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EMPIRICAL CHALLENGES IN THE ECONOMIC EVALUATION OF HEALTH PROGRAMS USING QUANTITATIVE AND QUALITATIVE METHODS

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ABSTRACT

Economic evaluations are often used to assess the impacts of health programs or available technologies. However, less attention has been paid in the literature to how to obtain evidence to answer key questions such as the effectiveness, costs and long-term impact on health and quality of life, as well as the long-term impact on other healthcare uses. This thesis addresses three specific methodological challenges in economic evaluation and shows practical measures that may improve and enrich this field of research. The first challenge is one that commonly occurs in economic evaluation alongside clinical studies, namely how to deal with missing data. The advantages and the weaknesses of the available methods are explained in a synthetic and didactic way by using a case study and commenting on the on the suitability of each method. The second challenge that we addressed was how evidence for economic evaluation can be collected and synthesised in a systematic literature review. The case study focused on quantifying the costs, survival and quality of life of patients in the months and years following spinal cord injury. This review collected data from 67 longitudinal and cross-sectional studies from different countries. Heterogeneity between studies was addressed using tabulation, meta-analysis, meta-regression and graphical analyses. The third challenge we addressed was how to understand healthcare from the perspective of the patient or the user. We conducted a qualitative study to gather more in-depth evidence of factors influencing healthcare access and financing in a community of immigrants residing in Spain that are poorly understood by the host society. This study shows gaps in public health protections for migrants in Spain. The study also revealed the significance to this community of services of cultural importance, specifically options to seek care in their country-of-origin, access to traditional medicine, and burial in their country of origin. Likewise, this study was the first to provide an understanding of the

community-based insurance scheme autonomously developed by this population to finance healthcare.

RESUMEN

Las evaluaciones económicas a menudo se utilizan para la evaluación de los impactos de los programas de salud o las tecnologías disponibles. Sin embargo, en la literatura se ha prestado menos atención a cómo obtener la evidencia para responder a cuestiones claves cómo la efectividad, los costes e impacto a largo plazo en la salud y la calidad de vida, así como el impacto a largo plazo en otros usos de la atención médica. Esta tesis aborda tres desafíos metodológicos específicos en la evaluación económica y muestra medidas prácticas que pueden mejorar y enriquecer este campo de investigación. El primer desafío es uno que ocurre comúnmente en la evaluación económica junto con los estudios clínicos, a saber, cómo lidiar con los datos faltantes. Las ventajas y las debilidades de los métodos disponibles se explican de forma sintética y didáctica utilizando un caso de estudio y comentando la idoneidad de cada método. El segundo desafío que abordamos fue cómo recopilar y sintetizar evidencia para la evaluación económica en una revisión sistemática de la literatura. Este estudio se centró en cuantificar los costes, la supervivencia y la calidad de vida de los pacientes en los meses y años posteriores a la lesión medular. Esta revisión recopiló datos de 67 estudios longitudinales y transversales de diferentes países. La heterogeneidad entre los estudios se abordó mediante tabulación, metaanálisis, meta-regresión y análisis gráficos. El tercer reto que abordamos fue cómo entender la asistencia sanitaria desde la perspectiva del paciente o del usuario. Hemos llevado a cabo un estudio cualitativo para recopilar evidencia, de manera más amplia, de los factores que influyen en el acceso y la financiación de la atención médica en una comunidad de inmigrantes residentes en España que son poco conocidos por la sociedad de acogida. Este estudio muestra lagunas en la protección de la salud pública para los inmigrantes en España. El estudio también reveló la importancia cultural de estos servicios comunitarios, en particular las

opciones para buscar atención medica en su país de origen, acceso a medicina tradicional y entierro en su país de origen. Asimismo, este estudio fue el primero en proporcionar una comprensión del esquema de seguro comunitario desarrollado, de manera autónoma, por esta población para financiar la atención en salud.

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CHAPTER I. INTRODUCTION

Due to advances and change in health policies or available technology, economic evaluations are often used to define the overall cost-effectiveness of a new health program or technology compared to other alternative(s) in order to provide the necessary information for an efficient decision on the use of society's resources (Drummond et al., 1998). Economic evaluation is a process related to cost-benefit analysis that allows explicit ordering of available information, objectifying value judgments as far as possible, to help establish priorities and make a comparative choice between alternative actions. This branch of "health economics" has allowed the development of a whole current of research that consists of identifying, measuring, valuing, and comparing the costs and consequences of the alternatives studied (A. Briggs et al., 2006; Drummond et al., 1998).

Identification of outcomes (costs and consequences) of interventions needs evidence that addresses four key questions:

i) Is the intervention effective?

ii) What is the long-term impact on quality of life or survival?

iii) What resources does the intervention require and what are the costs of those resources?

iv) What is the long-term impact on use of other healthcare (for example, in terms of adverse effects of treatment or preventing recurrence of disease)?

These four questions can be thought of as equivalent to a “microeconomic” analysis of the intervention. In economic evaluation, for pragmatic reasons, these questions are usually considered from the clinical or healthcare provider’s perspective, without taking account of the wider institutional context in which healthcare is provided and consumed, nor taking account of broader influences on public health - demographic, economic, behavioural and cultural

(Culyer & Maynard, 1997; Solar & Irwin, 2010) or the perceptions and motivations of the actors involved (see Figure 1.1).

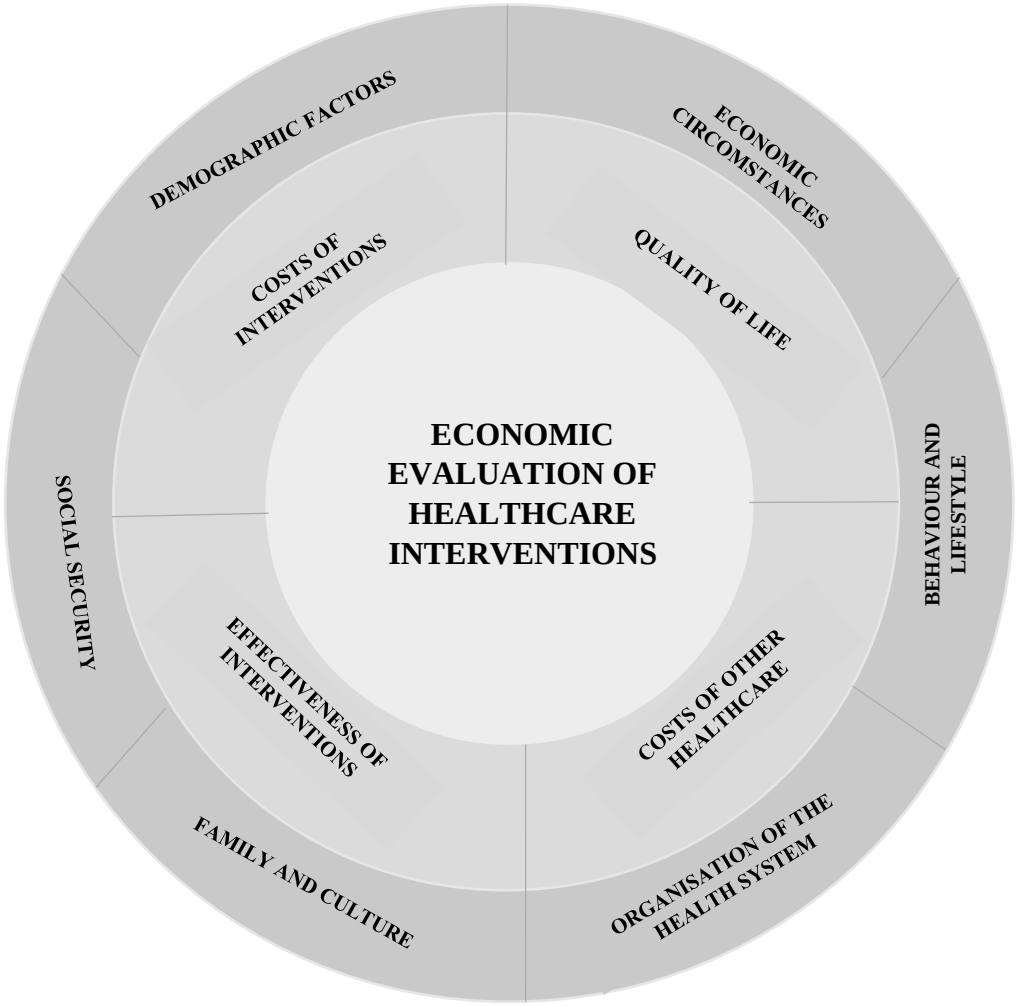


Figure 1.1 Factors associated with costs of healthcare and health outcomes

A micro-economic analysis of an intervention is typically a quantitative exercise in measuring the resources used in an intervention and the healthcare outcomes and then valuing those items from the provider's perspective. A societal analysis aims to take a wider perspective, taking account of impacts of an intervention on other sectors of society, such as family and employers. Nevertheless, even when economic evaluations take a societal perspective, the usual approach

is limited to quantitative data from surveys or questionnaires, for example, to estimate the number of days lost from employment. Health economists are increasing aware of the value of qualitative methods, to obtain a richer understanding of the perspective of those involved and affected (Coast 2017). This thesis includes examples of both types of empirical analysis (quantitative and qualitative), and focuses on some of the specific challenges for researchers wishing to use these methods.

Evidence for economic evaluation about the effectiveness of interventions is generally drawn from randomised clinical trials (RCT). RCTs are prospective studies that measure the effectiveness of a new intervention or treatment. Participants are randomly assigned to two (or more) groups and the outcomes are measured at specific times and any difference in response between the groups is assessed statistically (NICE, 2022; Tarnow-Mordi et al., 2017). An example of RCT is the Early Venous Reflux Ablation (EVRA) ulcer trial (Davies et al., 2017) (recently completed) - which aimed to assess the clinical and cost effectiveness of early endovenous treatment of superficial venous reflux compared to standard care alone in patients with chronic venous ulceration - or the ongoing PAPAARTIS clinical trial (Petroff et al., 2019) which tests the hypothesis that minimally invasive staged segmental artery coil embolisation can greatly reduce the incidence of ischaemic spinal cord injury (SCI) and mortality compared with standard open surgical or endovascular thoracoabdominal aneurysm repair alone.

There are well established protocols for conducting RCTs in a clinical setting (Akobeng, 2005; Tetzlaff et al., 2012). The second chapter in this thesis addresses a common methodological challenge the economic analysis of clinical studies ("within-trial" cost-effectiveness analysis, CEA), which is how to handle missing data. Missing data occur frequently in RCTs because

patients may be lost to follow-up, questionnaires may be lost or unreturned and responses to individual questionnaire items may be illegible, nonsensical or non-existent (Trials, 2010). This is a concern in within-trial CEAs because costs or health outcomes in individuals with missing data may be systematically different from those with fully observed information. Therefore, handling missing data inappropriately can bias the results, make inefficient use of the data available and ultimately mislead resource allocation decisions. In this chapter, we address a quantitative economic analysis of a RCT with missing data. We compared six different methods: complete case-analysis (CCA), multiple imputation by linear regression (MILR), multiple imputation by predictive mean matching (MIPMM), repeated measure mixed model (RMM) also known as random effect, repeated measure fixed effect (RMFE), and a Bayesian parametric approach (BPA) using the selection model in the R package missingHE for handling missing data, using a case study of EVRA trial. The study had a considerable amount of missing data arising from staggered recruitment, which means that the dataset was an unbalanced panel. The main advance of this chapter consists of explaining in a synthetic and didactic way the advantages and weaknesses of the available methods to handle missing data, and commenting on the suitability of each one.

If more than one RCT has evaluated the same intervention, one can conduct a systematic review (SR). SRs can identify broad trends in the data from diverse sources, bring together evidence about components and drivers of variation in outcomes. Synthesis of findings can be done qualitatively by a narrative synthesis. However, when the number of studies reviewed is high a narrative synthesis may be frustrating. Meta-analysis (MA) is a quantitative technique that combines the varied results together to get an overall impression about what the results from

all of the studies are saying and to get a single pooled result of how much a treatment is beneficial. Also, MA can help to test and confirm hypotheses about heterogeneity.

SR and meta-analysis of the results are recommended for the evaluation of the clinical effectiveness of interventions, and there are well-established methods and techniques available using random or fixed effect model (DiGuiseppi et al., 2001; Epstein et al., 2022). However, less attention has been given in the literature to how evidence should be obtained and synthesised to answer the other three key questions for economic evaluation: the costs of interventions, the long-term impact on health and quality of life, and the long-term impact on other use of healthcare. The third chapter of this thesis tackles some of the particular challenges of SR and quantitative synthesis of these kinds of data. This chapter investigated the costs following SCI in adults and the quality of life (QoL). This work aimed to inform the economic evaluation of the PAPAARTIS trial (Petroff et al., 2019) . Patients with thoracic abdominal aneurysms need an urgent surgical procedure that can save their life, but also carries a high risk of leaving them with SCI and possibly paraplegia or tetraplegia. Thus, to assess the benefit/risk profile of the procedure, it is essential to know and, if possible, quantify the impact of SCI on the quality of life of the patient and society in general. Surprisingly, so far there has been no SR on this topic.

The SR of these variables (long term costs and quality of life) in this population (people with SCI) raises a number of challenges for the investigator which are not present in the same degree in SR of clinical variables. The first challenge is the diversity of designs of studies conducted in these patients. Broadly, two types of primary study (that collect data from individuals) are prevalent in this area: cross sectional surveys, and longitudinal cohort studies. Cross sectional surveys can explore associations between variables, but comparisons may be confounded by

unobserved factors, and these studies cannot make any statements about cause and effect. Prospective longitudinal studies can show trends over time and can control to some extent for observed and unobserved variables at baseline but may be confounded by unobserved factors that change over time. Hence, we were careful to conduct separate analyses depending on the study design. The second challenge was the considerable diversity of patient types, outcome measures, time horizons and other factors that influence estimates of costs and quality of life and can confound attempts to synthesise these data. Hence, we were careful to filter studies for inclusion to increase the degree of homogeneity (for example, limiting quality of life measures to EQ-5D and SF-36) and to attempt to control for confounding variables where possible employing a variety of methods (tabulation, graphical analysis, meta-analysis and meta-regression).

When it comes to finding evidence about broader influences on health such as individual circumstances or perception, family, culture, etc. the quantitative approach (e.g., based on surveys or questionnaires) may be limited (Creswell et al., 2007) and a qualitative approach would be more appropriate (Coast, 2017). Qualitative research is an approach for exploring and understanding the meaning that individuals or groups attribute to social or human problem. The process of qualitative research involves emerging questions and procedure, data typically collected in the participants setting, data analysis inductively from particulars to general themes and the researcher making interpretation of the meaning of data. The fourth chapter carries out a qualitative analysis to understand the access to healthcare by a very marginalized group in Spain and exploring for the first time the role of a particular class of informal collective healthcare financing known as tontine. In Spain, the restrictions of Real Decreto Ley 16/2012

contributed to increased socioeconomic inequality, lower use of planned healthcare, lower levels of health and a higher mortality rate in the undocumented migrant community (Devillanova & Frattini, 2016; Jiménez-Rubio & Vall Castelló, 2020; Juanmarti Mestres et al., 2018; Lopez-Valcarcel & Barber, 2017). Thus, the condition of migrants is an axis of inequality defined by their own status in society, constituted by restrictions in health access, limitations in access to the labour market, cultural differences, and other structural factors on which their living conditions depend. Numerous studies analyse the condition of the immigrant population(Cottini et al., 2020; Hernández-Quevedo & Jiménez-Rubio, 2009; Jiménez-Rubio & Hernández-Quevedo, 2011). However, data often comes from national surveys, in which undocumented immigrants are under-represented or unidentified, and data on the use and funding of health access by undocumented immigrants is lacking. In sub-Saharan Africa, tontines - also known as rotating savings and credit associations (ROSCAs) - have established themselves as strong financial structures, operating autonomously and informally (lacking state or legal regulation) in parallel with the formal sector. Its members present themselves as a mediator between agents who alternatively have the capacity and need for financing. Therefore, their ability to assume the social protection of their members differentiates them from the formal sector (Kounou et al., 2013). In Spain, many immigrant communities use tontines "adapted" to a common and defined purpose: Help each other to healthcare access, taking much more into account people without resources, who may contribute less or even be exempt from contributing, in certain cases. However, the functioning of tontines in the migratory context has not received enough attention in the literature. In this chapter we analyse its use as a resource to access health services, which is a new topic. The qualitative methodology has been chosen, since it allows us to approach new social phenomena and social realities characterized by processes of change. This work

contributes to the literature by providing evidence on the healthcare use and financing of healthcare access in an underrepresented community.

CHAPTER II. COMPARING METHODS FOR HANDLING MISSING COST AND QUALITY OF LIFE DATA IN THE EARLY ENDOVENOUS ABLATION IN VENOUS ULCERATION TRIAL

ABSTRACT

OBJECTIVES: This study compares methods for handling missing data to conduct cost-effectiveness analysis in the context of a clinical study.

METHODS: Patients in the Early Endovenous Ablation in Venous Ulceration (EVRA) trial had between 1 year and 5.5 years (median 3 years) of follow-up under early or deferred endovenous ablation. This study compares Complete-Case-Analysis (CCA), multiple imputation using linear regression (MILR) and using predictive mean matching (MIPMM), Bayesian parametric approach using the R package missingHE (BPA), repeated measures fixed effect (RMFE) and repeated measures mixed model (RMM). The outcomes were total mean costs and total mean quality-adjusted life years (QALYs) at different time horizons (1 year, 3 years and 5 years).

RESULTS: All methods found no statistically significant difference in cost at the 5% level in all time horizons, and all methods found statistically significantly greater mean QALY at year 1. By year 3, only BPA showed a statistically significant difference in QALY between treatments. Standard errors differed substantially between the methods employed.

CONCLUSION: CCA can be biased if data are MAR and is wasteful of the data. Hence the results for CCA are likely to be inaccurate. Other methods coincide in suggesting that early intervention is cost-effective at a threshold of £30,000 per QALY 1, 3 and 5 years. However, the variation in the results across the methods does generate some additional methodological uncertainty, underlining the importance of conducting sensitivity analyses using alternative approaches.

KEYWORDS

Longitudinal missing outcome, repeated measure, mixed model, fixed effect, multiple imputation, complete-case-analysis, Bayesian parametric approach, cost-effectiveness analysis

2.1 INTRODUCTION

Missing data occurs when one or all variables are missing for a given subject. This often occurs in longitudinal studies and can particularly be a problem in within-study cost-effectiveness analysis (CEA) because accurate estimates of total mean cost and quality-adjusted life years require full data to be collected on each subject at each follow-up time point (Faria et al., 2014; Fitzmaurice et al., 2011; Myers, 2000).

This study compares six different methods for handling missing data in a cost-effectiveness analysis comparing early endovenous ablation versus delayed ablation for venous leg ulcer treatment (Gohel et al., 2020). The original cost-effectiveness analysis employed a repeated measure mixed model (RMM), and reported mean total cost of –£155 (95% CI, –£1262 to £953) and mean total QALY of 0.073 (95% CI, –0.06 to 0.20) at 3 years (Gohel et al., 2020). RMM has been shown to have acceptable properties in simulation studies (Gabrio et al., 2021). However, as missing data are always unknown, it is recommended to conduct sensitivity analyses to see how robust the results are to alternative methods, and this is the primary aim of this paper (Faria et al., 2014). This work is unable to demonstrate which approach is "correct" because we do not know the values of the missing data. Nevertheless, this paper provides an interesting case study of "revisional research" in health economics (Laxy et al., 2017), in which the original findings are challenged by employing more extensive methods to assess modelling uncertainty. The methods outlined in this paper may also be useful more generally to investigators wishing to explore the different ways that missing data approaches can be implemented with standard statistical software (STATA or R).

Due to the design of the trial, there was very low loss to follow-up, but considerable item missingness (see Methods: Data). There are several ways in which the chosen missing data approach might influence the results: different subjects used in the analysis, different number of observations used per subject, different statistical models of the missing data mechanism and the latent correlation between observed and missing observations, or different estimation model to estimate total mean costs and QALYs and the correlation between them (Gomes et al., 2013; Groenwold et al., 2014). This paper addresses this challenge using six alternative methods: complete case-analysis (CCA) (Carroll et al., 2020; Leurent et al., 2018; Manca & Palmer, 2005), multiple imputation by linear regression (MILR), multiple imputation by predictive mean matching (MIPMM) (Hayati Rezvan et al., 2015; Leurent et al., 2018; Manca & Palmer, 2005; White et al., 2011), repeated measure mixed model (RMM) also known as random effect, repeated measure fixed effect (RMFE) (Cox et al., 2020), and a Bayesian parametric approach (BPA) using the **selection** model in the R package **missingHE** (Z. Ma & Chen, 2018). All methods assume data are Missing Completely at Random, given covariates (CD-MCAR) or Missing at Random (MAR). Under CD-MCAR, the probability that data are missing only depends on observed baseline covariates, and under MAR, the probability depends only on values of observed outcome data and baseline covariates (Faria et al., 2014). The package **missingHE** also provides models to explore missing not at random (MNAR) situations but this is not considered here (Gabrio et al., 2021). Results are estimated over different time horizons (and hence with different quantities of missing data) of 1, 3 and 5 years. In each case we calculate the mean incremental total cost and QALY, standard errors, the incremental cost-effectiveness ratio (ICER) and the cost-effectiveness acceptability curve (CEAC). The focus in this paper is on alternative statistical methods for handling missing data. We do not explore other sources of

modelling uncertainty, such as use of different sets of covariates to make predictions or alternative statistical distributions of dependent variables (Hoch, 2008; Kreif et al., 2013).

2.2 METHODS

2.2.1 Data

The Early Endovenous Ablation in Venous Ulceration (EVRA) randomised clinical trial evaluated the cost-effectiveness of early versus deferred endovenous ablation to treat venous leg ulcers. The trial methods and patients are described elsewhere (Gohel et al., 2020). Briefly, resource use items in hospital, primary and community care and medications related to the treatment of venous ulceration, adverse events or complications were collected by case note review and questionnaires completed at baseline and monthly thereafter up to one year, plus one further telephone follow up between October 2018 and March 2019.

The baseline covariates included in all the estimation models were: *TREAT* is treatment randomised ("early" coded as 1 or "delayed" coded as zero). The variable $WEEK_t$ is the time variable (coded as a set of categorical (dummy or factor) variables) representing the week after randomisation at which data are observed, from t=0 (baseline) to t=16 (week 260). *SIZE, AGE* and *DURATION* are the ulcer size(cm^2), subject's age (years) and length of time with ulcer (years), respectively, measured at baseline and centred at the means. SITE was coded as a factor variable.

Each item of resource use was multiplied by UK unit costs obtained from published literature, NHS reference costs, and manufacturers' list prices to calculate overall costs within each of these categories for each patient (Gohel et al., 2020). The costs for each individual over their follow-up (from randomization to date of censoring for that individual) were assigned or

apportioned into discrete time periods, that corresponded to 12 monthly periods during the first year (as follow-ups were monthly) and then yearly periods thereafter. This allowed discounting to be applied (3.5% per year), and facilitated analysis using the MI and mixed model in long format (see below).

EQ-5D-5L was collected at baseline, 6 weeks, 6 months, 12 months, plus one further telephone follow up between October 2018 and March 2019, and a utility index was calculated at each time point using a published tariff (van Hout et al., 2012). SF-36 was also administered but only up to one year, so was not used in this paper.

Patients who died during the study were assigned zero costs and HRQOL thereafter. Code and example data are available in the Supplementary data, http://dx.doi.org/10.17632/j8fmdwd4jp.6.

2.2.2 Missing data

Due to rigorous trial design and conduct procedures (Mason et al., 2018), there were very few withdrawals or failures to complete questionnaires as planned in the study (see Supplementary Material table S5). Nevertheless, data are incomplete in this study for two reasons. First, recruitment of the 450 patients into the clinical study across the 20 vascular centres took place between October 2013 and September 2016. The study finalised on March 2019. This "staggered" recruitment into the trial meant that patients had a minimum of 1 years of follow-up and a maximum of 5.5 years (median 3 years).

Second, all patients had regular and periodically scheduled follow-up during the first year after recruitment, but to keep the cost of the research study low, only one further telephone follow-up per patient was conducted. This took place between October 2018 and March 2019. Figure

2.1 shows how this study design influences the missing data pattern. A patient recruited in 2014 will have complete follow-up during the first year, missing data at years 2, 3 and 4, and one follow-up at 5 years (patient A). A patient recruited in 2015 will have complete follow-up during the first year, missing data at years 2 and 3, one follow-up at year 4, and missing data for year 5. A patient recruited in 2016 (patient C) will have complete follow-up during the first year, missing data at year 2, one follow-up at year 3, and missing data for years 4 and 5. This mainly affected collection of EQ-5D, because in the absence of telephone questionnaire data, most types of resource use and clinical outcomes could be obtained from case-notes.

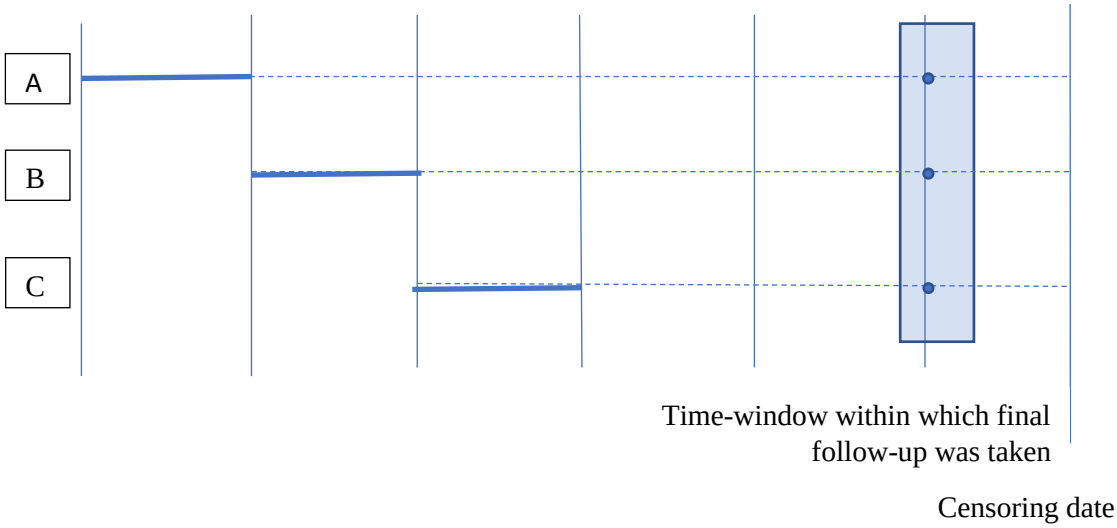


Figure 2.2 Schematic relation between recruitment date and missing data pattern for 3 hypothetical patients

The pattern of missingness was examined using descriptive statistics and via the linear logistic model of indicators of missing cost and EQ-5D data on treatment allocation and a selection of baseline variables. (Equation 2.1) (Faria et al., 2014).

$$logit(\pi_{it}) = \gamma_1 TREAT_i + \gamma_2 DURATION_i + \gamma_3 AGE_i + \gamma_4 SIZE_i + \gamma_5 Site_i + \gamma_6 WEEK_t \quad (2.1)$$

where π denotes the probability that an observation is missing in individual *i* at time *t*.

Cost-effectiveness analysis was conducted using aggregated data - CCA and BPA - and disaggregated (longitudinal) data - MI, RMM and RMFE. Table 2.1 summarises the approaches. Further details are also given in the Supplementary materials.

	RMM & RMFE	CCA	MILR & MIPMM	BPA
Number of patients included at 3 years	450	44	450	450
Total number of non-missing observations included at 3 years†	1,929 EQ-5D, 6,861 period costs	44 total costs, 44 QALY	450 EQ-5D, 450 period costs	377 total costs, 44 QALY
Format of data as input	Longitudinal	Aggregate	Longitudinal	Aggregate
Statistical model of the missing data	Implicit imputation of missing EQ-5D and period costs	None	Explicit imputation of missing EQ-5D and period costs	Logit model of probability of missingness
How are total costs and QALY over the desired time horizon predicted at individual level?	Not necessary	Not done	Passively in each imputed dataset	Missing total cost & QALY are parameters to estimate
How are mean total incremental costs and QALY over the desired time horizon estimated	Weighted sum of EQ5D and period cost coefficients estimated in the statistical model	Bivariate normal regression	Bivariate normal regression for each imputed dataset, synthesised using Rubin's rules	Bivariate normal regression
Estimation of standard errors and CEAC	Bootstrap	Parametrically	Parametrically	Parametrically

† If aggregate data are used, there will be one observation per patient. If longitudinal data are used, the inputs to the model may consist of several observations per patient. RMM. repeated measure mixed model; RMFE. repeated measure fixed effect; CCA. complete-case-analysis; MIPMM. Multiple Imputation using predictive mean matching; MILR. Multiple Imputation using linear regression; BPA. Bayesian parametric approach

Table 2.1 Overview of approaches employed to handle missing data.

2.2.3 Repeated measure: mixed model and fixed effect

The effects of the events on the HRQOL and costs were computed using repeated measures regression model with the differences between subjects (ς_i) modelled as a random effect (RMM) or fixed effects (RMFE) (equation 2.2). The RMFE method eliminates unobserved time-invariant confounders without imposing any additional assumptions on ς_i. The RMM

method assumes that unobserved heterogeneity ζ_i is not correlated with other controls (Kennedy, 2008).

$$Y_{it} = \beta_0 + \beta_1 TREAT_i + \beta_2 DURATION_i + \beta_3 AGE_i + \beta_4 SIZE_i + \beta_5 Site_i + \beta_6 WEEK_t + \delta TREAT_i * WEEK_t + \zeta_i + \epsilon_{it} \quad (2.2)$$

Y_{it} is the outcome variable (one model for costs during each period *t* and another for EQ-5D tariff at the end of each period *t*) for each subject *i* at time point *t.* Hence for the model where the dependent variable is cost, Y_{i0} is set to be zero for all subjects, Y_{i1} is the cost for patient *i* during the first 4 weeks Y_{i2} is the cost between the 4th and the 8th week, and so on up to Y_{i12} (week 52). After that, the periods are set to be yearly, so that Y_{i13} is the cost between week 52 and week 104 (year 2), and so on up to Y_{i16} (year 5 or week 260). ζ_i is the random deviation of subject *i*'s mean costs or EQ-5D tariff from the overall mean β_0 and ϵ_{it}, often called within-subject residual across time, is the random deviation of Y_{it} from subject *i*'s mean costs or EQ-5D tariff (Monsalves et al., 2020; Rabe-Hesketh, 2008). Y_i is the outcome variable for each subject *i.*

In RMM and RMFE estimates of the $\hat{\delta}$ are a (vector of) coefficients for the interactions between treatment assignment and period number and hence represents the mean incremental cost of early treatment (versus delayed) during period t (in the cost model) or the mean incremental EQ-5D tariff at follow-up time point t (in the EQ-5D model). These analyses were implemented using the **mixed** and **xtreg** command in STATA 15. To estimate total mean incremental cost per patient over a desired time horizon (e.g., 3 years), the relevant period coefficients are simply added up (**lincom**). Thus, for example, where the dependent variable is cost accrued during the preceding period, and $\hat{\delta}_1$ is the time-treatment interaction coefficient at 4 weeks (~month 1),

$\hat{\delta}_2$ at 8 weeks (~month 2), and $\hat{\delta}_3$ at 13 weeks (month 3), then the difference in total mean incremental cost over the first 3 months is $\hat{\delta}_1 + \hat{\delta}_2 + \hat{\delta}_3$. To estimate mean total incremental QALY over a given time horizon, the "area under the curve" applying the trapezium rule is calculated. Hence, using the coefficients from the EQ-5D model over the first 3 months (where $\hat{\beta}_1$ is the difference in EQ-5D at baseline, $\hat{\delta}_1$ at 4 weeks and $\hat{\delta}_2$ at 3 months), the estimated mean total incremental QALY over the first 3 months would be $0.5 * ((\beta_1 + \hat{\delta}_1) * \frac{4}{52} + (\hat{\delta}_1 + \hat{\delta}_2) * \frac{9}{52}$).

Uncertainty was estimated by bootstrapping incremental mean costs and QALYs (A. H. Briggs et al., 1997) and shown by the cost-effectiveness acceptability curve (CEAC). The bootstrap is used here because in the RMFE and RMM approaches, we run separate regressions for period costs and EQ-5D. In the MI, BPA and CCA approaches, we are able to analytically calculate the variance -covariance matrix using a joint regression of total costs and total QALY (assuming a bivariate normal distribution of the dependent variables) and so could estimate the CEAC parametrically. In the case of the RMM and RMFE models, this option is not available and so the bootstrap presents a pragmatic, numerical solution to this problem.

2.2.4 Multiple imputation

We implemented MI using 3 steps. Firstly (van Buuren, 2018), M imputations (completed datasets) were generated under an imputation model replacing missing values with "plausible" substitutes, based on distribution of the observed data using linear regression (MILR) and predictive mean matching (PMM). The variables included in the imputation models for costs and EQ-5D were treatment, age, duration, site, ulcer size, ethnicity, diabetes, history of deep vein thrombosis, trial leg and eq5d at baseline (Schafer, 2000).

This step was performed by multivariate imputation by chained equation (MICE) (also known as fully conditional specification (FCS) (van Buuren et al., 1999) or sequential regression multivariate imputation (Raghunathan et al., 2000)) which is a practical approach to generating imputations based on a set of inter-linked imputation models. The process using MILR begins by choosing the first variable to impute, say costs in the first period (Y_1). Values for all other variables (both EQ5D at each follow up and period costs) to be imputed were then filled in using a simple rule (simple random sampling with replacement from the observed values). Then, Y_1 was regressed on all other variables and baseline covariates, and then missing values for Y_1 were replaced by simulated draws from the corresponding posterior predictive distribution of Y_1. Then, the process was repeated for the next variable (e.g., Y_2), which was regressed on all other variables and using the newly imputed values in Y_1. Again, missing values in Y_2 were replaced by draws from the posterior predictive distribution of Y_2. The process was repeated for all other variables with missing values in turn: this is called a cycle. In order to stabilize the results, the procedure was repeated for 20 cycles to produce a single imputed data set, and the whole procedure was repeated M times to give M imputed data sets (Bartlett et al., 2015; Bartlett & Morris, 2015; Royston, 2005; van Buuren, 2007).

A second method for MI, predictive mean matching (PMM) was also used. PMM is an ad hoc method of imputing missing values which combines the standard linear regression and the closest-neighbour imputation approaches. For each missing value Y_i with covariates X_i, PMM identify k individual with the nearest value of observed Y_i – It uses the linear predictions as a distance measure to form the set of the nearest neighbours (suitable "donor") consisting of the complete value –, it then randomly draws an imputed value from this set. By drawing from the observed data, PMM preserves the distribution of the observed values in the missing part of the

data which makes it more robust than the fully parametric linear approach (Little, 2020). Possible donors were set with 10 closest neighbours as suggested in Morris et al., (Morris et al., 2014).

Step 2 was to perform M=40 imputations (Bodner, 2008), and finally, step 3, the results obtained from the 40 completed-data analyses were combined into a single multiple-imputation result using Rubin's rules (Asch et al., 2015). Analyses were implemented using the **mi** suite of commands in STATA 15.

Monte Carlo Errors (MCE) and the fraction of missing information (FMI) were calculated to indicate the stability of the model. FMI and MCE reflect the variability of MI results across repeated uses of the same imputation procedure and are useful for determining an adequate number of imputations to obtain stable MI results (White et al., 2011).

