Abstract

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

Design– Retrospective analysis of patient records.

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

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

Interventions - risk profiling/not applicable.

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

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

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

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

INTRODUCTION

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

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

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

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

METHODS

Participants

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

Experimental design

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

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

Framingham Risk Score

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

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

Statistical analysis

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

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

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

RESULTS

Survival analysis

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

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

FRS prediction model using SCI characteristics

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

DISCUSSION

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

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

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

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

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

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

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

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

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

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

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None

DISCLOSURES

The authors declare that there is no conflict of interest

REFERENCES

1. Savic G, DeVivo MJ, Frankel HL, Jamous MA, Soni BM, Charlifue S. Causes of death after traumatic spinal cord injury-a 70-year British study. Spinal Cord 2017.
2. Osterthun R, Post MW, van Asbeck FW, van Leeuwen CM, van Koppenhagen CF. Causes of death following spinal cord injury during inpatient rehabilitation and the first five years after discharge. A Dutch cohort study. Spinal Cord 2014;52(6):483-8.
3. Garshick E, Kelley A, Cohen SA, Garrison A, Tun CG, Gagnon D et al. A prospective assessment of mortality in chronic spinal cord injury. Spinal Cord 2005;43(7):408-16.
4. Grundy SM, Pasternak R, Greenland P, Smith S, Jr., Fuster V. Assessment of cardiovascular risk by use of multiple-risk-factor assessment equations: a statement for healthcare professionals from the American Heart Association and the American College of Cardiology. Circulation 1999;100(13):1481-92.
5. Yeo WW, Yeo KR. Predicting CHD risk in patients with diabetes mellitus. Diabet Med 2001;18(5):341-4.
6. Matheny M, McPheeters ML, Glasser A, Mercaldo N, Weaver RB, Jerome RN et al. U.S. Preventive Services Task Force Evidence Syntheses, formerly Systematic Evidence Reviews. Systematic Review of Cardiovascular Disease Risk Assessment Tools. Rockville (MD): Agency for Healthcare Research and Quality (US); 2011.
7. West CR, Mills P, Krassioukov AV. Influence of the neurological level of spinal cord injury on cardiovascular outcomes in humans: a meta-analysis. Spinal Cord 2012;50(7):484-92.
8. Phillips AA, Krassioukov AV. Contemporary Cardiovascular Concerns after Spinal Cord Injury: Mechanisms, Maladaptations, and Management. J Neurotrauma 2015;32(24):1927-42.
9. Cardus D, Ribas-Cardus F, McTaggart WG. Lipid profiles in spinal cord injury. Paraplegia 1992;30(11):775-82.
10. Krum H, Howes LG, Brown DJ, Ungar G, Moore P, McNeil JJ et al. Risk factors for cardiovascular disease in chronic spinal cord injury patients. Paraplegia 1992;30(6):381-8.
11. Bauman WA, Spungen AM. Disorders of carbohydrate and lipid metabolism in veterans with paraplegia or quadriplegia: a model of premature aging. Metabolism 1994;43(6):749-56.
12. Bauman WA, Adkins RH, Spungen AM, Herbert R, Schechter C, Smith D et al. Is immobilization associated with an abnormal lipoprotein profile? Observations from a diverse cohort. Spinal Cord 1999;37(7):485-93.
13. Jones LM, Legge M, Goulding A. Factor analysis of the metabolic syndrome in spinal cord-injured men. Metabolism 2004;53(10):1372-7.
14. Liang H, Chen D, Wang Y, Rimmer JH, Braunschweig CL. Different risk factor patterns for metabolic syndrome in men with spinal cord injury compared with able-bodied men despite similar prevalence rates. Arch Phys Med Rehabil 2007;88(9):1198-204.
15. Finnie AK, Buchholz AC, Martin Ginis KA, Group SSR. Current coronary heart disease risk assessment tools may underestimate risk in community-dwelling persons with chronic spinal cord injury. Spinal Cord 2008;46(9):608-15.
16. de Groot S, Dallmeijer AJ, Post MW, van Asbeck FW, Nene AV, Angenot EL et al. Demographics of the Dutch multicenter prospective cohort study 'Restoration of mobility in spinal cord injury rehabilitation'. Spinal Cord 2006;44(11):668-75.
17. Kirshblum SC, Burns SP, Biering-Sorensen F, Donovan W, Graves DE, Jha A et al. International standards for neurological classification of spinal cord injury (revised 2011). J Spinal Cord Med 2011;34(6):535-46.
18. Ravensbergen HJ, de Groot S, Post MW, Slootman HJ, van der Woude LH, Claydon VE. Cardiovascular function after spinal cord injury: prevalence and progression of dysfunction during inpatient rehabilitation and 5 years following discharge. Neurorehabil Neural Repair 2014;28(3):219-29.

