

Short title: Cause-specific mortality after TSCI

1 Title: Comparison of all-cause and cause-specific mortality of persons with traumatic spinal
2 cord injuries to the general Swiss population: Results from a national cohort study

3

4

5 Authors: Jonviea D Chamberlain ^{1, 2, 3}, Anne Buzzell ^{1, 2}, Hans Peter Gmünder ⁴, Kerstin Hug ⁵,
6 Xavier Jordan ⁶, André Moser ⁷, Martin Schubert ⁸, Marcel Zwahlen ³, Martin WG Brinkhof ^{1, 2}
7 for the SwISCI cohort study and the Swiss National Cohort

8

9

10

11 Affiliations:

12 ¹ Swiss Paraplegic Research, Nottwil, Switzerland

13 ² University of Lucerne, Health Sciences and Health Policy, Luzern, Switzerland

14 ³ Institute of Social and Preventative Medicine, University of Bern, Switzerland

15 ⁴ Swiss Paraplegic Center, Nottwil, Switzerland

16 ⁵ REHAB Basel, Basel, Switzerland

17 ⁶ Clinique Romande de Réadaptation, Sion, Switzerland

18 ⁷ Epidemiology, Biostatistics and Prevention Institute, University of Zurich

19 ⁸ Balgrist University Hospital, Zürich, Switzerland

20

21

22 Short title: Cause-specific mortality after TSCI

23

24

25 Corresponding Author:

26 Jonviea Chamberlain, PhD

27 Swiss Paraplegic Research, Guido A. Zäch Strasse 4, CH-6207 Nottwil, Switzerland

28 Tel: +41 41 939 65 92

29 E-mail: jonviea.chamberlain@paraplegie.ch

30

31

32

33 Keywords: Epidemiology, mortality, standardized mortality ratio, spinal cord injury

34 **1. ABSTRACT**

35

36 **Background:** Traumatic spinal cord injuries (TSCI) are a neurological condition associated
37 with reduced well-being, increased morbidity and reductions in life expectancy. Estimates of
38 all-cause and cause-specific mortality can aid in identifying targets for prevention and
39 management of contributors for premature mortality.

40

41 **Objectives:** To compare all-cause and cause-specific rates of mortality to that of the Swiss
42 general population; to identify differentials in risk of cause-specific mortality according to
43 lesion characteristics.

44

45 **Methods:** All-cause and cause-specific standardized mortality ratios (SMRs) were calculated
46 using data from the Swiss Spinal Cord Injury (SwiSCI) cohort study. Cause-specific subhazard
47 ratios (sHRs) were estimated within a competing risk framework using flexible parametric
48 survival models.

49

50 **Results:** Between 1990 and 2011, 2492 persons sustained a TSCI, of which 379 died. Persons
51 with TSCI had a mortality rate more than two times higher than that of the Swiss general
52 population (SMR=2.32; 95% CI=2.10-2.56). Tetraplegic lesions were associated with an
53 increased risk of mortality due to respiratory and cardiovascular diseases, infections, and
54 accidents. Cause-specific SMRs were notably elevated for SCI-related conditions such as
55 urinary tract infections and septicemia.

56

57 **Conclusions:** Elevated SMRs due to cardiovascular disease, urinary tract infections and
58 septicemia-related mortality suggest the need for innovation when managing associated
59 secondary health conditions.

60 **2. Introduction**

61 In a recent re-evaluation of the WHO Global Burden of Disease study [1], neurological
62 diseases were identified as the leading contributor to the global burden [2]. With overall
63 global aging, the number of people affected with neurological diseases is only expected to
64 augment, regardless of notable reductions in age-standardized rates [2]. Traumatic spinal
65 cord injuries (TSCIs), comprised within the assemblage of neurological diseases, are a
66 disabling condition associated with reduced functioning, and quality of life, increased
67 morbidity, and reductions in life expectancy. In comparison to the general population,
68 persons with TSCI have a roughly 2.5 times greater risk of mortality (standardized mortality
69 ratio [SMR]=2.5, 95% confidence interval [CI]=1.9-3.2) [3]. This burden of mortality is similar
70 to what has been estimated for other chronic neurological conditions such as multiple
71 sclerosis (MS) (SMR=2.8, 95% CI=2.7-2.9) [4] or traumatic brain injury (TBI) (SMR=2.3; 95%
72 CI=2.1-2.4) [5].

73 Reductions in premature mortality associated with neurological diseases would aid in
74 reduction of global burden of disease. Unfortunately, most research on long-term mortality
75 risk post-SCI have found little to no improvements in recent decades [3], and although
76 persons with SCI have the potential for a life expectancy similar to that of the general
77 population, within-population and between-country discrepancies in mortality and survival
78 estimates exist [3,6]. Importantly, these discrepancies reflect the influence of SCI
79 characteristics and health systems on risk of mortality, and can thereby be exploited to
80 identify targeted interventions and areas for innovation. To this aim, estimates of all-cause
81 and cause-specific mortality can aid in identifying targets for prevention and management of
82 contributors for premature mortality. Furthermore, cause-specific mortality comparisons to
83 the general population can help with benchmarking to identify target areas for health
84 system improvement. The purpose of this study is to thereby provide cause-specific
85 mortality estimates within the SCI population as well as in comparison to the general
86 population.

87

88 **3. Methods**

89 *Study population*

90 The present study employs data collected in the Swiss Spinal Cord Injury (SwiSCI) cohort on
91 incident cases of TSCI admitted to a specialized rehabilitation facility between 1990 and

92 2011 [7]. Information on cause of deaths (CoDs) was obtained through probabilistic linkage
93 [8] with the Swiss National Cohort (SNC) based on date of birth, date of death (when
94 available), geocoded address, age and sex; applying a similar methodology as that used in
95 previous studies [9,10]. New cases of SCI admitted to an active specialized rehabilitation
96 facility within Switzerland were eligible for linkage. Of the original 6,162 cases, including
97 incident cases of non-traumatic and traumatic SCI from pre-1960, 85.5% were linked
98 (N=5,266) to the SNC data. A weight was created corresponding to the likelihood of a correct
99 match for persons within the SwiSCI dataset with multiple potential matches (21.6%).
100 Records with the highest weight were used in analyses, secondary matches – alternative
101 links – were included in a sensitivity analysis.