For each of the m complete datasets, total cost and total QALY over 1 year, 3 years and 5 years for each subject were imputed passively using the same formulas given in the section for repeated measures. The difference between repeated measures and MI being that in the RMM and RMFE approaches, estimates of total mean cost and QALY for the group as a whole were made by linear combination (**lincom**) of the coefficients, while MI imputes a total cost and QALY for each subject, and then proceeds to estimate mean incremental cost and QALYs for the group as a whole using bivariate normal regression (**sureg** in STATA 15). Coefficients from this regression were then combined across the multiple imputed datasets using Rubin's rules (**mi estimate**) [34]. The bootstrap was not used with MI as this can be complex and time-consuming (Brand et al., 2019). Instead, the CEAC was calculated parametrically from the coefficients and covariance matrix of the bivariate normal regression.

2.2.5 Complete case analysis

Total cost and total QALY were calculated for each individual *i* over the relevant time horizon T (1, 3 or 5 years) (Equation 2.3). Any subject with a missing period cost or EQ-5D in one the relevant time horizon was dropped (as total cost and total QALY for individual i at time T cannot be calculated if any period costs or EQ-5D values up to T are missing). A bivariate normal regression was performed at each time horizon for total costs and total QALY (equation 3), where Y_i is a (cost, QALY) pair for individual i. The CEAC was calculated using the bootstrap (parametric estimates were also tried and made no noticeable difference to the results so are not reported).

$$Y_i = \beta_0 + \beta_1 eq5d0_i + \beta_2 TREAT_i + \beta_3 DURATION_i + \beta_4 AGE_i + \beta_5 SIZE_i + \beta_6 SITE_i + \varepsilon_i \quad (2.3)$$

2.2.6 Bayesian parametric approach (BPA)

The dataset for BPA consists of total observed cost and total observed QALY for each individual over the time period of interest (1, 3 or 5 years), along with baseline control variables. Hence one total cost and one total QALY observation per subject are used as dependent variables in the analyses, in the same way as the CCA approach. However, unlike CCA, all individuals are included in the analysis dataset. In BPA each unobserved quantity (total cost or total QALY) in the model is handled as if it were a parameter (Baio, 2012; Baio & Dawid, 2015; Daniels & Hogan, 2008; Gabrio et al., 2019).

The BPA was implemented based on Markov Chain Monte Carlo (MCMC) using the R function **selection,** within the **missingHE** package (Daniels & Hogan, 2008). BPA requires the specification of four models: the first two are the estimation models for the total QALY and total cost variables (*Y*) assuming these data are bivariate normally distributed (as Equation 3)

and the last two are the auxiliary models which are fitted (similarly to equation 1) to estimate the probability *Y* is missing using logistic regressions.

The four models include baseline covariates of treatment allocation, ulcer duration, ulcer size, age, and site. and the auxiliary models also include the length of follow-up in the study, as the probability of missingness increases with time since baseline. Non-informative priors were used for the precision of the dependent variables, which were varied from 0.001 to 0.01 in sensitivity analyses. Incremental mean costs and QALY were computed from the estimation models and the CEAC was calculated parametrically from the variance-covariance matrix.

The original cost-effectiveness analysis for the EVRA trial coded SITE as a random effect. The documentation for BPA states that covariates can be included either as fixed or random effects (Gabrio, 2020), but despite our best efforts and attempting to contact the software authors for advice without reply, we were unable to implement this feature. Hence in this paper we implemented all models using fixed effects for SITE for comparability.

2.3. RESULTS

2.3.1 Pattern of missingness

No baseline data were missing. 74% of subjects had complete data (costs and EQ-5D) at 1 year, 10% at year 3 and 25% at year 5 (Table 2.2). This pattern arises from the staggered recruitment and because the final questionnaire was administered at a fixed calendar point irrespective of when the subject was recruited.

Time point	Missing Pattern (Costs, EQ-5D)			
	Complete cost and complete EQ5D	Complete cost and missing EQ5D	Missing cost and complete EQ5D	Missing cost and missing EQ5D
At 1-Year	74% N=333	19% N=85	0.2% N=1	7% N=31
At 3-Years	9.7% N=44	74% N=333	0%	16.3% N=73
At 5-Years	25.3% N=114	7% N=31	0%	67.7% N=305

Table 2.2 Missing data pattern

The logistic model showed the probability that a value is missing in costs and EQ-5D are related to the time in follow-up, age at baseline and site ($p < 0.0001$), see supplementary table S2.6 and table S2.7. As EQ-5D tend to change over time since surgery (see Supplementary Material Table S2.9), and EQ-5D are more likely to be missing at longer follow-up, this suggests that the probability of an item being missing may be correlated with values of observed outcomes (MAR). However, it cannot be ruled out that data might be MNAR (that is, missingness correlated with unobserved outcomes).

Only subjects with complete aggregate data were used in CCA: year 1, n=338; year 3, n=44 and year 5, n=147. The BPA included all the 450 subjects. The data for RMM and MI included all the longitudinal observations for all follow-ups as an unbalanced panel.

2.3.2 Cost effectiveness analysis

Table 2.3 shows a summary of the results of the cost-effectiveness-analysis with the six different approaches at each time point. All methods agreed that there was no statistically significant difference in cost at the 5% level at any time horizon. Early intervention was associated with statistically significantly greater mean QALY among all methods at year 1.

BPA showed a statistically significant difference at year 3, while other methods tended towards greater QALY for the intervention, but this did not reach statistical significance.

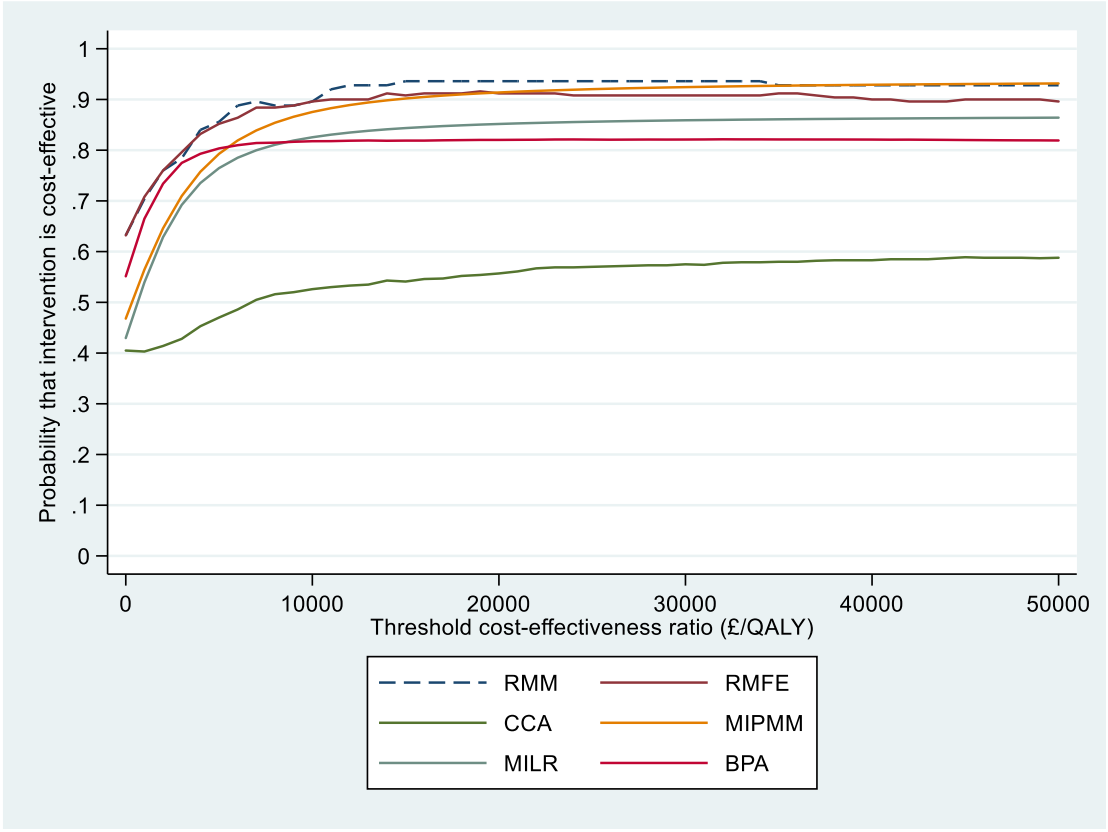
	Time Point	RMM	RMFE	CCA	MIPMM	MILR	BPA
Differences in mean Costs (standard error) (95% confidence interval) **(£)**	1-Year	N=450 -70 (482) CI (-1014 to 874)	N=450 -93 (525) CI (-1123 to 936)	N=338 -4 (326) CI (-644 to 636)	N=450 50 (295) CI (-528 to 627)	N=450 (307) CI (-534 to 669)	N=450 137(305) CI (-340 to 665)
	3-Years	N=450 -159 (565) CI (-1265 to 949)	N=450 -180 (610) CI (-1375 to 1015)	N=44 215 (831) CI (-1531 to 148)	N=450 25 (312) CI (-586 to 637)	N=450 58 (328) CI (-583 to 700)	N=450 -38 (360) CI (-637 to 556)
	5-Years	N=450 -93 (651) CI (-1369 to 1184)	N=450 -111 (697) CI (-1477 to 1255)	N=147 464 (751) CI (-1008 to 1936)	N=450 8 (333) CI (-645 to 661)	N=450 57 (354) CI (-637 to 751)	N=450 1200 (807) CI (-122 to 2536)
Differences mean QALY (standard error) (95% confidence interval)	1-Year	N=450 .05 (.02) CI (.02 to .08)	N=450 .05 (.02) CI (.02 to .08)	N=338 .04 (.02) CI (.01 to .07)	N=450 .05 (.02) CI (.01 to .08)	N=450 .05 (.02) CI (.01 to .08)	N=450 .05(0.02) CI (.02 to .78)
	3-Years	N=450 .07 (.07) CI (-.06 to .20)	N=450 .07 (.07) CI (-.06 to .20)	N=44 .04 (.13) CI (-.21 to .29)	N=450 .08 (.05) CI (-.04 to .20)	N=450 .09 (.08) CI (-.07 to .25)	N=450 .12(0.13) CI (.09 to .34)
	5-Year	N=450 .05 (.11) CI (-.16 to .26)	N=450 .05 (.11) CI (-.16 to .26)	N=147 .01(.12) CI (-.24 to .25)	N=450 .05 (.08) CI (-.10 to .20)	N=450 .05 (.12) CI (-.20 to .31)	N=450 .16(0.17) CI (-.03 to .58)
ICER £/QALY	1-year	Dominant (-1319)	Dominant (-1802)	Dominant (-98)	1082	1430	2728
	3-Years	Dominant (-2165)	Dominant (-2446)	6075	319	627	Dominant (-317)
	5-years	Dominant (-1803)	Dominant (-2250)	59500	159	1010	7394

Note: RMM. repeated measure mixed model; RMFE. repeated measure fixed effect; CCA. complete-case-analysis; MIPMM. Multiple Imputation using predictive mean matching; MILR. Multiple Imputation using linear regression; BPA. Bayesian parametric approach; QALY. quality-adjusted life years; ICER. incremental cost ratio.

Table 2.3 Results of the models.

At 3 years early intervention dominated according to RMM, RMFE and BPA methods. The ICER according to CCA was £6075/QALY, £319/QALY using PMM and £627/QALY using MILR. All methods suggested that early intervention is cost-effective at a threshold of £30,000 per QALY at 1-, and 3- year time horizons. At a threshold of £30000/QALY, the estimated

probability that the intervention was cost-effective was 93% using RMM, 91% using RMFE and 58% using CCA, see Figure 2.2.

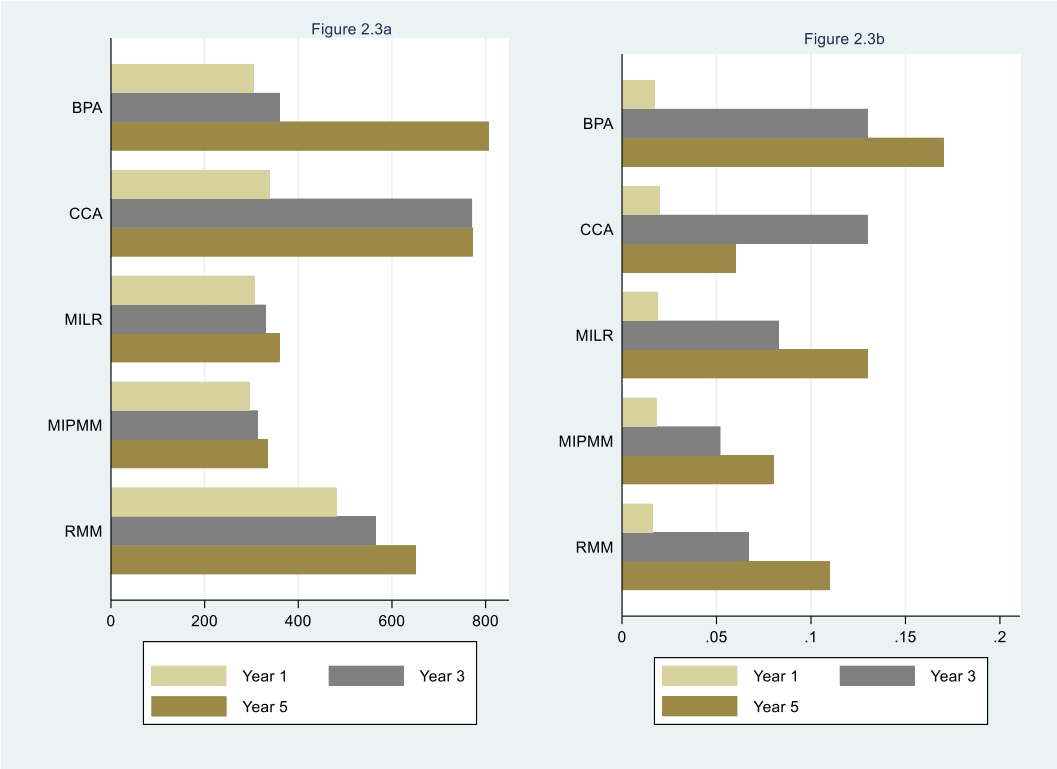


Note: RMM. Repeated measure mixed model; RMFE. Repeated measure fixed effect; MIPMM multiple imputation using predictive men matching; MILR. multiple imputation using linear regression; CCA. complete-case-analysis; BPA. Bayesian parametric approach.

Figure 2.2 Cost-effectiveness acceptability curves at 3 years

When we compare the two methods for multiple imputation, MIPMM show a loss of efficiency of 0.03% in costs using M=40 and 0.8% in QALY while MILR shows 0.20% and 1.3% for costs and QALY, respectively. MCE were less than 10% of the standard errors (SE) in both methods, indicating reasonable stability of the models. As would be expected, imputations with MIPMM correspond more closely than MILR to the distribution of observed data (Supplementary Figure S2.1).

RMM and RMFE showed greatest standard errors (SE), 482 and 525, respectively at year 1 for incremental mean costs than other methods (Figure 2.3a). CCA showed the greatest SE at year 3 and BPA at year 5, 831 and 807, respectively. MIPMM showed the lowest SE at all time horizons. Regarding QALY at year 1, CCA and BPA showed greater SE than other methods (Figure 2.3b). BPA presented the highest SE at year 3 and 5. Other methods showed similar SE for incremental mean QALY at years 1, 3 and 5.



RMM. repeated measure mixed model; RMFE. repeated measure fixed effect; CCA. complete-case-analysis; MIPMM. Multiple Imputation using predictive mean matching; MILR. Multiple Imputation using linear regression; BPA. Bayesian parametric approach.

Figure 2.3 Standard errors of a) incremental mean costs b) incremental mean QALY.

2.4 DISCUSSION

This paper compared six methods for handling missing data empirically, some in common use and others less so, using a real data set with several follow-up points over a long time period.

We have attempted to use a similar estimation model in each case, so that differences arise mainly from the number of subjects and observations per subject that comprise the data, and the assumed latent correlation between observed and missing data.

The original cost-effectiveness analysis employed RMM, and reported mean total cost of –£155 (95% CI, –£1262 to £953) and mean total QALY of 0.073 (95% CI, –0.06 to 0.20) at 3 years (Gohel et al., 2020) . The very small differences arise in this paper because the original paper coded SITE as a random effect. In this paper, we code SITE as a factor variable (fixed effect). All the approaches coincide in estimating statistically significantly greater QALY at 1 year, but only BPA showed a statistically significant difference in QALY at 3 years. RMM, RMFE, MILR, MIPMM and BPA suggest the mean difference in QALY is positive (in favour of early intervention). However, the mean coefficient for incremental cost is negative in some methods and positive in others, leading to differences in the ICER.

CCA is the simplest method to implement. However, because subjects with any incomplete observations are discarded, it can be considered wasteful of the available data. Hence it is likely that the standard errors are over-estimates, arising from the low number of observations. CCA can also be biased if data are MAR. Hence the ICER for CCA could be inaccurate. Other methods coincide in suggesting that early intervention is cost-effective at a threshold of £30,000 per QALY at 1-, 3- and 5- year time horizons. However, the variation in the ICER across the methods does generate some additional methodological uncertainty, underlining the importance of conducting sensitivity analyses using alternative methods.

BPA offers a principled framework for handling missing data under the assumption of MAR. BPA includes all individuals but uses aggregate data for the dependent variables. This means

that if a subject has one missing EQ-5D follow-up, then the QALY for that individual would be recorded as missing, and previous (or future) follow-ups for EQ-5D for that individual would be ignored. This means BPA can also be considered wasteful when (as is the case here) many individuals have some missing EQ-5D, in the sense that some relevant data is ignored. Hence it might be reasonable to conclude that the large standard errors generated by BPA at 3 and 5 years in this example are over-estimates.

MI, RMM and RMFE employ all the available longitudinal period cost and EQ-5D observations in all the subjects. Hence, they can be considered efficient methods in the sense that every item of observed data is used in the analysis model. This is important when there is substantial item missingness, as we have in this dataset. They are straightforward to implement using standard software. RMM and RMFE would not be a suitable option if there were considerable missing baseline covariates that needed to be included in the analysis model (**selection** and CCA share this limitation). There were slight differences between RMM and RMFE. This may be due to the cluster size.

MI has been widely recommended for cost-effectiveness analysis (A. Briggs et al., 2003; Burton et al., 2007; Faria et al., 2014; Marshall et al., 2009). MI can impute both missing outcome data and missing baseline data. Also, simulation studies have found that MIPMM offers a better fit to the data (Marshall et al., 2010). Some caution is needed when using MIPMM if there are few donors in the vicinity of an incomplete case, leading to a risk of bias (Morris et al., 2014). Also, if a donor is selected for many individuals or repeatedly used by the same individual across imputations this will lead to inefficiency, underestimating the between-imputation variance. MI can compute the variance-covariance matrix of total mean cost and total mean QALY using parametric assumptions, while RMM and RMFE estimates costs and EQ-5D separately and

uses bootstrap simulations to estimate the correlation between total mean cost and total mean QALY. This makes both RMM and RMFE rather slow to compute, though some analysts may favour semi-parametric methods such as bootstrap when data are not normally distributed.

2.4.1 Strengths and limitations

This study has compared the missing data approaches reported in Gohel et al. (Gohel et al., 2020) against a wider set of methods for handling missing data. We included approaches that are commonly used, and others less so (Faria et al., 2014; Leurent et al., 2018), in a case study with a long follow up and a high proportion of item missingness There are also some limitations that need to be taken into account. First, other missing data approaches are available (O'Kelly, 2014; Shah et al., 2014; Tilling et al., 2016). We only examined MAR mechanisms here. If data are MNAR then this may give rise to bias. The data could have been modelled as a three-level multilevel MI (time, subject and site). When the percentage of missing data is large MI strategies that do not take into account the intra-cluster correlation can underestimate the variance of the treatment effect (Andridge, 2011; Gomes et al., 2013; J. Ma et al., 2011). Other Bayesian models could also have been tried to model sites as random effects (Gabrio et al., 2021; Lambert et al., 2008). Also, costs and QALY were assumed normally distributed for the simplicity of modelling (Mihaylova et al., 2010). In this case study the standard errors for RM models were generally greater than for MIPMM. However, since we do not know the true values of the missing data, we cannot generalize about which method is "correct".

2.4.2 Conclusion

The variation in the results across the methods underline the importance of conducting sensitivity analyses using alternative approaches to missing data. Further work might consider models for handling non-normal distributions and more complex missing data mechanisms.

CHAPTER III. A SYSTEMATIC REVIEW OF THE IMPACT OF SPINAL CORD INJURY ON COSTS AND HEALTH RELATED QUALITY OF LIFE

ABSTRACT

OBJECTIVES: To systematically review the quality of life (QoL) burden and costs of spinal cord injury (SCI) on health services, patients, and wider society.

METHOD: A systematic review guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Statement was conducted through Scopus, PubMed and Embase databases. Descriptive analyses, random-effects direct meta-analysis and random-effects meta-regression were conducted.

RESULTS: A total of 67 studies were eligible for inclusion. SCI individuals tend to report higher QoL in mental than physical dimensions of the Short-Form 36. Neurological level of SCI affects negatively QoL. Cross-sectional studies find employment is associated with better QoL, but the effect is not observed in longitudinal studies. The estimated lifetime expenditure per individual with SCI ranged from $0.5 million to $2.0 million, with greater costs associated with earlier age at injury, neurological level, United States (US) healthcare setting, and the inclusion of non-healthcare items in the study.

CONCLUSION: SCI, and neurological level of injury, are associated with low QoL on mobility and physical dimensions. Mental health scores tend to be greater, and most dimensions of QoL appear to improve over time, at least over the first year. These conditions are associated with high costs which vary by country.

KEYWORDS

Spinal cord injury, Quality of life, Short-form 36, EQ5D, Costs

3.1 INTRODUCTION

Spinal cord injury (SCI), with an annual incidence of between 250,000 and 500,000 people worldwide (WHO, 2011), is a serious medical condition with important functional, psychological, and socioeconomic consequences on patients and their families (Bicknell et al., 2009; Huynh et al., 2002; V. Y. Ma et al., 2014; Zürcher et al., 2019) and a substantial burden on the medical and social care system (Hall et al., 2019). Medical advances in recent years have improved the life expectancy of people with SCI (Barker et al., 2009; Etz et al., 2015). However, treating and caring for people with SCI represents a substantial challenge (Doosti-Irani et al., 2018) aggravated by permanent disability, the severity of injury, the occurrence in younger people (Access Economics, 2009; Polinder, 2007), loss of employment (Lidal et al., 2007) and the need for family members to give up their time to provide informal care (Priebe et al., 2007).

Comparison between studies of costs and quality of life (QoL) of people with SCI needs to be undertaken cautiously. Studies differ in the resource items included. Some studies focus on "direct" costs related to use of health services, while others may include "indirect" cost (the broader opportunity costs of SCI on other persons and sectors, such as families, carers, loss of productivity, the education sector and so on). Measurement of health service unit costs can be influenced by the type of health system, price levels, accounting practices, and severity of the condition (Espín et al., 2022). Effective treatment of SCI often requires specialist health and social care, but these can of course only be accessed by the user if such services are available near to where the person lives. Countries will differ in the quality and quantity of relevant services on offer, and whether paid from insurance or if patients are expected to contribute financially out of pocket (Papanicolas et al., 2018). Likewise, QoL, as well as depending on the severity and duration of the injury itself, will also be influenced by the circumstances in which

people grow, live, work, and age, and the resources and infrastructure in place to help them live with their disability (WHO, 2008). QoL will be influenced by the person's neurological impairment, but also their perception of wellbeing, which may be conditioned by attitudes and prejudices of society at large towards people with disabilities (Ferdiana et al., 2017). Indeed, "cost" and "QoL" for SCI will be jointly determined to some extent by wider social and cultural factors beyond the influence of the healthcare service.

The interpretation of the evidence will also depend on the study design. Broadly, two types of primary study (that collect data from individuals) are prevalent in this area: cross sectional surveys, and longitudinal cohort studies (although, depending on the research question, other study designs such case-control would also be feasible). Cross sectional surveys can explore associations between variables, but comparisons may be confounded by unobserved factors, and these studies cannot make any statements about cause and effect. Prospective longitudinal studies can show trends over time, and can control to some extent for observed and unobserved variables at baseline, but may be confounded by unobserved factors that change over time. For example, if a longitudinal study finds that people who obtain employment after the injury have better QoL, it is unclear whether gaining employment benefited the person's wellbeing, or whether both employment opportunities and gains in QoL arose from an improvement in the underlying health condition. Results of studies will only be representative of the prevalent population with SCI if they have deliberately sampled with this aim, and this also needs to be borne in mind when comparing outcomes.

Furthermore, a wide range of measures for assessing QoL has been used in the literature (Wilson et al., 2011). França et al., (de França et al., 2013) measured QoL among SCI

population using the WHOQOL-BREF questionnaire. The authors reported that psychological health and social relationship domains tended to score higher than environmental and physical health. A prospective longitudinal study of patients from Northern India (Singh et al., 2008) found that Global QoL tended to increase 6 months from the time of injury. Kalyani et al., (Kalyani et al., 2015) employed the Ferrans and Powers quality of life questionnaire in Sri Lanka and found higher scores for the family and social/economic dimensions than health/functioning and psychological dimensions. Clayton et al., (Clayton & Chubon, 1994) using the life situation survey (LSS), found that patients with greater disability tended to report better QoL, though this may be a bias of the cross-sectional study design.

Given these uncertainties, there is a need for a comprehensive quantitative synthesis of previous research. Other systematic reviews have focused on specific interventions, outcomes, population or regions. Bagnall et al. (Bagnall et al., 2003), reviewed spinal fixation surgery and steroids for SCI. Malekzadeh et al. (Malekzadeh et al., 2021) examined direct (that is, health service) costs of living with SCI and found that annual cost ranged from $32,240 to $1,156,400, with variation between countries arising from differences of the components of cost, time horizon, level and severity of injury and the health system structure. Furlan et al., (Furlan et al., 2017) found the cost of spinal cord injury among war veterans to range from $30,770 to $62,563 per year, generally greater than the costs of other chronic diseases. Dalvand et al., (Dalvand et al., 2019) found that people with SCI in Iran reported half the QoL score on the SF-36 physical dimension compared with the general population. Ku, J. (Ku, 2007) conducted a narrative review of SF-36 but did not carry out evidence synthesis of these data. Bokaye et al. (Boakye et al., 2012) noted the biases associated with cross-sectional studies and the lack of longitudinal studies limited any conclusions that could be drawn from their data.

The objective of this paper is to provide a comprehensive systematic review of costs following SCI in adults and QoL, measured by SF-36 or EQ-5D, accompanied by quantitative evidence synthesis (meta-analysis) where appropriate. A systematic review can identify broad trends in the data from diverse sources, bring together evidence about components and drivers of variation in costs and QoL, and assess the degree of consensus across studies. Quantitative evidence on the underlying economic and health burden of this condition is essential information to inform the long-term economic evaluation of interventions and policies to prevent, treat or provide care for people with SCI, such as the ongoing PAPAARTIS clinical trial (Petroff et al., 2019) , which aims to prevent SCI arising as a complication of surgery.

3.2 METHODS

A systematic review was conducted and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement(Moher et al., 2009). The protocol was previously registered in the International Prospective Register Of Systematic Reviews (CRD42021235801).

3.2.1 Eligibility criteria

The inclusion criteria for articles included in the review were as follows:

- Empirical studies published in English, Spanish, Italian and French.
- Selected condition (SCI population)).
- Original research with primary data

- Outcomes of healthcare costs, social costs, and/or QoL measured with the Euroqol EQ5D (Devlin et al., 2017) or Short-form 36 or 12 instruments (Ware et al., 1996; Ware & Sherbourne, 1992).

The QoL outcomes were limited to these instruments to obtain some homogeneity, and because they are the most common QoL tools used in health economic evaluation (Shearer & Morshed, 2011). No publication date limits were applied. Exclusion criteria were:

a. Studies that focused on special SCI populations (e.g., diagnosed mental illness or other specific diseases)

b. Studies of specialized interventions to prevent, treat or care for SCI. Hence, randomised controlled trials of SCI interventions were excluded.

3.2.2 Search terms and databases

The search was conducted through Scopus, PubMed and Embase databases during March 2021. Search filters were grouped into four broad categories: costs of healthcare, impact on home living and families, employment and income, and QoL (Supplementary Table S3.1).

3.2.3 Study selection

Studies were selected in a sequential process (see the flow chart in Figure 3.1). Phase I identified articles that had the search terms in their title, abstract or keywords. Phase II eliminated duplicates in the different search sequences, or in more than one database. Phase III screened studies by title and abstract, and classified publications according to whether they address the research questions. In Phase IV the full text was obtained and read. In Phase V the final selection of included articles was made by the 2 authors by discussion and agreement. Study quality criteria were assessed, and data were extracted.

3.2.4 Data collection process and data items

The severity of SCI depends on which segments of the spinal cord are affected. While the specific assessment for a patient requires specialist expertise, there are some broad generalities. Damage to higher segments leads to greater levels of impairment. Damage to the upper cervical segments (C1-C4) can lead to substantial impairment of all four limbs (tetraplegia), while damage to lower cervical segments (C5 – C8) can permit some limited use of the arms or hands. Damage the thoracic segments (T1 – T12) will frequently allow use of hands but inhibit use of legs (paraplegia) (Kirshblum et al., 2013). The American Spinal Injury Association Impairment Scale (AIS) was used by many studies. The AIS is a universal classification tool for spinal cord injuries based on a standardized sensory and motor assessment of the degree of impairment below the neurological level of injury, with grade A meaning complete injury (loss of sensory and motor function), B (sensory but not motor function), C and D referring to levels of partial motor function (Alizadeh et al., 2019).

The SF-36 measures two distinct physical and mental dimensions of QoL, each consisting of four subscales. The Physical Component Summary (PCS) of QoL includes the subscales of physical functioning (PF), physical role (PR), bodily pain (BP), and general health (GH). The Mental Component Summary (MCS) includes the subscales of vitality (V), social role (SR), emotional role (RE), and mental health (MH). The EQ-5D assesses five dimensions of health related QoL (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) on a scale with 3 levels (EQ-5D-3L) or 5 levels (EQ-5D-5L). Overall health (where 1 is the best possible QoL and 0 represents a QoL equivalent to death) is scored using a published algorithm specific for each country (Euroqol, 2022) known as the EQ-5D tariff.

The mean and standard deviation (SD) of each SF-36 domain and for the EQ-5D tariff was extracted from cross-sectional studies, and from longitudinal studies at baseline and each follow-up. We were also interested in the factors associated with QoL, such as severity of injury, age at date of accident, current age, current marital status, current employment status, time since injury, time spent in hospital, current neurological level and AIS score. Where studies used regression or similar statistical analysis to estimate the association between QoL domains and other factors, the coefficients (or odds ratio) and level of statistical significance (p-value) were extracted.

Healthcare (direct) costs were classified as hospital (surgical procedures, intensive care unit, other), nursing home and rehabilitation. Non-healthcare (indirect) costs were classified as adaptions to home, productivity losses arising from loss of employment or sick leave, or premature death, payments for carers, and informal care (opportunity cost of unpaid carer time).

The type of study was classified as cross-sectional or longitudinal (for studies that collected primary data) or a mathematical model. Models are used to predict mean cost over the lifetime of a hypothetical cohort, based on aggregate data from the literature on the age distribution of people with SCI, the life expectancy for each age group, and the average yearly cost of treating and caring for SCI (McDaid et al., 2019). Local currency was updated to 2020 prices and converted into international dollars ($) at purchasing power parity (OECD & Eurostat, 2012).

3.2.5 Risk of bias in individual studies

The overall quality of the studies was assessed by one author using the 14 criteria of the "QualSyst" tool (Alberta Heritage Foundation for Medical Research) (Kmet et al., 2004). The 14 criteria were scored depending on the degree to which the specific criteria were met ("yes" = 2, "partial" = 1, "no" = 0). Criteria not applicable to study design were marked "n/a" and

excluded from the calculation of the summary score. A summary score was calculated for each paper by summing the total score obtained across relevant items and dividing by the total possible score.

3.2.6 Statistical analysis

QoL data were analysed using descriptive analyses (tabulation), random-effects direct meta-analysis (MA), and random-effects meta-regression(W-l Cheung et al., 2012). Mean QoL was tabulated for cross sectional studies, and for longitudinal studies at each time point. The factors associated with QoL were tabulated and graphical analyses were carried using **graph bar** command in STATA 15 to show the number of studies that reported a positive association or better score when two categories were compared; a negative association or worse score when two categories were compared; or no significant association between QoL and the factor.

Synthesis of mean QoL across cross-sectional studies was conducted using MA, stratified by low, middle- and high-income countries as defined by the World Health Organisation(WBG, 2022). Meta-regression analyses explore sources of variation in mean QoL and were used when heterogeneity was moderate or high in MA (I^2>25%) (Higgins & Thompson, 2002). Meta-regression analyses were conducted separately for the following variables where data were reasonably complete: mean time since injury, proportion of study sample in employment, and proportion of study sample who were paraplegic (rather than tetraplegic). Other variables were not employed because they were not reported in the majority of studies. MA and meta-regression analyses were implemented using the **metan** and **metareg** command in STATA 15. MA was not carried out for longitudinal studies as there were few such studies, and outcomes were reported in different formats that precluded quantitative synthesis.

Descriptive graphical analyses of mean costs estimate in primary studies were carried using the **ggplot** command in R, showing the association of mean costs with the length of follow-up, country, cost items included, and neurological level of SCI. Mean lifetime costs per person estimated by modelling studies were tabulated, along with a description of the main sources of input data in each case. Given the differences in study design and reporting, MA was not considered feasible for costs. Codes and data are available on Mendeley Data online (Diop, 2022).

3.3 RESULTS

The PRISMA chart for study selection is shown in Figure 3.1, 1083 publications were identified in Phase 1 of which 1018 were screened out leaving 67 (Andresen et al., 1999; Arango-Lasprilla et al., 2010; Ataoğlu et al., 2013; Cao et al., 2011; Carrillo et al., 1998; Chan et al., 1997; Charles et al., 1978; Cotner et al., 2018; Deutsch et al., 2011; DeVivo, 1997; DeVivo et al., 2011; Ebrahimzadeh, Golhasani-Keshtan, et al., 2014; Ebrahimzadeh, Soltani-Moghaddas, et al., 2014; Edwards et al., 2002; Elfström et al., 2005; Forchheimer et al., 2004; García-Altés et al., 2012; Glennie et al., 2017; Gurcay et al., 2010; Haran et al., 2005; Harvey et al., 1992; Horner-Johnson et al., 2010; Hossain et al., 2019; Johnson et al., 1998; Kawu et al., 2011; Krause et al., 2019; Kreuter et al., 2004; Leduc & Lepage, 2002; Lessing et al., 2022; Li et al., 2011; Lidal et al., 2008; Lucke et al., 2004; Mac-Thiong et al., 2012; Mahabaleshwarkar & Khanna, 2014; Margolis et al., 2014; McDaid et al., 2019; Middleton et al., 2007; Moghimian et al., 2015; Munce et al., 2013; Oh et al., 2005; Paul et al., 2013; Porgo et al., 2019; Price et al., 1994; Radhakrishna et al., 2014; Richard-Denis et al., 2017, 2018; Rivers et al., 2018; Sabour et al., 2015; Salamati et al., 2015; Schwartz et al., 2018; Seel et al., 2001; Seel & Tewksbury, 2001; Sikka et al., 2019; Smith et al., 2003; Sundance et al., 2004; Tate & Forchheimer, 2001; Tator et al., 1993; Tavakoli et al., 2016; Tsai et al., 2005; Unalan et al., 2007; Vaikuntam et al., 2019; Webster et al., 2004; Westgren & Levi, 1998; Yang et al., 2008; Yasami et al., 2017; Yazdanshenas Ghazwin et al., 2014; Yu

et al., 2008) which met our criteria of inclusion. Study design characteristics, population and measures of exposure and outcome are recorded in Supplementary Table S3.2. All studies included either patients with SCI or traumatic SCI.

