Mortality and Longevity after a Spinal Cord Injury: Systematic Review and Meta-Analysis

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Key Words

Epidemiology · Systematic review · Spinal cord injury · Mortality · Survival · Longevity · Meta-analysis · Standardized mortality ratio

Abstract

Background/Aims: Mortality and longevity studies of spinal cord injury (SCI) are essential for informing healthcare systems and policies. This review evaluates the current evidence among people with SCIs worldwide in relation to the WHO region and country income level; demographic and lesion characteristics; and in comparison with the general population. **Methods:** A systematic review of relevant databases for original studies. Pooled estimates were derived using random effects meta-analysis, restricted to traumatic SCI. **Results:** Seventy-four studies were included. In-hospital mortality varied, with pooled estimates of 24.1% (95% confidence interval (CI) 14.1–38.0), 7.6% (95% CI 6.3–9.0), 7.0% (95% CI 1.5–27.4), and 2.1% (95% CI 0.9–5.0) in the WHO regions of Africa, the Americas, Europe and Western Pacific. The combined estimate for low- and middle-income countries was nearly three times higher than for high-income countries. Pooled estimates of first-year survival were 86.5%

(95% CI 75.3–93.1), 95.6% (95% CI 81.0–99.1), and 94.0% (95% CI 93.3–94.6) in the Americas, Europe and Western Pacific. Pooled estimates of standardized mortality ratios in tetraplegics were 2.53 (2.00–3.21) and 2.07 (1.47–2.92) in paraplegics. **Conclusion:** This study found substantial variation in mortality and longevity within the SCI population, compared to the general population, and between WHO regions and country income level. Improved standardization and quality of reporting is needed to improve inferences regarding the extent to which mortality outcomes following an SCI are related to healthcare systems, services and policies.

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Introduction

All-cause mortality and life expectancy are key end-point measures of individual health after a spinal cord injury (SCI). Similar to other neurological conditions, such as traumatic brain injury [1, 2], epilepsy [3], Parkinson's disease [4], and multiple sclerosis [5, 6], previous studies in SCI have shown a heightened risk of mortality and reduced longevity as compared to the general population [7–10]. Within SCI, mortality

typically varies with lesion severity; higher-level (tetraplegia) as well as complete lesions are associated with heightened risk as compared to lower-level (paraplegia) and incomplete lesions [8, 11]. This variation observed between SCI-specific characteristics (e.g. tetraplegia versus paraplegia) has been associated with the level of impairment in vital body functions; SCI-specific morbidity; non-specific secondary health conditions and faster biological aging; and disability [12–16]. Other studies have indicated socioeconomic deprivation, depression, substance abuse and suicidal ideation as mediating factors to the heightened risk of mortality following SCI [17–20].

A comparative analysis of mortality outcomes and longevity may provide insights into a critical aspect of human rights in people living with SCI: the highest attainable standard of physical and mental health [21]. Systematic evaluations of mortality and life expectancy data may help identify real-world gaps in the quality or access to critical care provisioning, within the SCI population as well as in comparison to the general population. Global evaluations may also identify consistencies in outcomes across countries and settings, related to geographic variation as well as sociodemographic and socioeconomic gradients, and use of the cumulative evidence may improve the accuracy and reliability of health policy recommendations that aim to improve survival and life expectancy of people living with SCI. Broad measures of mortality are generally available, even in resource-limited countries, often making it possible to draw comparisons between countries and over time. Specific outcomes such as high in-hospital mortality may be indicative of particular shortcomings of the healthcare system, such as inadequate emergency service response, capacity problems, or the limited availability and delayed timing of critical medical interventions and rehabilitation. Thus, we may anticipate higher in-hospital mortality, especially with increasing severity of neurological lesion, among low-resourced as compared to high-resourced settings.

While comprehensive, methodologically rigorous reviews exist regarding mortality and longevity after SCI, they are narrative in nature; this review seeks to contextualize mortality and longevity through meta-analytic techniques, which is necessary to illuminate the potential impact of healthcare systems, while additionally updating and building upon extant reviews [8, 11, 22]. The aim of this systematic review and meta-analysis is to evaluate the variation in mortality and longevity among people with traumatic and non-traumatic SCIs worldwide, with the objective of evaluating variation in rela-

tion to WHO region, country-income level, demographic and lesion characteristics, and compared to the general population.

Materials and Methods

This review complies with PRISMA recommendations [23] and expands on the recent WHO Report International Perspectives on Spinal Cord Injury (IPSCI) [22].

Search Strategy

The literature search included studies published between January 1, 2000 and June 17, 2013. A variety of sources were used to find relevant papers including PubMed, EMBASE, and LILACS databases. A hand-search through relevant topic-specific journals was conducted. In addition, we screened bibliographies for relevant literature that were missed. The following MeSH terms were used in the search strategy: ‘spinal cord injury’, ‘paraplegia’, ‘quadriplegia’, ‘mortality’, ‘cause of death’, ‘survival’, ‘epidemiology’, ‘life expectancy’. Non-MeSH terms included: ‘SMR or standardized mortality ratio’, and ‘proportional hazards model’. Additional search phrases were added based on studies cited in previous literature but not found using pre-specified terms, including: ‘(non-traumatic spinal cord injury) OR (traumatic spinal cord injury)’ AND (mortality OR survival OR trend* OR outcome) and ‘spinal cord injuries/mortality’ (MeSH). The search was restricted to publications in English, French, German, Italian, or Spanish.

Inclusion/Exclusion Criteria

Original studies were eligible for inclusion if they reported at least one measure of survival or mortality on people with traumatic SCI, non-traumatic SCI, or both. Studies focusing on specific populations (e.g. pediatric or SCI caused by sports-related accident) were eligible, as well as descriptive studies that included the number of in-hospital deaths, irrespective of whether mortality was the main outcome of interest. We excluded randomized control trials (RCTs), studies not specific to SCI (e.g. spinal fractures without SCI), reviews, and case reports. Two reviewers independently assessed titles and abstracts in order to determine eligibility for the study (J.C. and S.M.). Any discrepancies were discussed and, if necessary, a third reviewer was consulted (L.M. or M.W.G.B.).

Data Extraction

A database was created and maintained using MS Access to ensure standardized data collection. Data collected included: author, year, country, study period, study design, study population, inclusion criteria, exclusion criteria, sample size, demographic and injury characteristics, type of mortality or survival estimate and its stratification (e.g. age, gender). All data were double-checked independently by a second reviewer (L.M. or S.M.) to ensure accuracy. Graphical digitizing software (PlotDigitizer) was used to extract estimates only included in graphs [24]. Hazard ratios (HR), when not reported, were calculated from available survival curves (e.g. Kaplan-Meier curves) using the methodology outlined by Tierney et al. [25].

Outcome variables of interest included in-hospital mortality (defined as death following admission to acute care and before discharge from acute care), median survival (i.e. the smallest survival time at which the cumulative survival function is equal or less than 0.5), and percent survival at 1, 5, 10, 20, and 30 years after SCI. Comparative measures included standardized mortality ratio (SMR) and percent longevity. Point estimates including a measure of variance (i.e. standard error or 95% confidence intervals (CI)) or crude information that would allow for the calculation of point estimates and variance (e.g. number of patients, number of deaths, person-years of follow-up, median survival time, expected number of deaths) were extracted. Available information on potential determinants or risk factors of mortality were also collected, including the age at injury, gender, lesion level, American Spinal Injury Association (ASIA) Impairment Scale (AIS) score, and completeness of lesion.

Quality Assessment

All studies were quality-assessed using criteria based on standard principles outlined by the Center for Review and Dissemination [26] and STROBE guidelines [27]. Guidelines proposed by Dekkers et al. were used to distinguish cohort and case series [28].

Statistical Analysis

Stata version 13.0 and R version 3.0 were used for analyses. Random effects meta-analyses were used to calculate pooled estimates of mortality and survival [29] for whole-population studies in TSCI, excluding selected TSCI (e.g. cervical TSCI-, pediatric- and geriatric-only populations). Meta-analyses of mortality outcomes for NTSCI were not feasible due to lack of sufficient data. We further refrained from combined analysis of TSCI and NTSCI data (including studies with mixed NTSCI/TSCI populations) as it would produce distorted estimates given the different nature of the two etiologies (e.g. age, sex ratio, mortality rates). Estimated proportions and their variances were logit transformed [30]. We performed separate meta-analyses on the ORs and HRs as potential risk factors for mortality for both age and gender and SMRs. Analyses of ratio measures were performed on the natural log scale. Statistical heterogeneity was identified using the I^2 statistic [31]. For the meta-analysis and meta-regression of in-hospital mortality, for which there was sufficient data (at least ten studies: http://handbook.cochrane.org/chapter_9/9_6_4_meta_regression.htm), WHO region and country income level were used as macro-level variables to investigate systematic sociodemographic, economic, and geographic variation; estimates of one-year were available only for high-income countries; therefore, only regional variation was investigated [32]. For all other outcomes (i.e. SMRs, ORs and HRs), there were insufficient data for sub-grouped analyses. Additional predictors used in the meta-regression of in-hospital mortality included the following study characteristics: male to female ratio, mean age, and tetraplegia-paraplegia ratio. Country income level was included as a macro indicator, which was dichotomized into high income versus medium and low income due to limited number of studies in low-income countries [33]. Regional data from China were excluded from the meta-regressions as the national GDP is not representative of regional economic resources and related variation in accessibility, level and quality of specialized healthcare [34]. Publication and reporting biases were examined using a funnel plot and linear regression of the effect estimate on their standard errors [35].

