Understanding functioning and its complexity in persons with spinal cord injury as a first step towards corresponding prediction modelling

Cumulative thesis

PhD in Health Sciences at the Department of Health Sciences and Medicine,

University of Lucerne

presented by

Jsabel Hodel

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SUMMARY

The objective of this doctoral thesis was to inform the development of future prediction models of functioning in spinal cord injury (SCI) by examining the complexity of functioning and its predictors in persons with SCI attending first rehabilitation in Switzerland as well as the current state of prediction research in the field of SCI rehabilitation. To achieve this objective, three related research studies were conducted.

Study 1 used the International Classification of Functioning, Disability and Health (ICF) as a conceptual framework and structural equation modelling (SEM) as methodology to investigate associations between body structures and functions, and activities as well as their relationship with contextual factors and characteristics of the health condition in persons with SCI in Switzerland at discharge from first rehabilitation. Findings revealed potential important direct and indirect effects within the tested association structures. Study 2 used latent process mixed models (LPMMs) and multinomial logistic regression as methodologies to identify classes of functioning trajectories and corresponding predictors of class membership in persons with SCI undergoing first rehabilitation in Switzerland. Results showed four distinct classes of functioning trajectories and revealed robust predictors for distinguishing between identified classes. Lastly, study 3 summarized current literature on prediction models of functioning in the field of SCI rehabilitation in the form of a scoping review. Results showed that the potential of functioning-based prediction models for use in clinical practice remains to be explored.

Altogether, the findings of this doctoral thesis will pave the way for discussions and future research on prediction models of functioning in SCI with the ultimate goal of enhancing clinical practice.

LIST OF ABBREVIATIONS

ADL	Activities of daily living
ICD	International Classification of Diseases
ICF	International Classification of Functioning, Disability and Health
FIM™	Functional Independence Measure
LPMM	Latent process mixed model
NRP74	National Research Programme 74 Smarter Health Care
SCI	Spinal cord injury
SCIM III	Spinal Cord Independence Measure version three
SEM	Structural equation modelling
StARS	Standardized Assessment and Reporting System
SwiSCI	Swiss Spinal Cord Injury Cohort Study
TREE	Transparency, Replicability, Ethics, and Effectiveness
WHO	World Health Organization

CHAPTER 1
Introduction

This doctoral thesis investigated the complexity of functioning and its predictors in persons with spinal cord injury (SCI) attending first rehabilitation in Switzerland as well as the current state of prediction research in the field of SCI rehabilitation. The results of this thesis have the potential to inform the development of future prediction models of functioning in SCI. The following introduction outlines the background and objective of this doctoral thesis as well as the context in which the corresponding research was conducted.

BACKGROUND

Understanding the lived experience of persons with SCI through functioning

SCI is a severe health condition with various and wide-ranging implications for the person living with SCI. It not only involves impairments in body structures (the spinal cord) and changes in body functions (the loss of neurological functions), it limits the performance of activities (such as self-care or mobility) as well as participation in major life areas (such as using transportation or employment) [1]. In order to enhance our knowledge of SCI and enable persons with SCI to live an autonomous life, we need to understand how SCI plays out in people's everyday life. In doing so, personal and environmental factors, for example a person's motivation or the availability of assistive devices and health care services, need to be taken into consideration.

SCI results from physical damage to the spinal cord inside the spinal column. The respective cause of the lesion can either be traumatic, for example due to an accident, a fall or violence, or non-traumatic, for example due to an infectious or musculoskeletal disease. As the spinal cord serves the transmission of the motor, sensory and autonomic information between the brain and the body, a lesion leads to partial or complete loss of body functions below the lesion site [2]. A lesion located at a lower level of the spinal cord (i.e. paraplegia) often involves the loss of lower limb movement and trunk control, whereas a lesion at a higher level (i.e. tetraplegia) usually involves additional loss in upper limb movement, and some persons might require breathing assistance [1]. In addition to the injury level, the extent of the loss of motor, sensory and autonomic functions is also affected by the severity of the injury. This is defined as complete or incomplete SCI depending on the extent motor or sensor functions below the level of injury and in the sacral segments have been preserved [2]. Persons with SCI experience various wide-ranging implications beyond the physical damage to the body and the loss of motor and neurological functions. SCI can lead to limitations in the performance of activities

of daily living (ADL), such as bladder and bowel management [3-6], and persons with SCI may also experience restrictions in participating in major life areas, such as employment [7-9]. In general, injury-related factors such as injury level and severity [10-12] as well as sociodemographic factors [13, 14] are associated with the overall functioning of persons living with SCI. Furthermore, persons with SCI are confronted with the emotional and psychological adaptation to the injury [15-17], and are at risk for developing secondary health conditions and complications [1, 18, 19], such as pain [20-22], depression [23], urinary tract infections [24] or pressure injuries [25, 26].

The lived experience of persons with SCI is currently most comprehensively described and operationalized by the World Health Organization's (WHO) International Classification of Functioning, Disability and Health (ICF) [27]. In the ICF, "functioning" encompasses a person's *body functions* and *structures*, and *activities and participation*. These components of functioning reflect both, the biological as well as the lived health of a person. Body functions and structures are the physiological and psychological functions and the anatomical parts of the human body. Activities and participation are all of the actions, behaviours and social roles that are performed by the person, from the simplest to the most complex [27]. Furthermore, the ICF specifically highlights the understanding of functioning as the outcome of the interaction between a *health condition* and *contextual factors*, i.e. *environmental* and *personal factors*. The term "health condition" is understood as a health problem impacting on a person's functioning, and includes both acute and chronic diseases as well as disorders, traumas or injuries. Contextual factors denote the full context of a person's life, identified by environmental factors external to a person, i.e. the surrounding physical, social, political, legal and attitudinal context, and personal factors intrinsic or specific to a person, including for example social status or upbringing [27]. Environmental factors may impact on a person's functioning positively, by acting as facilitator and improving functioning, or negatively, by acting as barrier and limiting functioning.

The ICF provides a classification for consistent documentation of functioning information. As such, the ICF complements WHO's International Classification of Diseases (ICD), which was developed to provide an international standard to document information about diseases and other health problems.

The conceptual basis of the ICF is the biopsychosocial model of functioning and disability shown in Figure 1. The essential characteristic of the biopsychosocial model is its understanding of functioning as a complex and dynamic interaction between its components [27]. This means that one component can impact one or more of the other components. In other words, a person's functioning status may change over time and is modifiable, for example by adapting environmental factors, e.g. by providing a wheelchair and assistive devices for persons with SCI. Functioning status is also on a continuum, i.e. the lived experience of health as outcome of the interaction between a health condition and contextual factors can range from the complete absence of functioning to full functioning. Overall, the model provides the building blocks – in the form of different components and possible interactions between them – for the study of different aspects of functioning and disability. Thus, the specific associations or causal links between the components need to be explored empirically by the collection and analysis of data on the specific components of interest.

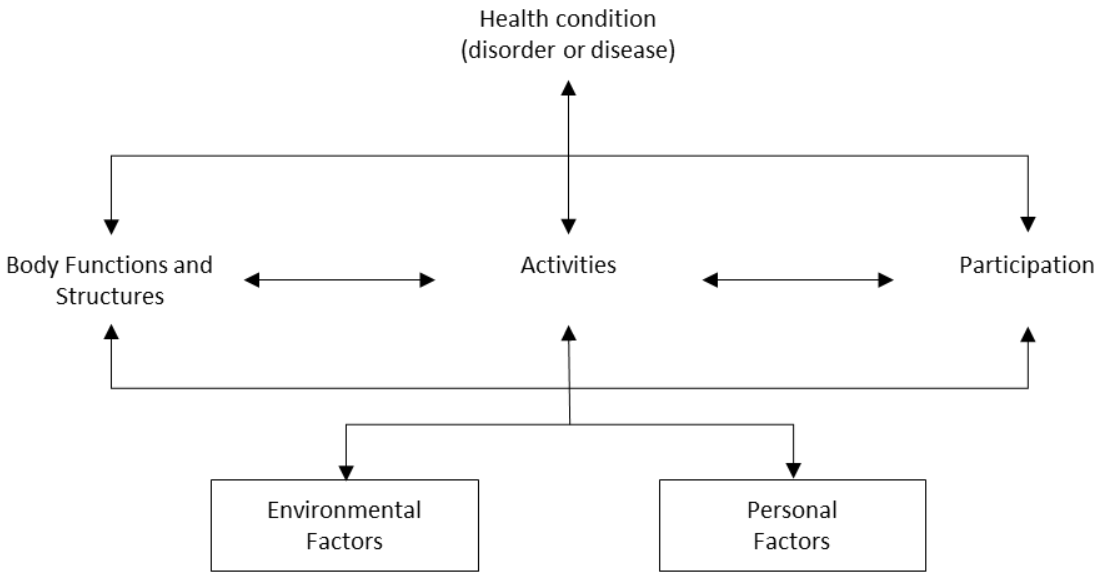

Figure 1: Representation of the biopsychosocial model of functioning and disability underlying the ICF and the interactions among its components, from WHO 2001, p. 18 [27].

In the context of this doctoral thesis, the ICF and its underlying biopsychosocial model of functioning and disability serve as the basis for the description, understanding, and analysis of functioning outcomes and their predictors in persons living with SCI in Switzerland.

The role of functioning information in first rehabilitation after SCI

Persons with SCI may require lifelong health services across the continuum of care: After a newly acquired injury, persons with SCI demand an immediate acute care which starts with the admission to the hospital. During this phase, the neurological state of the patient is stabilized and the focus of rehabilitation is on the medical prevention of complications [28]. In Switzerland, acute rehabilitation is generally followed by a specialized and interdisciplinary inpatient rehabilitation (referred to as "first rehabilitation" or "initial rehabilitation" in this thesis), in which persons with newly acquired SCI receive various interventions (such as physical, occupational, recreational, or speech therapy) [29]. These rehabilitation interventions generally aim to optimize a person's functioning in light of his/her environment [30, 31], and specifically to regain independence and autonomy in performing ADL, and to prepare the person's return home and participation in society [28, 29]. After returning home and in the long-term, persons with SCI require continued specialized outpatient rehabilitation services and other health and social services in order to maintain a healthy and autonomous life.

To monitor the lived experience of persons with SCI through the continuum of care, regularly documenting functioning is important. As shown by Kirchberger et al. [32], problems in functioning experienced by persons with SCI are diverse. Moreover, the prevalence of problems in specific components of the ICF might be different for different stages along the continuum of care from early post-acute to the long-term. For instance, in the component of activities and participation, aspects of mobility and self-care were more frequently reported in the early post-acute setting. With respect to environmental factors, attitudes and support of others were more frequently reported in early post-acute setting, whereas other aspects, such as climate or physical geography, were more frequently reported in the long-term setting. Similar findings have been reported by other researchers as well [33, 34].

First rehabilitation after SCI is a critical time point as it is when the focus in care shifts from stabilizing a person's health state to optimizing a person's functioning. Assessing and documenting functioning information and monitoring functioning status is crucial in first rehabilitation as it guides the planning and management of the rehabilitation process and clinical decision making and indicates whether rehabilitation goals have been achieved [35, 36]. The collection of comprehensive and relevant functioning information is important for

health professionals in order to describe the patient's health state at the time of assessment and to identify his/her functioning needs. Accordingly, specific short-, mid- and long-term rehabilitation goals are set together with the patient, a suitable programme of rehabilitation interventions are identified and conducted, and the patient's post-intervention functioning is evaluated [35]. The cycle of assessment, goal-setting, assignment and conduct of interventions and evaluation of post-intervention functioning is known as the Rehab-Cycle [35, 37, 38]. A Rehab-Cycle can be repeated within one phase to monitor rehabilitation progress and help decide on the adjustment of interventions. Moreover, a Rehab-Cycle can be employed across the continuum of care.

Fundamental to the clinical decision making in the rehabilitation process (or Rehab-Cycle) is the health professional's knowledge, experience and appraisal about impairments and restrictions in all functioning components as well as their interactions. In this regard, functioning is complex in two respects: First, there is a wide range of possible interactions and impacts among the components of functioning, and second, functioning may change over time. From a practice point of view, health professionals consider the person's functioning status at the time of assessment as well as expected functioning outcomes in the process of rehabilitation planning. In order to describe, investigate and understand the complexity of functioning in persons with SCI, prediction research is a promising field of study.

Prediction research as opportunity to enhance first rehabilitation practice after SCI

Prediction research is about the study of variables or test results and their ability to predict the occurrence of a certain outcome in the future, also referred to as prognosis, or the presence of a diagnosis for persons with a given health condition [39, 40]. Predicting an outcome is not an end by itself but rather serves as the foundation to enhance health care practice by informing the decision making of health professionals at specific time points along the care pathway [40]. Following the work of several research groups [39-44], different numbers of study types can be distinguished for prognostic and diagnostic prediction research. For the purpose of this doctoral thesis, we adapted the descriptions of Bouwmeester et al. [39] and summarized them as follows:

(1) *Predictor finding studies* are association studies with the aim to identify or explore which variables, out of different candidate predictors, are of potential importance for the prediction of a specific outcome of interest. These studies set the basis for further

testing of promising predictors in either prediction model studies or studies about causation [44].

(2) *Prediction model studies* generally aim to develop a prediction model for an intended clinical use and/or to externally validate an already existing prediction model within a given context (with or without model updating). Prediction models are always multivariable and are understood as "tools that combine multiple predictors by assigning relative weights to each predictor to obtain a risk or probability" [45]. Ideally, prediction model studies with focus on model development include an internal validation to assess any potential optimism in the performance of the model based on the development sample [45]. Prediction model studies with focus on external validation explicitly test the performance of a prediction model on a new participant sample which was not used for corresponding model development.