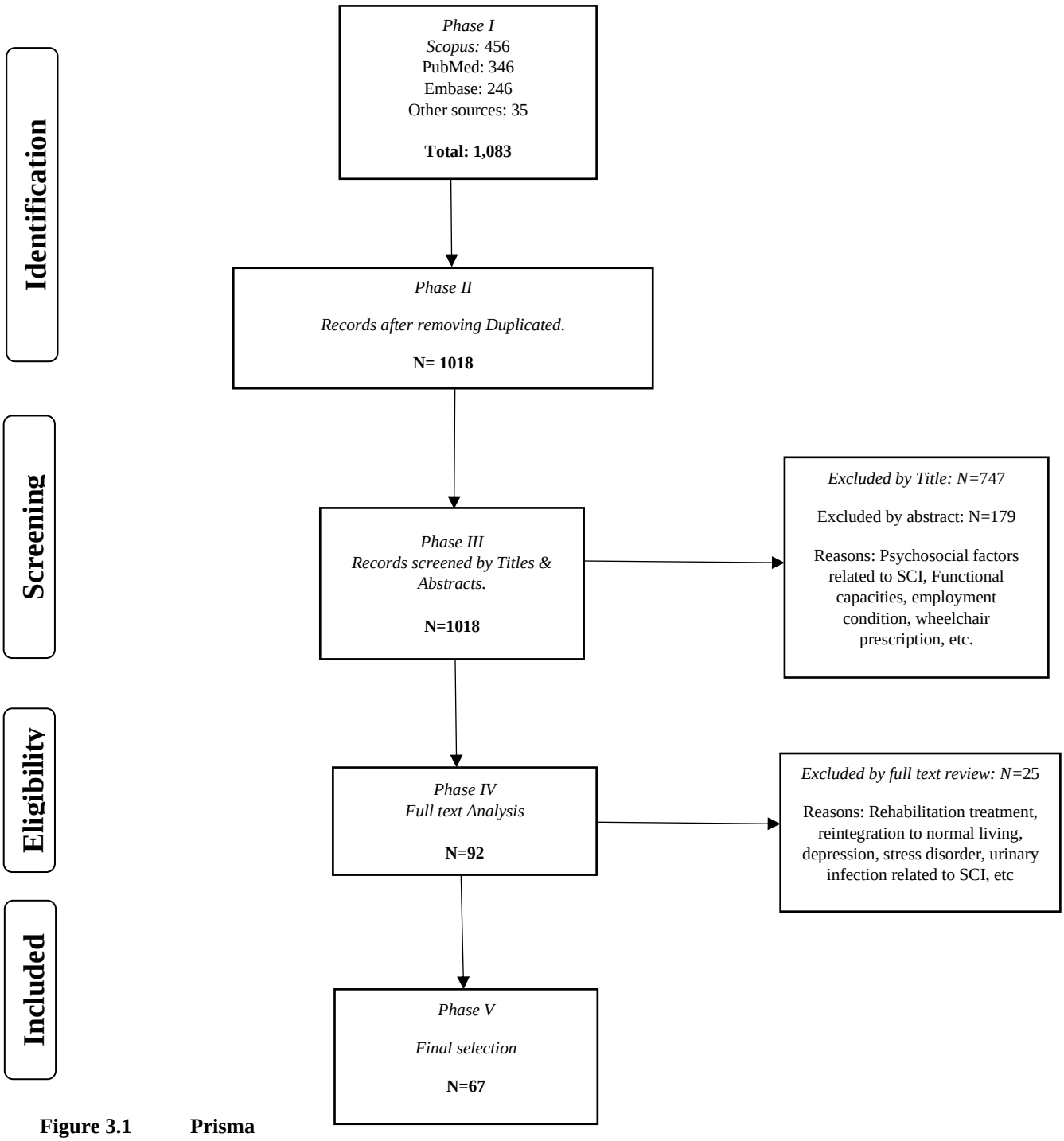


Figure 3.1 Prisma

3.3.1 Study characteristics

The overall score from the quality assessment ranged from 64% to 82% (Supplementary Table S3.3). 46 studies (69%) were conducted in high-income countries, and 21 (31%) in low- and middle-income countries, see Table 3.1. 56 (84%) were cross-sectional. The mean age at injury in the studies was between 23 and 44 years and the mean age at interview of patients was from 17 to 75 years. The mean time from injury to interview ranged from 1 to 27 years in the cross-sectional studies and ranged from 0 to 5 years in the longitudinal studies. The proportion of male patients in the studies was between 27% and 100%. 57 studies did not differentiate between the causes of SCI while the others stratified by causes such as falls, motor vehicle accident, violence and sports.

	High-income countries N=46	Low- and middle-income countries N=21	Total, N=67
Sample size, range of number of participants	10 to 50276	30 to 54484	10 to 54484
Type of study design			
Cross-section, N	35	21	56
Longitudinal, N	11	0	11
Outcomes studied			
Included cost variable, N	28	6	34
Included QoL variable, N	18	15	33[†]
Year of publication, range	1977 to 2019	2001 to 2020	1977 to 2020
Socio-demographic variables included			
Age at injury, range of mean of studies (N)	23-44 (6)	24 to 33 (4)	23 to 44 (10)
Age at interview, range of mean of studies (N)	17 to 75 (29)	33 to 53 (17)	17 to 75 (46)
Proportion of men, range (N)	27 to 99 (32)	68.5 to 100 (14)	27 to 100 (46)
Proportion of employed before injury, range (N)	25 to 55 (2)	22 to 67 (4)	22 to 67 (6)
Proportion of employed after injury, range (N)	20 to 100 (5)	12 to 39 (7)	12 to 100 (12)

Time since injury (cross-section studies), range (N)	1 to 27 (11)	2 to 12 (9)	1 to 27 (20)
Time since injury (longitudinal studies), range (N)	0 to 5 (5)	--	0 to 5 (5)
Level of injury			
Proportion of paraplegic, range (N)	0 to 79 (12)	49 to 100 (8)	0 to 100 (20)
Cause of injury			
SCI any cause, N	38	19	57[a]
SCI related to specific causes [b], N	8	2	10

[a] 1 study compared early versus late transfer to specialist spinal cord centre. [b] Specific causes were motor vehicle accident, violence, falls, sports and other mechanism. N number of studies. SCI spinal cord injury, QoL. Quality of life. [†]8 studies were on factors associated with QoL.

Table 3.1 Characteristics of included studies

3.3.2 Quality of life

Table 3.2 synthesises using MA the results of cross-section studies that reported QoL. SCI individuals tended to report greater QoL in mental than physical dimension scores. When comparing the 8 domains of SF-36 quality of life, PF showed the lowest score while MH and SR had the highest score. The MA showed moderate and high heterogeneity (I^2>25%) in PF for middle-income countries and PR, BP, GH, ER, MH, and SR for high-income countries (see Supplementary Material Figures 3.1-3.10). Reported Mean QoL tended to be greater in middle income countries than high income countries for nearly all dimensions of the SF-36.

Five studies collected longitudinal data on QoL (Table 3.3). Schwartz et al. (Schwartz et al., 2018), used SF-36 questionnaire and reported mean QoL scores at 1-, 2-, and 5-years' post-injury. However, no baseline data were reported (Table 3.3a). Non-significant increases in QoL were found in nearly all the subscales from 1- to 2-years. Lucke et al. (Lucke et al., 2004) reported SF-36 at 6-months, but no baseline data. SCI individuals reported low PF, PR, and ER scores, while reporting high GH, MH and SR scores.

	Mean (†)	95% Confidence Interval (†)		Range of means between studies	Heterogeneity (†)		Number of studies (Number of subgroups)
		Lower	Upper		I^2	P-value	
High income country							
Physical Functioning	25.42	21.28	29.56	(16.1-42.5)	5.6	0.4	12 (14)
Physical Role	40.47	28.06	52.87	(19.6-74.4)	71	0	11 (12)
Bodily Pain	54.86	48.67	61.04	(39-68)	32.2	0.13	11 (12)
General Health	52.18	45.88	58.48	(42.23-69.7)	50.4	0.02	11 (12)
Physical Component Score	*32.97*	*27.26*	*38.68*	*(28.7-34.1)*	*0*	*0.87*	*5 (6)*
Emotional Role	57.83	42.5	73.16	(31.4-90)	82.3	0	11 (12)
Vitality	46.04	43.2	48.88	(42.9-61.4)	0	0.5	11 (12)
Mental Health	59.75	51.62	67.88	(44.3-80.3)	67	0	11 (12)
Social Role	54.64	46.89	62.39	(38.7-85.4)	45	0.04	11 (12)
Mental Component Score	*55.11*	*47.27*	*62.96*	*(49.7-58.8)*	*0*	*0.98*	*5 (6)*
Middle income country							
Physical Functioning	27.62	17.05	38.18	(10-61.2)	58.7	0	11 (15)
Physical Role	42.33	32.67	51.99	(20-70.5)	0	0.97	11 (15)
Bodily Pain	52.72	45.91	59.54	(37.64-77)	0	0.9	11 (15)
General Health	54.2	46.87	61.53	(39-64)	0	1	11 (15)
Physical Component Score	*46.93*	*31.73*	*62.13*	*(31.75-65.2)*	*0*	*0.78*	*3 (5)*
Emotional Role	50.75	37.45	64.06	(29-74.1)	0	0.99	11 (15)
Vitality	59.1	49.8	68.38	(42-73)	0	0.98	11 (15)
Mental Health	54.03	53.44	54.62	(50-85.4)	0	0.93	11 (15)
Social Role	58.69	46.92	70.45	(38-83.5)	0	0.9	11 (15)
Mental Component Score	*63.79*	*48.19*	*79.4*	*(50-78.6)*	*0*	*0.62*	*3 (5)*

(†) estimated by random effects meta-analysis, see supplementary material

Table 3.2 Short-Form 36 quality of life, cross-sectional studies

3.3a. Mean quality of life in longitudinal studies								
Authors	Population	QoL	Baseline	1st Year	2nd Year	5th Year	Δ Year 1 – Baseline	Δ Year 2 – Baseline
		SF-36						
Schwartz et al. 2018	All SCI	Physical functioning		31.7 (30.3)	34.1 (31.1)	30.8 (29)		
		Physical role		40 (31.5)	45.4 (31.1)	46.6 (32.5)		
		Emotional role		69.7 (32.1)	70 (30.4)	71.5 (32)		
		Vitality		51.5 (20)	53 (19.1)	51 (20.2)		
		Mental health		69.1 (19.1)	69.5 (18.6)	69.1 (20)		
		Bodily pain		55.8 (25.7)	57.8 (25.4)	56.1 (27.3)		
		Social role		62.4 (26.7)	65.7 (25.2)	64.7 (26.3)		
		General health		61.5 (21.8)	58.6 (21.7)	59.2 (21.1)		
Lucke et al. 2004	All SCI	Physical functioning		19.3 (28.9)				
		Physical role		46.4 (41.9)				
		Emotional role		42.9 (41.7)				
		Vitality		55.7 (9.3)				
		Mental health		75.4 (11.4)				
		Bodily pain		59 (29)				
		Social role		73.2 (19.7)				
		General health		65 (18.4)				
		Physical component score		33.3 (12.5)				
		Mental component score		51.8 (8)				
3.3b. Factors associated with quality of life in longitudinal studies								
		EQ5D, proportion of people reporting problems (a score not equal to 1)						
Paul et al. 2013	SCI with Compensation	Problems of mobility	92.6%	80.2%	70.4%		-12.4%	-22.2%
		Problems of self-care	66.1%	53.5%	44.3%		-12.6	-21.8%
		Problems of usual activity	90.4%	81.9%	78.4%		-8.5%	-12%
		Problems of pain	86.8%	81.8%	77.3%		-5%	-9.5%
		Problems of anxiety/depression	50%	37.4%	31.8%		-12.6%	-18.2%

	SCI without Compensation	Problems of mobility	97%	78%	84%		-19%	-13%
		Problems of self-care	65%	52.5%	38%		-12.5%	-27%
		Problems of usual activity	90%	96%	76%		6%	-14%
		Problems of pain	88.6%	98%	78,3%		9.4%	-10.3
		Problems of anxiety/depression	49%	57%	30.8%		8%	-18.2%
		SF-36						
Cotner et al. 2018	SCI for people with competitively-gained employment during the study	Mental component score	56.8 (13.9)	59.9 (9.8)	59.2 (10.6)		3.1	2.4
		Physical component score	30.6 (9.1)	32.6 (9.5)	32.2 (9.8)		2	1.6
	SCI for people without competitive employment	Mental component score	56.7 (11.4)	57.5 (10.7)	56.6 (9.6)		0.8	-0.1
		Physical component score	26.5 (7.7)	29.1 (8)	28.9 (8.2)		2.6	2.4[a]
Richard-Denis et al., 2018	SCI with AIS Grade[†] A compared to SCI with AIS Grade[†] D	Mental component score		3.2[*] (0.1 to 6.2)				
		Physical component score		−7.1[*] (−9.5 to −4.6				
	SCI with AIS Grade[†] B compared to SCI with AIS Grade[†] D	Mental component score		1.4[*] (-2.1 to 4.8)				
		Physical component score		−4.5[*] (−7.3 to −1.6)				
	SCI with AIS Grade[†] C compared to SCI with AIS Grade[†] D	Mental component score		-0.2[*] (-3.2 to 2.8)				
		Physical component score		-3.4[*] (-6.3 to -0.4)				

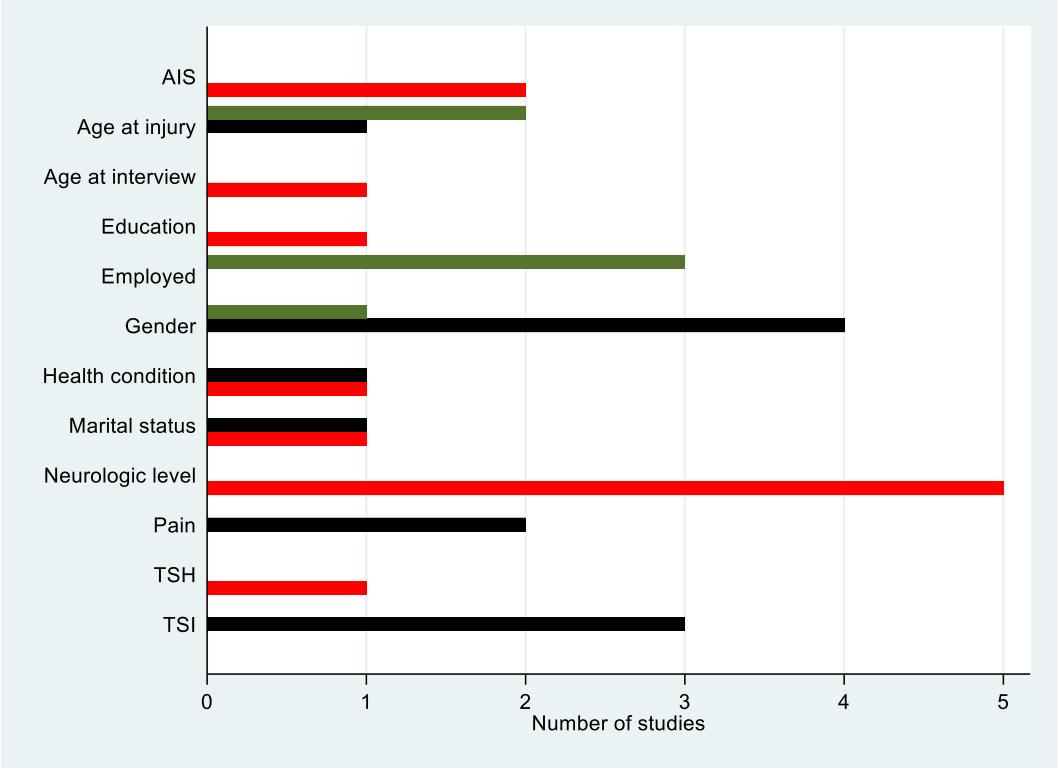
SF-36 short-for 36 questionnaire; EQ5D EuroQol-5D questionnaire; SCI spinal cord injury; AIS American spinal injury association impairment scale.; [†]AIS grade was measured at baseline; AIS Grade A = complete, there is no motor or sensory function left below the level of injury; AIS Grade B = incomplete, sensory function, but not motor function, is preserved below the neurologic level (the first normal level above the level of injury) and some sensation is preserved in the sacral segments S4 and S5.; AIS Grade C = incomplete, motor function is preserved below the neurologic level, but more than half of the key muscles below the neurologic level have a muscle grade less than 3 (i.e., they are not strong enough to move against gravity); AIS Grade D = incomplete, motor function is preserved below the neurologic level, and at least half of the key muscles below the neurologic level have a muscle grade of 3 or more (i.e., the joints can be moved against gravity); [*]Mean differences; [a]$p < 0.05$

Table 3.3 Mean quality of life and factors associated with quality of life, longitudinal studies

3.3.3 Within-study association between QoL and modifying factors

8 studies (Cotner et al., 2018; Forchheimer et al., 2004; Kreuter et al., 2004; Leduc & Lepage, 2002; Lidal et al., 2008; Paul et al., 2013; Richard-Denis et al., 2018; Westgren & Levi, 1998) reported the within-study association between QoL and observed potential modifiers such as age, gender, time since injury, level of injury, health problems, time spent at hospital education, marital status, financial support and employment.

3 of those studies reported longitudinal data, see Table 3.3b. Paul et al. (Paul et al., 2013), examined the effect of receiving financial compensation from an accident insurance scheme on QoL by comparing a population of SCI receiving this financial support to another group without support. The study found no significant differences in mean QoL after 18 months. The proportion reporting problems tended to diminish over time in both groups, and it was noteworthy that the proportion reporting problems of mental health was considerably lower than those reporting problems of mobility. Cotner et al. (Cotner et al., 2018) compared SCI individuals who had gained competitive employment during the study with those who had not. Employed people tended to report greater QoL, but differences were not significant. However, the authors reported that PCS increased significantly from baseline in the unemployed group. Richard-Denis et al., (Richard-Denis et al., 2018) compared mean QoL scores differentiated by the initial severity of the neurological injury. The authors reported that SCI individuals sustaining less severe neurological injury (grade D) reported higher PCS than individuals with grades A, B or C injury. However, individuals with initial grade A injury showed increased MCS, compared with individuals with incomplete grade B, C or D injury.



TSI time since injury; TSH time spent ah hospital; Neurologic level compared tetraplegic vs paraplegic
The figure shows the number of cross-sectional studies that show a statistically significant positive association between the factor and physical functioning (green bar), the number that show a significant negative association (red bar), and the number that show no significant effect (black bar). Not all studies reported the association with all factors.

Figure 3.2 Factors associated with physical functioning in cross sectional studies (N=5)

Figure 3.2 shows the results of the 5 cross-section studies reporting factors related to PF. All 5 studies reported that paraplegic individuals showed better PF than tetraplegic individuals. Employment was associated with better PF in 3 studies.

Results for factors associated with other dimensions of the SF-36 are reported in the Supplementary Material figures S3.32-S3.40. 3 studies showed no significant differences between paraplegic and tetraplegic people in GH scores, and no consensus were found among studies that looked at other physical domains. Neurologic level of injury did not seem to contribute to ER, V or SR. 1 study reported better MH for paraplegic individuals (compared with tetraplegic) whereas 3 studies did not find significant differences. One study found that

single individuals scored significantly lower V, ER and MH scores than those that were married (Westgren & Levi, 1998), but others did not find significant differences (Kreuter et al., 2004). 5 studies examined gender differences on QoL scores, of which 2 found higher PF, V or MH in men, though other studies did not find significant effects.

3.3.4 Between-study association between QoL and modifying factors

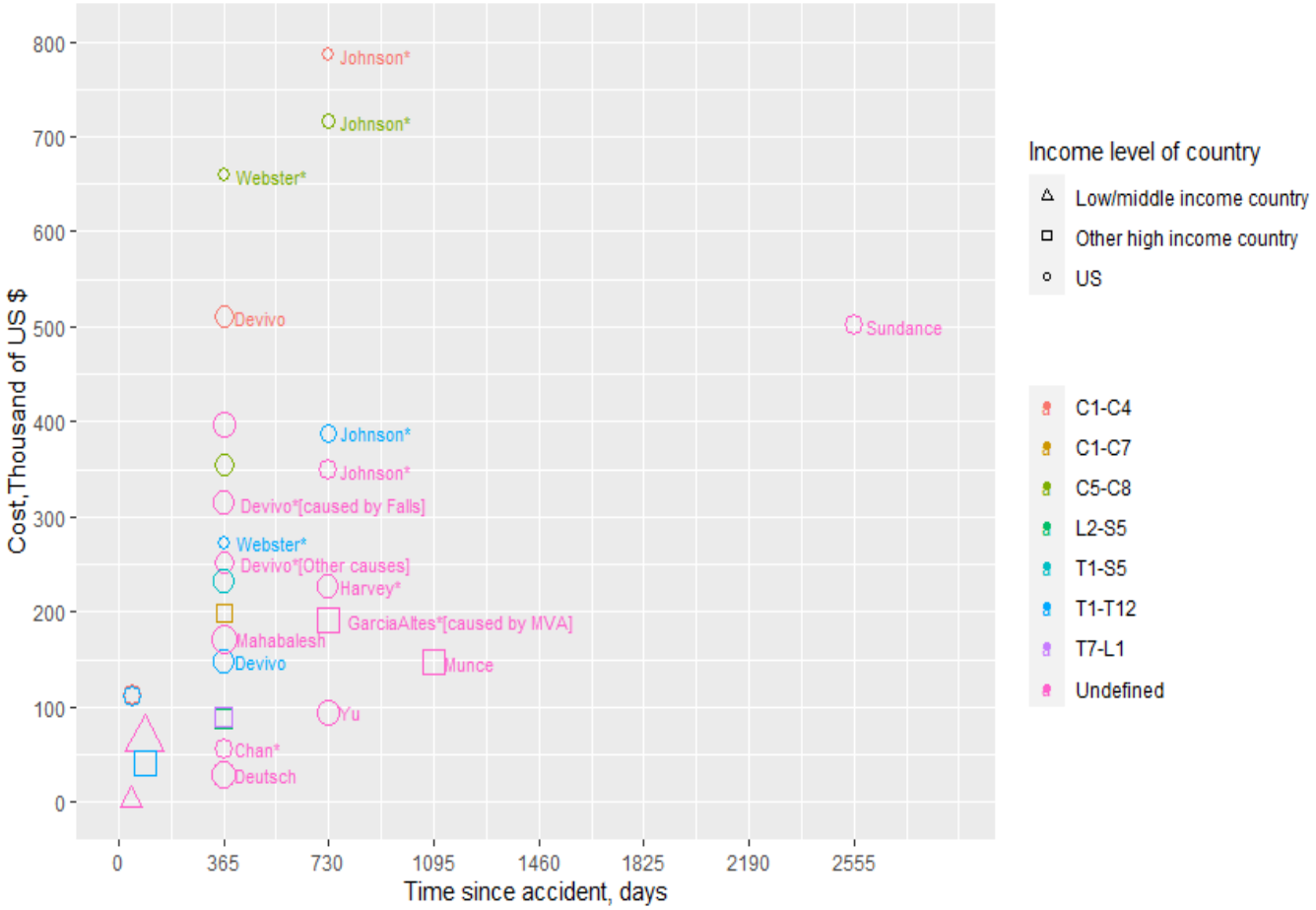
Random-effects meta-regression was conducted among the cross-sectional studies where the MA showed moderate or high between-study heterogeneity (Supplementary Material Figures S3.11-S3.31). No significant associations were found at the 5% level. At the 10% significance level, physical functioning tends to be greater in studies that measured QoL at a longer time since the injury, compared with those that measured QoL sooner after the injury. Studies with a greater proportion of paraplegic individuals (rather than tetraplegic) tended to report lower bodily pain scores and better emotional role scores.

3.3.5 Costs

34 studies reported mean costs of SCI over different time periods. Among the studies that estimated costs from primary data from the hospital admission period up to 7 years, Figure 3.3 shows results grouped by income level of country (US, other high-income countries Spain, Canada, and Australia and middle/low-income countries China, Taiwan, and Nigeria) neurological level of injury, and whether non-healthcare costs were included in the study (labelled with an asterisk).

Hospital costs from 30 to 90 days after the initial accident ranged from $1,927 (Kawu et al., 2011) to $112,978 (Charles et al., 1978), while the mean cost at 1-year ranged from $28,563

(Deutsch et al., 2011) to $858,330 (Webster et al., 2004). Low- and middle-income countries tended to report lower costs than the US, and costs tended to be greater for more severe injury.



*Includes non-healthcare costs; C1-C7 Tetraplegic; C1-C4 High tetraplegic; C5-C8 Low tetraplegic; T1-T12 paraplegic (paralysis in the thoracic area); T7-L1 paraplegia (affecting abdominal area); L2-S5 paraplegia (paralysis of lumbar and sacral area); T1-S5 paraplegia (paralysis in the thoracic, lumbar and sacral area). The size of the marker is proportional to the $\log_{10}$ of the sample size of the study
Not all studies are labelled to avoid overlapping.

Figure 3.3 Costs per injured person (price in US $ 2020)

Three modelling studies estimated lifetime mean costs in the United Kingdom or US of SCI individuals, differentiating by impairment level and cause of injury (Table 3.4). All studies used a discount rate of 4%. McDaid et al. (McDaid et al., 2019) estimated lifetime costs of tetraplegic injury to be around just under $2 million in the UK for a patient with mean age 46 years at

accident, and just under $1.5 million for paraplegic injuries. Cao et al. (Cao et al., 2011) estimated lifetime costs using a similar methodology in the US for C1 to C4 injuries and C5 to C8 injuries, respectively, with broadly similar results. Devivo (DeVivo, 1997) estimated mean lifetime costs (averaged across all neurological levels) between approximately $600,000 and $950,000, depending on the cause of the injury. Comparison of costs between studies should be undertaken cautiously because of different health and social care settings, different measurement of severity (AIS or affected segment of spinal cord) and whether productivity losses were included.

Authors, Year	Country	Population type	Societal perspective	Includes rehabilitation costs	Includes costs of productivity loss and family care (social)	% Paraplegic	Details of the study to estimate prevalence by age			Source of Resource Use and Cost Data	Modelling method	Discount rates	Costs
							Sample size, N	Age at injury, mean	Age at survey mean (range in sample)				
McDaid et al., 2019	UK	SCI all causes	Yes	No	Yes	18%	1,270		46 (0 to 85+)	§	Markov Model	4%	1,209,097
McDaid et al., 2019	UK	SCI all causes - tetraplegic ABC	Yes	No	Yes	0%	445		46 (0 to 85+)	§	Markov Model	4%	1,998,353
McDaid et al., 2019	UK	SCI all causes - paraplegic ABC	Yes	No	Yes	100%	229		46 (0 to 85+)	§	Markov Model	4%	1,485,600
McDaid et	UK	SCI all	Yes	No	Yes		596		46 (0 to 85+)	§	Markov	4%	513,564

al., 2019		causes - all D									Model		
Devivo, J. M., 1997	US	SCI caused by motor vehicle accident	No	Yes	No		1,010	30		¶	Annual weighted cost †	4%	947,758
Devivo, J. M., 1997	US	SCI caused by violence	No	Yes	No		830	27		¶	Annual weighted cost †	4%	616,389
Devivo, J. M., 1997	US	SCI caused by falls	No	Yes	No		647	24		¶	Annual weighted cost †	4%	650,298
Devivo, J. M., 1997	US	SCI caused by sports	No	Yes	No		208	42		¶	Annual weighted cost †	4%	935,574
Devivo, J. M., 1997	US	other causes of SCI	No	Yes	No		197	38		¶	Annual weighted cost †	4%	648,011
Cao et al. 2011	US	SCI all causes - C1 to C4	No	Yes	No			25		¶	Annual weighted cost †	4%	3,270,320
Cao et al. 2011	US	SCI all causes - C5 to C8	No	Yes	No			25		¶	Annual weighted cost †	4%	2,228,242
Cao et al. 2011	US	SCI all causes - T1 to S5	No	Yes	No			25		¶	Annual weighted cost †	4%	1,337,370
Cao et al. 2011	US	SCI all causes - AIS D	No	Yes	No			25		¶	Annual weighted cost †	4%	962,860
Cao et al. 2011	US	SCI all causes - C1 to C4	No	Yes	No			50		¶	Annual weighted cost †	4%	1,838,669
Cao et al. 2011	US	SCI all causes	No	Yes	No			50		¶	Annual weigh	4%	1,438,049

		- C5 to C8									ted cost †		
Cao et al. 2011	US	SCI all causes - T1 to S5	No	Yes	No			50		¶	Annual weighted cost †	4%	935,440
Cao et al. 2011	US	SCI all causes - AIS D	No	Yes	No			50		¶	Annual weighted cost †	4%	726,637

† The value of lifetime charges for an individual with SCI secondary to each cause was estimated using the mean first year and recurring annual charges for that cause (assuming that the recurring charges are constant after the first year), mean age at time of injury for all persons in the National Spinal Cord Injury Statistical Center database, and the most recent survival data. C1 to C4 High tetraplegic; C5 to C8 Low tetraplegic; T1-S5 paraplegia (paralysis in the thoracic, lumbar and sacral area); AIS Grade A = complete, there is no motor or sensory function left below the level of injury; AIS Grade B = incomplete, sensory function, but not motor function, is preserved below the neurologic level (the first normal level above the level of injury) and some sensation is preserved in the sacral segments S4 and S5.; AIS Grade C = incomplete, motor function is preserved below the neurologic level, but more than half of the key muscles below the neurologic level have a muscle grade less than 3 (i.e., they are not strong enough to move against gravity); AIS Grade D = incomplete, motor function is preserved below the neurologic level, and at least half of the key muscles below the neurologic level have a muscle grade of 3 or more (i.e., the joints can be moved against gravity); All studies included costs of surgical procedures, intensive care unit, normal hospital room, nursing home care and adaptions to home; Productivity losses incurred by carers or due to patient's sick leave or patient's death; § Literature and 2015–2016 English National Schedule of Reference Costs; ¶ hospital record or third parties

Table 3.4 Lifetime costs per injured person (price in US $ 2020)

3.4 DISCUSSION

3.4.1 Summary of findings

This study attempted to systematically review evidence on the underlying economic and health burden of SCI condition. Despite the heterogeneity in population, outcomes, study methodology, or timeframe, there seem to be some general trends that are consistent in the different analyses (meta-regression, the analysis of within-study factors, and longitudinal studies). First, as might be expected, SCI, and neurological level of injury, are associated with low QoL on mobility and physical dimensions. Second, the mental health scores of survivors of SCI appear considerably greater than physical scores. Third, most dimensions of QoL appear to improve over time, at least over the first year. These results might indicate that the degree of

impairment tends to ameliorate but could equally arise because people tend to adapt to the situation in which they find themselves.

Although some cross-sectional studies have linked employment status to higher QoL, neither the meta-regression analysis nor the longitudinal study found any significant differences. This could suggest that the effect found in cross-sectional studies is a confounded by unobserved or uncontrolled factors (Lidal et al., 2007). Given the results of this review, it appears more plausible that adequate physical functioning is a condition of gaining competitive employment, rather than the other way around.

Health and other costs for people living with SCI are substantial, accumulate over the lifetime and are conditioned on severity of injury and whether non-healthcare costs were included in the study. Most cost studies were in the US, and it seems that total expenditures in this country are higher than other systems. However, this result should be interpreted cautiously as access to treatment and care services in the US may depend on the insurance held by the patient. Devivo, et al. (DeVivo et al., 2011) highlighted differences when costs are charged to the patient, or covered by a third-party insurer. Hospital admission charges for acute care were three times higher when they were charged to a third-party payer, and twice as high for 1-year costs and inpatient rehabilitation.

3.4.2 Limitations

This review included both cross-sectional and longitudinal study designs. While cross sectional studies can use regression methods to adjust the measure of association for observed covariates, they nevertheless carry a risk of confounding from selection bias, reverse- causality or omitted variables. We aimed to be cautious in our conclusions and used different methods of analysis

(MA, meta-regression, tabulation and comparison with longitudinal studies). Throughout the study, we were conscious that quality of life (and expenditures) on people with SCI depend on wider cultural, institutional and environmental factors, including attitudes to disability.

3.4.3 Conclusion

SCI, and neurological level of injury, are associated with low QoL on mobility and physical dimensions. Mental health scores tend to be greater, and most dimensions of QoL appear to improve over time, at least over the first year. These conditions are associated with high costs which vary by country.

CHAPTER IV. HEALTHCARE ACCESS THROUGH COMMUNITY-BASED HEALTH INSURANCE AMONG SENEGALESE MIGRANTS

RESUMEN

OBJETIVO: Este trabajo evalúa los determinantes en la financiación del acceso a la atención médica y el papel de una clase particular de financiación informal propia conocida como tontina para el acceso a la atención médica en la población de migrantes de origen senegalés.

MÉTODO: Los datos fueron recogidos mediante técnicas cualitativas, entrevistas semiestructuradas (n=14) y grupo de discusión (n=10) en una población de migrantes senegaleses residente en Granada entre octubre y noviembre de 2019. Los participantes claves fueron procedentes de una tontina.

RESULTADOS: La falta de trabajo o recursos económicos, así como la condición de migrante indocumentada constituyen barreras para la adhesión a los seguros de salud públicos y privados. Asimismo, los participantes consideran que la asistencia sanitaria pública no tiene en cuenta la importancia que puede tener para ellos seguir un tratamiento cerca de sus familiares o tener la alternativa de las medicinas tradicionales. La tontina permite proteger a las personas más vulnerables como los y las indocumentados y permite financiar las prácticas de importancia cultural para las personas migrantes senegaleses.

CONCLUSIONES: Este estudio fue el primero en proporcionar una comprensión de un mecanismo de financiación propio de una colectiva de migrantes bastante desconocida por la sociedad española. Las tontinas continúan una larga tradición en la que las comunidades desfavorecidas y vulnerables resisten múltiples fuentes de discriminación y desigualdad mediante la autoayuda, la confianza y la solidaridad.

PALABRAS CLAVE

Accesibilidad a los Servicios de Salud, Seguros de Salud Comunitarios, Inmigrantes Indocumentados, Poblaciones Vulnerables, Salud Pública

4.1 INTRODUCCIÓN

El continuo aumento del flujo migratorio conlleva importantes desafíos de tipo político, cultural, social y sanitario en los países de acogida. Si bien la inmigración es un fenómeno social antiguo, su influencia en la política de salud en los países desarrollados ha aumentado en las últimas décadas (Mladovsky et al., 2012). Un ejemplo claro es el cese de cobertura de salud universal en España desde el Real Decreto-Ley (RDL) 16/2012, que excluyó a las personas migrantes indocumentadas del acceso al conjunto de los servicios de salud, a excepción de mujeres embarazadas, niños y la atención de urgencia (López-Fernández et al., 2012). Aunque en determinadas comunidades autónomas se han puesto en marcha otros programas alternativos para seguir dando acceso al sistema sanitario a las personas migrantes indocumentadas, como es el caso de Canarias, Andalucía y País Vasco (Cimas et al., 2016; Gallo & Gené-Badia, 2013), en España, las restricciones del RDL 16/2012 contribuyeron a un aumento de desigualdad socioeconómica, menor uso de atención sanitaria planificada, menores niveles de salud y una mayor tasa de mortalidad en la comunidad de migrantes indocumentadas (Jiménez-Rubio & Vall Castelló, 2020; Juanmarti Mestres et al., 2018). Una de las primeras medidas del nuevo gobierno que tomó posesión en julio de 2018 en España fue restablecer la cobertura sanitaria universal a los inmigrantes que acrediten haber residido más de 90 días en el país. Si bien los cambios resultantes mejoraron el acceso a la atención sanitaria, no restablecieron la cobertura sanitaria universal en España. El Real Decreto Ley 7/2018 fue aprobado en septiembre 2021 por el parlamento español, y se ha convertido en un tema político de primer orden, dada la tendencia generalizada en Europa y más allá de negar la cobertura sanitaria universal a las personas migrantes indocumentadas (Beck et al., 2017; Bruquetas-Callejo & Perna, 2020; Zaklaki, 2019).