Results

Literature Search

The search produced 1,749 potential articles, 607 of which were duplicates. Therefore, 1,142 titles and abstracts were screened for relevance; 120 publications were identified for further screening; and 78 articles were eligible for inclusion in the systematic review. Sixty-three studies were eligible for inclusion in at least one of the meta-analyses (fig. 1).

Study Characteristics

More than one third of all included studies were from the United States ($n = 28$) [18, 36–62]; roughly 13% of studies were conducted in Canada ($n = 10$) [17, 63–71], 5% in Israel ($n = 4$) [72–75], 5% in Australia ($n = 4$) [9, 76–78]; 4% in France ($n = 3$) [79–81]; 4% from Norway ($n = 3$) [7, 10, 19]; while the remaining were from countries including Brazil, China, Estonia, Finland, Greece, Germany, Iceland, Italy, Japan, the Netherlands, Nigeria, Poland, Scotland, Sierra Leone, South Africa, Sweden, Taiwan, and the United Kingdom (see online suppl. table; for all online suppl. material, see www.karger.com/doi/10.1159/000382079) [7, 82–107]. The study duration ranged from less than one year to more than 50 years, and included data beginning in 1935 until 2009. Sample sizes varied between 24 [99] and close to 100,000 individuals (see online suppl. table) [62]. A majority of studies involved traumatic SCI (TSCI) ($n = 68$), but a few studies were also included that considered non-traumatic SCI (NTSCI) only ($n = 7$) [43, 48, 69, 75, 76, 85, 86], or both NTSCI and TSCI ($n = 3$) [40, 41, 96] (see online suppl. table). Most studies measured completeness of motor and sensory impairments using the AIS. Among studies with an NTSCI population, the male to female ratio was much closer to 1.0 compared to studies with a TSCI population, which included greater proportions of men (see online suppl. table). For those studies that reported the mean age, the mean age ranged between 23 and 62 [74, 106] and between 48 [75] and 62 [48] among studies with adult TSCI and NTSCI populations. Among pediatric populations, the mean age was 11.8 for a TSCI-only population (among one year survivors-only) [83], and 5 years in an NTSCI population [86].

Study Quality

A large percentage of studies (62%) did not refer to ICD codes or a written clinical definition or classification for SCI (table 1). For studies from the World Health Organization (WHO) African region ($n = 7$), most had

Fig. 1. Flowchart of studies excluded and selected for systematic review and meta-analysis.

potential bias ($n = 4$), and although none defined SCI, the majority provided demographic information, including details on SCI characteristics ($n = 5$). A smaller proportion of studies from the WHO region of the Americas included potential sources of bias ($n = 8$). More than a third of studies failed to provide confidence intervals for main outcomes (40%) (table 1). Of the studies that employed survival analysis (i.e. Kaplan-Meier curves, Cox regression, or SMRs) ($n = 45$), only 16% provided adequate statistics, including censoring, median survival/person-years and follow-up on mortality ($n = 7$), while 9% failed to provide any information ($n = 4$) (table 1).

Traumatic Spinal Cord Injury

In-Hospital Mortality

In-hospital mortality among studies reporting on TSCI populations ranged between 10.8% [100] and 34.6% [101] in Africa; 3.1% [68] to 12.6% [58] in the Americas; 1.1% [107] and 15.9% [98] in Europe; and 1.4% [103] and 3.4% [87] in the Western Pacific, which included only

China (online suppl. table). Among studies with a cervical TSCI-only population in-hospital mortality varied between 4.2 and 26.2% [49, 56, 66, 94, 105]. Study estimates for one geriatric population was 23.1% (online suppl. table) [89].

Within WHO regions, the between-study heterogeneity was substantial, with I^2 values ranging from 73.9 to 98.0% and p values indicating statistical support for heterogeneity in three out of four regions (fig. 2). For whole-population studies in TSCI (i.e. TSCI-only population), the combined estimates from random effects meta-analysis for the WHO regions of Africa, the Americas, Europe and Western Pacific were 24.1% (95% CI 14.1–38.0; $I^2 = 75.0\%$), 7.6% (95% CI 6.3–9.0; $I^2 = 95.4\%$), 7.0% (95% CI 1.5–27.4; $I^2 = 97.5\%$), and 2.1% (95% CI 0.9–5.0; $I^2 = 73.9$), respectively. The combined in-hospital mortality in low- and middle-income countries (excluding regional data from China) was nearly three times higher than the estimate for high-income countries (20.5%, 12.4–32.0% vs. 7.0%, 3.7–12.7%; p from meta-regression model <0.01). Given the difference in the

Table 1. Assessment of study quality

	Number	Percent
Is the sample representative of a large population?		
Representative	38	49
Regional	40	51
Is there potential bias in study design? ¹		
No	50	64
Potential bias	28	36
Did authors include definition of SCI?		
Yes	30	38
No	48	62
Did the outcome of interest include a confidence interval?		
Yes	47	60
No	31	40
Were summary statistics reported for the population of interest?		
Basic	10	13
SCI only	2	3
SCI and basic	61	78
No	5	6
Did authors control for potential confounders?		
Yes	44	56
No	10	13
Not applicable	24	31
Relevant statistics for interpretation of reported survival analysis ²		
Mortality follow-up	7	16
Info on median survival/person-years	6	13
Info on censoring	7	16
Info on censoring and follow-up on mortality	5	11
Info on censoring and median survival/person-years	2	4
Info on median survival/person-years and follow-up on mortality outcome	7	16
Info on censoring and median survival/person-years and follow-up on mortality outcome	7	16
No	4	9

Number refers to the number of studies out of the total sample, percentage corresponds to the proportion of studies, which provided information. ¹ Potential sources of bias included: (1) bias in assessment of the outcome, (2) information bias (quality and extent of information obtained different for exposed versus non-exposed, (3) bias from non-response and loss to follow-up, (4) analytic bias (preconceptions regarding outcome – bias analyses and interpretation). ² Only for those studies reporting survival-related analysis (i.e. Kaplan-Meier curves, Cox regression, SMRs).

income level, there was little evidence for additional variation of in-hospital mortality with study characteristics, including the male to female ratio ($p = 0.44$), mean age ($p = 0.36$), and the tetraplegia-paraplegia ratio ($p = 0.28$).

Survival

Median survival ranged between 2.8 [7] and 43 years [73] after TSCI [7, 10, 37, 72, 73, 80, 81]. One-year survival ranged between 79 and 100%, 5-year survival between 85 and 96%, and 10-year survival between 81 and 93% [9, 10, 19, 39, 50, 51, 57, 72, 73, 77, 80, 84, 88, 106].

Studies comparing survival between males and females generally reported higher rates of survival among females.

Few studies reported information on survival according to SCI characteristics. Studies that reported survival information according to either lesion level or severity found decreasing survival with increasing severity and lesion level (table 2). An exceptional study by Middleton et al., which provided both long-term follow-up as well as detailed information related to SCI characteristics, found consistent trends for 5-, 10-, and 20-year survival, and also found that among people with an AIS A, B, or C,

Fig. 2. In-hospital mortality after traumatic SCI by WHO region. In-hospital mortality represents those deaths that occurred during acute care. The black circles with the corresponding line represent

the point estimate with 95% CI of in-hospital mortality. The area of the gray boxes represents the relative weight, which is inversely proportional to the variance of the estimate.

those with a C1–C4 lesion had better survival compared to those with a C5–C8 lesion, likely reflecting the higher mortality rate in the first year following TSCI for higher lesions (deaths in the first year were excluded from survival calculations in following years) [9].