102

103 *Causes of death*

104 For each linked mortality record, up to five causes or contributing causes of death were
105 recorded using ICD-8 (until 1994) and ICD-10 coding (1995 and later): the underlying CoD;
106 the initial cause of disease; the consecutive disease; and two concomitant diseases. Previous
107 studies using CoD information have used the underlying cause of death for analyses, which is
108 defined as the disease or injury that initiated events leading to death, including chronic
109 conditions [11]. A hierarchical approach was used to identify the CoD relevant for cause-
110 specific mortality analyses and the calculation of SMRs, as implemented in previous studies
111 [12]. This approach skips over CoDs related to an external injury code (e.g., sequelae from
112 traffic accident) or SCI-related ICD code to identify a CoD relevant for secondary prevention.
113 For example, when using this hierarchical approach, a CoD coded as „paraplegia/tetraplegia“
114 or „external injury“ at the primary, secondary, or tertiary level was ignored until a code
115 unrelated to SCI was identified, if available.

116

117 A categorical variable was created to group causes of death into six broad categories based
118 on expert opinion, previous literature [13], data availability, as well as identifying meaningful
119 groups for targeted prevention. These groups include: respiratory diseases (ICD-10
120 codes=J30-J99 – excluding respiratory infections); cardiovascular disease (I00-I99);
121 neoplasms (C00-D49); infections (including respiratory and urinary tract infections (UTI):
122 A00-B99, J00-J22, N390-392); accidents (S00-Y99, excluding X60-X84); and all other causes of
123 mortality.

124

125 *Statistical analysis*

126 Standardized mortality ratios (SMRs) were calculated using mortality rates for the general
127 population (GP) (obtained through the SNC) stratified by age, sex, year, and CoD. Flexible
128 parametric models within a competing-risk framework were used to estimate cause-specific
129 subhazard ratios (sHRs) [14]. Separate baseline hazards were estimated for circulatory and
130 respiratory diseases, as well as accidents and all other causes to allow for potential time-
131 varying effects according to cause of death. Attained age, lesion level and completeness
132 were assumed to have an influence on cause-specific mortality, and were therefore
133 interacted with each CoD to allow for the effect of these covariates to vary according to CoD.
134 Attained age at death or study end was accomplished with data splitting techniques.

135

136 Given the potential for coding inaccuracies in CoD statistics, two plausible alternative coding
137 scenarios were implemented to evaluate the robustness of results:

- 138 - *Sensitivity analysis 1*: Re-calculation of SMRs using the original underlying CoD, not
139 applying hierarchical coding scheme (Supplementary Table 1)
- 140 - *Sensitivity analysis 2*: Competing-risk analysis for pre-identified SCI-related causes of
141 interest (i.e., respiratory infections and UTI/renal failure) recorded *anywhere* on death
142 certificate (i.e., underlying CoD, initial disease, consecutive, or concomitant)
143 (Supplementary Table 2 and 3).

144

145 All analyses were carried out using Stata version 14.2 [15].

146 **4. Results**

147 *Summary statistics*

148 Between 1990 and 2011, 2,492 persons were admitted for first rehabilitation within a
149 specialized rehabilitation center; of which, 379 had a known date of death, contributing to
150 20,099.9 years of follow-up time. Cause of death information was available for 335 cases.
151 Excluding deaths due to accident- or SCI-related ICD-10 codes, cardiac disease (11.9%),
152 ischemic heart disease (10.1%), neoplasms (8.1%), and suicide (6.3%) were the most
153 commonly recorded CoDs (Table 1). Accidents were less frequently recorded when excluding
154 deaths that occurred less than one year post-injury (Table 1).

155 The overall mortality rate for persons with TSCI was more than two times higher than
156 that of the Swiss GP (SMR=2.32; 95% CI=2.10-2.56) (Table 2). SMRs were elevated for
157 women (SMR=2.61; 95% CI=2.18-3.13) and tetraplegics (SMR=2.65; 95% CI=2.31-3.04) (Table
158 2). The synergistic influence of lesion level and completeness on mortality rates was
159 evidenced in that the mortality rate for incomplete paraplegics was 1.6 times that of the GP
160 (SMR=1.64; 95% CI=1.32-2.03), while for complete tetraplegics, the difference was 8.5 times
161 higher than that of the GP (SMR=8.49; 95% CI=6.55-11.01) (Table 2).

162

163 *Cause-specific mortality*

164 Cause-specific SMRs are presented in Table 3. Relative to the GP, persons with TSCI
165 experienced the highest burden of mortality due to septicemia-related deaths (SMR=19.71;
166 95% CI=9.40-41.35) (Table 3). With the exception of a few specific causes of death (e.g.,
167 chronic obstructive pulmonary disease and neoplasms), mortality rates for persons with SCI
168 were higher overall in comparison with the GP (Table 3). For example, persons with SCI
169 experienced mortality rates due to cardiovascular disease 2.7 times greater than that of the
170 general population (SMR=2.67, 95% CI=2.23-3.19; including cardiac disease, ischemic heart
171 disease, and all circulatory diseases). Cause-specific SMRs further varied according to SCI
172 characteristics (Table 4). When not applying a hierarchical coding scheme, SMRs for
173 accidents and nervous system-related diseases augmented, while SMRs estimated for
174 respiratory infections, other respiratory and other circulatory diseases diminished and were
175 no longer different than mortality rates experienced by the GP (Supplementary Table 1).

176 Subhazard ratios are presented in Table 5. Regardless of specific CoD, sHRs were highest
177 for the oldest age group (60 years and older) (Table 5). Following adjustment, tetraplegic
178 lesions were associated with an increased risk of mortality due to respiratory and
179 cardiovascular diseases, infections, and accidents (Table 5). Complete lesions were also
180 associated with an elevated risk for mortality due to respiratory diseases and accidents
181 (Table 5). With the exception of age, there was no difference in risk of mortality due to
182 neoplasms or other causes according to lesion characteristics. In a separate analysis on risk
183 of mortality due to respiratory infections, sHRs were elevated for both for tetraplegic and
184 complete lesions (Supplementary Table 2). This relationship remained when including all
185 individuals with a respiratory infection coded on the death certificate, regardless of the

186 position (Supplementary Table 2). No differential in risk of mortality due to UTI/renal failure
187 was identified according to lesion characteristics (Supplementary Table 3).