A nivel internacional, las barreras más destacadas para el acceso y la utilización de los sistemas sanitarios por parte de las personas migrantes son: las diferencias culturales, el idioma, la zona residencial donde viven, sus condiciones laborales, el miedo a la deportación o la falta de conocimiento del sistema de los "recién llegados" (Badanta-Romero et al., 2021a; Scheppers, 2006). Para hacer frente a las desigualades en el uso y acceso a la asistencia médica, surgieron movimientos de solidaridad, como la Red de Denuncia y Resistencia al RDL 16/2012 (REDER) con el fin garantizar unas protecciones mínimas a las personas migrantes indocumentadas, defendiendo así el acceso universal a la atención médica (Urtaran-Laresgoiti et al., 2019). Asimismo, la comunidad de migrantes senegaleses utiliza las "tontinas" con la finalidad de proteger a sus miembros más vulnerables. Una tontina es un método de ahorro colectivo donde la noción de grupo es determinante en la recaudación y distribución de fondos. En la África subsahariana, las tontinas - también conocidas como asociaciones de ahorro y crédito rotativo (AACR) - se han asentado como sólidas estructuras financieras, y operan de forma autónoma e informal (carecen de regulación estatal o legal) en paralelo con el sector formal (Kounou et al., 2013). Sus miembros se presentan como un mediador entre agentes que tienen alternativamente capacidad y necesidad de financiación. Por lo tanto, su capacidad de asumir la protección social de sus miembros les diferencia del sector formal (Sow, 2006). Esta práctica se deriva de sus costumbres tradicionales de vivir en colectividad y de la existencia, en su sociedad de origen, de agrupaciones entre vecinos o entre personas de la misma edad con el propósito de ayudarse mutuamente por turnos entre diferentes labores u objetivos (construcciones o restauraciones de casas, cosechas, sanidad, etc.) (Henry & Guillerme-dieumegard, 1991; Semin, 2007; Servet & Akpaca, 1995).

La tontina se practica también entre personas migrantes senegaleses en Andalucía y en otras comunidades autónomas como Cataluña, Aragón, etc. (Sow, 2006) Además las tontinas son más utilizadas por las mujeres inmigrantes (Sow, 2006). Sin embargo, en España, muchas comunidades utilizan este sistema "adaptado" a un propósito común y definido: Ayudarse mutuamente a acceder a la atención sanitaria, teniendo mucho más en cuenta a las personas sin recursos, que pueden contribuir menos o incluso estar exentos de contribuir en determinados casos. En la África occidental, las tontinas utilizan sistemas de autogestión sofisticados donde la proximidad, la equidad, la confianza mutua entre los miembros de la tontina, la reciprocidad de acción, enmarcada en medidas coercitivas con respecto al comportamiento oportunista, son la base de los intercambios entre sus miembros (Mayoukou, 1977). Esto se halla además en conformidad con los resultados de la Premio Nobel de 2009 Elinor Ostrom (Ostrom & Merino Pérez, 2015), quien documentó una serie de casos en los que las comunidades cooperan con éxito en la gestión de intereses comunes. Uno de los factores destacados por Ostrom como detrás de este éxito es la importancia de las normas y reglas compartidas por las comunidades para mejorar el comportamiento cooperativo. No obstante, hay escasa literatura sobre el funcionamiento de la tontina fuera del contexto africano.

Este estudio emprende un trabajo cualitativo entre una comunidad de migrantes senegaleses legales e indocumentados residente en Granada (España), con tres objetivos: 1) conocer los factores influyentes en la cobertura de seguros de salud formales, tanto públicos como privados 2) los factores influyentes en la participación en la tontina 3) la contribución de la tontina para el acceso a la salud.

4.2 MATERIAL Y MÉTODOS.

4.2.1 Diseño y muestra

El funcionamiento de las tontinas en el contexto migratorio no ha recibido suficiente atención en la literatura. En este estudio se analiza su uso como un recurso para acceder a los servicios de salud, lo que constituye un tema novedoso. Se ha optado por la metodología cualitativa, puesto que esta permite aproximarnos a nuevos fenómenos sociales y a las realidades sociales caracterizadas por procesos de cambio. Las técnicas de recogida de datos utilizados fueron entrevistas semiestructuradas (Adams, 2015) y grupo de discusión (Krueger & Casey, 2015). El muestreo fue intencional y los participantes eran migrantes de origen senegaleses pertenecientes a una tontina de la provincia de Granada. Los participantes clave fueron identificados con la ayuda de los coordinadores de la tontina, seleccionados en función de su tiempo de participación en la tontina para proporcionar un conocimiento profundo sobre objeto de estudio. Los informantes debían tener una antigüedad en el lugar de trabajo como mínimo de un año. Otros criterios de selección tenían en cuenta la variación de ingresos, la edad y el sexo.

4.2.2 Colección de datos

Se realizaron 14 entrevistas semiestructuradas en octubre y noviembre de 2019 en el lugar de elección de las personas entrevistadas. Los participantes fueron invitados a reflexionar sobre cuatro cuestiones (Figura 4.1, Box 1) relacionadas con las barreras al acceso al sistema sanitario y la ausencia de cobertura de salud formal. Para recoger datos sobre su participación en la tontina y su influencia en el acceso a la sanidad, se realizó un grupo de discusión en el centro cultural senegalés en Granada el 25/10/2019. La guía de preguntas está descrita en la figura 4.1

Box 2. Las entrevistas y el grupo de discusión se realizaron en wolof (idioma nacional de Senegal) y con un investigador cuya lengua madre es wolof para garantizar que los participantes entiendan el propósito del estudio y asegurarse de que el idioma no sea una barrera para expresarse. Un breve cuestionario fue entregado a todos los participantes al inicio de la entrevista y discusión de grupo para recoger las variables edad, sexo, ocupación, estatus de inmigrante y nivel de educación.

Box 1. Temario de la entrevista

- Explicar su situación en España (regular, laboral, familiar, etc.)
- Barreras/Dificultades que han experimentado (experiencias personales o de personas cercanas) para el acceso a la salud
- Conocimientos sobre diferentes seguros formales en España (ejemplos: seguridad social, mutuas)
- Barreras/Dificultades que han experimentado (experiencias personales o de personas cercanas) /que pueden encontrar para la contratación de un seguro formal

Box 2. Temario de la Discusión de grupo

- Explicar las razones de su adherencia a la tontina.
- Cómo caracterizan las tontinas (en general), cómo le diferencian de los otros seguros formales que conocen (seguridad social, mutuas, etc.).
- Barreras/Dificultades que han experimentado (experiencias personales o de personas cercanas) para el acceso a la salud en España
- Soluciones aportadas a las barreras/dificultades que han discutido para el acceso a la salud.
- Otras contribuciones de las tontinas en el acceso a la salud (tanto de sus experiencias en España cómo en Senegal)

Figura 4.1 **Temario de las entrevistas y discusión grupo**

4.2.3 Análisis de datos

Las entrevistas y el grupo de discusión fueron grabadas y transcritas literalmente. Asimismo, las transcripciones fueron traducidos en castellano. Se realizó un análisis temático de contenido,

con el apoyo del software NVIVO 12 Plus. Las categorías y subcategorías se generaron de forma mixta: las derivadas de la guía de entrevista y las emergentes de los datos, mediante un proceso inductivo. Para ello se identificaron temas, se codificaron y clasificaron, se establecieron patrones comunes y se analizaron regularidades, convergencias y divergencias en los datos, mediante un proceso de comparación constante y volviendo a los datos (de lo particular a lo general) (Miles , Huberman, A. M.,, 1994). El análisis parte de la perspectiva de la interseccionalidad donde la desigualdad no puede ser reducida a un solo eje fundamental sino en su plasmación en contextos determinados, y que además permite desentrañar cómo los sujetos otorgan significados que no se corresponden con una visión de las categorías independientes y separadas (Constantinidis et al., 2019; Fajardo-Fernández et al., 2019).

4.2.4 Consideraciones éticas

El estudio fue aprobado por la comisión de ética en investigación de la Universidad de Granada quedando registrado con el no. 1038/CEIH/2020. Los/las participantes dieron su consentimiento informado y se garantizaron el anonimato y la confidencialidad.

4.3 RESULTADOS

4.3.1 Características de la muestra

Tabla 4.1 y 4.2 describen las características de los y las participantes en las entrevistas y en el grupo de discusión. 11 (79%) hombres y 3 (21%) mujeres fueron entrevistados, con una edad media de 41 años mientras que 8 (80%) hombres y 2 (20%) mujeres participaron en el grupo de discusión, con una edad media de 46 años. Las personas migrantes indocumentadas fueron un 63%. 87.5% de los participantes tenían empleo, de los cuales un 46% trabajan en la venta ambulante. La media de familiares dependientes económicamente de las personas migrantes

era 8 personas. Aunque un 86% de los entrevistados tenían conocimientos de los seguros formales públicos y privados, sólo un 7% tenía un seguro privado y un 24% no tenían ni seguros públicos ni privado. Sin embargo, un 29% dejaron su seguro privado cuando se inscribió a la tontina.

Características	Hombre n (%)	Mujer n (%)	Total n (%)
Edad (media), en años	Media (DT) 41 (10.5)	Media (DT) 40.3 (4.7)	Media (DT) 40.9 (9.4)
Sexo	11 (78.57)	3 (21.43)	14 (100)
Estatus de inmigrante en España			
Documentado/a	5 (45.45)	2 (66.67)	7 (50)
Indocumentado/a	6 (54.55)	1 (33.33)	7 (50)
Ocupación			
Venta ambulante	3 (27.27)	1 (33.33)	4 (28.57)
Ayudante cocinero	1 (9.09)	0	1 (7.14)
Estudiante	1 (9.09)	0	1 (7.14)
Agente de seguridad	0	1 (33.33)	1 (7.14)
Informático/a	1 (9.09)	0	1 (7.14)
Soldador/a	0	1 (33.33)	1 (7.14)
Obrero/a agrícola	3 (27.27)	0	3 (21.43)
Traductor/a Jurado/a	1 (9.09)	0	1 (7.14)
Desempleado/a	1 (9.09)		1 (7.14)
Educación			
Sin estudios	5 (45.45)	2 (67.67)	7 (50)
Secundario	3 (27.27)	1 (33.33)	4 (28.57)
Estudios universitarios	3 (27.27)	0	3 (21.43)
Nº de familiares dependientes	Media (DT) 8 (3.3)	Media (DT) 9 (3.5)	Media (DT) 8 (3.2)
Personas migrantes con conocimientos sobre seguros formales			
Si	10 (90.91))	2 (66.67)	12 (85.71)
No	1 (9.09)	1 (33.33)	2 (14.29)
Personas migrantes con seguro de salud privado			
Si	1 (9.09)	0	1 (7.14)
No	10 (90.91)	3 (100)	13 (92.86)
Personas migrantes con protección social publica			
Si	9 (81.82)	2 (66.67)	11 (78.57)
No	2 (18.18)	1 (33.33)	3 (21.43)
Personas que dejaron su seguro privado por participar en la tontina	3 (27.27)	1 (33.33)	4 (28.57)

DT, desviación típica

Tabla 4.1 Características de los participantes en las entrevistas

Características	Hombre n (%)	Mujer n (%)	Total n (%)
Edad (media), en años	Media (DT) 43.6 (16.4)	Media (DT) 56.5 (14.8)	Media (DT) 46.2 (16.2)
Sexo	8 (80)	2 (20)	10 (100)
Estatus de inmigrante en España			
Documentado/a	1 (12.5)	1 (50)	2 (20)
Indocumentado/a	7 (87.5)	1(50)	8 (80)
Ocupación			
Venta ambulante	7 (87.5)	0	7 (70)
Jubilado/a	0	1 (50)	2 (20)
Obrero/a agrícola	1 (12.5)	1 (50)	1 (10)
Educación			
Sin estudios	4 (50)	2 (100)	6 (60)
Secundario	4 (50)	0	4 (40)
Nº de familiares dependientes	Media (DT) 7.5 (3.6)	Media (DT) 8.5 (0.7)	Media (DT) 7.7 (3.7)

DT, desviación típica

Tabla 4.2 Características de los participantes en DGF

4.3.2 Factores influyentes en la ausencia de cobertura de las personas migrantes en seguros de salud formales.

4.3.2.1 Barreras/dificultades para acceso a seguros sanitarios formales (públicos y privados)

Las ideas principales se muestran en la tabla 4.3 con citaciones textuales de los participantes. Todos los y las entrevistados ven como condicionante a la inscripción de un seguro de salud formal (tanto público como privado) la necesidad de disponer de la documentación legal. Las personas migrantes indocumentadas con certificado de empadronamiento si tenían acceso a la sanidad pública. Sin embargo, los y las participantes relataron que aquellos que tienen dificultades en obtener el empadronamiento por diferentes motivos o que no pueden demostrar una residencia legal mayor de 3 meses no podrían tener acceso a la sanidad pública o atención primaria. Cuando están admitidas en urgencias debían financiar su uso de los servicios sanitarios por sus recursos propios o a través de los servicios sociales. La falta de trabajo u otros

ingresos periódicos, y el coste de los seguros de salud fueron las principales barreras señaladas para la contratación de los seguros privados.

4.3.2.2 Lagunas en los seguros formales

Por otra parte, los participantes relatan que los seguros de salud formales no permiten la repatriación de los pacientes que prefieren seguir un tratamiento cerca de sus familiares en Senegal. Según los participantes, mucho de las personas migrantes senegaleses carecían de apoyo familiar en España y no suelen tener la ayuda necesaria a domicilio para cuidarse durante la rehabilitación después del tratamiento médico- Además, afirmaron que seguir un tratamiento en su país de origen les permite poder optar a la medicina tradicional en la que mucho de ellos confían por sus creencias y tradiciones. No obstante, sólo el 20% de los participantes preferían la medicina tradicional que la occidental.

Además, para una persona que se acerque al final de su vida, la repatriación mientras todavía estuviera viva evitaría el coste mucho mayor de expatriación del cadáver a sus familiares en caso de fallecimiento. Las personas migrantes senegaleses piden ser sepultado en su tierra de origen por sus costumbres.

4.3.2 Factores influyentes en la participación en la tontina

4.3.3.1 Motivos de la participación en la tontina

Las personas migrantes senegaleses consideran relevantes, en su adhesión a la tontina, la necesidad de proteger los más vulnerables: indocumentados, personas mayores, personas migrantes en desempleo, etc. Asimismo, los participantes afirman que, gracias a su capacidad de compartir riesgos entre un gran número de personas, la tontina tiene un coste mensual menor que los seguros privados y tiene más en cuenta la situación de las personas migrantes: los

indocumentados sin protección social, la necesidad del apoyo familiar para la rehabilitación, etc. El coste de adhesión a la tontina varía según cada situación pudiendo llegar a ser cero para los más vulnerables (personas migrantes en desempleo, personas mayores o personas con determinadas enfermedades).

4.3.3.2 Transparencia y autogestión

Otro punto expresado por los y las participantes a favor de la tontina fue la transparencia. A través de sistemas colectivos de autogestión y gobernanza interna, los propios miembros de la tontina son responsables para su gestión, así como decidir sobre las normas de admisión de nuevos candidatos. Para ser miembro de la tontina es imprescindible ser apadrinado por un miembro de la tontina.

4.3.4 Contribución de la tontina para el acceso a la salud

4.3.4.1 Acceso a la asistencia medica

La tontina permite el acceso a la atención médica a las personas migrantes indocumentadas excluidos del acceso a la sanidad pública por barreras administrativas: no disponer de la tarjeta sanitaria por no tener el certificado de empadronamiento u otros motivos. Asimismo, permite a las personas migrantes indocumentadas sin protección social la financiación del acceso a los servicios hospitalarios públicos (alta hospitalaria programado o urgente y urgencia ambulatoria) así como el acceso a un tratamiento en centros privados y el acceso a los fármacos con receta.

4.3.4.2 Acceso a las prácticas de importancia cultural

La tontina permite financiar las prácticas de importancia cultural para las personas migrantes senegaleses como seguir un tratamiento con la medicina tradicional, así como, si fuese

necesario, la financiación de la expatriación de los cadáveres por avión a su país de origen. Además, la tontina permite seguir un tratamiento en su país de origen.

TEMAS		CITACIÓN
Factores influyentes en la cobertura de seguros de salud formales, tanto públicos como privados.	Barreras/dificultades para acceso a seguros formales	E8 “Por ejemplo el seguro de salud del banco es formal pero no todos podemos tenemos acceder a esta opción, los que no tienen papeles (refiriéndose a los inmigrantes irregulares) no pueden tenerlo” E4 “Si tengo conocimientos de los seguros privados porque lo tenía antes, Ahora no lo tengo. Es más caro también y no es asequible para los que no trabajan o aquellos que tienen trabajos precarios como la venta ambulante”
	Lagunas en los seguros formales	E13 “Nosotros no somos de aquí (España), si yo mañana estoy muy enfermo quien me cuida, mi familia está muy lejos y prefiero curarme allí y si me tengo que morir que no les suponga un coste. Todos los senegaleses que se mueren aquí ponemos dineros entre nosotros y pagamos para que pueda volver con su familia y descansa en su tierra. Ningún senegalés quiere que le sepulten aquí y los seguros de salud de aquí no te permiten eso”
Factores influyentes en la participación en la tontina	Motivos para la participación en la tontina	P4 “Nuestra tontina no tiene restricciones cómo los seguros formales y podemos permitir a los inmigrantes de orígenes senegaleses, especialmente los más vulnerables a participar en ella.” P10 “Yo pagaba 70 euros anuales en los bancos, pagaba más, pero también si pasa algo el beneficio que uno gana con los bancos es mayor. Pero aquí poniendo 25 euros estoy ayudando a otros que no podían pagar 70 euros en el banco. La tontina es más social”
	Transparencia y autogestión	P8 “Hay transparencia, es para todos los senegaleses, lo gestionamos nosotros y nos conocemos muy bien. Hay un grupo de persona que controlan todos los niveles y es como un sistema formal: Vamos y hablamos con la gente para decirle cómo funciona y en cada evento que tenemos le recordamos la importancia. Tenemos un tesorero y por cada aportación recibes una factura y todos tienen una tarjeta de miembro de la asociación”
Contribución de tontina para el acceso a la salud	Acceso a la asistencia medica	P7 “Actualmente, por ejemplo, la tontina es muy beneficioso en Senegal. Por ejemplo, los que los usan con objetivos de celebraciones matrimoniales u otras cosas son exitosos y solo lo usan gente que decimos que no pueden ahorrar nada al fin de mes. Así como tal si lo hacemos para la salud y funciona.

		Aquí, cotizamos no todos la misma cantidad, tenemos muy en cuenta la gente que no puede hacerlo porque nos conocemos muy bien y si le pasa algo alguien le damos una cantidad con el que se paga las consultaciones e incluso sus medicinas"
	Acceso a servicios de importancia cultural	P6 "Muchas gentes piensan en la medicina tradicional cuando llevan meses con tratamiento y no ven mejoras, y también hay otras personas que por ejemplo el medico les dice que le quedan poco tiempo de vida y prefieren volver con sus familiares, todo esto nuestra tontina lo garantiza con una ayuda económica" P1 "Es una ayuda mutua, el que es miembro imagínate, tocando madera, que le pase algo (refiriéndose a la muerte) eso permite que le llevamos de retorno a Senegal porque nadie quiere quedarse aquí. Todos queremos una sepultura en cementerio respecto a nuestra religión y que se no sepulten en nuestra tierra cerca de nuestros familiares. Ser miembro de esta tontina te permite esto".

Tabla 4.3 Resumen de citaciones textuales

4.4 DISCUSIÓN

Aunque hay literatura sobre otras funciones de las tontinas en España (Sow, 2006), hasta dónde sabemos este es el primer estudio sobre la financiación informal del acceso y uso de los servicios sanitarios para las personas migrantes.

Los relatos de los participantes muestran, en consonancia con otro estudio (Bas-Sarmiento et al., 2015), que, aunque en Andalucía no se aplicó el Real Decreto-Ley 16/2012, las personas migrantes indocumentadas recién llegadas o con dificultades administrativas de disponer de pruebas de residencia mayor de 3 meses estaban excluidas de los servicios sanitarios primarios y preventivas. Y como resultado, la condición de migrante indocumentado se convierte en un eje de desigualdad definido por su propio estatus en la sociedad, constituido por las restricciones en acceso sanitarias junto con las limitaciones en el acceso al mercado de trabajo, diferencias

culturales, y otros factores estructurales de que dependen sus condiciones de vida (Borrell et al., 2012; Gea-Sánchez et al., 2017a).

Contrariamente a otras colectivas de personas migrantes (Badanta-Romero et al., 2021b), el 80% de la muestra prefieren, como primera opción, la medicina occidental que la medicina tradicional, datos que coinciden con los resultados de Ojeleke (Ojeleke et al., 2020). Sin embargo, los resultados muestran que las personas migrantes senegaleses quieren tener la opción de la medicina tradicional. Estos hallazgos pueden explicarse por, en primer lugar, la tendencia de preservar su identidad cultural y tener la medicina tradicional como alternativa (Agudelo-Suárez et al., 2012), y, en segundo lugar, la "gravedad" de la enfermedad, tipo de atención recibida y recursos financieros (Chavez Rodriguez & Córdova Ramírez, 2018).

Finalmente, este estudio pone de manifiesto que, para las personas migrantes senegaleses, las protecciones sanitarias públicas no tienen en cuenta las opciones de ser tratado en su país de origen o sus prácticas culturales como el acceso a la medicina tradicional cómo alternativa, así como la expatriación de los cadáveres. En este sentido, la tontina complementa los servicios formales ofreciendo estos servicios con un sistema basado en la proximidad, la equidad, la confianza mutua entre sus miembros (Mayoukou, 1977). Las tontinas continúan una larga tradición en la que las comunidades desfavorecidas y vulnerables resisten estas múltiples fuentes de discriminación y desigualdad mediante la autoayuda, la confianza y la solidaridad (Schmid et al., 2010).

4.4.1 Fuertes y limitaciones del studio

En primer lugar, se utilizó una muestra de conveniencia, no incluyendo las personas migrantes senegaleses para quienes la tontina no ha funcionado tan bien o quienes por alguna razón no

pudieron o no quisieron participar en la tontina, lo que dificulta inferir que nuestra muestra fue representativa de la comunidad migrantes senegaleses en Andalucía o España. Asimismo, la participación de los hombres fue bastante dominante en la muestra (79%). Sin embargo, a pesar del pequeño tamaño de la muestra, es interesante notar el alto grado de acuerdos entre los participantes y los resultados son consistentes con otros estudios11,27. Otra limitación puede estar relacionada con la traducción de las transcripciones. A pesar de que la realización de las entrevistas y el grupo de discusión en el dialecto senegalés, wolof, limita las dificultades de comunicación y la negatividad de la participación, su traducción al castellano podría provocar la pérdida de significado de algunas palabras.

Este estudio se enfocó en el uso de los sistemas de financiación formales, así como la utilización y contribución de la tontina para el acceso a la atención médica. Se ha planificado investigaciones futuras para comparar las experiencias de los miembros de tontinas en otras ciudades españoles y profundizar en algunos factores tratados superficialmente en este trabajo, por ejemplo, para el rol de las mujeres en la asociación, su gobernanza, así como estimar de forma cuantitativa el uso y los costes de los servicios sanitarios formales y tradicionales para los miembros de la asociación(copagos, tarifas públicas y precios privados), y su método de financiación (pago de bolsillo, tontina o seguridad social).

4.4.2 Conclusión

Las personas migrantes senegaleses utilizan las tontinas para la financiación de los servicios de prácticas culturales no incluidos en el sistema de salud español, así como la financiación del acceso a la salud a las personas migrantes indocumentadas excluidas del acceso a la atención médica. Asimismo, este estudio fue el primero en proporcionar una comprensión de un

mecanismo de financiación propio de una colectiva de migrantes bastante desconocida por la sociedad española.

CHAPTER V. CONCLUSIÓN

Como la ambición y entorno de una investigación en políticas sanitarias es amplia, y las decisiones dependen tanto en la evidencia cuantitativa como en la cualitativa, el investigador en economía de la salud tiene que conocer y aplicar metodologías diversas. En ese marco, esta tesis presenta diversas herramientas metodológicas dirigidas a la economía de la salud que permiten evaluar nuevas programas o tecnologías sanitarias. En línea general, los resultados de este trabajo muestran que diversas metodologías pueden emplearse en la evaluación económica y los resultados son muy sensibles a los métodos empleados. Además, dado que muchos de los factores que impactan la salud quedan excluidos de la perspectiva clínica o del sistema de salud, es necesario salirse del paradigma de los análisis parciales o "microeconómicos" de la intervención hacia una evaluación de coste-beneficio más amplio de los impactos y la aceptabilidad de las políticas en las diferentes partes interesadas. En este sentido el enfoque cualitativo tiene el potencial de ayudar al investigador, y el público en general, a comprender el impacto de los factores en la salud de manera más amplio.

Al abordar los diferentes trabajos presentados, el capítulo dos compara siete metodologías diferentes para el tratamiento de los datos faltante en un análisis coste efectividad. Para cada método, se explica los supuestos que los identifican, se lleva a cabo un análisis de coste efectividad y se informa los coeficientes y las desviaciones típicas asociadas a cada intervención. Este capítulo ofrece una verdadera comprensión del uso de las diferentes estrategias, y más utilizadas en el campo de economía de la salud, para el manejo de los datos faltante. Asimismo, dado la variabilidad de los métodos, el investigador debe ser consciente de las limitaciones de cada uno de los métodos. Este trabajo subraya la importancia de realizar análisis de sensibilidad utilizando enfoques alternativos en el manejo de los datos faltantes. Futuras investigaciones podrían considerar modelos para manejar distribuciones no normales y mecanismos de datos faltantes más complejos.

El capítulo tres revisa sistemáticamente el impacto de los costes y de la calidad de vida de la lesión de la médula espinal en los servicios de salud, los pacientes y la sociedad en general. Este trabajo destaca que la heterogeneidad es inevitable en las revisiones sistemáticas. Por lo tanto, se necesita cautela en las conclusiones extraídas y puede ser necesario llevar a cabo diferentes tipos de análisis para manejar la heterogeneidad. Finalmente, el capítulo cuatro se enfocó en el uso de los sistemas de financiación formales, así como la utilización y contribución de la tontina para el acceso a la atención médica. Este estudio pone de manifiesto las carencias de las protecciones sanitarias públicas para las personas migrantes senegaleses como la no consideración de las opciones de ser tratado en su país de origen o no acceso a sus prácticas culturales como el acceso a la medicina tradicional cómo alternativa, así como la expatriación de los cadáveres.

Fuertes y limitaciones de los trabajos presentados

En este trabajo, hemos considerado los métodos para manejo de datos faltante comúnmente utilizado en evaluaciones de tecnologías sanitaria, Sin embargo, cabe mencionar la disponibilidad de otros modelos sofisticados, que no han sido tratado en este trabajo. Asimismo, cómo se mencionó en el capítulo 2, asumimos que los datos son faltantes al azar (missing at random) y no hemos investigado métodos para situaciones en las que los datos no son faltantes al azar (missing not at random). Los métodos para datos faltantes se han aplicado a un solo caso de estudio. Por lo tanto, hay que probar los métodos en otros ensayos y además realizar simulaciones para concluir sobre la generalización de nuestros resultados.

Aunque fuimos cauteloso en la revisión sistemática respecto a las diferencias en diseños de los estudios, zonas geográficas y metodologías, la calidad de vida, así como los costes de las personas con SCI pueden depender de otros factores tales como culturales, institucionales y

ambientales más amplios, incluidas las actitudes de la sociedad hacia la discapacidad. Asimismo, tales factores deben tenerse en cuenta para la transferibilidad de los resultados de un país a otro.

Finalmente, para la evaluación de los determinantes en la financiación del acceso a la atención médica y el papel de la tontina, se utilizó una muestra de conveniencia, no incluyendo las personas migrantes senegaleses para quienes la tontina no ha funcionado tan bien o quienes por alguna razón no pudieron o no quisieron participar en la tontina, lo que dificulta inferir que nuestra muestra fue representativa de la comunidad migrantes senegaleses. Asimismo, hay escaso estudios sobre el uso o acceso o la financiación de la salud de las personas migrantes indocumentadas y sobre la tontina fuera del contexto africano. En este aspecto, nuestro trabajo contribuye en la literatura aportando evidencia sobre la financiación informal del acceso y uso de los servicios sanitarios para las personas migrantes.

Esta tesis ha presentado tres trabajos originales dentro la disciplina de la evaluación económica de los programas de salud. Aunque se trate de trabajos en diferentes populaciones y contextos, el hilo unificador es la ambición de proporcionar medidas prácticas para abordar retos metodológicos corrientes en la evaluación económica y enriquecer este campo de investigación. Asimismo, esta tesis hace hincapié sobre la necesidad de tener conocimientos en diversas técnicas para un uso eficiente de las evidencias desde la perspectiva de todas la partes involucradas y afectadas. Sin embargo, la complejidad presente en las evidencias clínicas, accesos a la atención médica y la organización de los sistemas de salud requiere que un investigador en evaluación económica investiga a menudo cuestiones particulares de manera interdisciplinaria. Asimismo, el investigador en evaluación económica debe tener aptitudes en

diversas líneas de investigación como la estadística, epidemiologia, economía, ciencias de la salud, métodos cualitativos etc. así como saber trabajar en equipo multidisciplinario.

Futuros líneas de investigación

Futuros líneas de investigaciones podrían profundizar algunos factores tratados superficialmente en este trabajo. Uno de ellos es la integración de los enfoques cualitativos y cuantitativos en la misma línea de investigación. Se ha puesto en marcha un nuevo proyecto estimar de forma cuantitativa el uso y los costes de los servicios sanitarios formales y tradicionales utilizados para los miembros de la tontina y su método de financiación (pago de bolsillo, tontina o seguridad social) en comparación con los inmigrantes que no son miembros de una tontina, y en comparación con la población autóctona. También, este proyecto va a utilizar métodos cualitativos para profundizar en la investigación de la gobernanza de la tontina. Pretendemos seguir en esta línea de investigación y para ello contamos con la financiación de la Unidad de Excelencia de la Universidad de Granada de 2021 (en colaboración varios profesores e investigadores, del Departamento de Economía Aplicada, del Departamento de Sociología, y del Departamento de Anatomía Patológica e Historia de la Ciencia de la Universidad de Granada y Papa Sow, Investigador en African Basic Research Institute, Universidad de Cheikh Anta Diop de Dakar) y de la beca de la Asociación de Economía de la Salud en investigación de economía de la salud y servicios sanitarios de 2022.

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APPENDIX CHAPTER 2

Supplementary material

Description of the difference between models that use aggregate data and models that use longitudinal data

We present a hypothetical example to explain the different ways that the models use the available data. Table S1 shows 3 hypothetical stylised subjects, in a dataset with outcome variables for period costs and EQ-5D collected at the end of two time periods (year 1 and year 2). Subject 1 had complete data, subject 2 was missing cost data at follow-up, and subject 3 was missing EQ-5D data at one follow-up. Hence total cost over 2 years cannot be calculated for subject 2 and total QALY cannot be calculated over 2 years for subject 3.

Subject ID	Baseline EQ-5D	Costs during year 1	Costs during year 2	EQ-5D at the end of year 1	EQ-5D at the end of year 2
1	0.5	10	15	0.5	0.5
2	0.6	missing	20	0.6	0.6
3	0.4	5	10	missing	0.4

Table S2.1 Hypothetical dataset with missing data

Complete case analysis (CCA) would only include the aggregate observations from subject 1 in the model, and subjects 2 and 3 would be excluded from the analysis (see Table S2).

Subject ID	Total cost over 2 years	Total QALY over 2 years
1	25	1
2	Subjects 2 and 3 are excluded from the CCA analysis	
3		

Table S2.2 Aggregate data included in CCA

Bayesian Parametric Analysis (BPA) would include aggregate data for all 3 subjects as shown in Table S3. The missing data the total cost for subject 2 and the total QALY for subject 3 would be estimated as parameters by the software.

Subject ID	Total cost up to the end of year 2	Total QALY up to the end of year 2
1	25	1
2	missing	1.2
3	15	missing

Table S2.3 Aggregate data included in BPA

Multiple Imputation (MI) using chained equations would include all the longitudinal data from Table S1. MI imputes the missing data at each interim period and generates M complete data sets. Total cost and total QALY are then calculated passively for each imputed dataset for all 3 subjects. Both methods (MILR and MIPMM) described in the main paper allow the imputation. Total mean cost and total mean QALY are then estimated jointly for each imputed dataset using bivariate normal regression, and estimates are combined across the imputed datasets using Rubin's rules. The cost-effectiveness acceptability curve can be estimated parametrically from the variance-covariance matrix of the regression.

Subject ID	Total cost up to the end of year 2	Total QALY up to the end of year 2
1	25	1
2	missing	1.2
3	15	missing

Table S2.4 Disaggregate data included in MI

Choosing an imputation model

MILR: $Y_i \sim N(\beta_0 + \beta_1 X_, \sigma^2)$

a) Estimate $\beta = (\beta_{0,} \beta_1, \sigma)$ from complete cases, giving estimates $\widehat{\beta_{0,}}\ \widehat{\beta_1}, \widehat{\sigma}$
b) Draw β from its posterior
   - For linear regression this done exactly
   - Giving perturbed parameters ${\beta^*}_0 + {\beta^*}_1$ and σ^*
c) Impute missing values for subject 2 and 3. Here involves ${Y^*}_i \sim N({\beta^*}_0 + {\beta^*}_1 X_i, {\sigma^*}^2)$

b) and c) are repeated m times to create m datasets

MIPMM:

a) Regress Y on X using cases with Y observed, giving $\hat{\beta}$
b) Draw β^*
c) Impute all the missing values of Y:

- Predict all observed Y values using $\hat{\beta}$
- Predict all missing Y values using β^*
- For each missing Y value:
    i. Find the K individuals with observed Y whose $\hat{\beta}X$ are nearest to β^*X for the missing value
    ii. Select one of these K individual at random
    iii. Impute using the chosen individual's value of Y

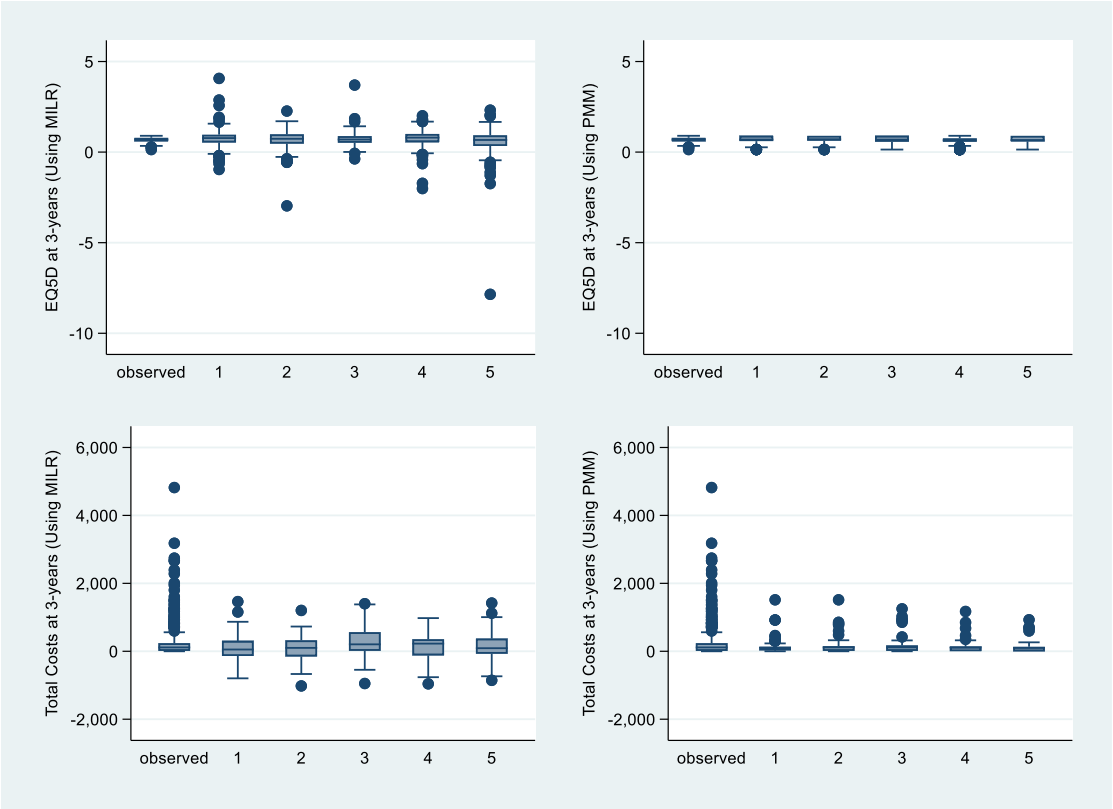
The repeated measures mixed model (RMM) and fixed effect (RMFE) also includes all the longitudinal data from Table S1. RMM and RMFE estimate separate models for the period costs and EQ-5D. All the available data (the period costs at each time point, and the EQ-5D at each time point) are used in the analysis model, and then the total mean costs and total mean QALY are predicted from the estimated coefficients. Bootstrap can be used to estimate the correlation between total mean cost and total mean QALY.

