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Burden of Cardiovascular Risk in Individuals With Spinal Cord Injury and Its Association With Rehabilitation Outcomes

Results From the Swiss Spinal Cord Injury Cohort

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Objectives: The aims of the study are to determine the cardiovascular risk burden rehabilitation discharge and to explore the association between recovery during rehabilitation and cardiovascular disease risk profile.

Methods: We included adults without cardiovascular disease admitted for rehabilitation. We evaluated rehabilitation outcomes on admission and discharge. Cardiovascular disease risk profile was assessed by Framingham risk score, high-density lipoprotein, and fasting glucose level.

Results: We analyzed data from 706 participants (69.6% men) with a median age of 53.5 yrs. The median time since injury was 14 days, and the admission length was 5.2 months. Majority had paraplegia (53.3%) and motor incomplete injury (53.7%). One third of the cohort had high cardiovascular risk profile before discharge. At discharge, poorer anthropometric measures were associated with higher Framingham risk score and lower high-density lipoprotein levels. Individuals with higher forced vital capacity (>2.72 l) and peak expiratory flow (>3.4 l/min) had 0.16 mmol/l and 0.14 mmol/l higher high-density lipoprotein compared with those with lower respiratory function, respectively. Individuals with higher mobility score (>12.5) and functional independence score (>74) had 0.21 and 0.18 mmol/l higher high-density lipoprotein compared with those with lower scores.

Conclusions: There is high cardiometabolic syndrome burden and cardiovascular disease risk profile upon rehabilitation discharge. Higher respiratory function, mobility, and overall independence were associated

What Is Known

- Individuals with spinal cord injury are at high risk for cardiovascular mortality and morbidity. However, cardiovascular screening is rarely done before discharge.

What Is New

- One third of the cohort had a high cardiovascular risk profile. Lower lung function, mobility, and overall functioning have higher cardiovascular disease risk and should be targeted for routine screening.

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CME Objectives: Upon reading this journal article, the reader is expected to: (1) Determine the burden of cardiometabolic disease in the early phase of spinal cord injury (SCI); (2) Differentiate the proposed SCI cutoff for high-risk obesity from the able-bodied population; and (3) Increase physicians' acuity for detecting cardiometabolic disease in their practice.

Level: Advanced

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PFR and MG conceptualized the study. PFR analyzed the data. GM, JS, IE-H, SS, MH-G, XJ, TM, and GS interpreted the data and drafted the manuscript. MG and TM supervised the study conduct. All authors approved the final version of the manuscript.

Peter Francis Raguindin is in training.

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with better cardiovascular disease risk profile, although with study design limitations and short follow-up. Future studies should explore whether rehabilitation outcomes could be used to prioritize screening.

Key Words: Cardiovascular Risk, Paraplegia, Tetraplegia, Cardiovascular Disease, Lung Volumes, Spirometry, Obesity, Functioning

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Spinal cord injury (SCI) results in dramatic changes in an individual's functioning that changes across the injury trajectory.[1] The injury causes skeletal muscle paralysis and spasticity that limit their independence over activities of daily living and their physical activity. The injury also results in lower cardiorespiratory function secondary to impaired neurologic control (autonomics) or respiratory muscle paralysis.[2] Furthermore, changes in metabolic milieu were reported within weeks after injury as the body shifted from a catabolic state in response to acute injury to an anabolic state in subacute injury, which promotes fat accumulation.[3] Therefore, subacute injury is a critical phase characterized by dynamic physiologic adaptation. A recent study on the subacute phase observed no deterioration of cardiovascular health during inpatient rehabilitation.[4] Thus, the inpatient rehabilitation program could have a beneficial effect on cardiometabolic health.

Rehabilitation programs are tailored to shorten hospital stays, decrease readmissions, and reduce the risks of secondary complications[5–7] by improving physical capacity (e.g., respiratory function and muscle strength) and functional independence,[8] which have been crucial for daily physical activities and social integration.[9,10] Among other activities, these programs focus on muscle strengthening, preventing spasticity, and improving cardiorespiratory fitness through exercises.[8] Few studies have associated rehabilitation outcomes with cardiovascular health in this group. A study has previously associated poorer lung volumes with higher odds of type 2 diabetes and hypertension.[11] Another study observed an association between lower limb spasticity and fasting glucose and adiposity.[12] Understanding these changes during inpatient rehabilitation could be important in cardiovascular disease (CVD) prevention because deterioration in lipid or glucose profile could lead to long-term complications and morbidity.[13] In a previous study, at discharge from initial rehabilitation, almost one third of patients can be classified as high risk for CVD.[4] Despite being considered for a high CVD risk group because of risk factors clustering as early as within weeks after injury,[14,15] CVD screening has not been routinely included before rehabilitation discharge.[16,17] Previous study has shown 20% of individuals with SCI are being screened for lipid profile and fasting glucose upon discharge[18] even though 30%–60% of them are at high cardiovascular risk.[4] The main determinants of poorer CVD risk profile in subacute injury phase remain largely unknown.

We hypothesize that better functional recovery during initial rehabilitation is associated with more favorable CVD risk profile at discharge and may be used to triage CVD screening in inpatient setting. Thus, for this study, we aimed to (1) determine the CVD risk and cardiometabolic syndrome burden during initial inpatient rehabilitation, (2) explore longitudinal changes in rehabilitation outcomes, and (3) associate these rehabilitation outcomes with cardiovascular risk profile before discharge from initial rehabilitation risk.

METHODS

This is a cohort study on rehabilitation outcomes over time (longitudinal analysis) and the association of these measures to cardiovascular risk profile at discharge during inpatient rehabilitation. Specific details on study procedures and data analysis can be found in the Online Appendix (Supplemental Digital Content 1, http://links.lww.com/PHM/C54).

Study Setting and Population

The Swiss Spinal Cord Injury cohort (SwiSCI) is a multicenter study across all four rehabilitation centers in Switzerland, namely, Swiss Paraplegic Center (Nottwil), Clinique Romande de Readaptation (Sion), Balgrist Spine Center (Zurich), and Basel Rehabilitation Clinic (Basel). The additional details of the study cohort can be found in previous publications.[19,20] In summary, this study enrolled individuals with a new diagnosis of SCI from each participating center. We collected demographic and clinical profiles, with detailed injury characteristics and additional information related to overall well-being and functioning, using the prescribed data collection form of the International Spinal Cord Society.[21,22] Data were collected upon admission and before discharge.

We enrolled adults (≥18 yrs) admitted for inpatient rehabilitation in one of the participating centers from May 2013 (cohort inception date) to September 2021. We excluded individuals with acute inflammatory and infectious causes of the injury and terminal cancers or those in palliative care. We also excluded those with a history of CVD to estimate the participant's risk for the first cardiovascular event. Participants were followed from admission until discharge to rehabilitation centers.