188

189 **5. Discussion**

190 Persons with a TSCI have a more than doubled rate of mortality in comparison with the GP,
191 with augmenting disparities associated with increasing severity. Furthermore, cause-specific
192 SMRs as well as risk for cause-specific mortality varied according to lesion level and
193 completeness, with tetraplegic and complete lesions exhibiting a higher risk in mortality due
194 to respiratory and cardiovascular disease, infections, and accidents in comparison with
195 paraplegic and incomplete lesions.

196 Cardiovascular diseases, suicide, and systemic infections are the leading causes of death
197 in the present study population when excluding accident and nervous system-related ICD
198 codes. In comparison with previous studies, some discrepancies in leading causes of death
199 can be noted; for example, Savic *et al* reported respiratory diseases (including infections),
200 circulatory diseases and neoplasms as the leading causes of mortality for individuals who
201 survived at least one year post-injury [13]. Additionally, in terms of direction and magnitude
202 of the effect, differences exist between country-level comparisons of cause-specific SMRs.
203 For example, in the United States, DeVivo *et al* reported a higher rate of cancer-related
204 mortality among the SCI population compared to the GP, and reported SMRs nearly half that
205 of what was estimated in this study for suicide [16]. In contrast, two studies from Estonia
206 and Norway estimated similarly heightened suicide-specific SMRs compared with the present
207 study [17,18]. Such differences could be impacted by incomplete and poorly informed coding
208 practices of death certificates [19]. Age- and sex-specific mortality stratified by ICD-10 coding
209 groups for the European standardized population could help improve comparability between
210 countries, and thereby aid in benchmarking across health systems for chronic disease
211 populations.

212 Mortality rates between two- to three-times that of the GP have been regularly reported
213 in recent SCI literature [3]. Unfortunately, despite advances in medical technology and
214 rehabilitation, a multitude of studies have found only limited or no improvement in long-
215 term mortality [20,21]. The cause-specific SMR estimates reported in this study help identify
216 potential causes that may be driving the overall mortality differential. For example, not only
217 was cardiovascular disease the leading CoD, but also persons with SCI were found to have

218 about a 2.5 times greater risk of mortality due to cardiovascular disease in comparison with
219 the GP. Modifications in cardiovascular disease risk post-SCI is likely related to physiologic
220 changes associated with lesion level and severity. For example, immediately following SCI,
221 the autonomic nervous system (ANS) incurs physiological alterations that have both acute
222 and chronic implications on cardiovascular functioning, such as unstable blood pressure,
223 autonomic dysreflexia (AD) and orthostatic hypotension (OH), associated with a multitude of
224 cardiovascular complications, including cardiac arrest, intracranial hemorrhage, stroke and
225 death [22]. Reflecting the influence of lesion characteristics on the risk of cardiovascular
226 disease, autonomic dysreflexia – a response to stimuli below the lesion level characterized
227 by an acute elevation of the systolic blood pressure – has been estimated to be three-times
228 more common in individuals with complete tetraplegic lesions in comparison to individuals
229 with incomplete lesions, with AD occurring primarily in high thoracic (paraplegic) and
230 cervical (tetraplegic) lesions [22]. However, although pharmaceutical interventions and
231 guidelines are available for management of AD, persons with SCI are still estimated to
232 experience an average of 11 AD episodes per day [22], with episodes continuing to occur
233 many years post-SCI [23]. The persistence of AD episodes as well as UTIs or pneumonia
234 despite following the guidelines of best clinical practice and management, suggest the need
235 for innovation in post-SCI care to improve long-term mortality outcomes [24].

236

237 *Strengths & limitations*

238 This study uses information from a large, nationally-representative cohort of persons
239 admitted for first rehabilitation within a specialized SCI center in Switzerland, therefore
240 study results are generalizable to other high-income rehabilitation settings. Unfortunately,
241 some limitations exist. For example, many CoDs had small case numbers, thereby requiring
242 caution when drawing conclusions from absolute numbers. Additionally, previous research
243 has found that the CoD information coded on death certificates lacks reliability when
244 identifying the true underlying CoD [25,26]. Assuming non-differential misclassification of
245 codes between the GP and the TSCI population, for the present study, relative estimates of
246 mortality would likely be attenuated towards the null, so over- or under-estimation of
247 mortality differentials is unlikely. Another potential limitation of the current study was the
248 use of probabilistic linkage to collect information on CoDs, and the resulting potential for
249 incorrect linkages. However, a sensitivity analysis using secondary alternative links found no

250 meaningful influence on study results that would modify interpretation (Supplementary
251 Table 4). Although unlinked deaths would bias absolute mortality rates, this study
252 investigates relative mortality, for which unlinked deaths have been shown to have limited
253 impact [27]. Finally, important targets for primary interventions include secondary health
254 conditions – such as bladder control, pain, or pressure ulcers – which are notably missing
255 from the present study. Currently, this information coupled with mortality outcomes is not
256 available within the context of the Swiss SCI population.

257

258 *Conclusion*

259 The particularly elevated cause-specific SMRs reported within this study for cardiovascular
260 diseases, urinary tract infections, and septicemia-related mortality require innovative
261 approaches for management of SCI-associated secondary health conditions, as well as
262 targeted interventions for known risk factors.