(3) *Impact studies* aim to assess the impact or effect of the use of an existing and externally validated prediction model in practice, for example in terms of patient outcomes, management or health professional and patient behaviour.

In practice, the assignment of a study to either type is not always straightforward [39]. Moreover, study types 2 and 3 also include the phases, which are necessary to implement in the development of a prediction model that will be used in clinical practice: Development, validation, and impact assessment [46-49].

The description of these different study types underscores that prediction research can support the understanding of associations among variables and outcomes of interest (in terms of predictor finding studies) as well as the translation of research evidence into practice (in terms of prediction model and impact studies). Since optimized functioning is the primary outcome of rehabilitation, the question is whether prediction research can assist in describing and understanding the complexity of functioning and translate it into practice to support clinical decision making and rehabilitation management.

In SCI literature, only few studies have investigated complex associations across the components of the biopsychosocial model [50-54]. These studies use, for example, path analysis and graphical modelling approaches. With respect to longitudinal investigations of functioning outcomes as operationalized by a sum score across various domains of functioning (e.g. mobility, self-care, and bladder and bowel management), only few studies have used

sophisticated methodologies to investigate change over time and its associations with different predictors such as person characteristics [55-57]. However, to enhance our understanding of functioning in SCI and in particular its complexity, the investigation of comprehensive association structures and the longitudinal course of functioning outcomes by means of predictor finding studies is fundamental. Findings from such studies can potentially inform the tailoring of first rehabilitation programmes and assist in clarifying specific functioning needs of persons with SCI. Moreover, they can serve as the basis for the development of corresponding prediction models of functioning in SCI.

The development of prediction models for use in clinical practice might be promising, for example, in the identification of persons with unfavourable outcomes or the allocation of suitable health services to reach a specific rehabilitation goal. More specifically, prediction models have the potential to support health professionals during the Rehab-Cycle in first rehabilitation after SCI, for example, in determining patients' rehabilitation needs according to their predicted outcomes. In SCI literature, prediction models have been developed for outcomes reflecting specific aspects of functioning, such as for bowel and bladder outcomes [58-60], or ambulatory outcomes [61-66]. Less is known about prediction models of functioning in SCI as operationalized in the ICF. Thus, an overview of corresponding literature is needed to assess the current state of prediction research in the field of SCI rehabilitation. Furthermore, by shedding light on existing research gaps and promising future research directions, such an overview can assist in the development of future prediction models of functioning in SCI.

OBJECTIVE AND OUTLINE

Building upon this background, the overall objective of this doctoral thesis was to inform the development of future prediction models of functioning in SCI by examining the complexity of functioning and its predictors in persons with SCI attending first rehabilitation in Switzerland as well as the current state of prediction research in the field of SCI rehabilitation. To achieve this objective, three related research studies were conducted according to the following specific aims:

(1) To examine the associations between components of functioning and their relationship with age, gender and aetiology in persons with SCI attending first rehabilitation while considering potential indirect effects and group differences.

(2) To identify different classes of functioning trajectories in persons with SCI attending first rehabilitation and to examine potential predictors of class membership.

(3) To explore existing prediction models of functioning in the field of SCI rehabilitation.

A description of each research study is provided in the next sections. The corresponding scientific publications can be found in chapters 2-4, respectively.

Study 1: Examination of functioning in persons with SCI

The first research study is related to specific aim 1 and can be understood as an exploratory association study investigating the understanding of functioning and its complexity in persons with SCI. To do so, the cross-sectional study examined associations between body structures and functions, and activities as well as their relationship with contextual factors and characteristics of the health condition in persons with SCI in Switzerland at discharge from first rehabilitation. The specific aims were to:

(a) Test indirect effects of body structures and functions on activities through different mental functions, and

(b) test the resulting models for differences in aetiology, age and sex groups.

The analysis methods applied were Rasch-analysis [67, 68] and structural equation modelling (SEM) [69]. The latter is able to handle complex structures of associations among multiple variables.

Study 2: Functioning trajectories in persons with SCI

The second research study related to specific aim 2 and is an explorative investigation on the longitudinal course of functioning in persons with SCI undergoing first rehabilitation and corresponding predictors. In particular, the study examined the heterogeneous individual courses of functioning (i.e. trajectories) of persons with SCI undergoing first rehabilitation in Switzerland with respect to homogeneous subgroups (i.e. classes) and their potential predictors. The specific aims were to:

(a) Identify classes of functioning trajectories in persons with SCI undergoing initial rehabilitation in specialized centres in Switzerland, and

(b) examine potential predictors of class membership in order to inform clinical planning in the rehabilitation process.

The analysis methods used were latent process mixed models (LPMMs) [70] and multinomial logistic regression.

Study 3: Prediction models of functioning in the field of SCI rehabilitation

The third research study relates to specific aim 3, in which current literature on prediction models of functioning in the field of SCI rehabilitation were summarized in the form of a scoping review [71]. The specific aims were to:

(a) Identify prediction models of functioning in SCI,
(b) examine their content by using the ICF as a reference language,
(c) examine their use from a systems perspective, and
(d) document which methods were used to develop them.

This study explored and highlighted current gaps as well as promising future directions in prediction research in SCI. Together with the findings from studies 1 and 2, it has the potential to set the basis for informing future developments or improvements of prediction models of functioning in the field of SCI rehabilitation.

CONTEXT

Swiss Spinal Cord Injury Cohort Study

Since 2010, the Swiss Spinal Cord Injury Cohort Study (SwiSCI) has been collecting population-based data on persons with SCI in Switzerland. The SwiSCI is hosted by the Swiss Paraplegic Research and collaborating partners are the four major specialized SCI rehabilitation centres in Switzerland (SCI Center, Balgrist University Hospital, Zurich; Centre for SCI and Severe Head Injury, REHAB Basel, Basel; Clinique Romande de Réadaptation, Sion; Swiss Paraplegic Centre, Nottwil). Its research programme is committed to improving the understanding of functioning in persons with SCI and to support health maintenance and quality of life of persons with SCI across their life span and along the continuum of care. Accordingly, the SwiSCI data model is based on the ICF and the underlying conceptualization of functioning [72-77], and incorporates three different streams of data collection [78]:

(1) A retrospective medical records data collection including all four collaborating clinics,
(2) a prospective data collection in the form of a survey in the community of persons living with SCI and performed every 5 years, and

(3) a prospective data collection in the form of an *Inception Cohort* including persons with newly acquired SCI undergoing first rehabilitation in one of the collaborating clinics.

Generally, SwiSCI includes persons with both traumatic and non-traumatic SCI. In addition, participants must be 16 years or older and have permanent residence in Switzerland. Persons with congenital conditions, such as spina bifida, or neurodegenerative disorders, such as amyotrophic lateral or multiple sclerosis, persons with Guillain-Barré syndrome leading to SCI and persons experiencing new SCI in the context of palliative care are excluded from SwiSCI [78].

This doctoral thesis used data collected within the SwiSCI Inception Cohort, which collects standardized data from admission to discharge and during yearly follow-up appointments: T1=at around 4 weeks after SCI diagnosis; T2=at around 12 weeks after SCI diagnosis; T3=at around 24 weeks after SCI diagnosis; T4=at discharge, T5=1-year follow-up appointment [79]. This specific design allows up to four assessments per person during his/her first rehabilitation stay and thus, supports cross-sectional as well as longitudinal examinations.

The measurement instrument in SwiSCI that was used in this doctoral thesis to operationalize functioning is the Spinal Cord Independence Measure version three (SCIM III) [80]. The SCIM III assesses functioning of persons with SCI, and generates a sum score that reflects independence in the performance of ADL in the areas of mobility, self-care, respiration and bowel and bladder management. The SCIM III has been shown to have favourable psychometric properties, i.e. reliability and validity, and to be sensitive to change [81].

National Research Programme 74 Smarter Health Care

This thesis is part of a research project within the National Research Programme 74 Smarter Health Care (NRP74) supported by the Swiss National Science Foundation. The NRP74 aims "to provide insights into the health care structure and utilisation in Switzerland, and into ways of improving health outcomes with a particular focus on prevention and the treatment of chronic conditions" [82]. Additionally, the programme sets a focus on health data with respect to improving availability and accessibility, as well as linkage and comparability. Among 34 NRP74 research projects, this thesis is part of project No. 21 entitled *Enhancing continuous quality improvement and supported clinical decision making by standardized reporting of functioning*, which is also referred to as NRP74 Standardized Assessment and Reporting System (StARS) project for functioning information in rehabilitation [83, 84].

The NRP74 StARS project specifically addresses questions about the standardization of functioning information with an example application in rehabilitation quality management (part A) [85-88]. It also addresses questions about potential use cases (i.e. application areas) for standardized functioning information and the translation of generated knowledge into practice with an example application in first rehabilitation of persons with SCI (part B). This doctoral thesis corresponds to the work performed in the subproject part B.

In order to foster collaboration with relevant stakeholders, the NRP74 StARS project incorporated several stakeholder involvement activities. Such activities included, for example, the formation of a project advisory board and the conduction of two advisory board meetings to discuss selected project results, as well as the conduction of a stakeholder dialogue with relevant stakeholders in the Swiss health system as part of the implementation strategy of the NRP74 StARS project.

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CHAPTER 2
Examining the complexity of functioning in persons with spinal cord injury attending first rehabilitation in Switzerland using structural equation modelling

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ARTICLE

Examining the complexity of functioning in persons with spinal cord injury attending first rehabilitation in Switzerland using structural equation modelling

This article has been corrected since Advance Online Publication and a correction is also printed in this issue

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Abstract

Study design Cross-sectional.

Objectives To examine the associations between activities, body structures and functions, and their relationship with aetiology, age and sex in persons with spinal cord injury (SCI) at discharge from first rehabilitation.

Setting Swiss SCI Cohort Study (SwiSCI).

Methods The study included 390 participants with newly acquired SCI and the International Classification of Functioning, Disability and Health (ICF) as conceptual frame of reference. Body structures were represented by injury level and severity; body functions by cardiovascular, pulmonary, skin, bowel and urinary functions and pain; mental functions by anxiety, depression, optimism and self-esteem; and activities by independence in performing activities of daily living (ADL). Using structural equation modelling (SEM), indirect effects of body structures and functions on independence in performing ADL through mental functions were tested for each mental function separately. For each structural model, fit was assessed using several indices and differences in aetiology, age and sex groups were explored.

Results The structural model about optimism showed good fit in all indices; the models about anxiety, depression and self-esteem showed conflicting fit indices, respectively. Within all models, effects on independence in performing ADL were mainly direct. Pain showed significant ($P < 0.05$) indirect effects on independence in performing ADL within the depression, optimism and self-esteem models. The model about anxiety showed differences in aetiology groups.

Conclusions Using an ICF-based modelling approach, this study presents an attempt towards a more comprehensive understanding of functioning in first rehabilitation of persons with SCI, which might be fundamental for rehabilitation planning.

Introduction

The objective of rehabilitation is to optimise functioning for people, who because of a health condition, have difficulties carrying out activities of everyday life [1]. By 'functioning' we mean the key concept in the World Health Organization's International Classification of Functioning, Disability and Health (ICF) [2], namely the sum of human body structures and functions, as well as activities and areas of participation. As the ICF makes clear, rehabilitation's focus must be both on optimising functioning at the body level as well as the person's capacity to perform actions and to transform this improvement in capacity by making changes in the person's environment, to optimise their performance in everyday life. To achieve this, rehabilitation requires information on people's functioning to guide intervention

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planning and, more generally, decision-making among health professionals and patients.

Spinal cord injury (SCI) is a health condition that has devastating impacts on people's life and functioning. The injury creates impairments in body structures and functions, including the neurological damage of the spinal cord and the loss of motor, sensory and autonomic neurologic functions [3]. These impairments adversely affect the person's independence in performing daily activities such as self-care, mobility, bladder and bowel management. Newly injured persons in acute care and first rehabilitation not only have to undergo a traumatic event, they are also placed at risk of complications such as pressure injuries, thromboembolism, cardiopulmonary arrest, cardiovascular, pulmonary and renal conditions [4]. The degree to which rehabilitation can optimise their functioning will be influenced by injury-related factors such as the cause of the injury [5], as well as sociodemographic factors [6, 7]. Factors such as depression have shown to influence functioning outcomes [8], however, how they impact the relationship between body structures and functions and activities and participation has not been examined yet. Given the wide and diverse range of impacts on body structures and functions, and resulting decrements in capacity to perform actions, SCI is associated with a high degree of complexity of people's functioning profile.

Deepening our understanding of this complexity, and in particular the associative linkages between health condition and components of functioning will be assisting in tailoring rehabilitation so as to meet the needs of people with SCI. Moreover, as countries put regulations in place that require an ICF-based documentation of assessment (as in Switzerland where ICF-based rehabilitation goals are required for quality assurance purposes [9]), empirical investigations into the associations described by the model of the ICF are important to ensure that evidence-based decisions can be made in rehabilitation practice.

To analyse these complex association structures, statistical modelling methods can be used [10]. In the SCI literature, we have found only a few studies that use these methods and the ICF model as a framework to analyse relationship structures among components of functioning [11] and interactions with the health condition and contextual factors [12–14].

