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

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STUDY DESIGN: Multicentre, cross-sectional study.
OBJECTIVES: To determine if clinical measures of poor mental health (MH-) and neuropathic pain (NP) are related to increased CVD risk in individuals with chronic spinal cord injury (SCI), and further elucidate the relationships between CVD risk, autonomic function, NP, and MH-.
SETTING: Eight SCI rehabilitation centres in the Netherlands.
METHODS: Individuals ($n = 257$) with a traumatic, chronic (≥10 yrs) SCI, with age at injury between 18–35 years, completed a self-report questionnaire and a one-day visit to a rehabilitation centre for testing. CVD risk was calculated using Framingham risk score. NP was inferred using The Douleur Neuropathique 4 clinical examination, and MH- was assessed using the five-item Mental Health Inventory questionnaire. Cardiovascular autonomic function was determined from peak heart rate during maximal exercise (HR_{peak}).
RESULTS: There was a high prevalence of both NP (39%) and MH- (45%) following SCI. MH- was significantly correlated with an adverse CVD risk profile ($r = 0.174$; $p = 0.01$), increased the odds of adverse 30-year CVD risk by 2.2 (CI 0.92–2.81, $p = 0.02$), and is an important variable in determining CVD risk (importance=0.74, $p = 0.05$). Females ($p = 0.05$) and those with a higher HR_{peak} ($p = 0.046$) tended to be more likely to have NP.
CONCLUSIONS: Clinical measures of MH-, but not NP, are important factors for increased CVD risk following SCI. NP tended to be more prevalent in those with more preserved cardiovascular autonomic function. The interrelationships between secondary consequences of SCI are complex and need further exploration.

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INTRODUCTION

Spinal cord injury (SCI) disrupts sensory, motor, and autonomic pathways, with higher, more severe injuries resulting in greater loss of sensorimotor function [1] and increasing autonomic impairment [2]. In particular, individuals with lesions above the 6th thoracic level (T6) may experience loss of descending control of sympathetic pathways that regulate the heart and key vascular resistance and capacitance beds in the splanchnic circulation [3], leading to abnormal control of heart rate and blood pressure [4, 5]. Accordingly, cardiovascular disease (CVD), the leading cause of morbidity and mortality among individuals with SCI [6], occurs earlier and progresses more rapidly following SCI [7]. In addition to traditional CVD risk factors, injury characteristics including the duration (DOI) and spinal level of injury (LOI), as well as autonomic function (using indices of systolic arterial pressure (SAP) and maximal exercise heart rate (HR_{peak})) have been identified as key predictors of an adverse CVD risk profile [8]. In order to build a comprehensive CVD risk profile for individuals living with SCI, potential risk factors that may have a compounding effect with the impacts of injury need to be further explored.

There is a high prevalence of neuropathic pain (NP) [9] and poor mental health (MH-) [10] in individuals with chronic SCI and these factors have been reported to be associated with increased CVD in this population [11]. However, in these and other studies NP and MH- have generally been derived from self-report questionnaires using broad questions with differing timeframes. Validated clinical measures, such as the Douleur Neuropathique 4 exam (DN4) [12] for NP and the 5-item Mental Health Inventory questionnaire (MHI-5) [13] for MH-, have not been employed when exploring these variables in relation to CVD risk and cardiovascular autonomic function following SCI.

Chronic pain is associated with CVD in the general population [14, 15]. Pain, and in particular NP, is prevalent after SCI [9]. There

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are conflicting results regarding the relationships between injury characteristics and the presentation of NP, with reports of NP being more common in people with tetraplegia [16], paraplegia [17, 18], or no difference with differing LOI [9, 19]. Following SCI, aberrant sprouting of sensory axons induces alterations to sympathetic pathways, contributing to increased sensitivity of sympathetic reflexes through morphological changes [20], enhanced input from primary sensory neurons [21], central sensitisation of nociceptive inputs [22], and hypersensitive postganglionic sympathetic responses [23], providing possible mechanistic links between NP and autonomic impairment. Furthermore, NP may intersect with autonomic dysreflexia (AD), a cardiovascular condition unique to high-level SCI related to injury to descending autonomic (sympathetic) pathways, manifesting as paroxysmal hypertension in response to sensory stimuli below the LOI [23]. It may be that the presence of NP as a pervasive sensory stimulus, coupled with central sensitisation of nociceptive input and excessive sympathetic responses link NP and AD, with adverse CVD consequences [21].