263

264 **6. Statements**

265 **7.1 Acknowledgements**

266 We thank the Swiss Federal Statistical Office for providing mortality and census data and for
267 the support which made the SNC and this study possible. The members of the SNC Study
268 Group include: Matthias Egger (Chairman of the Executive Board), Adrian Spoerri and Marcel
269 Zwahlen (all Bern), Milo Puhan (Chairman of the Scientific Board), Matthias Bopp (both
270 Zurich), Nino Künzli (Basel), Michel Oris (Geneva) and Murielle Bochud (Lausanne). We further
271 thank the members of the SwiSCI Steering Committee including: Xavier Jordan, Bertrand
272 Léger (Clinique Romande de Réadaptation, Sion); Michael Baumberger, Hans Peter Gmünder
273 (Swiss Paraplegic Center, Nottwil); Armin Curt, Martin Schubert (University Clinic Balgrist,
274 Zürich); Margret Hund-Georgiadis, Kerstin Hug (REHAB Basel, Basel); Thomas Troger (Swiss
275 Paraplegic Association, Nottwil); Daniel Joggi (Swiss Paraplegic Foundation, Nottwil); Hardy
276 Landolt (Representative of persons with SCI, Glarus); Nadja Münzel (Parahelp, Nottwil);
277 Mirjam Brach, Gerold Stucki (Swiss Paraplegic Research, Nottwil); Christine Fekete (SwiSCI
278 Coordination Group at Swiss Paraplegic Research, Nottwil).

279

280

281

282 **7.2 Statement of Ethics**

283 The SwiSCI cohort study has been approved by local ethics committees (reference numbers:
284 1008 [Luzern]; 37/11 [Basel]; CCVEM 015/11 [Valais]; 2012-0049 [Zürich]).

285

286 **7.3 Disclosure Statement**

287 The authors have no conflicts of interests to declare.

288

289 **7.4 Funding Sources**

290 This work was supported by the Swiss National Science Foundation (grant no. 166603 -
291 <http://p3.snf.ch/project-166603>) to MWGB and MZ.

292

293 **7.5 Author Contributions**

294 **JDC, MWGB** and **MZ** were responsible for initial conceptual framing. **AB** and **MWGB**
295 provided statistical support and critical feedback on manuscript content. **HPG, KH, XJ**, and
296 **SM** provided clinical support and feedback of the present manuscript. **MZ** and **AM** provided
297 statistical support for analyses, as well as critical evaluation of statistical methods
298 implemented. **JDC** was responsible for all analyses, drafting, and finalization of manuscript.

299 **7. Supplementary material**

300

301 **Supplementary Table 1:** Causes of death and associated SMRs according to decade, not
302 using hierarchical coding scheme

303

304 **Supplementary Table 2:** Competing risk analysis of risk factors for respiratory infections,
305 subhazard ratios

306

307 **Supplementary Table 3:** Competing risk analysis of risk factors for UTI/renal failure,
308 subhazard ratios

309

310 **Supplementary Table 4:** Causes of death and associated SMRs according to decade,
311 alternative links

312 **8. References**

313

- 314 1 Vos T, Allen C, Arora M, Barber RM, Bhutta ZA, Brown A, et al. Global, regional, and national
315 incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990–2015:
316 a systematic analysis for the Global Burden of Disease Study 2015. *The Lancet*.
317 2016;388:1545-1602.
- 318 2 Global, regional, and national burden of neurological disorders during 1990-2015: a systematic
319 analysis for the Global Burden of Disease Study 2015. *Lancet Neurol*. 2017;16:877-897.
- 320 3 Chamberlain JD, Meier S, Mader L, von Groote PM, Brinkhof MW. Mortality and longevity after
321 a spinal cord injury: systematic review and meta-analysis. *Neuroepidemiology*. 2015;44:182-
322 198.
- 323 4 Manouchehrinia A, Tanasescu R, Tench CR, Constantinescu CS. Mortality in multiple sclerosis:
324 meta-analysis of standardised mortality ratios. *J. Neurol. Neurosurg. Psychiatry*. 2016;87:324.
- 325 5 Harrison-Felix C, Kreider SE, Arango-Lasprilla JC, Brown AW, Dijkers MP, Hammond FM, et al.
326 Life expectancy following rehabilitation: a NIDRR Traumatic Brain Injury Model Systems study. *J*
327 *Head Trauma Rehabil*. 2012;27:E69-80.
- 328 6 Chamberlain JD, Gmunder HP, Hug K, Jordan X, Moser A, Schubert M, et al. Differential
329 survival after traumatic spinal cord injury: evidence from a multi-center longitudinal cohort study
330 in Switzerland. *Spinal Cord*. 2018
- 331 7 Post MW, Brinkhof MW, von Elm E, Boldt C, Brach M, Fekete C, et al. Design of the Swiss
332 spinal cord injury cohort study. *Am J Phys Med Rehabil*. 2011;90:S5-16.
- 333 8 Chevrette A: G-LINK: A Probabilistic Record Linkage System.
- 334 9 Weber R, Ruppik M, Rickenbach M, Spoerri A, Furrer H, Battegay M, et al. Decreasing mortality
335 and changing patterns of causes of death in the Swiss HIV Cohort Study. *HIV Med*.
336 2013;14:195-207.
- 337 10 Keiser O, Spoerri A, Brinkhof MW, Hasse B, Gayet-Ageron A, Tissot F, et al. Suicide in HIV-
338 infected individuals and the general population in Switzerland, 1988-2008. *Am J Psychiatry*.
339 2010;167:143-150.
- 340 11 Berlin C, Panczak R, Hasler R, Zwahlen M. Do acute myocardial infarction and stroke mortality
341 vary by distance to hospitals in Switzerland? Results from the Swiss National Cohort Study.
342 *BMJ Open*. 2016;6
- 343 12 Krause JS, Cao Y, DeVivo MJ, DiPiro ND. Risk and protective factors for cause-specific
344 mortality after spinal cord injury. *Arch Phys Med Rehabil*. 2016;97:1669-1678.
- 345 13 Savic G, DeVivo MJ, Frankel HL, Jamous MA, Soni BM, Charlifue S. Causes of death after
346 traumatic spinal cord injury-a 70-year British study. *Spinal Cord*. 2017;55:891-897.
- 347 14 Hinchliffe SR, Lambert PC. Extending the flexible parametric survival model for competing risks.
348 *Stata J*. 2013;13:344-355.
- 349 15 StataCorp. Stata Statistical Software: Release 15. StataCorp LP, College Station, TX, 2015,
- 350 16 DeVivo M, Chen Y, Krause J, Saunders L. Trends in age-adjusted cause-specific mortality rates
351 after spinal cord injury: Top Spinal Cord Inj Rehabil, 2012, 18, pp 214.