Therefore, the objective of this study is to examine the associations between activities, body structures and functions, and their relationship with contextual factors in persons with SCI. Since the Swiss SCI Cohort Study (SwiSCI) [15] was developed based on the ICF as a conceptual model, the study provides an optimal basis for our purposes. Considering the variables available in SwiSCI, the specific aims are (1) to test indirect effects of body structures and functions on activities through different mental functions, and (2) to test the resulting models for differences in aetiology, age and sex groups. We use the notion 'indirect effects' to account for our cross-sectional study design; it should not be used synonymously with 'mediations', since the latter is referring to causal hypotheses requiring longitudinal study designs [16]. In this study, body structures were specified by injury level and severity; body functions by cardiovascular, pulmonary, skin, bowel and urinary functions and pain; mental functions by anxiety, depression, optimism and self-esteem; and activities by the independence in performing activities of daily living (ADL). See Table 1 for further information.

Methods

Study design and participants

This study used data from the SwiSCI Inception Cohort Study [15] in which newly injured persons with SCI are recruited during first rehabilitation in one of the four collaborating rehabilitation centres (SCI Center, Balgrist University Hospital, Zürich; Centre for SCI and Severe Head Injury, REHAB Basel, Basel; Clinique Romande de Réadaptation, Sion; Swiss Paraplegic Centre, Nottwil). Inclusion criteria of the SwiSCI Inception Cohort are the following: (1) age of 16 years or older, (2) permanent residence in Switzerland, (3) diagnosis of traumatic or non-traumatic SCI; exclusion criteria can be found elsewhere [15]. Measurements are performed one month (T1), three months (T2) and six months (T3) after SCI diagnosis during the clinical rehabilitation setting and at discharge (T4).

Until November 12th 2018, 883 participants were enroled in the SwiSCI Inception Cohort Study and completed data collection at discharge. For the purpose of this study, patients with the following characteristics were excluded from the sample in specific order: (1) death during first rehabilitation ($N = 16$), (2) no observations in all items of the independence in performing ADL measure at T4 ($N = 174$), (3) no observations in all items of the measures of the mental functions at T4 ($N = 290$), (4) intact neurological level or normal degree of impairment [17] at T4 ($N = 13$).

Measures

The SwiSCI builds upon the ICF as conceptual foundation and during its development, instruments to operationalise the components of the ICF were identified [18, 19]. The ICF concepts reflected within the present study, measurement information, corresponding variables and response options are shown in Table 1.

Table 1 Overview of ICF concepts and corresponding operationalisations or measurement instruments and items considered within the analysis of this study.

ICF concept	Construct	Operationalization or instrument	Assessment mode	Time point	No. of items	Further specification	Response options	Item label
Body structures	Neurological level of injury	International SCI Core Data Set/ ISNCSCI [17, 45]	Clinical assessment	T4	1	Neurological level of injury	Tetraplegia (C1-C8)/paraplegia (T1-S5)[d]	Level of injury
	Severity of injury	International SCI Core Data Set/ ISNCSCI [17, 45]	Clinical assessment	T4	1	ASIA Impairment Scale	Incomplete (B, C, D)/complete (A)[d]	Severity of injury
Body functions	Bowel function	International SCI Bowel Function Basic Data Set [46]	Health record	T4	1	Normal defecation since T3	No/yes	Bowel function
	Cardiovascular function	International SCI Cardiovascular Function Basic Data Set [47]	Health record	T4	1	Occurrence of cardiovascular conditions or complications since T3	No/yes	Cardiovascular function
	Pain	International SCI Pain Basic Data Set [48]	Questionnaire [a] (self-reported)	T4	1	Presence of pain in the last week	No/yes	Pain
	Pulmonary function	International SCI Pulmonary Function Basic Data Set [49]	Health record	T4	1	Occurrence of pulmonary conditions or complications since T3	No/yes	Pulmonary function
	Skin function	International SCI Skin and Thermoregulation Function Basic Data Set [50]	Clinical assessment	T4	1	Presence of pressure injury since T3	No/yes	Skin function
	Urinary function	NA	Clinical assessment	T4	1	Presence of infection of urinary tract since T3	No/yes	Urinary function
	Anxiety	HADS [51, 52]	Questionnaire [a] (self-reported)	T4	7	Presence of anxiety symptoms in the last week	Four-level rating scales, where higher rates indicate the presence of anxiety symptoms	Stressed
								Scared
								Worried
								Relaxed
								Fearing
								Restless
								Panicked
	Depression	HADS [51, 52]	Questionnaire [a] (self-reported)	T4	7	Presence of depression symptoms in the last week	Four-level rating scales, where higher rates indicate the presence of depression symptoms	Enjoying as before
								Laughing
								Being cheerful
								Slowed down
								Interested in appearance
								Looking forward
								Enjoying a book
	Optimism	LOT-R [53]	Questionnaire [a] (self-reported)	T4	6[b]	Feeling of optimism of today	Five-level rating scales, where higher rates indicate higher optimism	Expecting the best
								Things go wrong if they can
								Optimistic about future
								Expecting things to go wrong
								Not relying on good things
								Expecting good things
	Self-esteem	RSES [54]	Questionnaire [a] (self-reported)	T4	4[c]	Self-esteem in general	Four-level rating scales, where higher rates indicate higher self-esteem	Having good qualities
								Feeling useless
								Being of worth
								Taking a positive attitude

Table 1 (continued)

ICF concept	Construct	Operationalization or instrument	Assessment mode	Time point	No. of items	Further specification	Response options	Item label
Activities	Performing ADL	SCIM III [55]	Health record	T4	19	Ability of performing ADL concerning self-care, respiration, sphincter management and mobility independently	Raw sum score ranging from 0 to 100, where a higher score indicates higher independency in performing ADL	Independence in performing ADL
NA	Age at injury	NA	Health record	T1	1	Age at SCI diagnosis	Younger than or equal/older than median age in years[d]	Age
	Aetiology	International SCI Core Data Set [45]	Health record	T1	1	Cause of injury	Traumatic/non-traumatic	Aetiology
	Sex	NA	Health record	T1	1	Sex	Male/female	Sex
	Language	NA	Health record	T1	1	Language of correspondence	German/French/Italian/Other	Language

ICF International Classification of Functioning, Disability, and Health, *SCI* spinal cord injury, *ISNCSCI* International Standards for Neurological Classification of Spinal Cord Injury, *ASIA* American Spinal Injury Association, *T1–T4* Swiss SCI Inception Cohort Study measurement time points, *HADS* Hospital Anxiety and Depression Score, *LOT-R* Life Orientation Test-Revised, *RSES* Rosenberg Self-Esteem Scale, *SCIM III* Spinal Cord Independence Measure version III, *ADL* activities of daily living, *NA* not applicable.

[a]Language versions: German, French, Italian.

[b]Selection of the six non-filler items of the questionnaire.

[c]Selection of the four items of the questionnaire that were administered at more than one time point within the Swiss SCI Inception Cohort Study.

[d]Dichotomization strategy (performed after missing data imputation).

Missing data imputation

Observations in the response options 'unknown' or 'unable to determine' were considered as missing. Missing observations of the injury level or severity at T4 were replaced by the last observation of the corresponding variable at T3 or T2 or T1. Missing observations in the other variables were replaced by using the non-parametric random forest method MissForest [20] which is able to handle data with continuous as well as categorical variables. The MissForest method has been shown to not only outperform established methods such as nearest neighbour imputation and multivariate imputation by using chained equations [20, 21], but also other random forest imputation methods [22]. See Supplementary Table 1 for further information on missing observations before data imputation.

Rasch measurement model for the independence in performing ADL

Using the Rasch measurement model [23, 24], the raw sum score of the Spinal Cord Independence Measure version III (SCIM III) was transformed to an interval sum score. Model fit was assessed by the individual and overall item fit, the person fit and the P value of the χ^2 test statistic of the item–trait interaction with good fit for non-significant χ^2 ($P > 0.05$). Score reliability was tested by the person separation index (PSI) with an adequate expectation of 0.70 or above at the group level. To test whether the data fulfils the underlying model assumptions, local independency among items, unidimensionality of the score and the absence of differential item functioning (DIF) were tested iteratively. If items showed local dependence, a testlet approach was used to introduce super-items created by summing the initial response options of local dependent items. The corresponding analysis approach is described elsewhere [25].

Measurement models for the mental functions

We hypothesised each mental function to be a single latent factor represented by the respective observed questionnaire items (indicators) with uncorrelated measurement errors. In this context, direct effects of latent factors on indicators are referred to as factor loadings. Confirmatory factor analysis (CFA) [16, 26] was used to test if the hypothesised measurement models fit the data and hence, represent a single latent factor. Model fit was assessed by the following fit indices: χ^2 test statistic, comparative fit index (CFI), root-mean-square error of approximation (RMSEA) and weighted-root-mean-square residuals (WRMR). The criteria to evaluate goodness of model fit were: non-significant χ^2 ($P > 0.05$), CFI > 0.95, RMSEA < 0.05 and WRMR < 1.0 [27]. If the initial CFA did not show good fit, the

modification indices (MI) and residual correlation matrix of the respective measurement model were examined and indicator error correlations were introduced iteratively, (1) starting from the largest MI with significant Bonferroni-adjusted *P* value, and (2) starting from the largest absolute residual correlation >0.10 [16]. In the final measurement models, only significant indicator error correlations were retained.

For all measurement models, invariance was tested on the level of the significance pattern (configural invariance) and the estimates (weak invariance) of the factor loadings for aetiology, age, sex, level and severity of injury and language (German, French) groups as described by Hirschfeld and von Brachel [28].

Structural models

By using structural equation modelling (SEM) [16], indirect effects of body structures and functions on the independence in performing ADL through the mental functions anxiety, depression, optimism and self-esteem were tested for each mental function separately. Starting from the biopsychosocial model underlying the ICF, the following considerations guided the development of these hypotheses: first, we assumed the effects of body structures and functions on activities to be the primary or focal relationship within first rehabilitation of persons with SCI, and this relationship and patient's state of health to be most stable at the point of discharge. Therefore, we have applied data from discharge. Second, we considered anxiety, depression, optimism and self-esteem as mental functions belonging to the ICF component of body structures and functions. Since body structures and functions can be influenced by other body structures and functions, we hypothesised possible indirect effects of the other body structures and functions on activities through the mental functions. Third, any variables on environmental factors were not considered in this study since we draw upon data collected in first rehabilitation settings which we assumed to be not significantly different in their setup. Any differences would be a reflection of differences related to the rehabilitation setting rather than the person's environment. Fourth, any variables on participation in life of persons with SCI were not considered in this study since we assumed that a meaningful participation indicator requires a follow-up time after first rehabilitation.

For the SEM, the interval sum score of the SCIM III and the measurement models for the mental functions as resulted from the previous analyses were used. Model fit was assessed by the χ^2 test statistic, the CFI and the WRMR. The following criteria were used to evaluate goodness of model fit: non-significant χ^2 ($P > 0.05$), CFI > 0.95 and WRMR < 0.90 [27].

Each structural model was explored for differences in aetiology, age and sex groups, provided that the measurement model for the corresponding mental function showed invariance for the respective group variable [29]. Whether a structural model shows differences in a specific group variable was assessed by comparing the χ^2 test statistics between the corresponding freed structural model (allowing path parameters of the model to differ across respective groups) and the corresponding constrained structural model (restricting path parameters to be the same across respective groups).

The Rasch analyses were performed using *RUMM2030* [30], other analyses were conducted by using *R 3.5.0* [31]. Imputation of missing observations was undertaken by the use of the package *missForest 1.4* [20]. CFA and SEM were conducted by using the package *lavaan 0.6–3* [32] and its weighted least squares mean- and variance-adjusted estimator able to compute robust standard errors of the model parameters and mean- and variance-adjusted test statistics. If not explicitly stated other, the significance level of *P* values refers to 0.05.

Results

In total, 390 participants were considered within this study. Sample descriptive information are presented in Table 2. Participants were mainly male (69.49%) with incomplete (83.59% after missing data imputation) paraplegia (60.77% after missing data imputation). Mean age was 53.82 years (s.d. = 16.47) and median length of stay in first rehabilitation was 133.5 days (25–75% percentiles = 75.25–192.5 days). The observed variance–covariance matrix among the imputed model relevant variables is presented in Supplementary Table 2.

Rasch measurement model for the independence in performing ADL

For the final model, two testlets were created: one testlet incorporated the items of the self-care subscale and the respiration and sphincter management subscale, the other testlet incorporated the items of the mobility subscale of the SCIM III. This testlet design showed good model fit with $\chi^2 = 18.28$ (df = 10, $P = 0.05$) and PSI (with extremes) = 0.92. Moreover, no DIF has been present for aetiology, age and sex.

Measurement models for the mental functions

None of the measurement models for the mental functions showed good fit in all indices in the initial CFA. The final model fit statistics after introducing indicator error correlations are reported in the following paragraph.

Table 2 Characteristics of SwiSCI Inception Cohort Study participants and participants included within this study.

