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**Traditional cardiovascular risk factors strongly underestimate the 5-year occurrence of cardiovascular morbidity and mortality in spinal cord injured individuals**

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### Article

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1 **Abstract**

2 **Objective**– To explore whether traditional models of cardiovascular disease (CVD) risk  
3 prediction correctly predict CVD events across a median 5.7-year follow-up in people with  
4 spinal cord injury (SCI), and if adding SCI-related characteristics (i.e. lesion level) to the  
5 prediction model can improve the prognostic value.

6 **Design**– Retrospective analysis of patient records.

7 **Setting** – Observation at the start of active rehabilitation of participants in a multicenter cohort  
8 study, ‘Restoration of (wheelchair) mobility in SCI rehabilitation’, in the Netherlands.

9 **Participants** – Patients with SCI (n=200; 74% male, 40±14 years, ASIA impairment A-D,  
10 tetraplegia 40%, motor complete 69%).

11 **Interventions** - risk profiling/not applicable.

12 **Main Outcome Measures** - Survival status and cardiovascular morbidity and mortality were  
13 obtained from medical records. 5-year Framingham Risk Scores (FRS) and the FRS ability to  
14 predict events assessed using receiver operating characteristics curves (ROC) with  
15 corresponding area under the curves (AUC) and 95% CIs. Kaplan–Meier curves and the log-  
16 rank test were used to assess the difference in clinical outcome between participants with a  
17 FRS > and < median FRS score for the cohort. SCI-related factors associated with CVD-events,  
18 ASIA impairment, motor completeness, level of injury and sports participation prior to injury,  
19 were explored using univariate and multivariate Cox proportional hazard regression.

20 **Results** - The median 5-year FRS was 1.36%. Across a median follow-up of 5.7-years, n=39  
21 developed a CVD event, including 10 fatalities. Although the FRS markedly underestimated  
22 the true occurrence of CVD events, the Kaplan–Meier curves and the log-rank test showed that  
23 the risk ratio for individuals with a <median FRS (e.g., low-risk) vs. a >median FRS (high-  
24 risk) was 3.2 (95% CI 1.6-6.5;  $p=0.001$ ). Moreover, receiver operating characteristics curves  
25 (ROC) with corresponding area under the curves (AUC) suggests acceptable accuracy of the  
26 FRS to identify individuals with increased risk for future CVD events (ROC-AUC of 0.71,  
27 95%-Confidence Interval(CI) 0.62-0.82). Adding ASIA impairment (0.74; 95% CI 0.66-0.82),  
28 motor impairment (0.74; 95% CI 0.66-0.83), level of injury (0.72; 95% CI 0.63-0.81) or active  
29 engagement in sport prior to injury (0.72; 95% CI 0.63-0.88) to the FRS did not improve the  
30 level of discrimination.

1 **Conclusions** – Our 5.7-year retrospective study reveals that cardiovascular risk factors and risk  
2 models markedly underestimate the true risk for CVD events in individuals with SCI.  
3 Nonetheless, these markers successfully distinguish between SCI individuals at high *versus*  
4 low-risk for future CVD events. Our data may have future clinical implications, both related to  
5 (cut-off values of) CVD risk factors, but also for (earlier) prescription of (non)pharmacological  
6 strategies against CVD in SCI individuals.

7 **Key Words:** Spinal cord injury, cardiovascular disease risk prediction.

## 1 INTRODUCTION

2 Cardio- and cerebro-vascular diseases (CVD) have become a major concern for individuals  
3 with a spinal cord injury (SCI). CVD constitutes 26.7% of all-cause mortality<sup>1</sup> and are  
4 responsible for the greatest proportion of morbidity and mortality in the SCI population.<sup>2, 3</sup>  
5 Assessing a person's risk for developing CVD is typically performed using traditional  
6 cardiovascular risk factors and, subsequently, risk is predicted using widely available  
7 algorithms such as the Framingham risk score (FRS). Since these algorithms are based on non-  
8 disabled populations, mainly including middle-aged and older Caucasian men from Western  
9 countries, one may question its generalizability to other populations,<sup>4-6</sup> including SCI.