Data quality

Did the trial involve a quality manager?	Trial manager
Measures taken to anticipate the extent, pattern, and causes of missing data at the study design stage	A follow-up on any missing data from the outset to keep to a minimum
Design of cost components of the questionnaires	The resource diary was designed in collaboration with the Health Economist and trial project team, based on previous experience
How were questionnaires piloted?	Patient resource use diaries were used in other vascular studies by this team with minor adaptions for this context
Use of measures for improving probabilities that respondents would answer the phone	Cost data was collected at the same time of clinical data so repeated calls were made if the phone was not answered. Interviewers would note convenient times to call individual participants
Did any data collection coordination exist between phone calls and photos?	Yes, the interviewers would be aware when the ulcer was healed or not and therefore could prompt the participants re: expected resource use
How were interviewers selected and trained?	The interviewers were Vascular nurses, trained by the Trial Manager at the outset and on an ongoing basis when required
Did data collectors use paper forms or enter data directly into an electronic device?	Paper forms were used which were transcribed into the electronic database. A subset of forms at each recruiting site were checked annually for data entry errors
Were random checks performed on completed forms and data completeness, accuracy, and consistency?	Reports were run on a bimonthly basis by the Trial Manager to review data completeness, accuracy, and consistency.
Did interviewers meet regularly with supervisors for feedback, discussion of quality control procedures, and observation checks?	The trial manager regularly fed back any observations from the data reviews, or monitoring visits to ensure consistency of the data collection between the research sites

Were proportions of missing data across interviewers compared?	No, but each site received feedback to ensure consistency between sites
Measures in response to detected errors	Data queries were raised in the database and followed up until completion or exhaustion of efforts.

Table S2.5 Data quality



MILR: Multiple imputation using linear regression MIPMM multiple imputation using predictive mean matching

Supplementary figure S2.1 Distribution of imputations at 3-year for MILR and MIPMM

Logistic regression — Number of obs = 7,200; LR chi2(24) = 1394.64; Prob > chi2 = 0.0000; Log likelihood = -1791.3125; Pseudo R2 = 0.2802

M_c_total_	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
trt	.0282749	.0899957	0.31	0.753	-.1481134	.2046632
size	-.0012455	.0021421	-0.58	0.561	-.0054439	.0029529
duration	-.0930757	.0341044	-2.73	0.006	-.1599191	-.0262323
age	-.015338	.0030682	-5.00	0.000	-.0213516	-.0093244
sitegroup	.0788522	.0088615	8.90	0.000	.0614839	.0962204
ethn	.1649945	.0506233	3.26	0.001	.0657747	.2642143
dvt	.3155367	.1498264	2.11	0.035	.0218824	.6091909
diabetic	.2002774	.1300238	1.54	0.123	-.0545646	.4551194
whichleg	.0458514	.0896908	0.51	0.609	-.1299394	.2216422
wk						
0	0	(empty)				
4	-5.202004	.4260024	-12.21	0.000	-6.036953	-4.367054
6	0	(empty)				
8	-4.786957	.3548074	-13.49	0.000	-5.482367	-4.091548
13	-4.489685	.3131752	-14.34	0.000	-5.103497	-3.875873
17	-4.125369	.271147	-15.21	0.000	-4.656807	-3.59393
19	-4.065003	.2650354	-15.34	0.000	-4.584463	-3.545544
26	-3.953224	.2543048	-15.55	0.000	-4.451653	-3.454796
30	-3.80382	.2410908	-15.78	0.000	-4.27635	-3.331291
34	-3.671557	.2304028	-15.94	0.000	-4.123138	-3.219975
39	-3.630592	.2272747	-15.97	0.000	-4.076042	-3.185141
43	-3.552676	.2215531	-16.04	0.000	-3.986912	-3.11844
47	-3.515542	.2189286	-16.06	0.000	-3.944634	-3.08645
52	-3.479517	.216444	-16.08	0.000	-3.90374	-3.055295
104	-3.195385	.1988453	-16.07	0.000	-3.585114	-2.805655
156	-2.590122	.1714137	-15.11	0.000	-2.926086	-2.254157
208	-1.668972	.1487187	-11.22	0.000	-1.960455	-1.377489
260	0	(omitted)				
_cons	-.2184967	.1964492	-1.11	0.266	-.60353	.1665365

Table S2.6 Missingness mechanism in costs

Logistic regression — Number of obs = 3,150; LR chi2(15) = 1749.16; Prob > chi2 = 0.0000; Log likelihood = -1228.5817; Pseudo R2 = 0.4158

M_eq5d	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
trt	-.0089402	.102411	-0.09	0.930	-.2096622	.1917817
size	.0007334	.0021134	0.35	0.729	-.0034087	.0048755
duration	.0461652	.0390633	1.18	0.237	-.0303975	.1227279
age	-.0114205	.0036461	-3.13	0.002	-.0185666	-.0042744
sitegroup	.038745	.0106635	3.63	0.000	.0178449	.0596452
ethn	.0734084	.0703374	1.04	0.297	-.0644505	.2112672
dvt	-.019235	.1776667	-0.11	0.914	-.3674554	.3289854
diabetic	.1243942	.1494422	0.83	0.405	-.1685071	.4172955
whichleg	.2007494	.1023966	1.96	0.050	.0000556	.4014431
wk						
4	0	(empty)				
6	2.815483	.7330868	3.84	0.000	1.378659	4.252307
8	0	(empty)				
13	0	(empty)				
17	0	(empty)				
19	0	(empty)				
26	3.7715	.7206433	5.23	0.000	2.359065	5.183935
30	0	(empty)				
34	0	(empty)				
39	0	(empty)				
43	0	(empty)				
47	0	(empty)				
52	3.960838	.7193332	5.51	0.000	2.550971	5.370705
104	0	(empty)				
156	7.534148	.7247638	10.40	0.000	6.113637	8.954659
208	6.297947	.7167442	8.79	0.000	4.893154	7.70274
260	6.406705	.7170898	8.93	0.000	5.001234	7.812175
_cons	-6.175076	.7400978	-8.34	0.000	-7.62564	-4.724511

Table S2.7 Missingness mechanism in EQ5D

```
Fixed-effects (within) regression               Number of obs     =      6,861
Group variable: subjectnum~r                    Number of groups  =        450

R-sq:                                           Obs per group:
     within  = 0.1077                                         min =          1
     between = 0.0023                                         avg =       15.2
     overall = 0.0843                                         max =         17

                                                F(32,6379)        =      24.05
corr(u_i, Xb)  = -0.0037                        Prob > F          =     0.0000
```

c_total_	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
size	0	(omitted)				
duration	0	(omitted)				
age	0	(omitted)				
sitegroup						
Cambridge University Hospitals NHS F..	0	(omitted)				
Frimley Park Hospital NHS Foundation..	0	(omitted)				
Gloucestershire Hospitals NHS Trust	0	(omitted)				
Heart of England NHS Trust	0	(omitted)				
Hull & East Yorkshire Hospitals NHS ..	0	(omitted)				
Imperial College NHS Healthcare Trust	0	(omitted)				
Leeds Teaching Hospitals NHS Trust	0	(omitted)				
North Cumbria University Hospitals N..	0	(omitted)				
North West London Hospitals NHS Trust	0	(omitted)				
Plymouth Hospitals NHS Trust	0	(omitted)				
Salisbury NHS Foundation Trust	0	(omitted)				
Sheffield Teaching Hospitals NHS Fou..	0	(omitted)				
Taunton and Somerset NHS Foundation ..	0	(omitted)				
The Dudley Group NHS Foundation Trust	0	(omitted)				
The Royal Bournemouth and Christchur..	0	(omitted)				
The Royal Wolverhampton Hospitals NH..	0	(omitted)				
University Hospitals Birmingham NHS ..	0	(omitted)				
Worcestershire Acute Hospitals NHS T..	0	(omitted)				
York Hospitals NHS Foundation Trust	0	(omitted)				
trt						
EVRA	0	(omitted)				
wk						
4	314.6783	41.73497	7.54	0.000	232.8637	396.4929
8	262.9023	41.87566	6.28	0.000	180.812	344.9927
13	217.8526	42.06686	5.18	0.000	135.3874	300.3178
17	249.8257	42.12755	5.93	0.000	167.2416	332.4099
19	266.8738	42.18627	6.33	0.000	184.1745	349.573
26	288.5732	42.24059	6.83	0.000	205.7674	371.3789
30	240.2317	42.29739	5.68	0.000	157.3146	323.1488
34	219.6135	42.40893	5.18	0.000	136.4778	302.7493
39	199.3411	42.4655	4.69	0.000	116.0945	282.5878
43	193.1009	42.52197	4.54	0.000	109.7435	276.4582
47	169.2793	42.52197	3.98	0.000	85.92199	252.6367
52	158.4613	42.52197	3.73	0.000	75.10394	241.8186
104	350.1617	42.85044	8.17	0.000	266.1605	434.163
156	306.6475	43.58525	7.04	0.000	221.2058	392.0893
208	194.362	45.81949	4.24	0.000	104.5404	284.1836
260	70.45295	59.64915	1.18	0.238	-46.47942	187.3853
trt#wk						
EVRA# 4	563.0859	59.26814	9.50	0.000	446.9004	679.2714
EVRA# 8	98.16214	59.4183	1.65	0.099	-18.3177	214.642
EVRA# 13	3.540809	59.55321	0.06	0.953	-113.2035	120.2851
EVRA# 17	-58.64266	59.76523	-0.98	0.327	-175.8026	58.51727
EVRA# 19	-96.15819	59.80663	-1.61	0.108	-213.3993	21.0829
EVRA# 26	-137.1768	59.88484	-2.29	0.022	-254.5712	-19.78238
EVRA# 30	-104.3542	60.0068	-1.74	0.082	-221.9877	13.27926
EVRA# 34	-93.61363	60.12626	-1.56	0.120	-211.4813	24.25404
EVRA# 39	-59.7594	60.16618	-0.99	0.321	-177.7053	58.18653
EVRA# 43	-96.41856	60.24624	-1.60	0.110	-214.5214	21.68432
EVRA# 47	-67.39876	60.28647	-1.12	0.264	-185.5805	50.78297
EVRA# 52	-44.73532	60.32678	-0.74	0.458	-162.9961	73.52543
EVRA#104	-51.32446	60.65976	-0.85	0.398	-170.238	67.58905
EVRA#156	-34.86661	61.85028	-0.56	0.573	-156.1139	86.38071
EVRA#208	25.27543	65.43716	0.39	0.699	-103.0034	153.5543
EVRA#260	43.84911	85.08868	0.52	0.606	-122.9533	210.6515
_cons	4.312527	20.98281	0.21	0.837	-36.82083	45.44588
sigma_u	235.79805					
sigma_e	442.00888					
rho	.22154103	(fraction of variance due to u_i)				

```
F test that all u_i=0: F(449, 6379) = 4.31                     Prob > F = 0.0000
```

Table S2.8 Treatment costs over 1 to five years using repeated measures fixed effect.

Fixed-effects (within) regression — Number of obs = 1,929
Group variable: subjectnum~r — Number of groups = 450

R-sq:
within = 0.1184
between = 0.0164
overall = 0.0546

Obs per group:
min = 1
avg = 4.3
max = 5

F(12,1467) = 16.42
corr(u_i, Xb) = 0.0009 — Prob > F = 0.0000

eq5d	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
size	0	(omitted)				
duration	0	(omitted)				
age	0	(omitted)				
sitegroup						
Cambridge University Hospitals NHS Found..	0	(omitted)				
Frimley Park Hospital NHS Foundation Trust	0	(omitted)				
Gloucestershire Hospitals NHS Trust	0	(omitted)				
Heart of England NHS Trust	0	(omitted)				
Hull & East Yorkshire Hospitals NHS Trust	0	(omitted)				
Imperial College NHS Healthcare Trust	0	(omitted)				
Leeds Teaching Hospitals NHS Trust	0	(omitted)				
North Cumbria University Hospitals NHS T..	0	(omitted)				
North West London Hospitals NHS Trust	0	(omitted)				
Plymouth Hospitals NHS Trust	0	(omitted)				
Salisbury NHS Foundation Trust	0	(omitted)				
Sheffield Teaching Hospitals NHS Foundat..	0	(omitted)				
Taunton and Somerset NHS Foundation Trust	0	(omitted)				
The Dudley Group NHS Foundation Trust	0	(omitted)				
The Royal Bournemouth and Christchurch H..	0	(omitted)				
The Royal Wolverhampton Hospitals NHS Tr..	0	(omitted)				
University Hospitals Birmingham NHS Foun..	0	(omitted)				
Worcestershire Acute Hospitals NHS Trust	0	(omitted)				
York Hospitals NHS Foundation Trust	0	(omitted)				
trt						
EVRA	0	(omitted)				
wk						
6	.0250647	.0149994	1.67	0.095	-.0043578	.0544872
26	.0540998	.0154189	3.51	0.000	.0238543	.0843453
52	.0598649	.0157072	3.81	0.000	.0290539	.0906759
156	.0304918	.0357066	0.85	0.393	-.0395495	.1005332
208	-.0077211	.0224712	-0.34	0.731	-.0518002	.0363579
260	-.0983242	.0229998	-4.28	0.000	-.1434402	-.0532083
trt#wk						
EVRA# 6	.0594229	.0211751	2.81	0.005	.0178862	.1009597
EVRA# 26	.0603568	.0219526	2.75	0.006	.017295	.1034186
EVRA# 52	.0412199	.0221877	1.86	0.063	-.0023031	.0847429
EVRA#156	-.0196394	.0497633	-0.39	0.693	-.1172542	.0779753
EVRA#208	-.0358757	.032179	-1.11	0.265	-.0989974	.027246
EVRA#260	.0427549	.033185	1.29	0.198	-.0223402	.10785
_cons	.6433117	.0074048	86.88	0.000	.6287866	.6578368
sigma_u	.17899004					
sigma_e	.15377115					
rho	.57535394	(fraction of variance due to u_i)				

F test that all u_i=0: F(449, 1467) = 5.73 — Prob > F = 0.0000

Table S2.9 EQ-5D over 1 to 5 years using repeated measures fixed effect.

APPENDIX CHAPTER 3

		Terms **TITLE ABSTRACT KEYWORD**
	Population	
1		"Spinal cord injury" or "spinal cord injuries"
	Outcomes	
	Health care	
2		"Health care" and (cost or costs)
3		Hospitalization or hospitalisation
4		"Length of stay"
5		Cost or costs
6		Rehabilitation or rehabilitate
7		"Mental health"
8		Psychiatry
9		Counsel*
	SCI and Healthcare	#1 AND (#2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9)
	Families	
10		"Informal care"
11		"Social care"
12		"Personal care"
13		(house or home) and (modification or refit*)
14		(vehicle or car) and (modification or refit*)
	SCI and Families	#1 AND (#10 OR #11 OR #12 OR #13 OR #14)
	Employment	
15		Employ*
16		Productivity
17		"sick day" or "sick leave" or "work absence" or "absence from work"
18		Earning*
19		Income
20		salary
	SCI and Employment	#1 AND (#15 OR #16 OR #17 OR 18 OR #19 OR #20)
	Quality of life	
21		SF-36 or "short form 36"
22		EQ-5D or euroqol
	SCI and Quality of life	#1 AND (#21 OR #22)
	SF-36 or "short form 36"	#1 AND (#21)
#1 AND (#2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22)		

Table S3.1 Search terms

Author	Year	Country	Sample	Population	Age at injury	Age at survey	Men (%)	TSI	EBI	EAI	Paraplegia (%)	Study type	Vble of interest
Johnson et al.	1996	US	195	SCI								Longitudinal	Costs
McDaid et al.	2019	UK	1270	Paraplegia ABC, Tetraplegia ABC and all D		46	72				18	Cross-section	Costs
Garcia-Altés et al.	2012	Spain	542	SCI								Cross-section	Costs
Richard-Denis	2017	Canada	87	SCI		46	78,2					Cross-section	Costs
Mahabaleshwarkar et al.	2014	US	11848	SCI	18 to 60							Cross-section	Costs
Cao et al.	2011	US		SCI	25 & 50							Cross-section	Costs
Tator et al.	1993	Canada	191	SCI	34							Cross-section	Costs
Sundance et al.	2004	US	130	Workers SCI		39	92			100		Cross-section	Costs
Carillo et al.	1998	US	19	quadriplegic and paraplegic		17	95			26	52	Cross-section	Costs
Edgard et al.	1977	US	142	SCI		0 to 60					56	Cross-section	Costs
Devivo, J. M.	1997	US	1010	SCI by motor vehicle accident, violence, falls, sports and other cases		24 to 38						Cross-section	Costs
Harvey et al.	1992	US	758	SCI			71					Cross-section	Costs
Margolis et al.	2014	US	546	SCI		41,5	45,2				35	Cross-section	Costs
Devivo et al.	2011	US	1508	SCI								Cross-section	Costs
Munce et al.	2013	Canada	936	SCI		47	74,1					Cross-section	Costs
Yang	2008	Taiwan	54484	SCI	0 to 80							Cross-section	Costs
Vainkuntam	2019	Australia	534	SCI		54	74,1					Cross-section	Costs
Radhakrishna	2014	Canada	481	SCI								Cross-section	Costs
Price	1994	US	121	SCI	2 to 87		80					Cross-section	Costs
Porgo	2019	Canada	50276	SCI		63	49					Cross-section	Costs
Sikka	2018	US	591	SCI		46	74					Cross-section	Costs
Wayne	2010	Australia	1320	SCI		46,3	77,5					Cross-section	Costs
Liu	2002	China	264	SCI		42	76					Cross-section	Costs
Kawu	2011	Nigeria	34	SCI		35,4						Cross-section	Costs
McKinley WO	2001	US	86	SCI								Longitudinal	Costs
Deutsch	2011	US	2919	SCI		65 to 85	54					Cross-section	Costs
Chan	1997	US	69	SCI		75	27					Longitudinal	Costs
Yu	2008	US	2008	SCI		42	98,6					Longitudinal	Costs
Webster	2004	US	62	SCI		38,7	92				0	Longitudinal	Costs
Krause	2018	US	303	SCI		49	71					Longitudinal	Costs
Smith	2003	US	47	SCI	24,7		93				78,7	Cross-section	Costs

Lessing	2020	Tanzania	260	SCI		34,8	84					Cross-section	Costs
Mac-Thiong	2012	Canada	477	SCI		41,4	78,4					Cross-section	Costs
Tsai	2005	Taiwan	184	SCI		41,5	68,5					Cross-section	Costs
Richard-Denis et al.	2018	Canada	119	Cervical TSCI		51,7	78,2		54,2			Longitudinal	Qol
Cotner et al.	2018	US	92	Veteran with SCI		51	96,7					Longitudinal	Qol
Lucke	2004	US	10	SCI		35,1	80					Longitudinal	Qol
Schwartz et al.	2018	Canada	1125	SCI			79					Longitudinal	Qol
Unalan et al.	2007	Turkey	41	SCI	33,07	39,15		6,31	61	22,2	95	Cross-section	Qol
Atoglu et al.	2013	Turkey	140	SCI (chronic pain vs without pain)		36	74	2,1	67			Cross-section	Qol
Arrango Laspirilla et al.	2001	Colombia	40	SCI		34,7	92	11,85		30	50	Cross-section	Qol
Leduc et al.	2002	Canada	587	SCI		44,75	80			31	67	Cross-section	Qol
Kreuter	2005	Australia	89	SCI		43,5						Cross-section	Qol
Kreuter	2005	Sweden	71	SCI		41,4		5,8		20	51,2	Cross-section	Qol
Haran et al.	2005	Australia	305	SCI		44	83	6,5		39	53,5	Cross-section	Qol
Glennie et al.	2016	Canada	338	SCI (Rural area vs Urban area)	43			9				Cross-section	Qol
Moghimian et al.	2015	Iran	106	SCI		37,1	82,1	7,3	51	34		Cross-section	Qol
Lidal et al.	2008	Norway	165	SCI (Male vs Female)	23	50	82	27			65	Cross-section	Qol
Hossein et al.	2019	Iran	184	SCI	33,2		81	4		39	48,91 3043 48	Cross-section	Qol
Gurcay et al.	2008	Turkey	54	SCI		33,87	68,5	2,79	22,2	12	70,3	Cross-section	Qol
Oh J.	2005	Korea	132	SCI		41,8	61,4	5,65			18,2	Cross-section	Qol
Yasami et al.	2016	Iran	35	SCI								Cross-section	Qol
Yazdanshenas Ghazwin et al.	2014	Iran	153	SCI		35,1	100					Cross-section	Qol
Salamati et al.	2014	Iran	47	Veteran SCI							100	Cross-section	Qol
Ebrahimzadeh et al.	2014	Iran	37	Veteran SCI		48,5	100					Cross-section	Qol
Celik et al.	2007	Turkey	30	SCI	34,36	39,33		3,74				Cross-section	Qol
Horner-Johnson et al.	2010	US	54	SCI		46,31	63					Cross-section	Qol
Middleton et al.	2007	Australia	106	SCI		46,7	75,47 16 98 11	8,6			63	Cross-section	Qol
Sabour et al.	2015	Iran	104	SCI		52,58	81,7	9,26			87,5	Cross-section	Qol
Ebrahimzadeh et al.	2014	Iran	52	Veteran SCI	23,6	49,3					88,5	Cross-section	Qol
Andressen	1999	US	183	Veteran SCI		50,5	98,9	17,9			53	Cross-section	Qol
Elfstrom	2005	Sweden	256	TSCI	43,9		74,6	5,65				Cross-section	Qol

Hossein Tavakoli	2016	Iran	184	SCI		33,2	81	4		35,3		Cross-section	Qol
Edward	2002	Canada	14	SCI		38		2,6				Cross-section	Qol
Paul et al.	2013	New zeland	91	SCI		41,3	76					Longitudinal	Qol
Forchemeir et al.	2001	US	2307	SCI (Male vs Female)		41,6	79,1	1		25,9		Cross-section	Qol
Rivers et al.	2017	Canada	340	SCI	41,6		79,1	11,7	25,9			Cross-section	Qol
Westgren et al.	1998	Sweden	353	SCI								Cross-section	Qol

SCI spinal cord injury; QoL quality of life; TSI time since injury; EBI employment before injury; EAI employment after injury

Table S3.2 Characteristics of included studies

Studies	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14	Score	Score (%)
Johnson et al. 1996	2	1	1	2	n/a	n/a	n/a	2	1	1	1	1	2	2	16	73
McDaid et al. 2019	2	1	2	2	n/a	n/a	n/a	2	1	1	1	2	2	2	18	82
Garcia-Altés et al. 2012	2	1	0	2	n/a	n/a	n/a	2	1	1	1	0	2	2	14	64
Leduc et al 2002	2	1	0	2	n/a	n/a	n/a	2	1	1	1	0	2	2	14	64
Moghimian et al 2015	2	1	0	2	n/a	n/a	n/a	2	1	1	1	0	2	2	14	64
Paul et al., 2013	2	1	2	2	n/a	n/a	n/a	2	1	1	1	2	2	2	18	82
Richard-Denis et al. 2016	2	1	0	2	n/a	n/a	n/a	2	1	1	1	0	2	2	14	64
Rivers et al., 2017	2	1	1	2	n/a	n/a	n/a	2	1	1	1	1	2	2	16	73
Sundance et al. 2004	2	1	0	2	n/a	n/a	n/a	2	1	1	1	0	2	2	14	64
Carillo et al. 1998	2	1	0	2	n/a	n/a	n/a	2	1	1	1	0	2	2	14	64
Edgard 1977	2	1	0	2	n/a	n/a	n/a	2	1	1	1	0	2	2	14	64
Hossain et al 2019	2	1	0	2	n/a	n/a	n/a	2	1	1	1	0	2	2	14	64
Devivo 1997	2	1	0	2	n/a	n/a	n/a	2	1	1	1	0	2	2	14	64
Harvey 1992	2	1	0	2	n/a	n/a	n/a	2	1	1	1	0	2	2	14	64
Margolis et al. 2014	2	1	1	2	n/a	n/a	n/a	2	1	1	1	1	2	2	16	73
Devivo 2011	2	1	0	2	n/a	n/a	n/a	2	1	1	1	0	2	2	14	64
Munce et al. 2013	2	1	0	2	n/a	n/a	n/a	2	1	1	1	0	2	2	14	64
Arango-Lasprilla 2010	2	1	1	2	n/a	n/a	n/a	2	1	1	1	1	2	2	16	73
Richard-Denis et al.	2	1	2	2	n/a	n/a	n/a	2	1	1	1	2	2	2	18	82
Cotner et al. 2018	2	1	1	2	n/a	n/a	n/a	2	1	1	1	1	2	2	16	73
Schwartz et al.	2	1	2	2	n/a	n/a	n/a	2	1	1	1	2	2	2	18	82
Unalan et al. 2007	2	1	0	2	n/a	n/a	n/a	2	1	1	1	0	2	2	14	64
Atoglu et al. 2013	2	1	1	2	n/a	n/a	n/a	2	1	1	1	1	2	2	16	73

Haran et al 2005	2	1	0	2	n/a	n/a	n/a	2	1	1	1	0	2	2	14	64
Glennie et al. 2016	2	1	0	2	n/a	n/a	n/a	2	1	1	1	0	2	2	14	64
Lidal et al. 2008	2	1	0	2	n/a	n/a	n/a	2	1	1	1	0	2	2	14	64
Gurcay et al. 2008	2	1	0	2	n/a	n/a	n/a	2	1	1	1	0	2	2	14	64
Forchemeir et al. 2001	2	1	1	2	n/a	n/a	n/a	2	1	1	1	1	2	2	16	73
Westgren and Levi 1998	2	1	2	2	n/a	n/a	n/a	2	1	1	1	2	2	2	18	82
Mahabaleshwarkar	2	1	0	2	n/a	n/a	n/a	2	1	1	1	2	2	2	16	73
Cao et al. 2011	2	1	0	2	n/a	n/a	n/a	2	1	1	1	1	2	2	15	68
Tator et al. 1993	2	1	0	2	n/a	n/a	n/a	2	1	1	1	0	2	2	14	64
Yang et al. 2008	2	1	2	2	n/a	n/a	n/a	2	1	1	1	1	2	2	17	77
Vainkuntam et al. 2019	2	1	2	2	n/a	n/a	n/a	2	1	1	1	2	2	2	18	82
Radhakrishna et al. 2014	2	1	2	2	n/a	n/a	n/a	2	1	1	1	2	2	2	18	82
Price et al. 1994	2	1	2	1	n/a	n/a	n/a	1	1	1	1	2	2	2	16	73
Porgo et al. 2019	2	1	2	2	n/a	n/a	n/a	2	1	1	1	2	2	2	18	82
Sikka et al. 2018	2	1	2	2	n/a	n/a	n/a	2	1	1	1	2	2	2	18	82
Wayne et al. 2010	2	1	2	2	n/a	n/a	n/a	2	1	1	1	2	2	2	18	82
Liu et al. 2002	2	1	2	2	n/a	n/a	n/a	2	1	1	1	2	2	2	18	82
Kawu et al. 2011	2	1	2	2	n/a	n/a	n/a	2	1	1	1	2	2	2	18	82
McKinley WO et al. 2002	2	1	2	1	n/a	n/a	n/a	2	1	1	1	1	2	1	15	68
Deutsch et al. 2011	2	1	2	2	n/a	n/a	n/a	2	1	1	1	2	2	2	18	82
Chan et al. 1997	2	1	2	2	n/a	n/a	n/a	2	1	1	1	2	2	2	18	82
Yu et al. 2008	2	1	2	2	n/a	n/a	n/a	2	1	1	1	2	2	2	18	82
Webster et al. 2004	2	1	2	2	n/a	n/a	n/a	2	1	1	1	2	2	2	18	82
Krause et al. 2018	2	1	2	2	n/a	n/a	n/a	2	1	1	1	2	2	2	18	82
Smith et al. 2003	2	1	2	2	n/a	n/a	n/a	2	1	1	1	1	2	2	17	77
Lessing et al. 2020	2	1	2	2	n/a	n/a	n/a	2	1	1	1	2	2	2	18	82
Mac-Thiong et al. 2012	2	1	2	2	n/a	n/a	n/a	2	1	1	1	1	2	2	17	77
Tsai et al. 2005	2	1	2	2	n/a	n/a	n/a	2	1	1	1	2	2	2	18	82
Lucke et al. 2018	2	1	2	2	n/a	n/a	n/a	2	1	1	1	2	2	2	18	82
Kreuter et al. 2005	2	1	2	1	n/a	n/a	n/a	2	1	1	1	2	2	2	17	77
Oh J. et al. 2005	2	1	2	2	n/a	n/a	n/a	2	1	1	1	2	2	2	18	82
Yasami et al. 2016	2	1	2	2	n/a	n/a	n/a	2	1	1	1	2	2	2	18	82
Yazdanshenas Ghazwin et al. 2014	2	1	2	2	n/a	n/a	n/a	2	1	1	1	2	2	2	18	82
Salamati et al. 2014	2	1	2	2	n/a	n/a	n/a	2	1	1	1	2	2	2	18	82
Ebrahimzadeh et al. 2014	2	1	2	1	n/a	n/a	n/a	2	1	1	1	2	2	2	17	77

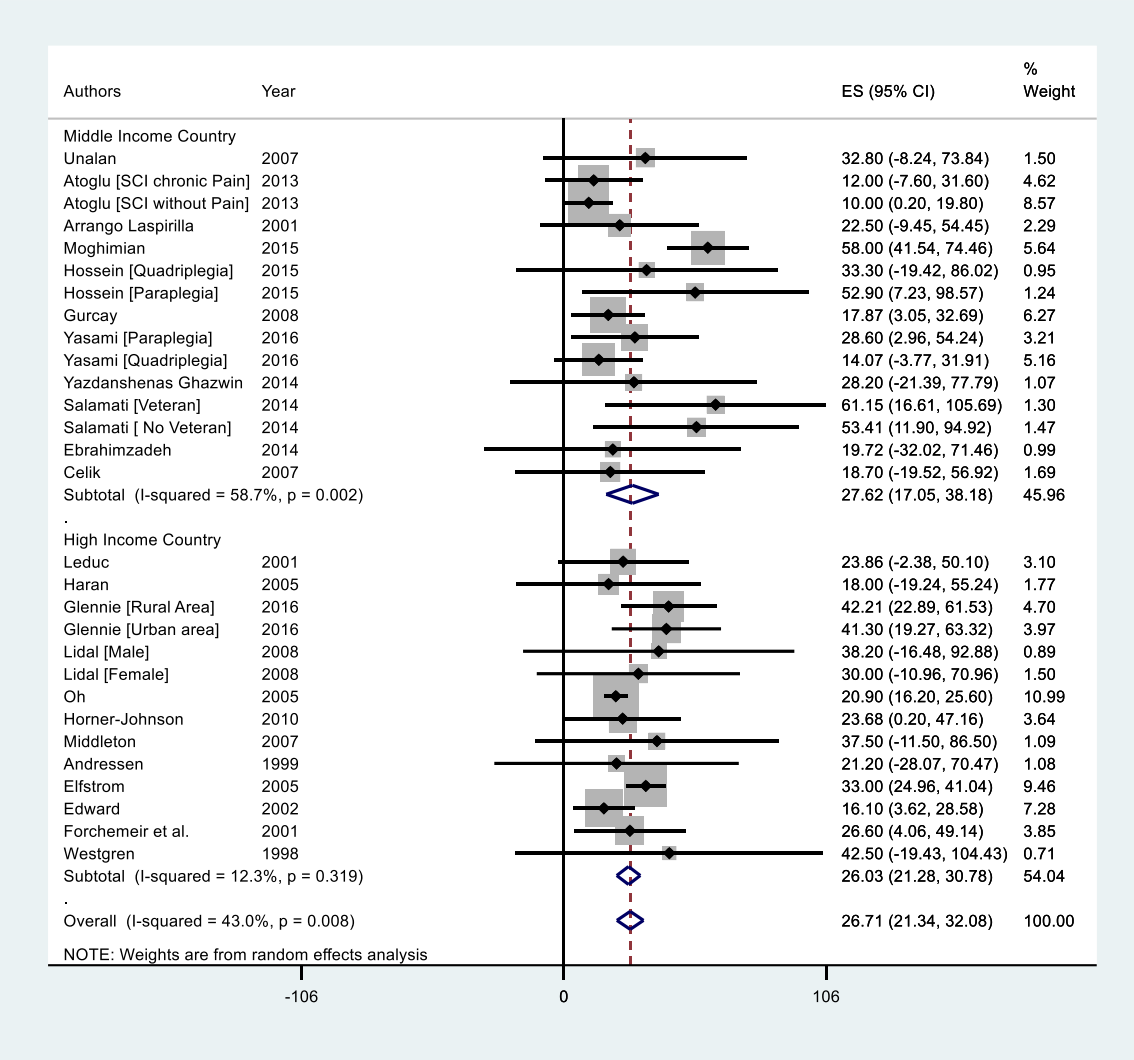
Celik et al. 2007	2	1	2	2	n/a	n/a	n/a	2	1	1	1	2	2	2	18	82
Horner-Johnson et al. 2010	2	1	2	2	n/a	n/a	n/a	2	1	1	1	2	2	2	18	82
Middleton et al. 2007	2	1	2	2	n/a	n/a	n/a	2	1	1	1	1	2	2	17	77
Sabour et al. 2015	2	1	2	1	n/a	n/a	n/a	2	1	1	1	2	2	2	17	77
Ebrahimzadeh et al. 2014	2	1	2	2	n/a	n/a	n/a	2	1	1	1	2	2	2	18	82
Andressen et al. 1999	2	1	2	2	n/a	n/a	n/a	2	1	1	1	2	2	2	18	82
Elfstrom et al. 205	2	1	2	2	n/a	n/a	n/a	2	1	1	1	2	2	2	18	82
Hossein Tavakoli et al. 2016	2	1	2	2	n/a	n/a	n/a	2	1	1	1	2	2	2	18	82
Edward et al. 2002	2	1	2	2	n/a	n/a	n/a	2	1	1	1	2	2	2	18	82

Q1. Question / objective sufficiently described? Q2. Study design evident and appropriate? Q3. Method of subject/comparison group selection or source of information/input variables described and appropriate? Q4. Subject (and comparison group, if applicable) characteristics sufficiently described? Q5. If interventional and random allocation was possible, was it described? Q6. If interventional and blinding of investigators was possible, was it reported? Q7. If interventional and blinding of subjects was possible, was it reported? Q8. Outcome and (if applicable) exposure measure(s) well defi ned and robust to measurement / misclassification bias? Means of assessment reported? Q9. Sample size appropriate? Q10. Analytic methods described/justified and appropriate? Q11. Some estimate of variance is reported for the main results? Q12. Controlled for confounding? Q13. Results reported in sufficient detail? Q14. Conclusions supported by the results? 1=Partial 2= yes 0=No; n/a= Not applicable