Pooled estimates for one-year survival after TSCI were calculated according to WHO regions (fig. 3). Sub-groups according to WHO region explained some of the heterogeneity observed in overall pooled estimate (ES = 92.8%; 95% CI 89.4–95.2; $I^2 = 96.9\%$). In the Americas, one-year

Table 2. SCI-specific survival following SCI

Author	Country	Study period	Study population	Category	Median survival	PYs	1-year survival	5-year survival	10-year survival	20-year survival	30-year survival
Ahoniemi et al., 2011 [84]	Finland	1976–2005	TSCI	Para Tetra	– –	– –	99.38 97.22	94.75 86.73	87.96 79.32	77.16 62.35	– –
Cao et al., 2013 [37]	USA	1998–2009	TSCI	Overall C1–C4 Other injury levels	4.58 3.46 5.01	13,361 – –	– 89 ¹ 95 ¹	– 80 ¹ 86 ¹	– – 78 ¹	– – –	– – –
Catz et al., 2002 ² [72]	Israel	1959–1992	TSCI	Overall Lumbar Thoracic Cervical	– – – –	– – – –	– 95 ¹ 86 ¹ 83 ¹	85 88 ¹ 68 ¹ 61 ¹	81.4 84 ¹ 60 ¹ 53 ¹	74.8 78 ¹ 46 ¹ 38 ¹	62.2 63 ¹ 24 ¹ 16 ¹
Hagen et al., 2010 [10]	Norway	1952–2008	TSCI	Overall Complete cervical Complete TLS Incomplete cervical Incomplete TLS	7.4 – – – –	– – – – –	79.2 – – – –	– 71 ¹ 88 ¹ 78 ¹ 93 ¹	– 62 ¹ 78 ¹ 67 ¹ 89 ¹	– 52 ¹ 74 ¹ 57 ¹ 83 ¹	– 36 ¹ – 33 ¹ 76 ¹
Middleton et al., 2012 ³ [9]	Australia	1955–2006	TSCI	Overall Para Tetra C1–C4 ABC C5–C8 ABC T1–S5 ABC	– – – – – –	– – – – – –	93.7 95.9 91.8 84.1 91.8 95.4	– 98 ¹ 94 ¹ 94 ¹ 92 ¹ 96 ¹	– 94 ¹ 88 ¹ 89 ¹ 85 ¹ 94 ¹	– 88 ¹ 78 ¹ 82 ¹ 74 ¹ 87 ¹	– 73 ¹ 62 ¹ 57 ¹ 59 ¹ 72 ¹
Prusmack et al., 2006 [51]	USA	1997–2002	TSCI	Overall Incomplete Complete	– – –	– – –	81.0 85.9 76.1	– – –	– – –	– – –	– – –
Ronen et al., 2004 [75]	Israel	1962–2000	NTSCI	Overall Cervical Thoracic Lumbar	– 22.7 23.4 27.7	– – – –	99.4 – – –	93.7 – – –	84.2 – – –	49.8 – – –	39.3 – – –

Includes only studies that reported survival by SCI-specific characteristics. ¹ Values extracted using PlotDigitizer. ² Survival for individuals aged ≥ 35 at time of injury. Additional survival information provided for individuals aged ≤ 35 at time of injury in original publication. ³ Excluding those who died during the first year from survival calculations (e.g. 5-year survival includes only those that survived the first year following SCI). TLS = Thoracolumbosacral.

survival following TSCI ranged between 80.9 and 90.0% (ES = 86.5%; 95% CI 75.3–93.1; $I^2 = 91.3\%$) (fig. 3) [51, 57]. In Europe, as well as the Western Pacific, the pooled estimates for one-year survival were slightly higher (ES = 95.6%; 95% CI 81.0–99.1; $I^2 = 97.7\%$ and ES = 94.0%; 95% CI 93.3–94.6; $I^2 = 0\%$, respectively) (fig. 3) [9, 10, 19, 77, 84, 106].

Risk of Mortality

Among studies that reported risk of mortality with age at injury, HRs ranged between 1.03 and 3.44 [7, 81], and ORs ranged between 1.02 and 1.31 [60, 97]. Comparing males to females across studies, HRs ranged between 0.94

and 1.40 [7, 77], and ORs ranged between 1.15 and 1.60 [44, 58]. Meta-analysis produced pooled estimates for HRs and ORs for age at injury showed moderate-to-high heterogeneity for a pooled estimates of 1.06 (1.05–1.07; $I^2 = 78.2\%$) and 1.06 (1.03–1.09; $I^2 = 94.6\%$), indicating that mortality risk increased on average by 6% with increasing age. HRs and ORs reported for gender had pooled estimates of 1.27 (1.13–1.43; $I^2 = 0.0\%$) and 1.29 (1.21–1.36; $I^2 = 0.0\%$), indicating consistently higher mortality in males as compared to females.

With the exception of a few studies, risk of mortality was found to consistently increase with higher lesion levels and was elevated for complete versus incomplete

Fig. 3. One-year survival following traumatic SCI by WHO region. The black circles with the corresponding line represent the point estimate with 95% CI of one-year survival. The area of the gray boxes represents the relative weight, which is inversely proportional to the variance of the estimate.

lesions (as measured by either AIS scores or Frankel grades) (table 3). HRs were calculated for two studies to estimate mortality risk by lesion characteristics from Kaplan-Meier curves [9, 10]. A pooled estimate of 1.79 (1.51–2.12; $I^2 = 51.2\%$) was calculated for the HR of tetraplegia compared to paraplegia (fig. 4). Unfortunately, comparability is difficult due to variation in grouping (e.g. age groups, lesions levels) methods and adjustment techniques (i.e. selection of potential confounding variables).

Comparison with the General Population

Standardized Mortality Ratio. SMRs were reported for a variety of characteristics including: cause of death, paraplegia, tetraplegia, incomplete/complete lesions, gender, age, and AIS grade. Seven studies reported overall SMRs, four stratified by gender, five by lesion level, and six reported SMRs for cause of death. The majority of studies reporting overall SMRs were from Europe [7, 10, 84], two studies were from the Americas [37, 41], and two from the Western Pacific [9, 90]; SMRs for people with SCI ranged between 1.47 [41] and 5.00 [7]. The study by Imai et al. did not report confidence intervals or standard errors and could therefore not be included in the meta-analysis [90]. SMRs were generally higher in women as

compared to men [7, 19, 84]; with increasing age [7, 9, 10, 37]; and with increasing severity of the lesion (related to level and completeness of lesion) [9, 10, 19, 37, 84]. SMRs related to cerebrovascular diseases; bacterial diseases; suicide/accidental poisoning; and pneumonia/influenza were often the most elevated [9, 10, 19, 37, 78, 90].

We derived an overall SMR estimate of 2.45 (1.86–3.22), although with high heterogeneity ($I^2 = 96.9\%$); excluding a study that included only males gave a similar result (2.64; 1.97–3.53; $I^2 = 97.3\%$) [41]. A pooled SMR of 2.07 (1.47–2.92; $I^2 = 94.0\%$) was calculated for paraplegia (fig. 5) [9, 10, 19, 37, 84], and 2.53 (2.00–3.21; $I^2 = 92.4\%$) for tetraplegia (fig. 6) [9, 10, 19, 37, 84].

Life Expectancy

Overall life expectancy among the SCI population was reduced as compared to the general population [9, 44]. In addition, the gap in life expectancy widened with increasing lesion severity and age [59, 60, 107]. For instance, Strauss et al., estimated a life expectancy as compared to the general population for a 25-year-old white male (with traumatic SCI due to nonviolent etiology, 3 years since injury, and a grade A, complete lesion) of 68.2% for C6–C8; 58.9% for C5; 51.9% for C4; and 49.9% C1–C3 lesions [57]. Middleton et al. calculated percent