10

11 Interpretation of traditional CVD risk factors is complicated in SCI population. For example,  
12 elevated arterial blood pressure is recognized as an independent risk factor for CVD in the  
13 general population. However, individuals with SCI, in particular those with high thoracic and  
14 cervical lesions, exhibit low resting arterial blood pressure that results from autonomic  
15 disturbances.<sup>7, 8</sup> Furthermore, despite the increased risk for CVD in individuals with SCI,  
16 classic cardiovascular risk factors, such as low-density lipoprotein, plasma triglycerides and  
17 fasting glucose, are not different between SCI and non-disabled populations.<sup>9-15</sup> This raises the  
18 question whether traditional cardiovascular risk factors and risk prediction models which use  
19 these risk factors can accurately predict future CVD in individuals with SCI.

20

21 The aim of this study was to examine the predictive value of traditional risk factors for future  
22 CVD using the Framingham risk score in individuals with SCI. For this purpose, we performed  
23 an observational cohort study to 1) determine whether the FRS accurately predicts  
24 cardiovascular morbidity and mortality across a median of 5.7-years after discharge from in-

1 patient rehabilitation in people with SCI, and 2) if adding SCI-related characteristics (i.e. lesion  
2 level) to the FRS can improve the prognostic value of the FRS. Based on the argument we  
3 raised earlier which suggests that SCI may affect interpretation of traditional CVD risk factors,  
4 we expect that the FRS underestimates future CVD, whilst adding SCI characteristics improves  
5 the prognostic value of the FRS in individuals with SCI.

6

## 7 **METHODS**

### 8 **Participants**

9 The data used in this study were collected as part of the Dutch prospective multicenter cohort  
10 study ‘Restoration of (wheelchair) mobility in SCI rehabilitation’<sup>16</sup> and obtained prospectively.  
11 The medical ethics committee of the Stichting Revalidatie Limburg/Institute for Rehabilitation  
12 Research in Hoensbroek approved the research protocol in 1999, and the medical ethics  
13 committee of the University Hospital of Utrecht approved for the follow-up research protocol  
14 in 2006. This resulted in a median follow-up of 5.7-years (Interquartile range 5.2-6.4 years).  
15 Participants (n=225) were recruited from 8 specialist SCI rehabilitation centers in the  
16 Netherlands. Written informed consent was obtained from all participants prior to the start of  
17 this study. Inclusion criteria required participants to have a traumatic or non-traumatic SCI  
18 classified as A, B, C or D on the American Spinal Cord Injury Association impairment scale  
19 (ASIA),<sup>17</sup> expected to remain wheelchair dependent, no evidence of pre-existing  
20 cardiovascular diseases and aged between 18-65.

21

### 22 **Experimental design**

23 The observation period began at the start of active rehabilitation when the participants could  
24 remain seated for a minimum of 3 hours (m=3 months after injury). Participants were asked to

1 eat only a light meal, to abstain from consuming tobacco, caffeine and alcohol at least 2 hours  
2 prior to testing and to void their bladders. All participants continued to take their regular  
3 medication. Blood samples were collected and analysed for serum concentrations of total and  
4 high-density lipoprotein cholesterol. Resting arterial blood pressure was measured by a  
5 physician using a manual sphygmomanometer whilst participants remained seated in their  
6 wheelchair.<sup>18</sup> Participants were considered to have diabetes when the primary care physician  
7 reported this or when medical records indicated the participant was taking diabetes medication.  
8 Lesion characteristics (level and completeness) were assessed by a specialist physician and  
9 according to the International Standards for Neurological Classification of Spinal Cord  
10 Injury.<sup>19</sup> Survival status and cardiovascular morbidity and mortality were obtained from  
11 medical records across the 5.7-year follow-up after discharge from inpatient rehabilitation. The  
12 follow up period of some individuals included in our analysis goes beyond the 5 years. All  
13 these individuals did however, develop CVD within the 5 years, and in some instances  
14 additional cardiovascular complications after the 5 years (Fig. 2). Cardiovascular  
15 complications and causes of death were identified according to the International Classification  
16 of Diseases and Related Disorders, 10<sup>th</sup> revision, volume 2 (codes I00-I99).