Characteristics	SwiSCI Inception Cohort Study ($N = 883$)	Present study before missing data imputation ($N = 390$)	P value
Sex			0.43
Female (%)	289 (32.73)	119 (30.51)	
Male (%)	594 (67.27)	271 (69.49)	
Missing (%)	0 (0)	0 (0)	
Mean age at SCI diagnosis, years (s.d.)	55.57 (18.44)	53.82 (16.47)	<0.05
Median age at SCI diagnosis, years (1./3. quantiles)	58 (43/71)	55 (42/67)	
Younger than or equal median age (%)	435 (49.26)	196 (50.26)	
Older than median age (%)	448 (50.74)	194 (49.74)	
Missing (%)	0 (0)	0 (0)	
Median length of stay, days (1./3. quantiles)	126 (67/185.5)	133.5 (75.25/192.5)	0.06
Missing (%)	0 (0)	0 (0)	
Language of correspondence			0.99
German (%)	678 (76.78)	299 (76.67)	
French (%)	172 (19.48)	78 (20.00)	
Italian (%)	23 (2.60)	11 (2.82)	
Other (%)	3 (0.34)	2 (0.51)	
Missing (%)	7 (0.79)	0 (0)	
Aetiology			0.47
Traumatic (%)	497 (56.29)	228 (58.46)	
Non-traumatic (%)	386 (43.71)	162 (41.54)	
Missing (%)	0 (0)	0 (0)	
Level of injury at discharge			<0.001
Tetraplegia (%)	271 (30.69)	152 (38.97)	
Paraplegia (%)	436 (49.38)	235 (60.26)	
Intact (%)	28 (3.17)	0 (0)	
Missing (%)	148 (16.76)	3 (0.77)	
Severity of injury at discharge			0.22
Complete (%)	140 (15.86)	63 (16.15)	
Incomplete (%)	586 (66.36)	324 (83.08)	
Missing (%)	157 (17.78)	3 (0.77)	
AIS-based neurological groups at discharge			<0.05
C1–4 AIS A, B or C (%)	41(4.64)	16 (4.10)	
C5–8 AIS A, B or C (%)	39 (4.42)	19 (4.87)	
T1-S5 AIS A, B or C (%)	162 (18.35)	80 (20.51)	
AIS D (%)	455 (51.53)	271 (69.49)	
AIS E (%)	27 (3.06)	0 (0)	
Missing (%)	159 (18.01)	4 (1.03)	

Distribution equality tests were performed using Pearson's χ^2 test (without continuity correction) for categorical variables and Mann–Whitney test (without continuity correction) for continuous variables.

AIS American Spinal Injury Association Impairment Scale, *SCI* spinal cord injury, *SwiSCI* Swiss Spinal Cord Injury Cohort Study.

Anxiety: no indicator error correlations were introduced according to the pre-defined criteria. The initial CFA model was retained and showed good model fit in two of four indices with $\chi^2 = 33.328$ (df = 14, $P = 0.003$), CFI = 0.992, RMSEA = 0.060, WRMR = 0.588; depression: after introducing one indicator error correlation, the model showed good fit in two of four indices with $\chi^2 = 40.112$ (df = 13, $P = 0.000$), CFI = 0.990, RMSEA = 0.073, WRMR = 0.661; optimism: after introducing four indicator error correlations, the final model showed good fit in all indices with $\chi^2 = 9.056$ (df = 5, $P = 0.107$), CFI = 0.998, RMSEA = 0.046, WRMR = 0.285; self-esteem: after introducing one indicator error correlation, the model showed good fit in two of four indices with $\chi^2 = 6.961$ (df = 1, $P = 0.008$), CFI = 0.994, RMSEA = 0.124, WRMR = 0.417.

The final measurement models for the mental functions including estimated factor loadings and indicator error correlations are shown in Supplementary Fig. 1. Model parameter estimates are presented completely standardised. Thus, the interpretation of the factor loadings is the following: given a change by one standard deviation unit in the latent factor, each factor loading estimates the corresponding amount of change in standard deviation units in the latent response variable assumed to underlie the respective observed indicator [16]. The factor loadings furthermore estimate the Pearson correlation between latent factor and respective latent response variable and their squares indicate the proportion of explained variance (R^2) of the latent factor by the latent response variables [16].

The residual correlation matrices indicating the difference between observed and model-implied correlations for each final model are shown in the Supplementary Table 3.

The full results of the invariance tests of the measurement models can be found in Supplementary Table 4. Within this section we only present the results relevant for the subsequent group difference tests of the structural models. At the level of factor loading estimates, the anxiety and depression measurement models are both invariant for aetiology, age and sex groups, the optimism measurement model is invariant for age groups, and the self-esteem measurement model is invariant for age and sex groups.

Structural models

The model fit statistics of the hypothesised structural models are reported in the following paragraph.

Anxiety: the model showed good fit in two of three indices with $\chi^2 = 120.030$ (df = 82, $P = 0.004$), CFI = 0.983, WRMR = 0.811; depression: the model showed good fit in two of three indices with $\chi^2 = 107.704$ (df = 81, $P = 0.025$), CFI = 0.990, WRMR = 0.770; optimism: the model showed overall good fit with $\chi^2 = 60.360$ (df = 62, $P = 0.535$), CFI = 1.000, WRMR = 0.588; self-esteem: the model showed good fit in two of three indices with $\chi^2 = 67.077$ (df = 36, $P = 0.001$), CFI = 0.971, WRMR = 0.825. The residual correlation matrices for each model are shown in the Supplementary Table 5.

The structural models and completely standardised parameter estimates are shown in Fig. 1a–d. The interpretation of

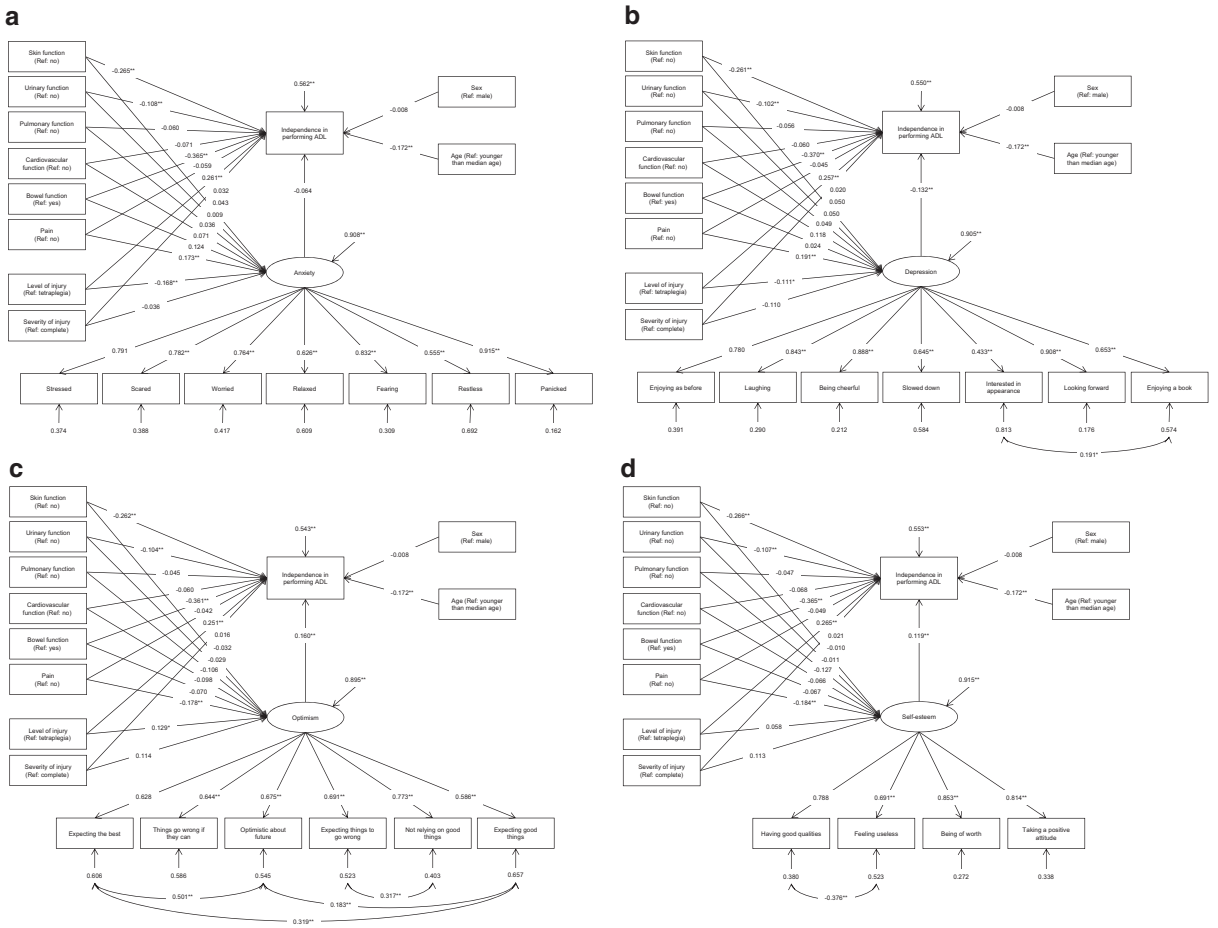

Fig. 1 Structural models showing the relationships of body structures and functions with activities of daily living. a Completely standardised parameter estimates of the structural model about anxiety ($N = 390$). **b** Completely standardised parameter estimates of the structural model about depression ($N = 390$). **c** Completely standardised parameter estimates of the structural model about optimism ($N = 390$). **d** Completely standardised parameter estimates of the structural model about self-esteem ($N = 390$). *ADL* activities of daily living, *Ref* reference response option of binary variables. Squares indicate observable variables including the independence in performing activities of daily living (ADL) specified by the interval sum score of the Spinal Cord Independence Measure version III (SCIM III); ellipses indicate latent factors; single-headed arrows indicate direct effects including measurement errors; double-headed arrows indicate correlations; correlations among and measurement errors of independent observable variables are omitted; $^{*}P < 0.05$; $^{**}P < 0.01$.

factor loadings is the same as already described in the previous section; the interpretation of the other path coefficients is analogous to the interpretation of coefficients in a multiple regression: given a change of one standard deviation unit in the independent variable, the path coefficient estimates the corresponding change in standard deviation units in the dependent variable, holding all other respective independent variables constant. Fig. 1c for example indicates that the presence of a pressure injury (skin function, response option yes) is associated with lower independence in performing ADL (path coefficient $\beta = -0.262$, $P < 0.01$) and lower optimism ($\beta = -0.032$); whereas a lower level of injury (paraplegia) is associated with higher independence in performing ADL ($\beta = 0.251$, $P < 0.01$) and higher optimism ($\beta = 0.129$, $P < 0.05$); and higher optimism is associated with higher independence in performing ADL ($\beta = 0.160$, $P < 0.01$). When looking at the squared factor loadings in this model, we see that the latent response variables represented by the indicator variables show proportions of explained variance of the latent factor optimism between 0.34 ('expecting good things') and 0.60 ('not relying on good things').

The respective model estimates for the indirect and total (direct plus indirect) effects of body structures and functions on the independence in performing ADL for the four structural models are shown in Table 3. Within all structural models, effects on independence in performing ADL were mainly direct with significant positive effects of a lower

Table 3 Completely standardised estimates for the indirect and total effects of body structures and functions on the independence in performing activities of daily living for the structural models about anxiety, depression, optimism and self-esteem.

ICF concept and variable	Indirect effects through:				Total effects
	Anxiety	Depression	Optimism	Self-esteem	
Body functions					
Bowel function (Ref: yes)	−0.008	−0.003	−0.011	−0.008	−0.373**
Cardiovascular function (Ref: no)	−0.005	−0.016	−0.016	−0.008	−0.076
Pain (Ref: no)	−0.011	−0.025*	−0.029*	−0.022*	−0.070
Pulmonary function (Ref: no)	−0.002	−0.006	−0.017	−0.015	−0.062
Skin function (Ref: no)	−0.003	−0.007	−0.005	−0.001	−0.267**
Urinary function (Ref: no)	−0.001	−0.007	−0.005	−0.001	−0.109**
Body structures					
Level of injury (Ref: tetraplegia)	0.011	0.015	0.021	0.007	0.272**
Severity of injury (Ref: complete)	0.002	0.015	0.018	0.013	0.035

The total effects are the same for all structural models.

Ref reference response option of binary variables.

*$P < 0.05$; **$P < 0.01$.

level of injury and significant negative effects of occurring complications or conditions in urinary, bowel and skin functions. Significant indirect effects were found for pain within the structural models about depression, optimism and self-esteem, respectively.

Table 4 shows the results of the structural model group difference tests. Significant group differences were found in aetiology groups for the structural model about anxiety.

Discussion

Using SEM to examine the possible influence of mental functions within the relationship of body structures, body functions and activities, pain showed significant indirect effects on the independence in performing activities of ADL in the structural models about depression, optimism and self-esteem. Group differences were found in aetiology groups for the structural model about anxiety.

However, the results need to be interpreted within its conceptual framework and the cross-sectional design of the study: first, personal factors are not classified yet in the ICF and there remains to be a debate about their definition and relationship to mental functions [33]. Regardless whether you consider anxiety, depression, optimism and self-esteem as mental functions or personal factors, they are important when looking at peoples' functioning. Second, this study reflects an attempt towards generating empirical evidence for a comprehensive understanding of functioning in first rehabilitation of persons with SCI as it is shown in the ICF. In this understanding, it can serve as a starting point for further model development and analyses. Since pain is the only body function that showed indirect effects on independence in performing ADL in the structural models about depression, optimism and self-esteem, it could be worthwhile to reconsider the relationship of pain and these mental functions in more detail and together with other pain items, e.g. clinical pain records.

The community survey of SwiSCI revealed that pain is highly prevalent in persons with SCI living in the community (with musculoskeletal type of pain most frequently reported) [34] and is perceived as one of the most important problems in functioning following SCI [35]. However, the relationships among pain, mental functions and independence in performing ADL appear to be complex, as for example literature about the pain–depression relationship often reflects both directions: in the general population, pain and depression symptoms are found to be commonly occurring and their relationship seem to be bidirectional [36]. Moreover, the bidirectional associations between depressive symptoms and pain seem to be similar for people with functioning problems and those without [37]. In the SCI community setting, increased pain was found to be a risk factor for developing of depression [38]. Moreover, chronic pain is suggested to be associated with increased depressive symptom levels and less participation [39], and with negative effects on psychological functioning, social integration and activities including mobility, self-care, social and recreational activities [40]. On the other hand, a meta-analysis of possible determinants for pain in persons with SCI has shown that depression prevalence is associated with pain prevalence [41]. Within the acute SCI setting, the pain–depression interaction remains unclear; different models have been tested and are conceivable [42], other studies have found that depressive symptoms are not related to pain or functional impairment [43]. Therefore, further research is needed to uncover comprehensive interactions among mental functions, possible changes in mental functions over time, and their associations with other body functions, body structures, activities and participation [44].