Definition of Rehabilitation Outcomes

Rehabilitation measure was divided into the following five components: anthropometric measures, respiratory function, spasticity, muscle strength (including frailty), and functional independence. All body anthropometrics were measured in the supine position. Waist circumference was measured after bowel care, at the end of normal expiration, approximately between the lower margin of the last palpable rib and the top of the iliac crest. It was measured using a pliable tape measure with a precision of 0.5 cm. Weight was measured using an electric wheelchair scale. The total weight of the subject with the wheelchair was subtracted from the wheelchair's weight to determine the subject's weight expressed in kilograms. Both waist circumference and weight were measured once per assessment. Body mass index (BMI) was computed using the standard formula (weight in kilograms/[height in meters]^2).

The respiratory function was assessed through functional vital capacity (FVC), forced expiratory volume in 1 sec (FEV1), and peak expiratory flow (PEF). Lung volumes (FVC and FEV1) are measured in liters, and the flow rate (PEF) was measured in liter per minute. These measure the extent of respiratory muscle innervation and function of the participants due to the injury. The best of the three efforts the participant made for respiratory function test was recorded and used in analysis. Spasticity was assessed on the biceps and gastrocnemius of the

upper and lower limbs from both sides. A rehabilitation specialist measured spasticity through modified Ashworth scale (0 as no spasticity to 5 maximum score). Handgrip strength was measured on both sides using a hand dynamometer using REACT protocol.

Functional independence was measured using the Spinal Cord Independence Measure (SCIM III).[23] The score has a minimum of 0 and a maximum 100 score. It is a composite of the following three main domains: self-care, respiration and sphincter management, and mobility. The mobility subcomponent has a maximum score of 40 and has six components, namely, indoor mobility (0–8), moderate distance 10- to 100-meter mobility (0–8), outdoor mobility more than 100 meters (0–8), mobility in stairs (0–3), wheelchair to car transfer (0–2), and wheelchair to ground (0–1) We used the functional independence (total score) and mobility subcomponent score for the analysis.

Definition of Cardiovascular Risk and Cardiometabolic Syndrome

Cardiovascular risk profile was assessed using the cardiovascular risk score, dyslipidemia, impaired fasting glucose, hypertension, overweight (high-risk obesity), and cardiometabolic syndrome. The Framingham risk score (FRS) predicted the risk of having the first cardiovascular event within 10 yrs and was based on a cohort of 5209 adults in Framingham, Massachusetts.[24] For this study, we computed the FRS of each patient at discharge for participants using the following variables: (*a*) age, (*b*) sex, (*c*) systolic blood pressure, (*d*) total cholesterol (units to be converted to milligrams per decilter), (*e*) high-density lipoprotein (units to be converted to milligrams per decilter), (*f*) diabetes, and (*g*) current smoking. The risk of the first cardiovascular event within 10 yrs is considered low when it is less than 10% and medium to high risk with those having 10% or more.[24] The FRS was chosen in the main analysis to be comparable with the previous attempt in validating the score with hard outcomes.[25] We also iterated cardiovascular risk score using SCORE2 (adjusted for Swiss population low-risk region)[26] and World Health Organization (WHO) CVD risk score (adjusted for Swiss population and the 2017 Global Burden of Disease).[27] The details of SCORE2 and WHO CVD risk score can be found in separate publications and have not yet been validated in the SCI population.

Venous blood samples were obtained from each participant after an overnight fast. The blood was sent to respective hospital laboratories, which measured high-density lipoprotein and glucose. Dyslipidemia was defined as those with high-density lipoprotein (HDL) at less than 1.0 mmol/l in males or less than 1.3 mmol/l in females, or with total cholesterol of 5.5 mmol/l or greater.[28] Impaired fasting glucose (high risk for diabetes) was defined as those with 7.0 mmol/l or greater from an international consensus.[29]

Hypertension was defined as having resting systolic blood pressure of 130 mm Hg or greater or diastolic blood pressure of 90 mm Hg or greater based on a clinical guideline.[30] Overweight (high risk for obesity) was defined as those having BMI greater than 22 kg/m^2 or waist circumference of 86.5 cm or greater according to SCI-specific cutoff,[31,32] and BMI greater than 25 kg/m^2 or waist circumference greater than 102 cm (males)/more than 88 cm (females) according to the cutoff for general population.[33] Finally, cardiometabolic syndrome is classified by having any three of the following (based on 2005 American Heart Association and National Heart, Lung and Blood Institute guideline): (*a*) overweight (SCI-specific cutoff), (*b*) elevated triglycerides, (*c*) low HDL, (*d*) impaired fasting glucose, and (*e*) hypertension.

Definition of Covariates

The level of injury was classified as tetraplegia (at level C2–C7) and paraplegia (level T1–S5), and the completeness of injury into complete motor injury (AIS A and B) and incomplete (AIS C and D) based on the International Standards for Neurological Classification of Spinal Cord Injury.[34] The SCI validated questionnaires were used to obtain some covariates. The dietary pattern is obtained using the Swiss Health Survey questionnaire,[35] and subsequently, a nutritional score was computed using the recommendations of the German Society for Nutrition.[36] Physical activity is measured through physical activity scale for individuals with physical disabilities.[37]

Data Analysis

We summarized the rehabilitation measures using median and interquartile range (IQR) as prescribed by the International Spinal Cord Society Standards of Data Analysis and Reporting.[22] We determined the changes in rehabilitation outcomes from admission to discharge using the Wilcoxon signed-rank test for paired samples. We summarized the rehabilitation outcomes by injury level and injury completeness. We iterated longitudinal analysis to determine whether injury characteristics affect the rehabilitation outcome changes. We also performed linear mixed model using random intercept and individuals as clusters, adjusted for age, sex, and injury level.

We selected cardiovascular risk score (FRS), HDL, and fasting glucose as main dependent variables based on previous literature on cardiometabolic risk in SCI. We used multivariable linear regression adjusted for age, sex, injury level, and body mass index (a surrogate for obesity). We drafted directed acyclic graphs to determine the minimum covariate adjustments in assessing the effect of independent variables (http://www.daggity.net) (Fig. S1, Supplemental Digital Content 1, http://links.lww.com/PHM/C54). We used the rehabilitation outcomes both as continuous and dichotomous variables. The use of independent variables (rehabilitation outcomes) as a continuous variable was done to determine the strength of association to the dependent variables (cardiovascular risk). Furthermore, we dichotomized the independent variables (rehabilitation outcomes) to determine the unit change in cardiovascular risk (dependent variables) for those with high versus lower rehabilitation measure (independent variables). We used SCI-adjusted cutoffs for waist circumference and body mass index. For other variables of rehabilitation, we divided the group into those above or below the medians. Furthermore, we log-transformed FRS before fitting in the regression model. No transformations were done for HDL and glucose before regression. We tested the normality of the residuals after regression fitting.