SHORT TITLE: All-cause and cause-specific mortality in the TSCI population

- 352 17 Sabre L, Remmer S, Adams A, Vali M, Rekand T, Asser T, et al. Impact of fatal cases on the
353 epidemiology of traumatic spinal cord injury in Estonia. *Eur J Neurol*. 2015;22:768-772.
- 354 18 Lidal IB, Snekkevik H, Aamodt G, Hjeltnes N, Biering-Sorensen F, Stanghelle JK. Mortality after
355 spinal cord injury in Norway. *J Rehabil Med*. 2007;39:145-151.
- 356 19 Messite J, Stellman SD. Accuracy of death certificate completion: the need for formalized
357 physician training. *JAMA*. 1996;275:794-796.
- 358 20 Hagen EM, Lie SA, Rekand T, Gilhus NE, Gronning M. Mortality after traumatic spinal cord
359 injury: 50 years of follow-up. *J Neurol Neurosurg Psychiatry*. 2010;81:368-373.
- 360 21 Middleton JW, Dayton A, Walsh J, Rutkowski SB, Leong G, Duong S. Life expectancy after
361 spinal cord injury: a 50-year study. *Spinal Cord*. 2012;50:803-811.
- 362 22 Phillips AA, Krassioukov AV. Contemporary Cardiovascular Concerns after Spinal Cord Injury:
363 Mechanisms, Maladaptations, and Management. *J Neurotrauma*. 2015;32:1927-1942.
- 364 23 Brinkhof MW, Al-Khodairy A, Eriks-Hoogland I, Fekete C, Hinrichs T, Hund-Georgiadis M, et al.
365 Health conditions in people with spinal cord injury: Contemporary evidence from a population-
366 based community survey in Switzerland. *J Rehabil Med*. 2016;48:197-209.
- 367 24 Anderson CE, Chamberlain JD, Jordan X, Kessler TM, Luca E, Mohr S, et al. Bladder emptying
368 method is the primary determinant of urinary tract infections in patients with spinal cord injury:
369 results from a prospective rehabilitation cohort study. *BJU Int*. 2018
- 370 25 Lloyd-Jones DM, Martin DO, Larson MG, Levy D. Accuracy of death certificates for coding
371 coronary heart disease as the cause of death. *Ann Intern Med*. 1998;129:1020-1026.
- 372 26 Mant J, Wilson S, Parry J, Bridge P, Wilson R, Murdoch W, et al. Clinicians didn't reliably
373 distinguish between different causes of cardiac death using case histories. *J Clin Epidemiol*.
374 2006;59:862-867.
- 375 27 Schmidlin K, Clough-Gorr KM, Spoerri A, Egger M, Zwahlen M. Impact of unlinked deaths and
376 coding changes on mortality trends in the Swiss National Cohort. *BMC Medical Informatics and
377 Decision Making*. 2013;13:1-1.
- 378
- 379

Table 1: Causes of death stratified by total, survival one year post-injury, and SCI characteristics

Cause of death	Total (N=335)	Survival more than 1 year post-injury	Completeness of SCI [Missing=17]		Level of SCI [Missing=1]	
		Total (N=229)	Incomplete	Complete	Tetraplegia	Paraplegia
Respiratory infection (J00-J22)	19 (5.7)	13 (5.7)	13 (6.2)	6 (5.6)	4 (2.9)	15 (8.3)
Chronic obstructive pulmonary disease (J40-J47)	2 (0.6)	1 (0.4)	2 (0.9)	-	-	2 (1.1)
Other respiratory disease (J30-J99)	19 (5.7)	10 (4.4)	7 (3.3)	11 (10.3)	8 (5.8)	11 (6.1)
Cardiac disease (I05-I09; I11; I30-I59)	40 (11.9)	25 (10.9)	24 (11.4)	15 (14.0)	14 (10.1)	26 (14.4)
Ischemic heart disease (I20-I25)	34 (10.1)	28 (12.2)	28 (13.3)	5 (4.7)	11 (7.9)	21 (11.6)
Cerebral, circulatory disease (I60-I69)	13 (3.9)	11 (4.8)	10 (4.7)	2 (1.9)	3 (2.2)	9 (5.0)
Pulmonary, circulatory disease (I26-I28)	16 (4.8)	9 (3.9)	9 (4.3)	7 (6.5)	7 (5.0)	9 (5.0)
Other circulatory disease (I10; I12-I15; I70-I99)	19 (5.7)	12 (5.2)	11 (5.2)	7 (6.5)	12 (8.6)	7 (3.9)
Neoplasms (C00-D49)	27 (8.1)	21 (9.2)	20 (9.5)	4 (3.7)	13 (9.4)	13 (7.2)
Urinary infection (N390-N392)	7 (2.1)	7 (3.1)	4 (1.9)	3 (2.8)	4 (2.9)	3 (1.7)
Renal failure (N17-N19)	2 (0.6)	-	2 (0.9)	-	1 (0.7)	1 (0.6)
Digestive-related disease (K00-K95)	17 (5.1)	13 (5.7)	15 (7.1)	1 (0.9)	10 (7.2)	5 (2.8)
Suicide (X71-X83)	21 (6.3)	18 (7.9)	14 (6.6)	7 (6.5)	12 (8.6)	5 (2.8)
Accidents (S00-T88; V00-X58)	28 (8.4)	7 (3.1)	11 (5.2)	14 (13.1)	8 (5.8)	20 (11.0)
Skin-related disease (L00-L99)	1 (0.3)	1 (0.4)	-	1 (0.9)	1 (0.7)	-
Infectious disease (A00-B99, excl. A41)	4 (1.2)	3 (1.3)	2 (0.9)	2 (1.9)	3 (2.2)	-
Septicemia (A41)	7 (2.1)	5 (2.2)	4 (1.9)	3 (2.8)	3 (2.2)	4 (2.2)
Ill-defined (R00-R99)	12 (3.6)	9 (3.9)	9 (4.3)	2 (1.9)	4 (2.9)	6 (3.3)
Nervous System-related disease (G00-G99)	19 (5.7)	16 (7.0)	9 (4.3)	9 (8.4)	10 (7.2)	9 (5.0)
Endocrine-related disease (E00-E89)	9 (2.7)	7 (3.1)	3 (1.4)	5 (4.7)	4 (2.9)	4 (2.2)
Musculoskeletal-related disease (M00-M99)	7 (2.1)	4 (1.7)	7 (3.3)	-	2 (1.4)	5 (2.8)
Mental-related disease (F01-F99)	11 (3.3)	8 (3.5)	6 (2.8)	3 (2.8)	5 (3.6)	5 (2.8)
Immune, blood, eye/ear-related disease (D50-D89; H00-H59)	1 (0.3)	1 (0.4)	1 (0.5)	-	-	1 (0.6)