Table 4 Group difference tests of the structural models for aetiology, age and sex groups.

Structural model and parameter constrains	χ^2_M	df_M	Model comparison	
			χ^2_D	df_D
Aetiology				
Anxiety				
Freed	134.939	164		
Constrained	207.347	183	31.157*	19
Depression				
Freed	130.289	162		
Constrained	172.903	181	20.509	19
Optimism				
Freed	–	–		
Constrained	–	–	–	–
Self-esteem				
Freed	–	–		
Constrained	–	–	–	–
Age				
Anxiety				
Freed	133.634	150		
Constrained	188.145	168	24.617	18
Depression				
Freed	113.641	148		
Constrained	140.591	166	13.927	18
Optimism				
Freed	72.815	112		
Constrained	112.368	130	20.790	18
Self-esteem				
Freed	64.630	64		
Constrained	89.555	82	15.876	18
Sex				
Anxiety				
Freed	96.295	150		
Constrained	127.982	168	16.770	18
Depression				
Freed	100.820	148		
Constrained	126.733	166	15.230	18
Optimism				
Freed	–	–		
Constrained	–	–	–	–
Self-esteem				
Freed	53.255	64		
Constrained	107.167	82	27.832	18

Freed, no constrains on parameter estimates across respective groups; Constrained, all path estimates constrained to be equal across respective groups. *M* model, *D* difference.

*$P < 0.05$.

Limitations

We note several methodological limitations to our study. First, the three measurement models for anxiety, depression and self-esteem are lacking good fit in terms of the *P* value of the χ^2 test statistic which is leading to unknown bias in the corresponding structural models, which likewise are lacking good fit in this index. Second, since the measurement models for the mental functions were modified in an exploratory and data-driven way by introducing indicator error correlations based on MI and residual correlation matrices, the results of this study are not generalisable and should be cross-validated. Moreover, indicator error correlations can be viewed as shared variance besides the common latent factor and the measurement models become multidimensional by their introduction. Third, we might not be able to detect invariances within our measurement models or group differences within our structural models due to the small sample sizes of some groups tested. Fourth, a selection bias on the sample used in this analysis could have occurred since (1) the filling in of the questionnaires within the SwiSCI Inception Cohort Study is optional and (2) we excluded participants with no observations in the ADL and the mental functions variables. Fifth, the cross-sectional design of the study does not allow for causal conclusions. Thus, a longitudinal study design is needed to clarify and extend the presented structural models.

Conclusion

Using an ICF-based modelling approach, this study presents an attempt towards a more comprehensive understanding of functioning in first rehabilitation of persons with SCI, which might be fundamental for rehabilitation planning and decision-making among health professionals and patients.

Data availability

The datasets generated and analysed during this study are not publicly available due to the commitment of SwiSCI to protect participants' privacy but are available at the SwiSCI Study Center (swisci.research@paraplegie.ch) on reasonable request.

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Author contributions JH contributed to the study design, conducted the analyses, interpreted the results and drafted the manuscript. CE contributed to the study design, conducted and supervised the analysis and interpreted the results. GS and JEB contributed to the study conceptualisation. BP contributed to the study design, supervised the analysis and drafting of the manuscript and interpreted the results. All authors revised earlier versions of the manuscript, approved the final version and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethics statement The SwiSCI was approved by the responsible ethics committees of the cantons of Lucerne, Zurich, Basel-Stadt and Valais.

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CORRECTION

Correction: Examining the complexity of functioning in persons with spinal cord injury attending first rehabilitation in Switzerland using structural equation modelling

Jsabel Hodel · Cristina Ehrmann · Gerold Stucki · Jerome E. Bickenbach · Birgit Prodinger · and the SwiSCI Study Group

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Correction to: *Spinal Cord*
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Following publication of this article, the authors noticed an error due to incorrect naming of two groups: 'paraplegia' and 'tetraplegia'. This affects Tables 1 and 2, and the Results section. The correction is as following: In Table 1 '**Paraplegia** (C1-C8)/**tetraplegia** (T1-S5)' has now been corrected to '**Tetraplegia** (C1-C8)/**paraplegia** (T1-S5)'. In the first paragraph of the Results section 'Participants were mainly male (69.49%) with incomplete (83.59% after missing data imputation) **tetraplegia** (60.77% after missing data imputation)', has now been changed to 'Participants were mainly male (69.49%) with incomplete (83.59% after missing data imputation) **paraplegia** (60.77% after missing data imputation)'. Finally, in Table 2, 'Paraplegia' and 'Tetraplegia' have been swapped to align with the correct, corresponding values. This has been corrected in both the PDF and HTML versions of the article, and does not change the interpretation of the data.

CHAPTER 3
Identification of classes of functioning trajectories and their predictors in individuals with spinal cord injury attending initial rehabilitation in Switzerland

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Original Research

Identification of Classes of Functioning Trajectories and Their Predictors in Individuals With Spinal Cord Injury Attending Initial Rehabilitation in Switzerland

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KEYWORDS
Latent class analysis;
Logistic models;
Longitudinal studies;
Observational study;
Rehabilitation;
Spinal cord injuries

Abstract *Objectives:* To identify classes of functioning trajectories in individuals with spinal cord injury (SCI) undergoing initial rehabilitation after injury and to examine potential predictors of class membership to inform clinical planning of the rehabilitation process.
Design: Longitudinal analysis of the individual's rehabilitation stay using data from the Inception Cohort of the Swiss Spinal Cord Injury Cohort Study (SwiSCI).
Setting: Initial rehabilitation in specialized centers in Switzerland.
Participants: Individuals with newly acquired SCI (N=748; mean age, 54.66±18.38y) who completed initial rehabilitation between May 2013 and September 2019. The cohort was primarily

List of abbreviations: ADL, activities of daily living; AIC, Akaike information criterion; AIS, American Spinal Injury Association Impairment Scale; BIC, Bayesian information criterion; LPMM, latent process mixed model; SCI, spinal cord injury; SCIM III, Spinal Cord Independence Measure version III; SSABIC, sample-size adjusted Bayesian information criterion; SwiSCI, Swiss Spinal Cord Injury Cohort Study.

Presented as a poster to the International Spinal Cord Society, November 5, 2019, Nice, France.
This study was conducted within the project "Enhancing continuous quality improvement and supported clinical decision making by standardized reporting of functioning," which is part of the National Research Programme "Smarter Health Care" (NRP74) supported by the Swiss National Science Foundation (grant no. 167412).
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composed of men (67.51%), persons with paraplegia (56.15%), incomplete injuries (67.51%), and traumatic etiologies (55.48%).
Interventions: Not applicable.
Main Outcome Measures: Functioning was operationalized with the interval-based sum score of the Spinal Cord Independence Measure version III (SCIM III). For each individual, the SCIM III sum score was assessed at up to 4 time points during rehabilitation stay. The corresponding time of assessment was recorded by the difference in days between the SCIM III assessment and admission to the rehabilitation program.
Results: Latent process mixed model analysis revealed 4 classes of functioning trajectories within the present sample. Class-specific predicted mean functioning trajectories describe *stable high functioning* (n=307; 41.04%), *early functioning improvement* (n=39; 5.21%), *moderate functioning improvement* (n=287; 38.37%), and *slow functioning improvement* (n=115; 15.37%), respectively. Out of 12 tested factors, multinomial logistic regression showed that age, injury level, injury severity, and ventilator assistance were robust predictors that could distinguish between identified classes of functioning trajectories in the present sample.
Conclusions: The current study establishes a foundation for future research on the course of functioning of individuals with SCI in initial rehabilitation by identifying classes of functioning trajectories. This supports the development of specifically tailored rehabilitation programs and prediction models, which can be integrated into clinical rehabilitation planning.

Spinal cord injury (SCI) is physical damage to the spinal cord with a resulting loss of autonomic, motor and sensory functions below the level of injury, which adversely affects an individual's ability to perform activities and participate in major areas of life.[1] A newly acquired SCI and its potentially life-changing consequences require a goal-oriented and interdisciplinary rehabilitation process starting as early as possible after the event to optimize an individual's functioning.[2] Following the World Health Organization's International Classification of Functioning, Disability and Health,[3] functioning describes the nature and extent of body functions and individual activities that result from an interaction between a health condition and environmental and personal contextual factors. Therefore, initial rehabilitation after SCI not only involves optimizing an individual's neurologic functions, it also addresses an individual's functioning requirements, including optimizing performance and independence in everyday life and adaptation and modification of the environment to enable full participation in the community.

As a result, monitoring functioning outcomes throughout the rehabilitation process is fundamental for individual goal setting, rehabilitation planning, and management, as well as for quality assurance.[4] Different instruments have been developed to capture an individual's functioning by means of a summary score. The Spinal Cord Independence Measure version III (SCIM III),[5] for example, describes an individual's independence in activities of daily living (ADL) in mobility, self-care, respiration, and bladder and bowel management and has demonstrated sensitivity to change.[6] If assessed longitudinally, such functioning sum scores are understood as an individual functioning trajectory (ie, an individual's course of functioning over time). Depending on their demographics,[7-9] injury characteristics,[10] the occurrence of complications,[10] and the availability of rehabilitation services,[11] people may develop differently during their initial rehabilitation stay and may show various individual functioning sum scores over time.

A nuanced picture of these heterogeneous individual functioning trajectories during the initial rehabilitation stay, including the identification of homogeneous subgroups of functioning trajectories and their predictors, can help to specifically tailor rehabilitation programs to the individual's functioning needs. In the SCI literature, studies have investigated classes of trajectories of musculoskeletal shoulder pain,[12] body mass index,[13] employment status,[14] life satisfaction,[15] mental health,[16] depression,[17] and self-efficacy and depressed mood[18] during initial rehabilitation and up to 5 years after discharge. As far as we are aware, no study has yet investigated classes of functioning trajectories assessed by a summary score for functioning such as the SCIM III. Therefore, this study aimed to identify classes of functioning trajectories in individuals with SCI undergoing initial rehabilitation in specialized centers in Switzerland and to examine potential predictors of class membership to inform clinical planning in the rehabilitation process.

Methods

Study design and participants

This study used data from the Inception Cohort of the prospective Swiss Spinal Cord Injury Cohort Study (SwiSCI).[19] The SwiSCI Inception Cohort included individuals with newly acquired and diagnosed SCI who were recruited upon entry to an initial rehabilitation program in a specialized SCI rehabilitation center in Switzerland (SCI Center, Balgrist University Hospital, Zurich; Centre for SCI and Severe Head Injury, REHAB Basel, Basel; Clinique Romande de Réadaptation, Sion; Swiss Paraplegic Centre, Nottwil). Further inclusion criteria were minimum age of 16 years and permanent residence in Switzerland. Criteria for exclusion were congenital conditions, palliative context, neurodegenerative disorders,

or Guillain-Barrée syndrome leading to SCI. A detailed description of the inclusion and exclusion criteria can be found elsewhere.[19] The longitudinal design of the SwiSCI Inception Cohort included up to 4 time points of data collection during initial rehabilitation stay (T1, 4wk after SCI diagnosis; T2, 12wk after SCI diagnosis; T3, 24wk after SCI diagnosis; T4, at discharge).[20] The responsible regional ethics committees approved the SwiSCI and all participants gave written informed consent.

Between May 2013 and September 2019, 1182 eligible individuals completed initial rehabilitation in a collaborating rehabilitation center, 1050 of whom consented to the SwiSCI Inception Cohort. For the purpose of comparability between centers and according to the longitudinal study design, we excluded participants based on the following criteria and in specific order: (1) implausible assessment time points of SCIM III (eg, SCIM measurements for T2 were dated to be assessed before the measurements for T1) or individuals whose first assessment occurred within intensive care after SCI (N=52), and (2) fewer than 2 SCIM III assessments during initial rehabilitation stay (N=250). In total, 748 participants were included in this study.

Measures

Main outcome and time of assessment

The main outcome of this study was functioning, which was operationalized by using the SCIM III sum score.[5] Previously derived interval-based SCIM III sum scores[21] based on Rasch analysis were used to accurately assess changes in functioning sum scores over time and to allow for their meaningful comparison. These interval-based sum scores range from 0-100, with larger numbers indicating more independence in performing ADL. In the SwiSCI Inception Cohort, the corresponding time of assessment of SCIM III was recorded in days since SCI diagnosis. Because patients spend different lengths of time in acute or intensive care prior to being admitted to initial rehabilitation, days since diagnosis is not representative for the start of inpatient rehabilitation. The respective assessment time points were recalculated into days since admission to the initial rehabilitation program. In what follows, assessment time points with respect to SCIM III refer to days since admission to initial rehabilitation program.

Predictors of class membership

Based on expert opinion and previously published studies on predictors of SCIM outcomes, we identified suitable variables collected in the SwiSCI as potential predictors of class membership (methods of assessments are described elsewhere).[22,23] Of these, only variables that showed less than 20% missing observations were included in the analysis.