MH- is more common in individuals living with SCI relative to the general population [10], particularly in those with high-level SCI [24]. In the general population, MH- is considered an independent risk factor for CVD as it induces dysregulation of the sympathoadrenal system, with increases in inflammation-related interleukins (IL-6, IL-1B), C-reactive protein, and triglycerides that promote systemic inflammation and dyslipidemia, predisposing to cardiovascular events [25]. Dyslipidemia and systemic inflammation are also increased following SCI, possibly creating an additive effect that further increases CVD risk in this population [26]. Coupling these effects with the sympathetic consequences of SCI, MH- could have a greater impact on CVD risk following SCI.

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

METHODS

This study is part of the Dutch multicentre research programme "Active LifestyLe Rehabilitation Interventions in aging Spinal Cord injury (ALLRISC)", a cross-sectional study among individuals with long-term SCI living in the Netherlands [27]. This study was approved by the Medical Ethics Committee of the University Medical Center Utrecht and the Department of Research Ethics at Simon Fraser University. Investigations were performed in accordance with the Declaration of Helsinki of the World Medical Association [28]. All participants gave written informed consent prior to participation. As part of the wider ALLRISC study, aspects of the methodology are similar to those reported previously [8].

Participants

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

Procedures

The study consisted of a one-day visit to a rehabilitation centre that included an extensive medical assessment, physical examination, oral interview, and several physical tests [8, 27]. Two weeks prior to the visit, participants were asked to complete a self-report questionnaire examining personal demographics, mental health, and secondary health conditions to SCI. On the day of the visit, participants were asked to fast (except for water) for 12 h prior to testing to ensure blood markers for the determination of cardiovascular disease risk (e.g. lipid profiles) were collected in the fasted state. They were asked to refrain from vigorous exercise on the day of testing, and to ensure appropriate bladder and bowel care was performed prior to testing to minimise the likelihood of AD during testing in susceptible individuals.

Personal characteristics. Age, sex, and DOI, were extracted from the self-report questionnaire. Waist circumference (WC) was measured in the supine position, at the narrowest part of the waist after a normal expiration, using a stretch-resistant measuring tape. A physiatrist determined the neurological level and severity of injury according to the International Standards for Neurological Classification of Spinal Cord Injury [1]. LOI was considered both linearly (C1 = 1, C2 = 2, etc.), and categorically according to three groups based on the known impact of LOI on cardiovascular autonomic pathways [29]: C1–C8 levels were defined as "high" injuries (potential loss of autonomic control of cardiac function and key vascular beds for blood pressure control); T1–T6 levels as "mid" injuries (potential loss of autonomic control of key vascular beds for blood pressure control, but minimal impairment to cardiac function); and SCI levels below T6 as "low" injuries (largely intact cardiovascular autonomic function). A complete lesion was defined as the absence of motor and sensory function in the sacral segments and classified as American Spinal Injury Association Impairment Scale (AIS) grade A. AIS grades B, C, and D were classified as incomplete lesions [1].

Neuropathic pain. For participants who indicated that NP had been a concern for them at some point post-injury, NP was objectified using the Douleur Neuropathique 4 (DN4) exam, administered by a physiatrist, which consists of 7 items related to symptoms of NP (burning, painful cold, electric shocks, tingling, pins and needles, numbness, and itching) and 3 related to a clinical examination (hypaesthesia to touch or pinprick and presence of allodynia) [12]. Individuals with SCI were included in the development of this assessment, and it is therefore validated for clinical use in populations with SCI [12]. NP was considered both linearly (1–10), and categorically (present=1, absent=0). For categorical analyses, individuals were considered to have NP if they had a DN4 score ≥4 or were taking medications with a primary indication for NP. Those who had never experienced NP were considered to have a score of zero.