Sensitivity Analyses

Detailed results of the sensitivity analyses can be found in the Online Appendix. To determine selection bias, we

compared the baseline characteristics of those with complete data with those with missing dependent variables using the χ^2 test or Wilcoxon test. We performed a post hoc test (Dunn test with Bonferroni adjustment) to confirm the differences between uneven group comparisons. We also fitted our main models with interaction term of sex and rehabilitation outcome (independent variable) to test for effect modification (sex). For statistically significant interactions, we iterated a subgroup estimate for each sex. We also restricted the analyses to those with paraplegia, motor complete injury, and traumatic SCI to create a more homogenous population based on injury characteristics. We performed subgroup analyses according to age (adults ≤ 50 yrs and older people >50 yrs). We performed Bonferroni corrections to adjust for multiple comparisons.

We also explored the association of longitudinal changes in rehabilitation outcomes and cardiovascular risk profile through a repeated measures approach. We used a multilevel mixed model using random intercept of each individual trajectory by residual maximum likelihood estimation. The longitudinal model was also adjusted for age, sex, injury level, and body mass index.

All analyses were performed using two-tailed tests, with *P* values less than 0.05 considered statistically significant. All analyses were performed using Stata 16.1 (StataCorp, TX).

Ethical Considerations

Written informed consent was obtained from all participants before data collection. The study is compliant with the Swiss Human Research Act (810.30 Federal Act of September 30, 2011, on Research involving Human Beings) and Federal Regulations on Data Protection (235.1 Federal Act of June 19, 1992, on Data Protection). The study has been cleared by ethics committees of participating centers, namely, Ethics Committee northwest/central Switzerland (EKNZ): PB_2016-00183, Ethics Committee Vaud (CEVD): 032/13 (CEVS), and Ethics Committee Zurich (KEKZH): 2013-0249. To protect the confidentiality of the participants, the investigators and data analysts only accessed deidentified datasets. The data set was kept under the secured servers of the Swiss Paraplegic Research. This study conforms to Strengthening the Reporting of Observational Studies in Epidemiology guidelines for reporting (see Supplementary Checklist, Supplemental Digital Content 2, http://links.lww.com/PHM/C55).

RESULTS

A total of 706 individuals with SCI were included in the analysis (Fig. 1). The median age is 53.5 yrs (IQR = 39–65), with the majority of the participants (59.02%) belonging to 46–60 yrs (32.72%) and 61–75 yrs (26.63%) age groups (Table 1). There were more males in the enrolled population compared with females (69.55% vs. 30.45%). The majority of individuals had paraplegia (53.26%), incomplete motor injury (53.68%), and traumatic injuries (60.20%). The list of nontraumatic causes can be found in the Appendix (Table S1, Supplemental Digital Content 1, http://links.lww.com/PHM/C54). The median length of rehabilitation was 5.2 mos (3.1–7.4).

Cardiovascular Risk Profile and Cardiometabolic Syndrome at Discharge

Dyslipidemia was observed in 46.7% and impaired fasting glucose was seen in 26.1% of the cohort (Fig. 2). Overweight (high risk for obesity) was seen in 72.6% using SCI-specific BMI cutoff and 49.9% using the cutoff for the general population. Moreover, 37.2% were considered high cardiovascular risk (>10% on FRS) and 35.4% have cardiometabolic syndrome (Table 2).

Longitudinal Changes in Rehabilitation Outcomes

Over the period of rehabilitation, we saw an overall improvement in respiratory function (Table 3), which was reflected in increasing FVC (from 2.65 l [IQR = 1.97–3.3] to 2.72 l [IQR = 2.12–3.33], $P < 0.001$) and PEF (from 3.2 l/min [IQR = 2.48–3.96] to 3.4 l/min [2.6–4.1], $P < 0.001$). Similar improvement were seen in individuals with tetraplegia and paraplegia (Table S2a, Supplemental Digital Content 1, http://links.lww.com/PHM/C54) and those with complete and incomplete injury (Table S2b). Changes in lung function and spasticity does not

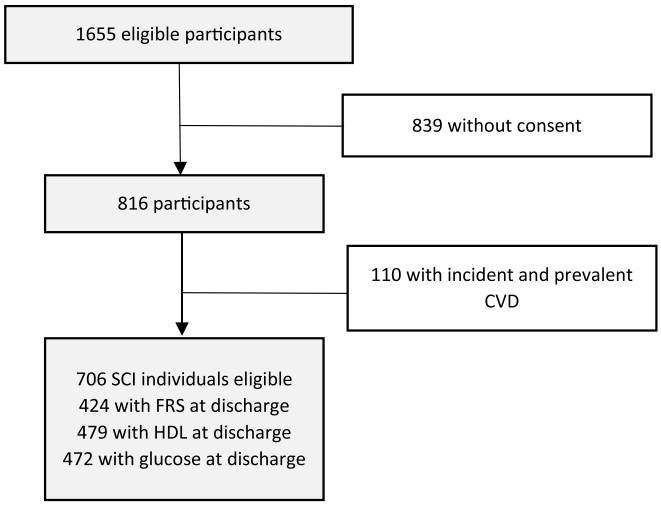

FIGURE 1. Flowchart of study participant enrollment.

TABLE 1. Baseline demographic and injury characteristics of study participants

Parameters	Eligible Population (N = 706)
Baseline demographics	
Age, median (IQR), year	53.5 (39–65)
Age groups, *n* (%)	
18–30	105 (14.87)
30–45	136 (19.26)
46–60	231 (32.72)
61–75	188 (26.63)
>76	46 (6.52)
Sex, *n* (%)	
Male	491 (69.55)
Female	215 (30.45)
Injury characteristics (T4)	
Injury level, *n* (%)[a]	
Tetraplegia (C2–C8)	208 (29.46)
Paraplegia (T1–S5)	376 (53.26)
Unknown	122 (17.28)
Injury completeness, *n* (%)[b]	
Motor complete	201 (28.47)
Motor incomplete	379 (53.68)
Unknown	126 (17.85)
Etiology of injury, *n* (%)	
Traumatic	425 (60.20)
Nontraumatic	281 (39.80)
AIS/ISNCSCI Impairment Scale, *n* (%)[c]	
A	134 (22.95)
B	67 (11.47)
C	79 (13.53)
D	299 (51.20)
E	1 (0.17)
Unable to determine	3 (0.51)
Unknown	1 (0.17)
Time since injury, median (IQR), days	14 (9–25)

[a] Injury level according to the International Spinal Cord Society standards of reporting.

[b] Complete injury (ASIA A and B) and incomplete injury (ASIA C, D, and E).

[c] Based on International Standards for Neurological Classification of Spinal Cord Injury, SCIM III, Spinal Cord Independence Measure version III.

seem to vary according to injury characteristics (Table S2c). Total SCIM score increased from 34 (IQR = 21–58) to 74 (IQR = 56–91) ($P < 0.001$), and mobility SCIM increased from 4 (IQR = 0–7) to 12.5 (IQR = 7–26) ($P < 0.001$). Individuals with incomplete injury has incremental change in functioning compared with those with complete injury (Table S2c).

