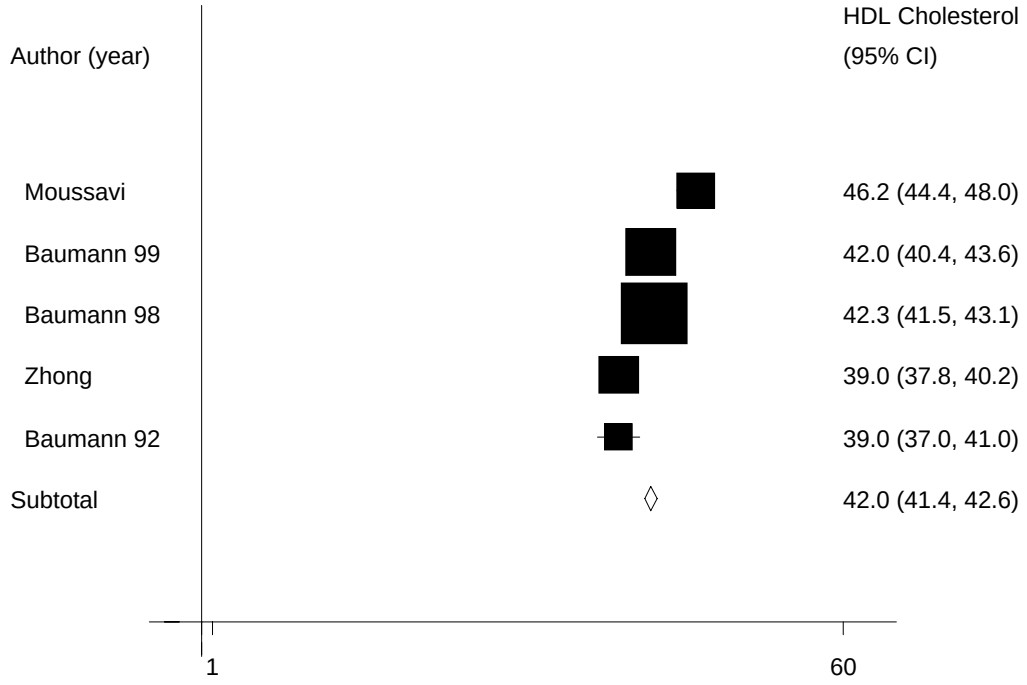


Figure 11. Mean levels of triglycerides, SCI studies

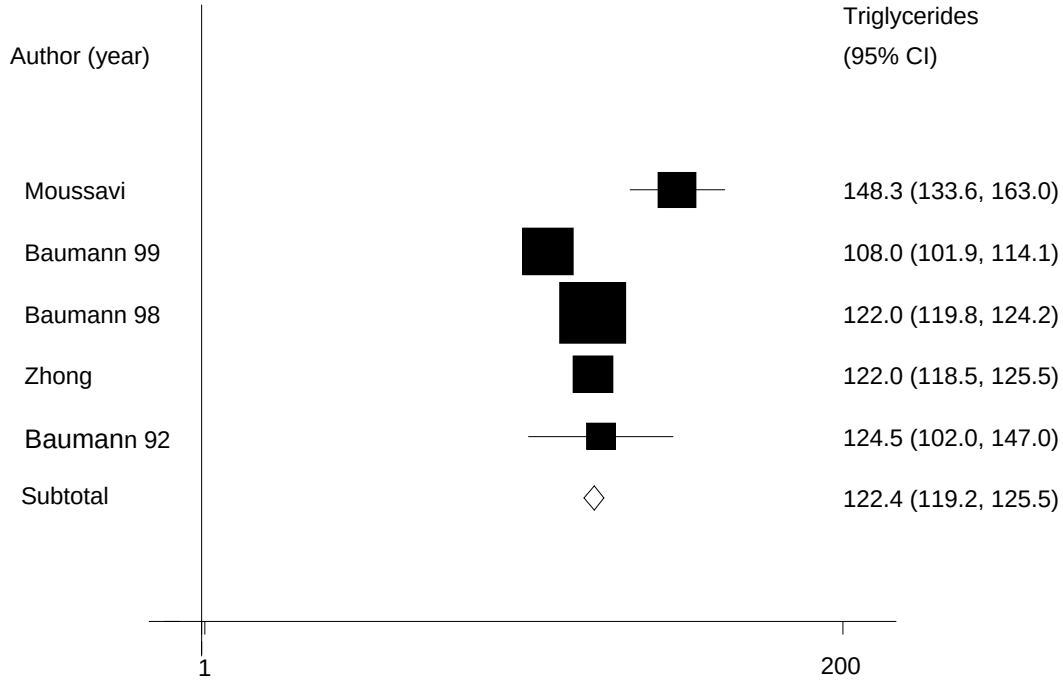


Figure 12. Total cholesterol, LDL-C and triglyceride levels of able-bodied males by age (NHANES)

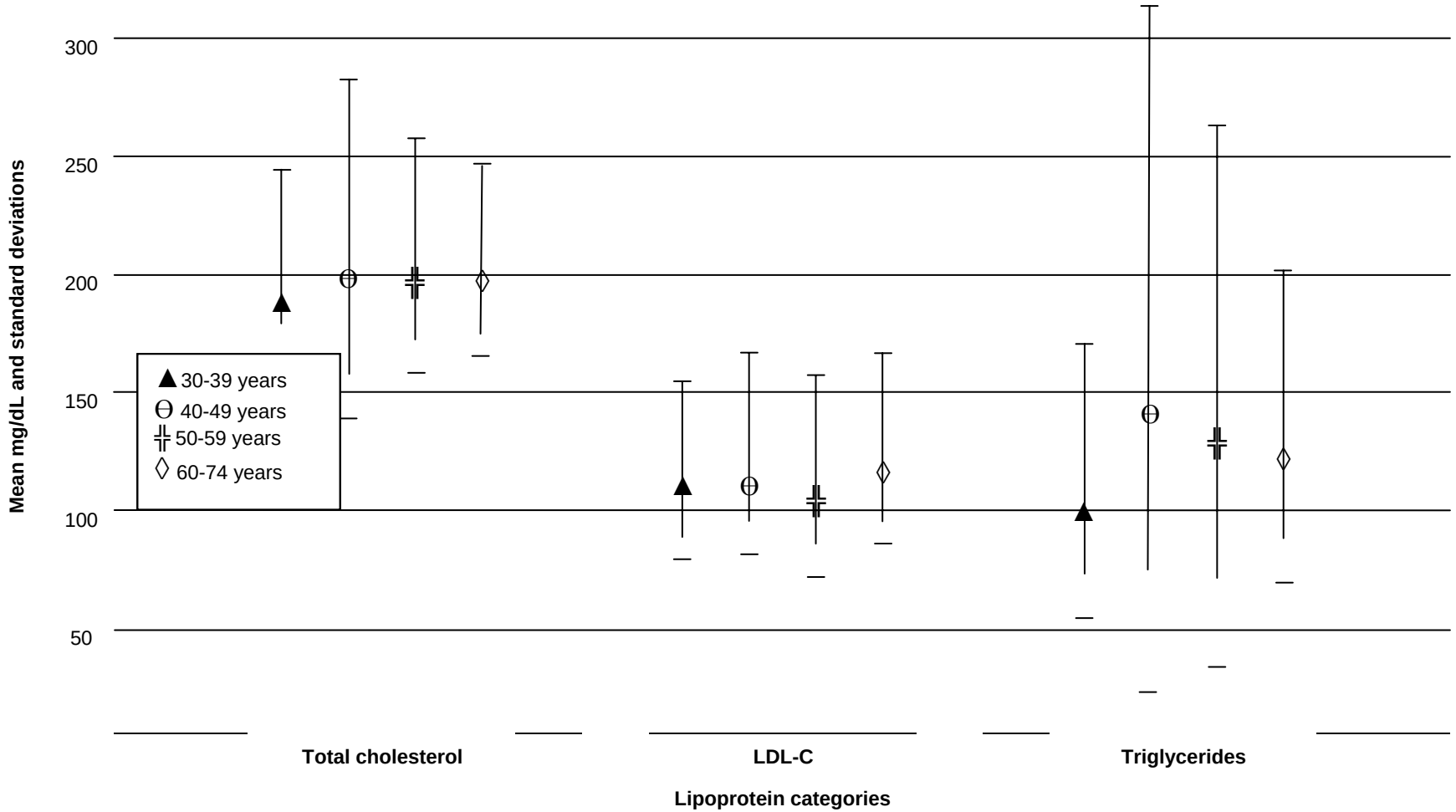


Figure 13. HDL cholesterol levels of able-bodied males by age (NHANES)

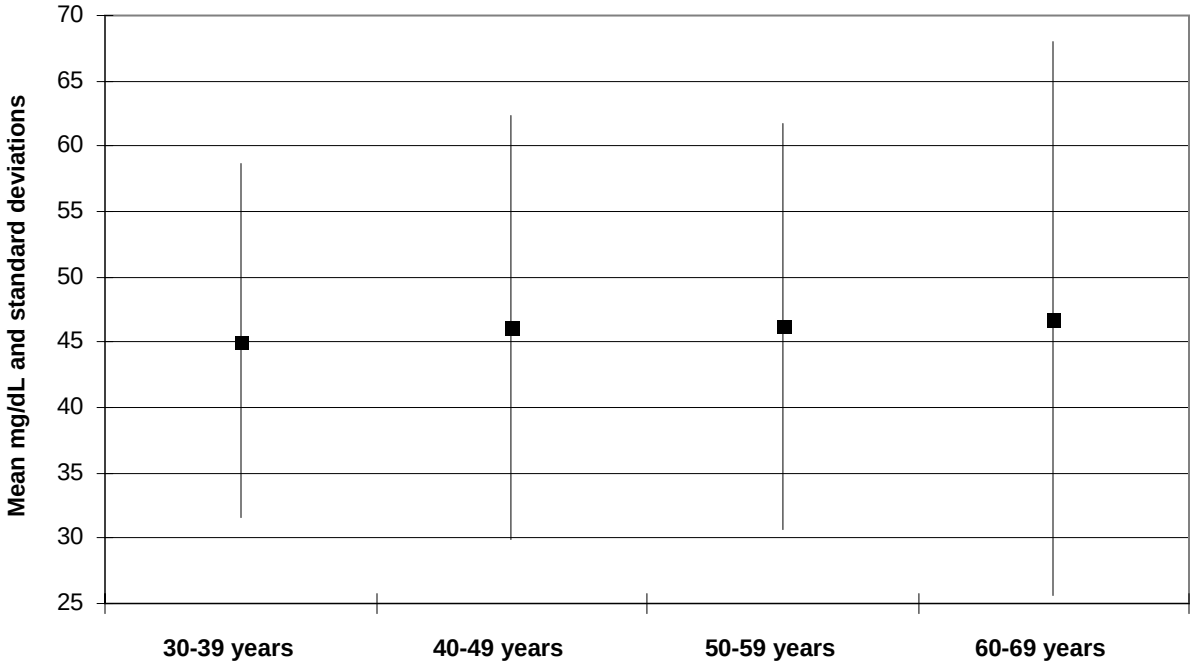


Figure 14. Mean BMI, SCI, and Control

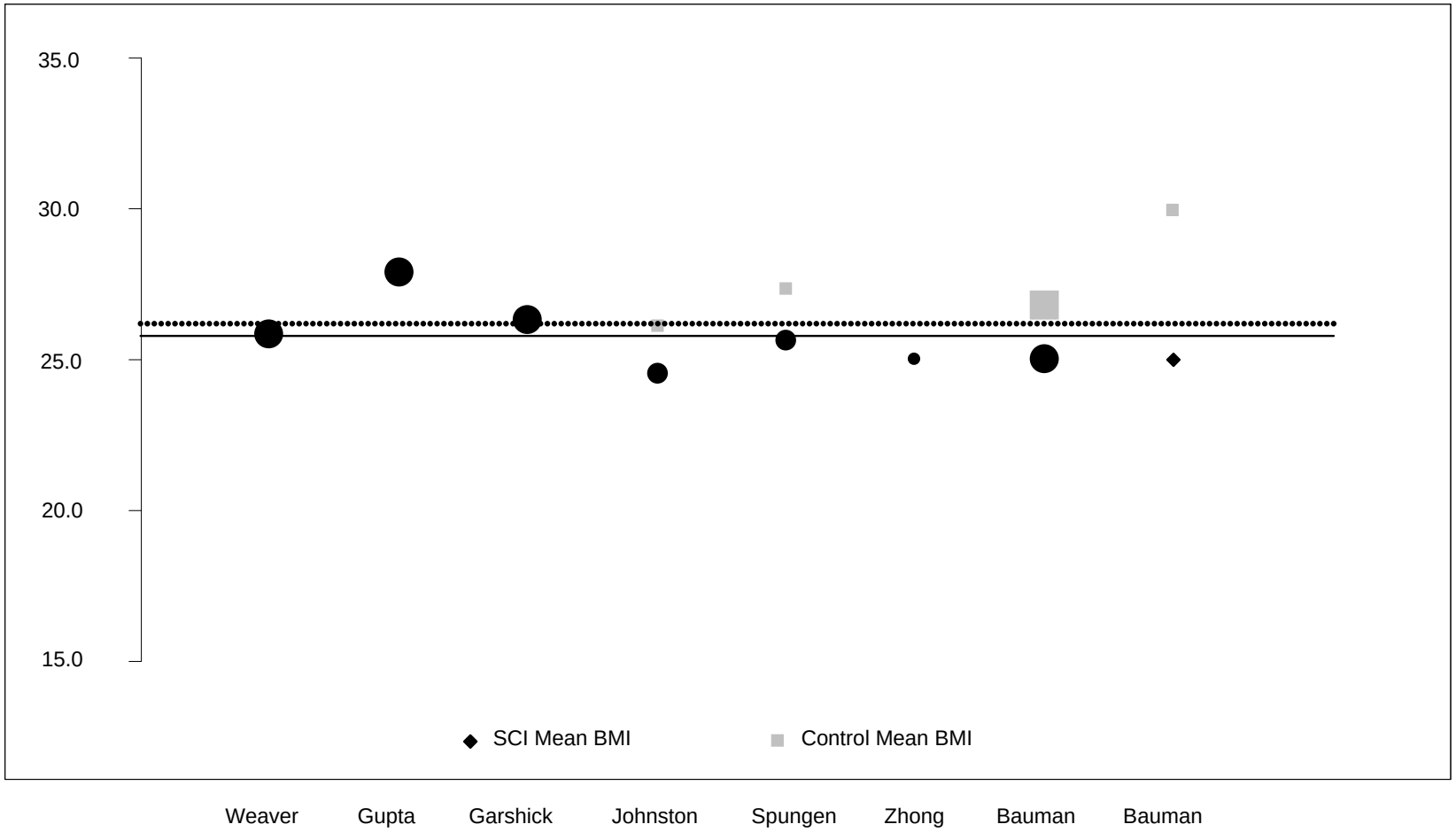
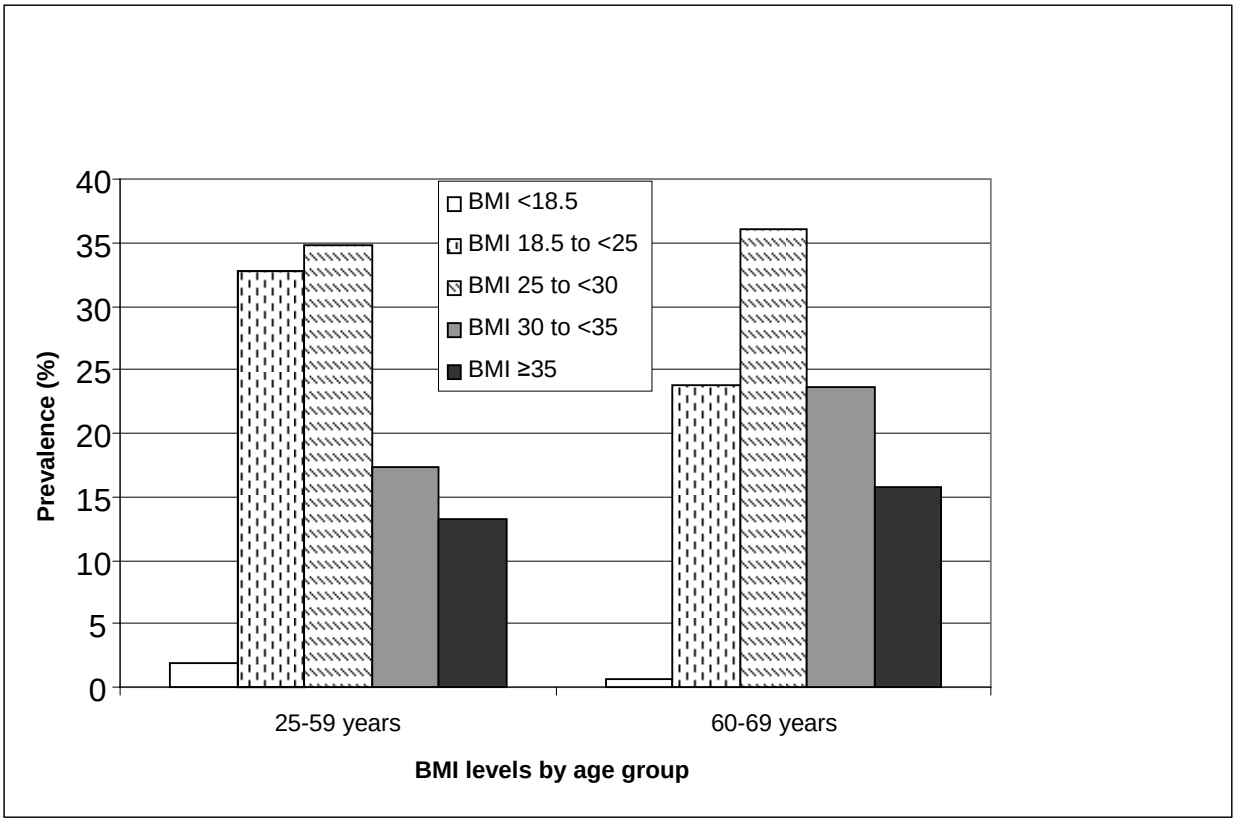


Figure 15. Prevalence of BMI levels by age group (NHANES 1999-2002)[105]



Question 2

Subject characteristics. The studies included more than 50,000 patients with SCI. Sample size ranged from 96[46] to 28,239.[49] Males (pooled prevalence 86 percent, 95 percent CI 80.4; 90.9) and Caucasians comprised the majority of individuals; all studies identified patients at clinics or administrative health care databases (Table 1 and Appendix E Table 2). Among American studies, large cohorts[2,49,50] (studies that analyzed nationally representative databases, including the Centers for Disease Control and Prevention and the national Behavioral Risk Factor Surveillance System Survey),[37] were considered to have higher generalizability. Applicability of several large studies from the VA Spinal Cord Injury Services can be generalized to veterans seeking care in the VA clinics and, to a lesser extent, general veterans with SCI or the overall adult SCI population.[3,34,37,48,51] Individuals differed by the level of injury, the time after injury, and functional status, but few studies included these factors in the analysis. Several studies reported prevalence of hypertension,[3,30,32,34,37,39,48,51,53,55] but only a few examined other risk factors of cardiovascular diseases, including smoking and lipid levels.[37,39,54] Furthermore, definitions of these comorbidities and methods to measure (and therefore, likely prevalence) varied across studies. The majority of the studies obtained events with ICD codes (the conceptual definition of outcomes is shown in Appendix F). However, the studies reported the prevalence of the outcomes obtained with different ICD codes. For example, one study[53] defined CVDs with ICD codes 390-448 and 745-747 that included rheumatic and hypertensive diseases as well as congenital anomalies of the heart while another[50] defined outcome as rehospitalization for diseases of the circulatory system, including heart disease, hypertension, pulmonary embolus, cerebrovascular diseases, and disease of the arteries and veins. Therefore, definitive comparisons of outcomes were not possible. The accuracy and reliability of the coding in different settings could not be estimated from the published articles.

Cardiovascular prevalence in adults with chronic SCI. Crude prevalence estimates were reported in the majority of the studies and ranged from 0.05 percent for cerebrovascular disease[53] to 58 percent for self reported cardiovascular symptoms[56] and differed, depending on how events were defined and measured (self reported or identified with ICD codes) and on age and time after SCI. Therefore, an overall summary estimate was not provided. The prevalence of cardiovascular diseases was <1 percent in two studies[32,50] and 2 to 3 percent in three studies[52,53,55] (Table 2). One smaller study of 140 patients used the London School of Hygiene Questionnaire on Chest Pain and Intermittent Claudication and reported a higher prevalence of CVDs (13.4 percent).[54] One study found an increase in prevalence in older patients to 19.3 percent after 60 years of age at time of injury and to 14.2 percent 30 or more years after injury (Table 3).[52] The prevalence of congestive heart failure was 2.7 percent in one study,[34] and the prevalence of other cardiac diseases 2 percent[55] or <2 percent.[53] The prevalence of cerebrovascular diseases varied from <1 percent,[53] to 1 percent[39] or 2 percent.[3] The prevalence of coronary heart disease was 2 percent or less in three studies,[32,39,53] 6 percent among patients from the Vietnam Head and Spinal Cord Injury Study Registry,[3] and the highest was 12 percent among members of Paralyzed Veterans of America.[37] The Stockholm Spinal Cord Injury Study[56] examined self reported prevalence of "cardiovascular symptoms" and included ankle-leg edema, chest pain, and palpitations. More than half of the patients with SCI reported symptoms (55 percent of males and 69 percent of injured females). However, prevalence of diagnosed cardiac diseases was only 2 percent.

Appendixes cited in this report are available at http://www.ahrq.gov/clinic/tp/carbliptp.htm

Whether this represents under diagnosis of cardiovascular diseases or classification of nonspecific symptoms which did not reflect CVD is not known. Seventy-two percent of patients with complete cervical and thoracic injury reported having cardiovascular symptoms. The prevalence of arterial hypertension was <3 percent in three studies,[30,32,53,55] 5-10 percent in four studies,[30,34,39,48] and more than 20 percent in four studies.[3,37,48,51] The Vietnam Head and Spinal Cord Injury Study reported that 21 percent of the injured adults had hypertension[3] and 25-49 percent of the patients of the Spinal Cord Injury Service of VA medical centers were diagnosed with arterial hypertension.[37,48,51] In addition, borderline hypertension was found in 33 percent of the injured veterans.[51] The prevalence of myocardial infarction was <5 percent in three studies.[3,39,53]

SCI veterans had higher prevalence of myocardial infarction, 14 percent[37] to 25 percent among those who were younger than 50 years at the time of injury and older than 50 years at the time of index admission to the Veterans hospital[48] (Table 3). The highest prevalence of 33 percent was reported among veterans who were older than 50 years at the time of injury representing the effect of age rather than injury [48] Patients with tetraplegia and ABC functional status had lower age adjusted rates of coronary heart diseases, including myocardial infarction, and higher rates of cerebrovascular diseases, dysrhythmia, and valvular disease (Table 4) by neurologic category among 834 patients.[53] Prevalence of cardiovascular symptoms and arterial hypertension appeared to vary by the level of injury, though statistical differences in rates were not provided (Appendix E Table 3).

Asymptomatic heart conditions in patients with SCI. Three studies reported cases of silent ischemia in asymptomatic adults with SCI.[10,106,107] Tomographic thallium-201 myocardial perfusion imaging detected scintigraphic evidence of ischemia in 3 of 6 patients (50 percent) with tetraplegia and signs of infarction in one patient.[106] A simple arm ergometry and radionuclide tomographic image test detected silent scintigraphic evidence of ischemia in 13 SCI patients with paraplegia from 20 tested having normal resting electrocardiograms (65 percent). Since five subjects had ECG evidence of ischemia on exercise testing, eight patients (62 percent) experienced undiagnosed coronary heart disease.[107] Latent coronary artery was diagnosed in 12 of 19 subjects with paraplegia (63 percent) using radionuclide myocardial perfusion imaging after upper body ergometry exercise.[10] A recently published case control study[108] of coronary scanning showed that 91 patients with chronic SCI had the higher mean calcium scores (75±218 versus 28±104, $p < 0.001$) compared to 273 age matched non-SCI controls. The prevalence of coronary artery calcification was greater in the SCI population than the control population (16 percent versus 7 percent, $p < 0.01$).

Pooled analysis detected a significant heterogeneity between studies in estimated prevalence of cardiovascular diseases (data not shown). Therefore, methodological heterogeneity made the pooled estimations not valid. Almost all variations in pooled prevalence of hypertension (14 percent) and myocardial infarction (8 percent) were attributable to heterogeneity between studies. The fact that the summarized prevalence of all CVD events, including coronary heart and non ischemic heart diseases, was less than different forms of CVDs reported in the studies. Such discrepancy can reflect overlap and different definitions and methods to measure outcomes, and, probably, some proportion of undiagnosed cardiac pathology in SCI populations. Three studies reported prevalence in subgroups[48,50,52] but not in the total sample. Conclusions and decisions based on pooled prevalence cannot be made.

Appendixes cited in this report are available at http://www.ahrq.gov/clinic/tp/carbliptp.htm

Cardiovascular mortality. Mortality from CVDs was more consistent than prevalence across five studies that reported this outcome (Table 5).[1-3,49,52] Patients with SCI died from diseases of the arteries (ICD codes 440-448) in 0.8[49] to 1.5[2] per 1,000 injured according to two large studies of more than 29,000 patients.[2,49] CVD (ICD codes 390-458) caused death in 1 percent[49] to 6.3 percent[1] to 10 percent[52] of those injured. Men with SCI had higher CVD mortality (5.3 percent) compared to women (1 percent), with no formal statistical test of the effect modification reported.[1] Results were not controlled for potential differences in other CVD risk factors such as smoking status, diabetes, hypertension, and family history. Mortality increased with the age of the patients, being the highest after 75 years (10 percent).[52] Less than 1 percent of SCI patients died from cerebrovascular diseases[1,2] and stroke.[49] Cerebrovascular deaths were more common in men (0.7 percent) than women (0.2 percent) with unknown statistical significance of the differences.[1] Mortality from cerebrovascular diseases was 0.1 percent[2] among patients with complete tetraplegia and 0.2 percent after cervical or thoracic injury with no functional motor preservation.[1] Mortality from ischemic heart disease was <1 percent in two studies.[2,3] One European study that obtained post mortem records found that 2.5 percent, including 2 percent men, died from ischemic heart disease.[1] One long-term followup study in U.S. veterans reported a two-fold increase in mortality from 5 years (0.4 percent) to 20 years (0.9 percent) after injury, representing the association between age and mortality rather than SCI.[3] Lung embolus caused death in 0.7 percent of patients with chronic SCI.[1] Three studies reported that coronary heart disease was the primary cause of death in approximately 9 percent of patients with SCI (Figure 16). The proportion of deaths attributable to CVDs varied from 7.1 percent for ischemic heart disease[49] to 24 percent for any CVD[1] (Table 6). CVDs are among the leading causes of death in patients with chronic SCI;[1,49,52] however, the contribution of age cannot be estimated by analyzing the crude proportion of aging SCI patients who died from heart diseases. One study of 402 veterans with chronic SCI followed for 55.6 months[36] showed that diabetes (relative risk 2.62, 95 percent CI 1.19; 5.77) and heart diseases (relative risk 3.66, 95 percent CI 1.77; 7.78) were significant risk factors for death after adjustment for age.

Cardiovascular prevalence and mortality in adults with chronic SCI compared to the general population according to age, race, and gender. Published evidence did not suggest that adults with chronic SCI experience CVDs more frequently than the general population. The Australian Risk Factor Prevalence Study of 327 patients with SCI and age and sex matched controls found that adults with SCI had a 50 percent reduction in arterial hypertension and no differences in odds of diabetes, myocardial infraction, angina pectoris, and cerebrovascular diseases (Table 7).[39] Crude odds of arterial hypertension were lower by 84 percent[34] in another study of 654 male veterans with SCI.[34] The same study reported lower odds of congestive heart failure in injured compared to able-bodied veterans.[34] The Stockholm Spinal Cord Injury Study showed that prevalence of circulatory diseases was lower by 75 percent in injured patients compared to healthy controls after adjustment for age, sex, socioeconomic status (odds ratio 0.25 p value = 0.014),[55] with no differences in rates of cardiac diseases, and use of cardiac medications. One larger study of 18,372 veterans with SCI, 6,433 able-bodied veterans, and 221,650 in the general population, using 2003 Behavioral Risk Factor Surveillance System survey data,[37] reported a three times higher rate of diabetes in injured veterans compared to the general population (20 percent versus 6.7 percent, odds ratio 3.32, 95 percent CI 1.34; 8.26),[37] but similar odds compared to other veterans (21 percent, odds ratio 0.94, 95 percent CI 0.47; 1.87). SCI adults with diabetes had higher adjusted rates of coronary heart disease by 280 percent, myocardial infarction by 270 percent, arterial hypertension by 250 percent, and stroke by 230

percent compared to SCI patients without diabetes (Figure 17).[37] Diabetes is associated with an increased risk of heart disease, independent of SCI. The authors did not compare relative risk of heart diseases in diabetics with and without injury to estimate the effect of injury.

Odds ratios of cardiovascular outcomes were reported after adjustment for age. However, age may modify the association with injury and diabetes. For example, odds of diabetes were higher in injured veterans compared to the general population in all age groups but higher compared to able bodied veterans in those of 45-59, 55-59, and older than 70 years of age (Appendix E Table 4). Despite no difference in management of diabetes, adults with SCI and diabetes had three to five times higher rates of foot sores compared with diabetics in the general population and able-bodied veterans with diabetes. Risk of diabetic retinopathy was 19 percent higher compared to diabetics in the general population (Table 8).

Evidence from one study suggested that neurological functional status may be associated with cardiovascular morbidity (Table 4). Patients with tetraplegia and no functional motor preservation had higher age adjusted odds ratio of cerebrovascular diseases, dysrhythmia, and valvular diseases and lower odds ratio of coronary heart disease compared to paraplegic patients (Figure 18). Adults with SCI and functional motor preservation had higher age adjusted odds of all CVDs, coronary atherosclerosis, dysrhythmia, and valvular disease compared to paraplegic and no functional motor preservation.[53]

Morbidity can be estimated using surrogate outcomes. ECG is the most important single diagnostic indicator of cardiac arrhythmias and myocardial infarction.[34] One large study of 26,734 able-bodied male veterans and 654 patients with SCI found a decreased relative risk of ECG abnormalities in injured patients, only ST segment elevation in younger injured was observed more often in younger patients (Appendix E Table 5). Injured veterans with intact sympathetic innervation to the heart (injury level T6 and below) had lower risk of any ECG abnormalities compared to impaired sympathetic activity (injury level T5 and above) (Appendix E Table 6). Younger patients had lower risk of ECG abnormalities (Appendix E Table 7). Nearly all examined ECG abnormalities were associated with increased risk of death in able-bodied veterans, but only left bundle branch block (LBBB), left ventricular hypertrophy with strain, and atrial fibrillation accompanied the higher hazard ratio of death in patients with SCI (Table 9). Furthermore, these abnormalities were associated with a greater risk of dying in SCI compared to able-bodied adults. The rates of diagnosed hypertension (44 percent vs. 7 percent), congestive heart failure (7 percent versus 1.7 percent), and coronary heart diseases (7 percent versus 1.7 percent) were lower among SCI veterans compared to able-bodied (Figure 19).[34] The contribution of undiagnosed heart disease on death in SCI patients is not known and requires future research.

In addition to reported relative risk, three studies[1,2,36] estimated age standardized mortality ratios from CVDs in SCI patients compared to the general population (Tables 10 and 11). Injured patients died from all cardiovascular diseases more often than age matched able-bodied adults (standardized mortality ratio 2.1, 95 percent CI 1.83; 2.37.[1] However, the ratio was significant only for lung embolus (standardized mortality ratio11, 95 percent CI 4.19; 24.8) but not for other forms of CVD. SCI was associated with comparable increase in rates of cardiovascular death in men and women (Table 11). Cardiovascular mortality was lower in those injured after 1972 (standardized mortality ratio 2.4, 95 percent CI 1.95; 3.01) compared to those injured from 1953-1971 (standardized mortality ratio 7.1, 95 percent CI 2.31; 9.32) (Table 12).[1] Standardized

mortality ratios in patients with cervical (standardized mortality ratio 1.1, 95 percent CI 0.72; 1.53) or thoracic injuries (standardized mortality ratio 1, 95 percent CI 0.82; 1.84) did not differ from the general population in the European study of 888 injured adults followed up from 1953 to 1992.[1]

The role of functional status was reported in one study. Patients with complete tetraplegia died from ischemic heart disease (ICD codes 410-414) (standardized mortality ratio 2.6, 95 percent CI 1.3; 3.9), non ischemic heart diseases (standardized mortality ratio 23.4, 95 percent CI 16.5; 30.3), and cerebrovascular diseases (standardized mortality ratio 5.4, 95 percent CI 1.8; 9) more often than would be expected from the same age able-bodied adults.[2]

Mortality from nonischemic heart diseases (standardized mortality ratio 5.6, 95 percent CI 4.4; 6.8), artery diseases (standardized mortality ratio 4.5, 95 percent CI 2.1; 6.9), and lung emboli (standardized mortality ratio 11.4, 95 percent CI 4.2; 24.8) was higher in all injured adults compared to the general population.[2] Mortality from lung emboli contributed the most to the overall differences within the total population. The role of carbohydrate and lipid disorders (the focus of this review) in nonischemic heart disease and biologic plausibility for this finding is not well known. Therefore, it is possible that these are spurious findings based on multiple comparisons.