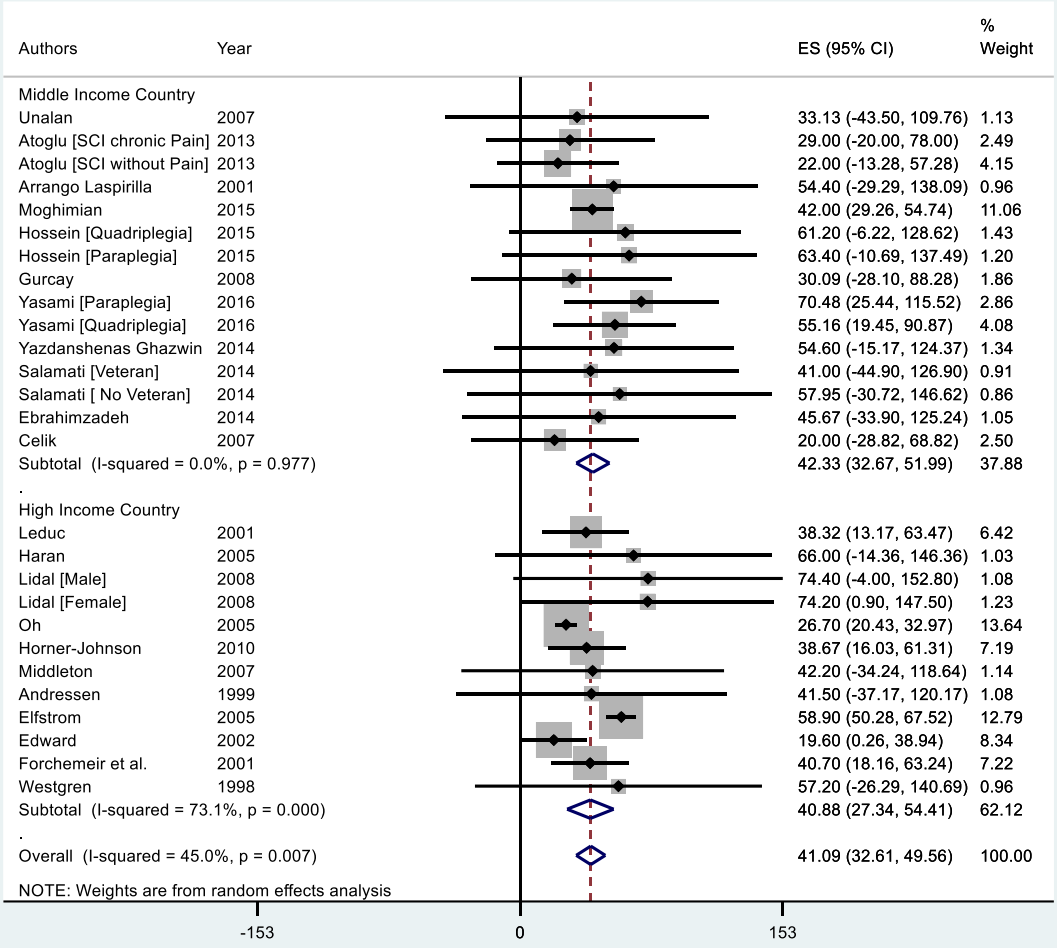
Table S3.3 Risk of Bias

Meta-analysis results

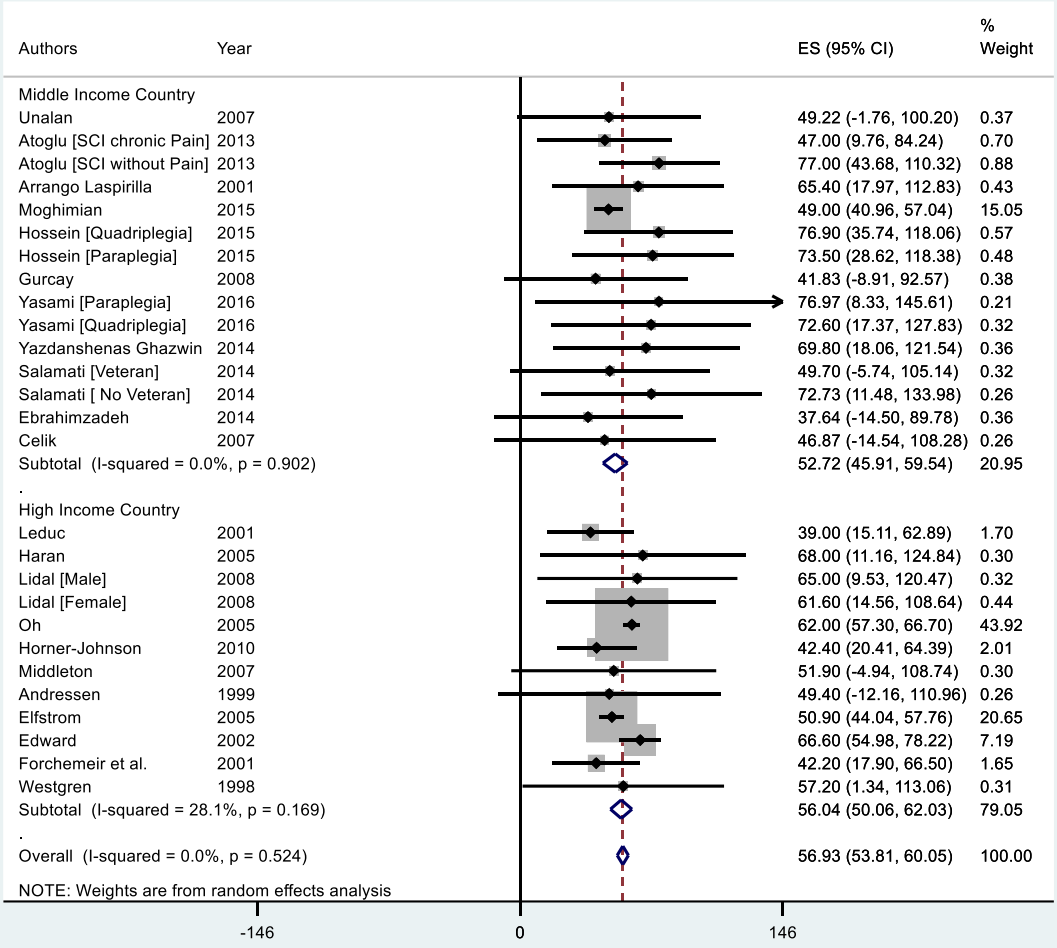
Figures S3.1 to S3.10 represent mean scores for the domains of Short-Form 36 quality of life between middle- and high-income countries. The 95% CI of each article is represented as horizontal lines near the main mean line; the dashed line at the mid represents an estimate of the total mean score and the rhomboid represents the CI of the mean score of QoL.



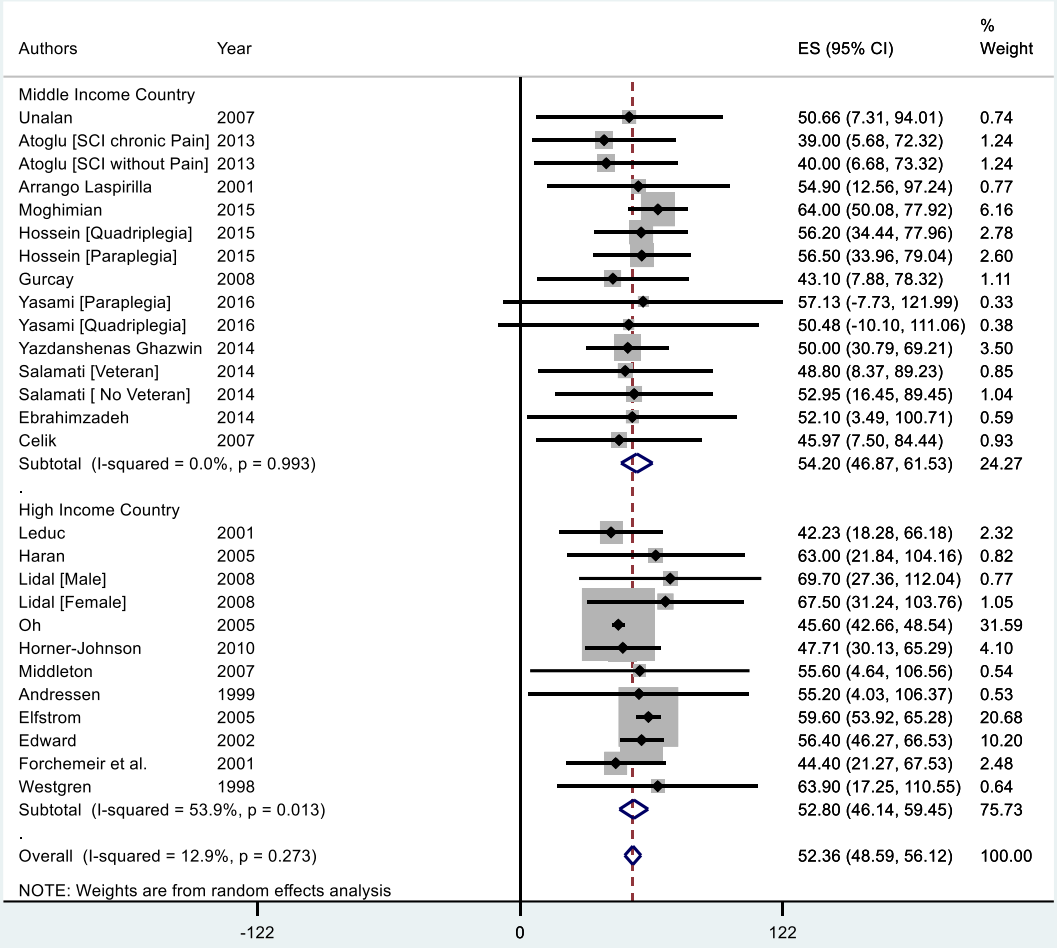
Supplementary figure S3.1 Physical functioning



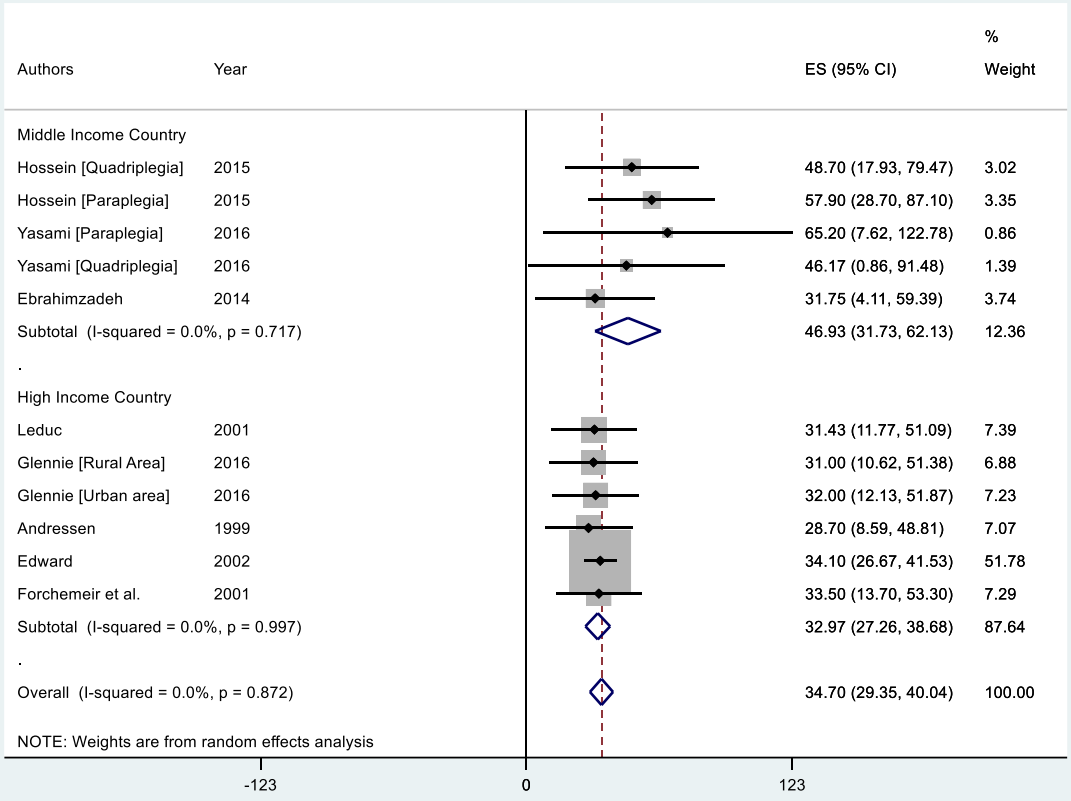
Supplementary figure S3.2 Physical role



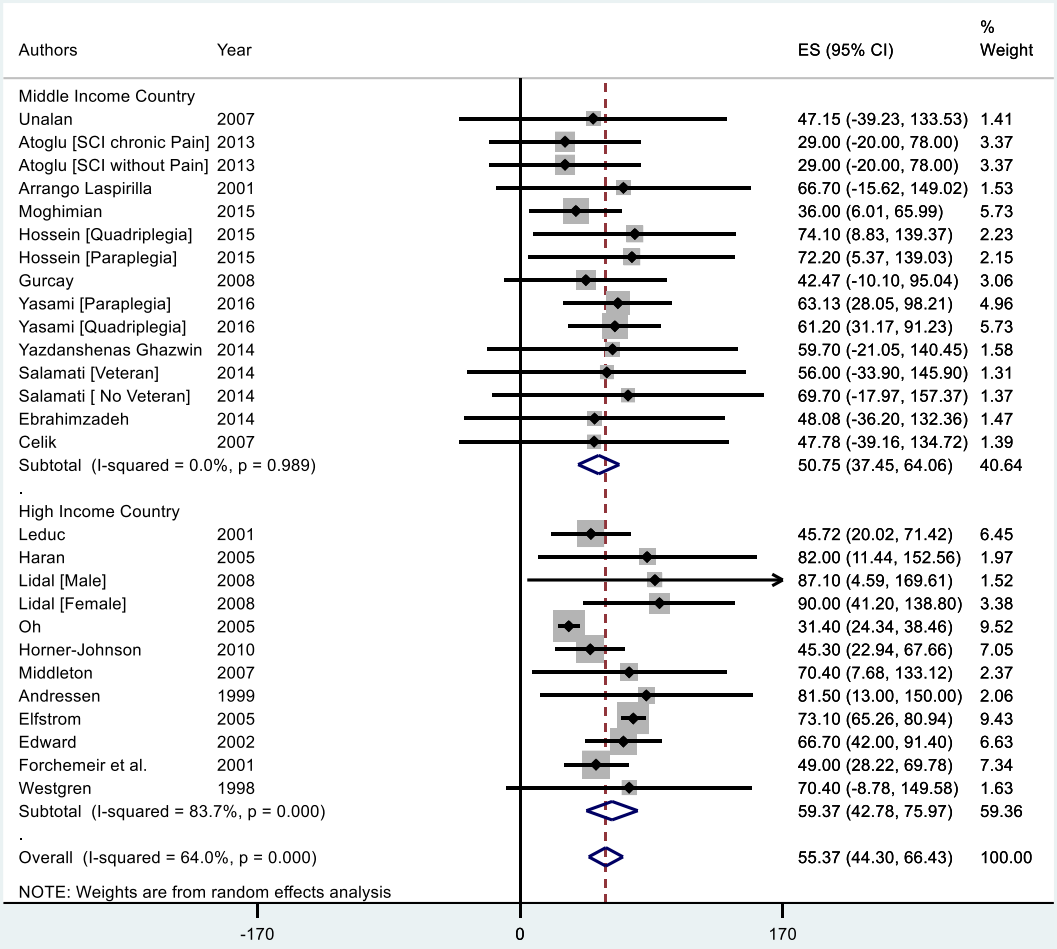
Supplementary figure S3.3 Bodily pain



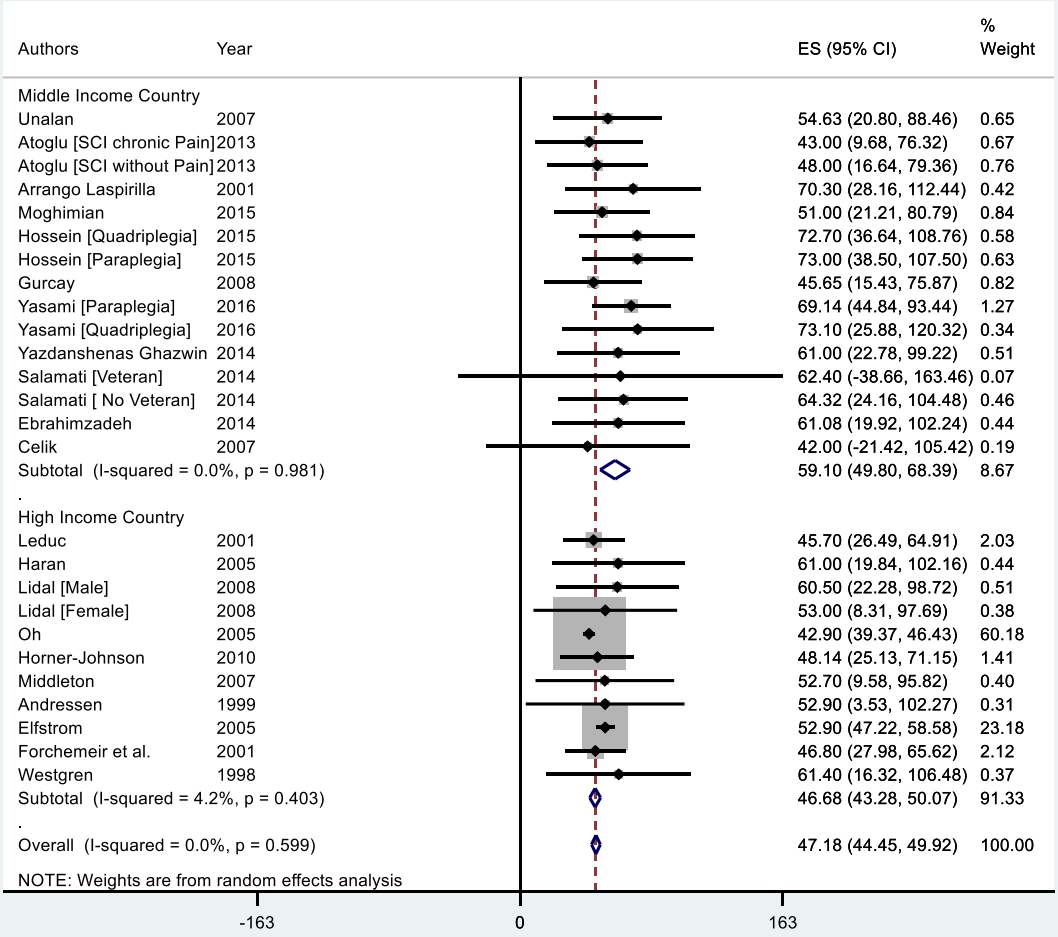
Supplementary figure S3.4 General health



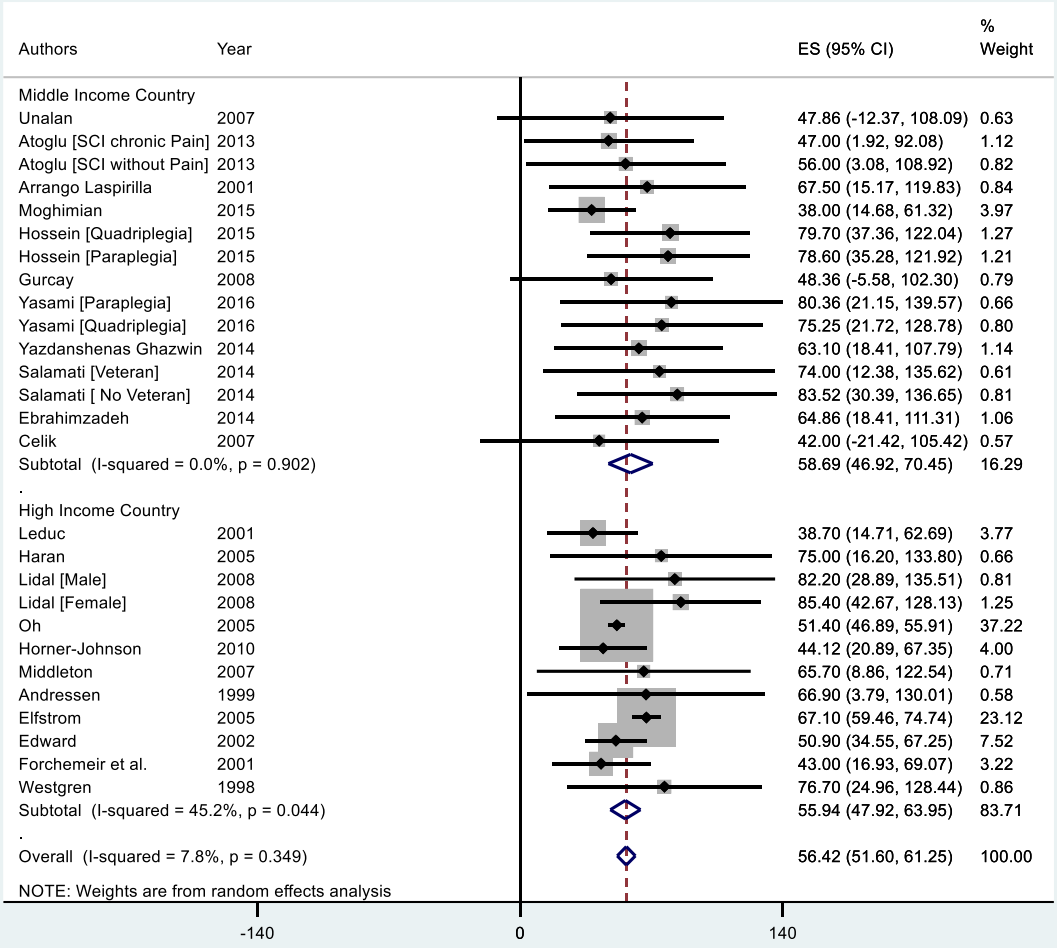
Supplementary figure S3.5 Physical component scores



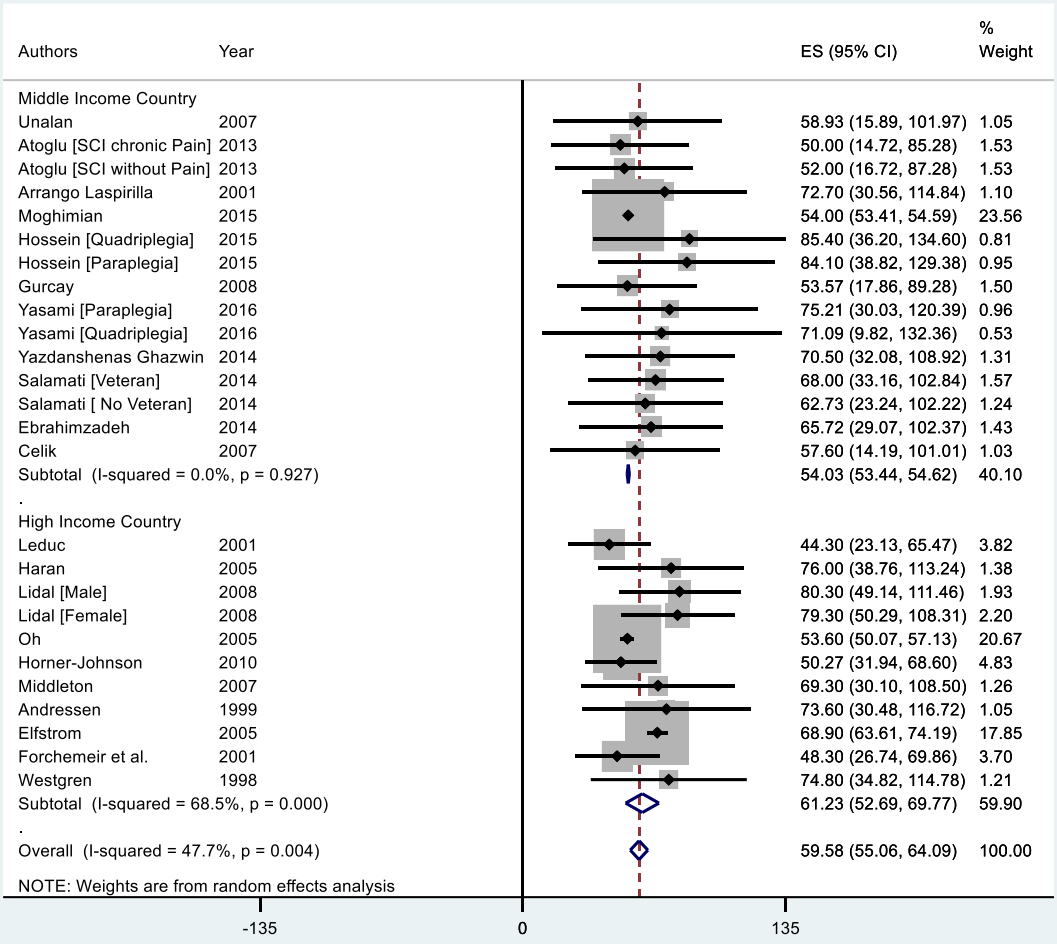
Supplementary figure S3.6 Emotional role



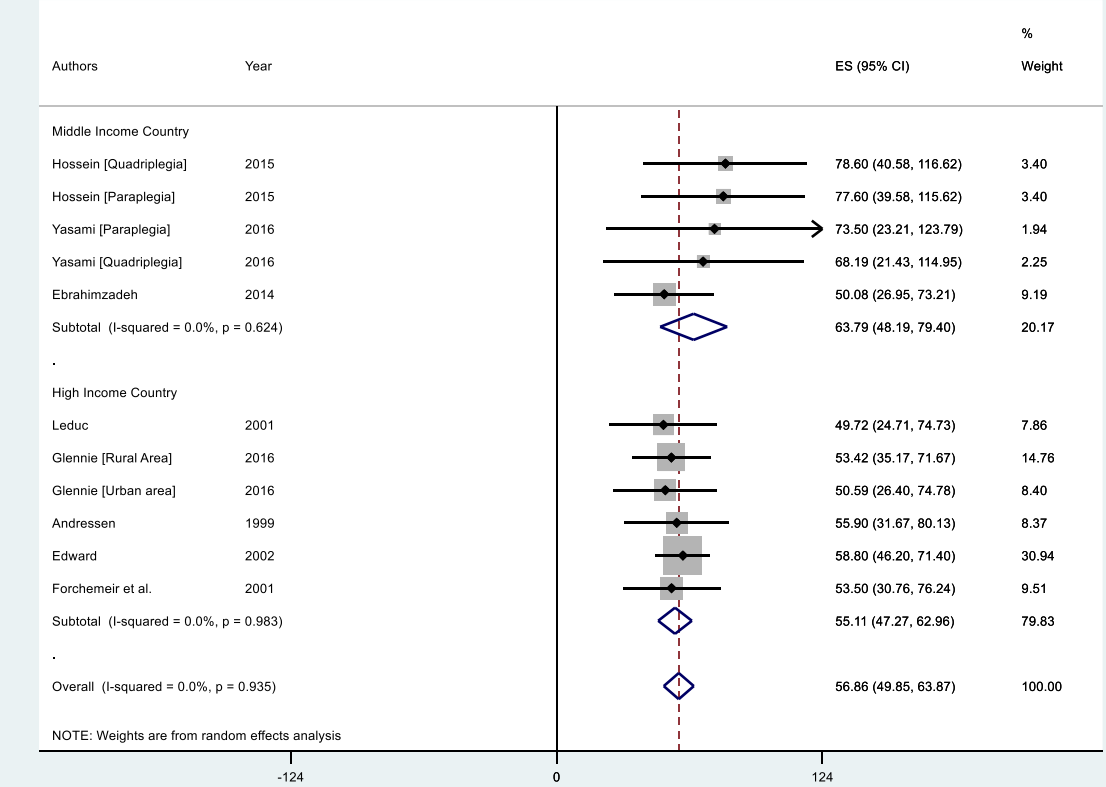
Supplementary figure S3.7 Vitality



Supplementary figure S3.8 Social role



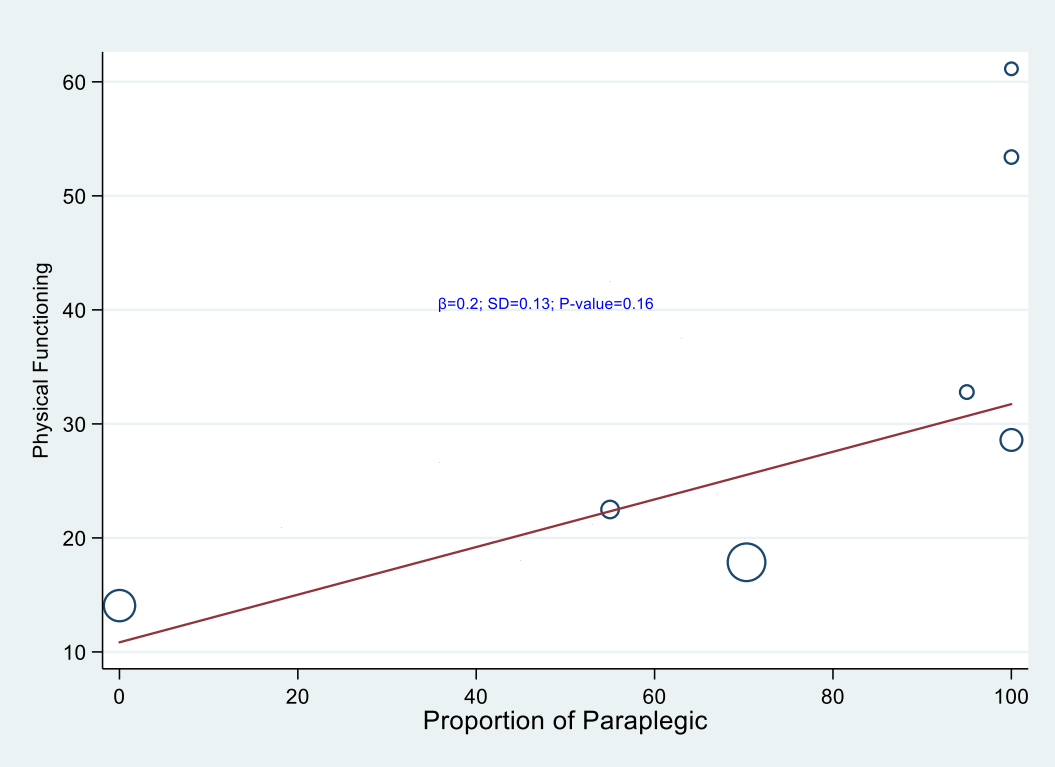
Supplementary figure S3.9 Mental health



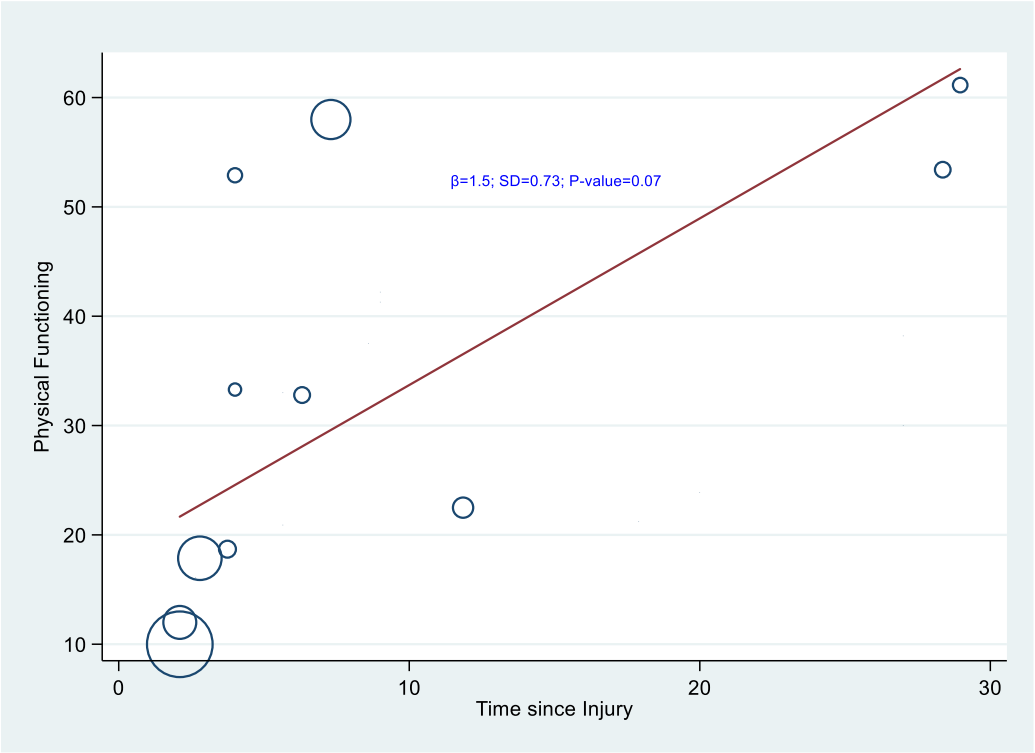
Supplementary figure S3.10 Mental component scores

Meta-regression results

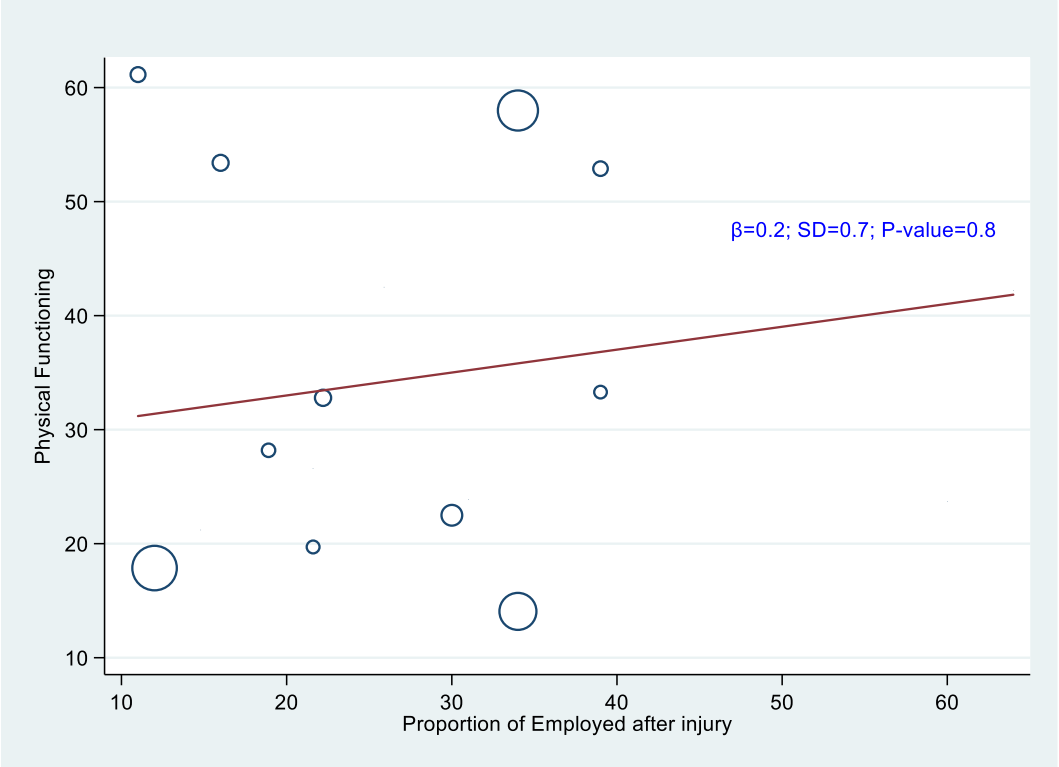
Figures S3.11 to S3.31 show the association between mean scores of 7 domains of Short-Form 36 quality of life (physical functioning, physical role, bodily pain, general health, emotional role, social role and mental health) and proportion paraplegic, years of injury and proportion of employed