There was an increase in spasticity in the lower limbs. At baseline, moderate to severe spasticity was observed in 9.28% of the left extremity and 9.58% of the right extremity, which increased to 19.94% and 18.63%, respectively (Table 3). We observed an increase in handgrip strength from 34.2 kg (IQR = 25.2–45.9) to 34.6 (IQR = 26–27.3) ($P < 0.001$). We observed no statistically significant changes in body anthropometrics over the rehabilitation period.

Rehabilitation Outcomes and Cardiovascular Risk

At discharge, almost one third of study participants were considered to have a poor cardiovascular risk profile. Specifically, 37.2% (162/435) had high FRS (≥10%), 40.9% (200/488) had low HDL (<1.0 mmol/l in males or <1.3 mmol/l in females), and 26.1% (125/479) had high fasting glucose levels (>7.0 mmol/l) (Table S3, Supplemental Digital Content 1, http://links.lww.com/PHM/C54). Cardiovascular risk scores were also computed based on SCORE2 and WHO risk score found in the Appendix (Table S4, Supplemental Digital Content 1, http://links.lww.com/PHM/C54). Waist circumference (>86.5 cm) and higher BMI (>22 kg/m^2) were associated with higher FRS compared with lower anthropometric measures (waist $\beta = 0.28$, 95% CI = 0.16–0.40; BMI $\beta = 0.32$, 95% CI = 0.19–0.46) (Table 4). Waist circumference was also associated with lower HDL-C by 0.10 and 0.09 mmol/l, respectively. Crude and age-adjusted models were consistent with fully adjusted models (Table S5a, Supplemental Digital Content 1, http://links.lww.com/PHM/C54). We also fitted an association models using SCORE2 and WHO CVD Risk score with comparable findings (Table S5b).

Higher PEF (>3.4 l/min) and FEV1 (>0.8 l) were associated with 0.16 and 0.14 mmol/l higher HDL-C compared with those with lower respiratory function (Table 4). These findings were consistent with age-, sex-, and medication-adjusted models (Table S6, Supplemental Digital Content 1, http://links.lww.com/PHM/C54). Likewise, age-, sex-, and medication-adjusted models of FVC showed higher HDL-C, but the fully adjusted model did not reach statistical significance.

Lastly, a high functional independence score (>74) and high mobility score (>12.5) are associated with 0.21 and 0.19 mmol/l higher HDL-C compared with those with lower scores. These associations are consistent across crude and incrementally adjusted models (Table S6).

We did not find any statistically significant association between rehabilitation outcomes and fasting glucose levels in fully adjusted models (Table 3) except for spasticity. Those with moderate-severe grade spasticity (+1–4/4) of the left lower extremity had 0.25 mmol/l higher fasting glucose compared with low-grade spasticity (0–1/4). Across crude and various adjusted models, no statistically significant association was seen (Table S7, Supplemental Digital Content 1, http://links.lww.com/PHM/C54).

We explored the association between longitudinal changes in rehabilitation outcomes and cardiovascular risk profile by fitting a multilevel mixed model approach (Table S8, Supplemental Digital Content 1, http://links.lww.com/PHM/C54). An increase in BMI and waist circumference during rehabilitation was associated with increase in FRS and decrease in HDL (high CV risk). An increase in respiratory function (FVC and PEF) and functioning are associated with increase in HDL (low CV risk).

Sensitivity Analyses

We iterated our models using independent variables treated as continuous data. The association between body anthropometrics, respiratory function, and functional independence scores with FRS and HDL-C were consistent with main analysis (Tables S9 and S10, Supplemental Digital Content 1, http://

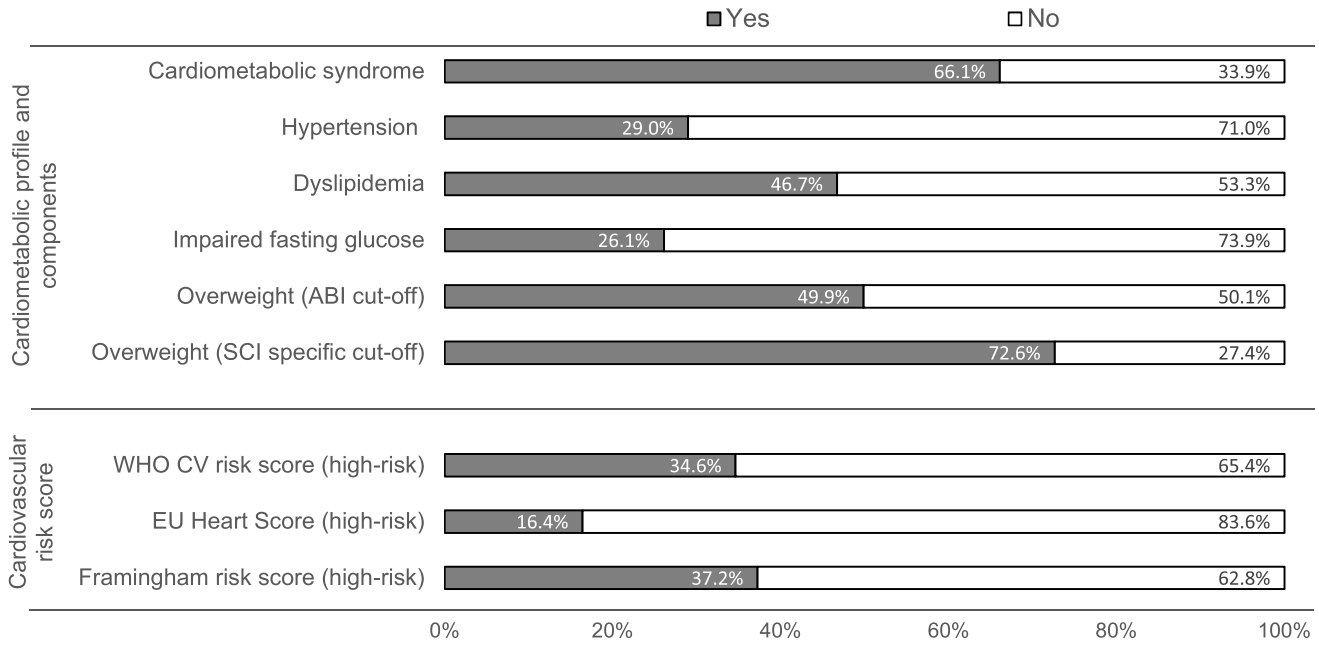

FIGURE 2. Cardiometabolic risk profile of individuals with SCI on discharge.

links.lww.com/PHM/C54). Higher waist circumference as a continuous variable was associated with higher fasting glucose (β = 0.01, 95% CI = 0.002–0.01) and were not observed in dichotomization (Table S11, Supplemental Digital Content 1, http://links.lww.com/PHM/C54).