Mental health. Mental health and well-being was evaluated with a bidirectional mental health model using the five-item Mental Health Inventory questionnaire (MHI-5) [13, 30], which consists of five questions on mood over the last 4 weeks. This clinical instrument has been validated for use in populations with SCI, with high internal consistency [31]. MH- was considered both linearly (0–100) and categorically (present=1, absent=0). For categorical analyses, individuals were considered to have MH- if they had an MHI-5 score ≤72 or were taking medications with a primary indication for depression [31].

Cardiovascular autonomic function. We inferred cardiovascular autonomic function from HR_{peak} (Polar Sport Tester, Polar Electro, Kempele, Finland) during graded maximal exercise testing as a marker of injury severity to descending autonomic (sympathetic) pathways [32]. HR_{peak} was determined as the highest 5 s average HR during the entire test. Chronotropic incompetence (CI) was defined as a HR_{peak} < 125 beats per minute and a normal HR_{peak} as ≥125 beats per minute (based on peak responses observed previously in those with high-level SCI and associated CI) [5]. We recorded resting systolic arterial blood pressure (SAP), which is heavily influenced by the integrity of cardiovascular autonomic pathways after SCI, using a digital sphygmomanometer while participants were seated in their wheelchair.

Cardiovascular disease risk. We calculated the Framingham risk score (FRS) for both 10-year [33] and 30-year [34] CVD risk. This score utilises the following risk factors: sex; age; smoking status; diabetes; SAP; antihypertensive treatment; high-density lipoprotein cholesterol; and total cholesterol. Since SCI can impair blood pressure regulation (particularly with lesions above T6) such that a lower SAP in a SCI population may not be associated with a reduced overall CVD risk in the same way as seen in able-bodied individuals, a neutral SAP of 120 mmHg was used when calculating the risk score. A risk score of 10% is considered "intermediate risk" and this was the cut-point used for classifying "at-risk" individuals [33].

Statistical analyses

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

RESULTS

Participants

A total of 282 individuals participated in the study. We were specifically interested in the effects of traumatic SCI, so data from 257 individuals (61 females) aged 47 ± 8 (SD) years with chronic (24 ± 9 (SD) years) traumatic SCI were included in the analyses. Participant characteristics are shown in Table 1. For various reasons not all data were collected in all participants; sample sizes for each measure are provided.

Table 1. Participant characteristics.

Characteristic	All	*n*	Male	*n*	Female	*n*	*p-value*
Age (years)	47 ± 8	257	47 ± 9	196	47 ± 9	61	0.98
Duration of injury (years)	24 ± 9	257	24 ± 9	196	23 ± 9	61	0.86
Level of injury (%)							
Cervical	45	114	47	93	34	21	0.07
Thoracic	50	128	47	92	59	36	0.10
Lumbar	5	14	6	11	5	3	0.77
Sacral	0	0					
Motor/sensory completeness of injury (%)							
Complete	71	183	70	138	75	45	0.45
Incomplete	29	73	30	58	25	15	0.45
Stratification by level based on known cardiovascular autonomic pathways (%)							
High (C1-C8)	45	114	47	93	34	21	0.07
Mid (T1-T6)	34	88	32	63	41	25	0.20
Low (Below T6)	21	54	20	40	23	14	0.61
Stratification by autonomic severity of injury (inferred from chronotropic incompetence) (%)							
High (C1-C8) with CI	64%	29	68	25	50	4	0.35
Mid (T1-T6) with CI	9%	6	8	4	11	2	0.73
Low (Below T6) with CI	2%	1	0	0	8	1	-
WC (cm)	97 ± 15	239	**100 ± 14**	**184**	**89 ± 14**	**55**	**<0.001**
SAP (mmHg)	126 ± 26	253	125 ± 26	192	126 ± 325	61	0.78
HR_{peak} (bpm)	147 ± 29	156	145 ± 30	118	152 ± 26	38	0.24
VO_{2peak} ($ml \cdot min^{-1} \cdot kg^{-1}$)	17.1 ± 6.1	160	**17.8 ± 6.2**	**118**	**15.2 ± 5.4**	**42**	**0.017**
Hypotension (%)	26	69	**30**	**57**	**13**	**8**	**0.01**
CI (%)	23	36	25	29	47	7	0.43
NP (%)	39	99	35	69	49	30	0.05
MH- (%)	45	116	46	91	41	25	0.46
NP and MH- (%)	19	49	18	36	21	13	0.61
10-year FRS (%)	10 ± 8	227	**12 ± 8**	**172**	**5 ± 4**	**55**	**<0.001**
10-year increased FRS (%)	38	87	**48**	**82**	**9**	**5**	**<0.001**
30-year FRS (%)	23 ± 16	228	**27 ± 16**	**172**	**14 ± 10**	**56**	**<0.001**
30-year increased FRS (%)	77	176	**87**	**149**	**50**	**27**	**<0.001**