17

### 18 **Framingham Risk Score**

19 The FRS-calculator is a method that uses equations derived from large prospective cohort  
20 studies such as the Framingham heart study and Framingham offspring study<sup>20</sup> to estimate the  
21 risk of developing CVD events in the proceeding 5-10 years.<sup>21</sup> CVD endpoints using the FRS  
22 prediction model can be defined as all coronary events (e.g. myocardial infarction, coronary  
23 death, coronary insufficiency, and angina), cerebrovascular disease (e.g. ischemic stroke,  
24 hemorrhagic stroke, and transient ischemic attack), rheumatic disease, heart arrhythmia,  
25 valvular disease, aortic aneurysms, peripheral artery disease, thromboembolic disease and

1 venous thrombosis.<sup>21</sup> Compared with other risk algorithms, the FRS-calculator is able to  
2 discriminate between those who will and will not develop a CV event<sup>22-26</sup> and has been  
3 validated in multiple populations.<sup>27</sup> For every individual, at the start of active rehabilitation,  
4 we calculated their 5-year risk score to develop CVD using the Framingham risk calculator  
5 from the Centre for Cardiovascular Sciences at the University of Edinburgh.<sup>28</sup> This particular  
6 tool is a spreadsheet-based calculator that uses age, sex, systolic blood pressure, total  
7 cholesterol, HDL cholesterol, smoking status and diabetes status to estimate the percentage  
8 based risk of developing CVD over a selected number of years.

9

## 10 **Statistical analysis**

11 Participant characteristics were summarized by means and standard deviations for normally  
12 distributed continuous variables, medians with interquartile ranges for not normally distributed  
13 continuous variables and percentages for categorical variables. Kaplan–Meier curves and the  
14 log-rank test were used to assess the difference in clinical outcome between participants with  
15 a FRS >1.36 (median score for the cohort) and FRS ≤1.36. For the context of this paper, the  
16 group of participants with a FRS ≤1.36 will be referred to as the ‘low FRS’ group and those  
17 with a FRS >1.36 will be referred to as the ‘high FRS’ group. The end-point was a CV event  
18 or CV mortality. Patients who did not reach the end-point were censored at the end of the  
19 observation period. Hazard ratios with 95% confidence intervals (CIs) were calculated using  
20 Cox proportional hazard regression.

21

22 The FRS ability to predict events in patients with SCI was assessed using receiver operating  
23 characteristics curves (ROC) with corresponding area under the curves (AUC) and 95% CIs.  
24 SCI-related factors associated with CVD-events were explored using univariate Cox



1 proportional hazard regression. Severity of injury as indicated by ASIA impairment, motor  
2 completeness and level of injury were included as factors in the regression analysis due to their  
3 direct association with impaired CV function.<sup>7,8</sup> Considering the beneficial effects of physical  
4 activity on CV health in the able bodied, we also decided to include sports participation prior  
5 to injury as a factor and explore its influence on predicting CVD after injury. These factors  
6 were separately added to the FRS and  $X*\beta$  values were calculated using multivariate Cox  
7 proportional hazard regression. Using the  $X*\beta$  values, receiver operating characteristics curves  
8 with corresponding AUC and 95% CI were determined. All statistical analyses were performed  
9 in SPSS 20.0. A  $p$ -value  $<0.05$  was considered statistically significant.

10

## 11 **RESULTS**

### 12 **Survival analysis**

13 Table 1 summarizes baseline characteristics and Table 2 indicates the cardiovascular events  
14 for the 200 individuals included in the analysis. In the 5.7-years following discharge from in-  
15 patient rehabilitation, a total of 39 participants (19.5%) developed a CVD event, 10 of which  
16 were fatal events. Deep venous thrombosis (DVT) was the most commonly observed CVD  
17 event with 5% of the study participants having an incidence of DVT.