We restricted our analysis to specific groups according to injury characteristics (motor complete, traumatic injury, and individuals with paraplegia) (Table S12, Supplemental Digital Content 1, http://links.lww.com/PHM/C54). The anthropometric measures were consistently associated with higher FRS in most of these groups but not with HDL-C. The association of functional independence was also consistent with higher HDL-C across different subgroups. We found that higher spasticity is associated with higher fasting glucose for individuals with paraplegia and traumatic injury.

We iterated our fully corrected models using sex as an interaction term (Table S13, Supplemental Digital Content 1, http://links.lww.com/PHM/C54). Sex-rehabilitation outcome interactions were statistically significant in fasting glucose-BMI, HDL-FVC, HDL-maximum grip, and HDL-spasticity. On fitting interaction terms in our fully adjusted models, statistically significant associations with respiratory function, spasticity, muscle strength, and functioning with HDL. We also found statistically significant association with anthropometric measures and FRS. In addition, we performed subgroup analyses to determine the influence of age in our estimates (Table S14, Supplemental Digital Content 1, http://links.lww.com/PHM/C54). The association of anthropometrics with FRS is consistent with adults (≤ 50 yrs). In addition, the association between respiratory function and HDL was also consistent with adults. The association between independent functioning and HDL was consistent across different subgroups.

Missing dependent (Table S15, Supplemental Digital Content 1, http://links.lww.com/PHM/C54) and independent (Table S16 a–c, Supplemental Digital Content 1, http://links.lww.com/PHM/C54) variables were tabulated accordingly. We compared the clinical profile of individuals with missing dependent variables (Table S16 a–c). We observed a higher proportion of females with missing dependent variables. Those with missing FRS (or lacking one component from the composite score) were older (Table S16a).

DISCUSSION

We found that at least a third of the cohort are considered at high cardiovascular risk and majority are classified high risk for obesity and cardiometabolic syndrome. Over the period of rehabilitation, we found that individuals with SCI improved in their respiratory function, muscle strength, and functioning. Furthermore, we showed an association between rehabilitation outcomes and cardiovascular risk profile. Future studies are to explore whether anthropometric measures, respiratory function, and functional independence may be used to prioritize screening in clinical settings when cardiovascular risk factors are not routinely measured. The summary of our main findings can be found in Figures 2 and 3 (graphical abstract).

During on average 5.2 mos in rehabilitation setting, our study participants improved respiratory function, muscle strength, and functional independence. This is in line with previous studies that reported improvements in gross motor and fine motor skills, a higher level of independence in activities of daily living, and higher motivation and outlook in life.[9,10,39] We also observed an increase in upper and lower limb spasticity that is also physiologically expected as a long-term consequence of paralysis and immobility.[40] We did not see significant changes in any of the body anthropometrics measures across time. Dynamic changes in fat, lean mass, bone, and water distribution in an individual with SCI in a subacute phase could have contributed to this null finding.[41,42] Lean muscle mass declines below the level of injury because of the loss of neural control and disuse. Bone mass also

TABLE 2. Lifestyle factors, health conditions, and cardiovascular risk profile at baseline

Parameters	Eligible Population (N = 706)
Lifestyle factors	
Special diet, *n* (%)	
No special diet	479 (89.70)
On medical diet[a]	55 (10.30)
Diet, *n* (%)	
Follow guideline on meat intake[b]	392 (73.82)
Follows guidelines on fruit and vegetables intake[c]	475 (88.95)
Nutritional score, median (IQR)[d]	4 (3–4)
Alcohol intake, *n* (%)	
Never	116 (16.43)
Drinker	590 (83.57)
Smoker, *n* (%)	
Never	229 (43.45)
Smoker	298 (56.55)
Physical activity (PASIPD), *n* (%)[e]	
Follows physical activity guidelines	305 (96.52)
Does not follow	11 (3.48)
Health conditions	
Medication intake, *n* (%)	
Steroid	24 (3.40)
Opioid	106 (15.01)
Antilipid medications/statins	62 (8.78)
Length of rehabilitation, median (IQR), mo	5.2 (3.1–7.4)
Cardiovascular risk profile (at T4)	
Framingham risk score, median (IQR)[f], %	7.16 (2.5–13.6)
Fasting glucose, median (IQR), mmol/l	5.0 (4.6–5.6)
Total cholesterol, median (IQR), mmol/l	4.7 (3.98–5.4)
Triglycerides, median (IQR), mmol/l	1.37 (1.0–1.89)
High density lipoprotein, median (IQR), mmol/l	1.18 (0.96–1.4)
Low density lipoprotein, median (IQR), mmol/l	2.8 (2.2–3.45)
HDL-C/total cholesterol ratio, median (IQR)	0.25 (0.20–0.31)

[a] Has special indication for diet.

[b] Recommended meat intake (<4 d/wk) according to the German Society for Nutrition (Deutsche Gesellschaft für Ernährung, 2013).

[c] Recommended fruits and vegetable intake (>3 portions/day) according to the German Society for Nutrition (Deustche Gesselschaft fur Ernahrung, 2013).

[d] Composite score computed using the dietary recommendation by the German Society for Nutrition (Deustche Gesselschaft fur Ernahrung, 2013). This comprises the score for liquid intake, fruit and vegetables, and meat intake with an overall score of 6 as best and 0 as poor diet and nutrition.

[e] Physical Activity Scale for Individuals with Physical Disabilities (PASIPD) based on modification (based on the study by Washburn et al.[38]). Physical activity was coded as active and sedentary based on the recommendation (30 mins of moderate or vigorous activity for 3 times per day, or 90 mins cumulative for cardiometabolic health).

[f] Ten-year risk for first cardiovascular event based on the study by D'Agostino et al.[24]

decreases because of the lack of weight-bearing and physical stress that is crucial for mineral deposition and bone development. The acute stress results in higher energy requirements and sequestration of fat storage to aid in energy production.[3,41] However, upon physiologic stability, the body shifts from catabolic to anabolic processes, which promote fat deposition.[41] This is also similar to water accumulation as a response to stress and eventual diuresis after injury stabilization. All body anthropometrics (waist circumference and BMI) then may depend on which body components change during the injury spectrum.