Table 2: All-cause standardized mortality ratios (SMRs)

	Num. of deaths	Expected deaths	SMR (95% CI)
Overall	376	162.19	2.32 (2.10-2.56)
Sex			
Male	257	116.63	2.20 (1.95-2.49)
Female	119	45.56	2.61 (2.18-3.13)
Lesion Level*			
Paraplegia	156	76.71	2.03 (1.74-2.38)
Tetraplegia	203	76.55	2.65 (2.31-3.04)
Completeness*			
Incomplete	218	116.15	1.88 (1.64-2.14)
Complete	125	32.42	3.86 (3.24-4.60)
Level & completeness*			
Incomplete paraplegia	83	50.64	1.64 (1.32-2.03)
Complete paraplegia	68	25.52	2.66 (2.10-3.38)
Incomplete tetraplegia	135	65.53	2.06 (1.74-2.44)
Complete tetraplegia	57	6.71	8.49 (6.55-11.01)

Note: *Excluding cauda equina lesions

Table 3: Cause-specific SMRs, overall and one year post-injury

Causes of death	Num. of deaths	Expected deaths	SMR (95% CI)	Survived at least one year post-injury	
				Num. of deaths	SMR (95% CI)
Respiratory infection	19	3.12	6.10 (3.89-9.56)	13	4.29 (2.49-7.38)
Chronic obstructive pulmonary disease	2	3.71	0.54 (0.13-2.16)	1	0.28 (0.04-1.95)
Other respiratory disease	19	5.04	3.77 (2.41-5.91)	10	2.02 (1.09-3.75)
Cardiac disease	40	10.62	3.77 (2.76-5.13)	25	2.41 (1.63-3.56)
Ischemic heart disease	34	18.27	1.86 (1.33-2.60)	28	1.56 (1.08-2.27)
Cerebral, circulatory disease	13	8.37	1.55 (0.90-2.67)	11	1.34 (0.74-2.42)
Pulmonary, circulatory disease	16	0.88	18.15 (11.12-29.63)	9	10.38 (5.40-19.95)
Other circulatory disease	19	7.21	2.50 (1.57-3.96)	12	1.70 (0.96-2.99)
Neoplasms	27	38.37	0.70 (0.48-1.03)	21	0.56 (0.36-0.85)
Urinary infection	7	0.39	18.16 (8.66-38.10)	7	18.54 (8.84-38.90)
Renal failure	2	0.65	3.06 (0.77-12.25)	0	-
Digestive disease	17	5.11	3.32 (2.07-5.35)	13	2.59 (1.50-4.45)
Suicide	21	3.16	6.65 (4.34-10.20)	18	5.76 (3.63-9.14)
Accidents	28	5.02	5.57 (3.85-8.07)	7	1.42 (0.67-2.97)
Skin-related disease	1	0.17	5.88 (0.83-41.77)	1	6.00 (0.84-42.57)
Infectious disease	4	1.54	2.59 (0.97-6.91)	3	1.97 (0.64-6.12)
Septicemia	7	0.36	19.71 (9.40-41.35)	5	14.35 (5.97-34.46)
Ill-defined	12	4.49	2.68 (1.52-4.71)	9	2.04 (1.06-3.92)
Nervous system-related disease	19	5.77	3.29 (2.10-5.16)	16	2.82 (1.73-4.61)
Endocrine-related disease	9	3.66	2.46 (1.28-4.72)	7	1.95 (0.93-4.08)
Musculoskeletal-related disease	7	1.02	6.88 (3.28-14.43)	4	4.01 (1.50-10.67)
Mental-related disease	11	6.28	1.75 (0.97-3.16)	8	1.30 (0.65-2.60)
Immune, blood, eye/ear-related disease	1	0.35	2.85 (0.40-20.27)	1	2.91 (0.41-20.65)

Table 4: Cause-specific SMRs stratified by lesion characteristics

	Para	Tetra	Incomplete	Complete
Causes of death	SMR (95% CI)	SMR (95% CI)	SMR (95% CI)	SMR (95% CI)
Respiratory infection	2.98 (1.12-7.94)	9.23 (5.57-15.32)	5.21 (3.03-8.98)	12.35 (5.55-27.50)
Chronic obstructive pulmonary disease	-	1.06 (0.27-4.24)	0.66 (0.17-2.65)	-
Other respiratory disease	3.58 (1.79-7.15)	4.33 (2.40-7.82)	1.71 (0.82-3.59)	14.12 (7.82-25.50)
Cardiac disease	2.97 (1.76-5.02)	4.85 (3.30-7.13)	2.84 (1.90-4.24)	8.73 (5.26-14.48)
Ischemic heart disease	1.35 (0.75-2.44)	2.30 (1.50-3.52)	1.91 (1.32-2.77)	1.72 (0.72-4.13)
Cerebral, circulatory disease	0.81 (0.26-2.52)	2.12 (1.10-4.07)	1.50 (0.81-2.79)	1.47 (0.37-5.87)
Pulmonary, circulatory disease	17.01 (8.11-35.68)	21.35 (11.11-41.03)	13.15 (6.84-25.26)	42.59 (20.30-89.34)
Other circulatory disease	3.44 (1.90-6.20)	1.93 (0.92-4.05)	1.73 (0.93-3.21)	6.15 (2.93-12.91)
Neoplasms	0.70 (0.41-1.21)	0.74 (0.43-1.28)	0.68 (0.44-1.05)	0.53 (0.20-1.40)
Urinary infection	23.73 (8.90-63.21)	15.17 (4.89-47.03)	12.74 (4.78-33.95)	52.54 (16.94-162.89)
Renal failure	3.42 (0.48-24.27)	3.07 (0.43-21.77)	3.76 (0.94-15.05)	-
Digestive disease	4.12 (2.22-7.65)	2.11 (0.88-5.06)	3.79 (2.28-6.28)	1.05 (0.15-7.42)
Suicide	6.82 (3.87-12.01)	4.42 (1.84-10.61)	6.63 (3.92-11.19)	7.87 (3.75-16.50)
Accidents	3.16 (1.58-6.31)	9.37 (6.04-14.52)	3.01 (1.67-5.43)	12.48 (7.39-21.07)
Skin-related disease	12.93 (1.82-91.76)	-	-	34.50 (4.86-244.88)
Infectious disease	3.90 (1.26-12.09)	-	1.76 (0.44-7.03)	5.89 (1.47-23.54)
Septicemia	18.54 (5.98-57.47)	23.04 (8.65-61.38)	14.20 (5.33-37.83)	50.09 (16.16-155.31)
Ill-defined	1.86 (0.70-4.96)	2.92 (1.31-6.50)	2.61 (1.36-5.02)	2.31 (0.58-9.24)
Nervous system-related disease	3.79 (2.04-7.04)	3.20 (1.66-6.15)	1.97 (1.03-3.79)	9.07 (4.72-17.42)
Endocrine-related disease	2.36 (0.89-6.29)	2.27 (0.85-6.04)	1.05 (0.34-3.25)	7.65 (3.18-18.37)
Musculoskeletal-related disease	4.30 (1.08-17.20)	10.04 (4.18-24.11)	8.78 (4.19-18.41)	-
Mental-related disease	1.74 (0.73-4.19)	1.64 (0.68-3.94)	1.21 (0.54-2.69)	2.81 (0.91-8.72)
Immune, blood, eye/ear-related disease	-	5.96 (0.84-42.28)	3.68 (0.52-26.09)	-