Three studies reported that coronary heart disease constitutes approximately 9 percent among primary causes of death in SCI patients.[1-3] The proportion of deaths attributable to all CVDs varied from 18.8 percent for diseases of the heart[49] to 24 percent for circulatory system disorders.[1] Cardiovascular diseases are among the leading causes of death in patients with chronic SCI.[1,49,52] However, the contribution of age cannot be estimated analyzing crude proportion of aging SCI patients who died from heart diseases. One study of 402 veterans with chronic SCI followed by 55.6 months[36] showed that diabetes (relative risk 2.62, 95 percent CI 1.19; 5.77) and heart diseases (relative risk 3.66, 95 percent CI 1.77; 7.78) were significant risk factors for death after adjustment for age.

The role of lipid disorders to increase the risk of cardiovascular morbidity and mortality has not been evaluated in the published articles. The Australian Risk Factor Prevalence Study examined the overall cardiovascular risk in 102 injured patients and age matched control with scores from the MRFIT study (age, diastolic blood pressure, total cholesterol level, cigarettes per day, and sex).[39] The injured patients had overall percentile position of risk <50 percent independent of age and years after injury. The authors concluded that increased blood pressure, elevated blood cholesterol, or smoking could not explain cardiovascular prevalence in SCI patients.[39] Physical activity, BMI, cigarette use, and alcohol consumption were not associated with increased risk of cardiovascular diseases in the study of 97 injured adults.[54] However, the size of this study was too small to rule out clinically meaningful associations. One study showed that diabetes in SCI patients was associated with an increased risk of coronary heart disease, myocardial infarction, arterial hypertension, high cholesterol, and stroke, the well known association in able-bodied adults.[37]

Interpretation of findings. Published evidence suggested that for people with SCI, diabetes mellitus contributed to an increased risk of CVDs.[37] The role of metabolic syndrome and lipid disorders had not yet been investigated. Increased rates of diabetes in SCI compared to able-bodied adults were reported in three articles[30,32,37] with no differences in the other three.[34,39,55] The degree of neurological impairment may be associated with cardiovascular mortality in SCI patients with no documented evidence of independent contribution of glucose and lipid disorders. Cardiovascular morbidity varied substantially among studies, being highest in injured

veterans. Many important confounders might explain such differences beyond the veteran status, since many veterans do not seek care from the VA.[74] The studied veterans are more likely to be poor, without private insurance, have minority status, and/or have a service connected injury.[74] Indirect comparisons of cardiovascular morbidity in injured patients with known incidence of CVD in the general population does not permit and accurately estimate the contribution of metabolic disorders in patients with SCI.

Summary. Cardiovascular diseases are among the leading causes of death in patients with chronic SCI. However, when compared to able-bodied adults, cardiovascular prevalence in SCI patients did not show significant differences.

a. Cardiovascular mortality in injured patients was compared to standardized by age mortality in the general population in three studies. Age adjusted mortality from nonischemic heart diseases (standardized mortality ratio 5.6, 95 percent CI 4.4; 6.8), artery diseases (standardized mortality ratio 4.5, 95 percent CI 2.1; 6.9), and lung emboli (standardized mortality ratio 11.4, 95 percent CI 4.2; 24.8) was higher in all injured adults compared to the general population. Cardiovascular mortality was lower in those injured after 1972 (standardized mortality ratio 2.4, 95 percent CI 1.95; 3.01) compared to those injured from 1953-1971 (standardized mortality ratio 7.1, 95 percent CI 2.31; 9.32).

   Limited inconsistent evidence suggested higher risk of morbidity and mortality in adults who were older at time of injury. The role of functional status was examined in two studies reporting that patients with tetraplegia had higher odds of having and dying from cerebrovascular diseases. Inconsistent evidence suggested that patients with complete tetraplegia died from ischemic heart disease (standardized mortality ratio 2.6, 95 percent CI 1.3; 3.9) and nonischemic heart diseases (standardized mortality ratio 23.4, 95 percent CI 16.5; 30.3) more often than would be expected from the same age able-bodied adults. However, these findings may be based on chance due to the multiple comparisons and lack of significant associations with other cardiovascular outcomes.

b. Diabetes contributed to higher risk of CVD in veterans with SCI compared to nondiabetic SCI veterans in one large study. No studies compared risk of CVD among diabetics with SCI to able-bodied diabetics. The role of lipid disorders to increase the risk of cardiovascular morbidity and mortality has not been evaluated in the published articles. One study concluded that increased blood pressure, elevated blood cholesterol, or smoking could not explain increased cardiovascular prevalence in SCI patients.

Table 1. Patient characteristics in studies that reported cardiovascular events in adults with SCI

Author	Sample Country	Patients
Cardus, 1992[46]	96 USA	Patients after traumatic SCI who resided in the county area and had to use assistive device for walking. Age: >18 years; Time after injury: >9 months. Controls: 96 nontrained able-bodied men matched by age.
Krum, 1992[39]	327 Australia	Patients with SCI and age and sex matched controls from the 1983 Australian Risk Factor Prevalence Study. Gender: 19% female; 25-64 years old; Time after injury: 34% more than 10 years after injury; Injury: 40% with cervical, 35% with lower thoracic, 13% with upper thoracic, and 12% with lumbar levels of injury; ~41% with Frankel Grade A of completeness - complete motor and sensory deficit.
Whiteneck, 1992[52]	834 UK	Patients with SCI, treated at the British spinal injury centers; Gender: 13% female; Age at time of injury was between 15 and 55 years—15-24 years 42%, 25-34 years 27%, 35-44 years 18%, 45-55 years; median survival time 32 years; Time after injury: >20 years; 412 survivors, Median survival time 32 years; 85% survived at 10 years, 71% at 20 years, 53% at 30 years, and 35% at 40 years after injury.
DeVivo, 1993[2]	9,135 USA	Patients injured between 1973 and 1984 and treated at any of 13 regional SCI care systems.
Imai, 1994[30]	244 Japan	Males with SCI identified during the National Livelihood Basic Survey in Japan engaged in light work at special centers, who had medical examination for blood pressure and medical history. Mean age: 49.5 years; Time after injury: average 17.9 years; Injury: 19 patients injured at level C-T5, 24 at T6-T10, 139 at T11-L1, and 13 at L2 or lower.
Nam, 1994[47]	1,027+2,007 USA	Patients admitted to medical centers with stroke and patients with traumatic SCI (paraplegia or quadriplegia). Population: average age 37.2±16.1 years.
Levi, 1995[55]	326 Sweden	Patients with traumatic SCI from the Stockholm Spinal Cord Injury Study, residents of the Greater Stockholm area. Control: participants in the Swedish Annual Level-of Living Survey (1,978 interviews).
Levi, 1995[56]	353 Sweden	Patients with traumatic SCI, participants in The Stockholm Spinal Cord Injury Study. Time after injury: 0-4 years after injury 23.97%; 5-17 years after injury 48.76%; 18-44 years after injury 24.52%.
McGlinchey-Berroth, 1995[48]	534 USA VA settings Time: 1989-1992	Patients with traumatic SCI admitted to the high quality Spinal Cord Injury Service of the VA Medical Center; mean age of 50 years (16-84 years), 23% were at least 65 years of age; Gender: 99% males; Time after injury: 16±13.1 years, 12 hospital admissions since injury.
Imai, 1996[32] (the same population as Imai, 1994)[30]	244, Japan	Males with traumatic SCI at several rehabilitation centers; ages 22 to 69 years (mean 47.6); Time after injury: 17.3 years; Injury: C-T5 level 1%; T6-T10 12%; T11-Ll 69%; L2 8%. Control group (general population) National Livelihood Basic Survey conducted by the Ministry of Health and Welfare in 1989, on 800,000 people in 240,000 households.
Hartkopp,1997[1]	888 Denmark	Patients (713 men and 175 women) who survived traumatic SCI and were rehabilitated at the Centre for Spinal Cord Injured in Hornbnk, Denmark. Population: median age at the time of injury 27.5 in 1953-1971 and 28.5 in 1972-1990.
Rish, 1997[3]	230 USA VA settings Time: 1967-1970 to 1995	Patients with traumatic SCI identified in the Vietnam Head and Spinal Cord Injury Study Registry who survived more then 72 hours, with significant myelopathy; mean age at injury 21.4 years, with previous excellent health (active duty military personnel) mean age at injury 21.4 years; median time after injury 25 years.
DeVivo, 1999[49]	28,239 USA	Patients admitted to the model system or to a Shriner's Hospital within 1 year of traumatic SCI who survived at least 24 hours after injury; Gender: 19% female; Race: 67.6% Caucasian, 20.7% African American, 8.1% Hispanic, 3.6% Asian, Native American, or other; Time at injury: 54% of injuries occurred between the ages of 16 and 30 years, and 23% between 31 and 45 years; Injury: 53% cervical, C5-C8 34.5% and C1-C4 18.5% of the population; 53.8% neurologically complete, 27.2% motor functional, 19% sensory sparing or motor nonfunctional; 2.9% were ventilator-dependent.

Table 1. Patient characteristics in studies that reported cardiovascular events in adults with SCI (continued)

Author	Sample Country	Patients
Groah, 2001[53]	834 UK	Patients alive >20 years after SCI identified in 2 British spinal Injury centers; Mean age 57±10 years; Gender: 14% females; Time after injury: 29±6 years.
Davies, 2002[54]	97 Canada	Patients with segmental, nonprogressive traumatic SCI; mean age 47.5±4.5; Gender: 10% females; Age at injury: 31.67±16.4; Time after injury: 15.9±10.1 years; Injury: Quadriplegic 42%; Paraplegic 57%; Undetermined 1%; Complete 33%; Incomplete 64%; Undetermined 3%; Traumatic 87%.
Prakash, 2002[34]	654 USA VA settings Time: 1987-1999	47,070 patients with at least one ECG obtained in the Palo Alto Veterans Affairs Health Care System; 26,734 able-bodied male veterans and 654 patients with SCI. Mean age: 50±14 years.
Cardenas, 2004[50]	8,668 USA	Patients with traumatic SCI identified in the Model System (hospitalized between acute hospitalization and comprehensive inpatient rehabilitation, admitted to a Model System within 365 days of injury) who reside in the geographic region in which the Model System facility is located; 3,904 patients with 11,047 followup interviews, Gender: 21.4% female; Race: 61.4% White Injury: C1-4 ASIA grades A, B, C: 4.6% C1-4 ASIA grade D: 6.1% C5-8 ASIA grades A, B, C: 19.1% C5-8 ASIA grade D: 8.5% T1-S5 ASIA grades A, B, C: 33.1% T1-S5 ASIA grade D: 4.2%.
Lavela, 2006[37]	5,690 USA VA settings Time: 2003	Veterans with SCI and disorders who use VA health services; Mean age 60 years; Gender: 97% males; Race: White 81%; Time after injury: 24 years; Injury: 52% with paraplegic level injury. Control: 2003 Behavioral Risk Factor Surveillance System survey data for veteran and general population from the Centers for Disease Control and prevention. 6,433 general veteran group and 221,650 general population group.
Lee, 2006[51]	168 USA VA settings	Patients with SCI identified in the Spinal Cord Injury Service of the Veterans Affairs Palo Alto Medical Center; Mean age 50.27±12.8 years; Gender: 11% female; Race: 62% White; Time after injury: 19.17±13 years; Injury: 73 (43%) had paraplegia and 95 (56%) tetraplegia.
Garshick, 2005[36]	361 USA VA settings Time: 1994-2000	Males with chronic SCI, >20 years of age previously treated by the SCI Service at Veterans Affairs Boston Healthcare System, registered in the National Spinal Cord Injury Association database in Massachusetts, New Hampshire, Vermont, Maine, and Rhode Island (289 veterans and 72 nonveterans); Mean age: 50.6±15.0 years (range 23-87), Race: 93% Caucasian, 5% African American, and 2% other races; Time after injury: 17.5±12.8 years (range 1.0-56.5); Injury: 92% SCI was due to traumatic injury; 37 deaths.

Table 2. Prevalence of CVD in adults with SCI

Author	Age, Years	Outcomes	Sample (n)	Prevalence, %
Garshick, 2005[36]	Mean 50.6±15.0	Hypertension	361	24.4
Groah,* 2001[53]	Mean 57±10	Hypertension	834	0.58
Krum, 1992[39]		Hypertension	102	9
Lavela, 2006[37]	Mean 60	Hypertension	18,372	49
Lee,* 2006[51]	Mean 50.27±12.8	Hypertension	168	45.14
Levi, 1995[55]		Hypertension	326	0
Prakash,* 2002[34]	Mean 50±14	Hypertension	654	7
Rish,* 1997[3]	Mean at injury 21.4, median time after injury 25	Hypertension	230	21
Imai, 1996[32]	Mean 47.6	Hypertension	244	16.39
Imai, 1996[32]	Mean 47.6	Hypotension	244	1.64
Lee,* 2006[51]	Mean 50.27±12.8	Prehypertension	168	32.74
		Stage 1 hypertension	168	16.07
		Stage 2 hypertension	168	8.33
Krum, 1992[39]	Range 25-64	Cerebrovascular accident	102	1
Rish,* 1997[3]	Mean at injury 21.4, median time after injury 25	Cerebrovascular accident	230	2
Groah,* 2001[53]	Mean 57±10	Cerebrovascular diseases	834	0.05
		Angina	834	0.07
Krum, 1992[39]	Range 25-64	Angina	102	2
Prakash,* 2002[34]	Mean 50±14	Coronary artery disease	654	1.7
Rish,* 1997[3]	Mean at injury 21.4, median time after injury 25	Coronary artery disease	230	6
Groah,* 2001[53]	Mean 57±10	Coronary atherosclerosis	834	0.27
Lavela, 2006[37]	Mean 60	Coronary heart disease	18,372	12
Groah,* 2001[53]	Mean 57±10	Ischemic heart diseases	834	0.65
Imai, 1996[32]	Mean 47.6	Ischemic heart diseases	244	1.64
Groah,* 2001[53]	Mean 57±10	Myocardial infarction	834	0.28
Krum, 1992[39]	Range 25-64	Myocardial infarction	102	1.9
Lavela, 2006[37]	Mean 60	Myocardial infarction	18,372	14
Rish,* 1997[3]	Mean at injury 21.4, median time after injury 25	Myocardial infarction	230	3
Levi, 1995[55]		Cardiac diseases	326	2
Davies, 2002[54]	Mean 47.5±4.5	Cardiovascular morbidity	140	13.4
Groah,* 2001[53]	Mean 57±10	Cardiovascular morbidity	834	2.72
Imai, 1996[32]	Mean 47.6	Circulatory diseases	244	0.82
Levi, 1995[55]		Circulatory diseases	326	2
Prakash,* 2002[34]	Mean 50 ± 14	Congestive heart failure	654	1.7
Groah,* 2001[53]	Mean 57±10	Dysrhythmia	834	0.43
		Left bundle branch block	834	0.02
		Other CVD	834	0.81
		Valvular disease	834	0.2
Levi, 1995[56]		Cardiovascular symptoms: ankle-leg edema, chest pain, palpitations	353	58

***** Outcomes events obtained with ICD codes
† Hospitalizations with CVD diagnosis

Table 3. Prevalence of CVD in adults with SCI by age and years after injury

Author	Sample (n)	Age at Injury	Prevalence, %
All CVD			
Whiteneck, 1992*[52]	834	<30 years	2
		30-39 years	2.9
		40-49 years	5.2
		50-59 years	8.1
		60+ years	19.3
CVD symptoms			
Levi, 1995[56]	162	21-40 years	57
		41-77 years	61
Hypertension			
McGlinchey-Berroth, 1995*†[48]	255	<50 years and <50 years at index submission	5.09
	162	<50 years and >50 years at the time of index admission	25.3
	93	Age at injury and index hospital admission >50 years	33.33
Myocardial infarction			
McGlinchey-Berroth, 1995†*[48]	255	<50 years and <5 years at index submission	5.09
	162	<50 years of age and >50 years at the time of index admission	25.3
	93	>50 years of age	33.33
		Years after Injury	
All CVD			
Whiteneck, 1992*[52]	834	<10 years	2.9
		10-19 years	5.4
		20-29 years	10
		30+ years	14.2
Cardenas, 2004*†[50]	3,978	1 year	0.73
	1,714	10 years	0.41
	1,653	15 years	0.79
	1,251	20 years	0.4
	2,451	5 years	0.53
CVD symptoms			
Levi, 1995[56]	87	0-4 years	48
	89	18-44 years	72
	177	5-17 years	55

***** Outcomes events obtained with ICD codes
† Hospitalizations with CVD diagnosis

Table 4. Prevalence of CVD* according to SCI neurological category[53]

Neurological Category	All SCI (N=834)		Tetra ABC (N=99)		Para ABC (N=285)		All D (N=161)	
	Number	Rate	Number	Rate	Number	Rate	Number	Rate
All CVD	458	27.2	64	35.2	279	29.9	115	21.2
Coronary heart disease	109	6.5	5	2.1	63	6.6	41	7.4
Myocardial infarction	47	2.8	1	0.3	31	3.2	15	2.6
Angina	12	0.7	0		4	0.4	8	1.7
Coronary atherosclerosis	46	2.7	3	1	25	2.7	18	3.1
LBBB	4	0.2	1	0.3	3	0.3	0	
Hypertension	98	5.8	5	1.7	71	7.6	22	4.5
Cerebrovascular disease	8	0.5	4	1.5	3	0.3	1	0.2
Dysrhythmia	73	4.3	20	13.1	42	3.3	11	1.3
Valvular disease	34	2	10	5	14	1.5	10	1.7
Other CVD	136	8.1	20	9.2	86	1.4	30	1.5

* Age adjusted rates per 1,000 SCI person years by neurological category

Table 5. Mortality from CVD in adults with SCI

Author	Sample	Patient Characteristics	Mortality, % Among all SCI Patients
Arterial diseases			
DeVivo, 1999[49] Time: 1973-1998	28,239	All SCI	0.08
DeVivo, 1993[2] Time: 1973-1985	9,135	All SCI	0.15
		Ages 25-54 years	0.04
		Age >54 years	0.10
		Incomplete paraplegia	0.03
		Complete paraplegia	0.03
		Incomplete quadriplegia	0.04
		Complete quadriplegia	0.04
		Survival 1-5 years	0.09
		Survival >5 years	0.01
Cardiovascular diseases			
Garshick, 2005[36] Time: 1994-2000 Mean age: 50.6±15	361	All SCI	2.2
DeVivo, 1999[49] Time: 1973-1998	28,239	All SCI	1.03
Hartkopp, 1997[1] Time: 1954-1992 Median age at time of injury: 27.5 from 1953-1971 and 28.5 from 1972-1990	888	All SCI	6.31
		Thoracic-lumbar injury/Frankel A-C	1.58
		Frankel D	3.04
		Frankel E	0.68
		Cervical lesion	0.00
		Thoracic/lumbar lesion	0.00
		Men	5.29
		Women	1.01
Whiteneck, 1992[52] Time: 1943-1970 Age at time of injury 15-55, 42% 15-24 years, 27% 25-34 years, 18% 35-44 years, 13% 45-55 years; Median survival time 32 years	834	All patients	10.07
		Paraplegia, ABC	5.76
		Quadriplegia, ABC	0.96
		All D and E	3.36
		15-24	0.08
		25-34	0.07
		35-44	0.24
		45-54	0.44
		55-64	1.33
		65-74	2.12
		75-84	10.20
Cerebrovascular diseases			
Hartkopp, 1997[1] Time: 1954-1992 Median age at the time of injury 27.5 in 1953-1971 and 28.5 in 1972-1990	888	All patients	0.90
		Thoracic-lumbar injury/Frankel A-C	0.23
		Frankel D	0.45
		Frankel E	0.00
		Men	0.68
		Women	0.23
DeVivo, 1993[2] Time:1973-1985	9,135	All patients	0.24
		Ages 25-54 years	0.15
		Age >54 years	0.04
		Incomplete paraplegia	0.03
		Complete paraplegia	0.02
		Incomplete quadriplegia	0.09
		Complete quadriplegia	0.10
		Survival 1-5 years	0.12
		Survival >5 years	0.07

Table 5. Mortality from cardiovascular diseases in patients with SCI (continued)

Author	Sample	Patient Characteristics	Mortality, % Among all SCI Patients
Ischemic heart disease			
Hartkopp, 1997[1]	888	All patients	2.48
Time: 1954-1992		Thoracic-lumbar injury/Frankel A-C	0.56
Median age at time of		Frankel D	1.13
injury: 27.5 from 1953-		Frankel E	0.56
1971 and 28.5 from		Men	2.14
1972-1990		Women	0.34
DeVivo, 1993[2]	9,135	All patients	0.67
Time: 1973-1985		Ages 25-54 years	0.19
		Age >54 years	0.44
		Incomplete paraplegia	0.14
		Complete paraplegia	0.12
		Incomplete quadriplegia	0.23
		Complete quadriplegia	0.18
		Survival 1-5 years	0.27
		Survival >5 years	0.12
Rish, 1997[3]	230	All patients	0.02
Time: 1954-1992		Survival 5 years	0.43
Mean age at injury 21.4		Survival 20 years	0.87
years, Median time after		Survival >20 years	0.87
injury 25 years			
Lung embolus			
Hartkopp, 1997[1]	888	All patients	0.68
Time: 1954-1992		Thoracic-lumbar injury/Frankel A-C	0.11
Median age at time of		Frankel D	0.34
injury 27.5 from 1953-		Frankel E	0.11
1971 and 28.5 from		Men	0.68
1972-1990		Women	0.00
Non ischemic heart disease			
DeVivo, 1993[2]	9,135	All patients	0.92
Time: 1973-1985		Ages 25-54 years	0.31
		Age >54 years	0.47
		Incomplete paraplegia	0.04
		Complete paraplegia	0.11
		Incomplete quadriplegia	0.28
		Complete quadriplegia	0.48
		Survival 1-5 years	0.32
		Survival >5 years	0.18
Stroke			
DeVivo, 1999[49]	28,239	All patients	0.19
Time: 1973-1998			

Figure 16. Percent of all deaths due to coronary heart disease among adults with SCI

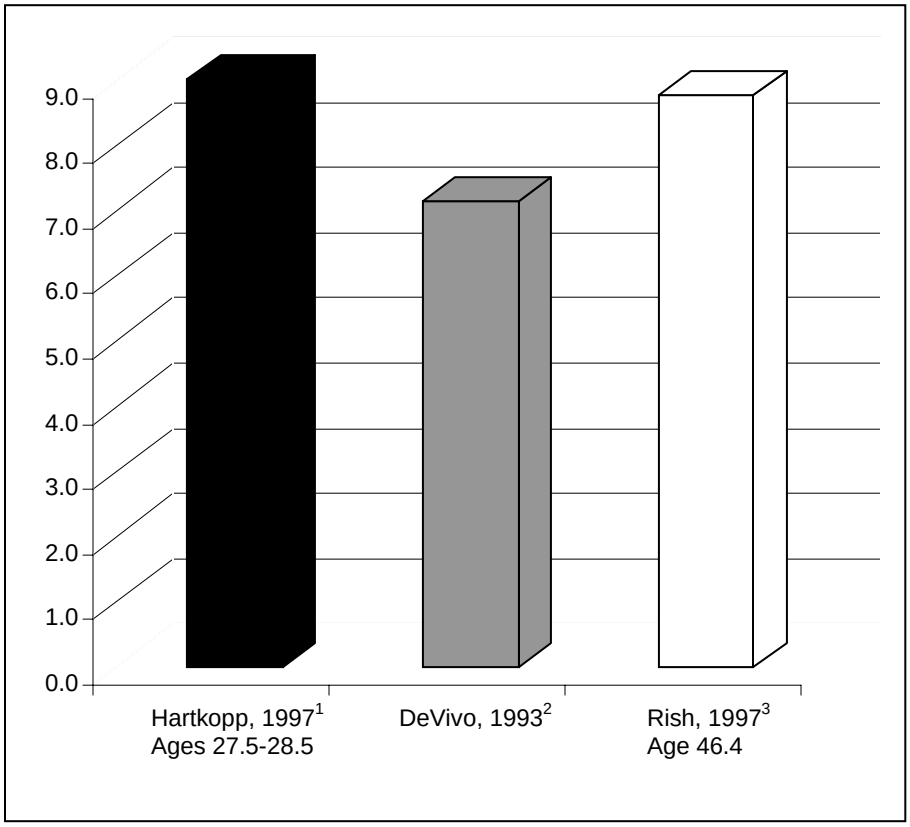


Table 6. Percent of all deaths from CVD among adults with SCI

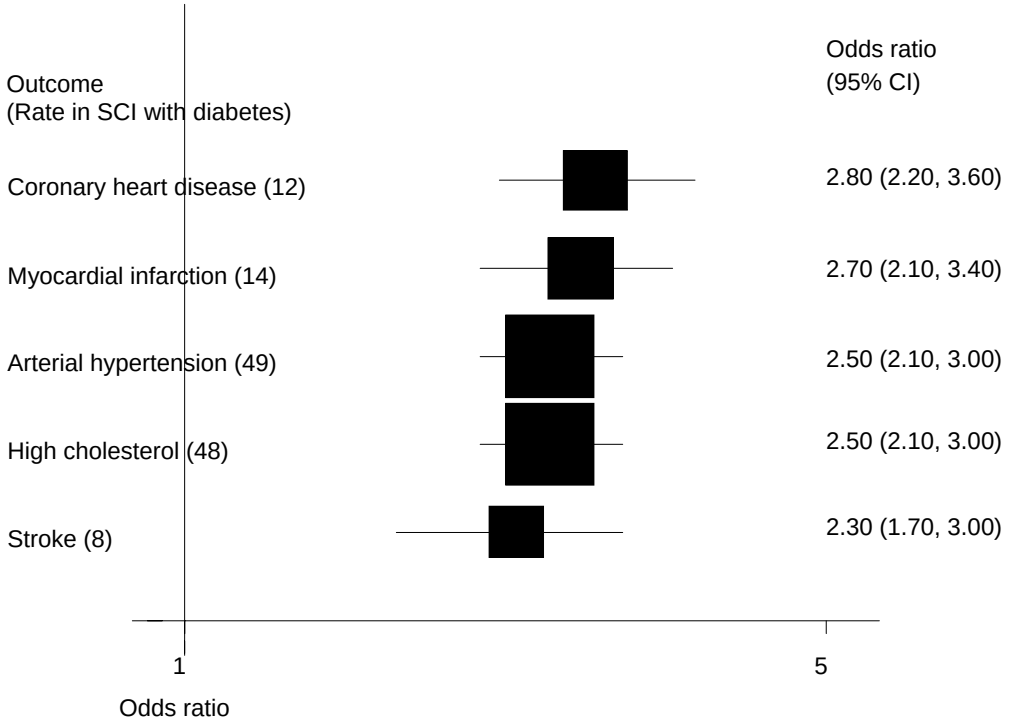
Author	Disease (ICD Codes)	% of all SCI Deaths
Hartkopp, 1997[1]	CVD (390-458)	24.0
	Ischemic heart disease (410-414)	9.0
DeVivo, 1999[49]	Heart	18.8
DeVivo, 1993[2]	Ischemic heart disease (410-414)	7.1
Garshick, 2005[36]	Circulatory system disorder (390-459)	21.6
	Circulatory system disorder (390-459) as contributing cause of death	18.9
Rish, 1997[3]	Myocardial infarction	8.8
Whiteneck, 1992[52]	CVD	23.2

Table 7. Odds ratios of diabetes or CVD in adults with SCI compared to able bodied

Conditions	Odds Ratio (95% CI)		
	Lavela, 2006[37] VA Settings %; Mean Age 60 Years	**Prakash, 2002[34] VA Settings Age 50±14**	**Krum, 1992[39] Ages 25-64**
Coronary heart disease		**0.24 (0.13; 0.43)**	
Myocardial infarction			1.00 (0.14; 7.24)†
Arterial hypertension		**0.16 (0.12; 0.21)**	**0.40 (0.17; 0.92)** †
High cholesterol			
Stroke			
Diabetes	**3.3 (1.3; 8.3)***	1.1 (0.88; 1.37)	3.13 (0.62; 15.89) †
Congestive heart failure		**0.24 (0.13; 0.43)**	
Angina			0.67 (0.11; 4.1) †
Cerebrovascular diseases			1.00 (0.06; 16.21) †

* Adjusted for age, race, marital status, duration of injury, employments status, and educational level
† Adjustment for age, matching by gender
Bold - significant association at 95% confidence level

Figure 17. Odds ratios* of cardiovascular outcomes in VA users with SCI and diabetes vs. SCI but no diabetes[37]



* Adjusted for age, race, marital status, duration of injury, employments status, and educational level

Table 8. Diabetes management and diabetes complications in VA users with SCI, in VA users without SCI, and non-VA user general population without SCI[37]

Diabetes Management or Complications	Prevalence in VA SCI (%)	Prevalence in VA Non SCI (%)	Odds Ratio in VA SCI Compared to the VA Non SCI Population (95% CI)	Prevalence in Non VA General Population (%)	Odds Ratio in VA SCI Compared to Non VA General Population (95% CI)
Duration of diabetes (>25 years)	13.55	10.94	1.27 (0.97; 1.66)	9.75	**1.44 (1.16; 1.79)**
Insulin therapy	26.03	28.51	0.88 (0.72; 1.08)	25.9	1.01 (0.85; 1.19)
Oral agent	62.97	69.54	**0.75 (0.62; 0.90)**	66.35	0.86 (0.74; 1.01)
Insulin + oral agent	11.25	12.82	0.86 (0.65; 1.13)	11.17	1.00 (0.79; 1.27)
Foot sores with >4 weeks to heal	41.37	17.85	**3.25 (2.65; 3.98)**	13.12	**4.68 (4.02; 5.46)**
Retinopathy	25.31	24.24	1.06 (0.86; 1.31)	22.27	**1.19 (1.00; 1.41)**
Diabetes education	63.04	60.16	1.13 (0.94; 1.36)	49.84	**1.72 (1.47; 2.00)**

Bold – significant association at 95% confidence level

Figure 18. Adjusted odds ratio of CVD in patients with SCI: Tetraplegia with no functional motor preservation compared to paraplegia and no functional motor preservation [53]

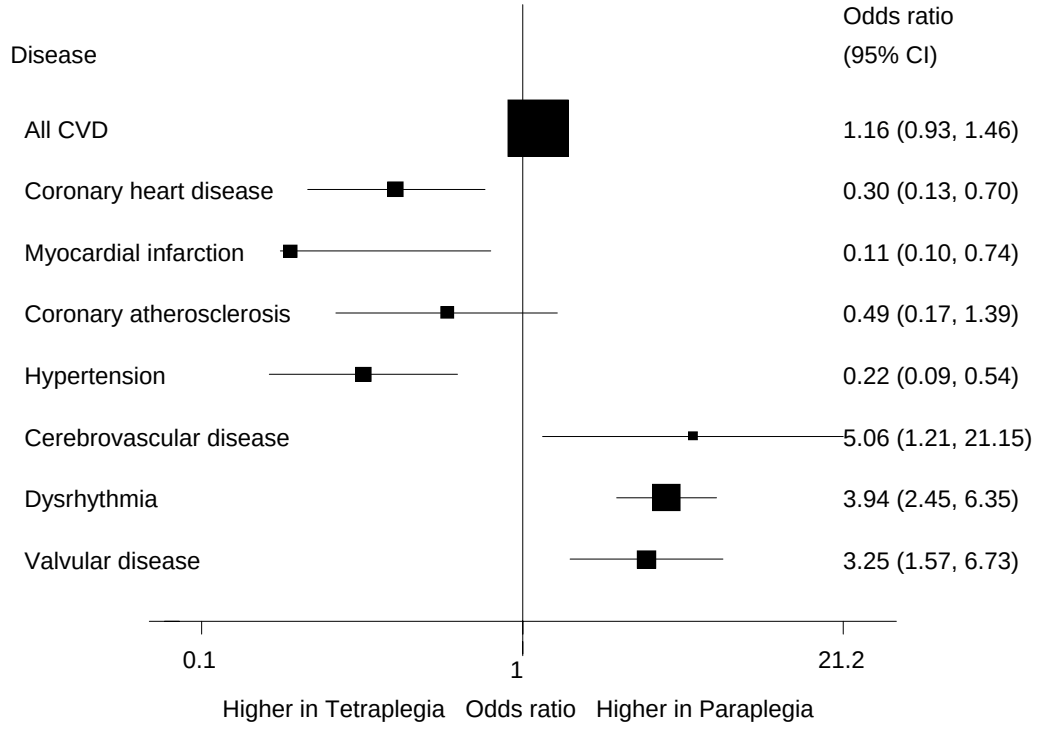


Table 9. Hazard ratio of dying having ECG abnormality vs. normal ECG among patients with SCI and able-bodied veterans [34]