We included the following variables as potential predictors of class membership: age at SCI diagnosis (in years), sex (female, male), language of correspondence (German, French, Italian, other), insurance type (health, disability, accident, self-pay), ward type (basic, semiprivate, private), etiology (traumatic, nontraumatic), injury level (according to the Neurological Classification of Spinal Cord Injury and the neurologic level of injury: tetraplegia, C1-C8; paraplegia, T1-S5; intact) and severity at T1 (according to the Neurological Classification of Spinal Cord Injury and the American Spinal Injury Association Impairment Scale [AIS]: complete, AIS grade A; incomplete, AIS grades B, C, or D; normal, AIS grade E), existence of comorbidities before SCI (any diagnosis other than SCI with diagnosis date before SCI diagnosis, no/yes), requiring ventilation assistance (no/yes), and cardiovascular (no/yes) and pulmonary (no/yes) conditions and complications at T1 since SCI diagnosis. Variables including associated injuries; partner at time of SCI diagnosis; the presence of pain, anxiety, and depression symptoms; normal defecation; urinary tract infections; or pressure injuries were identified as suitable potential predictors but were not included owing to the number of missing observations.

Data analysis

Classes of functioning trajectories

To identify the number of different classes of functioning trajectories within the present sample of individual interval-based SCIM III sum score trajectories, we used latent process mixed models (LPMMs)[24-26] because these models can handle unstructured assessment time points and individuals with different numbers of assessments.[26] The analysis included 2 steps: (1) Three LPMMs with different parameterized link functions—linear function and quadratic I-splines functions with 2 or 3 knots at percentiles—were estimated to identify the best-fitting link function able to account for non-normal and bounded longitudinal outcomes.[26] The models were compared using the Akaike information criterion (AIC) and the best-fitting link function was determined by the model with lowest AIC. (2) Two sets of 6 LPMMs, each with an increasing number of latent classes (1-6), were estimated to identify the number of classes of functioning trajectories. In the first set, the specification of the variability of between-person functioning trajectories was fixed across classes. In the second set, this variability was allowed to be proportionally varying across classes. Both sets incorporated the best-fitting link function from step 1. The models were compared using the Bayesian information criterion (BIC), the sample-size adjusted BIC (SSABIC), and the AIC. Better model fit was indicated by lower values for all 3 indices. In addition, they were evaluated and compared according to their convergence, interpretability, entropy indicator describing the degree of class separation (a higher value indicated better separation between classes and therefore better classification accuracy), and class sample sizes according to the most likely class membership (preference for models with class sample sizes including at least 5% of the study participants).

In both steps, all fitted models corresponded to unconditional models (ie, no covariates were integrated). Supplemental appendix S1 (available online only at http://www.archives-pmr.org/) presents detailed model specifications and R syntax of the final LPMM. Alternative model specifications were tested and are available from the authors on request.

Predictors of class membership

According to the standard 3-step method,[27] the following analysis was conducted to examine potential predictors of class membership: (1) the most likely class membership of each participant was extracted from the best-fitting LPMM;

(2) the extracted information was merged with the original data; and (3) a multinomial logistic regression was conducted based on the merged data to examine potential predictors of class membership. Before this step, missing observations in potential predictor variables were imputed using the nonparametric random forest method MissForest[28] and categorical variables were dichotomized. The robustness of the regression analysis was investigated by means of a sensitivity analysis including complete cases only.

All analyses were performed using the software R for Windows, version 3.6.0.[a] LPMMs were fitted using the R package lcmm (version 1.8.1),[b] missing data imputation was performed using the R package missForest (version 1.4),[c] and multinomial logistic regression was conducted using the R package nnet (version 7.3-12).[d] The study reporting followed the Guidelines for Reporting on Latent Trajectory Studies Checklist[27] and the Strengthening the Reporting of Observational Studies in Epidemiology statement.[29]

Results

Sample characteristics

Of the 748 participants included in this study, 2 SCIM III assessments were available for 408 individuals, 3 for 186 individuals, and 4 for 154 individuals (reasons for <4 assessments include late admission or consent, a short rehabilitation stay, or missing observations). Sample descriptive information including details about the time of assessment of SCIM III are presented in table 1. Participants had a mean age of 54.66±18.38 years, and the cohort was primarily composed of men (67.51%), persons with paraplegia (56.15%), incomplete injuries (67.51%), and traumatic etiologies (55.48%). The median time between SCI diagnosis and admission to initial rehabilitation was 14 days (first quartile, 9d; third quartile, 24d).

Classes of functioning trajectories

The observed individual functioning trajectories are shown in figure 1 and separated according to their respective number of assessments during initial rehabilitation stay in supplemental figure S1 (available online only at http://www.archives-pmr.org/). The analysis of the best-fitting link function for these individual trajectories according to lowest AIC showed that the quadratic I-splines with 3 knots at percentiles performed best (supplemental fig S2, available online only at http://www.archives-pmr.org/). However, because more than half of the participants had only 2 SCIM III assessments, a sensitivity analysis excluding these participants from the sample was conducted to assess the difference between quadratic I-splines with 2 or 3 knots at percentiles (supplemental fig S3, available online only at http://www.archives-pmr.org/). Because the 95% confidence interval of the quadratic I-splines with 2 knots mostly included the change described by the function with 3 knots, the function with 2 knots was chosen to be the best-fitting link function for this sample.

Table 2 presents the fit characteristics of the 2 tested sets of LPMMs, and supplemental figures S4 and S5 (available online only at http://www.archives-pmr.org/) show the class-specific predicted mean trajectories identified by each model within the 2 sets, respectively. Both model sets showed overall good visual interpretability of the class-specific predicted mean functioning trajectories. Because the class-specific variability of between-person trajectories used in the second model set allows more flexibility, this set was preferred. In this set the 6-class and 5-class models included classes with <5% of the study participants and were excluded as candidates for the best-fitting LPMM. Within the remaining candidate models, BIC, SSABIC, and AIC did not clearly point to a single model. The 4-class model was preferred by SSABIC and AIC and the 3-class model by BIC. Because the addition of a fourth class to the 3-class model splits an existing class into 2 different unique classes, both of which seemed meaningful and showed satisfying sample sizes, we considered the 4-class model as best-fitting. Moreover, it showed a good entropy value of 0.80. The identified class-specific predicted mean functioning trajectories are shown in figure 2 and describe *stable high functioning* (n=307; 41.04%), *early functioning improvement* (n=39; 5.21%), *moderate functioning improvement* (n=287; 38.37%), and *slow functioning improvement* (n=115; 15.37%), respectively. Figure 3 complements the class-specific predicted mean trajectories with the respective observed individual functioning trajectories. Corresponding posteriori classification accuracy is presented in table 3. Accordingly, the LPMM shows most difficulties classifying members of the *early improvement class* with mean posterior misclassification probability of 27.36% for the *moderate improvement class*. Class-specific sample characteristics are shown in table 4, and the model parameter estimates can be found in supplemental table S1 (available online only at http://www.archives-pmr.org/).

Predictors of class membership

Table 5 presents the results of the multinomial logistic regression analysis (n=709; AIC, 1401.83) with the *slow functioning improvement class* used as a reference class. Thereby, the coefficients of the regression analysis describe the estimated change of the relative logit of being in a specific class compared with the reference class. The coefficients are to be interpreted for 1 unit change in a continuous predictor variable and for changing from the reference category to a specific other category in a categorical predictor variable, holding all other respective predictor variables constant. Accordingly, the likelihood of being in any other than the reference class is decreased by higher age and the occurrence of pulmonary conditions and complications, whereas a lower injury level of or an incomplete injury increased this likelihood. Moreover, ventilation assistance decreased the likelihood of being in the *stable high* or the *moderate improvement class* compared with the reference class, and having a private ward type decreased the likelihood of being in the *early improvement class* compared with the reference class. Of the remaining predictors, sex, language of correspondence, etiology, comorbidities before SCI, cardiovascular conditions and complications, and insurance type did not show any significant associations.

Table 1 Characteristics of study participants

Characteristics	SwiSCI Inception Cohort Study (N=1050)	Excluded from present study (N=302)	Included in present study (N=748)	P-value
Female, n (%)	342 (32.57)	99 (32.78)	243 (32.49)	0.93
Age at SCI diagnosis, mean ± SD, y	55.21 ± 18.51	56.57 ± 18.81	54.66 ± 18.38	0.16
Length of stay, mean ± SD, d	137.22 ± 82.56	125.99 ± 91.23	141.75 ± 78.40	<0.001
Interval-based SCIM III sum score at T1,				<0.001
median [Q_1, Q_3]	71.36 [55.95, 88.62]	42.63 [16.96, 71.36]	73.31 [58.76, 88.69]	
Missing, n (%)	270 (25.71)	230 (76.16)	40 (5.35)	
Interval-based SCIM III sum score at T2,				<0.001
median [Q_1, Q_3]	86.11 [69.33, 91.87]	63.79 [51.39, 76.06]	86.84 [72.35, 91.87]	
Missing, n (%)	659 (62.76)	277 (91.72)	382 (51.07)	
Interval-based SCIM III sum score at T3,				<0.01
median [Q_1, Q_3]	85.28 [68.82, 91.17]	75.17 [55.95, 82.44]	87.00 [69.35, 91.81]	
Missing, n (%)	851 (81.05)	281 (93.05)	570 (76.20)	
Interval-based SCIM III sum score at T4,				0.04
median [Q_1, Q_3]	91.63 [84.29, 95.47]	90.44 [74.24, 95.47]	91.87 [85.33, 95.47]	
Missing, n (%)	183 (17.43)	173 (57.28)	10 (1.34)	
Assessment time point SCIM III T1 since admission to initial rehabilitation program,				<0.001
median [Q_1, Q_3], d	11.00 [1.00, 19.00]	-2.50* [-19.25, 4.00]	12.00 [3.00, 20.00]	
Missing, n (%)	266 (25.33)	226 (74.83)	40 (5.35)	
Assessment time point SCIM III T2 since admission to initial rehabilitation program,				<0.001
median [Q_1, Q_3], d	68.00 [56.00, 76.00]	51.00 [28.00, 58.00]	69.00 [57.00, 76.00]	
Missing, n (%)	659 (62.76)	277 (91.72)	382 (51.07)	
Assessment time point SCIM III T3 since admission to initial rehabilitation program,				<0.001
median [Q_1, Q_3], d	146.00 [134.00, 159.00]	128.00 [116.00, 143.00]	148.00 [137.00, 160.00]	
Missing, n (%)	851 (81.05)	281 (93.05)	570 (76.20)	
Assessment time point SCIM III T4 since admission to initial rehabilitation program,				0.01
median [Q_1, Q_3], d	129.00 [69.00, 186.00]	116.00 [28.00, 191.00]	132.00 [72.25, 185.75]	
Missing, n (%)	181 (17.24)	171 (56.62)	10 (1.34)	
Traumatic etiology, n (%)	596 (56.76)	181 (59.93)	415 (55.48)	0.19
Level of injury at T1, n (%)				<0.001
Tetraplegia	333 (31.71)	96 (31.79)	237 (31.68)	
Paraplegia	530 (50.48)	110 (36.42)	420 (56.15)	
Intact	8 (0.76)	2 (0.66)	6 (0.80)	
Missing	179 (17.05)	94 (31.13)	85 (11.36)	
Severity of injury at T1, n (%)				<0.001
Complete	200 (19.05)	53 (17.55)	147 (19.65)	
Incomplete	658 (62.67)	153 (50.66)	505 (67.51)	
Normal	7 (0.67)	2 (0.66)	5 (0.67)	
Missing	185 (17.62)	94 (31.13)	91 (12.17)	
Associated injuries, n (%)				<0.001
No	302 (28.76)	114 (37.75)	188 (25.13)	
Yes	419 (39.90)	121 (40.07)	298 (39.84)	
Missing	329 (31.33)	67 (22.19)	262 (35.03)	
Comorbidities before SCI diagnosis, n (%)				<0.001
No	147 (14.00)	20 (6.62)	127 (16.98)	
Yes	704 (67.05)	112 (37.09)	592 (79.14)	
Missing	199 (18.95)	170 (56.29)	29 (3.88)	
Language of correspondence, n (%)				0.05
German	797 (75.90)	246 (81.46)	551 (73.66)	
French	208 (19.81)	43 (14.24)	165 (22.06)	
Italian	30 (2.86)	10 (3.31)	20 (2.67)	
Other	7 (0.67)	1 (0.33)	6 (0.80)	
Missing	8 (0.76)	2 (0.66)	6 (0.80)	

(*continued*)

Table 1 (*Continued*)

Characteristics	SwiSCI Inception Cohort Study (N=1050)	Excluded from present study (N=302)	Included in present study (N=748)	P-value
Insurance type, n (%)				<0.001
Health	536 (51.05)	84 (27.81)	452 (60.43)	
Disability	7 (0.67)	0 (0.00)	7 (0.94)	
Accident	337 (32.10)	56 (18.54)	281 (37.57)	
Self-pay	1 (0.10)	1 (0.33)	0 (0.00)	
Missing	169 (16.10)	161 (53.31)	8 (1.07)	
Ward type, n (%)				<0.001
Basic	477 (45.43)	73 (24.17)	404 (54.01)	
Semi-private	244 (23.24)	41 (13.58)	203 (27.14)	
Private	125 (11.90)	22 (7.28)	103 (13.77)	
Missing	204 (19.43)	166 (54.97)	38 (5.08)	
Partner at time of SCI diagnosis, n (%)				<0.001
No	132 (12.57)	9 (2.98)	123 (16.44)	
Yes	334 (31.81)	29 (9.60)	305 (40.78)	
Missing	584 (55.62)	264 (87.42)	320 (42.78)	
Cardiovascular conditions and complications at T1 since SCI diagnosis, n (%)				<0.001
No	608 (57.90)	84 (27.81)	524 (70.05)	
Yes	262 (24.95)	41 (13.58)	221 (29.55)	
Missing	180 (17.14)	177 (58.61)	3 (0.40)	
Pulmonary conditions and complications at T1 since SCI diagnosis, n (%)				<0.001
No	583 (55.52)	64 (21.19)	519 (69.39)	
Yes	279 (26.57)	57 (18.87)	222 (29.68)	
Missing	188 (17.90)	181 (59.93)	7 (0.94)	
Ventilation assistance at T1 since SCI diagnosis, n (%)				<0.001
No	762 (72.57)	88 (29.14)	674 (90.11)	
Yes	98 (9.33)	30 (9.93)	68 (9.09)	
Missing	190 (18.10)	184 (60.93)	6 (0.80)	
Normal defecation at T1 since SCI diagnosis, n (%)				<0.001
No	317 (30.19)	24 (7.95)	293 (39.17)	
Yes	171 (16.29)	12 (3.97)	159 (21.26)	
Missing	562 (53.52)	266 (88.08)	296 (39.57)	
Urinary tract infection at T1 since SCI diagnosis, n (%)				<0.001
No	368 (35.05)	34 (11.26)	334 (44.65)	
Yes	148 (14.10)	3 (0.99)	145 (19.39)	
Missing	534 (50.86)	265 (87.75)	269 (35.96)	
Pressure injury at T1 since SCI diagnosis, n (%)				<0.001
No	419 (39.90)	27 (8.94)	392 (52.41)	
Yes	104 (9.90)	11 (3.64)	93 (12.43)	
Missing	527 (50.19)	264 (87.42)	263 (35.16)	
Pain at T1 in the past week, n (%)				<0.001
No	94 (8.95)	4 (1.32)	90 (12.03)	
Yes	277 (26.38)	17 (5.63)	260 (34.76)	
Missing	679 (64.67)	281 (93.05)	398 (53.21)	

NOTE. *P* values for distribution comparisons were calculated using the Mann-Whitney *U* test for continuous variables and Pearson chi-square test for categorical variables (both without continuity correction).
Abbreviations: Q_1, 1st quartile; Q_3, 3rd quartile; T1-T4, time point of assessment within the SwiSCI Inception Cohort Study.
* For some individuals, the first SCIM III assessment occurred in intensive care after SCI and before admission to the initial rehabilitation program.