Note: SMRs not calculated for those CoDs with insufficient cases.

Table 5: Competing risk analysis of risk factors for cause-specific mortality, subhazard ratios

	Respiratory diseases (N=21)		Cardiovascular diseases (N=122)		Neoplasms (N=27)	
	Univariable	Multivariable	Univariable	Multivariable	Univariable	Multivariable
Age at injury						
Less than 46 years	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
46-60 years	6.59 (0.74-58.96)	5.07 (0.53-48.83)	2.63 (1.09-6.33)	2.48 (1.02-5.99)	5.67 (1.18-27.29)	3.56 (0.69-18.38)
60 years and older	28.94 (3.84-218.26)	27.71 (3.62-212.31)	22.34 (10.86-45.94)	16.43 (7.87-34.31)	15.71 (3.63-68.01)	9.91 (2.24-43.78)
Lesion Level						
Paraplegia	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Tetraplegia	2.60 (1.08-6.28)	3.37 (1.29-8.80)	2.58 (1.79-3.73)	2.22 (1.50-3.30)	1.68 (0.78-3.63)	1.45 (0.62-3.37)
Completeness						
Incomplete	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Complete	2.25 (0.93-5.42)	4.95 (1.97-12.46)	0.78 (0.52-1.15)	1.50 (0.99-2.28)	0.36 (0.12-1.06)	0.55 (0.18-1.66)
	Infections (N=37)		Accidents (N=28)		Other (N=100)	
	Univariable	Multivariable	Univariable	Multivariable	Univariable	Multivariable
Age at injury						
Less than 46 years	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
46-60 years	0.69 (0.18-2.68)	0.67 (0.17-2.59)	1.43 (0.48-4.25)	1.38 (0.42-4.53)	1.44 (0.73-2.82)	1.16 (0.58-2.34)
60 years and older	6.87 (2.98-15.82)	5.53 (2.34-13.07)	3.74 (1.52-9.18)	3.57 (1.33-9.60)	5.75 (3.38-9.78)	4.31 (2.48-7.49)
Lesion Level						
Paraplegia	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Tetraplegia	2.65 (1.35-5.17)	2.65 (1.32-5.34)	3.79 (1.67-8.60)	3.93 (1.65-9.37)	1.41 (0.93-2.14)	1.30 (0.83-2.02)
Completeness						
Incomplete	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Complete	1.09 (0.56-2.13)	1.96 (0.96-4.00)	2.40 (1.09-5.30)	4.25 (1.86-9.72)	0.82 (0.52-1.29)	1.15 (0.72-1.84)

Note: The group "Respiratory diseases" excludes respiratory infections, while the group "Infections" includes respiratory infections, septicemia, urinary tract infections, and all other infections. Sex and cause of TSCI were included in the analyses as potential confounders.

Supplementary Table 1: Causes of death and associated SMRs according to decade, not using hierarchical coding scheme

Causes of death	Actual number of deaths	Expected deaths	SMR (95% Confidence Interval)	Comparison with SMRs using heirarchy
Respiratory infection	6	3.12	1.93 (0.87-4.29)	↓†
Chronic obstructive pulmonary disease	1	3.71	0.27 (0.04-1.91)	‡↓
Other respiratory	7	5.04	1.39 (0.66-2.91)	†↓
Cardiac disease	23	10.62	2.17 (1.44-3.26)	‡↓
Ischemic heart disease	30	18.27	1.64 (1.15-2.35)	‡↓
Cerebral, circulatory	13	8.37	1.55 (0.90-2.67)	‡
Pulmonary, circulatory	6	0.88	6.81 (3.06-15.15)	‡↓
Other circulatory	12	7.21	1.66 (0.94-2.93)	†↓
Neoplasms	27	38.37	0.70 (0.48-1.03)	‡
Urinary infection	3	0.39	7.78 (2.51-24.13)	‡↓
Digestive	17	5.11	3.32 (2.07-5.35)	‡
Suicide	21	3.16	6.65 (4.34-10.20)	‡
Accidents	88	5.02	17.52 (14.22-21.59)	‡↑
Skin	1	0.17	5.88 (0.83-41.77)	‡
Infectious	4	1.54	2.59 (0.97-6.91)	‡
Septicemia	3	0.36	8.45 (2.72-26.20)	‡↓
Ill-defined	11	4.49	2.45 (1.36-4.43)	‡
Nervous	44	5.77	7.62 (5.67-10.24)	‡↑
Endocrine	5	3.66	1.36 (0.57-3.28)	N.A.
Musculoskeletal	5	1.02	4.91 (2.05-11.81)	‡↓
Mental	6	6.28	0.96 (0.43-2.13)	↓†