ECG Abnormalities	Spinal Cord Injury Hazard Ratio 95% CI	Able-bodied Hazard Ratio 95% CI
Right bundle branch block	1.23 (0.4; 4)	**2.21 (1.97; 2.47)**
Left bundle branch block	**4.24 (1.5; 12)**	**1.98 (1.62; 2.42)**
Intraventricular conduction delay	1.15 (0.3; 5)	1.13 (0.99; 1.3)
LVH with strain	**3.28 (1.2; 9)**	**1.31 (1.14; 1.52)**
Left atrial abnormality	0.59 (0.2; 1.9)	**1.55 (1.39; 1.74)**
Anterior Q wave	1.44 (0.5; 4.6)	**2 (1.76; 2.28)**
Inferior Q wave	0.78 (0.3; 1.8)	**1.32 (1.21; 1.43)**
Atrial fibrillation	**3.54 (1.2; 11)**	**2.02 (1.79; 2.27)**
Premature ventricular contraction	0.33 (0.05; 2.5)	**1.51 (1.36; 1.67)**
Abnormal ST depression	1 (0.5; 1.9)	**1.9 (1.77; 2.04)**
Abnormal QT interval	0.27 (0.1; 18)	**1.91 (1.77; 2.06)**

Bold – significant association at 95% confidence level

Figure 19. Hazard ratio of dying based on ECG abnormality vs. normal ECG among VA users with SCI and able-bodied VA users[34]

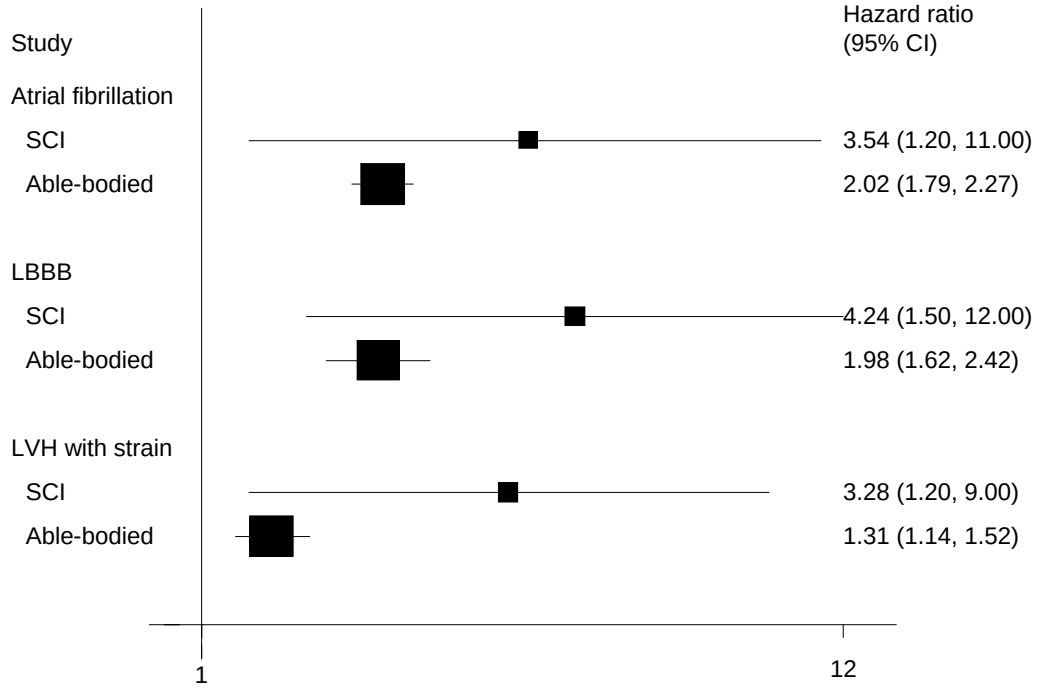


Table 10. Age standardized mortality ratios in adults with chronic SCI compared to the general population (no adjustment for other confounding factors)[2]

Risk Factors	Death (N)	Standardized Mortality Ratio (95% CI)
Ischemic heart disease (ICD codes 410-414)		
Age 25-54 years	17	1.4 (0.8; 2.0)
Age >54 years	40	1.1 (0.8; 1.4)
Incomplete paraplegia	13	1.4 (0.7; 2.1)
Complete paraplegia	11	1 (0.4; 1.6)
Incomplete quadriplegia	21	1 (0.6; 1.4)
Complete quadriplegia	16	**2.6 (1.3; 3.9)**
Survival 1-5 years	25	1.1 (0.7; 1.5)
Survival >5 years	11	0.6 (0.2; 1.0)
Non ischemic heart disease (ICD codes 420-429)		
Age 25-54 years	28	**6.5 (4.1; 10.8)**
Age >54 years	43	**4.2 (3; 5.4)**
Incomplete paraplegia	4	1.4 (0.4; 2.4)
Complete paraplegia	10	**2.8 (1.1; 4.5)**
Incomplete quadriplegia	26	**4 (2.5; 5.5)**
Complete quadriplegia	44	**23.4 (16.5; 30.3)**
Survival 1-5 years	29	**4.1 (2.6; 5.6)**
Survival >5 years	16	**3 (1.5; 4.5)**
Cerebrovascular diseases (ICD codes 430-438)		
Age 25-54 years	14	**4.6 (2.2; 7.0)**
Age >54 years	4	0.4 (0; 0.8)
Incomplete paraplegia	3	1.3 (0; 2.8)
Complete paraplegia	2	0.8 (0; 1.9)
Incomplete quadriplegia	8	1.4 (0.4; 2.4)
Complete quadriplegia	9	**5.4 (1.8; 9.0)**
Survival 1-5 years	11	2 (0.8; 3.2)
Survival >5years	6	1.3 (0.2; 2.4)
Diseases of arteries (ICD codes 440-448)		
Age 25-54 years	4	8.2 (0.2; 16.2)
Age >54 years	9	1.2 (0; 3.5)
Incomplete paraplegia	3	5.4 (0; 11.5)
Complete paraplegia	3	5 (0; 10.6)
Incomplete quadriplegia	4	2.7 (0.1; 5.3)
Complete quadriplegia	4	9.4 (0.2; 18.6)
Survival 1-5 years	8	**5.8 (1.8; 9.8)**
Survival >5 years	1	0.9 (0; 2.7)

Bold - significant association at 95% confidence level

Table 11. Age standardized mortality ratios for cardiovascular death by gender compared to able bodied[1]

Cause of Death	Standardized Mortality Ratio (95% CI)		
	Men	**Women**	**Both Genders**
Period of injury 1953-1990 (end of followup: December 31, 1992)			
CVD	1.2 (0.85; 1.53)	1 (0.52; 2.14)	1.2 (0.87; 1.49)
Ischemic heart disease	0.7 (0.41; 1.06)	1 (0.14; 1.96)	0.7 (0.42; 1.02)
Cerebrovascular disease	1 (0.35; 2.07)	1 (0.13; 3.98)	1 (0.43; 1.94)
Lung embolus	**14 (5.25; 31.1)**		**11 (4.19; 24.8)**
Total	**2.1 (1.79; 2.38)**	**2 (1.53; 2.94)**	**2.1 (1.83; 2.37)**
Period of injury 1953-1971 (end of followup: December 31, 1973)			
CVD	**3.2 (1.38; 6.29)**	4 (0.09; 19.5)	**3.2 (1.47; 6.12)**
Ischemic heart disease			1.1 (0.13; 3.91)
Cerebrovascular disease			
Lung embolus	**131 (27.1; 384)**		**107 (22.1; 313)**
Total	**6.5 (4.66; 8.74)**	**12 (5.81; 22.3)**	**7.1 (5.31; 9.32)**
Period of injury 1972-1990 (end of followup: December 31, 1992)			
CVD	1.3 (0.71; 2.09)	3 (0.86; 6.16)	1.5 (0.89; 2.25)
Ischemic heart disease	1.2 (0.58; 2.24)		1.2 (0.59; 2.13)
Cerebrovascular disease		4 (0.53; 15.9)	1.4 (0.28; 3.96)
Total	**2.3 (1.79; 2.90)**	**3 (1.91; 5.09)**	**2.4 (1.95; 3.01)**

Bold – significant association at 95% confidence level

Table 12. Age standardized mortality ratios from CVD in adults with SCI compared to the general population

Author Sample	Patient Characteristics	Mortality/1,000 SCI	Standardized Mortality Ratios (95% CI)
Artery diseases			
DeVivo, 1993[2] N = 9,135 (standardization by age, sex, and race)	Survival >5 years	0.11	0.9 (0; 2.7)
	Age >54 years	0.99	1.2 (0; 3.5)
	Incomplete quadriplegia	0.44	2.7 (0.1; 5.3)
	All patients	1.53	**4.5 (2.1; 6.9)**
	Complete paraplegia	0.33	5 (0; 10.6)
	Incomplete paraplegia	0.33	5.4 (0; 11.5)
	Survival 1-5 years	0.88	**5.8 (1.8; 9.8)**
	Age 25-54 years	0.44	8.2 (0.2; 16.2)
	Complete quadriplegia	0.44	9.4 (0.2; 18.6)
Garshick, 2005[36] N = 361	All patients		1.15 (0.13-4.15)
Cerebrovascular diseases			
DeVivo, 1993[2] N = 9,135 (standardization by age, sex, and race)	Age >54 years	0.44	**0.4 (0; 0.8)**
	Complete paraplegia	0.22	0.8 (0; 1.9)
	Incomplete paraplegia	0.33	1.3 (0; 2.8)
	Survival >5 years	0.66	1.3 (0.2; 2.4)
	Incomplete quadriplegia	0.88	1.4 (0.4; 2.4)
	All patients	2.41	1.8 (1; 2.6)
	Survival 1-5 years	1.20	2 (0.8; 3.2)
	Age 25-54 years	1.53	**4.6 (2.2; 7)**
	Complete quadriplegia	0.99	**5.4 (1.8; 9)**
Hartkopp, 1997[1] N = 888	Men	6.76	0.95 (0.35; 2.07)
	All patients	9.01	0.99 (0.43; 1.94)
	Women	2.25	1.1 (0.13; 3.98)
Cardiovascular diseases			
Hartkopp, 1997[1] N = 888	Cervical lesion		1.07 (0.72; 1.53)
	Women	10.14	1.13 (0.52; 2.14)
	Men	52.93	1.15 (0.85; 1.53)
	All patients	63.06	1.15 (0.87; 1.49)
	Thoracic/lumbar lesion		1.26 (0.82; 1.84)
Ischemic heart disease			
DeVivo, 1993[2] N = 9,135 (standardization by age, sex, and race)	Survival >5 years	1.20	0.6 (0.2; 1)
Hartkopp, 1997[1] N = 888	Women	3.38	0.67 (0.14; 1.96)
	Men	21.40	0.68 (0.41; 1.06)
	All patients	24.77	0.68 (0.42; 1.02)
DeVivo, 1993[2] N = 9,135 (standardization by age, sex, and race)	Complete paraplegia	1.20	1 (0.4; 1.6)
	Incomplete quadriplegia	2.30	1 (0.6; 1.4)
	Age >54 years	4.38	1.1 (0.8; 1.4)
	Survival 1-5 years	2.74	1.1 (0.7; 1.5)
	All patients	6.68	1.3 (1; 1.6)
	Age 25-54 years	1.86	1.4 (0.8; 2)
	Incomplete paraplegia	1.42	1.4 (0.7; 2.1)
	Complete quadriplegia	1.75	**2.6 (1.3; 3.9)**
Lung embolus			
Hartkopp, 1997[1] N = 888	All patients	6.76	**11.4 (4.19; 24.8)**
	Men	6.76	**14.3 (5.25; 31.1)**

Table 12. Age standardized mortality ratios from CVDs in adults with SCI compared to the general population (continued)

Author Sample	Patient Characteristics	Mortality/1,000 SCI	Standardized Mortality Ratios (95% CI)
Nonischemic heart disease			
DeVivo, 1993[2]	Incomplete paraplegia	0.44	1.4 (0.4; 2.4)
N = 9,135	Complete paraplegia	1.09	**2.8 (1.1; 4.5)**
	Survival >5 years	1.75	**3 (1.5; 4.5)**
	Incomplete quadriplegia	2.85	**4 (2.5; 5.5)**
	Survival 1-5 years	3.17	**4.1 (2.6; 5.6)**
	Age >54 years	4.71	**4.2 (3; 5.4)**
	All SCI	9.20	**5.6 (4.4; 6.8)**
	Age 25-54 years	3.07	**6.5 (4.1; 10.8)**
	Complete quadriplegia	4.82	**23.4 (16.5; 30.3)**
Diseases of the heart			
Garshick, 2005[36]	All patients		0.59 (0.19;1.38)
N = 361			
Other diseases of the circulatory system			
Garshick, 2005[36]	All patients		1.49 (0.31;4.36)
N = 361			

Bold - significant association at 95% confidence level

Question 3

Exercise in adults with SCI. Of the 19 peer reviewed original articles, there were none reporting results of RCTs. The majority consisted of small, uncontrolled intervention trials (case series) or cross-sectional surveys using measures of self-reported physical activity. Variation in study design, intervention, and reported outcomes precluded quantitative pooling of results. A summary of findings from individual studies according to intervention type and outcomes was conducted. To facilitate review, these studies were separated by outcomes of interest: Carbohydrate-related outcomes (n=10) (Table 13) and lipid-related outcomes (n=13) (Table 14). These were then further organized by type of reported exercise, as follows:

A. Active Exercise (AE): n=six studies of 57 individuals (40 males, five females, 12 unreported; 36 paraplegic, three tetraplegic, nine unclassified and nine other) (8-24 weeks exercise duration).[57-63]
B. Functional Electrical Stimulation Exercise (FES): n=five studies of 32 individuals (27 males, five females; eight paraplegic, 14 tetraplegic and ten unclassified) (8-52 weeks exercise duration)[64-68]
C. Passive Exercise (PE): n=0 studies
D. Self-Reported Physical Activity: n=six studies of 215 individuals (205 males, 14 females; 125 paraplegic, 93 tetraplegic, one unclassified) (no report of duration)[13,14,54,69-71]
E. Other: n=one study (nine males, seven females) (no report of duration)[72]

Description of exercise intervention studies with carbohydrate related outcomes (Table 13) (n=10 studies of 101 individuals).[13,14,58,60,62,64-68] The overall quality, quantity, and consistency of evidence for exercise as an intervention for carbohydrate disorders is poor. Study characteristics ranged from a case series using pre-post assessment of outcomes for six individuals randomly assigned to eight weeks of high- versus low-intensity arm crank exercise[58] to a cross-sectional survey of 22 individuals who provided self-assessed physical activity levels and metabolic variables.[13] The intervention type, frequency, intensity, and duration varied considerably across studies. Most involved several sessions of supervised exercise per week with a study duration ranging from eight weeks to one year. SCI level and severity, and duration since injury, varied across studies. More than 90 percent of subjects were men. One study was a survey of self-reported exercise or physical activity and assessed the impact of the respondent's activity on major cardiovascular endpoints.[54] Three studies examined the effects of active exercise (AE),[58,60,62] while five examined the effects of FES exercise,[64-68] on carbohydrate related measures. Two survey studies assessed the association between self-reported physical activity and these measures.[13,14] The most commonly assessed measures were fasting plasma glucose and oral glucose tolerance tests, measuring post-oral load levels of glucose and insulin. None assessed glycosylated hemoglobin.

Impact of exercise programs on carbohydrate related measures. There is mixed, low-quality evidence that a program of exercise improves carbohydrate-related measures. Of the five studies that measured fasting plasma glucose only one showed a statistically significant difference. Two (one AE; one FES) found no differences before and after intervention,[60,65] while one FES study found a nonstatistically significant trend for reduction.[67] Two surveys identified inverse correlations (r = -.53 and -.40 respectively) between self-reported physical activity and plasma glucose; one was statistically significant[13] while the other was not.[14] Measures of two-hour post-load glucose were mixed. One FES study found a significant (p = .014), 13 percent post-training reduction in glucose levels, averaged across participants,[66] while another FES study showed no

change.[68] Both survey studies of self-reported physical activity identified inverse correlations (r = -.59 and -.34 respectively) with two-hour post-load glucose; the prior was statistically significant ($p < 0.01$)[14] while the latter was not.[13] Impaired glucose tolerance and clearing were also reported. One AE study showed a statistically significant post-training 15 percent average reduction in area under the curve after glucose load,[62] and one FES study found a significant 33 percent average increase in glucose disposal.[65]

Measures of insulin levels were no more uniform than for glucose. Some studies assessed fasting insulin levels, while others assessed insulin levels after a standard glucose load or insulin area under the curve. One possible consistency in these studies is the lack of change in fasting plasma insulin levels after training. Two FES studies found no difference in fasting plasma insulin,[65,67] while one identified decreased levels that were not significant.[64] One survey study showed no correlation between self-reported physical activity and insulin;[14] the other survey study did identify an inverse correlation (r = -.40), but it was not statistically significant ($p > 0.05$).[13] Plasma insulin concentrations after oral glucose load were also inconsistent. One FES study identified a nonsignificant 26 percent average reduction in two-hour post-load levels,[66] while another FES study found no change.[68] Similarly, one survey study identified a statistically significant inverse correlation (r = -.79. $p < 0.01$) between self-reported physical activity and post-load insulin,[14] while the other found no correlation.[13] One AE study identified a significant 33 percent average reduction in area under the curve for plasma insulin concentrations after glucose load.[62] To further complicate any possible conclusions, the AE study comparing two programs of exercise (low intensity vs. high intensity)[58] found insulin sensitivity to be decreased by an average of 33 percent for those assigned the low intensity intervention, but increased an average of 56 percent for those in the high intensity intervention.

Description of exercise intervention studies with lipid or cardiovascular related outcomes (Table 14) (n=13 studies of 292 individuals).[13,14,54,57-61,63,69-72] The quality, quantity, and consistency of evidence for studies reporting lipid related measures is also poor. Study designs were primarily reports of case series and cross-sectional surveys, with intervention type, frequency, intensity, and duration varied across studies. Nearly 90 percent of subjects were men, thus limiting extrapolation of findings in women. Six studies examined the effects of AE on lipid related measures.[57-61,63] No eligible studies examined FES exercise. There were six survey studies that assessed the association between self-reported physical activity and lipid measures.[13,14,54,69-71] One of these examined the association between physical activity and cardiovascular morbidity.[54] One study, categorized as "other," examined the effects of a weight management training program, including curriculum on exercise, on lipid outcomes.[72] The most common lipid related measures were TC, HDL-C, LDL-C, the ratio of TC to HDL-C (TC/HDL-C), and TG.

Impact of exercise programs on lipid or cardiovascular related measures. Evidence may point to improved levels of TC after a training intervention, or with self-reported physical activity. Among the studies examining effects of AE interventions, two identified statistically significant reductions in TC levels (on average, 8 percent and 10 percent less than pre-training);[60,63] these involved training programs with a body-weight supported treadmill[63] or a wheelchair aerobic fitness trainer.[60] One study found a nonsignificant 9 percent average decrease,[61] while two showed no changes;[58,59] all three of these studies involved arm crank exercise. Three survey studies examined self-reported exercise and TC levels.[69-71] While one found no difference in TC levels between those who were physically active and those who were sedentary,[69] two others identified significant inverse correlations (r = -.35 and -.33, p = 0.008 and

p <0.05, respectively). The study examining the weight management training program also identified a nonsignificant decrease in TC.[72]

Six AE studies reported outcomes for HDL-C.[57-61,63] While three reported no changes,[57,58,60] one reported a statistically significant increase[59] and two reported very small, nonsignificant increases (10 percent and 8 percent).[61,63] Four survey studies reported on HDL-C, with one identifying a significantly significant 14 percent decrease (p <0.05) for individuals who were physically active compared to those who were sedentary.[69] Two others identified significant positive correlations (r = .46 and .63, p <0.05),[13,14] while another reported no correlation.[71] Oddly, the weight management study reported a significant decrease in HDL-C.[72] Measures for TC/HDL-C were similarly inconclusive. Of five AE studies, two reported no changes,[57,60] while three reported statistically significant reductions in values ranging from 18 percent to 23 percent.[58,61,63] Two survey studies identified significant inverse correlations between physical activity and TC/HDL-C (r = -.49, p <0.05 for both),[14,70] one identified a significant reduction (p <0.05) among those who were physically active compared to sedentary,[69] and one showed no correlation.[71]

In two of four AE studies reporting LDL-C measures, levels were significantly decreased by 15 percent and 25 percent (p = .05 for both);[61,63] no changes were observed in the others.[57,58] However, two of three survey studies identified significant inverse correlations between self-reported physical activity and LDL-C levels (r = -.28 and -.40, p = 0.003 and p <0.01 respectively).[70,71] The third survey study found no difference between groups.[69] The weight management program was associated with a nonsignificant decrease.[72]

While one study identified a statistically significant 31 percent average decrease in TG among those assigned a high intensity AE training protocol,[58] two others showed decreases that were nonsignificant,[61,63] and still two others found no change.[59,60] Among the four self-report surveys, one identified a nonsignificant 32 percent decrease among those who were physically active compared to sedentary.[69] Three others identified no correlation between physical activity and TG levels.[13,70,71]

The study by Davies and McColl[54] identified no association between physical activity levels and overall cardiovascular morbidity.

Summary. Evidence on effects of exercise on lipid and carbohydrate metabolism disorders is inconclusive. Studies to date have been short in duration, involved few subjects, and relied on study designs highly susceptible to error. Future collaborative research is needed to study both efficacy and effectiveness of such interventions in the population of individuals with SCI.

Dietary and pharmacologic intervention studies with carbohydrate or lipid related outcomes in adults with SCI.

Carbohydrate outcomes. There were no prospective studies that evaluated dietary and/or lifestyle interventions on carbohydrate related outcomes.

Lipid related outcomes (Table 15.). Only two prospective studies that evaluated dietary and/or lifestyle interventions to reduce lipid levels were identified and met inclusion criteria.[20,72] No studies assessing pharmacologic interventions were identified. The two dietary/lifestyle case series studies included 238 subjects, overwhelmingly male (87 percent). Quality of the two studies was poor.

One controlled clinical trial compared the effect of a dietary intervention referral compared to no dietary referral over a mean of 16 months.[20] Overall, mean age was 38.5 years and 89 percent were male. All subjects must have had an SCI of at least two years in duration. Group 1 (n=86) received a dietary intervention referral based on the recommendations of the American

Heart Association and American Dietetic Association Guidelines. These subjects had a total cholesterol level greater than 200 mg/dL. Group 2 (n=136) received no dietary intervention referral. All subjects had a total cholesterol level ≤200 mg/dL. Group 1 subjects were significantly older (mean 42.8 versus 35.7, p <0.0001) and had a longer post-injury duration (15.6 versus 11.1 years, p <0.0001) compared to Group 2 subjects. Dietary intervention was effective in reducing some lipid parameters. There were significant reductions in total and low density lipoprotein cholesterol levels from baseline in Group 1, 234 to 224 (p <0.001) and 159 to 151 (p = 0.004), respectively. Levels increased slightly but not significantly in Group 2. In Group 1, 67 percent had decreases in LDL-C compared to 47 percent in Group 2 (p = 0.007). Secondary analysis found 15 percent had reductions ranging from 30 to 69 mg/dL and the LDL-C values declined from greater than 135 mg/dL to <135 mg/dL in 21 percent. There were no significant effects on high density lipoprotein cholesterol or triglyceride levels in either group.

The second uncontrolled pilot study evaluated a weight management program consisting of 12 classes for 12 weeks, primarily led by a registered dietician.[72] Classes covered nutrition, exercise, and behavior modification. The dietary approach utilized a time-calorie displacement diet. The study followed 16 overweight subjects (BMI ≥25), up to 24 weeks. Subjects were on average 44 years of age, nine were men, 13 were White, and three were African American. There were no significant changes in total and LDL cholesterol levels from baseline at weeks 12 and 24. At week 12, TCl was reduced by 5.8 mg/dL (p = 0.28) and LDL cholesterol by 1.8 mg/dL (p = 0.76). By week 24, the mean changes were 0.3 mg/dL (p = 0.96) and -4.2 mg/dL (p = 0.42), respectively. HDL cholesterol was reduced significantly by 3.2 mg/dL from a baseline value of 43.1 mg/dL (p = 0.03) at week 12 and -0.9 mg/dL (p = 0.59) by week 24.

Table 13. Description of exercise intervention studies with carbohydrate related outcomes in people with SCI

Reference	Study Design; Sample Size	Intervention Type	Frequency; Intensity; Duration	Subject Characteristics	Outcomes of Interest	Findings
A. Active exercise						
de Groot, 2003[58]	Case series n=6 Random assignment to high vs. low intensity	Arm crank exercise	3 sessions/week; 60 minutes/session; High-intensity (HI; 70-80% heart rate reserve (HRR)) vs. low-intensity (LI; 40-50% HRR) 8 weeks of training	4 males, 2 females; Age range 19-54 years; Mean duration since injury 116±77 days; 6 paraplegic (C5-L1)	Insulin sensitivity (post-test/pre-test)	Nonsignificant decline in HI group (67%±9%) and nonsignificant improvement in LI group (156%±55%) from baseline
Midha, 1999[60]	Case series n=12 (Includes 2 nonSCI subjects)	Wheelchair aerobic fitness trainer (WAFT) training program	2-3 sessions/week; 20-30 minutes, until target heart rate of 90% age-predicted maximum reached; mean intensity 177 watts 10 weeks of training	11 males, 1 female; Age range 22-58; Duration since injury range 4-29 years; 3 quadriplegic; 7 paraplegic; 1 stroke; 1 amputee	Fasting serum glucose (mg/dL)	No change from pre-training to post-training (86±35 to 85±32)
Phillips, 2004[62]	Case series n=9	Body-weight supported treadmill training program	68 sessions (2.8±0.2 sessions/week); Velocity and % weight supported varied for each participant; 6.0±0.3 months of training	8 males, 1 female; Mean age 31±3 years; Mean duration since injury 8.1 years; 9 incomplete (C4-T12)	A. Glucose tolerance (area under glucose x time curve) B. Blood insulin concentration (area under insulin x time curve)	A. 15%±4% (range 6-26%) reduction from baseline ($p < .05$) B. 33%±8% (range 17-47%) reduction from baseline ($p < .01$)
B. Functional electrical stimulation exercise						
Chilibeck, 1999[64]	Case series n=5	Electrically stimulated leg cycling program	3 sessions/week; 30 minutes/session; Power 6.0 watts, increased as possible each session; 50 revolutions/minute;	4 males, 1 female; Age range 31-50 years; Duration since injury range 3-25 years; 5 complete (C5-T8)	A. Glucose tolerance (area under glucose x time curve) B. Fasting serum insulin (area under insulin x time curve) C. Insulin sensitivity	A. Nonsignificant decreases from pre-training to post-training B. Nonsignificant decreases from pre-training to post-training C. Increase from pre-

Table 13. Description of exercise intervention studies with carbohydrate related outcomes in people with SCI (continued)

Reference	Study Design; Sample Size	Intervention Type	Frequency; Intensity; Duration	Subject Characteristics	Outcomes of Interest	Findings
			8 weeks of training		index	training (~0.9) to post-training (~1.3) (p <.05)
Hjeltnes, 1998[65]	Case series n=5	Electrically stimulated leg cycling program	7 sessions/week; 30 minutes/session or until fatigued; Power 6.0 watts, increased by 6.1 watts each session; 50 revolutions/minute; 8 weeks of training	5 males, 0 females; Mean age 35±3 years; Mean duration since injury 10.2±3.4 years; 5 tetraplegic; 5 complete (C5-C7)	A. Insulin-mediated glucose disposal (uM/kg/minute) B. Mean steady-state insulin (uU/mL) C. Mean steady-state glucose (mM)	A. 33%±13% increased whole body insulin-stimulated glucose uptake from baseline (p <.05) B. No change from pre-training to post-training (97±1 to 94 ±1) C. No change from pre-training to post-training (5.8±0.4 to 5.9±0.4)
Jeon, 2002[66]	Case series n=7	Electrically stimulated leg cycling program	3 sessions/week; 30 minutes/session; 50-60% VO2 maximum; 8 weeks of training	5 males, 2 females; Age range 30-53 years; Duration since injury range 3-40 years; 3 tetraplegic 4 paraplegic 7 complete (C5-T10)	A. 2-hour postload glucose (mg/dL); B. 2-hour postload insulin (uU/mL)	A. Reduction from pre-training to post-training (139.9±16 to 122.4±10; p = .014); B. Nonsignificant reduction from pre-training to post-training (118.4±42.6 to 87.5±10)
Mahoney, 2005[67]	Case series n=5	Resistance exercise training program	2 sessions/week; 4 sets of 10 unilateral, dynamic knee extensions; 12 weeks of training	5 males, 0 females; Mean age 35.6±4.9 years; Mean duration since injury 13.4±6.5 years; 5 complete (C5-T9)	A. Plasma glucose levels (mg/dL) B. Insulin concentration	A. Nonsignificant trend for reduction from pre-training to post-training (p = .074) B. No change from pre-training to post-training
Mohr, 2001[68]	Case series n=10	Exercise program with functional electrical stimulation cycling ergometer	3 sessions/week; 30 minutes/session; 50 revolutions/minute; 1 year of training	8 males, 2 females; Mean age 35±2 years; Mean duration since injury 12±2; 6 tetraplegic (C6); 4 paraplegic (T4)	A. 2-hour postload insulin (uU/mL) B. 2-hour postload glucose (mM/L) C. Insulin-stimulated glucose uptake rates (mg/min/kg)	A. No change from pre-training to post-training (93±7 to 88±8) B. No change from pre-training to post-training C. Increased from pre-training to post-training (4.9±0.5 to 6.2±0.6; p

Table 13. Description of exercise intervention studies with carbohydrate related outcomes in people with SCI (continued)

Reference	Study Design; Sample Size	Intervention Type	Frequency; Intensity; Duration	Subject Characteristics	Outcomes of Interest	Findings
						<0.05)
C. Passive exercise						
No eligible studies						
D. Self-reported physical activity						
Jones, 2004[14]	Cross-sectional case-control survey n=20	NA Assessed physical activity levels (minutes/week) and metabolic variables	NA	20 males, 0 females; Age range 16-52 years; Mean duration since injury 10.3±1.8 years; 11 tetraplegic (C4-C7); 9 paraplegic (T5-L5)	A. Fasting plasma glucose (mM/L) B. Log 2-hour postload glucose (mM/L) C. Log fasting plasma insulin (uU/mL) D. Log 2-hour postload insulin (uU/mL)	A. Nonsignificant inverse association with physical activity (r = -0.40) B. Inverse association with physical activity (r = -0.59; p <.01) C. No association with physical activity (r = -0.07) D. Inverse association with physical activity (r = -0.79; p <.01)
Manns, 2005[13]	Cross-sectional survey n=22	NA Assessed physical activity levels and metabolic variables	NA	22 males, 0 females; Mean age 39±-9 years; Mean duration since injury 17±9 years; 22 paraplegic (T2-L2); 22 complete	A. Fasting plasma glucose (mM/L) B. 2-hour postload glucose (mM/L) C. Fasting plasma insulin (uM/ml) D. 2-hour postlload insulin (uM/ml)	A. Inverse association with physical activity (r = -0.525; p <.05) B. Nonsignificant inverse association with physical activity (r= -0.34) C. Nonsignificant inverse association with physical activity (r = -0.40) D. No association with physical activity (r = -0.16)
E. Other						
No eligible studies						

Table 14. Description of exercise intervention studies with lipid or cardiovascular related outcomes in people with SCI

Reference	Study Design; Sample Size	Intervention Type	Frequency; Intensity; Duration	Subject Characteristics	Outcomes of Interest	Findings
A. Active exercise						
Durán, 2001[57]	Case series n=13	Training program including mobility, strength, coordination, aerobic resistance, and relaxation activities	3 sessions/week; 120 minutes/session; Target HR 40%-80% of maximal HR; 16 weeks of training	12 males, 1 female; Mean age 26.3±8.3 years; Duration since injury range 2-120 months; 13 paraplegic 4 T6 or higher; 9 T6 or lower	A. HDL (mg/dL) B. LDL (mg/dL) C. TC/HDL	A. No change from pre-training (38±11.6) to post-training (p <008) B. No change from pre-training (94±39.8) to post-training (p <0.25) C. No change from pre-training (4.75+/-2.15) to post-training (p <0.076)
de Groot, 2003[58]	Case series n=6 Random assignment to high vs. low intensity	Arm crank exercise program	3 sessions/week; 60 minutes/session; High intensity (HI; 70-80% heart rate reserve) vs. low intensity (LI; 40-50% HRR); 8 weeks of training	4 males, 2 females; Age range 19-54 years; Mean duration since injury 116±77 days; 6 paraplegic (C5-L1)	A. TC (post-test/pre-test) B. HDL (post-test/ pre-test) C. LDL (post-test/pre-test) D. TC/HDL-C (post-test/pre-test) F. TG (post-test/pre-test)	A. No significant differences for HI or LI groups (-11% and -6%) B. No significant differences for HI or LI groups (+13% and -5%) C. No significant differences for HI or LI groups (-14% and -5%) D. Reduction in HI group (-23%) but not LI group (0%) F. Reduction in HI group (31%) but not LI group (-5%)
El-Sayed, 2005[59]	Controlled case series n=12	Arm crank exercise program	3 sessions/week; 30 minutes/session; 60-65% VO2 peak; 12 weeks of training	5 paraplegic (SCI); 7 able-bodied (AB); Mean age 32±1.6 years for AB; Mean age 31±2.9 years for SCI	A. TC (mM/L) B. HDL-C (mM/L) C. TG (mM/L)	A. No change from pre-training to post-training in AB or SCI B. Increase (p <0.05) from pre-training to post-training in SCI C. No change from pre-training to post-training in AB or SCI