18

19 Figure 2 shows the survival analysis for the groups with a low FRS ( $\leq 1.36$  (median)) and a  
20 high FRS ( $>1.36$ ). One individual was excluded from the survival analysis due to missing  
21 follow-up data. We found a significant difference in CVD events between both groups (hazard  
22 ratio for high FRS vs low FRS was 3.2, 95% confidence interval [CI] 1.6-6.5;  $p=0.001$ ). A total  
23 of 10 and 29 CVD events were recorded in the low and high FRS groups, respectively.

## 1 **FRS prediction model using SCI characteristics**

2 Table 3 illustrates the calculated hazard ratios with 95% CI, regression coefficients and  
3 statistical significance for various SCI characteristic individual predictors for CVD events.  
4 Each factor is assessed through separate univariate Cox regressions. Older age at time of SCI  
5 (1.05, 95% CI 1.02-1.07;  $p<0.001$ ), a higher 5-year FRS (1.10, 95% CI 1.05-1.16;  $p<0.001$ )  
6 and no participation in sport activities before the SCI injury (1.25, 95% CI 0.65-2.41;  $p=0.013$ )  
7 were identified as significant independent predictors for CVD events across the mean 5.7-year  
8 follow-up period. When the predictive value of the FRS alone was assessed by receiver  
9 operating characteristic curves (Figure 3), the area-under-the-curve was 0.71 (95% CI 0.62-  
10 0.82). For the new models, which included the FRS combined with SCI characteristics, we  
11 found no significant improvement in ROC-curves. More specifically, the predictive power of  
12 the FRS was not improved when adding ASIA impairment (0.74; 95% CI 0.66-0.82), motor  
13 impairment (0.74; 95% CI 0.66-0.83), level of injury (0.72; 95% CI 0.63-0.81) or active  
14 engagement in sport prior to injury (0.72; 95% CI 0.63-0.88).

15

## 16 **DISCUSSION**

17 The purpose of this study was to investigate whether traditional cardiovascular risk factors,  
18 through the calculation of the commonly used Framingham risk score, can predict the  
19 occurrence of CVD events over a 5.7-year follow-up in individuals with SCI. To our  
20 knowledge, this is the first study to test the accuracy of the FRS to predict future CVD events  
21 in individuals with SCI. First, we found that the FRS markedly underestimates the occurrence  
22 of CVD mortality and morbidity in individuals with SCI. Second, despite this marked  
23 underestimation of the true CVD event rate, the FRS was able to successfully identify  
24 individuals with SCI at increased risk for future CVD. These novel observations have important

1 clinical impact, since our findings suggest that aggressive (pharmaceutical) interventions may  
2 be required in individuals with SCI to lower risk for future CVD events, even when traditional  
3 CVD risk factors suggest a low-to-moderate risk.

4

5 A FRS of <10% in non-disabled individuals is classified to be “low” risk of 10 year CVD.  
6 Although difficult to translate this number to a 5 year CVD risk calculation, we expected to  
7 see very few events in our relatively young population (40±14 years) of SCI individuals across  
8 the 5.7-year period. In marked contrast, we found 39 CVD events, 10 of which were fatalities,  
9 which represent an unexpectedly high rate of CVD events. Although previous work suggested  
10 that the FRS may underestimate the actual CVD risk in the SCI population,<sup>15, 29, 30</sup> our study  
11 represents the first retrospective study to support this hypothesis. The CVD events were quite  
12 varied and featured typical CVD incidents but ~25% originated from venous  
13 thromboembolism, which might be over represented in this sample/model. Observations of  
14 events began within three months after injury which might have caused the capture of acute  
15 cardiovascular changes secondary to SCI in addition to chronic events. Despite the marked  
16 underestimation, the FRS was successful in distinguishing individuals who were at an  
17 increased risk for a CVD event. When comparing the ‘high’ vs ‘low’ risk group, our survival  
18 analysis indicated that the group of SCI individuals with a >median FRS had a 3.2-fold greater  
19 risk for developing a CVD event than those with a <median FRS. Interestingly, data from the  
20 ROC-curve indicates that the ability of the FRS to predict CVD events in SCI (i.e., 0.71) is  
21 comparable to that typically observed in non-disabled populations (0.68-0.75).<sup>31,32,33</sup> Taken  
22 together, this indicates that the FRS successfully identifies subjects with SCI who have an  
23 increased risk for CVD, but markedly underestimates the true risk.