Legend

Increased	↑
Remained significant/non-significant	‡
Decreased	↓
No longer significant	†

Supplementary Table 2: Competing risk analysis of risk factors for respiratory infections, subhazard ratios

	Respiratory Infection		All other causes	
	Hierarchical coding (N=19)	SA coding scheme (N=44)	Hierarchical coding (N=316)	SA coding scheme (N=291)
Age at injury				
Less than 46 years	Ref.	Ref.	Ref.	Ref.
46-59 years	3.16 (0.21-47.55)	1.54 (0.49-4.83)	1.53 (1.23-1.90)	1.57 (1.28-1.92)
60 years and older	21.65 (1.31-356.75)	16.89 (6.22-45.88)	7.17 (6.16-8.34)	6.78 (5.79-7.94)
Lesion Level				
Paraplegia	Ref.	Ref.	Ref.	Ref.
Tetraplegia	5.90 (2.35-14.76)	3.02 (1.12-8.17)	1.90 (1.46-2.47)	1.90 (1.42-2.52)
Completeness				
Incomplete	Ref.	Ref.	Ref.	Ref.
Complete	2.01 (1.34-3.04)	1.62 (1.06-2.47)	1.58 (1.26-1.98)	1.60 (1.28-2.00)

* Notes: (1) "SA coding schema" refers to the identification of a "respiratory infection" ICD code anywhere on death certificate (i.e., underlying CoD, initial disease, consecutive, or concomitant). For example, individuals coded under the hierarchical coding schema as having died from a cardiovascular-related disease, but for which the respiratory infection code was included as a concomitant disease, would be included as having died due to a respiratory infection in the SA coding schema. (2) Cause of SCI and sex were also included within the multivariable models as potential confounders.

Supplementary Table 3: Competing risk analysis of risk factors for UTI/renal failure, subhazard ratios

	Respiratory Infection		All other causes	
	Hierarchical coding (N=19)	SA coding scheme (N=44)	Hierarchical coding (N=316)	SA coding scheme (N=291)
Age at injury				
Less than 46 years	Ref.	Ref.	Ref.	Ref.
46-59 years	1.51 (1.30-1.75)	2.25 (2.06-2.47)	1.57 (1.23-2.00)	1.53 (1.21-1.94)
60 years and older	10.46 (3.04-35.99)	14.87 (4.98-44.39)	7.44 (6.54-8.47)	7.15 (6.18-8.27)
Lesion Level				
Paraplegia	Ref.	Ref.	Ref.	Ref.
Tetraplegia	1.16 (0.39-3.44)	1.11 (0.48-2.56)	2.05 (1.57-2.69)	2.13 (1.59-2.86)
Completeness				
Incomplete	Ref.	Ref.	Ref.	Ref.
Complete	1.33 (0.55-3.21)	1.27 (0.66-2.45)	1.61 (1.27-2.04)	1.63 (1.24-2.15)

* Notes: (1) "SA coding schema" refers to the identification of a UTI or renal failure ICD code anywhere on death certificate (i.e., underlying CoD, initial disease, consecutive, or concomitant). For example, individuals coded under the hierarchical coding schema as having died from a cardiovascular-related disease, but for which the renal failure code was included as a concomitant disease, would be included as having died due to UTI/renal failure in the SA coding schema. (2) Cause of SCI and sex were also included within the multivariable models as potential confounders.

Supplementary Table 4: Causes of death and associated SMRs according to decade, alternative links

Causes of death	Actual number of deaths	Expected deaths	Alternative link	Primary link
			SMR (95% Confidence Interval)	SMR (95% Confidence Interval)
Respiratory infection	17	3.12	5.46 (3.39-8.78)	6.10 (3.89-9.56)
Chronic obstructive pulmonary disease	3	3.71	0.81 (0.26-2.51)	0.54 (0.13-2.16)
Other respiratory	19	5.04	3.77 (2.41-5.91)	3.77 (2.41-5.91)
Cardiac disease	38	10.62	3.58 (2.60-4.92)	3.77 (2.76-5.13)
Ischemic heart disease	34	18.27	1.86 (1.33-2.60)	1.86 (1.33-2.60)
Cerebral, circulatory	12	8.37	1.43 (0.81-2.52)	1.55 (0.90-2.67)
Pulmonary, circulatory	15	0.88	17.01 (10.26-28.22)	18.15 (11.12-29.63)
Other circulatory	17	7.21	2.36 (1.47-3.79)	2.50 (1.57-3.96)
Neoplasms	25	38.37	0.65 (0.44-0.96)	0.70 (0.48-1.03)
Urinary infection	7	0.39	18.16 (8.66-38.10)	18.16 (8.66-38.10)
Renal failure	2	0.65	3.06 (0.77-12.25)	3.06 (0.77-12.25)
Digestive	17	5.11	3.32 (2.07-5.35)	3.32 (2.07-5.35)
Suicide	20	3.16	6.34 (4.09-9.82)	6.65 (4.34-10.20)
Accidents	25	5.02	4.98 (3.36-7.37)	5.57 (3.85-8.07)
Skin	1	0.17	5.88 (0.83-41.77)	5.88 (0.83-41.77)
Infectious	4	1.54	2.59 (0.97-6.91)	2.59 (0.97-6.91)
Septicemia	7	0.36	19.71 (9.40-41.35)	19.71 (9.40-41.35)
Ill-defined	12	4.49	2.68 (1.52-4.71)	2.68 (1.52-4.71)
Nervous	18	5.77	3.12 (1.96-4.95)	3.29 (2.10-5.16)
Endocrine	8	3.66	2.18 (1.09-4.37)	2.46 (1.28-4.72)
Musculoskeletal	7	1.02	6.88 (3.28-14.43)	6.88 (3.28-14.43)
Mental	12	6.28	1.91 (1.09-3.37)	1.75 (0.97-3.16)
Immune, blood, eye/ear	1	0.35	2.85 (0.40-20.27)	2.85 (0.40-20.27)