Table 3. SCI-specific determinants of mortality after traumatic SCI

Author	Country	Study design	Study period	Sample size	Study population	Measure	Category	Estimate	LCI	UCI
Ahoniemi et al., 2011 [84]	Finland	Retrospective cohort	1976–2005	1,647	TSCI	HR HR	Complete vs. incomplete (ref) Tetra vs. para (ref)	1.81 1.75	1.45 1.42	2.23 2.16
Cao et al., 2013 [36]	USA	Retrospective cohort	1995–2011	8,183	TSCI	OR OR OR OR OR	C1–C4 vs. non-cervical (ref) C5–C8 vs. non-cervical (ref) AIS A vs. AIS grade D (ref) AIS B vs. AIS grade D (ref) AIS C vs. AIS grade D (ref)	1.41 1.55 2.14 1.82 1.51	1.20 1.36 1.82 1.48 1.24	1.66 1.77 2.52 2.24 1.85
Cao et al., 2013 [37]	USA	Retrospective cohort	1998–2009	2,685	TSCI	HR HR HR HR	C1–C4 vs. C5–C8 and T1–S3 (ref) Frankel grade B vs. Frankel grade A (ref) Frankel grade C vs. Frankel grade A (ref) Frankel grade D vs. Frankel grade A (ref)	1.60 0.40 0.50 0.30	1.20 0.20 0.30 0.20	2.20 0.50 0.70 0.50
Espagnacq et al., 2011 [79]	France	Prospective cohort	1995–2006	1,241	TSCI	OR OR OR	C1–C4 complete vs. C5–C8 incomplete (ref) C1–C4 incomplete vs. C5–C8 incomplete (ref) C5–C8 complete vs. C5–C8 incomplete (ref)	1.40 1.00 1.40	0.70 0.40 0.60	3.00 2.40 2.90
Garshick et al., 2005 [41]	USA	Prospective cohort	1994–2000	361	TSCI and NTSCI	RR RR RR	Motor complete cervical vs. other motor incomplete (ref) Cervical ASIA C vs. other motor incomplete (ref) Other motor complete vs. other motor incomplete (ref)	1.23 1.77 1.07	0.45 0.65 0.48	3.37 4.84 2.36
Hagen et al., 2010 [10]	Norway	Retrospective cohort	1952–2008	401	TSCI	RMR RMR RMR HR HR HR	Incomplete tetra vs. incomplete para (ref) Complete para vs. incomplete para (ref) Complete tetra vs. incomplete para (ref) Complete cervical vs. incomplete TLS Complete TLS vs. incomplete TLS Incomplete cervical vs. incomplete TLS	1.35 2.49 4.56 4.75 1.31 3.57	0.79 1.44 2.60 4.01 0.63 2.97	2.30 4.30 8.00 5.50 1.99 4.18
Krause et al., 2010 [44]	USA	Prospective cohort	1997–1998	1,303	TSCI	OR OR OR	C1–C4 vs. ASIA D (ref) C5–C8 vs. ASIA D (ref) Non-cervical vs. ASIA D (ref)	3.28 1.94 1.90	2.04 1.26 1.25	5.28 2.97 2.89
Krause et al., 2004 [46]	USA	Prospective cohort	1995–2002	5,948	TSCI	OR OR OR OR OR	C1–C4 vs. T1–S5 (ref) C5–C8 vs. T1–S5 (ref) ASIA A vs. ASIA D/E (ref) ASIA B vs. ASIA D/E (ref) ASIA C vs. ASIA D/E (ref)	1.48 1.34 2.39 1.86 1.78	1.11 1.05 1.70 1.23 1.21	1.97 1.71 3.37 2.82 2.63
Krause et al., 2011 [45]	USA	Prospective cohort	1995–2009	8,027	TSCI	OR OR OR OR OR	C1–C4 vs. non-cervical (ref) C5–C8 vs. non-cervical (ref) ASIA A vs. ASIA D/E (ref) ASIA B vs. ASIA D/E (ref) ASIA C vs. ASIA D/E (ref)	2.56 2.14 1.70 1.27 1.01	2.09 1.81 1.28 0.91 0.72	3.12 2.54 2.26 1.78 1.41
Lhéritier et al., 2001 [80]	France	Retrospective cohort	1949–1999	697	TSCI	RR RR	C5 vs. C2–C4 (ref) C6–C8 vs. C2–C4 (ref)	0.64 0.48	0.33 0.25	1.23 0.91
Liang et al., 2001 [93]	Taiwan	Retrospective cohort	1989–1997	109	Cervical TSCI	HR	Complete tetra vs. incomplete tetra (ref)	1.14	0.14	9.54
Lidal et al., 2007 [19]	Norway	Retrospective cross-sectional	1961–2002	387	TSCI	HR HR	Frankel A–C vs. Frankel D–E (ref) Tetra vs. para (ref)	1.84 1.64	1.24 1.12	2.73 2.39

Table 3. (continued)

Author	Country	Study design	Study period	Sample size	Study population	Measure	Category	Estimate	LCI	UCI
Middleton et al., 2012 [9]	Australia	Retrospective cohort	1955–2006	2,014	TSCI	HR	Tetra vs. para (ref)	1.54	1.41	1.67
						HR	C1–C4 vs. T1–S1 ABC (ref)	1.33	1.03	1.64
						HR	C5–C8 vs. T1–S1 ABC (ref)	1.66	1.45	1.87
Neumann et al., 2009 [94]	Brazil	Retrospective cohort	2001–2005	84	Cervical TSCI	OR	Frankel A vs. Frankel B–D and inconclusive (ref)	4.52	1.62	12.70
O'Connor et al., 2005 [77]	Australia	Retrospective cohort	1986–1997	2,892	TSCI	HR	C1–C4 vs. T1–S5 (ref)	2.76	2.06	3.70
							C5–C8 vs. T1–S5 (ref)	1.71	1.31	2.24
Ronen et al., 2004 [75]	Israel	Retrospective cohort	1962–2002	1,087	TSCI	HR	Cervical vs. lumbar (ref)	1.33	0.98	1.81
						HR	Thoracic vs. lumbar (ref)	1.10	0.82	1.49
Sabre et al., 2013 [7]	Estonia	Retrospective cohort	2001–1997	244	TSCI	HR	Complete vs. incomplete (ref)	1.83	1.18	2.84
						HR	Tetra vs. para (ref)	1.84	1.17	2.89
Sabre et al., 2013 [7]	Norway	Retrospective cohort	2001–1997	71	TSCI	HR	Complete vs. incomplete (ref)	0.97	0.42	2.22
						HR	Tetra vs. para (ref)	3.72	1.40	9.87
Saunders et al., 2009 [52]	USA	Retrospective cohort	1981–1998	4,353	TSCI	OR	Frankel A vs. Frankel D/E (ref)	2.90	1.40	5.80
						OR	Frankel B vs. Frankel D/E (ref)	0.50	0.20	1.20
						OR	Frankel C vs. Frankel D/E (ref)	4.60	1.90	11.30
						OR	Tetra vs. para (ref)	2.00	1.30	3.00
Selassie et al., 2013 [53]	USA	Retrospective cohort	1998–2009	3,389	TSCI	HR	Tetra vs. para/other (ref)	2.54	1.73	3.73
						HR	Incomplete tetra vs. para/other (ref)	1.63	1.21	2.21
Shao et al., 2011 [97]	China	Retrospective cohort	1995–2008	1,163	Cervical TSCI	OR	C1–C3 vs. C6–C8 (ref)	5.03	1.84	13.73
						OR	C4–C5 vs. C6–C8 (ref)	2.14	1.13	4.06
						OR	ASIA A vs. ASIA D (ref)	64.73	20.66	202.78
						OR	ASIA B vs. ASIA D (ref)	15.08	3.86	58.86
						OR	ASIA C vs. ASIA D (ref)	4.64	1.07	20.07
Shavelle et al., 2006 [59]	USA	Prospective cohort	1973–2003	319	TSCI	OR	C1–C5 ASIA A vs. (ref)	2.27	1.48	3.48
Varma et al., 2010 [58]	USA	Retrospective cohort	1993–2005	1,997	TSCI	OR	Frankel B vs. Frankel A (ref)	0.40	0.20	0.70
						OR	Frankel C vs. Frankel A (ref)	0.80	0.40	1.30
						OR	Frankel D vs. Frankel A (ref)	0.70	0.30	1.50
						OR	Tetra vs. para (ref)	1.50	0.70	3.30

Includes only those studies that reported risk of mortality by SCI-specific characteristics. HR = Hazard ratio; OR = odds ratio; RMR = relative mortality ratio; RR = risk ratio.

life expectancy for individuals aged 25 with a T1–S5 AIS A, B, or C level and severity of 88%; 74% for C5–C8 AIS A, B, or C; and 69% C1–C4 AIS A, B, or C lesion [9]. In a US pediatric population (i.e. 21 years and younger), percent life expectancy for males two or more years post-injury, with nonviolent SCI etiology and an attained age of 5 years, was 72.5% among incomplete paraplegia (AIS grades B, C) and 60.2% for complete tetraplegia (C5) [60]. There were insufficient data on life expectancy for meta-analysis.

Leading Causes of Death

Among those studies that investigated the causes of death, the reported leading causes of death were diverse ($n = 22$) [9, 10, 19, 37, 40, 42, 51, 65, 74, 78, 84, 86–90, 92, 94, 97, 106–109]. The most commonly reported leading cause of death was pneumonia ($n = 5$) [19, 51, 78, 94, 109], followed by heart disease ($n = 3$) [10, 74, 84]. Only one study reported the crude number of deaths for causes of mortality by gender, and found that the leading cause of death among males was heart disease, compared to an

Fig. 4. Hazard ratio (HR) of all-cause mortality in tetraplegia as compared to paraplegia. The black circles represent the HR, with the corresponding line through the circle representing the 95% CI. The area of the gray boxes represents the weight, which is inversely proportional to the variance of the HR. * Represents HR derived from Kaplan-Meier curves.

Fig. 5. Age- and sex-standardized mortality ratio (SMR) for paraplegia. The black circles represent the SMR, with the corresponding line through the circle representing the 95% CI. The area of the gray boxes represents the weight, which is inversely proportional to the variance of the SMR.

Fig. 6. Age- and sex-standardized mortality ratio (SMR) for tetraplegia. The black circles represent the SMR, with the corresponding line through the circle representing the 95% CI. The area of the gray boxes represents the weight, which is inversely proportional to the variance of the SMR.

equal number of deaths due to digestive disorders as well as heart disease for females [84]. In the study by Hagen et al., SMRs were reported by gender for a few select causes of death; a large difference in SMRs between men and women was observed for accidental poisoning and suicide (3.7 compared to 37.6, respectively) [10].

Trends in Survival and Mortality

Lastly, a few studies have also looked at survival and mortality trends over time, albeit with mixed results. Among those studies that investigated trends, all were in high-resourced countries, with extended periods of follow-up (between 12 and 51 years of follow-up) and a tradition of modern SCI management [9, 10, 19, 52, 54, 55, 57, 77, 110]. For example, Middleton et al. found evidence of improvements in life expectancy and survival, especially among paraplegics, Saunders et al. found an overall decrease in the TSCI mortality rate, while Hagen et al. found no significant change in SMRs over time [9, 10, 52]. Other studies identified improvements in mortality rates during the first year post-injury, although not since the 1980s [54, 55]. Conflicting results were published in another study with roughly 40 years of follow-up, which found higher SMRs in the period of 1976 to 1982 compared to 1961 to 1975 [19].