19. Maynard FM, Jr., Bracken MB, Creasey G, Ditunno JF, Jr., Donovan WH, Ducker TB et al. International Standards for Neurological and Functional Classification of Spinal Cord Injury. American Spinal Injury Association. Spinal Cord 1997;35(5):266-74.
20. Anderson KM, Wilson PW, Odell PM, Kannel WB. An updated coronary risk profile. A statement for health professionals. Circulation 1991;83(1):356-62.
21. D'Agostino RB, Sr., Vasan RS, Pencina MJ, Wolf PA, Cobain M, Massaro JM et al. General cardiovascular risk profile for use in primary care: the Framingham Heart Study. Circulation 2008;117(6):743-53.
22. Menotti A, Puddu PE, Lanti M. Comparison of the Framingham risk function-based coronary chart with risk function from an Italian population study. Eur Heart J 2000;21(5):365-70.
23. Liao Y, McGee DL, Cooper RS, Sutkowski MB. How generalizable are coronary risk prediction models? Comparison of Framingham and two national cohorts. Am Heart J 1999;137(5):837-45.
24. D'Agostino RB, Sr., Grundy S, Sullivan LM, Wilson P, Group CHDRP. Validation of the Framingham coronary heart disease prediction scores: results of a multiple ethnic groups investigation. JAMA 2001;286(2):180-7.
25. Grundy SM, D'Agostino Sr RB, Mosca L, Burke GL, Wilson PW, Rader DJ et al. Cardiovascular risk assessment based on US cohort studies: findings from a National Heart, Lung, and Blood institute workshop. Circulation 2001;104(4):491-6.
26. Liao Y, McGee DL, Cooper RS. Prediction of coronary heart disease mortality in blacks and whites: pooled data from two national cohorts. Am J Cardiol 1999;84(1):31-6.
27. Menotti A, Lanti M, Puddu PE, Kromhout D. Coronary heart disease incidence in northern and southern European populations: a reanalysis of the seven countries study for a European coronary risk chart. Heart 2000;84(3):238-44.
28. Payne R. Edinburgh: Framingham CVD, ASSIGN, BNF, and Framingham CHD. Payne R. Cardiovascular Risk Calculators [Internet]. Edinburgh, UK: University of Edinburgh; 2005 [updated 2010 May 28]. Available from: http://cvrisk.mvm.ed.ac.uk/calculator/calc.asp. (Accessed March 4, 2018).
29. Wahman K, Nash MS, Lewis JE, Seiger A, Levi R. Cardiovascular disease risk and the need for prevention after paraplegia determined by conventional multifactorial risk models: the Stockholm spinal cord injury study. J Rehabil Med 2011;43(3):237-42.
30. Sullivan SD, Nash MS, Tefara E, Tinsley E, Groah S. Relationship Between Gonadal Function and Cardiometabolic Risk in Young Men With Chronic Spinal Cord Injury. PM R 2017.
31. DeFilippis AP, Young R, Carrubba CJ, McEvoy JW, Budoff MJ, Blumenthal RS et al. An analysis of calibration and discrimination among multiple cardiovascular risk scores in a modern multiethnic cohort. Ann Intern Med 2015;162(4):266-75.
32. Erbel R, Mohlenkamp S, Moebus S, Schmermund A, Lehmann N, Stang A et al. Coronary risk stratification, discrimination, and reclassification improvement based on quantification of subclinical coronary atherosclerosis: the Heinz Nixdorf Recall study. J Am Coll Cardiol 2010;56(17):1397-406.
33. Cook NR, Paynter NP, Eaton CB, Manson JE, Martin LW, Robinson JG et al. Comparison of the Framingham and Reynolds Risk scores for global cardiovascular risk prediction in the multiethnic Women's Health Initiative. Circulation 2012;125(14):1748-56, S1-11.
34. Laclaustra M, Van Den Berg EL, Hurtado-Roca Y, Castellote JM. Serum lipid profile in subjects with traumatic spinal cord injury. PLoS One 2015;10(2):e0115522.
35. Grove JS, Reed DM, Yano K, Hwang LJ. Variability in systolic blood pressure--a risk factor for coronary heart disease? Am J Epidemiol 1997;145(9):771-6.
36. Rothwell PM, Howard SC, Dolan E, O'Brien E, Dobson JE, Dahlof B et al. Prognostic significance of visit-to-visit variability, maximum systolic blood pressure, and episodic hypertension. Lancet 2010;375(9718):895-905.
37. Lee IM, Shiroma EJ, Lobelo F, Puska P, Blair SN, Katzmarzyk PT et al. Effect of physical inactivity on major non-communicable diseases worldwide: an analysis of burden of disease and life expectancy. Lancet 2012;380(9838):219-29.