Table 14. Description of exercise intervention studies with lipid or cardiovascular related outcomes in people with SCI (continued)

Reference	Study Design; Sample Size	Intervention Type	Frequency; Intensity; Duration	Subject Characteristics	Outcomes of Interest	Findings
Midha, 1999[60]	Case series n=12 (includes 2 non-SCI subjects)	WAFT training program	2-3 sessions/week; 20-30 minutes, until target heart rate of 90% age-predicted maximum reached; Mean intensity 177 watts; 10 weeks of training	11 males, 1 female; Age range 22-58; Duration since injury range 4-29 years; 3 tetraplegic; 7 paraplegic; 1 stroke; 1 amputee	A. TC (mg/dL) B. TG (mg/dL) C. HDL-C (mg/dL) D. TC/HDL-C	A. Reduction from pre-training to post-training (185±42 to 170±32, p = 0.04) B. No change from pre-training to post-training (117±52 to 110±60) C. No change from pre-training to post-training (48±10 to 48±10) D. No change from pre-training to post-training (4±1 to 3.8±1)
Nash, 2001[61]	Case series n=5	Arm crank exercise program, with focus on resistance and endurance	3 sessions/week; 45 minutes/session; Power output 400 kpm + 100 kpm every 3 minutes until peak VO2 maximum; 3 months of training	5 males, 0 females; Age range 34-43 years; Mean duration since injury 4.8±1.4 years; 6 paraplegic; 5 complete (T6-L1)	A. TC (mg/dL) B. HDL (mg/dL) C. LDL (mg/dL) D. TC/HDL-C E. TG (mg/dL)	A. Nonsignificant decrease pre-training to post-training (183±26 to 167±33) B. Nonsignificant increase pre-training to post-training (41±5 to 45±12) C. Decrease pre-training to post-training (118±22 to 88±30, p = 0.05) D. Decrease pre-training to post-training (5.0±1.1 to 3.9±0.7, p = 0.05) E. Nonsignificant decrease pre-training to post-training (202±120 to 190±91)

Table 14. Description of exercise intervention studies with lipid or cardiovascular related outcomes in people with SCI (continued)

Reference	Study Design; Sample Size	Intervention Type	Frequency; Intensity; Duration	Subject Characteristics	Outcomes of Interest	Findings
Stewart, 2004[63]	Case series n=9	Body-weight supported treadmill training program	68 sessions (2.8±0.2 sessions/week); Velocity and % weight support varied for each participant; 6.0±0.3 months of training	8 males, 1 female; Mean age 31±3 years; Mean duration since injury 8.1 years; 9 incomplete (C4-T12)	A. TC (mM) B. HDL-C (mM) C. LDL-C (mM) D. TC/HDL-C (mM) E. TG (mM)	A. Decrease from pre-training to post-training (4.9±0.2 to 4.4±0.1, p = 0.021) B. Nonsignificant increase pre-training to post-training (1.3±0.2 to 1.4±0.3, p = .19) C. Decrease from pre-training to post-training (3.3±0.2 to 2.8±0.3, p = 0.046) D. Decrease from pre-training to post-training (3.8±0.3 to 3.1±0.3, p = .041) E. Nonsignificant decrease pre-training to post-training (1.5±0.2 to 1.3±0.2, p = .17)
B. Functional electrical stimulation exercise						
No eligible studies						
C. Passive exercise						
No eligible studies						
D. Self-reported physical activity						

Table 14. Description of exercise intervention studies with lipid or cardiovascular related outcomes in people with SCI (continued)

Reference	Study Design; Sample Size	Intervention Type	Frequency; Intensity; Duration	Subject Characteristics	Outcomes of Interest	Findings
Dallmeijer, 1999[70]	Case-series survey n=19	NA Assessed risk profiles and sport activity (hours/week) at t1 (during rehab) and t2 (1 year post-discharge)	NA	15 males, 4 females; Mean age 40.7±14.7 years; Mean duration since injury 760±169 days; 9 tetraplegic; 10 paraplegic	A. Difference TC (mM/L) B. Difference LDL-C (mM/L) C. Difference TC/HDL-C (mML) D. TG (mM/L)	A. Inverse association with sport activity (r = -0.35; p = 0.008) B. Inverse association with sport activity (r = -0.28; p = 0.003) C. Inverse association with sport activity (r = -0.49; p = 0.035) D. No change in values from t1 to t2
Dallmeijer, 1997[69]	Cross-sectional survey n=24	NA Compared lipid levels between physically active (1.5-6.0 hours/week) and sedentary SCI patients	NA	24 males, 0 females 11 physically active 13 sedentary 24 tetraplegic 4 incomplete 20 complete	A. TC (mM/L) B. HDL (mM/L) C. LDL-C (mM/L) D. TC/HDL-C E. TG	A. No difference between groups B. Higher for physically active (1.1±0.21) than sedentary (0.95±0.20) (p <0.05) C. No difference between groups D. Lower for physically active (1.34±0.67) than sedentary (1.96±1.01) (p <0.05) E. Nonsignificantly lower for physically active (1.34±0.67) than sedentary (1.96±1.01)

Table 14. Description of exercise intervention studies with lipid or cardiovascular related outcomes in people with SCI (continued)

Reference	Study Design; Sample Size	Intervention Type	Frequency; Intensity; Duration	Subject Characteristics	Outcomes of Interest	Findings
Davies, 2002[54]	Cross-sectional survey n=97	NA Assessed physical activity as determinant of cardiovascular morbidity (both measurements made with valid and reliable scale)	NA	87 males, 10 females; Mean age 47.5±4.5 years; Mean duration since injury 15.9±10.1 years; 41 tetraplegic 55 paraplegic 1 undetermined 32 complete 62 incomplete 3 undetermined	Cardiovascular morbidity	No association with physical activity
Janssen, 1997[71]	Cross-sectional survey n=37	NA Assessed sport activity (hours/week) as determinant of lipid profiles	NA	37 males, 0 females; Age range 19-71 years; Duration since injury range 4-33 years; 8 tetraplegic 29 paraplegic 23 complete	A. TC (mM/L) B. HDL (mM/L) C. LDL-C (mM/L) E. TC/HDL-C F. TG	A. Inverse association with physical activity ($r = -0.33$; $p < 0.05$) B. No association with physical activity ($r = -0.14$) C. Inverse association with physical activity ($r = -0.40$; $p < 0.01$) E. No association with physical activity ($r = -0.17$) F. No association with physical activity ($r = 0.06$)

Table 14. Description of exercise intervention studies with lipid or cardiovascular related outcomes in people with SCI (continued)

Reference	Study Design; Sample Size	Intervention Type	Frequency; Intensity; Duration	Subject Characteristics	Outcomes of Interest	Findings
Jones, 2004[14]	Cross-sectional case-control survey n=20	NA Assessed physical activity levels (minutes/week) and metabolic variables	NA	20 males, 0 females; Age range 16-52 years; Mean duration since injury 10.3±1.8 years; 11 tetraplegic (C4-C7) 9 paraplegic (T5-L5)	A. TC/HDL (mM/L) B. Log HDL (mM/L)	A. Inverse association with physical activity (r = -0.49; p <0.05) B. Direct association with physical activity (r = 0.46; p <0.05)
Manns, 2005[13]	Cross-sectional survey n=22	NA Assessed physical activity levels and metabolic variables	NA	22 males, 0 females; Age range 39±9 years; Mean duration since injury 17±9 years; 22 paraplegic (T2-L2); 22 complete	A. HDL-C (mM/L) B. TG (mM/L)	A. Direct association with physical activity (r = 0.625; p <0.05) B. No association with physical activity (r = -0.256)
E. Other						
Chen, 2006[72]	Case series n=16	NA Participation in weight management program where exercise behavior was taught	Followup testing at 12 weeks and 24 weeks	9 males, 7 females; Age range 21-66 years; Mean duration since injury 17.5 years 15 SCI 1 spinal cord illness	A. TC (mg/dL) B. HDL-C (mg/dL) C. LDL-C (mg/dL)	A. Nonsignificant decrease pre-program to post-program (-5.8±20.9, p = 0.28) B. Decrease from pre-program to post-program (-3.2±5.4, p = .03) C. Nonsignificant decrease pre-program to post-program (-1.8±22.1, p = .76)

Table 15. Diet and pharmacologic therapy studies for prevention and/or treatment of carbohydrate and lipid metabolism disorders in people with spinal cord injury and disease

Reference Study Design	Intervention Type	Subject Characteristics; Duration	Outcomes of Interest	Findings
A. Diet therapy				
Szlachcic, 2001[20] Clinical controlled trial	Group 1 (subjects had total cholesterol >200mg/dl): Dietary intervention referral (Seen ≥2 times/week, followed recommendations of American Heart Association and American Dietetic Association Guidelines) (n=86) Group 2 (subjects had total cholesterol <200mg/dl): Not referred for dietary intervention (n=136)	222 subjects with SCI ≥2 years. Male 89% (n=198), females 11% (n=24). Mean age 38.5±11 years White: 22% (n=49) African American: 21% (n=47) Hispanic: 54% (n=120) Asian: 2% (n=4) Mean duration since injury Group 1 subjects significantly older (42.8 vs. 35.7, p <0.0001) and had longer post-injury duration (15.6 vs. 11.1, p <0.0001). Paraplegia, complete: 38% Paraplegia, incomplete: 12% Tetraplegia, complete: 38% Tetraplegia, incomplete: 16% Study duration: 16 months (mean)	A. TC B. LDL C. TG D. HDL	<u>Comparison of baseline to followup values</u> A. TC Group 1: 234±31 to 224±34, p <0.001 Group 2: 162±23 to 166±30, p = 0.06 B. LDL Group 1: 159±28 to 151±28, p = 0.004 Group 2: 101±21 to 104±27, p not significant C. TG Group 1: 183±161 to 162±103, p not significant Group 1: 99±59 to 104±71, p not significant D. HDL No significant effects
Chen, 2006[72] Single group uncontrolled trial	Weight management program consisting of 12 classes for 12 weeks, primarily led by registered dietician. Classes covered nutrition, exercise, and behavior modification. Dietary approach utilized a time-calorie displacement diet.	16 overweight (BMI ≥25) subjects, Male 56% (n=9), female 44% (n=7) Mean age 44: (range 21-66) White: 81% (n=13) African American: 19% (n=3) Mean duration since injury: 17.5 Years since injury (15) or illness (1) Study duration: 12 weeks and 24 weeks	A. TG B. LDL C. HDL	<u>Mean change from baseline during program intervention (week 12) (mg/dl)</u>. A. TG -5.8±20.9 (baseline 201.7±30.2), p = 0.28 B. LDL -1.8±22.1 (baseline 136.2±20.5), p = 0.76 C. HDL -3.2±5.4 (baseline 43.1±14.9), p = 0.03 <u>Mean change from baseline</u>

Table 15. Diet and pharmacologic therapy studies for prevention and/or treatment of carbohydrate and lipid metabolism disorders in people with spinal cord injury and disease (continued)

Reference Study Design	Intervention Type	Subject Characteristics; Duration	Outcomes of Interest	Findings
				during postintervention followup (week 24) (mg/dl). A. TG 0.3±24.1, p = 0.96 B. LDL -4.2±18.1, p = 0.42 C. HDL -0.9±5.4, p = 0.59
B. Pharmacologic therapy				
No studies reporting				

Chapter 4. Discussion

Prevalence and Risk Estimates

The present systematic review evaluated published evidence regarding the prevalence of lipid and carbohydrate disorders, CVDs, and mortality in adults with chronic posttraumatic SCI. We attempted to assess the contribution of risk of these disorders to CVD morbidity and mortality and whether they vary according to SCI status or compared to able-bodied individuals. The potential efficacy and harms of interventions to improve carbohydrate and lipid disorders in this population was also examined. This information was synthesized to determine if compared to able-bodied adults individuals with SCI:

1. have a different prevalence of carbohydrate disorders;
2. have increased risk of CVD morbidity and mortality,
3. have CVD and/or carbohydrate/lipid benefits from specific interventions;
4. should have thresholds/methods for detection or treatment modified.

The level of evidence addressing these issues is low. Most studies were retrospective, small, lacked adequate controls, and did not assess or adjust for confounding factors. Outcome measure definitions varied widely. However, limited low quality data suggest that adults with SCI are not at markedly higher risk of carbohydrate and lipid disorders or CVD than appropriately matched able-bodied individuals. Except for assessment of body composition/obesity, evidence does not support that diagnostic and treatment thresholds or methods for carbohydrate and lipid disorders should differ in SCI compared to able-bodied individuals. Assessment of insulin resistance and impaired glucose tolerance are not routinely performed in able-bodied individuals. The effectiveness of screening to improve clinical outcomes by detection of pre-diabetes (impaired fasting glucose or impaired glucose tolerance), insulin resistance, and diabetes in asymptomatic adults has not been demonstrated.[73] Use of these tests is limited due to their inconvenience, complexity of testing requirements, costs, and current lack of accuracy. The OGTT is inconvenient and not ordered by most physicians to diagnose diabetes, even among those at risk. Additionally, about one-half with IGT or OGTT would have normal tests if repeated. Similar concerns exist with the criteria used to define impaired fasting glucose. Because the glucose concentration distribution is unimodal, the choice of cutpoints used to designate abnormalities of carbohydrate metabolism is arbitrary. Very little high quality data exist on the independent role of gender, race, disease severity, level, or duration. Any observed differences in prevalence or risk is relatively small in magnitude, inconsistent in direction according to study or risk characteristic, and/or could be confounded by differences in other known risk factors: age, smoking, exercise status, family history, etc.).

Assessment of obesity using BMI, is likely to be inaccurate and underestimate body fat assessment in adults with SCI. For other measures of carbohydrate and lipid abnormalities there is no high quality evidence to indicate that different thresholds (or biomarkers) should exist for SCI individuals compared to able-bodied adults to identify patient risk level, define disease status, or initiate treatment. Little data exist on the effects of interventions to improve carbohydrate and lipid abnormalities, including the effect of exercise.

Several previous reports and reviews have suggested that the prevalence of carbohydrate and lipid disorders, as well as cardiovascular morbidity and mortality, is much higher in adults with SCI compared to able-bodied individuals. However, the prevalence of insulin resistance, metabolic syndrome, diabetes mellitus, impaired glucose tolerance, dyslipidemia, and obesity in

a population is highly dependent upon demographics of the population, including most importantly the age distribution, but also socioeconomic status and race/ethnicity. The dependence of these conditions on population characteristics makes it difficult to make between study comparisons, since the population characteristics vary greatly both between and within studies. These factors may explain the wide variation in study prevalence estimates as well as the relative risk compared to different able-bodied control populations. Additionally, definitions of disease or condition may also alter prevalence estimates. In the one included study assessing metabolic syndrome, the definitions used by the authors for hypertension, obesity, diabetes, and lipid disorders are not widely accepted or utilized in studies in able-bodied adults. Their definitions increase the estimated prevalence of disease in their population and relative to studies of able-bodied individuals that use established definitions.

Our findings of cardiovascular disease prevalence and mortality were lower than frequently reported. Previous reviews often incorporated a broad definition of CVD.[76] Definitions included in these reports were hypertension, as well as self-reported signs and symptoms of leg swelling or palpitations.[56] The clinical significance and the relation to CVD of leg swelling and palpitations are not clear. Accurate assessment of blood pressure in SCI individuals is problematic. No validated definitions or thresholds for hypertension interventions exist in SCI patients due to blood pressure measurement issues related to autonomic dysreflexia, muscle spasticity or hypotonicity, use of arms for wheelchair transportation, and, most importantly, the lack of long-term data correlating blood pressure and treatment with morbidity and mortality in SCI individuals. These highly prevalent conditions are much more common and inflate prevalence estimates of cardiovascular disease in SCI individuals but result in less morbidity than myocardial infarction or stroke. Use of self-reported disease classification or death certificates for cause of death may also result in biased estimates of disease prevalence or mortality. Several factors may contribute to the increased prevalence of undiagnosed CVD in SCI individuals, including access and quality of care, asymptomatic angina in patients with diabetes or upper level injury,[77,78] and metabolic syndrome, unstable blood pressure, and cardiac rhythm.[79,80] Screening to detect asymptomatic heart diseases, including coronary heart disease, arrhythmias, and autonomic dysreflexia, may result in higher prevalence of CVD in this population.

Prevalence of CVD in aging SCI individuals can be attributable to age rather than injury. Patients differed by the prevalence of risk factors prior to injury and by age at the time of injury, both could modify the association between SCI and CVD. Indeed, recently published retrospective analysis found that presence of cardiovascular disease prior to injury was associated with a 280 percent increase in risk of death (relative risk 2.8, 95 percent CI 1.22; 6.40).[81] For each additional year of age at injury, the relative risk of dying was increased by 8 percent (RR 1.08, 95 percent CI 1.06; 1.09).[81]

Whether the reported increased risk of all CVD in tetraplegic compared to paraplegic individuals can be interpreted as an evidence of higher morbidity[53,76] requires additional studies. Limited evidence suggests that CVD may contribute to approximately 20 percent of all deaths in SCI patients[1,36,49,52] and coronary heart disease in 9[1-3] to 13[81] percent of all deaths.[1-3,81] There is insufficient evidence to determine whether percentage of deaths due to CVD differs in SCI adults compared to appropriately matched able-bodied individuals. One study suggested that presence of heart diseases was associated with an increased risk of death by 3.7 fold in SCI patients independent of age and other risk factors.[52] Limited evidence suggests that the contribution of

different forms of heart disease (e.g., ischemic versus nonischemic coronary heart disease) to overall CVD mortality in SCI patients may differ from the general population.

CVD morbidity and mortality in SCI patients showed inconsistent differences compared to the general population. Survival rates in aging injured patients can depend on severity of CVD and quality of care. Whether the incidence of CVD was not well documented in the studies or the prognosis of CVD is worse in the SCI than in the able-bodied population is unclear. Case fatality from CVD in SCI patients compared to the general populations is not well established. However, some evidence suggested that case fatality rate for pneumonia was higher in injured than in the general population.[109]

The independent contribution of diabetes and impaired glucose tolerance on CVD prevalence in adults with versus without SCI has not been reported. The association between metabolic control and CVD in adults with SCI remains unclear. Vascular complications were not different in SCI users of the VA health care system who were diabetic compared to diabetic able-bodied veterans.[37] The role of lipid disorders on CVD in SCI individuals is not well documented and needs future investigation.

Some potentially eligible studies that may be cited as evidence of altered risk were excluded due to small sample size that limited generalizability (n=45, number of SCI individuals in each study ranged from 1-77). These studies were also of low quality and relevance because they were from a single center, not from the United States, lacked controls, and/or did not assess clinically relevant carbohydrate and lipid disorders. The impact of these studies on our overall findings regarding carbohydrate, lipid and body composition disorder prevalence, and subsequent clinical decision making is likely to be small. Only 17 excluded studies had control groups. The largest study reporting glucose intolerance and insulin resistance in the United States lacked controls, was comprised of 57 adults from a single center, and was published in 1983. The largest excluded *controlled* study of lipid disorders was a single center report comprised of 60 young SCI adults (mean age = 28 years) and 28 age and gender matched healthy able-bodied controls. Serum LDL cholesterol was higher (109 mg/dL vs. 91 mg/dL; $p = 0.04$) and HDL cholesterol lower (33 mg/dL vs. 44 mg/dL; $p = 0.004$) in SCI adults versus controls. The authors concluded that "serum lipoprotein levels should not be ignored for the followup of the patients with spinal cord injury."[75] We agree with their conclusion. Other excluded studies were of even lower quality and relevance to health care in the United States because they were smaller, from a single center, not from the United States, lacked controls, and/or did not assess clinically relevant carbohydrate and lipid disorders.

Role of Exercise, Diet, and Pharmacologic Interventions

The evidence that exercise programs alter carbohydrate and lipid outcomes is of poor quality and inconclusive. There were relatively few consistent findings pertaining to plasma glucose, two-hour post-load glucose, fasting insulin, or two-hour post-load insulin. Similarly, little consistency was reported between studies for HDL-C, TC/HDL, and TG. Results may have indicated some overall post-training benefits for outcomes of TC and LDL-C. While many reported findings appear to be encouraging and are suggested as such in the primary papers as well as past reviews,[85,110] caution is warranted when interpreting these studies. There was a general lack of quantity, quality, and consistency in methods and outcomes across studies. Overall, reports were based on short-term exercise protocols, often involved carefully recruited hospital- and/or clinic-based patients, and failed to consider implementation or sustainability of

exercise interventions in community-based populations. Only one study examined the effects of exercise on coronary heart disease outcomes.[54]

The exercise described in these papers varied considerably from one study to the next. In the cross-sectional surveys,[13,14,54,69-71] parameters of physical activity were rarely reported. Generally, questions pertaining to amount of physical activity per week were asked.[14,69-71] In exercise intervention studies, little consistency in duration, mode, frequency, or intensity of the exercise programs existed. The length of the exercise protocols ranged from 8 to 52 weeks; most were only 8 to 16 weeks in duration.[57-61,64-67] These studies may not have been long enough to impart measurable physiological benefits to study participants. Further, the types of exercise, frequency of sessions, and intensity of exertion were also varied, making results about preferred forms of exercise inconclusive.

Patient populations and outcome measures were also highly inconsistent. Study designs consisted only of case series, involving small numbers of subjects in hospital or clinical settings, or the cross-sectional surveys. The total number of subjects participating was low (n=101 for carbohydrate studies and n=292 for lipid studies) and, for the most part, subjects were not randomly selected from broader patient or community populations. These methods are considered highly susceptible to bias. Subjects that participated in the case series studies were likely a highly-motivated group of individuals, nonrepresentative of the broader population of those with SCI. Little information was presented on those asked to participate but who chose to abstain. Further, the measures of self-reported exercise or physical activity utilized in the cross-sectional surveys likely led to misclassification through recall error and social desirability issues. Even if measurement of physical activity was accurate, the cross-sectional nature of these surveys leaves results highly questionable due to possible confounding. For example, those who did not exercise may have had underlying carbohydrate and/or lipid metabolism disorders. This would make physical activity positively correlated, but not necessarily causally associated, with better carbohydrate and lipid measures.

None of the intervention studies used improvement in glycated hemoglobin (A1C) as an outcome. The effect of exercise on blood glucose often is delayed for several hours. A1C reflects the integrated effect on blood glucose throughout the day and A1C is easy to measure. Therefore, it would likely be preferable for future studies to track A1C changes rather than transient and more difficult to measure insulin or glucose levels or areas under the insulin and glucose curves for a few hours.

Even if consistent, convincing data were generated from these types of studies, there is no evidence for subsequent, successful translation of exercise interventions to a lesser motivated or community-based SCI population. Effectiveness of exercise interventions has yet to be studied in a population of individuals with SCI. Implementation and sustainability of exercise in this population is likely to be more challenging than in an able-bodied population, given the environmental barriers and physical risks, such as exercise-induced autonomic dysfunction and musculoskeletal injury.[8,26] The risk of further, unperceived health problems, such as silent ischemia, in denervated subjects should be carefully considered prior to implementing exercise-related recommendations or policies.

Exercise and dietary programs among able-bodied individuals have demonstrated a modest improvement in carbohydrate and lipid parameters among selected highly motivated individuals. Translation of these findings to community settings of SCI adults has not been demonstrated, and even the effectiveness in the general able-bodied population is unclear. For example, a recent randomized trial evaluated the effects of 22 weeks of aerobic training, resistance training, or both

(three times per week) on glycemic control in 251 able-bodied adults with Type 2 diabetes.[86] Combined training resulted in a 1 percent absolute reduction in glycated hemoglobin values versus sedentary controls. Reductions due to either resistance or aerobic training alone were about one-half that seen with combination therapy. Their was no difference in lipid values, blood pressure, lean body mass, fat mass, or percent body fat of any of the exercise programs versus controls. Adverse events were more common in the exercise group, and 14 percent of those randomized to exercise dropped out.

Ultimately, higher-quality studies examining effects of exercise on the health of subjects with SCI need to be conducted. While carbohydrate and lipid metabolism measurements are important, intermediate measures, extending such studies into longer term outcomes such as diabetes mellitus, coronary heart disease, and survival are important. In addition, clinical and research questions pertaining to obesity in individuals with SCI remain to be answered. The most appropriate measurements and definition of obesity for those with SCI have not been identified at this time. To continue the use of BMI as a measurement of obesity, it must be assessed whether current BMI cutpoints for the general population can be extrapolated to those with SCI, or whether cutpoints need to be specific to this population, considering both SCI type and level.

Little information exists regarding the impact of dietary or pharmacologic interventions on adults with SCI. Recommendations currently exist for disease definitions for diabetes and lipid abnormalities in able-bodied adults. Several large RCTs have established the effectiveness of statins used for primary prevention in able-bodied adults with mean baseline LDL cholesterol of approximately 150 mg/dL. Many of these individuals had other competing risks such as hypertension and cigarette use. Use of statins in able-bodied adults with diabetes have been demonstrated to be effective even if baseline LDL-C is less than 130 mg/dL. The mean baseline LDL-C in populations of SCI individuals included in this review was 125 mg/dl. Effectiveness and harms associated with statins may differ in SCI individuals compared to able-bodied adults. However, unless contrary data exist, it seems reasonable to extrapolate these findings and recommendations for similar pharmacologic intervention thresholds for treatment of lipid abnormalities in SCI individuals as used in able-bodied adults. There have been no primary prevention studies among individuals with low HDL-C. Recent studies of treatments to raise HDL-C have been stopped due to harm. Existing recommendations to assess cardiovascular risk for able-bodied individuals suggest that all adults should have a complete lipid profile, including HDL and LDL cholesterol levels, as well as family history, smoking status, and gender. The treatment recommendations should be based on that comprehensive risk assessment. Future studies are needed to determine if SCI should be included as an independent risk factor.

With regard to interventions to prevent and treat diabetes, currently no large scale randomized trials have demonstrated that aggressive control of Type 2 diabetes reduces cardiovascular complications. A recent systematic review assessed the comparative effectiveness and safety of oral medications for Type 2 diabetes mellitus. The authors reported that there was no definitive evidence about the comparative effectiveness of oral diabetes agents on all-cause mortality, cardiovascular mortality or morbidity, peripheral arterial disease, neuropathy, retinopathy, or nephropathy.[82] Two more recent meta-analyses of thiazolidinediones have been conducted. Among able-bodied patients with impaired glucose tolerance or Type 2 diabetes (n=14,291), rosiglitazone use for at least 12 months was associated with an increased risk of myocardial infarction and heart failure. There was no difference in increase risk in cardiovascular mortality.[83] A review of pioglitazone (n=16,390) showed a significantly lower risk of death myocardial infarction or stroke among patients with Type 2 diabetes and

inadequately glycemic control. Serious heart failure was increased.[84] Unless future RCTs demonstrate evidence to the contrary, a reasonable policy would be to implement existing diabetes detection and management guidelines used for able-bodied adults.

Conclusions and Policy Implications

Available evidence regarding the prevalence, impact, and outcomes of carbohydrate and lipid disorders in adults with chronic SCI is weak. Evidence is limited by relatively few studies, small sample size, lack of appropriate control groups, failure to adjust for known confounding variables, and variation in reported outcomes. However, the existing evidence does not indicate that adults with SCI are at markedly greater risk for carbohydrate and lipid disorders or subsequent cardiovascular sequelae than able-bodied adults. Cardiovascular diseases are among the leading causes of death in aging patients with chronic SCI. Therefore, patients with SCI should be assessed and treated according to existing guidelines for able-bodied individuals to reduce cardiac morbidity and mortality in this population associated with carbohydrate and lipid disorders.

BMI to assess obesity and body composition is likely inaccurate and underestimates fat mass in adults with SCI. Available evidence does not support establishing different thresholds to define and treat abnormal traditional lipid and carbohydrate measures or to utilize other markers (e.g., insulin sensitivity or impaired glucose tolerance) for SCI individuals compared to able-bodied adults. Because evidence is weak, it is not possible to conclude that an increased risk of these disorders and their subsequent cardiovascular sequelae do not exist or that use of alternative measures of abnormality may not someday be found beneficial.

Individuals with SCI may have unique physiologic differences compared to able-bodied individuals. Therefore, caution is advised in attempting to extrapolate findings from studies conducted in able-bodied adults evaluating efficacy and harms of interventions to improve carbohydrate, lipid disorders and subsequent coronary vascular disease.

If clinical uncertainty regarding carbohydrate and lipid disorder risks in adults with SCI and determining the most appropriate interventions remain high priority areas, then future high quality research is needed. Until that time, a reasonable policy would be to use similar criteria to identify and treat carbohydrate and lipid disorders (outside of body composition assessment) in adults with SCI as currently recommended for able-bodied adults. The role of exercise in SCI individuals also represents a unique challenge and requires further exploration into the benefits, risks, and potential implications of broader based exercise programs. This systematic review did not assess the diagnosis and treatment of hypertension in SCI individuals or the other potential benefits of diagnosis and management of SCI individuals, such as improved wound healing. Additional clinical and research activities are needed to address these issues.

Future Research

A major gap in the evidence is the lack of high-quality prospective epidemiologic studies assessing the prevalence and impact of lipid and carbohydrate abnormalities and corresponding CVD complications in SCI individuals, especially compared to appropriately matched able-bodied controls. Future research could include a large prospective multicenter cohort study of adults with SCI. Risk assessment should be started at the time of injury and continued during long-term followup. Prevalence and incidence assessment needs to be objective rather than self

reported. Inclusion of baseline and followup physiologic and serologic values (e.g., body composition measures, actual lipid and carbohydrate laboratory values) and standardized outcomes are made according to well-recognized diagnostic criteria of heart diseases. Expansion of existing cohort studies in the VA, a large non-VA cohort study, and future RCTs that aim to test whether more aggressive screening or treatment within SCI populations actually reduces disease prevalence, morbidity, and mortality could be initiated. Additional information on women is needed.

To a large extent, research within the VHA patient population has provided an important foundation to the current knowledge, particularly within the United States, regarding the prevalence of carbohydrate and lipid disorders and relevant considerations in persons with SCI. If there is continued concern that adults with chronic SCI have a different prevalence than adults without SCI, then future research would benefit from an expansion of the existing cohort studies in the VA, a large non-VA cohort study, and future RCTs that aim to test whether more aggressive screening or treatment within SCI populations actually reduces disease prevalence, morbidity, and mortality.

The VA administrative and clinical datasets and data from other large health care systems provide researchers with a wealth of information regarding the epidemiology of carbohydrate and lipid disorders with SCI patients. These datasets allow for rapid estimation of the magnitude of disease burden from carbohydrate and lipid disorders and can help to develop hypotheses about the role SCI may play in the development of disease. However, administrative datasets often suffer from selection bias in terms of the persons included and the measurements obtained. Therefore, such datasets need to be enriched with prospective cohort style data collection. This can be accomplished by designing a registry of adults with SCI and collecting a baseline battery of key measurements on all persons. This comprehensive set of baseline measurements can then be combined with standard outcomes data collected in these healthcare settings to provide a detailed description of the natural history and etiology of various diseases.

While in many ways the VHA provides an ideal U.S. setting to obtain important information on persons with SCI, it must be accompanied by complementary research on representative SCI persons from health systems outside of the VA. This is particularly important, since women are currently underrepresented in VHA datasets, and veterans have often been found to have more competing comorbidities than nonveteran populations,[37] which can make generalizations difficult without complementary non-VA data. Additionally, current reports indicate that approximately 90 percent of SCI subjects were men. It is not known if this is representative of the U.S. SCI population or only those reporting this information.

RCTs will be needed to further extend the information obtained from future prospective observational studies. Regardless of whether or not future trials indicate that individuals with SCI are at an increased risk of carbohydrate and/or lipid disorders, it is clear that, like the general population, a significant number of SCI individuals do have carbohydrate and lipid disorders and techniques for treating these disorders may need to be modified to meet the specific needs of those with SCI to ensure that they are being most appropriately treated. RCTs will therefore be needed to compare the effectiveness of any such modifications in treatment technique and intensity, including the same pharmacological agents recommended for the general population and specific for SCI patients' treatment options that would target impaired glucose tolerance and insulin sensitivity.

If prospective cohort studies identify an increased risk in adults with SCI, RCTs will be needed to further extend the information. Techniques for identifying and treating these

carbohydrate and lipid disorders and CVDs may need to be modified to meet the specific needs of those with SCI. In addition, continued clinical and research questions pertaining to obesity in individuals with SCI remain to be answered. These include identification of the most appropriate measurements and definition of obesity for those with SCI, and whether current BMI cutpoints for the general population can be validly extrapolated to those with SCI.

RCTs evaluating the potential effectiveness and harms of interventions to alter CVD risk factors and reduce CVD incidence, morbidity, and mortality are needed. The level of injury, neurological impairment, and other known or potential confounders including smoking status, hypertension, family history, race, age, diabetes, infections including, socioeconomic status, and quality of health care should be analyzed as possible effect modifiers of the association between well-known risk factors and cardiovascular morbidity and mortality.