The results of the corresponding sensitivity analysis (n=546; AIC, 1100.19) are shown in supplemental table S2 (available online only at http://www.archives-pmr.org/). Compared with the results in table 5, supplemental table S2 (available online only at http://www.archives-pmr.org/) also shows a decreased likelihood of being in the *stable high*

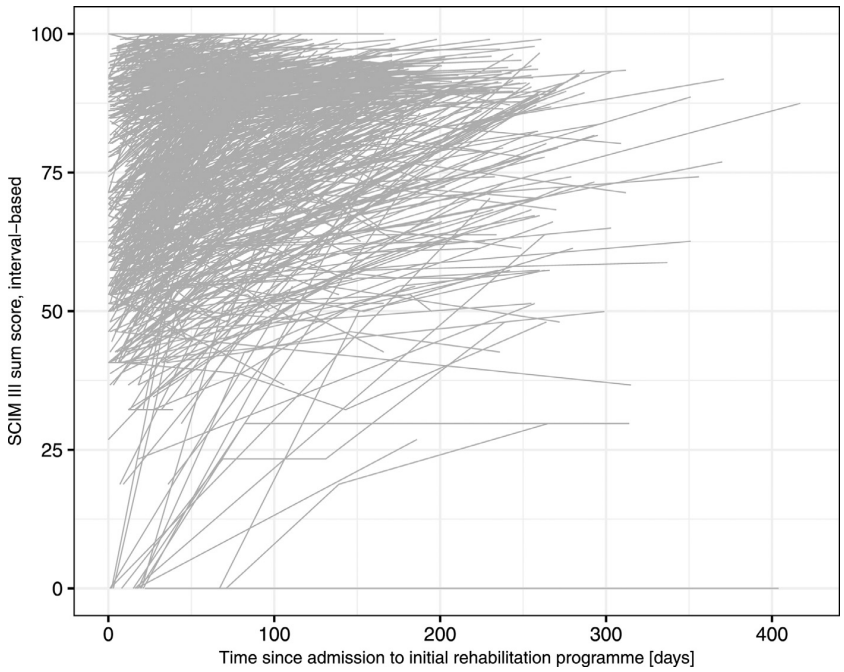

Fig 1 Observed individual functioning trajectories according to the interval-based SCIM III sum score.

class for private ward type and of being in the *moderate improvement class* for having a traumatic etiology, compared with the reference class. The occurrence of pulmonary conditions and complications was only associated with a lowered likelihood for being in the *stable high class*. Overall, age, injury level, injury severity, and ventilator assistance appeared to be robust predictors of class membership across both analyses within the present sample.

Discussion

This study revealed 4 distinct classes of functioning trajectories in individuals with SCI who underwent initial rehabilitation in specialized centers in Switzerland. According to the class-specific predicted mean functioning trajectories, the identified classes describe *stable high functioning* (n=307; 41.04%), *early functioning improvement* (n=39; 5.21%), *moderate functioning improvement* (n=287; 38.37%), and *slow functioning improvement* (n=115; 15.37%), respectively. To our knowledge, this is the first study identifying classes of functioning trajectories in individuals with SCI according to SCIM III sum scores. Given the limited body of empirical knowledge on this topic, there is a limited extent to which our results can be compared with other studies, such as individual growth curve models of change in functioning outcomes according to the FIM[30-32] or the identification of classes of trajectories of different outcomes in SCI.[12-18]

Although LPMMs and individual growth curve models share some commonalities, the latter do not incorporate any assumption about underlying, unobserved classes. Thus, individual growth curve models can be used to study individual change in functioning, whereas LPMMs can be used to study classes of similar change in functioning. Pretz et al[32] have described several potential applications of individual growth curve models in practice such as rehabilitation goal setting, intervention planning, and individual patient benchmarking. Nevertheless, we believe that for the monitoring of functioning throughout the rehabilitation process, it is also meaningful to be able to see how an individual patient is changing in comparison to similar patients. The identification of classes of functioning trajectories can be a first step toward enabling such monitoring. However, further research is needed for it to be implemented in practice.

Trajectory studies on outcomes such as life satisfaction[15] or employment status[14] have shown that independence in performing ADL assessed by the FIM is a predictor of the respective classes of trajectories. Although we do not know if these findings also hold for the SCIM, we believe that the importance of the longitudinal relationships between functioning and other outcomes should be investigated in future research.

Multinomial logistic regression showed that age, injury level, injury severity, and ventilator assistance are robust predictors that can distinguish between the identified classes of functioning trajectories in the present sample. Given the exploratory nature of our study, these findings are preliminary and need to be confirmed by other studies. Although age, injury level, and severity have also been identified as relevant predictors of the SCIM in previous studies,[10,33,34] these findings are only comparable to a limited extent because a relevant predictor for SCIM outcomes at a specific endpoint is not necessarily relevant for classes of change according to SCIM within a specific time frame. Nevertheless, having a look beyond the predictors assessed within our study, variables such as smoking status, different strength values, acute care length of stay, postacute length of stay, occurrence of complications, and SCIM score at

Table 2 Fit characteristics of the LPMMs

Model Specifications	No. of Classes	Random Starts (Departures/ Iterations)	No. of Model Parameters	BIC	SSABIC	AIC	Entropy	Class 1 Sample Size, n (%)	Class 2 Sample Size, n (%)	Class 3 Sample Size, n (%)	Class 4 Sample Size, n (%)	Class 5 Sample Size, n (%)	Class 6 Sample Size, n (%)
Set 1:	1	100/50	8	15146.91	15121.50	15109.97	1.00	748 (100.00)					
LPMMs with	2	100/50	11	15027.35	14992.42	14976.56	0.83	323 (43.18)	425 (56.82)				
class-invariant	3	100/50	14	14983.97	14939.52	14919.33	0.79	304 (40.64)	320 (42.78)	124 (16.58)			
variability	4	100/50	17	14967.75	14913.77	14889.25	0.81	269 (35.96)	45 (6.02)	117 (15.64)	317 (42.38)		
of between-person	5	100/50	20	14980.99	14917.48	14888.64	0.75	233 (31.15)	314 (41.98)	66 (8.82)	42 (5.61)	93 (12.43)	
trajectories	6*	100/50	23	15000.13	14927.10	14893.93	0.75	228 (30.48)	314 (41.98)	2 (0.27)	70 (9.36)	41 (5.48)	93 (12.43)
Set 2:	1	100/50	8	15146.91	15121.50	15109.97	1.00	748 (100.00)					
LPMMs with	2	100/50	12	15103.06	15064.95	15047.65	0.85	110 (14.71)	638 (85.29)				
class-specific	3	100/50	16	14979.32	14928.52	14905.45	0.77	340 (45.45)	112 (14.97)	296 (39.57)			
variability	4†	100/50	20	14980.76	14917.25	14888.41	0.80	39 (5.21)	115 (15.37)	307 (41.04)	287 (38.37)		
of between-person	5	100/50	24	15002.72	14926.51	14891.90	0.79	255 (34.09)	43 (5.75)	311 (41.58)	103 (13.77)	36 (4.81)	
trajectories	6	100/50	28	15025.92	14937.01	14896.63	0.77	271 (36.23)	7 (0.94)	308 (41.18)	18 (2.41)	102 (13.64)	42 (5.61)

* Indicates convergence problems.
† Best-fitting LPMM.

administration have been significantly associated with SCIM III outcomes up to 1 year after SCI in respective other studies[10,33,35] and thus should be checked as predictors of class membership of functioning trajectories in future research.

From a statistical point of view, it is important to validate and, if possible, update the identified classes of functioning trajectories in larger study populations and study designs that include more assessment time points, outcome measures, and predictors. Moreover, the number of classes might increase with increasing sample sizes. This is reflected in figure 3, which reveals that the *slow functioning improvement class* covers a wide range of observed individual functioning trajectories. This class might be split into new distinct classes for an increased sample size including more observations on low individual functioning trajectories. From a practical point of view, it is essential to evaluate with qualitative studies the meaning and value of the identified classes of functioning trajectories for clinical practice from the perspective of rehabilitation professionals. In the future, the findings of the present study might assist in developing clinical prediction models of functioning able to assign newly injured individuals to a specific class of functioning trajectories. In addition, classes of functioning trajectories, analyzed together with information on rehabilitation practices may support monitoring patient outcomes, contribute to the development of patient pathways for SCI initial rehabilitation, and support rehabilitation planning and management.

Study limitations

The limitations of this study are consistent with the use of existing data for secondary analysis in which no influence is possible on the initial data collection. First, there are limitations related to the SwiSCI and the corresponding operationalization of functioning used in the present study. SCIM is an instrument representing independence in ADL and does not include restrictions in "activities and participation" as defined in the International Classification of Functioning, Disability and Health. Despite the fact that it was specifically developed for individuals with SCI and has been demonstrated to be superior to the FIM, there are some disadvantages to mention within the scope of this study, including its proneness for floor and ceiling effects. In addition, although the SwiSCI Inception Cohort includes a comprehensive study design, the number of available SCIM III assessments and potential predictor variables in rehabilitation stay restricted the study results. For example, the included predictor variables level of injury, pulmonary conditions and complications, and ventilator assistance cover related characteristics of individuals with SCI. Furthermore, a selection bias could have occurred owing to the exclusion of study participants with implausible time points of assessments and individuals with less than 2 SCIM III observations during initial rehabilitation stay. Country specific differences with regard to clinical rehabilitation practice (eg, availability, eligibility, comprehensiveness, and duration of inpatient rehabilitation) might further limit the generalizability of the results. Second, class membership probabilities might depend on participant characteristics, and results can

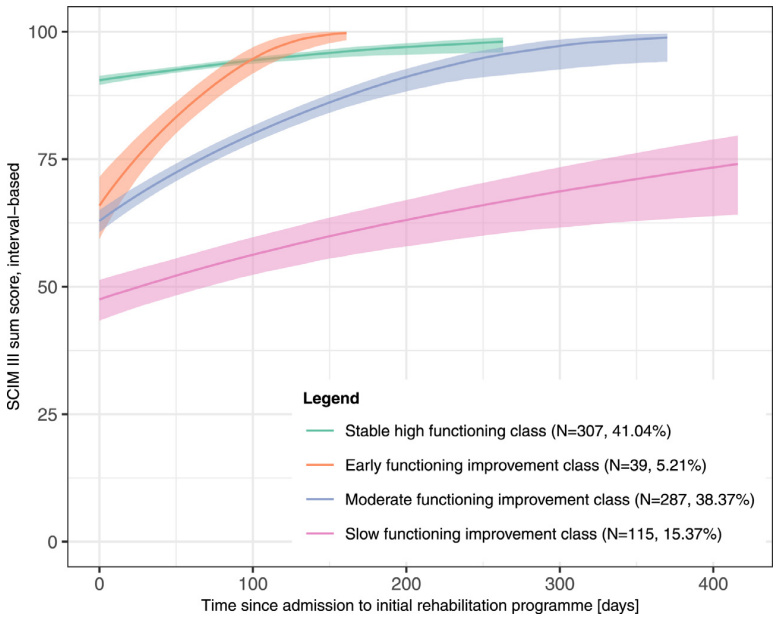

Fig 2 Class-specific predicted mean functioning trajectories according to the best-fitting LPMM and 95% confidence interval. Note that the class-specific predicted mean trajectories were plotted up the respective maximum observed time of assessment within each class.