Non-Traumatic Spinal Cord Injury

Due to limited data availability, it was not possible to perform meta-analyses for mortality or longevity outcomes following NTSCI. For two adult NTSCI populations, in-hospital mortality varied between 9.6 and 11.4% [48, 76] and was 7.2% for a pediatric population [86]. Median survival ranged between 0.16 [85] and 24 years [75], one-year survival between 19.7 and 99.4% [69, 75], 5-year survival was 93.7%, 10-year survival 84.2%, 20-year survival 49.8%, 30-year survival of 39.3% [75]. Studies reporting on factors affecting survival following an NTSCI diagnosis found age at lesion onset, sex, severity of lesion, and tumor site to be important predictors [43, 69, 75]. One study investigated trends in survival and found improvement in survival for NTSCI, albeit only in the past decade [75], while another study found no evidence of improvement in the risk of in-hospital mortality over time [48].

Discussion

Summary of Key Results

SMRs for people with SCI ranged between one and a half to five times that of the general population; SMRs

were higher for complete versus incomplete lesions. We found pooled in-hospital mortality and 1-year survival rates of roughly 8 and 93%, respectively, although heterogeneity was present; some variation in mortality measures was explained by sub-group analyses according to the WHO region.

In-Hospital Mortality

In-hospital mortality rates among people with SCI varied greatly according to WHO region and country-income level, which suggests a strong influence of healthcare capacity on in-hospital mortality. In-hospital mortality is considered to be an outcome indicator directly related to the quality of clinical care, which is closely related to the income level of countries, explaining the higher mortality in low-income countries as compared to high-income countries. Inclusion of studies from lower-resourced countries for the calculation of a pooled in-hospital mortality estimate may also explain why this estimate exceeds first-year mortality that is indicated by the pooled 1-year survival estimate. The heterogeneity identified within the WHO region sub-groups of in-hospital mortality estimates could be in part due to more micro-related differences in WHO regions such as different models of healthcare systems; specifically, urban versus rural, for which previous research has found discrepancies in health equity, especially in the case of China [34]. Although China is not considered a high-income country, reported in-hospital mortality was among the lowest compared to all other countries, which might reflect data availability from higher resource areas, such as Shanghai, and similarly resourced populations from a university hospital in Tianjin, China, as well as non-purposeful exclusion of more severe cases which, as detailed in the manuscript, were likely transferred to hospitals in nearby Beijing due to better medical facilities [111]. It is likely that if regional, rural estimates were available, in-hospital mortality would be higher, reflecting rates similar to lower-resource countries.

Comparison within SCI

Mortality and longevity outcomes vary according to lesion characteristics. Risk of mortality was generally higher, while survival and longevity decreased with increasing severity and increasing lesion level [9, 51, 75, 84], supporting what was observed in the systematic review conducted by van den Berg et al. [8]. From this it can be assumed that specialized care (e.g. care provided by specialized centers of care for SCI), or more generally, care

focused on management of SCI-specific health conditions (e.g. respiratory functioning, urinary tract infections), is necessary, particularly for those individuals with high lesion levels and severity in order to assuage the current gap in survival and life expectancy within the SCI population [112]. For example, following a cervical SCI, respiratory complications emerge shortly after the injury due to paralysis of respiratory muscles; specialized care aimed at respiratory management has been proven effective in improving respiratory status [113, 114]. Variation existed in terms of the magnitude of gaps in mortality and longevity outcomes according to lesion characteristics; differences in access and level of care, as well as other non-clinical factors may influence inconsistencies between studies, such as referral pattern, admission criteria, and therapy intensity [115]. These differences could also be attributed in part to variation in study design. For example, Cao et al. excluded those individuals who died during hospitalization, right-censored all observations at the end of the study period in 2009, and had a follow-up duration of 11 years [37].

Comparison with the General Population

Individuals with SCI have consistently higher mortality rates as compared to the general population, with higher SMRs reported for tetraplegia as compared to paraplegia. The discrepancies between mortality rates of the general population and the SCI population can be related to SCI-specific conditions and causes of death. Exemplifying this is the study by Lidal et al., which reported much higher mortality rates among both males and females due to urogenital disease (SMRs = 21.9 and 23.4, respectively), while mortality rate of ischemic heart disease mimicked that of the general population (SMR = 0.9) [19]; this reflects the long-term consequences associated with SCI. Due to the variation in study characteristics (e.g. inclusion/exclusion criteria, male to female ratio, proportion tetraplegics, etc.), as well as the paucity of data, it should be noted that a decent amount of uncertainty exists around the pooled estimates calculated; uncertainty that cannot be completely explained by predefined sub-groups such as WHO region or income level [7, 37]. For example, one study conducted in Estonia has a disproportionately high SMR in comparison with the other included countries. However, Estonia has a lower socioeconomic status and 75% of the deaths that occurred within the study population were among people younger than 60 years – as the SMRs were calculated using a life table based on the entire European Union, this could cause the observed discrepancy in SMRs [7]. Finally, a

higher pooled estimate of SMR for tetraplegia reflects the consistent evidence of higher risk of mortality for tetraplegia as compared to paraplegia.

Strengths

Systematic reviews are methodologically rigorous and strive to provide the reader with an up-to-date accumulation of evidence with a limited amount of bias [116]. In addition, meta-analyses summarize data and can provide increased evidence regarding the strength and direction of estimates through increasing power, precision, and limiting bias. Efforts were made to extract as much information possible in an attempt to provide the most comprehensive meta-analysis possible. For the purpose of the study, we, for instance, derived confidence intervals when not reported, and extracted/digitized estimates from graphical display items. To account for potential study-level heterogeneity, meta-regression was used to examine sources of systematic variation that might account for variation between studies included in meta-analyses (i.e. ratio of paraplegia versus tetraplegia, male to female ratio, and average age). However, although heterogeneity remained, lending to a more conservative interpretation of meta-analyses, the meta-analyses provide an indication of the strength and direction of effect, which could nevertheless help inform interventions for prevention purposes. WHO regions and country income levels were used as macro-level variables in sub-group analyses to explain heterogeneity. We expect the use of WHO region and country income level to at least crudely capture unmeasured traits related to setting, as these are broad indicators of geographic and economic traits, healthcare capacity, cultural, and other potential unmeasured influencers on mortality and longevity. In addition, this systematic review and meta-analysis followed guidelines proposed by both MOOSE [117] as well as PRISMA guidelines [23] where possible.

Limitations

Reporting Issues

Lack of standardization makes it difficult to discern the differences between studies and to compare study results, potentially contributing to the variation observed in results; this issue has been previously underlined (<http://www.nature.com/sc/journal/v44/n9/pdf/3101893a.pdf>). Existing recommended guidelines for reporting on observational studies (STROBE), as well as guidelines specific to spinal cord injury literature (ISCOS) [118] are enforced by few journals in the field, and seldom adhered to by authors own account; this results in non-uniform

quality of reporting. Variation in reporting was evident when comparing studies, which could be due to a number of reasons including (but not limited to): different sample sizes, different inclusion/exclusion criteria, study population characteristics (e.g. majority tetraplegic or paraplegic, more young than old, etc.), and variation in etiology of SCI (e.g. NTSCI versus TSCI, which has been shown to influence risk of mortality) [7, 41, 57, 119]. It was virtually impossible to compare Kaplan-Meier curves of age as some studies reported in 10-year bands, others 5-year bands, and others old vs. young, etc. [7, 10, 19, 40, 60, 72, 73, 75–77, 84]. Also, many studies excluded individuals based on age, but there was no uniform exclusion criterion for age. Difficulties arose in comparability as studies often did not start follow-up at the same time after SCI, or excluded deaths occurring before 1-year, which could lead to an underestimation of, for example, the true estimate of SMR after SCI [9]. In addition, variation in definitions by authors of in-hospital mortality, or in documentation methods of in-hospital mortality, may contribute to the heterogeneity observed in calculated pooled estimates.

Data Quality

Pooled estimates are only as good as the data used to make them, and therefore, it is necessary to temper conclusions by referring to the reporting issues intrinsic within the SCI literature. Unfortunately, the meta-analyses reported in this study often included a limited number of studies, and generally included a large amount of heterogeneity that could not be explained by a priori determined factors (including: study size, mortality assessment). Therefore, we restricted our focus to those studies that reported comparable statistics, and relied on information reported in articles (i.e. we did not contact authors), both of which might induce selection bias. However, we were generally able to calculate the necessary statistics from data available within the paper with the exception of one study that reported SMRs but neither provided confidence intervals nor the expected number of deaths [90]. Inadequate reporting of censoring procedures in survival analyses, such as when follow-up started (left-censoring), ended (right-censoring) and attrition in particular, may lead to biased estimates in mortality ascertainment. For example, pre-hospital deaths were often excluded in analyses and information thereof was generally not collected; this could lead to case ascertainment bias and overestimate survival. When interpreting survival and the pooled estimate of 1-year survival, it is therefore important to note that the statistic represents one-

year survival after surviving the initial phase before hospitalization. In addition, the meta-regression and sub-group analyses did not completely explain the differences observed between in-hospital mortality estimates, indicating the involvement of additional factors that we are unable to control for, and which could be related to data collection, methodological issues (e.g. difference in definition of in-hospital mortality or other outcomes), or true differences. Unfortunately, data are not available that would allow investigation of these potential sources of heterogeneity.