24

1 One potential implication of our observations is that different cut-off values for factors such as  
2 blood pressure and cholesterol should be adopted to calculate the correct CVD risk in SCI.<sup>10</sup>  
3 Indeed, in our study sample, cholesterol levels were within healthy ranges specified for non-  
4 disabled individuals and therefore a low FRS was calculated, despite being at an apparently  
5 higher risk for CVD . This finding supports previous work indicating the presence of low-to-  
6 normal levels of triglycerides, total and LDL cholesterol for individuals with SCI.<sup>9, 12, 15, 34</sup> In  
7 addition, systolic blood pressure in the subset of individuals who developed a CVD event was  
8 also within the normal range. Future studies adopting a prospective design should explore  
9 whether adjustment of cut-off values is required for the traditional CVD risk factors. One  
10 aspect to consider here is that it is not known how many participants might have been taking  
11 medications for hypertension, dyslipidemia or dysglycemia either before and/or after their  
12 injury which could have affected these key CVD risk factors and morbidity and mortality  
13 outcomes. Similarly, the study in which data were collected for the current retrospective study  
14 was first approved in 1999. In the proceeding ~20 years assessment methods for CVD risk  
15 factors and level of SCI and impairment and risk determination could have changed and  
16 possibly modified the study's current findings.

17 In addition to adjusting the cut-off values of traditional risk factors, one should also consider  
18 alternative risk factors in this population. First, although blood pressure is recognized as a  
19 strong predictor for CVD in the non-disabled population, frequent exposure to blood pressure  
20 variability may pose an additional risk. Individuals with SCI often experience episodes of  
21 autonomic dysreflexia, which represents an important CVD risk factor, independent of basal  
22 mean arterial blood pressure.<sup>35,36</sup> Second, current models of CVD risk prediction do not include  
23 a measure of physical activity. This is of special importance since recent work has revealed  
24 that physical inactivity has overtaken smoking as the leading cause of non-communicable  
25 diseases<sup>37</sup>, whilst individuals with SCI are exposed to marked physical inactivity<sup>38</sup>. Their life-

1 long exposure to an extreme form of sedentary behavior may accelerate the atherosclerotic  
2 processes. A final alternative explanation relates to the detrimental impact of a SCI on vascular  
3 health<sup>38, 39</sup> This is of special importance, since independent from known risk factors, impaired  
4 vascular function and structure may increase CVD risk.<sup>40-43</sup>

5

6 We tested individual predictors for CVD events using separate univariate cox regressions and  
7 to establish whether adding SCI characteristics to the Framingham model can improve the  
8 accuracy and prognostic value of the FRS. Unlike ASIA impairment and level of the injury,  
9 older age at time of injury, no sports participation prior to injury and a higher FRS were all  
10 significant predictors for CVD events. When comparing the models' accuracy and ability to  
11 identify individuals who will develop a CVD event, adding these individual predictors did not  
12 improve the FRS model. This is somewhat surprising considering that CVD risk increases  
13 relative to serum HDL levels<sup>44</sup> and direct associations have been reported between lipid  
14 concentrations (e.g. low HDL) and neurological deficit or severity of the spinal injury.<sup>34</sup>  
15 Possibly, the link between lipids and lesion level may be caused by the strong physical  
16 inactivity experienced by individuals with a higher level SCI rather than the lesion  
17 characteristics per se. The lack of the ability of the no sports participation prior to injury  
18 question to identify individuals who will develop a CVD event in this current sample may have  
19 been influenced by the method of assessment (e.g., recall) and it may not be relevant to those  
20 patients that develop a CVD event several years after their injury. Although SCI lesion  
21 characteristics did not improve the accuracy of the FRS, older age at time of injury was a  
22 significant independent predictor. These results corroborate with others who report that older  
23 age at time of injury accelerates the aging process and is an independent predictor of mortality  
24 in the first 5-years after injury.<sup>45</sup> Additionally, advancing age is associated with a higher  
25 prevalence of risk factors such as metabolic syndrome,<sup>46</sup> and possibly further accelerates the