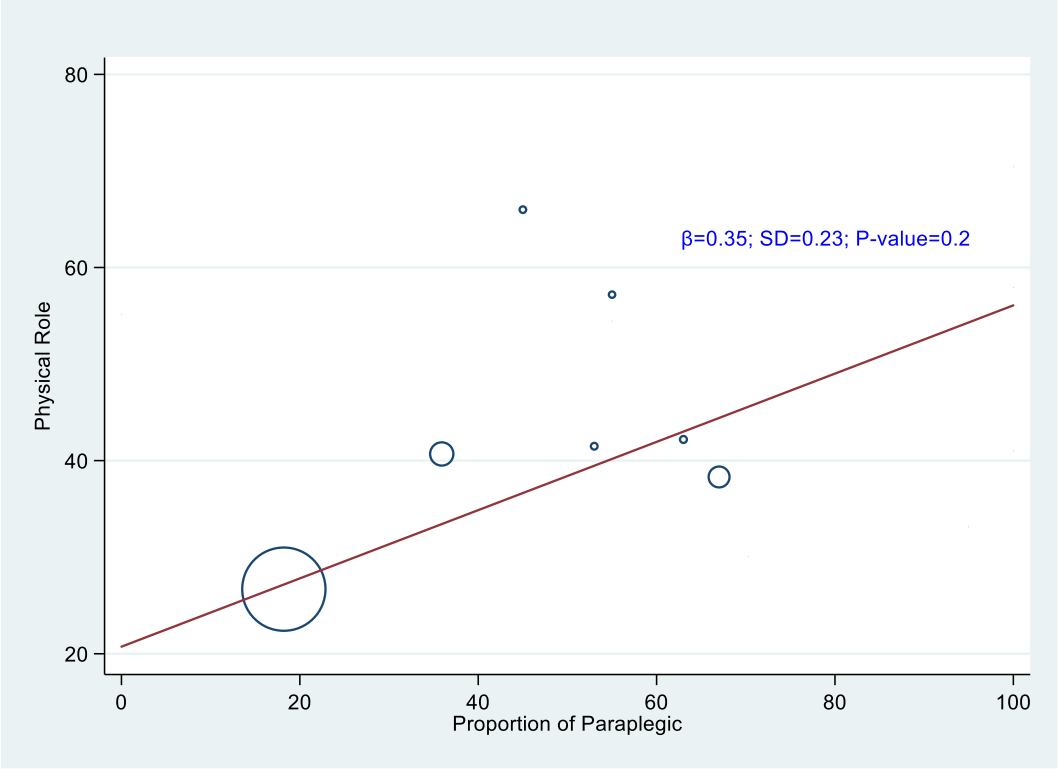
Supplementary figure S3.11 Association between physical functioning and proportion of paraplegic (compared with tetraplegic) individuals



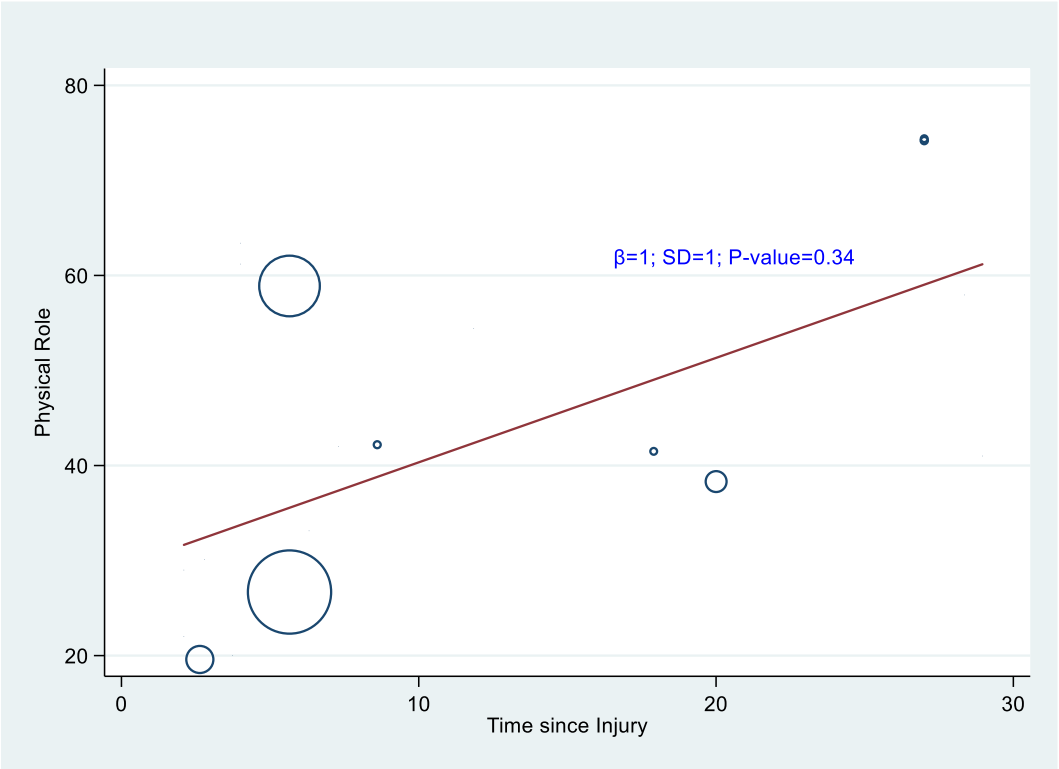
Supplementary figure S3.12 **Association between physical functioning and mean years of injury**



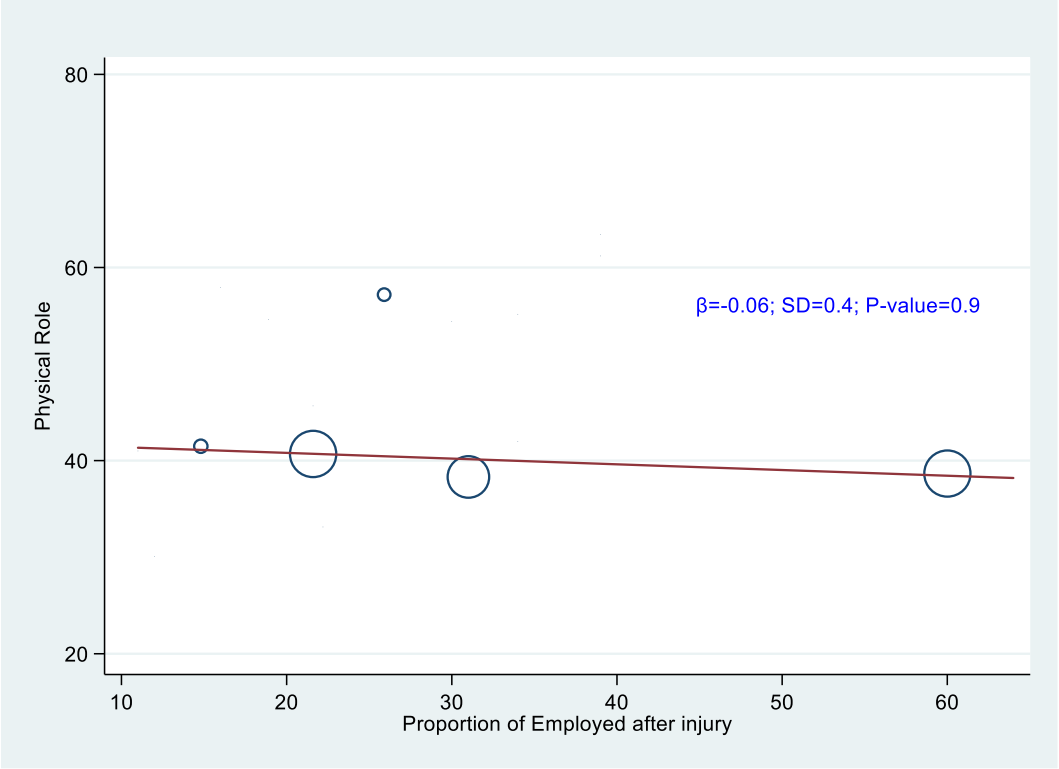
Supplementary figure S3.13 **Association between physical functioning and proportion of employment after injury**



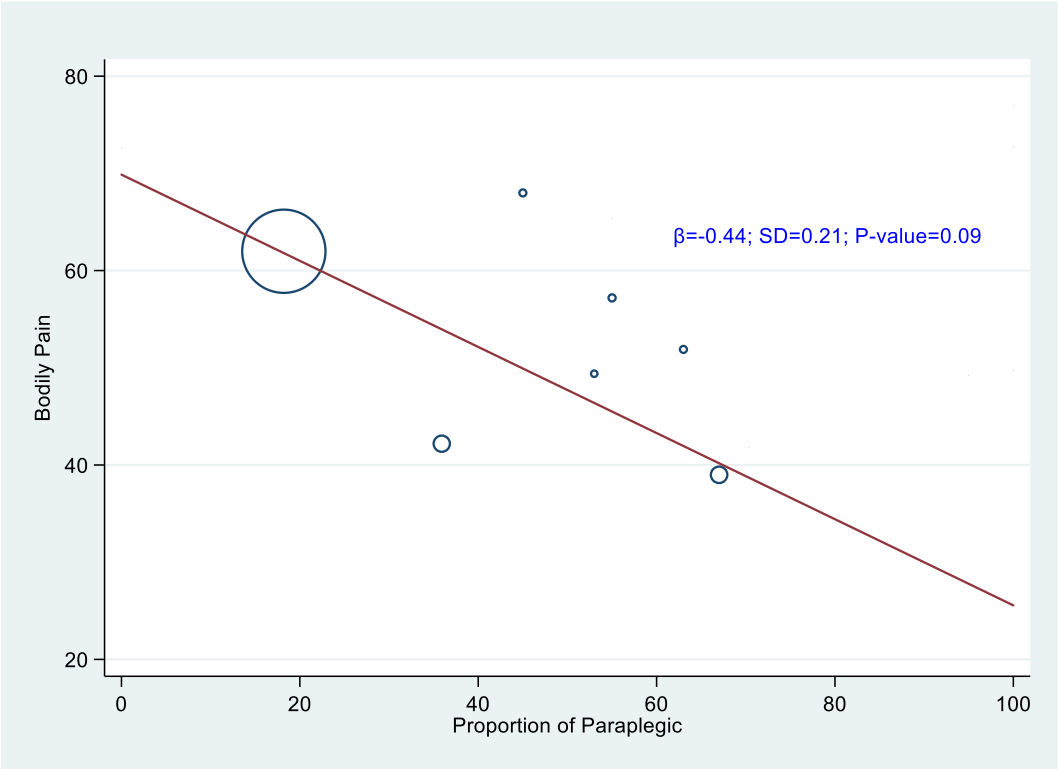
Supplementary figure S3.14 **Association between physical role and proportion of paraplegic (compared with tetraplegic) individuals**



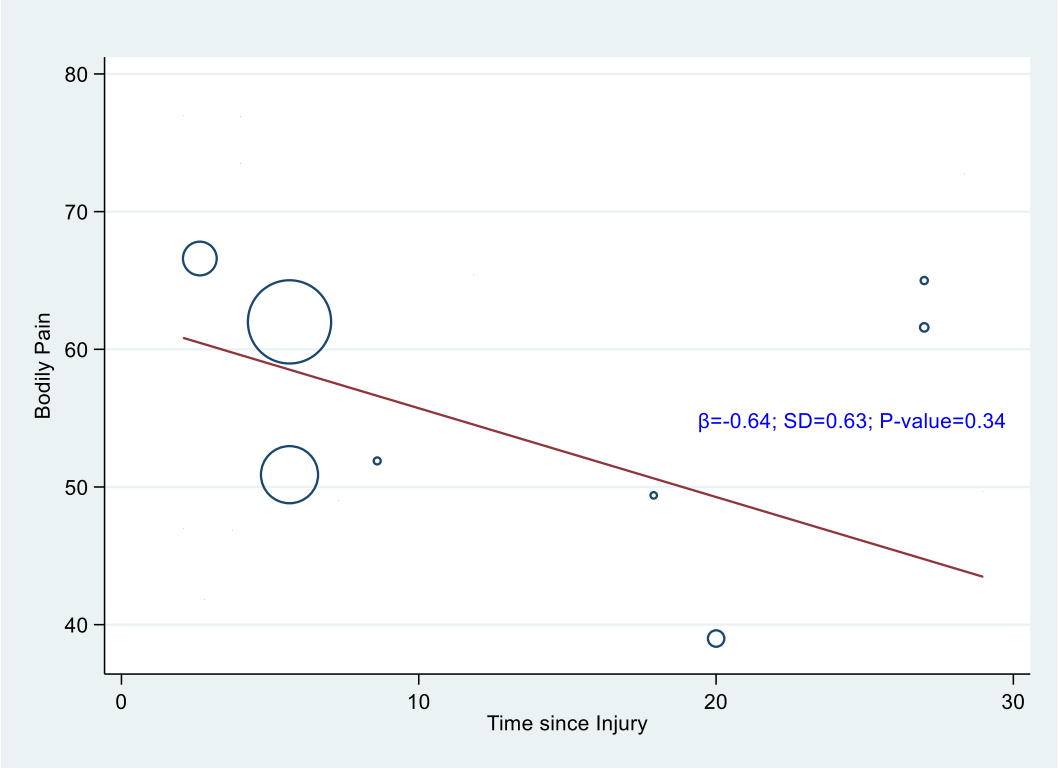
Supplementary figure S3.15 **Association between physical role and mean years since injury**



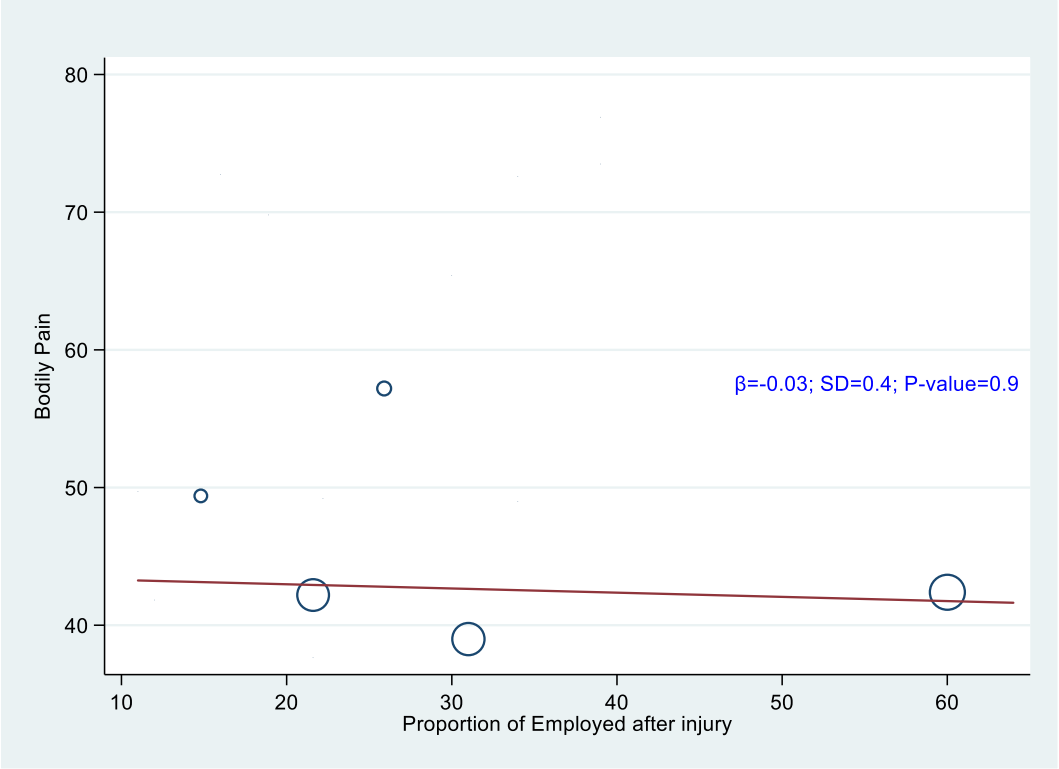
Supplementary figure S3.16 **Association between physical role and proportion with employment after injury**



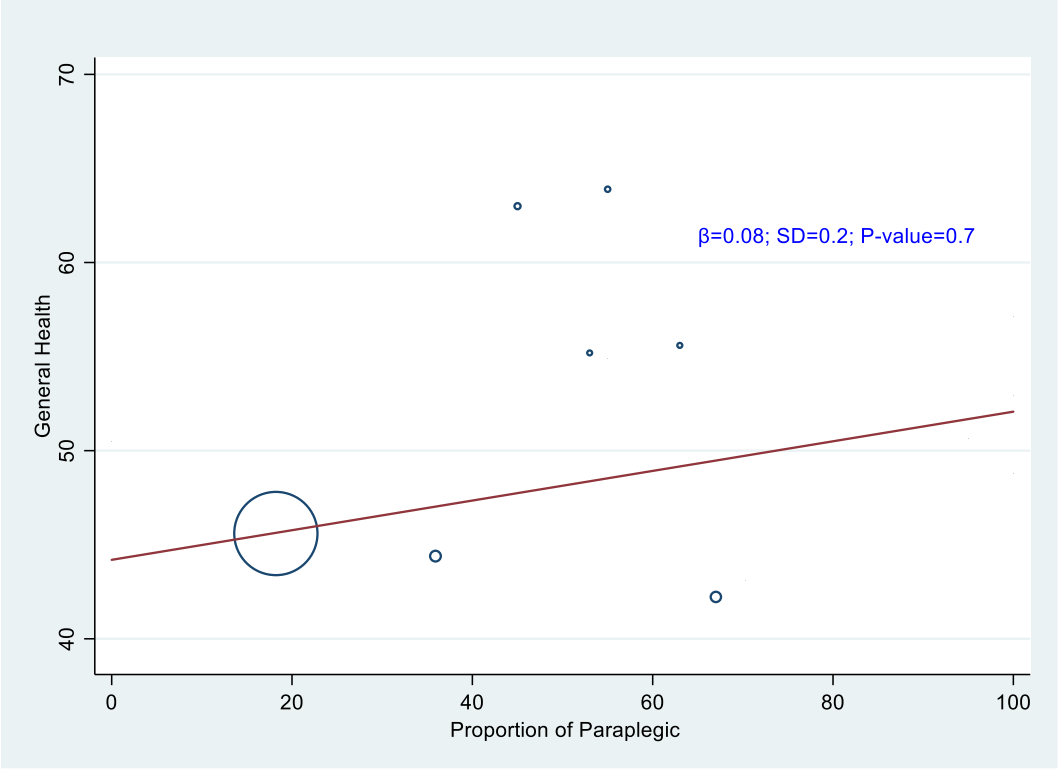
Supplementary figure S3.17 **Association between bodily pain and proportion of paraplegic (compared with tetraplegic) individuals**



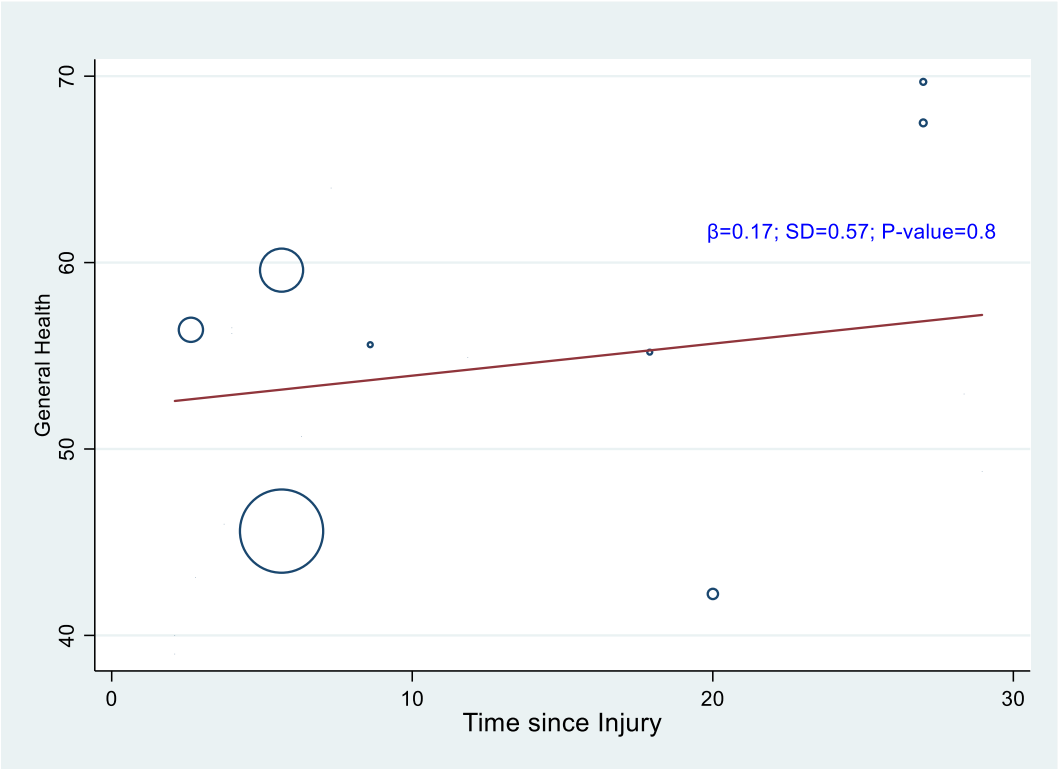
Supplementary figure S3.18 **Association between bodily pain and mean years since injury**



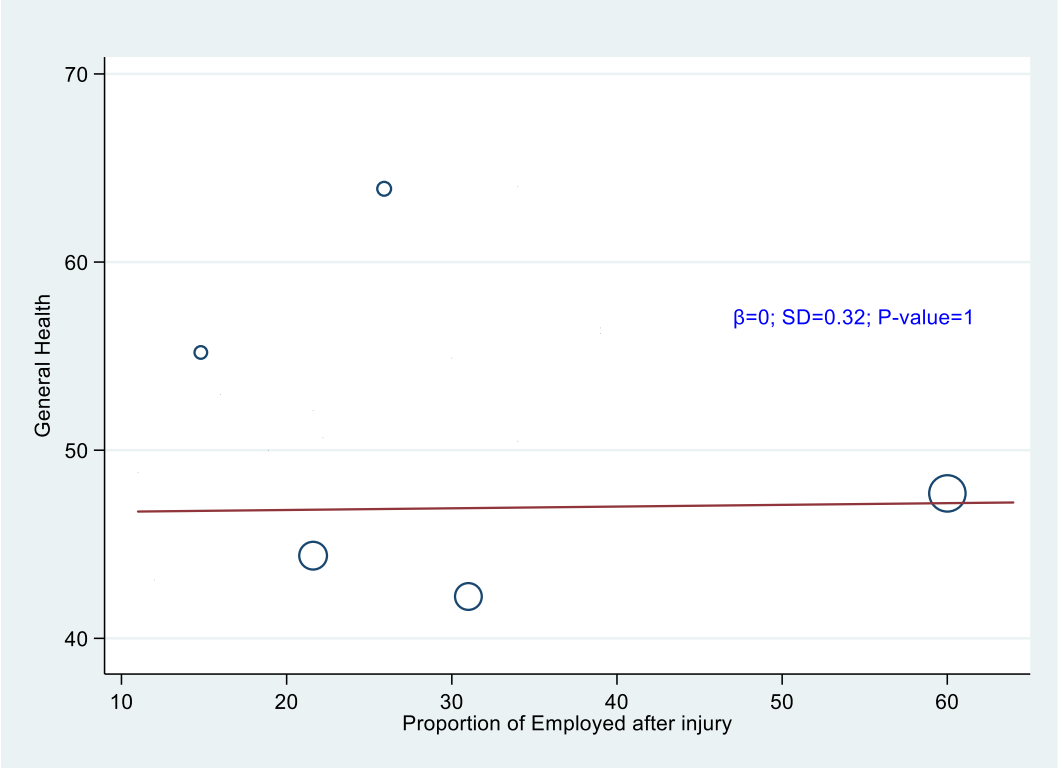
Supplementary figure S3.19 **Association between bodily pain and proportion with employment after injury**



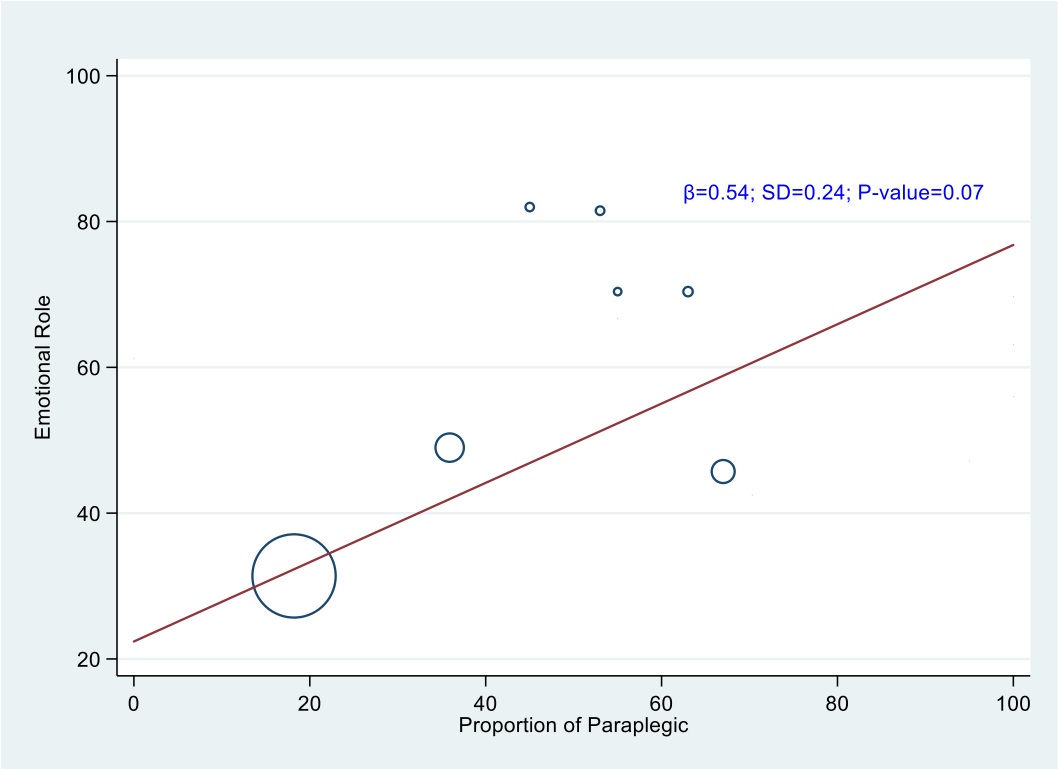
Supplementary figure S3.20 **Association between general health and proportion of paraplegic (compared with tetraplegic) individuals**



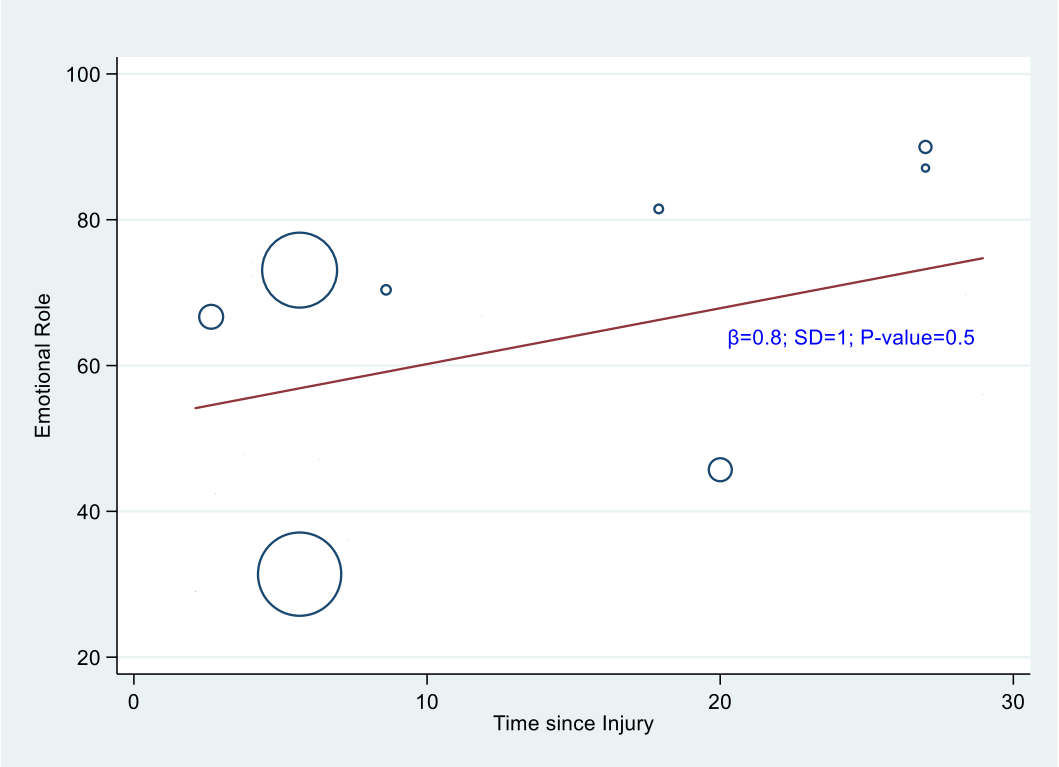
Supplementary figure S3.21 **Association between general health and mean years since injury**



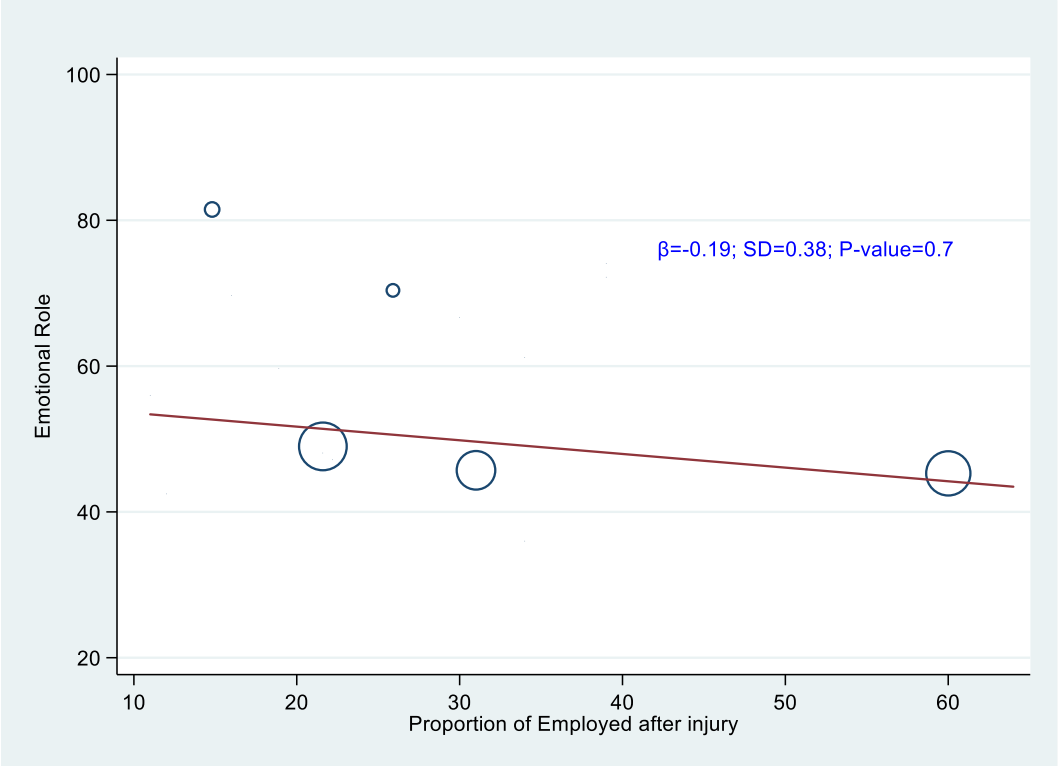
Supplementary figure S3.22 Association between general health and proportion with employment after injury



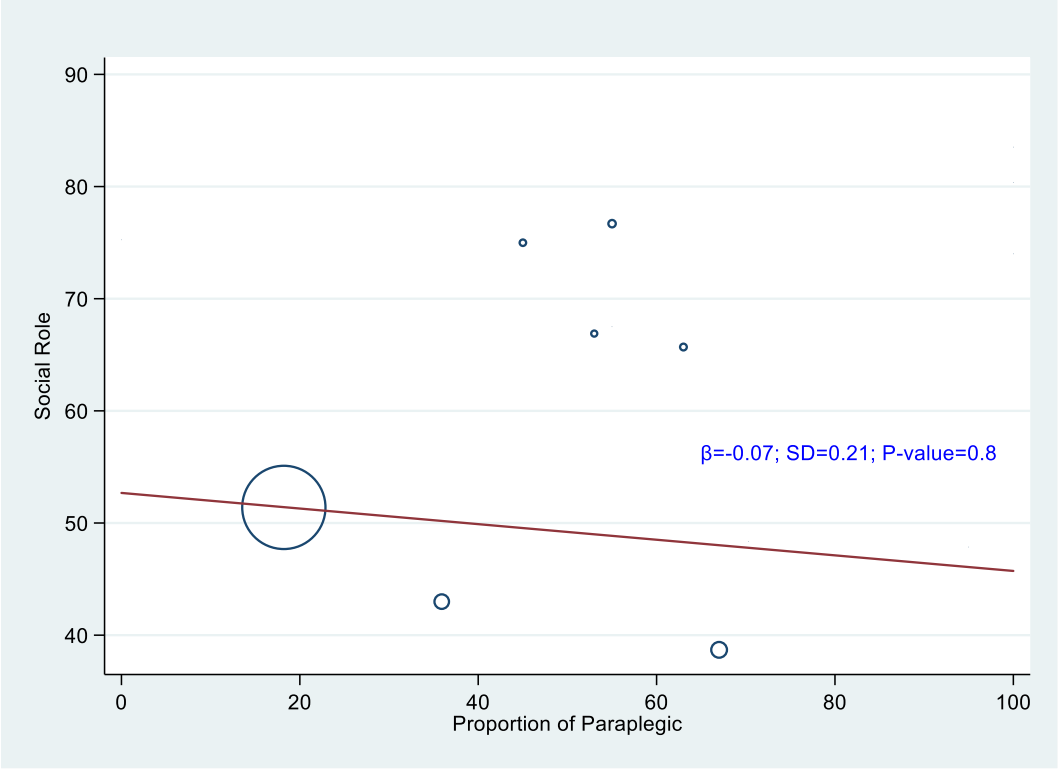
Supplementary figure S3.23 Association between emotional role and proportion of paraplegic (compared with tetraplegic) individuals