Moving Forward

To identify issues on the global level regarding SCI, we need comparative analyses and an accumulation of evidence. Systematic evaluation of mortality and life expectancy data aimed at identifying real-world gaps in quality and/or access to critical care remains difficult as, within the field of SCI, there lacks uniformity in reporting; even after strongly voiced calls for standardization and adherence to quality control [22, 120]. Efforts aimed at improving quality of reporting, should follow the guidelines proposed by STROBE [27], and ISCOS [118]. A possible solution to limit future issues of comparison could be to access an individual-based meta-database including data from multiple sources. This would also allow for a meta-analysis on individual-level data instead of aggregate data, which has been cited to reduce the amount of bias and comparison issues often associated with meta-analyses, and would allow for global comparisons, identification of studies with overlapping participants, and incorporation of results from unpublished studies (<http://www.bmj.com/content/340/bmj.c221>). Some fields of research that include population-based registries include cancer and HIV research (<http://www.uicc.org/programmes/gicr/response>). In addition, due to the limited number of studies, especially in lower-resourced countries, more studies that more thoroughly cover further regions of the world are needed.

Summary

This review builds on previous narrative reviews and provides an update of available literature, while also adding a quantitative component allowing for the presentation of pooled outcomes related to mortality and longevity as well as for the investigation of the impact of contextual factors [8, 11, 22]. The variation in longevity and mortality outcomes established within the scope of this

systematic review and meta-analysis points toward the influence of demographic and lesion characteristics. The impact of contextual factors such as the capacity of the healthcare system including emergency and early response services is most evidently displayed within in-hospital survival data, which has recently contributed to a call by the WHO to improve health sector response to SCI [121]. Variation in mortality and longevity outcomes is of ethical concern, particularly the between-country variation, as it could indicate inequities in access to adequate healthcare. Reduction of inequities and discrepancies, both within the SCI population as well as compared to the general population, could be achieved through focused management of SCI-specific health issues. This review

demonstrates the reporting issues intrinsic within SCI literature, which make it difficult to combine summary measures. In addition, it underscores the necessity of a meta-database of individual patient data as it would help researchers when making global comparisons and would facilitate identification of potential drivers behind mortality and longevity. Finally, standardization of reporting requires more emphasis.

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References

- Brooks JC, Strauss DJ, Shavelle RM, Paculdo DR, Hammond FM, Harrison-Felix CL: Long-term disability and survival in traumatic brain injury: results from the national institute on disability and rehabilitation research model systems. *Arch Phys Med Rehabil* 2013; 94:2203–2209.
- Himanan L, Portin R, Hämäläinen P, Hurme S, Hiekkänen H, Tenovu O: Risk factors for reduced survival after traumatic brain injury: a 30-year follow-up study. *Brain Inj* 2011;25: 443–452.
- Forsgren L, Hauser WA, Olafsson E, Sander JW, Sillanpää M, Tomson T: Mortality of epilepsy in developed countries: a review. *Epilepsia* 2005;46(suppl 11):18–27.
- Diem-Zangerl A, Seppi K, Wenning GK, Trinka E, Ransmayr G, Oberaigner W, Poewe W: Mortality in Parkinson's disease: a 20-year follow-up study. *Mov Disord* 2009;24:819–825.
- Rodríguez-Antigüedad Zarranz A, Mendibe Bilbao M, Larena González C, Audicana C: Mortality and cause of death in multiple sclerosis: findings from a prospective population-based cohort in Bizkaia, Basque country, Spain. *Neuroepidemiology* 2014;42: 219–225.
- Ragonese P, Aridon P, Salemi G, D'Amelio M, Savettieri G: Mortality in multiple sclerosis: a review. *Eur J Neurol* 2008;15:123–127.
- Sabre L, Hagen EM, Rekand T, Asser T, Körv J: Traumatic spinal cord injury in two European countries: why the differences? *Eur J Neurol* 2013;20:293–299.
- van den Berg ME, Castellote JM, de Pedro-Cuesta J, Mahillo-Fernandez I: Survival after spinal cord injury: a systematic review. *J Neurotrauma* 2010;27:1517–1528.
- Middleton JW, Dayton A, Walsh J, Rutkowski SB, Leong G, Duong S: Life expectancy after spinal cord injury: a 50-year study. *Spinal Cord* 2012;50:803–811.
- Hagen EM, Lie SA, Rekand T, Gilhus NE, Grønning M: Mortality after traumatic spinal cord injury: 50 years of follow-up. *J Neurol Neurosurg Psychiatry* 2010;81:368–373.
- Hagen EM, Rekand T, Gilhus NE, Grønning M: Traumatic spinal cord injuries – incidence, mechanisms and course. *Tidsskr Nor Laegeforen* 2012;132:831–837.
- Furlan JC, Noonan V, Singh A, Fehlings MG: Assessment of impairment in patients with acute traumatic spinal cord injury: a systematic review of the literature. *J Neurotrauma* 2011;28:1445–1477.
- Furlan JC, Noonan V, Singh A, Fehlings MG: Assessment of disability in patients with acute traumatic spinal cord injury: a systematic review of the literature. *J Neurotrauma* 2011;28: 1413–1430.
- Capoor J, Stein AB: Aging with spinal cord injury. *Phys Med Rehabil Clin N Am* 2005;16: 129–161.
- Krause JS, Saunders LL: Health, secondary conditions, and life expectancy after spinal cord injury. *Arch Phys Med Rehabil* 2011;92: 1770–1775.
- Hitzig SL, Eng JJ, Miller WC, Sakakibara BM; SCIRE Research Team: An evidence-based review of aging of the body systems following spinal cord injury. *Spinal Cord* 2011;49:684–701.
- Dryden DM, Saunders LD, Rowe BH, May LA, Yiannakoulis N, Svenson LW, Schopflocher DP, Voaklander DC: Depression following traumatic spinal cord injury. *Neuroepidemiology* 2005;25:55–61.
- Findley PA, Banerjee R, Sambamoorthi U: Excess mortality associated with mental illness and substance use disorders among veteran clinic users with spinal cord injury. *Disabil Rehabil* 2011;33:1608–1615.
- Lidal IB, Snekkevik H, Aamodt G, Hjeltne N, Biering-Sørensen F, Stanghelle JK: Mortality after spinal cord injury in Norway. *J Rehabil Med* 2007;39:145–151.
- Krause JS, Saunders LL, Acuna J: Gainful employment and risk of mortality after spinal cord injury: effects beyond that of demographic, injury and socioeconomic factors. *Spinal Cord* 2012;50:784–788.
- World Health Organization: Constitution of the World Health Organization. *Am J Public Health Nations Health* 1946;36:1315–1323.
- WHO: International Perspectives on Spinal Cord Injury. Geneva, World Health Organization, 2013.
- Moher D, Liberati A, Tetzlaff J, Altman DG; The PRISMA Group: Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med* 2009; 6:e1000097.
- Huwaldt JA: Plot digitizer, 2010.
- Tierney JF, Stewart LA, Ghersi D, Burdett S, Sydes MR: Practical methods for incorporating summary time-to-event data into meta-analysis. *Trials* 2007;8:16.
- Tacconelli E: Systematic reviews: CRD's guidance for undertaking reviews in health care. *Lancet Infect Dis* 2010;10:226.
- von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP; STROBE Initiative: The strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. *PLoS Med* 2007; 4:e296.
- Dekkers OM, Egger M, Altman DG, Vandenbroucke JP: Distinguishing case series from cohort studies. *Ann Intern Med* 2012;156:37–40.
- DerSimonian R, Laird N: Meta-analyses in clinical trials. *Control Clin Trials* 1986;7:177–188.
- Barendregt JJ, Doi SA, Lee YY, Norman RE, Vos T: Meta-analysis of prevalence. *J Epidemiol Community Health* 2013;67:974–978.
- Higgins JP, Thompson SG, Deeks JJ, Altman DG: Measuring inconsistency in meta-analyses. *BMJ* 2003;327:557–560.