38. Thijssen DH, Maiorana AJ, O'Driscoll G, Cable NT, Hopman MT, Green DJ. Impact of inactivity and exercise on the vasculature in humans. Eur J Appl Physiol 2010;108(5):845-75.
39. Green DJ, Hopman MT, Padilla J, Laughlin MH, Thijssen DH. Vascular Adaptation to Exercise in Humans: Role of Hemodynamic Stimuli. Physiol Rev 2017;97(2):495-528.
40. Chomistek AK, Chiuve SE, Jensen MK, Cook NR, Rimm EB. Vigorous physical activity, mediating biomarkers, and risk of myocardial infarction. Med Sci Sports Exerc 2011;43(10):1884-90.
41. Hamer M, Ingle L, Carroll S, Stamatakis E. Physical activity and cardiovascular mortality risk: possible protective mechanisms? Med Sci Sports Exerc 2012;44(1):84-8.
42. Taylor RS, Unal B, Critchley JA, Capewell S. Mortality reductions in patients receiving exercise-based cardiac rehabilitation: how much can be attributed to cardiovascular risk factor improvements? Eur J Cardiovasc Prev Rehabil 2006;13(3):369-74.
43. Mora S, Cook N, Buring JE, Ridker PM, Lee IM. Physical activity and reduced risk of cardiovascular events: potential mediating mechanisms. Circulation 2007;116(19):2110-8.
44. National Cholesterol Education Program Expert Panel on Detection E, Treatment of High Blood Cholesterol in A. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. Circulation 2002;106(25):3143-421.
45. Casper DS, Zmistowski B, Schroeder GD, McKenzie JC, Mangan J, Vatson J et al. Pre-Injury Patient Characteristics and Post-Injury Neurological Status Are Associated with Mortality following Spinal Cord Injury. Spine (Phila Pa 1976) 2017.
46. de Groot S, Adriaansen JJ, Tepper M, Snoek GJ, van der Woude LH, Post MW. Metabolic syndrome in people with a long-standing spinal cord injury: associations with physical activity and capacity. Appl Physiol Nutr Metab 2016;41(11):1190-6.
47. Gater DR, Jr., Farkas GJ, Berg AS, Castillo C. Prevalence of metabolic syndrome in veterans with spinal cord injury. J Spinal Cord Med 2019;42(1):86-93.
48. Cholesterol Treatment Trialists C, Mihaylova B, Emberson J, Blackwell L, Keech A, Simes J et al. The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trials. Lancet 2012;380(9841):581-90.
49. Thanassoulis G, Williams K, Altobelli KK, Pencina MJ, Cannon CP, Sniderman AD. Individualized Statin Benefit for Determining Statin Eligibility in the Primary Prevention of Cardiovascular Disease. Circulation 2016;133(16):1574-81.
50. Folkow B. The fourth Volhard lecture: cardiovascular structural adaptation; its role in the initiation and maintenance of primary hypertension. Clin Sci Mol Med Suppl 1978;4:3s-22s.
51. O'Leary DH, Polak JF, Kronmal RA, Manolio TA, Burke GL, Wolfson SK, Jr. Carotid-artery intima and media thickness as a risk factor for myocardial infarction and stroke in older adults. Cardiovascular Health Study Collaborative Research Group. N Engl J Med 1999;340(1):14-22.
52. Bots ML, Grobbee DE, Hofman A, Witteman JC. Common carotid intima-media thickness and risk of acute myocardial infarction: the role of lumen diameter. Stroke 2005;36(4):762-7.
53. Szlachcic Y, Adkins RH, Reiter JC, Yee F, Shaw SJ, Hodis HN. Predictors of subclinical atherosclerosis in women with spinal cord injury. Top Spinal Cord Inj Rehabil 2014;20(2):90-5.

Figure Legends

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

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

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