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

Prevalence of CVD risk and cardiovascular autonomic dysfunction

There were 87 individuals (38%: 5 females) considered to be at risk of CVD utilising the 10-year FRS, and 176 individuals (77%: 27 females) at risk utilising the 30-year FRS. Most lesions were cervical (45%) or thoracic (50%), with 79% ($n = 202$: 46 females) having mid- or high-level injuries that could affect cardiovascular autonomic control. HR_{peak} was collected in 156 individuals (61%: 38 females). There were 36 individuals (23%: 7 females) who presented with CI, implying cardiovascular autonomic dysfunction. Some of these data were previously published and further discussed by Dorton et al. [8].

Prevalence of NP and MH-

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

Relationships between NP, cardiovascular autonomic function and CVD risk

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

Correlations revealed a tendency for NP to be associated with female sex ($r = 0.122$, $p = 0.05$) and more intact cardiovascular autonomic function ($r = -0.156$, $p = 0.052$), although criteria for statistical significance were not met. Individuals with low- and mid-level injuries tended to present with NP more often than those with high-level injuries ($p = 0.065$) although this did not meet statistical criteria. Multiple linear regression (Table 2) and AIC analyses (Fig. 1) showed that NP was not a key predictor of 10-year or 30-year FRS. The presence of NP did not impact the odds of an adverse 10-year (0.73, $p = 0.27$) or 30-year (0.78, $p = 0.42$) CVD risk profile.

We considered whether the type of pain experienced was influenced by autonomic severity of injury (inferred from the presence or absence of CI) ($n = 156$). Overall, the presence of NP was more likely in those with less autonomically severe injuries (22% vs 40%, $p = 0.047$). Those with less autonomically severe lesions were more likely to report sensations of painful cold (0% vs 14%, $p = 0.0063$) or electric shock (3% vs 21%, $p = 0.013$).

Relationships between MH-, cardiovascular autonomic function and CVD risk

There tended to be a higher prevalence of CVD risk in those with MH- (55%) than those without MH- (43%, $p = 0.09$), although this did not reach criteria for statistical significance. MH- was significantly correlated with an adverse 10-year ($r = 0.174$, $p = 0.01$) and 30-year ($r = 0.141$, $p = 0.038$) CVD risk profile. Older individuals were more likely to experience MH-, although this did not meet criteria for statistical significance ($r = 0.124$, $p = 0.055$). MH- was identified as an important predictor using AIC analyses for both the 10-year and 30-year CVD risk (Fig. 1), with similar results using multiple linear regression (Table 2). Additionally, individuals with MH- were 1.6 (10-year FRS; $p = 0.09$) and 2.2 (30-year FRS; $p = 0.02$) times more likely to present with an adverse CVD risk profile, although the MH- relationship with the 10-year FRS did not achieve criteria for statistical significance.