- 32 Definition of Region Groupings: Health Statistics and Information Systems. World Health Organization, 2013.
- 33 GDP (Current US\$): World Development Indicators. The World Bank, 2014.
- 34 Li Y, Dorsten L: Regional and urban/rural differences of public health in China. *Global J Health Sci* 2010;2:20–30.
- 35 Egger M, Davey Smith G, Schneider M, Mindes C: Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;315:629–634.
- 36 Cao Y, Krause JS, Dipiro N: Risk factors for mortality after spinal cord injury in the USA. *Spinal Cord* 2013;51:413–418.
- 37 Cao Y, Selassie AW, Krause JS: Risk of death after hospital discharge with traumatic spinal cord injury: a population-based analysis, 1998–2009. *Arch Phys Med Rehabil* 2013;94:1054–1061.
- 38 Claridge JA, Croce MA, Weinberg JA, Forsythe RM, Miller C, Fabian TC: The real predictors of disposition in patients with spinal cord injuries. *J Trauma* 2006;60:178–186.
- 39 Fassett DR, Harrop JS, Maltenfort M, Jeyamohan SB, Ratliff JD, Anderson DG, Hilibrand AS, Albert TJ, Vaccaro AR, Sharan AD: Mortality rates in geriatric patients with spinal cord injuries. *J Neurosurg Spine* 2007;7:277–281.
- 40 Frisbie JH: Anemia and hypoalbuminemia of chronic spinal cord injury: prevalence and prognostic significance. *Spinal Cord* 2010;48:566–569.
- 41 Garshick E, Kelley A, Cohen SA, Garrison A, Tun CG, Gagnon D, Brown R: A prospective assessment of mortality in chronic spinal cord injury. *Spinal Cord* 2005;43:408–416.
- 42 Greenwell MW, Mangold TM, Tolley EA, Wall BM: Kidney disease as a predictor of mortality in chronic spinal cord injury. *Am J Kidney Dis* 2007;49:383–393.
- 43 Guo Y, Young B, Palmer JL, Mun Y, Bruera E: Prognostic factors for survival in metastatic spinal cord compression: a retrospective study in a rehabilitation setting. *Am J Phys Med Rehabil* 2003;82:665–668.
- 44 Krause JS, Saunders LL: Risk of mortality and life expectancy after spinal cord injury: the role of health behaviors and participation. *Top Spinal Cord Inj Rehabil* 2010;16:53–60.
- 45 Krause JS, Saunders LL, DeVivo MJ: Income and risk of mortality after spinal cord injury. *Arch Phys Med Rehabil* 2011;92:339–345.
- 46 Krause JS, DeVivo MJ, Jackson AB: Health status, community integration, and economic risk factors for mortality after spinal cord injury. *Arch Phys Med Rehabil* 2004;85:1764–1773.
- 47 Macias CA, Rosengart MR, Puyana JC, Linde-Zwirble WT, Smith W, Peitzman AB, Angus DC: The effects of trauma center care, admission volume, and surgical volume on paralysis after traumatic spinal cord injury. *Ann Surg* 2009;249:10–17.
- 48 Mak KS, Lee LK, Mak RH, Wang S, Pile-Spellman J, Abraham JL, Prigerson HG, Balboni TA: Incidence and treatment patterns in hospitalizations for malignant spinal cord compression in the United States, 1998–2006. *Int J Radiat Oncol Biol Phys* 2011;80:824–831.
- 49 Martin ND, Marks JA, Donohue J, Giordano C, Cohen MJ, Weinstein MS: The mortality inflection point for age and acute cervical spinal cord injury. *J Trauma* 2011;71:380–385; discussion 385–386.
- 50 Pickelsimer E, Shiroma EJ, Wilson DA: Statewide investigation of medically attended adverse health conditions of persons with spinal cord injury. *J Spinal Cord Med* 2010;33:221–231.
- 51 Prusmack C, Rochman AS, Levi AD: The effect of age on survival following traumatic spinal cord injury. *Top Spinal Cord Inj Rehabil* 2006;12:49–57.
- 52 Saunders LL, Selassie AW, Hill EG, Nicholas JS, Varma AK, Lackland DT, Patel SJ: Traumatic spinal cord injury mortality, 1981–1998. *J Trauma* 2009;66:184–190.
- 53 Selassie AW, Varma A, Saunders LL, Well-daregay W: Determinants of in-hospital death after acute spinal cord injury: a population-based study. *Spinal Cord* 2013;51:48–54.
- 54 DeVivo MJ: Sir Ludwig Guttmann lecture: trends in spinal cord injury rehabilitation outcomes from model systems in the United States: 1973–2006. *Spinal Cord* 2007;45:713–721.
- 55 DeVivo MJ: Epidemiology of traumatic spinal cord injury: trends and future implications. *Spinal Cord* 2012;50:365–372.
- 56 Sokolowski MJ, Jackson AP, Haak MH, Meyer PR Jr, Sokolowski MS: Acute mortality and complications of cervical spine injuries in the elderly at a single tertiary care center. *J Spinal Disord Tech* 2007;20:352–356.
- 57 Strauss DJ, DeVivo MJ, Paculdo DR, Shavelle RM: Trends in life expectancy after spinal cord injury. *Arch Phys Med Rehabil* 2006;87:1079–1085.
- 58 Varma A, Hill EG, Nicholas J, Selassie A: Predictors of early mortality after traumatic spinal cord injury: a population-based study. *Spine (Phila Pa 1976)* 2010;35:778–783.
- 59 Shavelle RM, DeVivo MJ, Strauss DJ, Paculdo DR, Lammertse DP, Day SM: Long-term survival of persons ventilator dependent after spinal cord injury. *J Spinal Cord Med* 2006;29:511–519.
- 60 Shavelle RM, DeVivo MJ, Paculdo DR, Vogel LC, Strauss DJ: Long-term survival after childhood spinal cord injury. *J Spinal Cord Med* 2007;30(suppl 1):S48–S54.
- 61 Buechner JS, et al: Hospitalizations for spinal cord injuries, 1994–1998. *Med Health R I* 2000;83:92–93.
- 62 Boake M, Patil CG, Santarelli J, Ho C, Tian W, Lad SP: Laminectomy and fusion after spinal cord injury: national inpatient complications and outcomes. *J Neurotrauma* 2008;25:173–183.
- 63 Couris CM, Guilcher SJ, Munce SE, Fung K, Craven BC, Verrier M, Jaglal SB: Characteristics of adults with incident traumatic spinal cord injury in Ontario, Canada. *Spinal Cord* 2010;48:39–44.
- 64 Dryden DM, Saunders LD, Rowe BH, May LA, Yiannakoulis N, Svenson LW, Schopflocher DP, Voaklander DC: Utilization of health services following spinal cord injury: a 6-year follow-up study. *Spinal Cord* 2004;42:513–525.
- 65 Furlan JC, Kattail D, Fehlings MG: The impact of co-morbidities on age-related differences in mortality after acute traumatic spinal cord injury. *J Neurotrauma* 2009;26:1361–1367.
- 66 Furlan JC, Krassioukov AV, Fehlings MG: The effects of gender on clinical and neurological outcomes after acute cervical spinal cord injury. *J Neurotrauma* 2005;22:368–381.
- 67 Krassioukov AV, Furlan JC, Fehlings MG: Medical co-morbidities, secondary complications, and mortality in elderly with acute spinal cord injury. *J Neurotrauma* 2003;20:391–399.
- 68 Lenehan B, Street J, Kwon BK, Noonan V, Zhang H, Fisher CG, Dvorak MF: The epidemiology of traumatic spinal cord injury in British Columbia, Canada. *Spine (Phila Pa 1976)* 2012;37:321–329.
- 69 Loblaw DA, Laperriere NJ, Mackillop WJ: A population-based study of malignant spinal cord compression in Ontario. *Clin Oncol (R Coll Radiol)* 2003;15:211–217.
- 70 Pickett GE, Campos-Benitez M, Keller JL, Duggal N: Epidemiology of traumatic spinal cord injury in Canada. *Spine (Phila Pa 1976)* 2006;31:799–805.
- 71 Pirouzmand F: Epidemiological trends of spine and spinal cord injuries in the largest Canadian adult trauma center from 1986 to 2006. *J Neurosurg Spine* 2010;12:131–140.
- 72 Catz A, Thaleisnik M, Fishel B, Ronen J, Spasser R, Fredman B, Shabtay E, Gepstein R: Survival following spinal cord injury in Israel. *Spinal Cord* 2002;40:595–598.
- 73 Tchvaloon E, Front L, Gelernter I, Ronen J, Bluvshstein V, Catz A: Survival, neurological recovery and morbidity after spinal cord injuries following road accidents in Israel. *Spinal Cord* 2008;46:145–149.
- 74 Zeilig G, Dolev M, Weingarten H, Blumen N, Shemesh Y, Ohry A: Long-term morbidity and mortality after spinal cord injury: 50 years of follow-up. *Spinal Cord* 2000;38:563–566.
- 75 Ronen J, Goldin D, Bluvshstein V, Fishel B, Gelernter I, Catz A: Survival after nontraumatic spinal cord lesions in Israel. *Arch Phys Med Rehabil* 2004;85:1499–1502.
- 76 New PW, Epi MC: Influence of age and gender on rehabilitation outcomes in nontraumatic spinal cord injury. *J Spinal Cord Med* 2007;30:225–237.
- 77 O'Connor PJ: Survival after spinal cord injury in Australia. *Arch Phys Med Rehabil* 2005;86:37–47.
- 78 Soden RJ, Walsh J, Middleton JW, Craven ML, Rutkowski SB, Yeo JD: Causes of death after spinal cord injury. *Spinal Cord* 2000;38:604–610.