Given the variation in design across studies, the lack of consistent findings in this review was not surprising. While improved studies will be challenging due to limited resources, complicated study questions, a relatively small subject population, and invasive intervention, policy recommendations cannot be generated until higher quality evidence is available. Consistent, higher quality research on exercise and metabolic and cardiovascular health in SCI patients is needed. Studies examining efficacy as well as effectiveness of exercise interventions are needed.

Continued research should be conducted to gain a better idea of the important barriers to exercise experienced by individuals with SCI and to develop novel methods to overcome these barriers. Preliminary studies may also assess which patients are most in need of intervention, the best types of exercise programs and equipment, and how to modify them based on characteristics of the injury. For example, telemedicine approaches to home-based exercise programs could potentially help overcome barriers to accessing traditional facilities or equipment. Whether qualitative or quantitative, this preliminary work would not only inform the development of exercise programs but also the research used to evaluate efficacy and effectiveness.

Accomplishing the level of research needed will likely require a collaboration of researchers across sites. Convening a consortium of experts is a practical first step. Cooperative research groups could determine the most appropriate and pragmatic study parameters, including intervention type and outcome measures, and could propose the most feasible quality studies. RCTs and prospective epidemiologic studies for individuals with SCI could both contribute enhanced knowledge to the current evidence base. While such studies are resource intensive, these accomplishments could perhaps be better achieved through the pooling of resources, either by funding agencies, or by researchers through multiple site collaborations. The VA medical system, the SCI model systems sites, or the National SCI Statistical Center at the University of Alabama Birmingham may be poised to lead such multi-site collaboration and studies.

Short-term, intermediate outcomes of exercise, as were typically reported in the current studies, may not be ideal or definitive measurements for this type of research. Studies ideally would focus on long-term clinically relevant outcomes such as prevention of diabetes mellitus, coronary heart disease, and mortality.

An RCT would provide the best evidence for or against the use of exercise to prevent or control carbohydrate and lipid disorders among those with SCI, though conducting adequately sized studies would be difficult and would require cooperative group participation. Studies on exercise and metabolic and cardiovascular outcomes in the SCI population will be more definitive if important demographic and injury parameters are considered. Key variables that should be included in future studies are patient age, race, and gender; comorbid conditions; baseline lipid and carbohydrate related measures; duration, level, and completeness of SCI;

functional status; baseline physical activity; exercise program type, frequency, intensity, and duration; and life satisfaction and other important psychosocial variables. RCTs and prospective epidemiologic studies with adequate numbers of participants should provide the least confounded evidence for or against exercise programs if the intervention and control groups are appropriately balanced and/or stratified by these variables.

Further research will be needed to translate any findings of exercise efficacy into effective community-based interventions. Even if efficacy is promising, it will remain to be seen if these interventions are feasible in a community setting, and if the interventions, as well as health outcomes, are sustainable over time. Further evidence on how best to motivate individuals to sustain exercise, while preventing and identifying potential harms, will be needed.

RCTs evaluating the potential effectiveness and harms of pharmacologic and dietary interventions to alter CVD risk factors (diabetes, lipid abnormalities, and/or obesity) and reduce CVD incidence, morbidity, and mortality may be needed if there is continued concern that results may differ in SCI populations compared to able-bodied adults.

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(Note that there is a separate set of references at the end of the evidence tables in Appendix E and reference numbers are different than those in the text of the report)

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List of Acronyms/Abbreviations

AB	Able bodied
AE	Active exercise
AHRQ	Agency for Healthcare Research and Quality
BMI	Body mass index
C	Cholesterol
CDC	Centers for Disease Control
CI	Confidence interval
CVD	Cardiovascular disease
DXA	Dual energy x-ray absorptiometry
ECG	Electrocardiogram
EPC	Evidence-based Practice Center
FES	Functional electrical stimulation
HDL	High-density lipoprotein
HI	High intensity
HRR	Heart rate reserve
ICD	International classification of diseases
IGT	Impaired glucose tolerance
LBBB	Left bundle branch blocks
LDL	Low-density lipoprotein
LI	Low intensity
LVH	Left ventricular hypertrophy
MET	Metabolic equivalents
N	Number
NA	Not applicable
OGTT	Oral glucose tolerance test
OR	Odds ratio
PE	Passive exercise
RCT	Randomized controlled trial
SCI	Spinal cord injury
TC	Total cholesterol
TEP	Technical expert panel
TG	Triglycerides
VA	Veterans Affairs
VHA	Veterans Health Administration
WAFT	Wheelchair aerobic fitness trainer
WMD	Weighted mean difference

Appendixes

Appendix A: Technical Expert Panel Members and Affiliation

TEP Member	Affiliation
Yuying Chen, MD, PhD	Physical Medicine and Rehabilitation University of Alabama at Birmingham
David R. Gater, Jr, PhD, MD	Department of Veterans Affairs Hunter Holmes McGuire Medical Center
Leonard Pogach, MD	Department of Veterans Affairs New Jersey Health Care System
Suparna Rajan, PhD, RD	Department of Veterans Affairs Puget Sound Health Care System

Appendix B. Exact Search Strings

Medical Subject Headings Terms and Key Words	Number of Retrieved References
"Spinal Cord Injuries" [MeSH] AND ("Cardiovascular Diseases" [MeSH] OR "Cardiology" [MeSH]) NOT review NOT letter NOT editorial NOT Case Reports Limits: All Adult: 19+ years, Entrez Date from 1990/01/01 to 2007/07/01, English, Humans	233
"Spinal Cord Injuries" [MeSH] AND Cardiovascular Diseases Limits: English, Humans	1,467
"Spinal Cord Injuries" [MeSH] AND Cardiovascular Diseases Limits: English, Randomized Controlled Trial, Humans	20
"Spinal Cord Injuries" [MeSH] AND Cardiovascular Diseases Limits: English, Clinical Trial, Humans	55
"Spinal Cord Injuries" [MeSH] AND "Cardiovascular Diseases" [MeSH] Limits: English, Clinical Trial, Humans	55
"Spinal Cord Injuries" [MeSH] AND "Cardiovascular Diseases" [MeSH] Limits: English, Randomized Controlled Trial, Humans	20
"Spinal Cord Injuries" [MeSH] AND "Cardiovascular Diseases" [MeSH] Limits: English, Meta-Analysis, Humans	1
"Spinal Cord Injuries" [MeSH] AND "Cardiovascular Diseases" [MeSH] Limits: English, Humans	1,464
"Spinal Cord Injuries" [MeSH] AND "Cardiovascular Diseases" [MeSH] AND "Insulin Resistance" [MeSH] Limits: English, Humans	2
"Cardiovascular Diseases" [MeSH] Limits: English, Humans	780,975
("Cardiovascular Diseases" [MeSH] OR "Cardiology" [MeSH]) NOT review NOT letter NOT editorial Limits: Adult: 19-44 years, Middle Aged: 45-64 years, Middle Aged + Aged: 45+ years, Aged: 65+ years, 80 and over: 80+ years, English, Humans	402,080
("Cardiovascular Diseases" [MeSH] OR "Cardiology" [MeSH]) Limits: Adult: 19-44 years, Middle Aged: 45-64 years, Middle Aged + Aged: 45+ years, Aged: 65+ years, 80 and over: 80+ years, English, Humans	456,995
“Spinal Cord Injuries” [MeSH] NOT review NOT Letter NOT editorial AND "Diabetes Complications" [MeSH] NOT review NOT letter NOT editorial Limits: Adult: 19-44 years, Middle Aged: 45-64 years, Middle Aged + Aged: 45+ years, Aged: 65+ years, 80 and over: 80+ years, English, Humans	19
"Trauma, Nervous System" [MeSH] AND ("Spinal Cord" [MeSH] OR "Spinal Cord Injuries" [MeSH] OR "Spinal Cord Diseases" [MeSH]) NOT review NOT letter NOT editorial AND ("Cardiovascular Diseases" [MeSH] OR "Cardiology" [MeSH]) Limits: Adult: 19-44 years, Middle Aged: 45-64 years, Middle Aged + Aged: 45+ years, Aged: 65+ years, 80 and over: 80+ years, English, Humans	669

"Autonomic Dysreflexia" [MeSH] AND ("Cardiovascular Diseases" [MeSH]) NOT review NOT letter NOT editorial	
Limits: Adult: 19-44 years, Middle Aged: 45-64 years, Middle Aged + Aged: 45+ years, Aged: 65+ years, 80 and over: 80+ years, English, Humans	17
"Autonomic Dysreflexia" [MeSH] AND ("Cardiovascular Diseases" [MeSH])	
Limits: Adult: 19-44 years, Middle Aged: 45-64 years, Middle Aged + Aged: 45+ years, Aged: 65+ years, 80 and over: 80+ years, English, Humans	23
"Brown-Sequard Syndrome" [MeSH] AND ("Cardiology" [MeSH])	
Limits: Adult: 19-44 years, Middle Aged: 45-64 years, Middle Aged + Aged: 45+ years, Aged: 65+ years, 80 and over: 80+ years, English, Humans	0
"Brown-Sequard Syndrome" [MeSH] AND ("Cardiovascular Diseases" [MeSH])	
Limits: Adult: 19-44 years, Middle Aged: 45-64 years, Middle Aged + Aged: 45+ years, Aged: 65+ years, 80 and over: 80+ years, English, Humans	8
"Quadriplegia" [MeSH] NOT review NOT letter NOT editorial AND ("Cardiovascular Diseases" [MeSH] OR "Cardiology" [MeSH])	
Limits: Adult: 19-44 years, Middle Aged: 45-64 years, Middle Aged + Aged: 45+ years, Aged: 65+ years, 80 and over: 80+ years, English, Humans	299
"Paraplegia" [MeSH] NOT review NOT letter NOT editorial AND ("Cardiovascular Diseases" [MeSH] OR "Cardiology" [MeSH])	
Limits: Adult: 19-44 years, Middle Aged: 45-64 years, Middle Aged + Aged: 45+ years, Aged: 65+ years, 80 and over: 80+ years, English, Humans	587
"Spinal cord injury" AND ("Cardiovascular Diseases/epidemiology" [MeSH] OR "Cardiovascular Diseases/etiology" [MeSH] OR "Cardiovascular Diseases/prevention and control" [MeSH]) NOT review Not letter Not editorial	
Limits: Adult: 19-44 years, Middle Aged: 45-64 years, Middle Aged + Aged: 45+ years, Aged: 65+ years, 80 and over: 80+ years, English, Humans	259
Related Articles for PubMed (Select 16823238)	302
Select 3 document(s)	3
Search "Cardiovascular Diseases" [MeSH] AND "Spinal Cord Diseases" [MeSH] NOT review NOT case report NOT letter NOT editorial	
Limits: All Adult: 19+ years, English, published in the last 10 years, Humans	288
Search "Cardiovascular Diseases" [MeSH] AND "Spinal Cord Diseases" [MeSH] NOT review NOT case report NOT letter NOT editorial	
Limits: All Adult: 19+ years, English, Humans	888
Search "Cardiovascular Diseases" [MeSH] AND "Spinal Cord Diseases" [MeSH] NOT review NOT case report NOT letter NOT editorial	
Limits: All Adult: 19+ years, Humans	1,320
Search "Cardiovascular Diseases" [MeSH] AND "Spinal Cord Diseases" [MeSH]	
Limits: All Adult: 19+ years, Humans	3,040
Search "Cardiovascular Diseases" [MeSH] AND "Spinal Cord Diseases" [MeSH]	5,414
Search "Cardiovascular Diseases" [MeSH]	1,366,747
Search "Spinal Cord Diseases" [MeSH]	71,345

Appendix C: Data Abstraction Form

- ID of the study from PubMed or Cochrane _____
- Number of the study _____
- First author _____
- Year of the publication_____
- Design of the study:
- Observational prospective
- Observational retrospective
- Case-control

Level of evidence:
Description of the target population _____
Description and clear definition of primary outcomes_____
Description and clear definition of secondary outcomes_____
Validation of the measurements of the exposure_____
Validation of the measurements of the outcomes_____
Process of the subject selection_____
Adequacy of the sampling (random selection or not)_____
Assessment of selection bias_____
Loss of followup_____
Length of followup (when applicable) in months_____
Validity of the measurements of confounding factors_____
Appropriateness matching_____
Appropriateness of adjustment_____
Appropriateness of standardization_____
Measurement of possible effect measure modification_____
External validity of the study_____
Years of observation, interval_____
Number of patients selected_____
Number of patients analyzed_____
Data used in the analysis_____
Adjustment for age of the patients, years_____
Adjustment for race of the patients_____
Adjustment for functional status, level of injury_____
Adjustment for socioeconomic status of the patients_____
Adjustment for comorbidities of the patients_____
Patient age_____
Patient race, % of blacks_____
Patient gender, % of females_____
Time after injury in years_____
Diagnosis of insulin resistance and diagnostic criteria of insulin resistance_____
Diagnosis of metabolic syndrome_____
Diagnosis of diabetes mellitus _____
Diagnosis of impaired glucose tolerance_____
% with insulin resistance_____
% with metabolic syndrome_____

% with diabetes mellitus_____
% with glucose tolerance_____
% with elevated cholesterol_____
% with elevated LDL_____
% with elevated TG_____
% with decreased HDL_____
% with dyslipidemia_____
% with obesity_____
% with abdominal obesity_____
Diagnosis of hypertension_____
Proportion of fat in total body mass_____
Proportion of abdominal fat in total body fat_____
Waist-hip ratio_____
% of subjects with I class of obesity_____
% of subjects with II class of obesity_____
% of subjects with III class of obesity_____
Proportion of patients in the sample with upper cervical SCI_____
Proportion of patients in the sample with low cervical SCI_____
Proportion of patients in the sample with upper thoracic SCI_____
Proportion of patients in the sample with lower thoracic SCI_____
Proportion of patients in the sample with lumbar SCI_____
Proportion of patients in the sample with sacral SCI_____
Proportion of patients in the sample with coccygeal SCI_____
Proportion of patients in the sample with tetraplegia _____
Proportion of patients in the sample with paraplegia _____
Functional status of the patients (definition and level)_____
Incidence of arrhythmia, events/year in 1,000 patients with SCI_____
% of patients with SCI with arrhythmia_____
Incidence of heart arrest, events/year in 1,000 patients with SCI_____
% of patients with SCI with heart arrest_____
Incidence of congestive heart failure, events/year in 1,000 patients with SCI_____
% of patients with SCI with congestive heart failure_____
Incidence of coronary disease, events/year in 1,000 patients with SCI_____
% of patients with SCI with coronary disease_____
Incidence of stroke, events/year in 1,000 patients with SCI_____
% of patients with SCI with stroke_____
Incidence of hypertension, events/year in 1,000 patients with SCI_____
% of patients with SCI with hypertension_____
Incidence of chronic renal failure, events/year in 1,000 patients with SCI_____
% of patients with SCI with chronic renal failure_____
Mean of glomerular filtration rate in ml per min_____
Mortality, all causes, events/year in 1,000 patients with SCI_____
% of patients with SCI who died within year of followup_____
Cardiovascular mortality, events/year in 1,000 patients with SCI_____
% of patients with SCI who died from CVD events within year of followup_____
Relative risk of arrhythmia, 95% CI_____

Relative risk of arrest, 95% CI_____
Relative risk of CHF, 95% CI_____
Relative risk of coronary heart disease, 95% CI_____
Relative risk of stroke, 95% CI_____
Relative risk of hypertension, 95% CI_____
Relative risk of CFR, 95% CI_____
Relative risk of all cause mortality, 95% CI_____
Relative risk of CVD mortality, 95% CI_____
Number of patients with arrhythmia _____
Number of patients with cardiac arrest_____
Number of patients with congestive heart failure_____
Number of patients with coronary heart disease_____
Number of patients with stroke_____
Number of patients with hypertension_____
Number of patients who died from CVD_____

Appendix D: List of Excluded Studies

1. Case records of the Massachusetts General Hospital. Weekly clinicopathological exercises. Case 23-1998. Tachypnea, changed mental status, and pancytopenia in an elderly man with treated lymphoma. N Engl J Med 1998;339(4):254-61. *No relevant outcomes*
2. Case records of the Massachusetts General Hospital. Weekly clinicopathological exercises. Case 8-2001. A 61-year-old man with transient quadriplegia and apnea. N Engl J Med 2001;344(11):832-9. *No relevant outcomes*
3. Prevention of venous thromboembolism in the acute treatment phase after spinal cord injury: a randomized, multicenter trial comparing low-dose heparin plus intermittent pneumatic compression with enoxaparin. J Trauma 2003 Jun;54(6):1116-24; discussion 25-6. *Not eligible target population*
4. Prevention of venous thromboembolism in the rehabilitation phase after spinal cord injury: prophylaxis with low-dose heparin or enoxaparin. J Trauma 2003 Jun;54(6):1111-5. *Not eligible target population*
5. Abel R, Schablowski M, Rupp R, Gerner HJ. Gait analysis on the treadmill - monitoring exercise in the treatment of paraplegia. Spinal Cord 2002;40(1):17-22. *No relevant outcomes*
6. Abel T, Schneider S, Platen P, Struder HK. Performance diagnostics in handbiking during competition. Spinal Cord 2006;44(4):211-6. *No relevant outcomes*
7. Adams MM, Ditor DS, Tarnopolsky MA, Phillips SM, McCartney N, Hicks AL. The effect of body weight-supported treadmill training on muscle morphology in an individual with chronic, motor-complete spinal cord injury: A case study. J Spinal Cord Med 2006;29(2):167-71. *No relevant outcomes*
8. Adkins VK, Mathewson C, Ayllon T, Jones ML. The ethics of using contingency management to reduce pressure ulcers: data from an exploratory study. Ostomy Wound Management 1999;45(3):56-8. *No relevant data*
9. Agarwal S, Kobetic R, Nandurkar S, Marsolais EB. Functional electrical stimulation for walking in paraplegia: 17-year follow-up of 2 cases. J Spinal Cord Med 2003;26(1):86-91. *No relevant outcomes*
10. Agarwal S, Triolo RJ, Kobetic R, Miller M, Bieri C, Kukke S, et al. Long-term user perceptions of an implanted neuroprosthesis for exercise, standing, and transfers after spinal cord injury. J Rehabil Res Dev 2003;40(3):241-52. *No relevant outcomes*
11. Alaedeen DI, Jasper J. Gastric bypass surgery in a paraplegic morbidly obese patient. Obesity Surgery 2006;16(8):1107-8. *Less than 100 patients in study*
12. Algood SD, Cooper RA, Fitzgerald SG, Cooper R, Boninger ML. Impact of a pushrim-activated power-assisted wheelchair on the metabolic demands, stroke frequency, and range of motion among subjects with tetraplegia. Arch Phys Med Rehabil 2004;85(11):1865-71. *No relevant outcomes*
13. al-Mahroos S, Malik AK, Sangam K, Burashid K. Progressive neurological symptoms in a diabetic patient. Postgraduate Medical Journal 1998;74(877):699-700. *Not adult spinal cord injury patients*
14. Ampil FL, Chin HW. Radiotherapy alone for extradural compression by spinal myeloma. Radiat Med 1995 May-Jun;13(3):129-31. *Not eligible target population*
15. Andersen JL, Mohr T, Biering-Sorensen F, Galbo H, Kjaer M. Myosin heavy chain isoform transformation in single fibres from m. vastus lateralis in spinal cord injured individuals: effects of long-term functional electrical stimulation (FES). Pflugers Arch 1996;431(4):513-8. *No relevant outcomes*
16. Andersen JT, Bradley WE. Neuro-urological investigation in urinary bladder dysfunction. International Urology & Nephrology 1977;9(2):133-43. *No relevant data*
17. Anonymous. Spinal cord injury and obesity. Nephrology News & Issues 2005;19(3):23. *No relevant data*
18. Apstein MD, George BC. Serum lipids during the first year following acute spinal cord injury. Metabolism: clinical and experimental 1998;47(4):367-70. *Not adult chronic SCI patients*
19. Attal N, Gaude V, Brasseur L, Dupuy M, Guirimand F, Parker F, et al. Intravenous lidocaine in central pain: a double-blind, placebo-controlled, psychophysical study. Neurology 2000 Feb 8;54(3):564-74. *Not eligible outcomes*
20. Averill A, Cotter AC, Nayak S, Matheis RJ, Shiflett SC. Blood pressure response to acupuncture in a population at risk for autonomic dysreflexia. Arch Phys Med Rehabil 2000 Nov;81(11):1494-7. *Not eligible exposure*
21. Ayas NT, Epstein LJ, Lieberman SL, Tun CG, Larkin EK, Brown R, et al. Predictors of loud snoring in persons with spinal cord injury. Journal of Spinal Cord Medicine 2001;24(1):30-4. *No relevant data*
22. Ayas NT, Garshick E, Lieberman SL, Wien MF, Tun C, Brown R. Breathlessness in spinal cord injury depends on injury level. Journal of Spinal Cord Medicine 1999;22(2):97-101. *No relevant data*
23. Badami JP, Hinck VC. Symptomatic deposition of epidural fat in a morbidly obese woman. Ajnr: American Journal of Neuroradiology 1982;3(6):664-5. *Not adult spinal cord injury patients*
24. Bailes JE, Miele VJ. The science of sports medicine. Clinical Neurosurgery 2004;51:91-101. *No relevant data*
25. Baker HW. Reproductive effects of nontesticular illness. Endocrinology & Metabolism Clinics of North America 1998;27(4):831-50. *Not adult spinal cord injury patients*

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Appendix E: Evidence Tables

Appendix E Table 1. Prevalence of metabolic syndromes, diabetes, glucose, lipid abnormalities, and BMI in adults with chronic posttraumatic SCI

Reference	Study Design	Subject Characteristics	Prevalence
Prevalence of metabolic syndrome and insulin resistance in people with SCI and disease			
Lee, 2005[1]	Convenience sample of 93 SCI patients from a Veterans Affairs hospital and local community. All were diagnosed for lipid panel, insulin, and glucose values. USA	Male: 86.0% (n=80) Female: 14.0% (n=13) Paraplegia: 58.1% (n=54) Tetraplegia: 41.9% (n=39)	Metabolic syndrome and insulin resistance 22.6% (21 of 93 subjects)
Bauman, 1999[2]	Cross-sectional study including a convenience sample of 201 SCI patients from a single clinical center who had oral glucose tolerance tests. Patients were subgrouped by level of injury. USA	Mean age (years): 39 Male: 84% (n=169) Female: 16% (n=32) White: 27% (n=54) Latino: 57% (n=114) African American: 14% (n=28) BMI: 25 Injury: Mean duration of SCI (years): 13 Mean age at injury: 25 Tetra complete: 28% (n=56) Tetra incomplete: 12% (n=25) Para complete: 42% (n=84) Para incomplete: 18% (n=36)	Hyperinsulinemia Tetraplegia group 53% (n=43) Paraplegia group 37% (n=44) P <0.05
Prevalence of diabetes in people with SCI and disease			
Bauman, 1999[2]	Cross-sectional study including a convenience sample of 201 SCI patients from a single clinical center who had oral glucose tolerance tests. Patients were subgrouped by level of injury. USA	Mean age (years): 39 Male: 84% (n=169) Female: 16% (n=32) White: 27% (n=54) Latino: 57% (n=114) African American: 14% (n=28) BMI: 25 Injury: Mean duration of SCI (years): 13 Mean age at injury: 25 Tetra complete: 28% (n=56) Tetra incomplete: 12% (n=25) Para complete: 42% (n=84) Para incomplete: 18% (n=36).	Diabetes: 13.4% (n=27) Results from fasting glucose testing: Overall diabetes: 3% (n=7) Tetraplegia complete: 4% (n=2) Tetraplegia incomplete: 0% (n=0) Paraplegia complete: 1% (n=1) Paraplegia incomplete: 11% (n=4) Results from 2 hour glucose challenge testing: Overall diabetes: 13% (n=27) Tetraplegia complete: 23% (n=13) Tetraplegia incomplete: 16% (n=4) Paraplegia complete: 6% (n=5) Paraplegia incomplete: 11% (n=4)

Appendix E Table 1. Prevalence of metabolic syndromes, diabetes, glucose, lipid abnormalities, and BMI in adults with chronic posttraumatic SC (continued)

Reference	Study Design	Subject Characteristics	Prevalence
Lavela, 2006[3]	National cross-sectional survey of 3,737 Veterans Affairs SCI subjects. USA	Veterans with SCI subgroups 1. Veterans with spinal disease (VSD) A. With diabetes (n=741) Mean age (years): 64.1* Male: 98.2% (n=728) White: 76.6% (n=568) Nonwhite: 23.4% (n=173)* Mean duration of SCI (years): 23.9 Paraplegia: 67.3% (n=499)* Tetraplegia: 32.7% (n=242) Mean age at injury: 40.0* B. Without diabetes (n=2,967) Mean age (years): 59.2 Male: 96.8% (n=2,872) White: 82.7% (n=2,454) Nonwhite: 17.3% (n=513) Mean duration of SCI (years): 23.8 Paraplegia: 61.6% (n=1,828) Tetraplegia: 38.4% (n=1,139) Mean age at injury: 35.4 * p=0.000, A vs. B 2. GVP = General Veteran Population (n=6,413) 3. GP = General Population, from Centers for Disease Control Behavioral Risk Factor Surveillance System 2003 survey data (n=221,650)	<u>Diabetes prevalence</u> VSD 20.0%; GVP 21.0%; GP 7.6%* *p <0.0001, VSD vs. GP <u>Diabetes prevalence by comparison group by age</u> Age (years) <40: VSD 4.6%; GVP 3.9%; GP 1.9% 40-44: VSD 6.7%; GVP 13.7%; GP 5.0% 45-49: VSD 10.2%; GVP 8.0%; GP 6.7% 50-54: VSD 17.5%; GVP 16.2%; GP 9.4% 55-59: VSD 20.2%; GVP 18.7%; GP 13.0% 60-64: VSD 23.1%; GVP 35.2%; GP 16.0% 65-69: VSD 24.9%; GVP 28.6%; GP 15.7% 70+: VSD 26.2%; GVP 24.0%; GP 15.6% <u>Duration of diabetes: comparison of groups</u> VSD n=741; GVP n=1,342; GP n=16,676 Mean duration (years): VSD 25.5; GVP 10.7; GP 9.7 Duration >25 years: VSD 13.6%*; GVP 10.9%; GP 9.8% *p ≤0.01, VSD vs. GP <u>Risk for clinical conditions, SCI veterans with diabetes compared to SCI veterans without diabetes</u> A. Coronary Heart Disease (n=3,177) Percent in SCI/D group: 12%; OR 2.8 [95% CI 2.2 to 3.6]. B. Myocardial infarction (n=3,230) Percent in SCI/D group: 14%; OR 2.9 [95% CI 2.1 to 3.4]. C. High cholesterol (n=3,415) Percent in SCI/D group: 48%; OR 2.5 [95% CI 2.1 to 3.0]. D. Stroke (n=3,170) Percent in SCI/D group: 8%; OR 2.3 [95% CI 1.7 to 3.0]. E. Hypertension (n=3,438) Percent in SCI/D group: 49%; OR 2.5 [95% CI 2.1 to 3.0]
Frisbie, 2005[4]	Chart review of 166 Veterans Affairs patients admitted for SCI rehabilitation within 108 days of paralysis using discharge diagnosis. Patients ≥40 years at time of injury (n=87) were followed for five years. USA	Veterans with SCI subgroups A. Age <40 years at time of injury (n=79) Mean age (years): 27 Male: 94.9% (n=75) SCI, cervical: 56% (n=44) Complete motor: 72% (n=56) A. Age ≥40 years at time of injury (n=87) Mean age (years): 60 Male: 97.7% (n=85) SCI, cervical: 67% (n=58) Complete motor: 43% (n=37) B subgroups	<u>Diabetes prevalence by comparison group by age at the time of acute SCI</u> Age (years) 16-39: 0% (n=79) ≥40: 21% (18 of 87 subjects) <u>Diabetes prevalence at 5-year followup in patients ≥40 years at time of SCI</u> 20% (13 of 64* subjects) *excludes subjects lost to death and followup. Three subjects in non-diabetic subgroup developed diabetes. <u>5-year mortality in patients ≥40 years</u> Diabetic subgroup (n=17, one lost to followup): 7 deaths; mortality rate 41%* Non-diabetic subgroup (n=64, 5 lost to followup): 10 deaths;

Appendix E Table 1. Prevalence of metabolic syndromes, diabetes, glucose, lipid abnormalities, and BMI in adults with chronic posttraumatic SC (continued)

Reference	Study Design	Subject Characteristics	Prevalence
		B[1]. Diabetic subgroup n=18 (21%) (all males) Mean age: 66 SCI, cervical: 72% (n=13) Complete motor: 33% (n=6) B[2]. Non-diabetic subgroup n=69 (79%) Mean age: 59 SCI, cervical: 65% (n=45) Complete motor: 45% (n=31) Inclusion: treatment for DM; 2 fasting blood glucose levels >140mg%, a single random glucose of >200mg%, or a single hemoglobin A1C >7mg% Exclusion: DM was rejected if related to administration of corticosteroids	mortality rate 16%. p=0.04 between groups
Garshick, 2005[5]	A prospective mortality study of 361 SCI males injured ≥1 year	A. Survivors (n=324) Mean age (years): 48.9 White: 93.2% (n=302) Nonwhite: 6.8% (n=22) BMI: 26.3 Age at SCI: 32.2 Mean duration of SCI (years): 16.7 Level of Injury Complete cervical: 21.3% (n=69) T1-T4: 14.8% (n=48) T5-T12: 12.4% (n=40) Others: 10.8% (n=35) Incomplete Cervical ASIA C: 10.8% (n=35) Cervical ASIA D: 12.4% (n=40) Other ASIA C: 7.7% (n=25) Other ASIA D: 9.9% (n=32) B. Deceased (n=37) Mean age (years): 65.0 White: 94.6% (n=35) Nonwhite: 5.4% (n=2) BMI: 26.0 Age at SCI: 40.8 Mean duration of SCI (years): 24.2 Level of Injury Complete cervical: 16.2% (n=6) T1-T4: 10.8% (n=4) T5-T12: 18.9% (n=7)	Diabetes prevalence 10.0% A. Survivors (n=324) 8.3% (n=27) B. Deceased subjects (n=37) 24.3% (n=9) Observed/expected deaths 2.0/0.53 Standardized mortality ratio 3.74 [95%CI 0.45 to 13.51]

Appendix E Table 1. Prevalence of metabolic syndromes, diabetes, glucose, lipid abnormalities, and BMI in adults with chronic posttraumatic SC (continued)

Reference	Study Design	Subject Characteristics	Prevalence
		Others: 8.1% (n=3) Incomplete Cervical ASIA C: 16.2% (n=6) Cervical ASIA D: 5.4% (n=2) Other ASIA C: 16.2% (n=6) Other ASIA D: 8.1% (n=3)	
Lee, 2005[1]	Convenience sample of 93 SCI patients from a Veterans Affairs hospital and local community. All were diagnosed for lipid panel, insulin, and glucose values. USA	Male: 86.0% (n=80) Female: 14.0% (n=13) Paraplegia: 58.1% (n=54) Tetraplegia: 41.9% (n=39)	Diabetes prevalence 21.3% (20 of 93 subjects)
Prakash, 2002[6]	Population:26,734 able-bodied male veterans and 654 patients with spinal cord injuries 47,070 patients with at least one ECG obtained in the Palo Alto Veterans Affairs Health Care System. Retrospective cohort to examine prevalence of ECG abnormalities in individuals with spinal cord injuries.	A. SCI (n=654) Mean age: 50 Annual mortality: 2.6% Duration of followup: 8 years Hypertension: 7% (p<0.001 vs. B) Congestive heart failure: 1.7% (p<0.001 vs. B) Coronary artery disease: 1.7% (p<0.001 vs. B) Pulmonary disease: 4.8% (p=0.01 vs. B) B. Able-bodied controls (n=26,734) Mean age: 56 Annual mortality: 3.0% Duration of followup: 8 years Hypertension: 44.0% Congestive heart failure: 7.0% Coronary artery disease: 7.0% Pulmonary disease: 5.5% Exclusion criteria: inpatient setting or emergency room at the time of ECG.	Diabetes prevalence A. SCI: 11.0% (72 of 654 subjects) B. Able-bodied controls: 10.0% (2,673 of 26,734 subjects)
Imai, 1996[7]	Questionnaire of 244 male SCI patients at 8 rehabilitation centers compared to general population. Japan *Likely same cohort as Imai 1994)*[8]	Mean age: 47.6 (range: 22-69) Mean duration of SCI: 17.3 Site of injury subgroups: A. Cervical (C) Thoracic (T) 5: 11.0% (n=23) B. T6-T10: 12.0% (n=30) C. T11-Lumbar (L) 1: 69.0% (n=173) D. L2-or below: 8.0% (n=18) Incomplete motor: 4.1% (n=10, 5 cervical and 5 thoracolumbar)	Comparison of diabetes prevalence between SCI patients and the general population, Outpatient rate per 1,000 population SCI: 61.5 General population: 12.2 Comparison of diabetes prevalence by SCI site of injury subgroup, Outpatient rate per 1,000 population A. C-T5: 0.0 B. T6-T10: *28 (extracted from graph)* C. T11-L1: *62* D. E. L2-or below: *165*