Furthermore, increase in anthropometric measures (BMI and waist circumference) were associated with poorer CV profile (increased FRS and decreased HDL) from our longitudinal models. Similarly, at discharge, higher mobility and overall functional independence scores were associated with a better lipid profile, which is consistent over several sensitivity tests and upon fitting to a longitudinal model. This strong association is consistent with previous studies and systematic reviews on physical activity and cardiometabolic health.[43] Furthermore, longitudinal studies on chronic and subacute injuries have reiterated these findings.[44] Exercise or a high level of physical activity had been associated with higher HDL because of improved cholesterol efflux capacity that promotes the transport of LDLs back to the liver for excretion.[45] This is the purported mechanism on how anaerobic exercise confers its beneficial effects on atherosclerosis. As such, there is a current trend of standardizing the measurement and prescription of exercises or physical activity in individuals with SCI.[46]

Better respiratory function was associated with a better cardiovascular risk profile. Higher peak expiratory flow and expiratory volume is used as a measure of cardiorespiratory fitness, which directly influences cardiometabolic health.[47,48] Another hypothesis to support is the loss of elastic recoil and reduced chest wall compliance, which were both associated with reduced vascular elasticity related to hypertension.[48,49] Finally, reduced oxygen uptake and relative hypoxia are associated with systemic inflammation, with a concomitant increase in inflammatory cytokines (C-reactive protein and interleukin 6) that have a crucial role in lipid profile and atherogenesis.[47] This association was previously observed in 253 chronic SCI individuals (4 yrs from injury), such that lower FEV1 and FVC were associated with hypertension and diabetes in a univariate model,[11] but did not show any significant association with HDL. The previous study had a younger study population and thus, had a lower prevalence of dyslipidemia compared with our group. Thus, the previous study may have been underpowered to detect any significant findings.[11]

A previous study found an association between severe spasticity with reduced adiposity and lower fasting glucose.[12] It was hypothesized that the higher muscle mass recruitment and contraction from severe spasticity were protective against fat cell deposition resulting in a lower total body fat percentage. Our fully adjusted model showed the higher spasticity group had 0.25 mmol/l higher fasting glucose compared with the lower spasticity (Table 3). Our focus was more on subacute injury without a history of CVD, which could have led to the divergence in our findings and the past study. The past study was focused on chronic injury with a smaller sample size and did not adjust for important confounders, although the past study has broader range of individuals with mild spasticity to severe spasticity.[12] Our hypothesis, instead, is that increased physical capacity and activity as shown by higher functional independence result in a better glucose profile with an opposite relationship with spasticity.

TABLE 3. Changes in the rehabilitation outcomes during rehabilitation period

	Admission[a]	Discharge[a]	P^b	LMM (Δ Time)[c]	P^b
Anthropometric measure					
Body mass index, kg/m^2	24.7 (21.6 to 28.0)	24.7 (21.9 to 27.9)	0.564	0.01 (−0.18 to 0.19)	0.95
Waist circumference, cm	90.1 (81 to 100.3)	91.2 (82 to 100)	0.824	0.46 (−0.72 to 1.65)	0.44
Lung function					
FVC, L	3.22 (2.48 to 3.96)	3.4 (2.6 to 4.1)	<0.001	−0.28 (−0.35 to −0.22)	<0.01
PEF, l/min	363 (271 to 456)	406 (308 to 499)	<0.001	−46.83 (−56.87 to −36.79)	<0.01
FEV1, l	2.65 (1.97 to 3.3)	2.72 (2.12 to 3.33)	<0.001	−0.20 (−0.25 to −0.15)	<0.01
Spasticity[d]					
Left gastrocnemius	1 (1 to 2)	1 (1 to 2)	0.002	-	-
Left gastrocnemius moderate-severe spasticity (+1–4/4), *n* (%)	34 (9.28)	73 (19.94)			
Right gastrocnemius	1 (1 to 2)	1 (1 to 2)	0.004	-	-
Right gastrocnemius mild spasticity (+1–4/4), *n* (%)	35 (9.58)	68 (18.63)			
Muscle strength[e]					
Right hand, kg	34.1 (24 to 45.4)	34.4 (25.8 to 46.6)	<0.001	4.00 (−0.26 to 8.26)	0.07
Left hand, kg	32.2 (22.6 to 42.7)	32.7 (23.3 to 43)	<0.001	2.99 (−0.60 to 6.57)	0.10
Best grip, kg	34.8 (25.5 to 46.3)	36 (27.2 to 47.8)	<0.001		
Functional Independence Scale (SCIM III)[f]					
Mobility total	4 (0 to 7)	12.5 (7 to 26)	<0.001	−8.58 (−9.20 to −7.97)	<0.01
Total SCIM	34 (21 to 58)	74 (56 to 91)	<0.001	−30.46 (−32.13 to −28.79)	<0.01

[a] Expressed in medians and IQR.

[b] Wilcoxon signed-rank test for paired samples.

[c] Linear mixed model using individual patient as cluster and time as predictor variables. β (95% CI) is the change at discharge from baseline. Model is adjusted for age, sex, and injury level.

[d] Spasticity is based on modified Ashworth scale comprising 6 grades of spasticity assessed by a rehabilitation specialist (0 increase in tone, and 5 rigidity in flexion or extension). Linear mixed models not provided as the scores did not satisfy regression assumptions.

[e] Hand grip strength is measured by hand dynamometer from 0 to 100 kg.

[f] Spinal Cord Independence Measure measures the functional independence score in different domains, namely, self-care, respiration and sphincter management, and mobility. Mobility subtotal comprise indoor mobility, mobility in moderate distances (10–100 m), outdoor mobility (>100 m), mobility using stairs, and transfer from wheelchair to car.

Finally, the FRS was higher and HDL-C was lower in individuals whose waist circumference and BMI were higher than this SCI-specific cutoff as compared with individuals with lower BMI and waist circumference values. Current anthropometric measures seem to underestimate the fat composition in SCI population.[50,51] Studies have been done to validate the use of waist circumference and body mass index and the association of cardiovascular risk including cutoff range for high risk.[31,32,52] Body mass index was validated using fat composition measured through bioelectrical impedance and C-reactive protein to approximate the high-risk groups.[32] Waist circumference cutoff was established using fat composition measured through magnetic resonance imaging and inflammatory biomarkers.[31,52] These studies were mostly done in individuals with chronic SCI, and none, yet, has explored this SCI-specific cutoff in subacute SCI. Although our study did not aim to validate these cutoffs in subacute SCI, our findings seem to be consistent with the current literature.

Few studies, to date, have ventured on the role of sex or gender with cardiovascular risk factors in individuals with SCI.[53] By fitting sex-rehabilitation outcome interaction term in our models, we identified sex as an effect modifier in our main finding. This means that the association between cardiovascular risk and rehabilitation outcome differs according to sex. Males have poorer cardiovascular profile than females.[54] For rehabilitation outcome, a previous longitudinal assessment showed males having better improvement in functionality compared with females.[55] As such, our findings were expected. Our main analysis was driven mostly by the high proportion of males. The small number of females in our study is a main limitation to fully understand effect modification by sex in some of our dependent variables.

Clinical Implications and Outlook

Clinical guidelines recommended cardiometabolic screening of individuals with SCI at 1- to 3-yr intervals, yet they do not specify the optimal timing for initial screening.[56] Our data showed that there is huge proportion of individuals with SCI being at high cardiovascular risk before discharge (e.g., high proportion of study population was with metabolic syndrome). As such, early cardiometabolic screening, at least for those at risk, should be considered before rehabilitation discharge.