- 79 Espagnacq MF, Albert T, Boyer FC, Brouard N, Delcey M, Désert JF, Lamy M, Lemouel MA, Meslé F, Ravaut JF: Predictive factors of long-term mortality of persons with tetraplegic spinal cord injury: an 11-year French prospective study. *Spinal Cord* 2011; 49:728–735.
- 80 Lhéritier K, Ravaut JF, Desert JF, Pedelucq JP, O'Hanna F, Daures JP: [Survival of tetraplegic spinal cord injured persons after the first admission of a rehabilitation center and prognosis factors: a multicenter study of 697 subjects in French centers]. *Rev Epidemiol Sante Publique* 2001;49:449–458.
- 81 Seguin P, Godard A, Le Maguet P, Launey Y, Laviolle B, Mallédant Y: [Impact of age on mortality in patients with acute traumatic spinal cord injury requiring intensive care]. *Ann Fr Anesth Reanim* 2012;31:196–202.
- 82 Ahidjo KA, Olayinka SA, Ayokunle O, Mustapha AF, Sulaiman GA, Gbolahan AT: Pre-hospital transport of patients with spinal cord injury in Nigeria. *J Spinal Cord Med* 2011;34:308–311.
- 83 Augutis M, Levi R: Pediatric spinal cord injury in Sweden: incidence, etiology and outcome. *Spinal Cord* 2003;41:328–336.
- 84 Ahoniem E, Pohjolainen T, Kautiainen H: Survival after spinal cord injury in Finland. *J Rehabil Med* 2011;43:481–485.
- 85 Conway R, Graham J, Kidd J, Levack P; Scottish Cord Compression Group: What happens to people after malignant cord compression? Survival, function, quality of life, emotional well-being and place of care 1 month after diagnosis. *Clin Oncol (R Coll Radiol)* 2007;19:56–62.
- 86 Fatunde OJ, Lagunju IA, Adeniyi OF, Orimadegun AE: Non-traumatic paraplegia in Nigerian children presenting at the University College Hospital, Ibadan. *Afr J Med Med Sci* 2006;35:37–41.
- 87 Feng HY, Ning GZ, Feng SQ, Yu TQ, Zhou HX: Epidemiological profile of 239 traumatic spinal cord injury cases over a period of 12 years in Tianjin, China. *J Spinal Cord Med* 2011;34:388–394.
- 88 Fielingsdorf K, Dunn RN: Cervical spine injury outcome – a review of 101 cases treated in a tertiary referral unit. *S Afr Med J* 2007;97:203–207.
- 89 Gulati A, Yeo CJ, Cooney AD, McLean AN, Fraser MH, Allan DB: Functional outcome and discharge destination in elderly patients with spinal cord injuries. *Spinal Cord* 2011; 49:215–218.
- 90 Imai K, Kadowaki T, Aizawa Y: Standardized indices of mortality among persons with spinal cord injury: accelerated aging process. *Ind Health* 2004;42:213–218.
- 91 Knútsdóttir S, Thórisdóttir H, Sigvaldason K, Jónsson H Jr, Björnsson A, Ingvarsson P: Epidemiology of traumatic spinal cord injuries in Iceland from 1975 to 2009. *Spinal Cord* 2012;50:123–126.
- 92 Leal-Filho MB, Borges G, Almeida BR, Aguiar Ade A, Vieira MA, Dantas Kda S, Morais RK, Santos CR, Mendes Sde S, Pinheiro LM: Spinal cord injury: epidemiological study of 386 cases with emphasis on those patients admitted more than four hours after the trauma. *Arq Neuropsiquiatr* 2008;66:365–368.
- 93 Liang HW, Wang YH, Lin YN, Wang JD, Jang Y: Impact of age on the injury pattern and survival of people with cervical cord injuries. *Spinal Cord* 2001;39:375–380.
- 94 Neumann CR, Brasil AV, Albers F: Risk factors for mortality in traumatic cervical spinal cord injury: Brazilian data. *J Trauma* 2009; 67:67–70.
- 95 Pagliacci MC, Franceschini M, Di Clemente B, Agosti M, Spizzichino L; GISEM: A multicentre follow-up of clinical aspects of traumatic spinal cord injury. *Spinal Cord* 2007; 45:404–410.
- 96 Scovil CY, Ranabhat MK, Craighead IB, Wee J: Follow-up study of spinal cord injured patients after discharge from inpatient rehabilitation in Nepal in 2007. *Spinal Cord* 2012;50:232–237.
- 97 Shao J, Zhu W, Chen X, Jia L, Song D, Zhou X, Yan W, Zhang Y: Factors associated with early mortality after cervical spinal cord injury. *J Spinal Cord Med* 2011;34:555–562.
- 98 van Asbeck FW, Post MW, Pangalila RF: An epidemiological description of spinal cord injuries in the Netherlands in 1994. *Spinal Cord* 2000;38:420–424.
- 99 Gosselin RA, Coppotelli C: A follow-up study of patients with spinal cord injury in Sierra Leone. *Int Orthop* 2005;29:330–332.
- 100 Nwankwo OE, Katchy AU: Outcome of a 12-week programme for management of the spinal cord injured with participation of patient's relations at Hilltop Orthopaedic Hospital, Enugu, Nigeria. *Spinal Cord* 2003;41:129–133.
- 101 Nwadinigwe CU, et al: Traumatic spinal cord injuries (SCI): a study of 104 cases. *Niger J Med* 2004;13:161–165.
- 102 Pietraszkiewicz F, Tysiewicz-Dudek M: Epidemiology of spinal injuries in Lubuskie Province. *Ortop Traumatol Rehabil* 2010; 12:435–442.
- 103 Ning GZ, Yu TQ, Feng SQ, Zhou XH, Ban DX, Liu Y, Jiao XX: Epidemiology of traumatic spinal cord injury in Tianjin, China. *Spinal Cord* 2011;49:386–390.
- 104 Solagberu BA: Spinal cord injuries in Ilorin, Nigeria. *West Afr J Med* 2002;21:230–232.
- 105 Wu Q, Li YL, Ning GZ, Feng SQ, Chu TC, Li Y, Hao Y, Wu QL: Epidemiology of traumatic cervical spinal cord injury in Tianjin, China. *Spinal Cord* 2012;50:740–744.
- 106 Divanoglou A, Westgren N, Seiger A, Hulting C, Levi R: Late mortality during the first year after acute traumatic spinal cord injury: a prospective, population-based study. *J Spinal Cord Med* 2010;33:117–127.
- 107 Thietje R, Pouw MH, Schulz AP, Kienast B, Hirschfeld S: Mortality in patients with traumatic spinal cord injury: descriptive analysis of 62 deceased subjects. *J Spinal Cord Med* 2011;34:482–487.
- 108 Krause JS, Carter R, Zhai Y, Reed K: Psychologic factors and risk of mortality after spinal cord injury. *Arch Phys Med Rehabil* 2009; 90:628–633.
- 109 New PW, McFarlane CL: Survival following spinal cord infarction. *Spinal Cord* 2013;51:453–456.
- 110 Lieutaud T, Ndiaye A, Laumon B, Chiron M: Spinal cord injuries sustained in road crashes are not on the decrease in France: a study based on epidemiological trends. *J Neurotrauma* 2012;29:479–487.
- 111 Ning GZ, Yu TQ, Feng SQ, Zhou XH, Ban DX, Liu Y, Jiao XX: Epidemiology of traumatic spinal cord injury in Tianjin, China. *Spinal Cord* 2011;49:386–390.
- 112 Parent S, Barchi S, LeBreton M, Casha S, Fehlings MG: The impact of specialized centers of care for spinal cord injury on length of stay, complications, and mortality: a systematic review of the literature. *J Neurotrauma* 2011;28:1363–1370.
- 113 Wong SL, Shem K, Crew J: Specialized respiratory management for acute cervical spinal cord injury: a retrospective analysis. *Top Spinal Cord Inj Rehabil* 2012;18:283–290.
- 114 Berly M, Shem K: Respiratory management during the first five days after spinal cord injury. *J Spinal Cord Med* 2007;30:309–318.
- 115 New PW, Townson A, Scivoletto G, Post MW, Eriks-Hoogland I, Gupta A, Smith E, Reeves RK, Gill ZA: International comparison of the organisation of rehabilitation services and systems of care for patients with spinal cord injury. *Spinal Cord* 2013;51:33–39.
- 116 Mulrow CD: Rationale for systematic reviews. *BMJ* 1994;309:597–599.
- 117 Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, Moher D, Becker BJ, Sipe TA, Thacker SB: Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis of observational studies in epidemiology (MOOSE) group. *JAMA* 2000;283:2008–2012.
- 118 DeVivo MJ, Biering-Sørensen F, New P, Chen Y: International Spinal Cord Injury Data Set: Standardization of data analysis and reporting of results from the international spinal cord injury core data set. *Spinal Cord* 2011;49:596–599.
- 119 DeVivo MJ, Krause JS, Lammertse DP: Recent trends in mortality and causes of death among persons with spinal cord injury. *Arch Phys Med Rehabil* 1999;80:1411–1419.
- 120 Harvey LA: Improving the quality of systematic reviews in spinal cord. *Spinal Cord* 2013; 51:174–175.
- 121 WHO: International Perspectives on Spinal Cord Injury. Geneva, World Health Organization, 2013.