Appendix E Table 1. Prevalence of metabolic syndromes, diabetes, glucose, lipid abnormalities, and BMI in adults with chronic posttraumatic SC (continued)

Reference	Study Design	Subject Characteristics	Prevalence
McGlinchey-Berroth, 1995[9]	Cross-sectional analysis of hospitalizations among 534 patients with SCI admitted to the high quality Spinal Cord Injury Service of the VA medical center (part of the Aging with a Long-Term Disability Research Program database). 510 discharged from the hospitals were included in the analysis.	Mean age: 50 (range 16-84) Mean duration of SCI: 16 Male: 99.0%. Group 1 (N=225) persons <50 years of age at the time of injury and <5 years at index submission. Group 2 (N=162) <50 years of age at the time of injury but >50 years at the time of index admission. Group 3 (N=93) persons >50 years of age at the time of injury. Exclusion criteria: not available discharge summary; current hospitalization, transfer to the long term care facility.	Diabetes prevalence 9.8% (47 of 480 subjects) A. Group 1 (N=225) 3.9% B. Group 2 (N=162) 12.3% C. Group 3 (N=93) 22.6%
Zhong, 1995[10]	SCI men (Veterans Affairs patients) studied during annual physical exam. USA	197 men with chronic SCI, 103 paraplegia and 94 tetraplegia Mean age: 50 (21-77) Mean duration of SCI: 18 (1-49) Mean BMI: 25 (15.8-47.8) Exclusion criteria: No prior history of diabetes or gout	Diabetes prevalence Diabetes: 18.3% (n=36)
Bauman, 1994[11]	Veteran SCI patients, matched for age and BMI were compared to veteran controls. USA	SCI (n=100) A. Paraplegia 50.0% (n=50) Mean age: 51.2 Mean BMI: 25.7 Mean duration of SCI: 19 B. Tetraplegia 50.0% (n=50) Mean age: 47.2 Mean BMI: 24.6 Mean duration of SCI: 17 Controls n=50 Mean age: 51 years Mean BMI: 26.9	Diabetes prevalence SCI: 22.0% (n=22) Control: 6.0% (n=3) Comparison of mean fasting plasma glucose (mg/dL) among groups A. Paraplegia: Normal 91; IGT 97; Diabetes 99* B. Tetraplegia: Normal 87; IGT 90; Diabetes 102*† C. Control: Normal 97; IGT 104; Diabetes 115* *p<0.05 versus Normal, † p<0.05 versus IGT
Imai, 1994[8]	Survey of 195 SCI male patients in Japan	Mean age: 49.5 Mean duration of SCI: 17.9 Site of injury subgroups: C-T5: 9.7% (n=19) T6-T10: 12.3% (n=24) T11-L1: 71.3% (n=139) L2-or below: 6.7% (n=13)	Prevalence of diabetes by level of injury All subjects: 5.6% C-T10: 0.0% (32 subjects) T11-L2: 6.5% (9 of 139 subjects) L2-or below: 15.4 (2 of 13 subjects) Outpatient rate per 1,000 population T11-L2: 65 L2-or below: 154

Appendix E Table 1. Prevalence of metabolic syndromes, diabetes, glucose, lipid abnormalities, and BMI in adults with chronic posttraumatic SC (continued)

Reference	Study Design	Subject Characteristics	Prevalence
			Standard outpatient morbidity ratio (general population = 100) T11-L2: 326* L2-or below: 945* *p<0.01 versus general population
Charlifue, 1999[12]	A longitudinal, cross-sectional study of 315 SCI patients	Mean age: 37.1 Male: 80.3% (n=253) Mean duration of SCI: 9.3 Subgroups A. Paraplegia ABC*: 46.7% (n=147) Mean age: 37.2 Male: 76.4% (n=112) Mean duration of SCI: 9.3 B. Tetraplegia ABC*: 42.2% (n=133) Mean age: 35.9 Male: 84.2 (n=112) Mean duration of SCI: 9.5 C. All D*: 11.1% (n=35) Mean age: 40.6 Male: 82.9 (n=29) Mean duration of SCI: 8.9 ASIA Impairment Scale: A = complete, no function; B = incomplete, sensory only; C = incomplete, some sensory and motor function; and D = incomplete, useful motor function.	Prevalence of diabetes (baseline) Overall: 2.5% (8 of 315 subjects) Paraplegia ABC: 3.4% (5 of 147 subjects) Tetraplegia ABC: 1.5% (2 of 133 subjects) All D: 2.9% (1 of 35 subjects) Prevalence of diabetes (at 5 years) Overall: 3.8% (12 of 315 subjects) Paraplegia ABC: 4.8% (7 of 147 subjects) Tetraplegia ABC: 3.0% (4 of 133 subjects) All D: 2.9% (1 of 35 subjects) Diagnosis of DM by age group (baseline) <30 years: 0.0% (n=82) 30-50 years: 2.1% (4 of 190 subjects) 50+ years: 9.3% (4 of 43 subjects) Diagnosis of DM by age group (at 5 years) <30 years: 0.0% (n=82) 30-50 years: 4.1% (8 of 190 subjects) 50 + years: 11.6% (5 of 43 subjects)
Rish, 1997[13]	230 Vietnam vets with SCI were reviewed for a 25 year followup USA	Mean age: 21.4 years with previous excellent health at baseline Site of injury: C2-T1: 21.0% (n=48) T2-T10: 31.0% (N=71) T11-L1: 23.0% (n=52) L2-sacrum: 14% (n=32) No vertebral injury noted: 11.0% (n=27) Paraplegia, complete: 47.0% (n=109) Paraplegia, incomplete: 28.0% (n=64) Tetraplegia, complete: 14.0% (n=31) Tetraplegia, incomplete: 9.0% (n=21) Not delineated: 2.0% (n=5)	Prevalence of diabetes: 29/230 (13%)

Appendix E Table 1. Prevalence of metabolic syndromes, diabetes, glucose, lipid abnormalities, and BMI in adults with chronic posttraumatic SC (continued)

Reference	Study Design	Subject Characteristics	Prevalence
Prevalence of glucose intolerance in people with SCI and disease			
Zhong, 1995[10]	SCI men (Veterans Affairs patients) studied during annual physical exam. USA	197 men with chronic SCI, 103 paraplegia and 94 tetraplegia Mean age: 50 years (21-77) Mean duration of SCI: 18 (1-49) Mean BMI: 25 (15.8-47.8) Exclusion criteria: No prior history of diabetes or gout	Impaired glucose tolerance prevalence Impaired Glucose Tolerance: 29.4% (n=58)
Bauman, 1994[11]	Veteran SCI patients, matched for age and BMI were compared to veteran controls. USA	SCI (n=100) A. Paraplegia 50.0% (n=50) Mean age: 51.2 Mean BMI: 25.7 Mean duration of SCI: 19 B. Tetraplegia 50.0% (n=50) Mean age: 47.2 Mean BMI: 24.6 Mean duration of SCI: 17 Controls n=50 Mean age: 51 years Mean BMI: 26.9	Impaired glucose tolerance prevalence SCI: 34.0% (n=34) Controls: 12.0% (n=6) Comparison of mean fasting plasma glucose (mg/dL) among groups A. Paraplegia: Normal 91; IGT 97; Diabetes 99* B. Tetraplegia: Normal 87; IGT 90; Diabetes 102*† C. Control: Normal 97; IGT 104; Diabetes 115* *p<0.05 versus Normal, † p<0.05 versus IGT
Bauman, 1999[2]	Cross-sectional study including a convenience sample of 201 SCI patients from a single clinical center who had oral glucose tolerance tests. Patients were subgrouped by level of injury. USA	Mean age (years): 39 Male: 84% (n=169) Female: 16% (n=32) White: 27% (n=54) Latino: 57% (n=114) African American: 14% (n=28) BMI: 25 Injury: Mean duration of SCI (years): 13 Mean age at injury: 25 Tetra complete: 28% (n=56) Tetra incomplete: 12% (n=25) Para complete: 42% (n=84) Para incomplete: 18% (n=36).	Impaired glucose tolerance: 27.9% (n=56) Comparison of mean fasting serum glucose (FS Glu) in mg/dl, peak serum glucose (Pk Glu) in mg/dl, fasting plasma insulin (FP Ins) in microU/ml, peak plasma insulin (Pk Ins) in microU/ml among groups (p-value for 3 df F-statistic): Tetra complete: FS Glu=97; PK Glu=193; FS Ins=10; Pk Ins= 216 Tetra incomplete: FS Glu=102; Pk Glu=178; FS Ins=10; Pk Ins= 148 Para complete: FS Glu=97; Pk Glu=158; FS Ins=9; Pk Ins= 152 Para incomplete: FS Glu=106; Pk Glu=158; FS Ins=10; Pk Ins= 144 P-value by groups: p <0.0001; p <0.0001; p <0.01; p <0.005
Mean lipid values in subjects with SCI and disease			
Moussavi, 2001[14]	A cross-sectional study of 189 community-dwelling SCI patients USA	Mean age (years): 43.1 (range 19.2-81.9) Men: 76.7% (n=145) Women: 23.3% (n=44) White: 59.3% (n=112) African American: 22.2% (n=42) Hispanic: 17.5% (n=33)	Mean serum lipid values Total cholesterol (TC): 195.9 Low Density Lipoprotein (LDL): 120.2 High Density Lipoprotein (HDL): 46.2 Triglyceride (TG): 148.3 Mean lipids values by gender Male (n=138): TC 193.9; LDL 120.8; HDL 43.7; TG 148.6

Appendix E Table 1. Prevalence of metabolic syndromes, diabetes, glucose, lipid abnormalities, and BMI in adults with chronic posttraumatic SC (continued)

Reference	Study Design	Subject Characteristics	Prevalence
		Other: 1.1% (n=2) Mean duration of SCI (years): 12.5 (0.5-47.0 Tetraplegia (A,B,C*): 41.3% Paraplegia (A,B,C*): 39.2% Tetraplegia or paraplegia, level D*: 19.6% *Based on American Spinal Injury Association Impairment Scale. (A) no function, (B) sensory only, (C) some sensory and motor preservation, (D) useful motor function, and (E) normal.	Female (n=41): TC 202.4; LDL 118.1; HDL 54.2; TG 147.2 Mean lipids values by race White (n=104): TC 194.9; LDL 117.9; HDL 45.9; TG 155.4 African American (n=41): TC 190.9; LDL 122.2; HDL 47.5; TG 106.8 Hispanic American (n=32): TC 203.4; LDL 123.2; HDL 45.7; TG 177.4
Bauman, 1999[15]	Cohort of outpatient SCI patients (n=320) seen for annual exam vs. able-bodied controls (n=303) matched by age and ethnicity USA	SCI subjects (n=320) Mean age: 41 (20-77) Male: 73% (n=234) Female: 27% (n=86) White: 47% (n=150) African American: 28% (n=90) Hispanic: 26% (n=83) Mean BMI: 25 (13.8-54.8) Body fat: 36% (21.1-72.3) BMI ≥27.8: 28% Mean duration of SCI: 15 (1-57) Motor complete: 65.6% Motor incomplete: 34.4% Sedentary able-bodied controls (n=303) Mean age: 42 (21-75) Male: 81.0% (n=245) Female: 16.0% (n=48) White: 56.0% (n=170) African American: 29% (n=88) Hispanic: 16.0% (n=48) Mean BMI: 29.9 (19.7-49.9) (p<0.0001 vs. SCI) Body fat: 31.0% (10.2-72.5) (p<0.0001 vs. SCI) BMI ≥27.8: 64.0% (p<0.0001 vs. SCI)	Comparison of mean lipid values between groups TC: SCI 190; Control 207* LDL: SCI 126; Control 137* HDL: SCI 42; Control 47** TG: SCI 108; Control 118† * p<0.0001 (between groups), ** p<0.0005, † p<0.05 Comparison of mean lipid values between genders A. Males: SCI n=233; Control n=244 TC: SCI 191; Control 209* LDL: SCI 129; Control 139** HDL: SCI 39; Control 45* TG: SCI 114; Control 126† * p<0.0001, ** p<0.01, † p<0.0005 B. Females: SCI n=87; Control n=59 TC: SCI 188; Control 199 LDL: SCI 118; Control 129 HDL: SCI 51; Control 54 TG: SCI 94; Control 82 Comparison of mean lipid values among ethnicities A. White: SCI n=149; Control n=169 TC: SCI 187; Control 209* LDL: SCI 125; Control 138** HDL: SCI 41; Control 46* TG: SCI 105; Control 119† * p<0.0001, ** p<0.005, † p<0.01 B. African American: SCI n=88; Control n=87 TC: SCI 195; Control 204 LDL: SCI 128; Control 133 HDL: SCI 49; Control 51 TG: SCI 91; Control 101 C. Hispanic: SCI n=83; Control n=43 TC: SCI 190; Control 209*

Appendix E Table 1. Prevalence of metabolic syndromes, diabetes, glucose, lipid abnormalities, and BMI in adults with chronic posttraumatic SC (continued)

Reference	Study Design	Subject Characteristics	Prevalence
			LDL: SCI 126; Control 138** HDL: SCI 49; Control 51 TG: SCI 91; Control 101 * p<0.01, ** p<0.05
Bauman, 1998a[16]	A cohort of 600 SCI patients was investigated for lipid profiles and by ethnicity subgroups in a SCI clinic over 24 months. USA	Mean age: 37.6 BMI: 25.0 White race: 26.5% (n=159) Hispanic: 47.0% (n=282) African American: 26.5% (n=159) Mean duration of SCI: 12.4 Tetraplegia, complete: 30.8% (n=185) Tetraplegia, incomplete: 18.7% (n=112) Paraplegia, complete: 32.8% (n=197) Paraplegia, incomplete: 17.7% (n=106) A. White (n=159) Mean age: 41.4 BMI: 24.9 Mean duration of SCI: 17.4 A. White (n=159) Mean age: 41.4 BMI: 24.9 Mean duration of SCI: 17.4 B. Hispanic (n=282) Mean age: 36.0 BMI: 25.3 Mean duration of SCI: 10.6 C. African American (n=159) Mean age: 36.6 BMI: 24.5 Mean duration of SCI: 10.6	<u>Overall Mean lipid values</u> TC: 190 LDL: 124 HDL: 42 TG: 122 <u>Mean lipid values between groups</u> TC: White 190; Hispanic 190: African American (AA) 191 LDL: White 125; Hispanic 124: AA 125 HDL: White 40; Hispanic 39: AA 47* TG: White 121; Hispanic 137: AA 96* * p<0.05 for African American versus White and Hispanic <u>Categorical Groupings by Ethnic Group</u> 1. LDL (mg/mL) <100: White 24.0%; Hispanic 27.0%: AA28.0% 100-130: White 38.0%; Hispanic 34.0%: AA 30.0% 131-160: White 24.0%; Hispanic 22.0%: AA 24.0% ≥161: White 14.0%; Hispanic 17.0%: AA18.0% 2. HDL (mg/mL) <30: White 19.0%; Hispanic 21.0%: AA 6.0%* 30-34: White 17.0%; Hispanic 15.0%: AA13.0% 35-40: White 18.0%; Hispanic 24.0%: AA16.0% >40: White 46.0%; Hispanic 40.0%: AA 65.0%* * p<0.05 for African American versus White and Hispanic
Bauman, 1998b[17] Same cohort as Bauman 1998a[16]	A cohort of 541 SCI patients were investigated for lipid profiles and by neurological deficit subgroups over a period of 2 years in a SCI clinic in CA USA	A. Tetraplegia (n=247) Mean age: 38 Male: 90.0% (n=222) Female: 10.0% (n=25) White race: 35.0% (n=86) African American: 20.0% (n=49) Hispanic: 45.0% (n=111) Mean duration of SCI: 13 Motor complete: 63.2% Motor incomplete: 36.8%	<u>Comparison of mean lipid profiles between groups and subgroups</u> A. Tetraplegia (n=247) TC: 184; Complete 181; Incomplete 190 LDL: 121; Complete 122; Incomplete 190 HDL: 39; Complete 38; Incomplete 40 TG: 122; Complete 118; Incomplete 125 B. Paraplegia (n=294) TC: 198; Complete 205; Incomplete 196 LDL: 122; Complete 129; Incomplete 119 HDL: 45; Complete 47; Incomplete 44

Appendix E Table 1. Prevalence of metabolic syndromes, diabetes, glucose, lipid abnormalities, and BMI in adults with chronic posttraumatic SC (continued)

Reference	Study Design	Subject Characteristics	Prevalence
		B. Paraplegia (n=294) Mean age: 37 Male: 84% (n=247) Female: 16.0% (n=47) White race: 17.0% (n=50)* African American: 28.0% (n=82) Hispanic: 55.0% (n=162) Mean duration of SCI: 12 Motor complete: 70.1% Motor incomplete: 29.9% * p<0.01 between groups	TG: 129; Complete 132; Incomplete 128
Zhong, 1995[10]	SCI men (Veterans Affairs patients) studied during annual physical exam USA	197 men with chronic SCI, 103 paraplegia and 94 tetraplegia Mean age: 50 (21-77) Mean duration of SCI: 18 (1-49) Mean BMI: 25 (15.8-47.8) Exclusion criteria: No prior history of diabetes or gout	<u>Mean lipid values in the study groups</u> A. All SCI subjects TC: 188 LDL: 124 HDL: 39 TG: 122 B. Paraplegia (n=103) vs. Tetraplegia (n=94) TC: Paraplegia 191; Tetraplegia 185 LDL: Paraplegia 125; Tetraplegia 123 HDL: Paraplegia 38; Tetraplegia 39 TG: Paraplegia 130; Tetraplegia 114 <u>Mean lipid values between subgroups with normal and elevated insulin levels</u> A. Normal insulin levels (n=119) LDL: 123 HDL: 39 TG: 109 B. Hyperinsulinemia (n=78)* LDL: 126 HDL: 37 TG: 143 (p=0.004 vs. normal insulin group) *Defined as peak plasma insulin >150*u*l/mL during oral glucose tolerance test (75g)
Bauman, 1992[18]	Veteran SCI patients, matched for age and BMI, were compared to veteran controls USA	A. Paraplegia: n=50 Mean age (years): 49.5 Mean BMI: 26.0 Mean duration of SCI: 17.6 B. Tetraplegia: n=50 Mean age: 46.2 Mean BMI: 24.0	<u>Mean lipid values in the study groups</u> A. Paraplegia (n=50) TC: 191* LDL: 124 HDL: 37** TG: 148 B. Tetraplegia (n=50)

Appendix E Table 1. Prevalence of metabolic syndromes, diabetes, glucose, lipid abnormalities, and BMI in adults with chronic posttraumatic SC (continued)

Reference	Study Design	Subject Characteristics	Prevalence
		Mean duration of SCI: 15.0 C. Controls: n=50 Mean age: 48.8 Mean BMI: 26.8	TC: 188* LDL: 128 HDL: 40** TG: 101† Controls (n=50) TC: 210 LDL: 136 HDL: 48 TG: 134 * p<0.01, ** p<0.0001, † p<0.05 across groups (ANOVA) <u>HDL cholesterol levels by SCI and subgroups</u> A. All SCI subjects (n=100) <30: 13.0% (n=13) 30-34: 24% (n=24) ≥35: 63.0% (n=63) B. Paraplegia (n=50) <30: 18.0% (n=9) 30-34: 22% (n=11) ≥35: 60.0% (n=30) B. Paraplegia (n=50) <30: 8.0% (n=4) 30-34: 26% (n=13) ≥35: 66.0% (n=33)
Krum, 1992[19]	Risk factors for cardiovascular disease in 327 consecutive SCI patients, matched for age and sex, were compared to controls from the Australian population	Age range: 25-64 Male: 84.0% (n=275) Female:16.0% (n=52) Duration of SCI: 34% had SCI for more than 10 years Control subjects (n not reported)	<u>Total cholesterol levels by age in males</u> All ages: SCI 208; Control *217(estimated from graph)* Age 25-29: SCI 185; Control *198* Age 30-34: SCI 197; Control *204* Age 35-39: SCI 216; Control *217* Age 40-44: SCI 206; Control *214* Age 45-49: SCI 216; Control *226* Age 50-54: SCI 216 ; Control *227* Age 55-59: SCI 209 ; Control *229* Age 60-64: SCI 206; Control *232* <u>Total cholesterol levels, female gender and duration of SCI</u> Female: SCI 190; Control *217* SCI, >10 years: SCI 192 <u>Total cholesterol levels by level of spinal lesion</u> Cervical: *188* Low thoracic: *182* High thoracic: *199* Lumbar: *205*

Appendix E Table 1. Prevalence of metabolic syndromes, diabetes, glucose, lipid abnormalities, and BMI in adults with chronic posttraumatic SC (continued)

<table>
<tr><th>Reference</th><th>Study Design</th><th>Subject Characteristics</th><th>Prevalence</th></tr>
<tr><td colspan="4">Prevalence of obesity and mean BMI categories in people with SCI and disease</td></tr>
<tr><td>Weaver, 2007[20]</td><td>Observational, retrospective review of clinical and administrative data of 7,959 veterans with SCI/D (5% had injuries <1 year)

USA</td><td>Mean age (years): 58.2
Age ≥65 years: 35.0% (n=2,786)
Age 50-64 years: 38.0% (n=3,024)
Age <50 years: 27.0% (n=2,149)

Male: 98% (n=7,800)
White race: 75.0% (n=5,969)
African American: 20.0% (n=1,592)
Hispanic and other race: 6.0% (n=478)

Mean duration of SCI (years): 20
Complete: 37.0%
Incomplete: 28.0%
Paraplegia: 56.0%</td><td><u>Mean BMI and categories</u>
Mean BMI: 25.8
BMI <25: 47% (n=3,741)
BMI 25-29.9: 33% (n=2,650)
BMI ≥30: 20% (n=1,592)
<u>BMI categories by level of injury</u>
Paraplegia (n=4,457)
<25 (normal weight): 45.0%
25-29.9 (overweight): 33.0%
≥30 (obese): 23%Tetraiplegia (n=3,502)
<25 (normal weight): 50.0%
25-29.9 (overweight): 35.0%
≥30 (obese): 17.0%
*P<0.0001, paraplegia vs. tetraplegia

OR for BMI in Veterans. Reference category for BMI is <25 (normal weight)
<table>
<tr><th>N=7,959</th><th>Overweight* OR (CI)</th><th>Obese** OR (CI)</th></tr>
<tr><td>Age <50</td><td>1.0 (reference)</td><td>1.0 (reference)</td></tr>
<tr><td>Age 50-64</td><td>†1.4 (1.2-1.5)</td><td>†1.4 (1.2-1.5)</td></tr>
<tr><td>Age 65+</td><td>†1.3 (1.2-1.5)</td><td>1.11 (1.0-1.3)</td></tr>
<tr><td>White</td><td>1.0 (reference)</td><td>1.0 (reference)</td></tr>
<tr><td>Black</td><td>‡0.8 (0.8-0.9)</td><td>1.0 (0.9-1.1)</td></tr>
<tr><td>Hispanic</td><td>1.1 (0.9-1.3)</td><td>1.1 (0.9-1.3)</td></tr>
<tr><td>Tetraplegia</td><td>1.0 (reference)</td><td>1.0 (reference)</td></tr>
<tr><td>Paraplegia</td><td>†1.2 (1.1-1.3)</td><td>†1.5 (1.3-1.7)</td></tr>
</table>
*BMI 25-29.9. **BMI ≥30. †P <0.001. ‡P <0.05.</td></tr>
<tr><td>Gupta, 2006[21]</td><td>Retrospective chart review of 408 (387 analyzed) Veterans Affairs patients

USA</td><td>Mean age: 55.8 (median 56 years; (range 21-85)
Males: 98.3% (n=401)
Females: 1.7% (n=7)

Mean duration of SCI: 19 (range 2 months-60 years)
Paraplegia: 52.2% (n=213)
Tetraplegia: 47.7% (n=195)</td><td><u>Mean BMI</u>
Paraplegia (n=213): 28.36
Tetraplegia (n=195): 27.29
<u>Prevalence by BMI cut points</u>
BMI <18.5 (underweight): 3.6% (n=14)
BMI 18.5-25 (normal weight): 27.9% (n=108)
BMI ≥25 (overweight): 68.8% (n=255) of which 29.9% were obese (BMI ≥30; n=76)
<u>Mean BMI and duration of injury</u>
0-5 years: 28.11 (n=60)
5-10 years: 28.86 (n=46)
10-15 years: 27.49 (n=39)
15-20 years: 28.76 (n=49)
20-25 years: 26.28 (n=52)
>25 years: 27.55 (n=133)</td></tr>
</table>

Appendix E Table 1. Prevalence of metabolic syndromes, diabetes, glucose, lipid abnormalities, and BMI in adults with chronic posttraumatic SC (continued)

Reference	Study Design	Subject Characteristics	Prevalence
			Prevalence of those overweight and obese by age Age, years 20-39: BMI ≥25 33.3% (n=11); BMI ≥30 2.8% (n=1) 40-59: BMI ≥25 65.0% (n=147); BMI ≥30 38.0% (n=86) 60-74: BMI ≥25 70.1% (n=68); BMI ≥30 17.6% (n=17) >75: BMI ≥25 61.3% (n=19); BMI ≥30 4.9% (n=2)
Garshick, 2005[5]	A prospective mortality study of 361 SCI males injured ≥1 year	A. Survivors (n=324) Mean age (years): 48.9 White: 93.2% (n=302) Nonwhite: 6.8% (n=22) Age at SCI: 32.2 Mean duration of SCI (years): 16.7 Level of Injury Complete cervical: 21.3% (n=69) T1-T4: 14.8% (n=48) T5-T12: 12.4% (n=40) Others: 10.8% (n=35) Incomplete Cervical ASIA C: 10.8% (n=35) Cervical ASIA D: 12.4% (n=40) Other ASIA C: 7.7% (n=25) Other ASIA D: 9.9% (n=32) B. Deceased (n=37) Mean age (years): 65.0 White: 94.6% (n=35) Nonwhite: 5.4% (n=2) Age at SCI: 40.8 Mean duration of SCI (years): 24.2 Level of Injury Complete cervical: 16.2% (n=6) T1-T4: 10.8% (n=4) T5-T12: 18.9% (n=7) Others: 8.1% (n=3) Incomplete Cervical ASIA C: 16.2% (n=6) Cervical ASIA D: 5.4% (n=2) Other ASIA C: 16.2% (n=6) Other ASIA D: 8.1% (n=3)	Mean BMI: A. Survivors (n=324): 26.3 B. Deceased (n=37): 26.0

Appendix E Table 1. Prevalence of metabolic syndromes, diabetes, glucose, lipid abnormalities, and BMI in adults with chronic posttraumatic SC (continued)

Reference	Study Design	Subject Characteristics	Prevalence
Johnston, 2005[22]	Cross-sectional survey of SCI (n=199) patients in New Jersey (patients from database & community were recruited) compared to national population (n=246,025) USA	SCI subjects (n=199) Mean age: 39.6 Male: 74.9% (n=149) Female: 25.1% (n=50) White race: 74.4% (n=148) African American: 20.1% (n=40) Asian: 1.5% (n=3) Other race: SCI 4.0% (n=8) Mean weight: 168.2 Mean duration of SCI: 8.11 Paraplegia incomplete: 27% Paraplegia complete: 71% Paraplegia minimal: 3% Tetraplegia incomplete: 53% Tetraplegia complete: 42% Tetraplegia minimal: 2% Control (n=246,025) Mean age: 45.1 Male: 48.3% (n=115,632) Female: 53% (n=130,393) White race: 46.2% (n=113,664) African American: 16.4% (n=40,348) Asian: 11.1% (n=27,309) Other race: 26.3% (n=64,705) Mean weight: 171.9 Inclusion: >18 years old; traumatic SCI; >1 year post injury Exclusion: normal neurological exam; non-traumatic injury; inability to understand English without translator.	<u>Mean BMI</u> SCI subjects (n=199): 24.5 Control (n=246,025): 26.1 <u>BMI Categories</u> A. <18.5 (underweight): SCI 7.1%; Control 4.0% B. 18.5-24.9 (normal weight) SCI 48.9% Control 39.3% C. 25-25.9 (overweight) SCI 31.3% Control 35.2% ≥30 (obese) SCI 12.6% Control 20.9% <u>Use physical activity or exercise to lose weight among overweight/obese</u>: SCI 50.0% Control 69.8%
Spungen, 2003[23]	In a cross-sectional study, 133 male SCI patients were compared to 100 controls matched to age, ethnicity and height USA	Tetraplegia (n=66) Mean age: 40 White race: 31.8% (n=21) African American: 7.6% (n=5) Hispanic: 60.6% (n=40) Mean duration of SCI: 14 Motor complete: 68.2% Motor Incomplete: 31.8% Paraplegia (n=67) Mean age: 37 (p<0.0005 vs. control) White race: 16.4% (n=11)	<u>Mean BMI</u> Tetraplegia (n=66): 25.4 Paraplegia (n=67): 25.8 Control (n=100): 27.3 <u>Comparisons among groups of total body fat</u> A. Mean total body fat (kg) Tetraplegia: 24.1* Paraplegia: 23.9† Control: 18.7 *p <0.005, tetraplegia vs. control. †p <0.01, paraplegia vs. control B. Mean total body fat (kg) by age among groups Tetraplegia: <40 (years) 20.3; ≥40 29.2, p<0.01

Appendix E Table 1. Prevalence of metabolic syndromes, diabetes, glucose, lipid abnormalities, and BMI in adults with chronic posttraumatic SC (continued)

Reference	Study Design	Subject Characteristics	Prevalence
		African American: 9.0% (n=6) Hispanic: 74.6% (n=50) Mean duration of SCI: 12 Motor complete: 73.1% Motor Incomplete: 26.9% Complete (n=94) Incomplete (n=39) Control (n=100) Mean age: 44 White race: 19% (n=19) African American: 6% (n=6) Hispanic: 75% (n=75)	Paraplegia: <40 22.7; ≥40 26.2 Control: <40 18.7; ≥40 18.8 C. Mean percent of body fat by age among groups Tetraplegia: <40 31%; ≥40 39%, p<0.01 Paraplegia: <40 30%; ≥40 36%, p<0.01 Control: <40 21%; ≥40 23% D. Mean total body fat (kg), motor-complete and incomplete: mean total body fat (kg) Tetraplegia: Complete 23.3; Incomplete 26.1 Paraplegia: Complete 24.7; Incomplete 21.7 E. Mean percent of body fat, motor-complete and incomplete: Tetraplegia: Complete 34%; Incomplete 35% Paraplegia: Complete 33%; Incomplete 28%
Bauman, 1999[15]	Cohort of outpatient SCI patients (n=320) seen for annual exam vs. able-bodied controls (n=303) matched by age and ethnicity USA	SCI subjects (n=320) Mean age: 41 (20-77) Male: 73.0% (n=234) Female: 27.0% (n=86) White: 47.0% (n=150) African American: 28.0% (n=90) Hispanic: 26.0% (n=83) Mean duration of SCI: 15 (1-57) Motor complete: 65.6% Motor incomplete: 34.4% Sedentary able-bodied controls (n=303) Mean age: 42 (21-75) Male: 81.0% (n=245) Female: 16.0% (n=48) White: 56.0% (n=170) African American: 29.0% (n=88) Hispanic: 16.0% (n=48)	<u>Mean BMI and Body Fat</u> A. SCI subjects (n=320) Mean BMI: 25 (13.8-54.8) Estimated body fat: 36.0% (21.1-72.3) BMI ≥27.8: 28.0% B. Sedentary able-bodied controls (n=303) Mean BMI: 29.9 (19.7-49.9) (p<0.0001 vs. SCI) Estimated body fat: 31.0% (10.2-72.5) (p<0.0001 vs. SCI) BMI ≥27.8: 64.0% (p<0.0001 vs. SCI)
Bauman, 1999[2]	Cross-sectional study including a convenience sample of 201 SCI patients from a single clinical center who had oral glucose tolerance tests. Patients were subgrouped by level of injury. USA	Mean age (years): 39 Male: 84% (n=169) Female: 16% (n=32) White: 27% (n=54) Latino: 57% (n=114) African American: 14% (n=28) BMI: 25 Injury: Mean duration of SCI (years): 13 Mean age at injury: 25 Tetra complete: 28% (n=56) Tetra incomplete: 12% (n=25)	<u>Mean BMI (kg/m^2):</u> Overall: 25 Tetra complete: 23 Tetra incomplete: 26 Para complete: 25 Para incomplete: 25 Total body fat (%): Overall: 34 Tetra complete: 34 Tetra incomplete: 35 Para complete: 34

Appendix E Table 1. Prevalence of metabolic syndromes, diabetes, glucose, lipid abnormalities, and BMI in adults with chronic posttraumatic SC (continued)

Reference	Study Design	Subject Characteristics	Prevalence
		Para complete: 42% (n=84) Para incomplete: 18% (n=36)	Para incomplete: 31
Anson, 1996[24]	Data from 348 post-acute SCI patients were collected during routine followup in Georgia USA	Mean age: 36.6 (median 33 years; range 32.4-44.2) Male: 81.9% (n=285) Female: 18.1% (n=63) White 80.2% (n=279) Non-white 19.5% (n=69) <u>Time since injury</u> 1-2 years 25.9% (n=90) 3.5 years 25.3% (n=88) 6-10 years 29.3% (n=102) 11-15 years 11.8% (n=41) >15 years 7.8% (n=27)	<u>Weight status</u> Underweight 22.3% (n=69); Ideal weight 37.9% (n=117) Overweight 26.9% (n=83); Obese 12.9% (n=40) <u>Weight status by years since injury</u> Time since injury A. 1-2 years Underweight 21.6% (n=19); Ideal weight 39.8% (n=35) Overweight 29.5% (n=26); Obese 9.1% (n=8) B. 3-5 years Underweight 20.3% (n=16); Ideal weight 41.8% (n=33) Overweight 24.1% (n=19; Obese 13.9% (n=11) C. 6-10 years Underweight 25.6% (n=21); Ideal weight 37.8% (n=31) Overweight 24.4% (n=20); Obese 12.2% (n=10) D. 11-15 years Underweight 27.0% (n=10); Ideal weight 24.3% (n=9) Overweight 27.0% (n=10); Obese 21.6% (n=8) E. >15 years Underweight 13.0% (n=3); Ideal weight 39.1% (n=9) Overweight 34.8% (n=8); Obese 13.0% (n=3) *Weight categories not defined
Zhong, 1995[10]	SCI men studied during annual physical exam. Veterans Affairs patients, USA	197 men with chronic SCI, 103 paraplegia and 94 tetraplegia Mean age: 50 (21-77) Mean duration of SCI: 18 (1-49) Exclusion criteria: No prior history of diabetes or gout	<u>Mean BMI</u> 25 (15.8-47.8) BMI >27.8 (n=48) There was a positive correlation between BMI and % body fat (r=0.59, p<0.001) By linear regression analysis, there was a positive correlation between BMI (r=0.20, p<0.01) and LDL (r=0.17, p<0.05), but not with age, date of injury, peak plasma glucose, or any other lipoprotein value.
Bauman, 1992[18]	Veteran SCI patients, matched for age and BMI, were compared to veteran controls USA	Paraplegia: n=50 Mean age (years): 49.5 Mean duration of SCI: 17.6 Tetraplegia: n=50 Mean age: 46.2 Mean duration of SCI: 15.0 Control: n=50 Mean age: 48.8	<u>Mean BMI</u> Paraplegia: n=50: 26.0 Tetraplegia: n=50: 24.0 Control: n=50: 26.8

Appendix E Table 2. Cardiovascular events in adults with chronic traumatic SCI

Study	Sample	Risk factors	Outcomes
Cardus, 1992[25] Case-control study to compare probability of cardiovascular diseases in patients with SCI compared to the able-bodied persons. Adjustment not reported. Matching by age.	640 patients over 18 year of age, more than 9 months after traumatic SCI who resided in the county area and had to use assistive device for walking. 96 eligible. Controls: 96 non trained able bodied men matched by age.	Risk factors of cardiovascular disease; age, blood pressure, blood cholesterol, fasting glucose, ECG abnormalities, self reported smoking. Age at injury and the time after injury.	Risk of cardiovascular diseases using Framingham risk calculation with cut off for low risk as 3% - probability of healthy 50 year old men, non smoker, non diabetic, with normal ECG, systolic blood pressure blow 125 mmHg, and blood cholesterol less than 200 mg.