Use of medications with a primary indication for NP and MH-

There were 136 individuals that completed the DN4 examination (suggesting concern for, or had experienced NP), with 99 individuals identified as presenting with NP at the time of evaluation (87 with DN4 score ≥ 4, 12 based on medication use). Of these 99 individuals, 37 indicated medication use directly targeting NP; of these, 12 individuals (32%) presented with a DN4 score <4, indicating effective pain management. Regarding MH-, 116 individuals presented with MH- (102 with MHI-5 score ≤72, 14 based on medication use). Of these 116 individuals, 32 indicated pharmacological treatment of MH- with 14 individuals (44%) having an MHI-5 score ≥75, indicating effective medicinal management. In total, 64% of individuals classified as having NP and 72% as having MH- were not taking a primary use medication for these conditions (Table 3).

Table 2. Regression model outcomes for multivariate regression between personal and injury characteristics, NP, MH-, and 10-year and 30-year CVD risk.

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

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

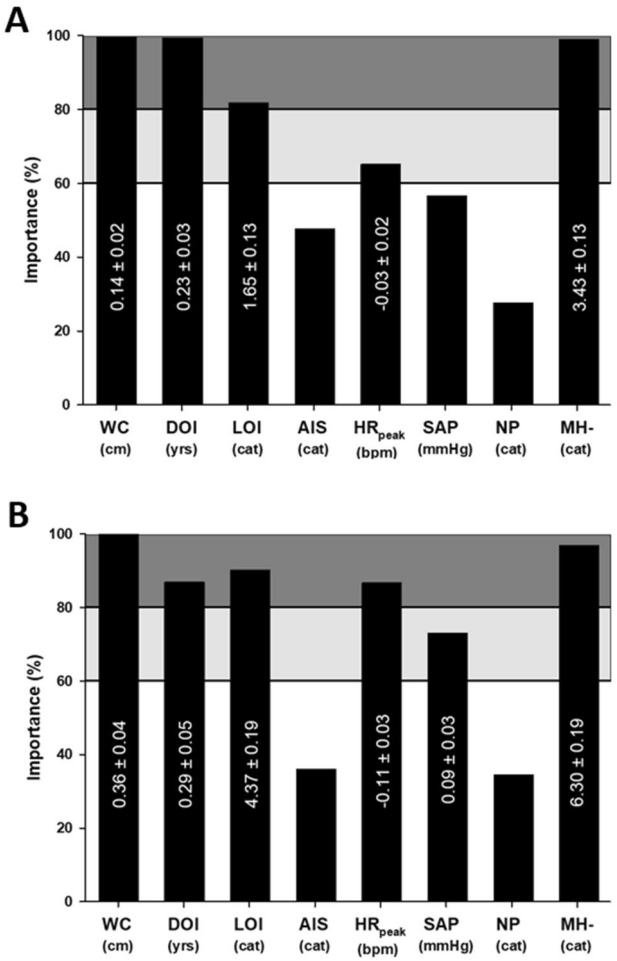

Fig. 1 Akaike Information Criterion model-averaged importance of predictors of CVD risk. WC, DOI, LOI (cat), and MH- (cat) were highly important predictors, with HR_{peak} being a moderately important predictor of increased CVD risk for the 10-year FRS (**A**). WC, DOI, LOI (cat), HR_{peak}, and MH-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

DISCUSSION

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

MH- and CVD risk

MH- is a known CVD risk factor for the general population through increases in inflammatory substrates and triglycerides [25]. MH- is more prevalent in those living with an SCI relative to the general population [11], and was present in 45% of individuals within our cohort. MH- can impact CVD risk from a physiological (e.g. impaired autonomic function, increased inflammatory responses, dyslipidemia, and endothelial dysfunction) and behavioural (e.g. decreased physical activity, increased smoking, and disrupted sleep patterns) perspective [35]. Individuals presenting with MH- had a two-fold greater likelihood of an adverse CVD risk profile. Considering that SCI independently impacts each of these variables, mental health should be a primary consideration in risk evaluation and management after injury. While others have shown causality for MH- to negatively impact CVD risk after SCI [11], it may also be that some part of this association relates to the devastating impact of cardiovascular dysfunction after SCI and its possible association with MH- [36] and poorer quality of life [37]. The possibility of this bidirectional component to the relationship should be considered in future studies.