Discharge planning from inpatient rehabilitation is mostly based on physiologic stability, functional independence, and readiness to reintegrate into society. Although CVDs have been recognized as an increasingly important cause of mortality,[57,58] cardiovascular screening may not be a medical priority before discharge. A retrospective assessment of hospital records participating in SwiSCI showed that only one fifth of the study population was screened for lipid profile (51), even though more than

TABLE 4. Association of cardiovascular risk factors and rehabilitation parameters[a]

Parameter (Cutoff)	Framingham Risk Score[b]	*P*	HDL	*P*	Glucose	*P*
Anthropometric measure						
Waist (86.5 cm)[c]	**0.28* (0.16 to 0.40)**	**<0.001**	**−0.10* (−0.20 to −0.001)**	**0.047**	0.14 (−0.09 to 0.37)	0.238
Body mass index (22 kg/m^2)[d]	**0.32* (0.19 to 0.46)**	**<0.001**	−0.09 (−0.20 to 0.02)	0.118	−0.004 (−0.24 to 0.23)	0.973
Respiratory function						
Forced vital capacity (2.72 l)	0.08 (−0.08 to 0.24)	0.341	0.12 (−0.002 to 0.25)	0.054	−0.03 (−0.27 to 0.22)	0.842
Peak expiratory flow (3.4 l/min)	0.02 (−0.14 to 0.18)	0.806	**0.16* (0.03 to 0.29)**	**0.013**	0.02 (−0.24 to 0.27)	0.902
Forced expiratory volume at 1 min (0.8 l)	−0.03 (−0.19 to 0.13)	0.731	**0.14* (0.02 to 0.26)**	**0.021**	0.07 (−0.19 to 0.32)	0.605
Spasticity[e]						
Left lower extremity spasticity (1/4)	−0.05 (−0.19 to 0.09)	0.481	−0.10 (−0.20 to 0.01)	0.075	**0.26* (0.03 to 0.47)**	**0.023**
Right lower extremity spasticity (1/4)	−0.02 (−0.15 to 0.12)	0.784	−0.08 (−0.18 to 0.02)	0.114	0.19 (−0.03 to 0.40)	0.088
Muscle strength and frailty[f]						
Left handgrip (33.3 kg)	0.02 (−0.19 to 0.24)	0.834	0.13 (−0.04 to 0.31)	0.128	−0.09 (−0.41 to 0.23)	0.579
Right handgrip (32.0 kg)	0.10 (−0.10 to 0.31)	0.321	**0.16* (0.001 to 0.32)**	**0.049**	0.01 (−0.30 to 0.33)	0.926
Best grip (34.63 kg)	0.13 (−0.10 to 0.35)	0.270	−0.02 (−0.19 to 0.16)	0.844	−0.05 (−0.39 to 0.28)	0.758
Functioning[g]						
Total SCIM (12.5)	0.09 (−0.05 to 0.21)	0.383	**0.21* (0.11 to 0.30)**	**<0.001**	−0.008 (−0.21 to 0.12)	0.937
Mobility SCIM (74)	0.06 (−0.07 to 0.18)	0.210	**0.19* (0.09 to 0.29)**	**<0.001**	0.003 (−0.20 to 0.20)	0.980

[a] Adjusted for age, sex, injury level, medication use (statins and steroids) and body mass index (except for body anthropometrics as independent variables). Independent variables (rehabilitation outcomes) as dichotomous variables and dependent variables as continuous variables. **P* values <0.05 in bold.

[b] Log-transformed values.

[c] Waist circumference adjusted for SCI cutoff at 86.5 cm (based on the study by Gill et al.[31]).

[d] BMI adjusted for SCI cutoff at 22 kg/m^2 (based on the study by Laughton et al.[32]).

[e] Spasticity is based on modified Ashworth scale comprising 6 grades of spasticity assessed by a rehabilitation specialist (0 increase in tone, and 5 rigidity in flexion or extension).

[f] Hand grip strength is measured by hand dynamometer from 0 to 100 kg.

[g] Spinal Cord Independence Measure measures the functional independence score in different domains, namely, self-care, respiration and sphincter management, and mobility. Mobility subtotal comprise indoor mobility, mobility in moderate distances (10–100 m), outdoor mobility (>100 m), mobility using stairs, and transfer from wheelchair to car.

one third may be at increased CVD risk and 39.5% met criteria for metabolic syndrome.[4] Our study revealed that higher rehabilitation outcomes relate to better cardiovascular health. To put into context, the use of statins result to 3%–5% increase in HDL (2 mg/dl or 0.05 mmol/l).[59] In our study, a higher functional independence score has 0.2 mmol/l higher than those with lower score. The functional independence score we used has self-care, respiration, and sphincter function (bladder and bowel), and mobility subcomponents. A high score on self-care, respiration, bladder, and bowel function is extremely important to achieve before discharge as this usually translates to less need for specialized care provided by a rehabilitation facility. Individuals with lower mobility scores might require less specialized care that could prompt early discharge, and they would likely benefit from cardiovascular screening before discharge. Furthermore, individuals with lower respiratory ventilation should also be prioritized for screening. As of time of writing, only one study has explored this association[11] and would further be useful if validated in other centers or countries with different rehabilitation programs. This information would be essential in healthcare settings with earlier discharge and shorter lengths of stay.[39,60,61]

In addition, future studies should explore sex differences on CV risk and CV diseases. More studies should report sex-disaggregated or female-specific results on the association of rehabilitation outcomes and CV risk. The SCI epidemiology, as of now, still occurs more commonly in males. This is rapidly changing as there are more and more nontraumatic and elderly sustaining injuries, of which sex disparity is less evident. As such, the epidemiology of comorbidities in women with SCI are increasingly becoming more important.

Finally, although current risk prediction tools are able to predict cardiovascular events within 5 yrs, the true burden of the disease is grossly underestimated by the FRS.[25] Individuals with SCI have lower blood pressure and lower lipid profiles, which computationally result in lower risk scores, yet remain at high-risk in reality.[62] Physical activity and baseline inflammation status are factors not considered and should be used to increase predictive ability. Thus, future studies should validate, adjust, or develop a new cardiovascular risk-scoring tool based on hard outcomes (cardiovascular events or cardiovascular deaths) in this group using long-term follow-up in this cohort. Novel cardiovascular biomarkers should also be explored to shed light on the pathophysiology and provide acuity in predictive tools.