Age	Time After Injury (Months)	Number	% with Risk >3% in SCI vs. Controls
21±3.2	65±27	25	0 vs.1
19.1±3.5	252±96	30	3.1 vs. 8.3
44.7±12	57±21	29	13.5 vs.14.5
37.4±6.6	232±122	12	9.4 vs. 7.2

| Krum, 1992[19]
Cross sectional analysis of cardiovascular morbidity in association with risk factor scores among Australian adults with spinal cord injury.
Time: 1983
Adjustment: age
Matching by gender and age | 327 patients with SCI and age and sex matched controls from the 1983 Australian Risk Factor Prevalence Study.
Exclusion criteria not reported but only 102 patients who completed questionnaire were analyzed.
Population: 102 patients, 19% female, 25-64 years old; 34% more than 10 years after injury; 40% with cervical, 35% with lower thoracic, 13% with upper thoracic, and 12% with lumbar levels of injury; ~41% with Frankel Grade A of completeness complete motor and sensory deficit | Cardiovascular risk factor score (RFS) derived from the MRFIT study (age, diastolic blood pressure (DBP), total cholesterol (TC) level, cigarettes/day, sex):
=0.1091*Age+0.288*DBP+0.008*Total cholesterol+0.227*cigarettes/day. | Prevalence of arterial hypertension, angina, myocardial infarction, cerebrovascular accident, and diabetes. Age adjusted percentile position of scores were compared to the general population. |

Prevalence	SCI	General Population
Hypertension	9	20
Angina	2	2.5
MI	1.9	1.8
Cerebrovascular accident	1	0.7
Diabetes	6	2

	Odds Ratio (95% CI)		
Hypertension	**0.40**	**0.17**	**0.92**
Angina	0.67	0.11	4.08
MI	1.00	0.14	7.24
Cerebrovascular diseases	1.00	0.06	16.21
Diabetes	3.13	0.62	15.89

Cardiac risk factor score

Age	Mean of Percentile Position in Comparison to Age Matched Subjects in the National Heart Foundation Study	STD
25-29	11	15
30-34	18	18
35-39	30	15.5
40-44	21	21

Appendix E Table 2. Cardiovascular events in adults with chronic traumatic SCI (continued)

Study	Sample	Risk factors	Outcomes		
			45-49	45	28
			50-54	34	37.5
			55-59	26	17
			60-69	44	17.5
			all ages	27.5	16.5
			>10 years after injury	34	29
Whiteneck, 1992[26] Retrospective analysis to examine morbidity and mortality in SCI patients compared to the general population. Time: 1943-1970 Adjustment age, gender, level of injury, time after injury	834 individuals with 20 or more years after SCI treated at the British spinal injury centers Exclusion criteria: childhood injuries, injuries in older adults (>55 years), not willing to complete interview. Population: 13% female, 412 survivors, 282 (68%) completed the interview, Age at time of injury was between 15 and 55 years—15-24 years 42%, 25-34 years 27%, 35-44 years 18%, 45-55 years 13%; median survival time 32 years; 85% survived at 10 years, 71% at 20 years, 53% at 30 years, and 35% at 40 years after injury.	Level and completeness of injury and age at injury. Paraplegia with Frankel grades A, B, or C – no functional motor preservation; Quadriplegia with Frankel grades A, B, or C – no functional motor preservation; Para- or quadriplegia with Frankel grades D or E – functional motor preservation	Disease-specific mortality. Cardiovascular deaths 84 (23.2%), 38 patients died from acute myocardial infarction, 31 from other disease of heart, 10 from cerebrovascular diseases, 5 from other circulatory problems. **CVD Mortality** / **N** / **% among Total Deaths** All cases: 84 / 23.2 Para ABC: 48 / 23.2 Quadriplegia ABC: 8 / 14.1 All D and E: 28 / 28.3 Annual CVD mortality rates/1,000 SCI cases and age matched **Age** / **SCI** / **General Population** 15-24: 0.8 / 0.1 25-34: 0.7 / 0.2 35-44: 2.4 / 0.8 45-54: 4.4 / 3.2 55-64: 13 / 9.4 65-74: 21 / 25.1 75-84: 102 / 61.4 CVD Incidence by age (episodes/100 cases per year) **Age at Episode** / **Heart-Circulatory** <30: 2 30-39: 2.9 40-49: 5.2 50-59: 8.1 60+: 19 **Years After Injury** <10: 2.9 10-19y: 5.4 20-29y: 10 30+: 14	

Appendix E Table 2. Cardiovascular events in adults with chronic traumatic SCI (continued)

<table>
<tr><th>Study</th><th>Sample</th><th>Risk factors</th><th>Outcomes</th></tr>
<tr><td>DeVivo, 1993[27]
Retrospective analysis to compare age, sex, race, and cause-specific mortality rates in patients with SCI 12 years after injury vs. the general population.
Time: 1973-December 21, 1985
Adjustment: standardization by age, sex, and race</td><td>9,135 persons injured between 1973 and 1984 and treated at any of 13 regional spinal cord injury care systems
Exclusion criteria: not reported.
Population: 854 SCI patients who died during followup time.</td><td>Age, neurological level, and extent of spinal cord lesion</td><td>Standardized mortality ratios versus general population (ratio of 1 = no increase in cause-specific death rate) (SMR)
Ischemic heart disease (ICD codes 410-414)
Non ischemic heart disease (ICD codes 420-429)
Cerebrovascular diseases (ICD codes 430-438)
Diseases of arteries (ICD codes 440-448)
Mortality in SCI patients:
<table>
<tr><th>Cause</th><th>Actual Death</th><th>SMR</th><th>SMR 95% CI</th></tr>
<tr><td>Ischemic heart disease (ICD codes 410-414)</td><td>61</td><td>1.3</td><td>1-1.6</td></tr>
<tr><td>Non ischemic heart disease (ICD codes 420-429)</td><td>84</td><td>5.6</td><td>4.4-6.8</td></tr>
<tr><td>Cerebrovascular diseases (ICD codes 430-438)</td><td>22</td><td>1.8</td><td>1-2.6</td></tr>
<tr><td>Diseases of arteries (ICD codes 440-448)</td><td>14</td><td>4.5</td><td>2.1-6.9</td></tr>
</table></td></tr>
<tr><td>Imai, 1994[8]
Cross-sectional analysis of morbidity rates and standardized morbidity ratios according to the site of injury compared to the general population.
Time: 1990
Adjustment: age</td><td>307 (244 responded) men with SCI identified during the National Livelihood Basic Survey in Japan engaged in light work at special centers, who had medical examination for blood pressure and medical history.
Exclusion criteria: 195 were analyzed among 228 eligible for not reported reasons.
Population: mean age was 49.5 years old; the average post-injury period 17.9 years; 19 patients injured at level C-T5, 24 at T6-T10, 139 at T11-L1, and 13 at L2 or lower.</td><td>Level of injury: C-T5; T6-T10; T11-L2; L2 ; Age: 40th, 50th, 60th</td><td>Outpatient rate of hypertension, renal diseases, and diabetes = (number of outpatients/population studied) * 1,000
Standardized morbidity ratios=(total number of outpatients/ expected number of outpatients) * 100
Obesity. Self reported treatment with anti-hypertensive medications.
<table>
<tr><th>Level of Injury</th><th>N</th><th>Prevalence/ 1,000</th><th>Standardized Morbidity Ratios
General Population = 100</th></tr>
<tr><td>C-T5</td><td></td><td></td><td></td></tr>
<tr><td>Renal diseases</td><td>2</td><td>105</td><td>2,049</td></tr>
<tr><td>T6-T10</td><td></td><td></td><td></td></tr>
<tr><td>Renal diseases</td><td>6</td><td>250</td><td>4,187</td></tr>
<tr><td>Hypertension</td><td>5</td><td>208</td><td>300</td></tr>
<tr><td>T11-L2</td><td></td><td></td><td></td></tr>
<tr><td>Hypertension</td><td>21</td><td>151</td><td>221</td></tr>
<tr><td>Renal diseases</td><td>18</td><td>129</td><td>2,194</td></tr>
<tr><td>Diabetes mellitus</td><td>9</td><td>65</td><td>326</td></tr>
<tr><td>Hypotension</td><td>3</td><td>22</td><td>607</td></tr>
<tr><td>L2</td><td></td><td></td><td></td></tr>
<tr><td>Hypertension</td><td>5</td><td>385</td><td>697</td></tr>
<tr><td>Renal diseases</td><td>4</td><td>308</td><td>5,569</td></tr>
<tr><td>Diabetes mellitus</td><td>2</td><td>154</td><td>945</td></tr>
</table></td></tr>
</table>

Appendix E Table 2. Cardiovascular events in adults with chronic traumatic SCI (continued)

<table>
<tr><th>Study</th><th>Sample</th><th>Risk factors</th><th>Outcomes</th></tr>
<tr><td></td><td></td><td></td><td>Prevalence of obesity:
<table><tr><th>Age</th><th>Obesity</th></tr><tr><td>40th</td><td>6.8</td></tr><tr><td>50th</td><td>2.5</td></tr><tr><td>60th</td><td>1</td></tr></table>
<table><tr><th colspan="3">Treatment with Antihypertensive Medications</th></tr><tr><th>Age</th><th>SCI</th><th>General Population</th></tr><tr><td>30th</td><td>9.1</td><td>2</td></tr><tr><td>40th</td><td>15.6</td><td>5.1</td></tr><tr><td>50th</td><td>21.8</td><td>14.4</td></tr><tr><td>60th</td><td>45.5</td><td>22.8</td></tr></table></td></tr>
<tr><td>Nam, 1994[28]
Retrospective medical chart review to test the hypothesis that the SCI population has an increased incidence of stroke, and to identify stroke risk factors unique to SCI patients.
Time: 1980-1990.
Adjustment not reported</td><td>1,027 patients admitted to medical centers with stroke and 2,007 patients with SCI (paraplegia or quadriplegia) including 13 patients with stroke.
Exclusion criteria: non traumatic SCI, stroke before SCI. Population: 2 patients with traumatic SCI followed by stroke.
Population: average age 37.2±16.1years</td><td>Traumatic SCI</td><td>Prevalence of stroke after traumatic SCI: 0.10 percent (2 cases/2,007 SCI patients.</td></tr>
<tr><td>Levi,1995[29]
Cross-sectional Stockholm Spinal Cord Injury Study.
Time: 1988-89.
Adjustment: age, sex, socioeconomic status</td><td>326 patients with SCI from the Stockholm Spinal Cord Injury Study, residents of the Greater Stockholm area.
Control participants in the Swedish Annual Level of Living Survey (1,978 interviews)
Exclusion criteria: residents of Gotland
Population: 80% males</td><td>Spinal cord injury</td><td>Prevalence of diabetes, hypertension, obesity, cardiac problems and self reported use of cardiac medications.
<table><tr><th>Disorder</th><th>SCI</th><th colspan="4">SCI/Controls</th></tr><tr><th></th><th>%</th><th>Crude Odds Ratio</th><th>p Value</th><th>Adjusted Odds Ratio</th><th>p Value</th></tr><tr><td>Diabetes mellitus</td><td>1</td><td>1.01</td><td>0.98</td><td>1.2</td><td>0.74</td></tr><tr><td>Circulatory</td><td>2</td><td>0.22</td><td>0.0003</td><td>0.25</td><td>0.01</td></tr><tr><td>Hypertension</td><td>0</td><td></td><td></td><td></td><td></td></tr><tr><td>Cardiac</td><td>2</td><td>0.64</td><td>0.35</td><td>0.72</td><td>0.5</td></tr><tr><td>Use of cardiac medication</td><td>2</td><td>0.46</td><td>0.07</td><td>0.69</td><td>0.4</td></tr></table></td></tr>
</table>

Appendix E Table 2. Cardiovascular events in adults with chronic traumatic SCI (continued)

<table>
<tr><th>Study</th><th>Sample</th><th>Risk factors</th><th>Outcomes</th></tr>
<tr>
<td>Levi, 1995[30]
Cross-sectional analysis of the associations between patient characteristics and prevalence of internal diseases and symptoms.
Adjustment: age, gender, duration of injury, functional status</td>
<td>353 subjects with traumatic SCI, participants in The Stockholm Spinal Cord Injury Study.
Exclusion criteria- not reported.
Population: 19% female
0-4 years after injury 23.97%
5-17 years after injury 48.76%
18-44 years after injury 24.52%</td>
<td>ASIA/IMSOP Impairment Scale Grade level of injury as cervical complete, thoracic incomplete, lumbo-sacral complete, lumbo-sacral incomplete; age at injury as continuous variable; duration of injury as shorter (0-4 years), intermediate (5-17 years), longer (18-44 years)</td>
<td>Prevalence of cardiovascular symptoms: ankle-leg edema, chest pain, palpitations.
<table>
<tr><th>Risk Factors</th><th>N</th><th>% with CVD Symptoms</th></tr>
<tr><td>Total</td><td>353</td><td>58</td></tr>
<tr><td>Males</td><td>286</td><td>55</td></tr>
<tr><td>Females</td><td>67</td><td>69</td></tr>
<tr><td>Age at injury 21-40</td><td>162</td><td>57</td></tr>
<tr><td>Age at injury 41-77</td><td>89</td><td>61</td></tr>
<tr><td>Duration of injury 0-4 years</td><td>87</td><td>48</td></tr>
<tr><td>Duration of injury 5-17 years</td><td>177</td><td>55</td></tr>
<tr><td>Duration of injury 18-44 years</td><td>89</td><td>72</td></tr>
<tr><td>Cervical injury, complete</td><td>53</td><td>72</td></tr>
<tr><td>Cervical injury, incomplete</td><td>93</td><td>57</td></tr>
<tr><td>Thoracic injury, complete</td><td>78</td><td>72</td></tr>
<tr><td>Thoracic injury, incomplete</td><td>48</td><td>58</td></tr>
<tr><td>Lumbosacral injury, complete</td><td>8</td><td>62</td></tr>
<tr><td>Lumbosacral injury, incomplete</td><td>47</td><td>38</td></tr>
</table>
</td>
</tr>
<tr>
<td>McGlinchey-Berroth, 1995[9]
Cross-sectional analysis of hospitalizations among patients surviving late life injury.
Time: 1989-1992.
Adjustment not reported.</td>
<td>534 patients with SCI admitted to the high quality Spinal Cord Injury Service of the VA medical center (part of the Aging with a Long-Term Disability Research Program database).
Exclusion criteria: not available discharge summary; current hospitalization, transfer to the long term care facility.
Population: 510 discharged from hospitals were included in the analysis; mean age of 50 years (16-84 years); 23% were at least 65 years of age; 16±13.1 years after injury, 12±12 hospital admissions since injury; 99% male.</td>
<td>Group 1 (N=225) persons <50 years of age at the time of injury and <5 years at index submission.
Group 2 (N=162) <50 years of age at the time of injury but >50 years at the time of index admission.
Group 3 (N=93) persons >50 years of age at the time of injury.</td>
<td>Hospitalization due to myocardial infarction (ICD-9-CM 401.9), diabetes (ICD 250.00 to 250.9), and hypertension (ICD 401.0 to 401.9).
Prevalence of CVD in SCI group
<table>
<tr><th>Outcomes</th><th>Group 1</th><th>Group 2</th><th>Group 3</th><th>Total</th></tr>
<tr><td>N</td><td>255</td><td>162</td><td>93</td><td></td></tr>
<tr><td>Myocardial infarction</td><td>5.09</td><td>25.3</td><td>33.33</td><td></td></tr>
<tr><td>Diabetes</td><td>3.92</td><td>12.34</td><td>22.58</td><td>9.8</td></tr>
<tr><td>Hypertension</td><td>5.09</td><td>25.3</td><td>33.33</td><td>16.67</td></tr>
<tr><td>Stroke</td><td>0</td><td>0</td><td>0</td><td></td></tr>
</table>
</td>
</tr>
<tr>
<td>Imai, 1996[7]
Cross-sectional analysis of morbidity in SCI patients compared to the general Japanese population.
Time: 1989.
Adjustment not reported,</td>
<td>244 males with SCI at several Rehabilitation Centers (Workman's Accident Compensation Rehabilitation Workshops).
Exclusion criteria: 20% did not respond to the questionnaire.
Population: Age 22 to 69 years (mean 47.6); mean postinjury periods 17.3 years; C-T5 level -1%; T6-T10 12%;</td>
<td>Level of injury: C-T5; T6-T10; T11-L2; L2-
Age: 40th, 50th, 60th</td>
<td>Outpatient rate = (number of outpatients/population studied) * 1,000
Standardized morbidity ratios (SMR) = (total number of outpatients/expected number of outpatients) * 100
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</tr>
</table>

Appendix E Table 2. Cardiovascular events in adults with chronic traumatic SCI (continued)

<table>
<tr><th>Study</th><th>Sample</th><th>Risk factors</th><th>Outcomes</th></tr>
<tr><td>standardization by age with general population</td><td>T11-Ll 69%; L2 -8%.
Control group (general population). National Livelihood Basic Survey conducted by the Ministry of Health and Welfare in 1989, on 800,000 people in 240,000 households.</td><td></td><td>
<table>
<tr><th></th><th>SCI Male</th><th>General Pop, Male</th><th>N Outpatients with SCI/244</th><th>SMR</th></tr>
<tr><td>All CVD</td><td>536.9</td><td>224.8</td><td>127</td><td>337</td></tr>
<tr><td>Hypertension</td><td>163.9</td><td>45.4</td><td>40</td><td>250</td></tr>
<tr><td>Hypotension</td><td>16.4</td><td>2.5</td><td>4</td><td>472</td></tr>
<tr><td>Ischemic heart diseases</td><td>16.4</td><td>9.0</td><td>4</td><td>146</td></tr>
<tr><td>Other diseases of circulatory system</td><td>8.2</td><td>7.0</td><td>2</td><td>93</td></tr>
<tr><td>Diabetes mellitus</td><td>61.5</td><td>12.2</td><td>15</td><td>323</td></tr>
</table>
</td></tr>
<tr><td>Hartkopp,1997[31]
Retrospective cohort to examine mortality among SCI compared to the general population.
Time: SCIs that occurred between January 1, 1953, and December 31, 1990; deaths before December 31, 1992.
Adjustment standardization by age</td><td>888 individuals (713 men and 175 women) who survived SCI and were rehabilitated at the Centre for Spinal Cord Injured in Hornbnk, Denmark.
Exclusion criteria: permanent respiratory support, severe SCI with specialized treatment
Population: median age at the time of injury 27.5 in 1953-1971 and 28.5 from 1972-1990</td><td>Neurological level of last preserved segment at time of injury, functional level according to Frankel scale at last followup: functionally complete tetraplegia (cervical cord lesions and Frankel class A-C), functionally complete paraplegia (thoracic and lumbar cord lesions and Frankel class A-C), Frankel class D, and Frankel class E.
Years of injury: 1953-1971 and 1972-1990</td><td>Mortality from cardiovascular diseases from The National Registry of Causes of Death and the general public records of vital statistics Denmark Statistic; medical records, death certificates, and post mortem records.
<table>
<tr><th></th><th colspan="2">Men</th><th colspan="2">Women</th><th colspan="2">All</th></tr>
<tr><td>Death (ICD codes)</td><td>N</td><td>%</td><td>N</td><td>%</td><td>N</td><td>%</td></tr>
<tr><td>Cardiovascular disease (390-458)</td><td>47</td><td>24</td><td>9</td><td>23</td><td>56</td><td>24</td></tr>
<tr><td>Ischemic heart disease (410-414)</td><td>19</td><td>10</td><td>3</td><td>8</td><td>22</td><td>9</td></tr>
<tr><td>Cerebrovascular disease (430-438)</td><td>6</td><td>3</td><td>2</td><td>5</td><td>8</td><td>3</td></tr>
<tr><td>Lung embolus (450)</td><td>6</td><td>3</td><td>0</td><td>0</td><td>6</td><td>3</td></tr>
<tr><td>Total</td><td></td><td></td><td></td><td></td><td>236</td><td>100</td></tr>
</table>
<table>
<tr><th></th><th colspan="2">Tetraplegia C</th><th colspan="6">Paraplegia, T-L</th></tr>
<tr><td>Frankel</td><td colspan="2">A-C</td><td colspan="2">A-C</td><td colspan="2">D</td><td colspan="2">E</td></tr>
<tr><td></td><td>N</td><td>%</td><td>N</td><td>%</td><td>N</td><td>%</td><td>N</td><td>%</td></tr>
<tr><td>Cardiovascular disease</td><td>9</td><td>13</td><td>14</td><td>20</td><td>27</td><td>36</td><td>6</td><td>24</td></tr>
<tr><td>Ischemic heart disease</td><td>2</td><td>3</td><td>5</td><td>7</td><td>10</td><td>14</td><td>5</td><td>20</td></tr>
<tr><td>Cerebrovascular disease</td><td>2</td><td>3</td><td>2</td><td>3</td><td>4</td><td>5</td><td></td><td></td></tr>
<tr><td>Lung embolus</td><td>1</td><td>1</td><td>1</td><td>1</td><td>3</td><td>4</td><td>1</td><td>4</td></tr>
<tr><td>Total</td><td>67</td><td></td><td>69</td><td></td><td>75</td><td></td><td>25</td><td></td></tr>
</table>
Standardized mortality ratios (SMR) = observed to expected number of deaths</td></tr>
</table>

Appendix E Table 2. Cardiovascular events in adults with chronic traumatic SCI (continued)

<table>
<tr><th>Study</th><th>Sample</th><th>Risk factors</th><th>Outcomes</th></tr>
<tr><td>Rish, 1997[13]
Retrospective review of the charts to analyze incidence and causes of deaths among Vietnam veterans over 25 periods after SCI.
Time: 1967-1970 to 1995.
Adjustment not reported.</td><td>230 patients with SCI identified in the Vietnam Head and Spinal Cord Injury Study Registry who survived more than 72 hours, with significant myelopathy; and with available medical records.
Exclusion criteria not reported.
Population: mean age at injury 21.4 years, with previous excellent health (active duty military personnel); median time after injury 25 years</td><td>Level of injury; Myelopathy (quadriplegic, paraplegic, complete, incomplete); Mechanism of injury (penetrating wounds, closed injuries)</td><td>The initial diagnosis of hypertension, obesity, diabetes, coronary artery disease, myocardial infarction, cerebral vascular accidents. Death from myocardial infarction.
Prevalence of diabetes and CVD n SCI patients:
<table><tr><th>Diagnosis</th><th>N</th><th>%</th></tr><tr><td>Hypertension</td><td>48</td><td>21</td></tr><tr><td>Obesity</td><td>32</td><td>14</td></tr><tr><td>Diabetes</td><td>29</td><td>13</td></tr><tr><td>Coronary artery disease</td><td>14</td><td>6</td></tr><tr><td>Myocardial infarction</td><td>8</td><td>3</td></tr><tr><td>Cerebrovascular accidents</td><td>4</td><td>2</td></tr></table>
Mortality from Myocardial infarction 2.2% (5 cases/230 patients)
<table><tr><th>Year After Injury</th><th>Death from Myocardial Infarction</th></tr><tr><td>5</td><td>1</td></tr><tr><td>20</td><td>2</td></tr><tr><td>>20</td><td>2</td></tr></table></td></tr>
<tr><td>DeVivo, 1999[32]
Retrospective cohort to examine trends in mortality and causes of death among patients with SCI.
Time: 1973-1998
Adjustment: age at injury, sex, race, etiology of injury, number of days from injury, neurological level of injury, Frankel grade or, American Spinal Injury Association (ASIA) Impairment Scale, ventilator dependency, sponsor of care, autopsy.</td><td>28,239 consecutive patients admitted to the model system or to a Shriner's Hospital within 1 year of traumatic SCI who survived at least 24 hours after injury.
Exclusion criteria not reported.
Population: 19% females; 67.6% Caucasian, 20.7% African American, 8.1% Hispanic, 3.6% Asian, Native American, or other; 54% of injuries occurred between the ages of 16 and 30 years, and 23% between 31 and 45 years; 53% cervical, C5-C8 34.5% and C1-C4 18.5% of the population; 53.8% neurologically complete, 27.2% motor functional, 19% sensory sparing or motor nonfunctional; 2.9% were ventilator-dependent.</td><td>Age at injury, neurological level of injury (C1-C4, C5-C8, T1-S5), Frankel grade or ASIA Impairment Scale (each grade separately), injury year (1973-1977, 1978-1982, 1983-1987, 1988-1992, 1993-1998).</td><td>Length of survival confirmed with the Social Security Death Index and cause of death from the National Spinal Cord Injury Statistical Center, hospital discharge summaries, death certificates, and autopsy reports.
Standardized mortality ratio - ratio of actual to expected deaths for each neurological category and ventilator status from each of three starting points (time of injury, first anniversary of injury, and fifth anniversary of injury) until followup termination. These standardized mortality ratios were then applied to 1994 general population mortality rates (the most recent available) to determine life expectancies.

CVD mortality after 1 year of injury:
<table><tr><th>Year of Death</th><th>N of Deaths</th><th>Heart, %</th><th>Stroke, %</th><th>Arteries, %</th></tr><tr><td>1973-77</td><td>74</td><td>10.8</td><td>1.4</td><td>0.0</td></tr><tr><td>1978-82</td><td>278</td><td>15.8</td><td>4.0</td><td>1.1</td></tr><tr><td>1983-87</td><td>370</td><td>20.3</td><td>3.5</td><td>2.2</td></tr><tr><td>1988-92</td><td>340</td><td>18.5</td><td>3.8</td><td>1.8</td></tr><tr><td>1993-98</td><td>481</td><td>20.6</td><td>2.9</td><td>1.2</td></tr><tr><td>Total</td><td>1,543</td><td>18.8</td><td>3.4</td><td>1.5</td></tr></table>.
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.</td></tr>
</table>

Appendix E Table 2. Cardiovascular events in adults with chronic traumatic SCI (continued)

Study	Sample	Risk factors	Outcomes
			Adjusted Odds Ratios for CVD Death Occurring After the First Post-injury Year Relative to All Other Causes: **Heart, Stroke, and Arteries** 1978-82: 1.62 (0.74-3.55) 1983-87: 1.86 (0.86-4.05) 1988-92: 1.35 (0.61-2.99) 1993-1998: 1.37 (0.61-3.07)
Groah, 2001[33] Prospective observation to examine incidence of cardiovascular disease in people with long-term SCI. Time: 1970-1993 Followup after injury: 20 years Adjustment: age	834 patients alive >20 years after spinal cord injury identified in 2 British Spinal Injuries Centers Eligible 545, 15-55 years old at the time of injury, initially admitted to one of the 2 British SCI centers within 1 year of injury, residence in a 13-county catchment area at the time of injury. Exclusion criteria: death during 20 years after injury, congenital cardiovascular diseases, subclinical disease. Population: mean age 57±10 years, duration of SCI 29±6 years, females 14%	Level of injury and Frankel/ASIA grade: 1. Tetraplegia Frankel/ ASIA Impairment grade A, B, or C (Tetra ABC) 2. Paraplegia Frankel/ ASIA Impairment grade A, B, or C (Para ABC) 3. All Frankel/ASIA Impairment grade Ds (All D) (37% between C4 and C7 and 40% between T11 and L4)	Incidence of cardiovascular diseases calculated by dividing the number of new CVD events by the total SCI person-time for each neurological category. Cardiovascular disease outcomes defined by ICD/9 codes 390-448 and 745-747 and obtained through medical record review: All CVD, coronary heart disease, hypertension, cerebrovascular disease, valvular disease, and dysrhythmia, "other cardiovascular disease" cardiomegaly, congestive heart failure, thrombophlebitis, endocarditis, deep venous thrombosis, and venous insufficiency.
Davies, 2002[34] Cross-sectional analysis to assess the risk of cardiovascular morbidity in adults with SCI relative to lifestyle risk factors. Time: 1972-1992 Adjustment: age, duration of cigarette use	140 patients with segmental, nonprogressive traumatic SCI, benign tumors, transverse myelitis, vascular infarcts, and congenital defects. Exclusion criteria: death (20), refusal to participate (10), poor health (1) Loss of followup: 12.3% Population: 97 patients, mean age 47.5±4.5; 10% female; age at injury 31.67±16.4; duration of disability 15.9±10.1 years. Quadriplegia 42% Paraplegic 57% Undetermined 1% Complete 33% Incomplete 64% Undetermined 3% Traumatic 87% Nontraumatic 13%	Self reported current lifestyle risks using selected sections of Lyndhurst Computerized Health Risk Assessment (LCHRA): Physical activity, BMI, cigarette use and alcohol consumption. Variation in lifestyle since SCI. Internal consistency reliabilities for the subscales used in this study ranged from a low a = 0.56 for bladder management to a high a = 0.82 for physical activity.	Cardiovascular morbidity measured using the London School of Hygiene Questionnaire on Chest Pain and Intermittent Claudication (LSHQCPIC) validated against physician diagnosis in general and patient populations with specificity 48-98% and sensitivity from 25-83%. In univariate analyses (correlations and chi-squares), cardiovascular morbidity was associated at the p <0.25 level with duration of cigarette use, age, monthly alcohol consumption, bladder self-care, frequency of excessive alcohol use, BMI, and a complete lesion. **OR** **95% CI** Age 1.04 0.99 1.08 Duration of cigarette use 1.03 0.99 1.07 **N** **Prevalence** Cardiovascular morbidity 13 13.4

Appendix E Table 2. Cardiovascular events in adults with chronic traumatic SCI (continued)