Table 3. Description, prevalence, and efficacy of pharmacological treatments used primarily for managing NP and MH-.

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

Medications with more than one primary use were only considered if primary use was specified. Note that one individual could be concurrently taking multiple medications. Treatment efficacy is the percentage of individuals receiving pharmacological treatment for the condition in whom the clinical scores were within the relevant cut point, relative to total cases. *MH-* poor mental health, *n* sample size, *NP* neuropathic pain, *SSRI* selective serotonin reuptake inhibitors, *TCA* tricyclic antidepressants.

NP and CVD risk

NP was present in 39% of participants, consistent with previous reports [9, 16]. However, NP was not significantly associated with CVD risk, contrary to previous literature [11]. There are several factors that could explain these conflicting results. First, we used a clinical measure to assess the presence of NP at the time of the examination. This clinically relevant snapshot could have underestimated the prevalence of NP in the long term and impacted the association with CVD risk. Indeed, previous studies showing associations between NP and CVD used questionnaires regarding the presence of pain spanning back 12 months [11, 16, 38]. Second, we used a calculated CVD risk with an "at-risk" threshold, while previous studies used the presence of CVD events (e.g. heart disease or stroke) [7, 11, 26]. We calculated 38% of individuals with chronic SCI to be "at-risk" of CVD compared to estimates of 5–10% using the presence of CVD [26]. Finally, it is possible that previous associations between NP and CVD events reflect commonality, where the two conditions coexist, rather than causality, with one condition leading to another.

Relationships between lesion characteristics and NP are unclear, with previous literature reporting an increased risk for NP in those with high-level lesions [16], those with paraplegia [17, 18] or no

differences based on LOI [9, 19]. Our data suggest that those with mid- and low-level lesions are at a greater risk for NP. These discrepancies suggest further investigation of the relationships between level of injury and NP and highlight that it should be considered in all individuals with SCI, regardless of lesion characteristics.

MH-, NP, and autonomic function

A secondary aim of this study was to further explore the relationships between MH- and NP and remaining cardiovascular autonomic function, inferred from HR responses to exercise, to better understand and establish a CVD risk profile in chronic SCI. Impaired autonomic function was previously shown to be an important independent factor in predicting increased CVD burden following SCI [8], however it is unclear whether this association is a direct effect of the loss of descending control of autonomic pathways, or an indirect effect of other factors presenting as a consequence of autonomic impairment. This is the first study to investigate the relationship between NP, MH-, and remaining autonomic function following SCI. As outlined above, there are several physiological and behavioural mechanisms that may link NP and MH- with autonomic function [22, 23, 35] and help elucidate their relationships with CVD risk. Our findings suggest that females and those with low-level injuries with more intact cardiovascular autonomic function might be more likely to experience NP. Given the relationships between impaired autonomic function and CVD risk, and lower likelihood of NP in those with impaired autonomic function, it is not surprising that pain was not a predictor of CVD risk. While there were no strong associations between MH- and autonomic function, shared mechanisms should be investigated further as they are both associated with increased CVD risk. Of note, preserved autonomic function was associated with a higher prevalence of painful cold and electric shock pain. It may be that those with preserved autonomic (sympathetic) function have a stronger substrate for aberrant sprouting within and between sensory and autonomic pathways, providing a mechanistic association between NP and cardiovascular autonomic function. Future research should emphasize more direct measures of remaining autonomic function to robustly explore these relationships. The observation that females tended to experience more severe NP has been reported before both in humans [39] and in animal models [40] but the mechanism underlying this observation remains unclear.