1 development of CVD in older individuals after SCI. Similarly, some of the older individuals  
2 may have been asymptomatic or had subclinical CVD at the time of their injury and/or CVD  
3 events after study enrolment may reflect a carryover from pre-injury states of  
4 hypercholesterolemia, low HDL and/or hypertension. Furthermore, the prevalence of diabetes  
5 was low for the general population and especially for the SCI population.<sup>47</sup> Taken together,  
6 our data do not support adding SCI-specific factors to the FRS to improve the prediction of  
7 future CVD events in SCI individuals.

8

9 *Clinical relevance.* Accurate CVD estimation is essential to balancing the risks and benefits of  
10 prescribing preventive therapies and interventions. The findings in the current study may have  
11 important clinical consequences as they suggest that individuals with SCI, even in the presence  
12 of risk factors that are within the low range of non-disabled individuals, may benefit from  
13 (pharmaceutical) interventions to prevent CVD. Some evidence also shows that in the non-  
14 disabled population, using interventions that lower the risk of CVD in those with risk factors  
15 within the “normal” range can have beneficial effects on overall CVD risk development.<sup>48</sup>  
16 <sup>49</sup>Although future work is required to better understand this area, adjustment of current risk-  
17 prediction models and exploring their clinical implication for individuals with SCI seems  
18 warranted. In this light, one should also consider adding novel risk factors (e.g. physical  
19 inactivity) and/or alternative screening methods. For the latter, carotid intima-media thickness  
20 (CIMT) is a known surrogate marker for CVD in the general population<sup>50-52</sup>. In SCI individuals,  
21 no correlation was found between lipid profile and CIMT, despite signs of subclinical  
22 atherosclerosis.<sup>53</sup> Possibly, vascular imaging techniques may be an appropriate CVD screening  
23 tool that, independent of current risk factors, provide independent predictive capacity. In  
24 conclusion, our findings suggest that, although a higher FRS corresponds with an increased  
25 rate of CVD, the FRS/traditional cardiovascular risk factors significantly underestimate the 5-

1 year risk of CVD morbidity and mortality in individuals with SCI. Furthermore, the increased  
2 risk and greater prevalence of a CVD event was independent of SCI lesion characteristics.  
3 Therefore, these data suggest that CVD risk estimation using the FRS and/or traditional  
4 cardiovascular risk factors should be interpreted with caution in this vulnerable population of  
5 SCI individuals. Given the high risk of CVD in this population, prospective follow-up studies  
6 are required to better understand CVD risk estimation in individuals with SCI, but also how  
7 this could adjust current medical care in individuals with SCI to prevent future CVD.

8

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10 None

#### 11 DISCLOSURES

12 The authors declare that there is no conflict of interest

13

14

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1 **Figure Legends**

2 **Figure 1.** Flow diagram of subject inclusion and retention from the initial measurement  
3 period up to follow up.

4

5 **Figure 2.** Survival analysis for individuals with a spinal cord injury (n=200) across a 5 year  
6 follow-up. Subjects were divided into individuals with a Framingham Risk Score (FRS)  $\leq 1.36$   
7 (i.e. median; grey line, 10 CVD events) and those with a FRS  $> 1.36$  (i.e. median; black line,  
8 29 CVD events).

9

10 **Figure 3.** Receiver operating characteristics (ROC) curve for the Framingham Risk Score for  
11 the prediction of 5-year occurrence of an CVD event individuals with a spinal cord injury  
12 (n=200) across a 5 year follow-up.

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