Study	Sample	Risk factors	Outcomes
Prakash, 2002[6] Retrospective cohort to examine prevalence of ECG abnormalities in individuals with spinal cord injuries. Time: 1987-1999 Followup: 5.6 years Adjustment not reported	47,070 patients with at least one ECG obtained in the Palo Alto Veterans Affairs Health Care System Exclusion criteria: inpatient setting or emergency room at the time of ECG Population: 26,734 able-bodied male veterans and 654 patients with SCI (age 50 ± 14)	Level of injury by the effect on sympathetic innervation of heart: intact injury Level T6 and below or impaired injury level T5 and above. Age below and above 65 years	Clinical events: Diabetes, hypertension, coronary heart disease, congestive heart failure, pulmonary disease. Standardized computerized ECG. Left ventricular hypertrophy: R wave >11mm in lead aVL, an S wave of >24mm in lead V1, an R wave of >26mm in lead V5, or SV1 + RV5 or V6 >35mm. Abnormal ECG as the presence of one of: right or left bundle branch blocks, intraventricular conduction delay, right ventricular hypertrophy or LVH, abnormal ST depression, atrial fibrillation, or QTc greater than 450 msec. Abnormal ST depression: ST depression >0.5mm in any one of leads II, V2, or V5. LVH with strain as LVH voltage criteria with abnormal ST depression. Mortality obtained from the Social Security Death Index.
Cardenas, 2004[35] Cross-sectional analysis at several time points to examine the reasons for rehospitalization in persons with acute traumatic spinal cord injury. Time: 1995-2002; 20 years of followup. Adjustment: age, gender, education, ethnicity, marital and vocational status.	Patients with traumatic SCI identified in the Model System (hospitalized between acute hospitalization and comprehensive inpatient rehabilitation, admitted to a Model System within 365 days of injury) who reside in the geographic region in which the Model System facility is located. 5,180 patients analyzed, 4,251 (82.1%) had year-1 followup interviews; 3,904 (91.8%) were matched by the Model System data. Exclusion criteria: no followup interviews with system identification code and unique patient identifier in the Model Systems Form II at first year anniversary; refusal to participate (1 site); small sample size of patients at sites. Loss of followup: 17.9 %. Population: 3,904 patients with 11,047 followup interviews, 21.4% female, 61.4% White; C1-4 ASIA grades A, B, C: 4.6% C1-4 ASIA grade D: 6.1% C5-8 ASIA grades A, B, C: 19.1% C5-8 ASIA grade D: 8.5% T1-S5 ASIA grades A, B, C: 33.1% T1-S5 ASIA grade D: 4.2%	Residence at discharge; payer, length of stay at time of initial rehabilitation; level of injury and functional status at discharge from initial rehabilitation.	A rehospitalization is any overnight hospitalization, even a 1-night hospitalization for observation, but does not include an emergency department visit obtained by subject interview and not by documentation of hospital. No cardiovascular disease specific multivariate risk for rehospitalization reported. Hospitalization for CVD: **Year of Followup / Total / % of CVD** 1 / 930 / 5 5 / 411 / 4 10 / 364 / 4 15 / 323 / 4 20 / 294 / 3 Total / 2,249 / 4

Appendix E Table 2. Cardiovascular events in adults with chronic traumatic SCI (continued)

<table>
<tr><th>Study</th><th>Sample</th><th>Risk factors</th><th>Outcomes</th></tr>
<tr><td>Garshick, 2005[5]
Prospective cohort study to examine the association between comorbid medical conditions and other health related factors and mortality in patients with chronic SCI.
Time: 1994-2000
Followup: 55.6 months (interquartile range 42.0-67.5 months; range 0.33-74.4 months); 1,544 person-years.
Adjustment age</td><td>402 subjects with chronic SCI, >20 years of age previously treated by the SCI Service at Veterans Affairs Boston Healthcare System, registered in the National Spinal Cord Injury Association database in Massachusetts, New Hampshire, Vermont, Maine, and Rhode Island
Exclusion criteria: other neurological diseases (polio, stroke, or multiple sclerosis), mechanical ventilation or tracheotomy.
Population: 361 males (289 veterans and 72 nonveterans), mean age: 50.6 ± 15.0 years (range 23-87), mean years since injury 17.5 ± 12.8 years (range 1.0-56.5); 93% Caucasian, 5% African American, and 2% other races, 92%, SCI was due to traumatic injury. 37 deaths.</td><td>Hypertension and diabetes diagnosed by a doctor, heart disease as treatment for 'heart trouble' reported in the 10 years prior to study entry using the respiratory health questionnaire based on the ATS DLD-78 adult respiratory questionnaire. Medical records were reviewed for subjects who reported diabetes, hypertension, or heart disease for doctor-confirmed diagnosis in a discharge summary, problem list, or in a progress note.</td><td>Date of death and cause-specific mortality through December 2000 using the National Death Index. Standardized mortality ratios (SMR) using the Life Table Analysis System (LTAS) provided by the National Institute of Safety and Health.
Causes of death using ICD codes: Diabetes (250); Diseases of the heart (390-398, 402, 404, 410-414, 420-429); Other diseases of the circulatory system (401, 403, 405, 415-417, 430-438, 440-459); Diseases of the arteries, veins, and pulmonary circulation (415-417,440-459).
<table>
<tr><th></th><th colspan="2">Alive</th><th colspan="2">Died</th></tr>
<tr><td>Heart Disease</td><td>19</td><td>5.90%</td><td>12</td><td>32.40%</td></tr>
<tr><td>Hypertension</td><td>79</td><td>24.40%</td><td>18</td><td>48.70%</td></tr>
<tr><td>Diabetes</td><td>27</td><td>8.30%</td><td>9</td><td>24.30%</td></tr>
</table>
<table>
<tr><th></th><th>Underlying Cause of Death</th><th>Contributing Cause of Death</th><th>Total</th></tr>
<tr><td>Circulatory system disorder</td><td>21.60%</td><td>18.90%</td><td>40.50%</td></tr>
<tr><td>390-59</td><td>8 in 37</td><td>7 in 37</td><td>15 in 37</td></tr>
</table>
<table>
<tr><th></th><th colspan="2">SMR (95% CI)</th></tr>
<tr><td>Diabetes</td><td>3.74</td><td>0.45-13.51</td></tr>
<tr><td>Diseases of the heart</td><td>0.59</td><td>0.19-1.38</td></tr>
<tr><td>Other diseases of the circulatory system</td><td>1.49</td><td>0.31-4.36</td></tr>
<tr><td>Diseases of the arteries, veins, and pulmonary circulation</td><td>1.15</td><td>0.13-4.15</td></tr>
</table>
Age Adjusted relative risk of death
<table>
<tr><th></th><th colspan="2">RR (95%CI)</th></tr>
<tr><td>Hypertension</td><td>1.65</td><td>0.86-3.16</td></tr>
<tr><td>Heart disease</td><td>3</td><td>1.47-6.12</td></tr>
<tr><td>Diabetes</td><td>2.03</td><td>0.95-4.34</td></tr>
</table>
Multivariate relative risk of death
<table>
<tr><td>Diabetes</td><td>2.62</td><td>1.19-5.77</td></tr>
<tr><td>Heart disease</td><td>3.66</td><td>1.73-7.78</td></tr>
</table></td></tr>
</table>

Appendix E Table 2. Cardiovascular events in adults with chronic traumatic SCI (continued)

Study	Sample	Risk factors	Outcomes
Lavela, 2006[3] A national cross-sectional survey of veterans with spinal cord injuries to analyze prevalence of diabetes and its complications compared to the general population. Time: 2003 Adjustment: age, race, marital status, duration of injury, employment, and education.	18,372 veterans with SCI and disorders who use VA health services. Exclusion criteria: veterans who used non VA care, gestational diabetes, multiple sclerosis. Control: 2003 Behavioral Risk Factor Surveillance System survey data for veteran and general population from the Centers for Disease Control and prevention. Population: 5,690 responders (rate 31%), 3,737 eligible. 6,433 general veteran group and 221,650 general population group. Males 97%; Whites 81%; mean age 60 years; 52% with paraplegic level injury; mean years after injury 24 years.	Presence of spinal cord injury; race; mean duration of injury; level of injury, age at injury; behavioral risk factors: smoking and alcohol intake; diabetes mellitus.	Self reported diabetes with 72-item Spinal Cord Dysfunction Health Care Questionnaire (SCD-HCQ). Self reported coronary heart disease, myocardial infarction, arterial hypertension, stroke, hyperlipidemia, asthma, hepatitis, pressure sore, tooth or gum diseases; quality of care indicators; quality of life indicators.
Lee, 2006[36] Cross sectional analysis of the association between plasma homocysteine and arterial hypertension in patients with SCI. Time: not reported. Adjustment not reported	168 patients with SCI identified in the Spinal Cord Injury Service of the Veterans Affairs Palo Alto Medical Center Exclusion criteria: not reported. Population: mean age 50.27±12.8 years; mean duration of injury of 19.17±13 years; 73 (43%) had paraplegia and 95 (56%) had tetraplegia; 11% female; 62% White.	Functional status: paraplegia; tetraplegia	Absolute rates of hypertension, dyslipidemia, insulin resistance, and the presence of metabolic syndrome obtained from medical records within 6 months of the evaluation date. Prevalence of hypertension in SCI patients **N=168** / **N** / **%** Total / 76 / 45.24 Pre hypertension / 55 / 32.74 Stage 1 hypertension / 27 / 16.07 Stage 2 hypertension / 14 / 8.33

Bold - significant association at 95% confidence level; STD - standard deviation; SMR - standardized morbidity ratios

Appendix E Table 3. Prevalence of cardiovascular symptoms* and hypertension depending on level on injury

Author	Sample (n)	Level of injury	Prevalence, %
CVD symptoms			
Levi, 1995[30]	53	Cervical injury, complete	72
	93	Cervical injury, incomplete	57
	8	Lumbosacral injury, complete	62
	47	Lumbosacral injury, incomplete	38
	78	Thoracic injury, complete	72
	48	Thoracic injury, incomplete	58
Hypertension			
Imai, 1994[8]	244	L2 level of injury	2.05
		T11-L2 level of injury	8.61
		T6-T10 level of injury	2.05

*Cardiovascular symptoms included ankle and leg edema, chest pain and/or palpitations

Appendix E Table 4. Prevalence and odds of diabetes in adults with SCI, able bodied veterans, and the general population[3]

Age	Prevalence in SCI, %	Prevalence in Veterans, %	Odds Ratio of Diabetes in SCI vs. Veterans			Prevalence in Population, %	Odds Ratio of Diabetes in SCI vs. General Population		
<40	4.6	3.9	1.19	0.97	1.45	1.9	2.48	2.12	2.91
40-44	6.7	13.7	0.45	0.39	0.52	5	1.36	1.20	1.55
45-59	10.2	8	1.31	1.14	1.50	6.7	1.58	1.42	1.42
50-54	17.5	16.2	1.09	0.99	1.22	9.4	2.05	1.88	1.88
55-59	20.2	18.7	1.1	0.99	1.22	13	1.69	1.56	1.56
60-64	23.1	35.2	0.55	0.50	0.61	16	1.58	1.46	1.46
65-69	24.9	28.6	0.83	0.75	0.91	15.7	1.78	1.65	1.65
>70	26.2	24	1.12	1.02	1.23	15.6	1.92	1.78	1.78

Appendix E Table 5. Relative risk of ECG abnormalities in adults with SCI compared to able-bodied controls[6]

Electrocardiogram Abnormalities	Age <65 years Relative Risk (95% CI)	Age >65 years Relative Risk (95% CI)
Any ECG abnormalities	1.01 (0.87; 1.16)	**0.81 (0.66; 0.99)**
Left ventricular hypertrophy with strain	**0.47 (0.26; 0.88)**	0.48 (0.16; 1.45)
PVC	**0.39 (0.18; 0.87)**	0.70 (0.32; 1.53)
Any Q wave	**0.65 (0.47; 0.91)**	1.10 (0.74; 1.64)
Anterior Q wave	1.11 (0.62; 2.02)	1.11 (0.42; 2.92)
Inferior Q wave	**0.61 (0.41; 0.93)**	1.09 (0.67; 1.78)
Abnormal QTc	1.11 (0.85; 1.45)	0.69 (0.41; 1.14)
Left atrial abnormality	1.51 (1.00; 2.27)	0.46 (0.12; 1.81)
IVCD	**0.47 (0.24; 0.94)**	0.67 (0.17; 2.67)
Atrial fibrillation	0.67 (0.25; 1.81)	0.72 (0.30; 1.69)
ST elevation	**1.20 (1.00; 1.44)**	1.17 (0.73; 1.88)
ST depression	1.06 (0.82; 1.36)	**0.38 (0.22; 0.66)**

Bold – significant association at 95% confidence level

Appendix E Table 6. Relative risk of electrocardiogram abnormalities in patients with SCI with intact sympathetic innervation to the heart (injury level T6 and below) compared to impaired sympathetic activity (injury level T5 and above)[6]

ECG Abnormalities	Relative Risk (95% CI)
Any ECG abnormalities	**0.49 (0.39; 0.62)**
LVH with strain	0.57 (0.19; 1.66)
Inferior Q wave	1.04 (0.54; 1.99)
Anterior Q wave	0.44 (0.16; 1.22)
Any Q wave	0.69 (0.41; 1.15)
Left atrial abnormality	**0.13 (0.04; 0.36)**
IVCD	0.28 (0.07; 1.08)
Abnormal QTc	**0.60 (0.39; 0.94)**
Atrial fibrillation	**0.19 (0.04; 0.90)**
ST depression	0.72 (0.46; 1.14)
ST elevation	**0.19 (0.12; 0.28)**

Bold – significant association at 95% confidence level

Appendix E Table 7. Relative risk of ECG abnormalities in patients with SCI younger vs. older than 65 years of age[6]

ECG Abnormalities	Relative Risk (95% CI)
Any ECG abnormalities	**0.56 (0.44; 0.72)**
RBBB	**0.17 (0.07; 0.43)**
LBBB	**0.19 (0.04; 0.93)**
LVH with strain	0.64 (0.18; 2.27)
Any Q wave	**0.32 (0.19; 0.53)**
Anterior Q wave	0.53 (0.17; 1.62)
Inferior Q wave	**0.30 (0.16; 0.57)**
Abnormal QTc	0.75 (0.42; 1.33)
Left atrial abnormality	2.20 (0.53; 9.17)
IVCD	0.76 (0.16; 3.55)
Atrial fibrillation	**0.15 (0.04; 0.56)**
ST elevation	1.25 (0.76; 2.06)
ST depression	0.97 (0.53; 1.79)

Bold - significant association at 95% confidence level

References for Appendix E

(Note that reference numbers are different than those in the text of the report)

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Appendix F: Conceptual Definition of Outcomes

Cardiovascular diseases[1] (CVD). Pathological conditions involving the cardiovascular system including the heart; the blood vessels; or the pericardium.

Operational definition: Prevalence of CVD and diabetes and incidence rate of CVD events. Definitions of CVD events are presented below.

Variable	Definition
Arrhythmia	Any variation from the normal rhythm or rate of the heartbeat
Arrhythmia, sinus	Irregularity of the heart rate related to functioning of the sinoatrial node
Atrial fibrillation	Disorder of cardiac rhythm characterized by rapid, irregular atrial impulses and ineffective atrial contractions
Atrial flutter	Rapid, irregular atrial contractions due to an abnormality of atrial excitation
Bradycardia	Excessive slowness in the action of the heart, usually with a heart rate below 60 beats per minute
Cardiac complexes, premature	A premature contraction of the heart that is initiated somewhere other than the sinoatrial node
Atrial premature complexes	Premature contractions of the heart arising from an ectopic atrial focus
Ventricular premature complexes	Premature contractions of the ventricle, the most common of all arrhythmias
Heart block	Impairment of conduction in heart excitation. It is often applied specifically to atrioventricular heart block
Long QT syndrome	A syndrome characterized by history of syncopal episodes and a long QT interval, sometimes leading to sudden death due to paroxysmal ventricular arrhythmia
Sick sinus syndrome	Dysfunction of the sinoatrial node manifested by persistent sinus bradycardia, sinus arrest, sinoatrial exit block, chronic atrial fibrillation and inability of the heart to resume sinus rhythm following cardioversion for atrial fibrillation
Tachycardia	Excessive rapidity in the action of the heart, usually with a heart rate above 100 beats per minute
Ventricular fibrillation	Turbulent, disorganized electrical activity of the heart in such a way that the recorded electrocardiographic deflections continuously change in shape, magnitude, and direction
Heart arrest	Abrupt cessation of cardiac pump function which may be reversible by a prompt intervention but will lead to death in its absence
Cardiovascular collapse	A sudden loss of effective blood flow due to cardiac and/or peripheral vascular factors which may reverse spontaneously (e.g., neurocardiogenic syncope; vasovagal syncope) or only with interventions (e.g., cardiac arrest)
Congestive heart failure	Defective cardiac filling and/or impaired contraction and emptying, resulting in the heart's inability to pump a sufficient amount of blood to meet the needs of the body tissues or to be able to do so only with an elevated filling pressure

Coronary disease	An imbalance between myocardial functional requirements and the capacity of the coronary vessels to supply sufficient blood flow Coronary artery abnormalities 1. Chronic atherosclerotic lesions 2. Acute (active) lesions (plaque fissuring, platelet aggregation, acute thrombosis) 3. Anomalous coronary artery anatomy
Myocardial infarction	Gross necrosis of the myocardium, as a result of interruption of the blood supply to the area 1. Healed 2. Acute
Pericarditis	Inflammation of the pericardium
Stroke	Sudden, nonconvulsive loss of neurological function due to an ischemic or hemorrhagic intracranial vascular event. In general, cerebrovascular accidents are classified by anatomic location in the brain, vascular distribution, etiology, age of the affected individual, and hemorrhagic vs. nonhemorrhagic nature.
Hypertension	Persistently high systemic arterial blood pressure. Based on multiple readings, hypertension is currently defined as when systolic blood pressure is consistently greater than 140 mm Hg or when diastolic pressure is consistently 90 mm Hg or more**.**
Death	Irreversible cessation of all biologic functions
Cardiovascular mortality	Death from cardiovascular diseases (considered as immediate and underlying cause of death)

International Classification of Diseases Codes to Identify Outcomes[2]

404 Hypertensive heart and kidney disease
Includes: disease: cardiorenal; cardiovascular renal; any condition classifiable to 402 with any condition classifiable to 403
Additional code to specify type of heart failure (428.0-428.43), if known
Additional code to identify the stage of chronic kidney disease (585.1-585.6), if known
The following fifth-digit sub-classification is for use with category 404:
0 without heart failure or chronic kidney disease
1 with heart failure
2 with chronic kidney disease
3 with heart failure and chronic kidney disease

402 Hypertensive heart disease
Includes: hypertensive: cardiomegaly; cardiopathy; cardiovascular disease; heart (disease) (failure), any condition classifiable to 429.0-429.3, 429.8, 429.9 due to hypertension
Use additional code to specify type of heart failure (428.0-428.43), if known

427 Cardiac dysrhythmias

427.0 Paroxysmal supraventricular tachycardia
Paroxysmal tachycardia: atrial [PAT]; atrioventricular [AV]; junctional nodal

427.1 Paroxysmal ventricular tachycardia
Ventricular tachycardia (paroxysmal)
427.2 Paroxysmal tachycardia, unspecified
Bouveret-Hoffmann syndrome
Paroxysmal tachycardia
427.3 Atrial fibrillation and flutter
427.31 Atrial fibrillation
427.32 Atrial flutter
427.5 Cardiac arrest
Cardiorespiratory arrest
427.6 Premature beats
427.60 Premature beats, unspecified
Ectopic beats
Extrasystoles
Extrasystolic arrhythmia
Premature contractions or systoles NOS
427.8 Other specified cardiac dysrhythmias
427.81 Sinoatrial node dysfunction
Sinus bradycardia: persistent severe
Syndrome: sick sinus; tachycardia-bradycardia
427.9 Cardiac dysrhythmia, unspecified
Arrhythmia (cardiac) NOS
428.0 Congestive heart failure, unspecified
Congestive heart disease
Right heart failure (secondary to left heart failure)
428.1 Left heart failure
Acute edema of lung with heart disease NOS or heart failure
Acute pulmonary edema with heart disease NOS or heart failure
Cardiac asthma
Left ventricular failure
428.9 Heart failure, unspecified
Cardiac failure NOS
Heart failure NOS
Myocardial failure NOS
Weak heart
428 Heart failure
Code, if applicable, heart failure due to hypertension first (402.0-402.9, with fifth-digit 1 or 404.0-404.9 with fifth-digit 1 or 3)
429.2 Cardiovascular disease, unspecified
Arteriosclerotic cardiovascular disease [ASCVD]
Cardiovascular arteriosclerosis
Cardiovascular: degeneration (with mention of arteriosclerosis) disease (with mention of arteriosclerosis)
Sclerosis (with mention of arteriosclerosis)
Additional code to identify presence of arteriosclerosis
794 Nonspecific abnormal results of function studies

250 Diabetes mellitus
250.0 Diabetes mellitus without mention of complication
Diabetes mellitus without mention of complication or manifestation classifiable to 250.1-250.9
Diabetes (mellitus) NOS
250.6 Diabetes with neurological manifestations
Additional code to identify manifestation, as:
diabetic:
amyotrophy (358.1)
gastroparalysis (536.3)
gastroparesis (536.3)
mononeuropathy (354.0-355.9)
neurogenic arthropathy (713.5)
peripheral autonomic neuropathy (337.1)
polyneuropathy (357.2)
250.7 Diabetes with peripheral circulatory disorders
Use additional code to identify manifestation, as:
diabetic:
gangrene (785.4)
peripheral angiopathy (443.81)
250.8 Diabetes with other specified manifestations
Diabetic hypoglycemia
Hypoglycemic shock
Use additional code to identify manifestation, as:
any associated ulceration (707.10-707.9)
diabetic bone changes (731.8)

International Classification of Diseases Codes to Identify Outcomes in Individual Studies:

Groah, 2001:[3] Cardiovascular disease outcomes defined by ICD/9 codes 390-448 and 745-747:
DISEASES OF THE CIRCULATORY SYSTEM (390-459)
ACUTE RHEUMATIC FEVER (390-392)
CHRONIC RHEUMATIC HEART DISEASE (393-398)
HYPERTENSIVE DISEASE (401-405)
ISCHEMIC HEART DISEASE (410-414)
Includes: that with mention of hypertension
Additional code to identify presence of hypertension (401.0-405.9)
DISEASES OF PULMONARY CIRCULATION (415-417)
OTHER FORMS OF HEART DISEASE (420-429)
CEREBROVASCULAR DISEASE (430-438)
Includes: with mention of hypertension (conditions classifiable to 401-405)
DISEASES OF ARTERIES, ARTERIOLES, AND CAPILLARIES (440-448)
745 Bulbus cordis anomalies and anomalies of cardiac septal closure
746 Other congenital anomalies of heart
747 Other congenital anomalies of circulatory system

McGlinchey-Berroth, 1995[4] Hospitalization due to myocardial infarction (ICD-9-CM 410.9), diabetes (ICD 250.00 to 250.9), and hypertension (ICD 401.0 to 401.9).
410 Acute myocardial infarction
Includes: cardiac infarction; coronary (artery):embolism; occlusion; rupture; thrombosis; infarction of heart, myocardium, or ventricle; rupture of heart, myocardium, or ventricle; ST elevation (STEMI) and non-ST elevation (NSTEMI) myocardial infarction; any condition classifiable to 414.1-414.9 specified as acute or with a stated duration of 8 weeks or less
The following fifth-digit subclassification is for use with category 410:
0 episode of care unspecified
1 initial episode of care
The fifth-digit 1 to designate the first episode of care (regardless of facility site) for a newly diagnosed myocardial infarction. The fifth-digit 1 is assigned regardless of the number of times a patient may be transferred during the initial episode of care.
2 subsequent episode of care
The fifth-digit 2 to designate an episode of care following the initial episode when the patient is admitted for further observation, evaluation or treatment for a myocardial infarction that has received initial treatment, but is still less than 8 weeks old.
410.0 Of anterolateral wall
ST elevation myocardial infarction (STEMI) of anterolateral wall
410.1 Of other anterior wall
Infarction:
anterior (wall) NOS (with contiguous portion of intraventricular septum)
anteroapical (with contiguous portion of intraventricular septum)
anteroseptal (with contiguous portion of intraventricular septum)
ST elevation myocardial infarction (STEMI) of other anterior wall
410.2 Of inferolateral wall
ST elevation myocardial infarction (STEMI) of inferolateral wall
410.3 Of inferoposterior wall
ST elevation myocardial infarction (STEMI) of inferoposterior wall
410.4 Of other inferior wall
Infarction: diaphragmatic wall NOS (with contiguous portion of intraventricular septum)
inferior (wall) NOS (with contiguous portion of intraventricular septum)
ST elevation myocardial infarction (STEMI) of other inferior wall
410.5 Of other lateral wall
Infarction: apical-lateral; basal-lateral; high lateral; posterolateral
ST elevation myocardial infarction (STEMI) of other lateral wall
410.6 True posterior wall infarction
Infarction: posterobasal; strictly posterior
ST elevation myocardial infarction (STEMI) of true posterior wall
410.7 Subendocardial infarction
Non-ST elevation myocardial infarction (NSTEMI)
Nontransmural infarction
410.8 Of other specified sites
Infarction of: atrium; papillary muscle; septum alone
ST elevation myocardial infarction (STEMI) of other specified sites

410.9 Unspecified site
401 Essential hypertension
Includes: high blood pressure ; hyperpiesia; hyperpiesis; hypertension (arterial) (essential) (primary) (systemic); hypertensive vascular: degeneration; disease

DeVivo, 1993:[5] Ischemic heart disease (ICD codes 410-414); Non ischemic heart disease (ICD codes 420-429); Cerebrovascular diseases (ICD codes 430-438); Diseases of arteries (ICD codes 440-448)
ISCHEMIC HEART DISEASE (410-414)
Includes:
that with mention of hypertension
Additional code to identify presence of hypertension (401.0-405.9)
410 Acute myocardial infarction
Includes:
cardiac infarction
coronary (artery):
embolism
occlusion
rupture
thrombosis
infarction of heart, myocardium, or ventricle
rupture of heart, myocardium, or ventricle
ST elevation (STEMI) and non-ST elevation (NSTEMI) myocardial infarction
any condition classifiable to 414.1-414.9 specified as acute or with a stated duration of 8 weeks or less
The following fifth-digit subclassification is for use with category 410:
0 episode of care unspecified
Use when the source document does not contain sufficient information for the assignment of fifth-digit 1 or 2.
1 initial episode of care
Use fifth-digit 1 to designate the first episode of care (regardless of facility site) for a newly diagnosed myocardial infarction. The fifth-digit 1 is assigned regardless of the number of times a patient may be transferred during the initial episode of care.
2 subsequent episode of care
Use fifth-digit 2 to designate an episode of care following the initial episode when the patient is admitted for further observation, evaluation or treatment for a myocardial infarction that has received initial treatment, but is still less than 8 weeks old.
411 Other acute and subacute forms of ischemic heart disease
412 Old myocardial infarction ;Healed myocardial infarction
Past myocardial infarction diagnosed on ECG [EKG] or other special investigation, but currently presenting no symptoms
413 Angina pectoris
414 Other forms of chronic ischemic heart disease
Excludes:
arteriosclerotic cardiovascular disease [ASCVD] (429.2)
cardiovascular:

arteriosclerosis or sclerosis (429.2)
degeneration or disease (429.2)
OTHER FORMS OF HEART DISEASE (420-429)
420 Acute pericarditis
Includes:
acute:
mediastinopericarditis
myopericarditis
pericardial effusion
pleuropericarditis
pneumopericarditis
Excludes:
acute rheumatic pericarditis (391.0)
postmyocardial infarction syndrome [Dressler's] (411.0)
421 Acute and subacute endocarditis
422 Acute myocarditis
Excludes:
acute rheumatic myocarditis (391.2)
423 Other diseases of pericardium
Excludes:
that specified as rheumatic (393)
424 Other diseases of endocardium
Excludes:
bacterial endocarditis (421.0-421.9)
rheumatic endocarditis (391.1, 394.0-397.9)
syphilitic endocarditis (093.20-093.24)
425 Cardiomyopathy
Includes:
Myocardiopathy
426 Conduction disorders
427 Cardiac dysrhythmias
428 Heart failure
Code, if applicable, heart failure due to hypertension first (402.0-402.9, with fifth-digit 1 or 404.0-404.9 with fifth-digit 1 or 3)
CEREBROVASCULAR DISEASE (430-438)
Includes:
with mention of hypertension (conditions classifiable to 401-405)
Use additional code to identify presence of hypertension
430 Subarachnoid hemorrhage
Meningeal hemorrhage
Ruptured:
berry aneurysm
(congenital) cerebral aneurysm NOS
432 Other and unspecified intracranial hemorrhage
433 Occlusion and stenosis of precerebral arteries
The following fifth-digit subclassification is for use with category 433:

0 without mention of cerebral infarction
1 with cerebral infarction
Includes:
embolism of basilar, carotid, and vertebral arteries
narrowing of basilar, carotid, and vertebral arteries
obstruction of basilar, carotid, and vertebral arteries
thrombosis of basilar, carotid, and vertebral arteries
434 Occlusion of cerebral arteries
The following fifth-digit subclassification is for use with category 434:
0 without mention of cerebral infarction
1 with cerebral infarction
435 Transient cerebral ischemia
Includes:
cerebrovascular insufficiency (acute) with transient focal neurological signs and symptoms
insufficiency of basilar, carotid, and vertebral arteries
spasm of cerebral arteries
436 Acute, but ill-defined, cerebrovascular disease
Apoplexy, apoplectic:
NOS
attack
cerebral
seizure
Cerebral seizure
437 Other and ill-defined cerebrovascular disease
438 Late effects of cerebrovascular disease
Note: This category is to be used to indicate conditions in 430-437 as the cause of late effects. The "late effects" include conditions specified as such, or as sequelae, which may occur at any time after the onset of the causal condition.
DISEASES OF ARTERIES, ARTERIOLES, AND CAPILLARIES (440-448)
440 Atherosclerosis
Includes:
arteriolosclerosis
arteriosclerosis (obliterans) (senile)
arteriosclerotic vascular disease
atheroma
degeneration:
arterial
arteriovascular
vascular
endarteritis deformans or obliterans
senile:
arteritis
endarteritis
Excludes:
atheroembolism (445.01-445.89)
atherosclerosis of bypass graft of the extremities (440.30-440.32)

440.0 Of aorta
440.1 Of renal artery
440.2 Of native arteries of the extremities
440.3 Of bypass graft of the extremities
440.8 Of other specified arteries
440.9 Generalized and unspecified atherosclerosis

Garshick, 2005:[6] Diseases of the heart (390-398, 402, 404, 410-14, 420-429); Other diseases of the circulatory system (401, 403, 405, 415-417, 430--38, 440-459); Diseases of the arteries, veins, and pulmonary circulation (415-417,440-459).
DISEASES OF THE CIRCULATORY SYSTEM (390-459)
ACUTE RHEUMATIC FEVER (390-392)
CHRONIC RHEUMATIC HEART DISEASE (393-398)
402 Hypertensive heart disease
403 Hypertensive kidney disease
405 Secondary hypertension
415 Acute pulmonary heart disease
416 Chronic pulmonary heart disease
417 Other diseases of pulmonary circulation
CEREBROVASCULAR DISEASE (430-438)
DISEASES OF ARTERIES, ARTERIOLES, AND CAPILLARIES (440-448)
DISEASES OF VEINS AND LYMPHATICS, AND OTHER DISEASES OF CIRCULATORY SYSTEM (451-459)

<u>Analytical framework for pooled analysis of prevalence of cardiovascular diseases in adults with chronic SCI.</u>
Prevalence was calculated as number of CVD events among total number of SCI patients in the study, standard error and confidence interval for population prevalence were calculated with Wilson estimate as followed:[7]

$SE\rho=\sqrt{\ [\rho*(1-\rho)]/[n+4]}$

95% level C confidence interval $\rho \pm 1.96*SE\rho$
Where p – prevalence, n- sample size

Pooled estimate as a weighted average:[8]

$$\theta_{IV} = \frac{\sum_i w_i \theta_i}{\sum_i w_i}$$

Weights are inverse of variance (standard error):

$$w_i = \frac{1}{SE(\theta_i)^2}$$

Standard error of pooled estimate:

$$SE(\theta_{IV}) = \frac{1}{\sqrt{\sum_i w_i}}$$

Heterogeneity (between-study variability) measured by:

$$Q = \sum_i w_i (\theta_i - \theta_{IV})^2$$

Assumptions for random effects model: true effect sizes *qi* have a normal distribution with mean *q* and variance *t2*; *t2* is the between-study variance
Between study variance:

$$\tau^2 = \frac{Q - (k-1)}{\sum_i w_i - \left(\frac{\sum_i w_i^2}{\sum_i w_i} \right)}$$

Where:
wi are the weights from the fixed effect inverse-variance method
Q is the heterogeneity test statistic from before (either from inverse-variance method or Mantel-Haenszel method)
k is the number of studies, and
t2 is set to zero if $Q<k-1$
Random effect pooled estimate is weighted average:

$$\theta_{DL} = \frac{\sum_i w'_i \theta_i}{\sum_i w'_i}$$

Weights used for the pooled estimate are similar to the inverse-variance, but now incorporate a component for between-study variation:

$$w'_i = \frac{1}{SE(\theta_i)^2 + \tau^2}$$

Standard error of pooled estimate

$$SE(\theta_{DL}) = \frac{1}{\sqrt{\sum_i w'_i}}$$

Heterogeneity between studies was quantified using the I-squared statistic.[9]. Statistical significance was analyzed at the 95% confidence level. All calculations were conducted using STATA software.[10]

References for Appendix E

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