Consideration of medicinal management for NP and MH-

Individuals living with SCI commonly use a variety of medications to manage secondary health conditions related to their injury, including MH-, NP, and CVD. Primary use medications for a specific condition often impact another condition, positively or negatively, and these effects are not always known or possible to account for. We considered medications with a primary indication for MH- and NP and found that relatively few individuals were well managed, with 56 and 68% still meeting clinical thresholds for the disorder, despite taking medications with a primary indication for the condition. It is likely, however, that although symptoms were not reduced below the clinical thresholds, symptom severity with medication use may have decreased. Interestingly, a high number of individuals presenting with MH- and NP did not report taking any primary use medications for these conditions (64 and 72%), with ongoing symptomology beyond clinical thresholds, highlighting the importance of considering medicinal management for NP and MH- in individuals with chronic SCI. Particular consideration should be given to those at higher risk for MH- and NP; MH- tended to be more present in older individuals and NP tended to be more prevalent in females. Of note, LOI and AIS were not associated with MH-, suggesting it be considered in all individuals with SCI, regardless of lesion characteristics.

Analytical considerations

The FRS incorporates resting blood pressure as a positive correlate of CVD risk, however, it is unclear if resting hypotension, prevalent in high-level SCI and strongly associated with severe autonomic impairment, provides the same cardio-protective benefit seen in the able-bodied [41]. Accordingly, we used a neutral SAP (120 mmHg) in the determination of the FRS. When we repeated our analysis using the recorded SAP, our results were essentially unchanged.

We assumed that individuals taking a primary use medication for MH- or NP at the time of testing had either experienced or been diagnosed with that condition. We did not change the respective raw scores of the DN4 or MHI-5, however, in the categorical analysis, they were classified as presenting with that condition. When we repeated our analyses using the recorded DN4 or MHI-5 scores, without accounting for medication use, our results were essentially unchanged.

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

Another consideration is the use of HR_{peak} to evaluate autonomic impairment in this study. The strengths of this approach are the ability to effectively and simply discriminate autonomic severity of injury, with clear translation and accessibility to the lived experience–clinicians and individuals with SCI can readily monitor peak heart rate using simple wearable devices during a bout of moderate-severe exercise to evaluate whether chronotropic incompetence is present. The challenge with this approach is that some individuals with high-level SCI were not able to complete the exercise testing protocol, representing a selection bias, with loss of those individuals likely to have the most severe autonomic impairment based on their high-level of injury.

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

CONCLUSIONS

These data show that a validated, clinical measure of MH-, but not NP, is an important predictor of increased CVD risk in individuals with chronic SCI. MH- is associated with a two-fold increased likelihood of an adverse CVD risk profile, likely impacted by both physiological and behavioral factors. NP tended to be more present in those with more preserved cardiovascular autonomic function, suggesting a link between the preservation of spinal autonomic pathways and NP. In general, many individuals had clinically relevant NP and MH-, but were not taking medication for these conditions, or their medication use did not improve symptoms below clinical thresholds. Medication use for MH- and NP needs to be carefully considered, including evaluation of individual treatment efficacy, adherence, and side-effects. The onset and progression of CVD following SCI is complex, combining traditional, SCI-specific, and non-traditional risk factors that need to be considered when creating a risk profile and determining appropriate management.

DATA AVAILABILITY

The datasets generated and/or analysed during the current study are available from the corresponding author on reasonable request.

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AUTHOR CONTRIBUTIONS

JKK, MCD, and VEC conceived the idea for the study. MWMP and SDG designed the study protocol and collected the data. MCD and VEC analysed the data. JKK, MWMP, and SDG assisted in interpreting the results. MCD and VEC wrote the manuscript. VEC supervised the research. All authors contributed to the critical revision of the manuscript.

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COMPETING INTERESTS

The authors declare no competing interests.

ETHICS

We certify that all applicable institutional and governmental regulations concerning the ethical use of human volunteers were followed during the course of this research.

ADDITIONAL INFORMATION

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