Strengths and Weaknesses

We presented results from prospectively collected data from a multicenter study that has less selection bias compared with most studies that which are based on registries and administrative data from hospitals. The use of administrative data from hospitals is problematic as physicians decide when and

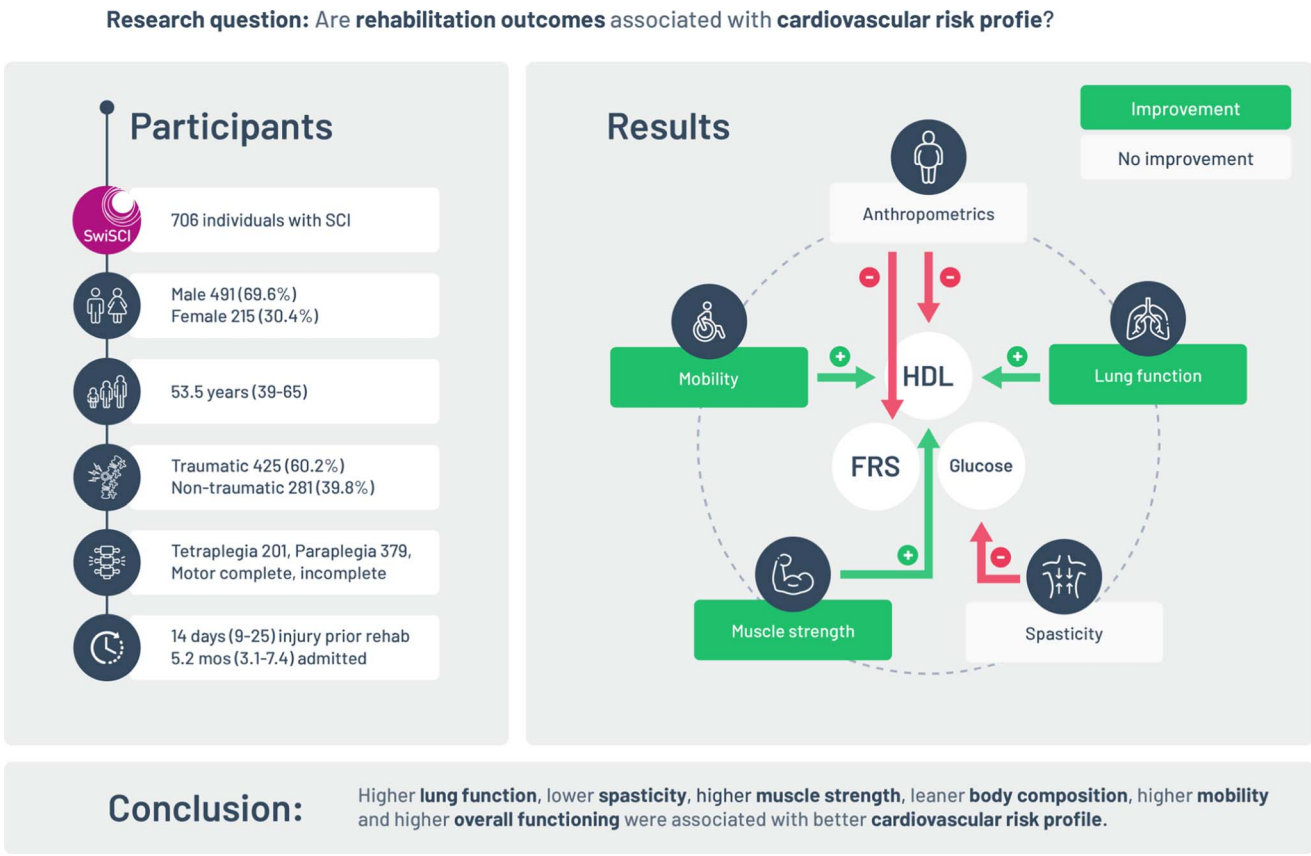

FIGURE 3. Graphical abstract.

what clinical outcomes to measure (confounding by indication). Using the SwiSCI cohort, we routinely collected and used SCI-specific dependent and independent variables on all participants. As one of the largest SCI cohorts in the literature, we provided a more precise estimate, adjusted for important confounding variables, performed subgroup analyses (by age and sex), and iterated restrictive analysis (according to injury characteristics). Our population is more homogenous as we removed all individuals with incident and prevalent CVDs, and because of the inpatient setting, which standardizes diet and physical activity to a healthy level. Our cohort has a huge proportion of elderly compared with other cohorts. This makes our cohort more ideal in determining cardiometabolic changes as we do not expect any abnormal findings in a cohort with young participants. Lastly, our final model was iterated, not only by different subgroups according to age, sex, and injury characteristics, but also by longitudinal multilevel mixed model analysis with consistent findings. As such, our findings are robust as the β estimates maintain their statistical significance across different scenarios.

Although our findings found important associations that may have implications for future clinical guidelines, these were based on cross-sectional study that are prone to reverse causation. This would mean that those with higher cardiovascular risk factors (independent variables) might be those with rehabilitation measure (dependent variables), and what we observed is a reversed cause-and-effect. Although we analyze longitudinally as part of sensitivity, the short latency period between dependent and independent variables could still make reverse causality possible. In addition, we used study sample medians of rehabilitation outcomes because there are no SCI-specific cutoffs in the literature and because sample size would mostly likely be underpowered for comparisons of unequal groups. Except for SCI-specific BMI and waist circumference, a cutoff on other rehabilitation outcomes that predicts a cardiovascular outcome would be more useful. However, this is impossible with our prospectively collected data as we still lack hard outcomes (e.g., incident CVD events) in our cohort. Another important limitation is the enrollment bias that was previously established in another publication.[19] Underreporting of women, the older people, and those with lower functional independence should be considered in interpreting our findings. Lesser women in our analysis group could make our findings less representative. It is also likely that the true association is underestimated, considering the underrepresentation of the older people and more severe SCI. Our analysis was also limited to common laboratory measures available in the clinics. It would have been ideal to have high-sensitivity C-reactive protein and other cardiovascular inflammatory makers that aids in characterizing the risk. The use of HDL-C for cardiovascular risk profiling could also be imprecise considering previous study on nonlinear relationship[63] and noncausal associations.[64] However, low HDL profile is more frequently seen in SCI compared with the general population.[65] This was hypothesized as the reason for high cardiovascular risk in SCI.[65,66] We also lack detailed interventions that a participant received during inpatient admission. Although we collected the diet and physical activity data, we lacked information on the detailed exercise

regimen, occupational training, and psychological interventions. Our information on the rehabilitation regimen does not have the adequate granularity to point out a specific intervention that provided cardiovascular benefit.

Finally, we used cardiometabolic risk profile, FRS, WHO CV score, and SCORE 2 to approximate cardiovascular risk. We have observed discrepancies when comparing the change in proportion of individuals classified as high risk over rehabilitation stay when using the three scores. This can be driven by lack of validation of such scores in SCI population, inherent differences in risk estimation, and disparities in components. Cardiovascular health promotion focuses on preventing hard cardiovascular event such as myocardial infarction, coronary diseases or cardiovascular deaths, none of which were observed during our study period. As such, care should be taken in interpreting our findings not to over extrapolate in disease prevention.

CONCLUSIONS

We observed a high burden of cardiometabolic syndrome and high CVD risk upon initial rehabilitation stay discharge. We also observed a significant improvement in rehabilitation outcomes (i.e., respiratory function, mobility, and SCIM score) during rehabilitation. Higher respiratory function, mobility, and functional independence score were associated with a better cardiovascular profile at discharge and sex was identified as effect modifier. Thus, aside from established cardiovascular risk factors, rehabilitation outcomes may be useful to improve current CVD prediction models in the SCI population. However, this remains to be verified in future studies, considering our limitations in study design and short follow-up period.

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