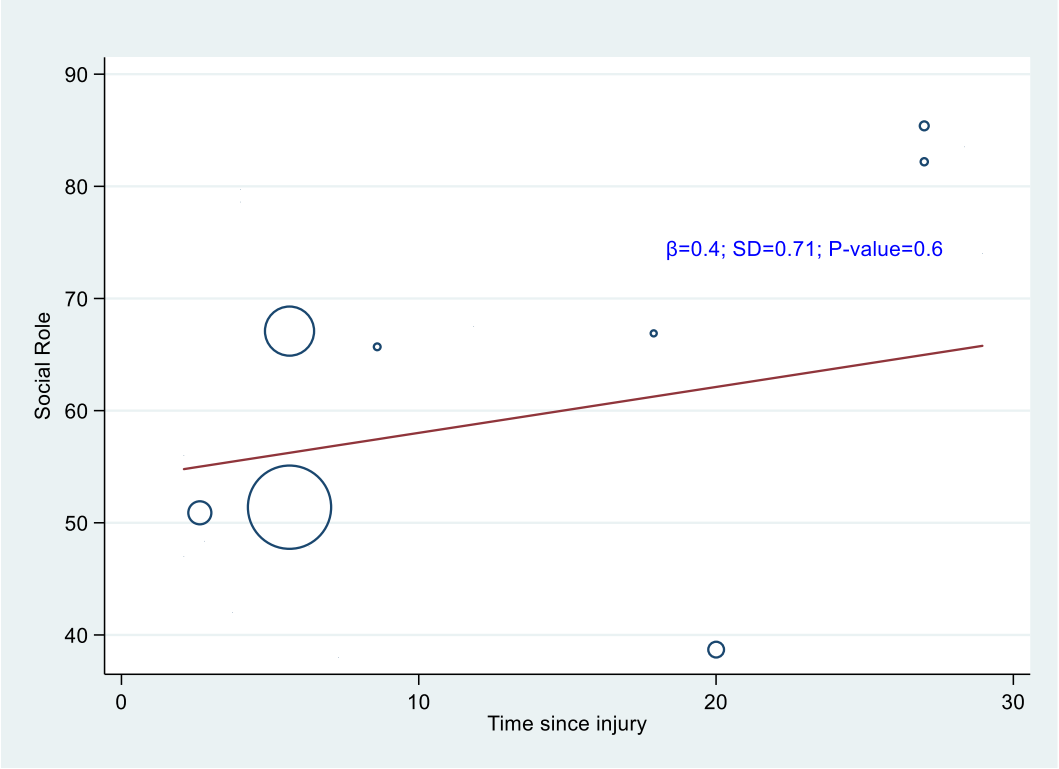
Supplementary figure S3.24 **Association between emotional role and mean years since injury**



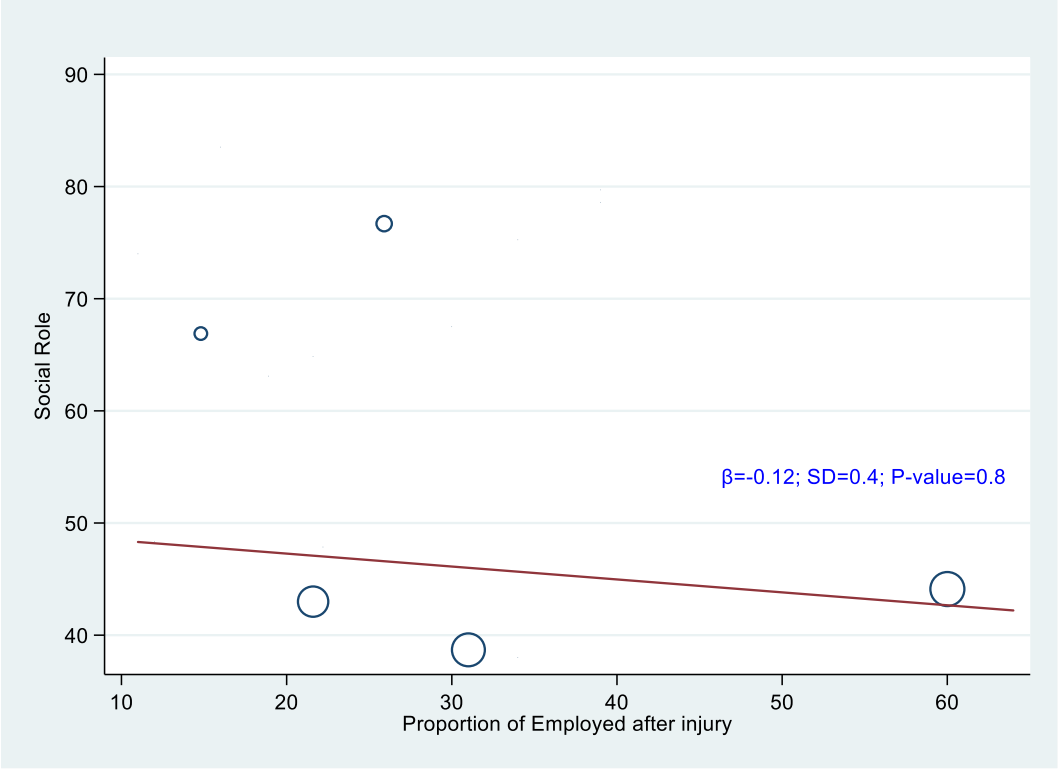
Supplementary figure S3.25 **Association between emotional role and proportion with employment after injury**



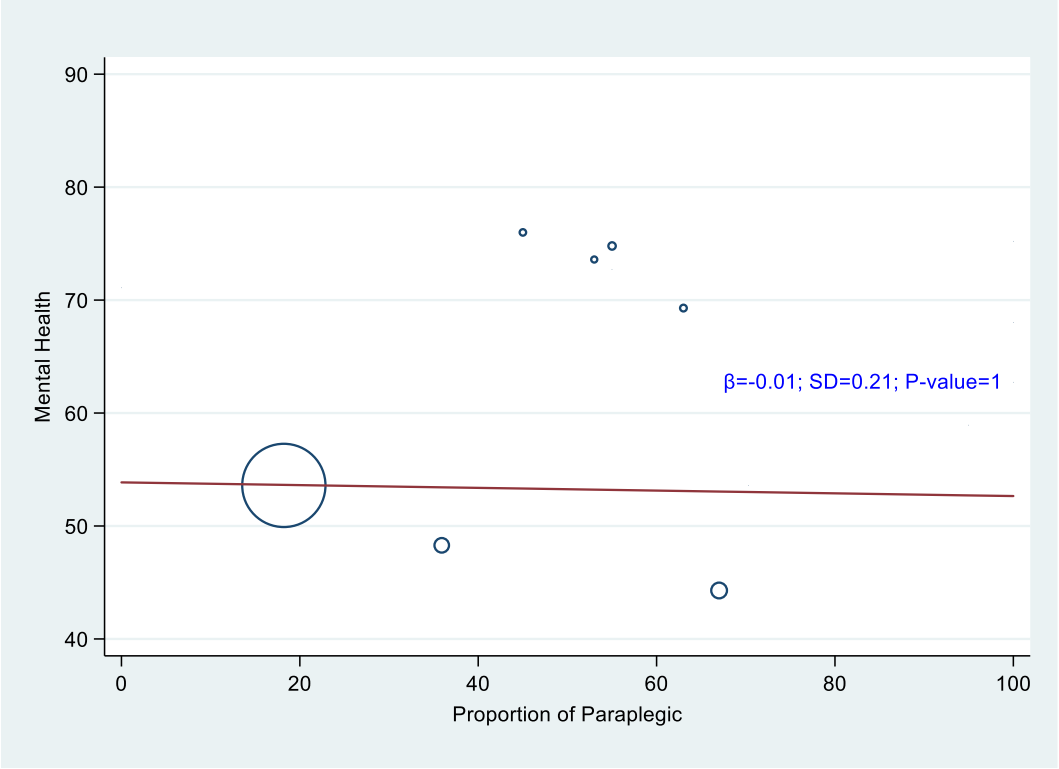
Supplementary figure S3.26 **Association between social role and proportion of paraplegic (compared with tetraplegic) individuals**



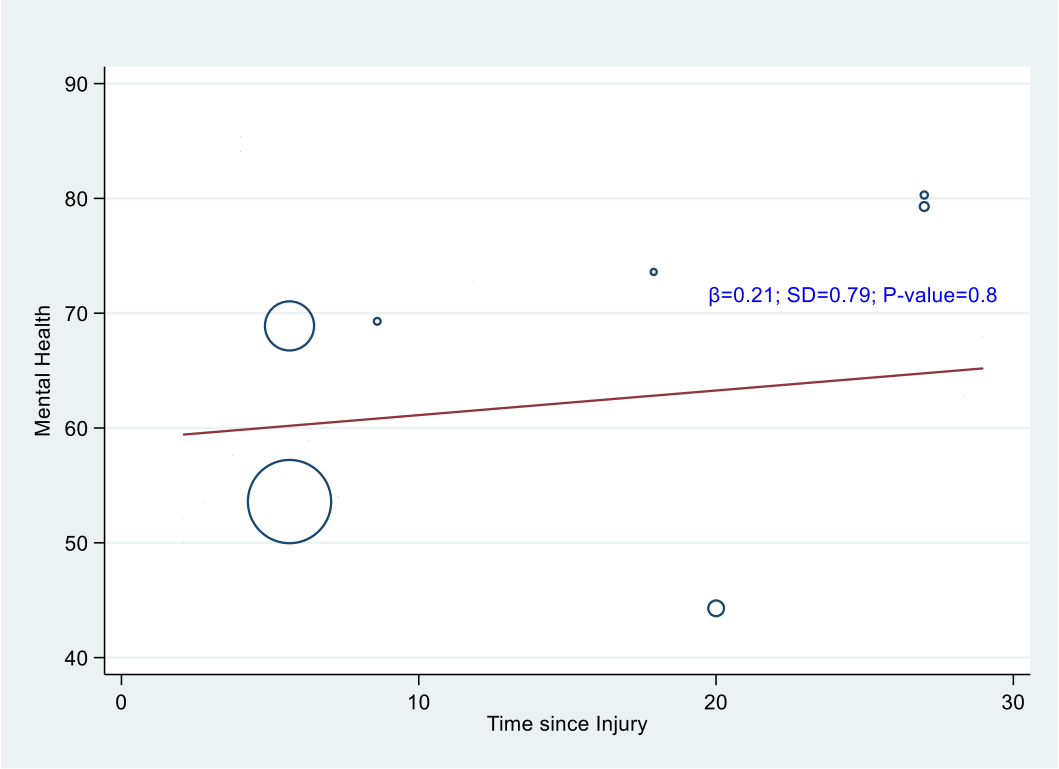
Supplementary figure S3.27 **Association between social role and mean years since injury**



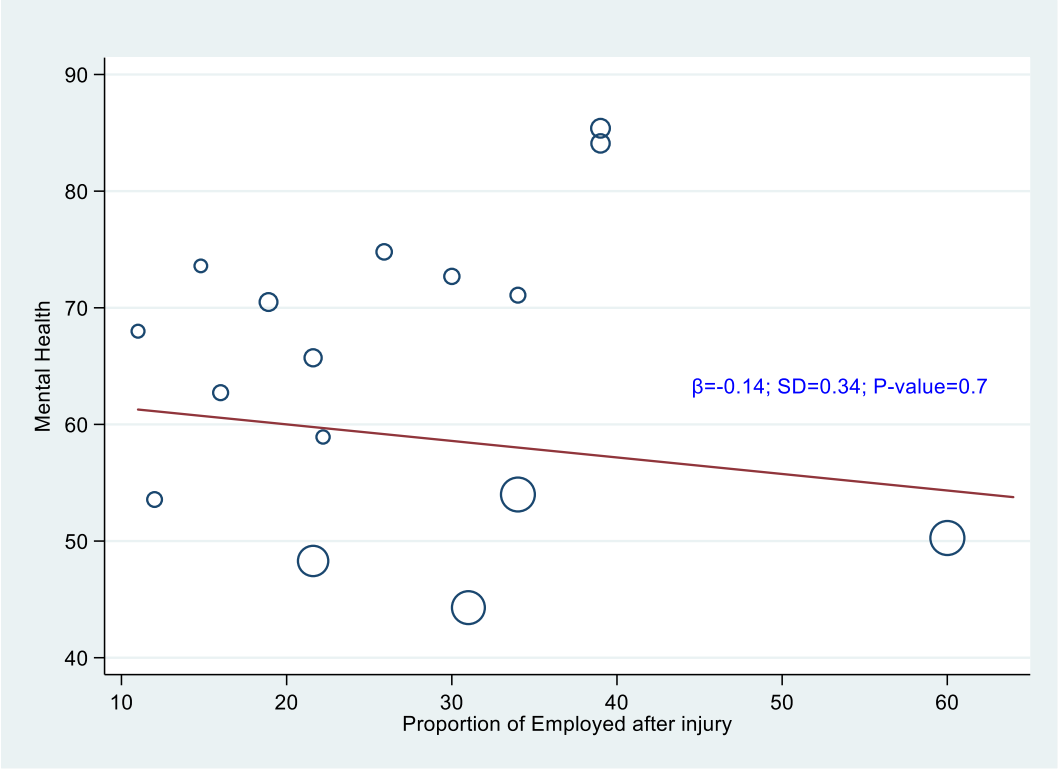
Supplementary figure S3.28 Association between social role and proportion with employment after injury



Supplementary figure S3.29 Association between mental health and proportion of paraplegic (compared with tetraplegic) individuals

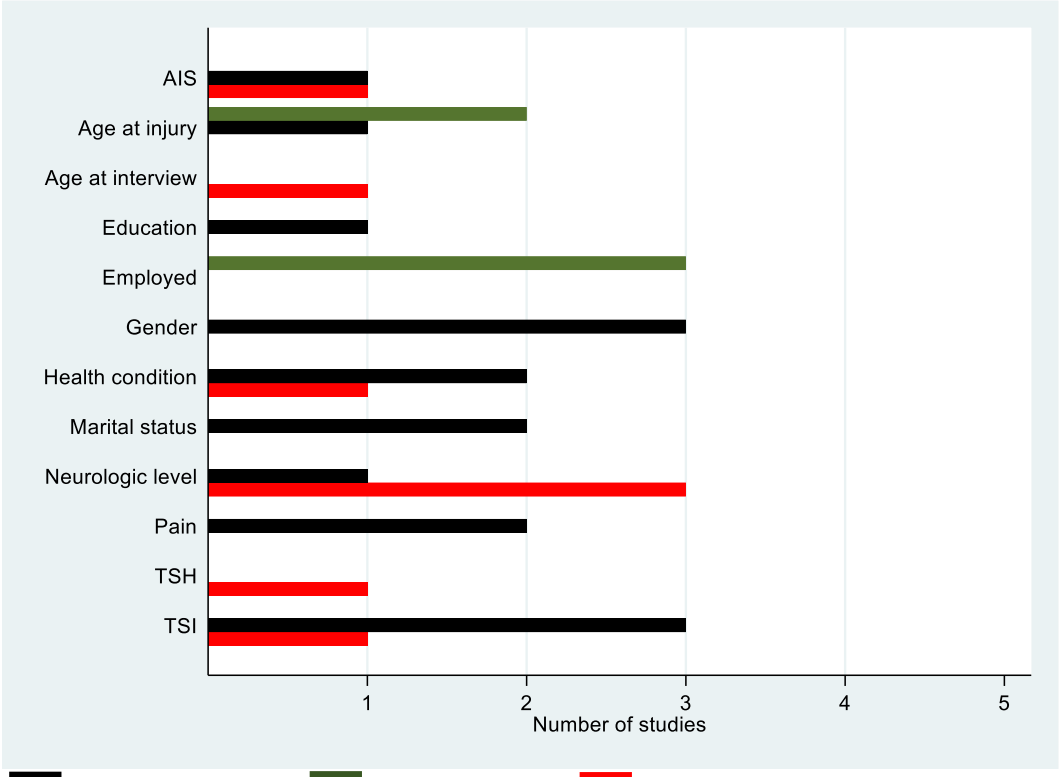


Supplementary figure S3.30 **Association between mental health and mean years since injury**



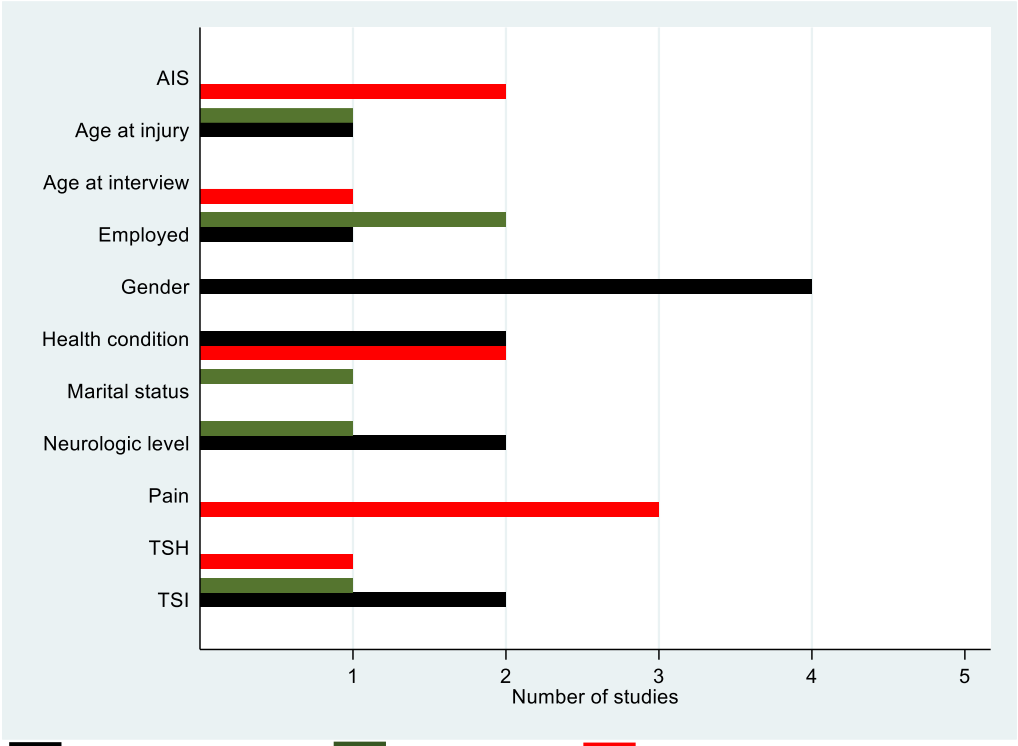
Supplementary figure S3.31 **Association between mental health and proportion with employment after injury**

Figure S3.32 to S40 show the number of cross-sectional studies that show a statistically significant positive association between the factor and domains of Short-Form 36 quality (green bar), the number that show a significant negative association (red bar), and the number that show no significant effect (black bar). Not all studies reported the association with all factors



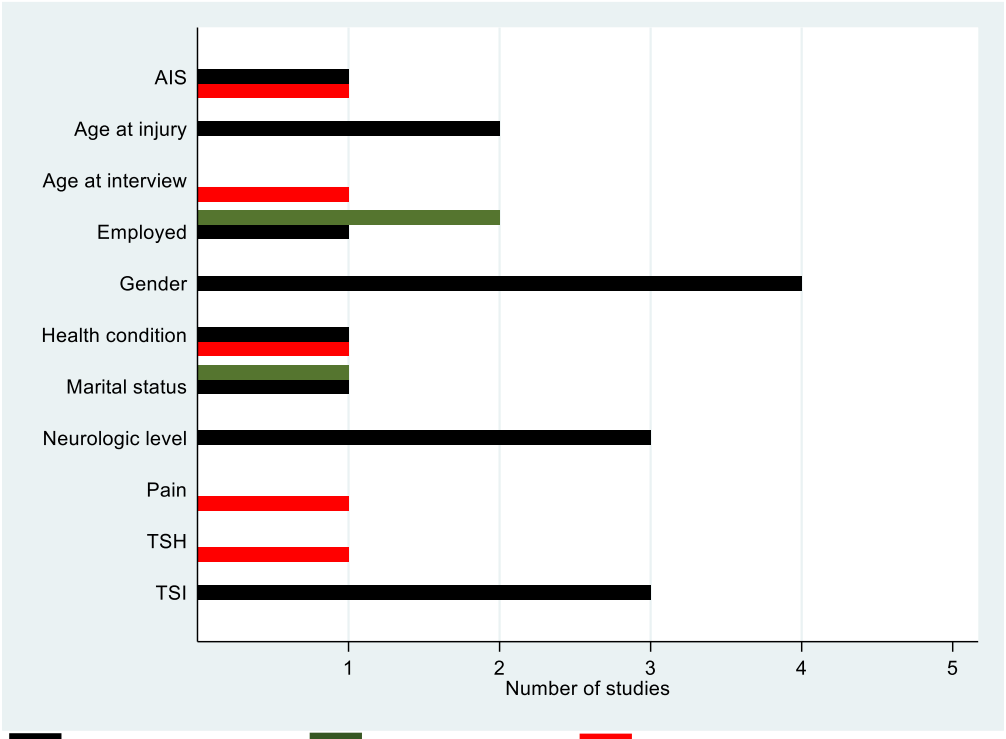
TSI time since injury; TSH time spent ah hospital; Neurologic level compared tetraplegic vs paraplegic

Supplementary figure S3.32 Factors associated with physical role in cross sectional studies (N=5)



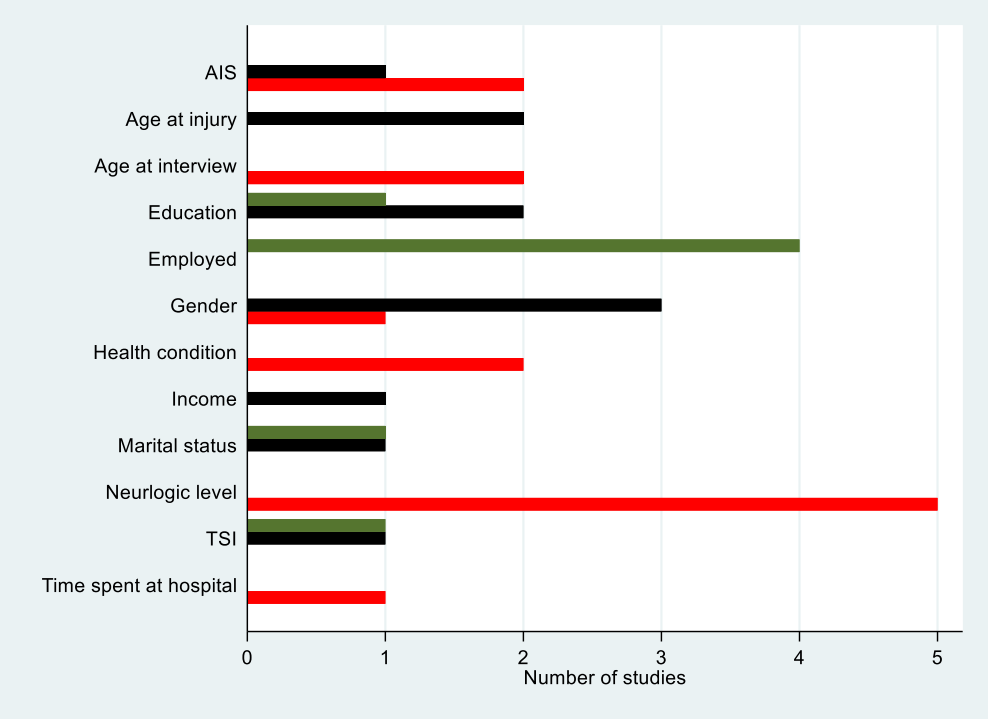
TSI time since injury; TSH time spent ah hospital; Neurologic level compared tetraplegic vs paraplegic

Supplementary figure S3.33 Factors associated with bodily pain in cross sectional studies (N=5)



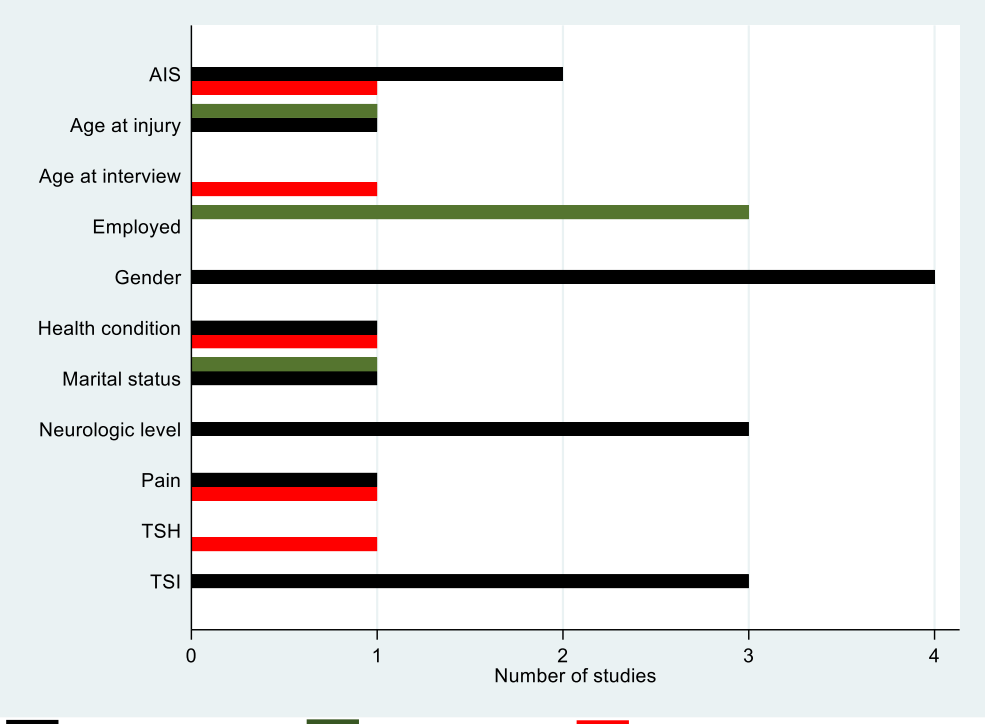
TSI time since injury; TSH time spent ah hospital; Neurologic level compared tetraplegic vs paraplegic

Supplementary figure S3.34 Factors associated with general health in cross sectional studies (N=5)



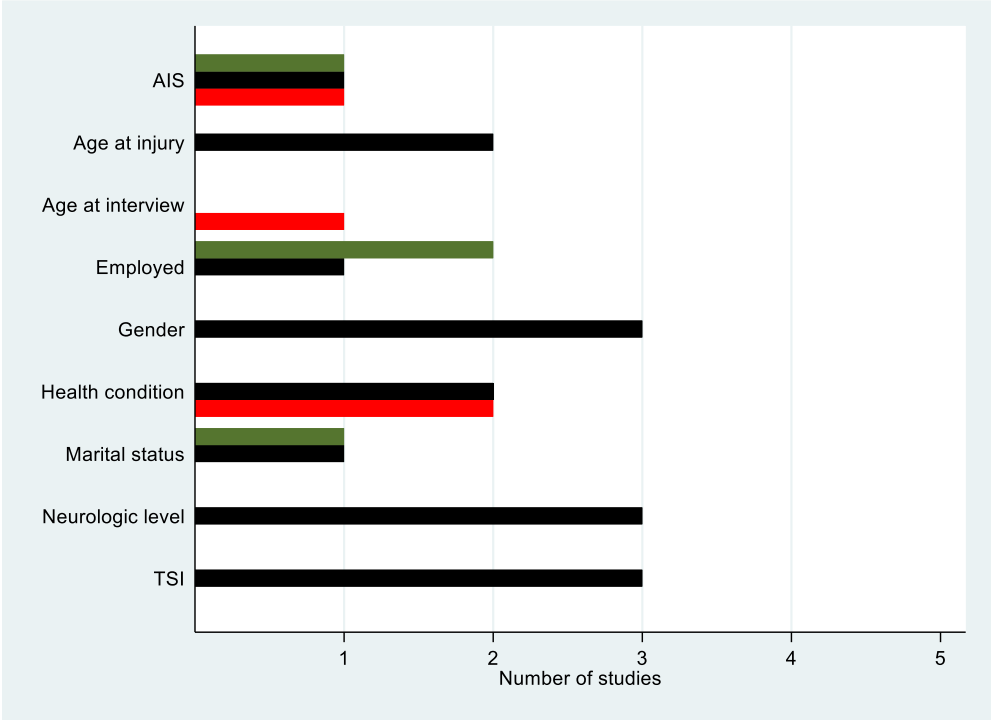
TSI time since injury; TSH time spent ah hospital; Neurologic level compared tetraplegic vs paraplegic

Supplementary figure S3.35 Factors associated with physical component scores in cross sectional studies (N=5)



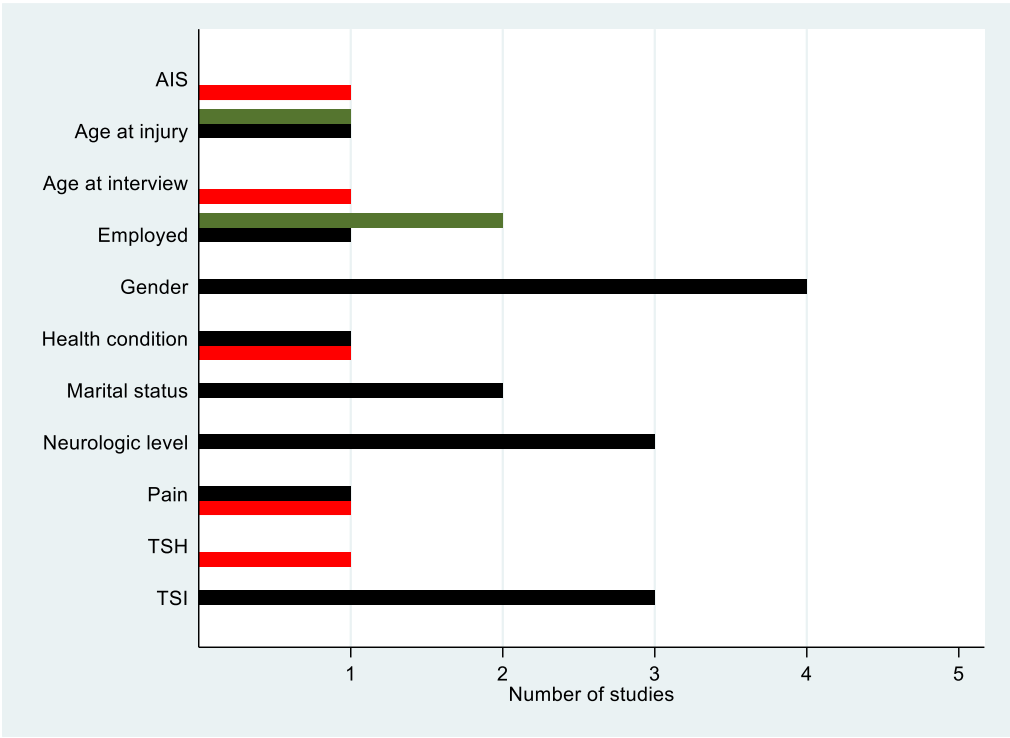
TSI time since injury; TSH time spent ah hospital; Neurologic level compared tetraplegic vs paraplegic

Supplementary figure S3.36 Factors associated with emotional role in cross sectional studies (N=5)



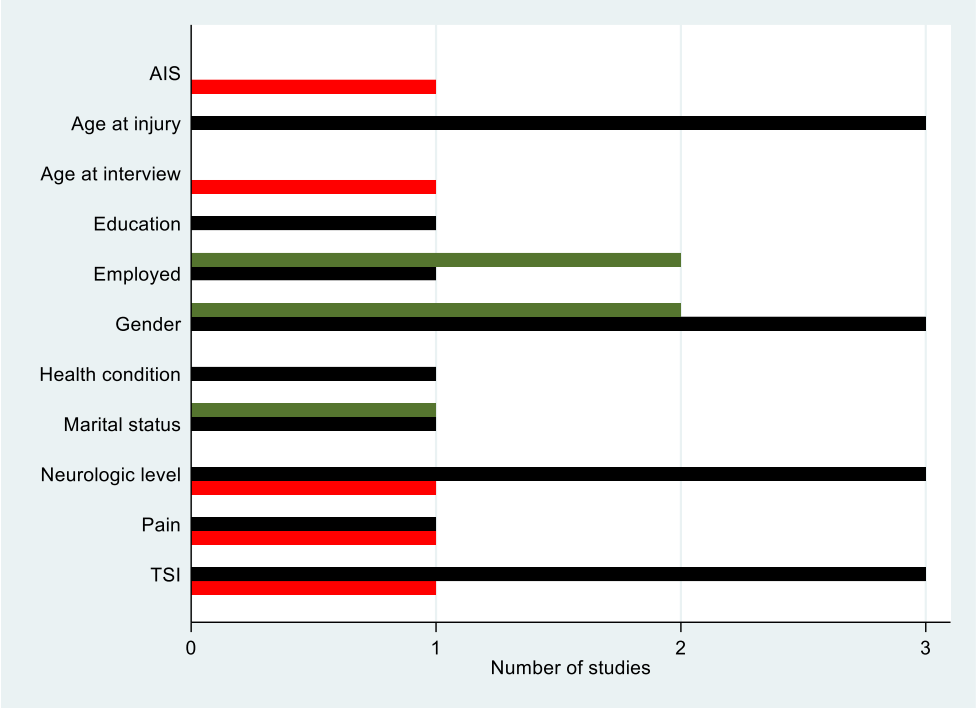
TSI time since injury; TSH time spent ah hospital; Neurologic level compared tetraplegic vs paraplegic

Supplementary figure S3.37 Factors associated with vitality in cross sectional studies (N=5)



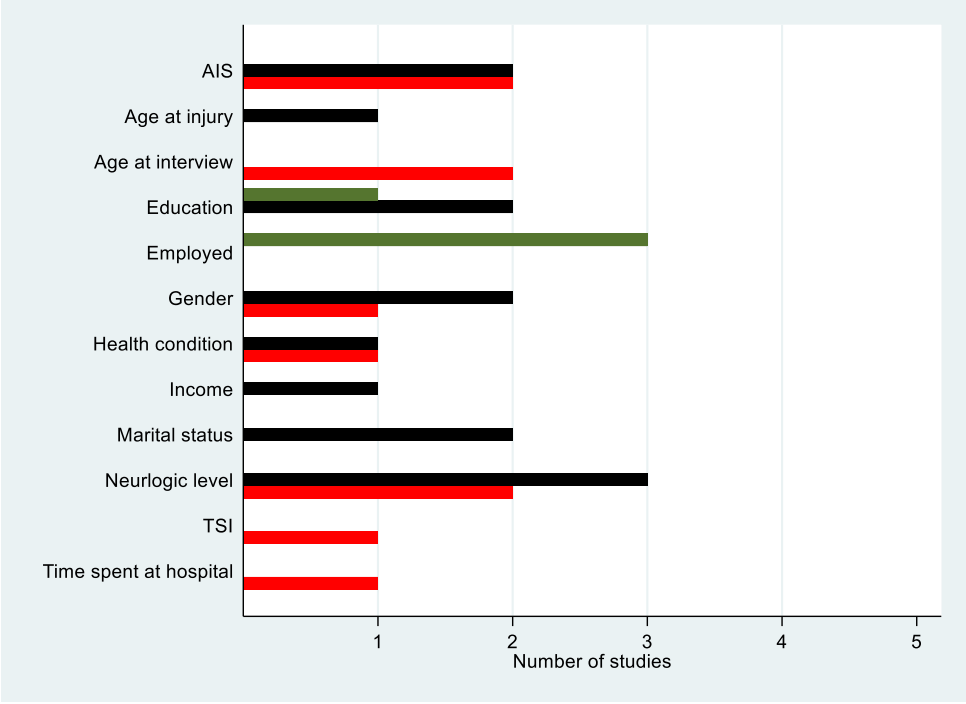
TSI time since injury; TSH time spent ah hospital; Neurologic level compared tetraplegic vs paraplegic

Supplementary figure S3.38 Factors associated with social role in cross sectional studies (N=5)



TSI time since injury; TSH time spent ah hospital; Neurologic level compared tetraplegic vs paraplegic

Supplementary figure S3.39 Factors associated with mental health in cross sectional studies (N=5)



TSI time since injury; TSH time spent ah hospital; Neurologic level compared tetraplegic vs paraplegic

Supplementary figure S3.40 Factors associated with mental component scores in cross sectional studies (N=5)