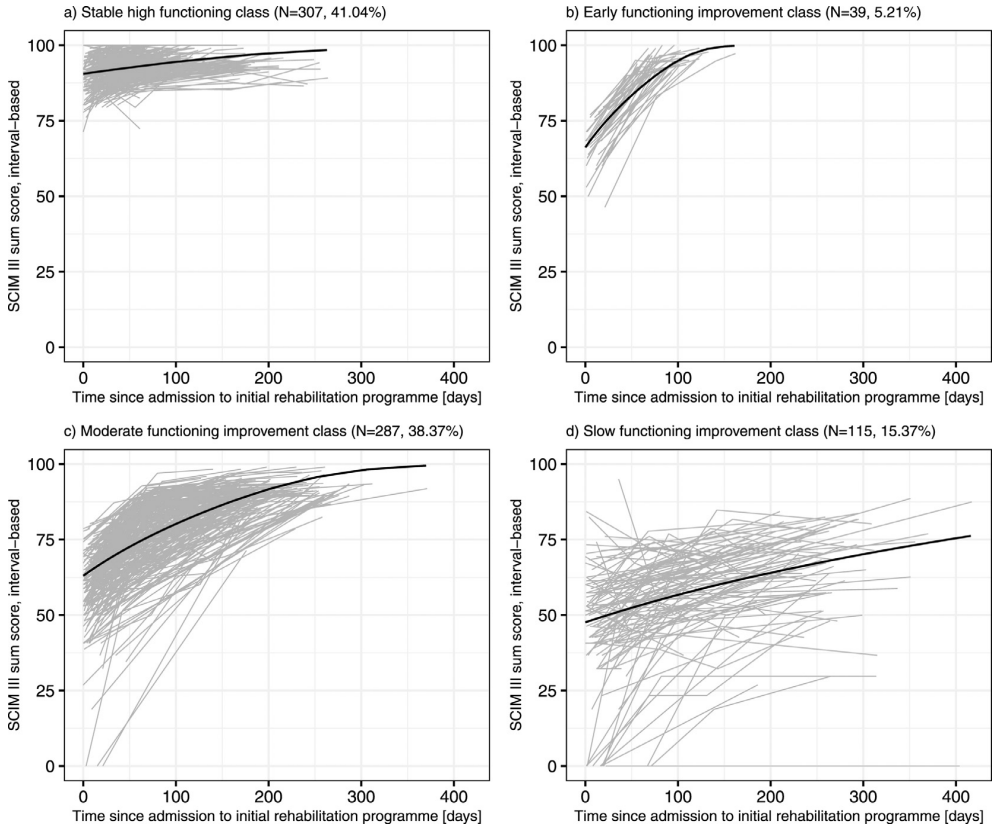

Fig 3 Observed individual (gray) and predicted mean (black) functioning trajectories of the best-fitting latent process mixed model for the (a) stable high functioning class (n=307; 41.04%), (b) early functioning improvement class (n=39; 5.21%), (c) moderate functioning improvement class (n=287; 38.37%), and (d) slow functioning improvement class (n=115; 15.37%).

Table 3 Posterior classification table of the best-fitting LPMM

Classes	n (%)	Mean Posterior Class Membership Probabilities, %			
		Stable High Functioning	Early Functioning Improvement	Moderate Functioning Improvement	Slow Functioning Improvement
Stable high functioning	307 (41.04)	93.20	1.50	5.24	0.06
Early functioning improvement	39 (5.21)	5.96	66.64	27.36	0.04
Moderate functioning improvement	287 (38.37)	3.08	3.50	87.71	5.71
Slow functioning improvement	115 (15.37)	0.20	0.01	14.49	85.31

Table 4 Characteristics of classes of functioning trajectories according to the best-fitting LPMM

Characteristics	Stable High Class (n=307)	Early Improvement Class (n=39)	Moderate Improvement Class (n=287)	Slow Improvement Class (n=115)
Female, n (%)	111 (36.16)	15 (38.46)	82 (28.57)	35 (30.43)
Age at SCI diagnosis, mean ± SD, y	51.77±17.26	54.15±16.84	55.09±19.06	61.50±18.37
Length of stay, mean ± SD, d	91.91±53.06	100.33±23.10	170.89±66.08	216.16±81.18
Interval-based SCIM III sum score at T1, median [Q_1, Q_3]	90.18 [86.11, 93.75]	68.78 [62.90, 74.93]	63.79 [54.50, 70.37]	49.93 [40.71, 57.37]
Missing, n (%)	18 (5.86)	1 (2.56)	10 (3.48)	11 (9.57)
Interval-based SCIM III sum score at T2, median [Q_1, Q_3]	92.53 [90.94, 94.81]	91.98 [89.98, 94.59]	84.29 [73.31, 88.33]	55.95 [49.93, 64.98]
Missing, n (%)	192 (62.54)	17 (43.59)	119 (41.46)	54 (46.96)
Interval-based SCIM III sum score at T3, median [Q_1, Q_3]	92.76 [90.92, 94.59]	94.81 [94.81, 94.81]	88.86 [83.58, 91.87]	62.60 [54.50, 69.35]
Missing, n (%)	280 (91.21)	38 (97.44)	191 (66.55)	61 (53.04)
Interval-based SCIM III sum score at T4, median [Q_1, Q_3]	95.80 [93.45, 97.75]	95.01 [93.45, 96.99]	89.65 [85.28, 91.87]	66.10 [54.50, 73.31]
Missing, n (%)	6 (1.95)	2 (5.13)	0 (0.00)	2 (1.74)
Assessment time point SCIM III T1 since admission to initial rehabilitation program, median [Q_1, Q_3], d	13.00 [4.00, 20.00]	10.50 [3.00, 16.25]	12.00 [2.00, 20.00]	9.00 [2.00, 18.25]
Missing, n (%)	18 (5.86)	1 (2.56)	10 (3.48)	11 (9.57)
Assessment time point SCIM III T2 since admission to initial rehabilitation program, median [Q_1, Q_3], d	67.00 [55.50, 75.00]	70.00 [56.00, 75.00]	69.00 [58.75, 77.00]	69.00 [60.00, 77.00]
Missing, n (%)	192 (62.54)	17 (43.59)	119 (41.46)	54 (46.96)
Assessment time point SCIM III T3 since admission to initial rehabilitation program, median [Q_1, Q_3], d	152.00 [138.50, 162.50]	141.00 [141.00, 141.00]	148.00 [137.00, 159.25]	146.00 [137.25, 158.50]
Missing, n (%)	280 (91.21)	38 (97.44)	191 (66.55)	61 (53.04)
Assessment time point SCIM III T4 since admission to initial rehabilitation program,				

(*continued*)

Table 4 (*Continued*)

Characteristics	Stable High Class (n=307)	Early Improvement Class (n=39)	Moderate Improvement Class (n=287)	Slow Improvement Class (n=115)
median [Q_1, Q_3], d	75.00 [47.00, 118.00]	93.00 [77.00, 108.00]	170.00 [128.50, 201.00]	225.00 [162.00, 263.00]
Missing, n (%)	6 (1.95)	2 (5.13)	0 (0.00)	2 (1.74)
Traumatic etiology, n (%)	143 (46.58)	27 (69.23)	168 (58.54)	77 (66.96)
Level of injury at T1, n (%)				
Tetraplegia	80 (26.06)	11 (28.21)	83 (28.92)	63 (54.78)
Paraplegia	182 (59.28)	22 (56.41)	177 (61.67)	39 (33.91)
Intact	5 (1.63)	1 (2.56)	0 (0.00)	0 (0.00)
Missing	40 (13.03)	5 (12.82)	27 (9.41)	13 (11.30)
Severity of injury at T1, n (%)				
Complete	15 (4.89)	1 (2.56)	90 (31.36)	41 (35.65)
Incomplete	244 (79.48)	32 (82.05)	167 (58.19)	62 (53.91)
Normal	4 (1.30)	1 (2.56)	0 (0.00)	0 (0.00)
Missing	44 (14.33)	5 (12.82)	30 (10.45)	12 (10.43)
Associated injuries, n (%)				
No	94 (30.62)	12 (30.77)	48 (16.72)	34 (29.57)
Yes	86 (28.01)	19 (48.72)	141 (49.13)	52 (45.22)
Missing	127 (41.37)	8 (20.51)	98 (34.15)	29 (25.22)
Comorbidities before SCI diagnosis, n (%)				
No	50 (16.29)	6 (15.38)	57 (19.86)	14 (12.17)
Yes	247 (80.46)	30 (76.92)	217 (75.61)	98 (85.22)
Missing	10 (3.26)	3 (7.69)	13 (4.53)	3 (2.61)
Language of correspondence, n (%)				
German	233 (75.90)	30 (76.92)	207 (72.13)	81 (70.43)
French	63 (20.52)	9 (23.08)	71 (24.74)	22 (19.13)
Italian	6 (1.95)	0 (0.00)	6 (2.09)	8 (6.96)
Other	4 (1.30)	0 (0.00)	2 (0.70)	0 (0.00)
Missing	1 (0.33)	0 (0.00)	1 (0.35)	4 (3.48)
Insurance type, n (%)				
Health	209 (68.08)	24 (61.54)	155 (54.01)	64 (55.65)
Disability	3 (0.98)	0 (0.00)	2 (0.70)	2 (1.74)
Accident	91 (29.64)	15 (38.46)	129 (44.95)	46 (40.00)
Missing	4 (1.30)	0 (0.00)	1 (0.35)	3 (2.61)
Ward type, n (%)				
Basic	180 (58.63)	28 (71.79)	142 (49.48)	54 (46.96)
Semiprivate	76 (24.76)	2 (5.13)	86 (29.97)	39 (33.91)
Private	34 (11.07)	7 (17.95)	42 (14.63)	20 (17.39)
Missing	17 (5.54)	2 (5.13)	17 (5.92)	2 (1.74)
Partner at time of SCI diagnosis, n (%)				
No	56 (18.24)	4 (10.26)	43 (14.98)	20 (17.39)
Yes	148 (48.21)	21 (53.85)	108 (37.63)	28 (24.35)
Missing	103 (33.55)	14 (35.90)	136 (47.39)	67 (58.26)
Cardiovascular conditions and complications at T1 since SCI diagnosis, n (%)				
No	233 (75.90)	25 (64.10)	198 (68.99)	68 (59.13)
Yes	73 (23.78)	14 (35.90)	87 (30.31)	47 (40.87)
Missing	1 (0.33)	0 (0.00)	2 (0.70)	0 (0.00)
Pulmonary conditions and complications at T1				

(*continued*)

Table 4 (*Continued*)

Characteristics	Stable High Class (n=307)	Early Improvement Class (n=39)	Moderate Improvement Class (n=287)	Slow Improvement Class (n=115)
since SCI diagnosis, n (%)				
No	257 (83.71)	28 (71.79)	185 (64.46)	49 (42.61)
Yes	45 (14.66)	11 (28.21)	101 (35.19)	65 (56.52)
Missing	5 (1.63)	0 (0.00)	1 (0.35)	1 (0.87)
Ventilation assistance at T1 since SCI diagnosis, n (%)				
No	298 (97.07)	37 (94.87)	258 (89.90)	81 (70.43)
Yes	5 (1.63)	2 (5.13)	27 (9.41)	34 (29.57)
Missing	4 (1.30)	0 (0.00)	2 (0.70)	0 (0.00)
Normal defecation at T1 since SCI diagnosis, n (%)				
No	82 (26.71)	15 (38.46)	149 (51.92)	47 (40.87)
Yes	131 (42.67)	8 (20.51)	15 (5.23)	5 (4.35)
Missing	94 (30.62)	16 (41.03)	123 (42.86)	63 (54.78)
Urinary tract infection at T1 since SCI diagnosis, n (%)				
No	177 (57.65)	16 (41.03)	103 (35.89)	38 (33.04)
Yes	47 (15.31)	11 (28.21)	69 (24.04)	18 (15.65)
Missing	83 (27.04)	12 (30.77)	115 (40.07)	59 (51.30)
Pressure injury at T1 since SCI diagnosis, n (%)				
No	208 (67.75)	23 (58.97)	125 (43.55)	36 (31.30)
Yes	13 (4.23)	3 (7.69)	55 (19.16)	22 (19.13)
Missing	86 (28.01)	13 (33.33)	107 (37.28)	57 (49.57)
Pain at T1 in the past week, n (%)				
No	48 (15.64)	7 (17.95)	28 (9.76)	7 (6.09)
Yes	127 (41.37)	15 (38.46)	97 (33.80)	21 (18.26)
Missing	132 (43.00)	17 (43.59)	162 (56.45)	87 (75.65)

Abbreviations: Q_1, 1st quartile; Q_3, 3rd quartile; T1-T4, time point of assessment within the SwiSCI Inception Cohort Study.

change if such covariates are included within LPMMs. However, Hu et al have shown that the approach used in this study is acceptable with a large sample size and good class separation.[36] Generally, classification accuracy of the final LPMM will improve if the available number of the *early functioning improvement class* members will increase. Third, the multinomial logistic regression of potential predictors of class membership did not take into account the classification errors of the LPMM. This leads to bias in the regression models and, in general, true effects might be underestimated.[27] Furthermore, the small sample size of the *early functioning improvement class* resulted in small numbers of observations in response categories of some predictors within this class, such as ward types, and might influence the performed analysis and corresponding results.

Conclusions

The present study establishes a foundation for future research on the course of functioning of individuals with SCI in initial rehabilitation by identifying classes of functioning trajectories. This supports the development of specifically tailored rehabilitation programs and prediction models, which can be integrated into clinical rehabilitation planning.

Suppliers

a. R, version 3.6.0; R Foundation for Statistical Computing.
b. lcmm R package, version 1.8.1; Proust-Lima C, Philipps V, Liquet B.
c. missForest R package, version 1.4; Stekhoven DJ, Bühlmann P.
d. nnet R package, version 7.3-12; Venables WN, Ripley BD.

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Table 5 Multinomial logistic regression of class membership for best-fitting LPMM (n=709)

Variable	Estimates (95% confidence interval)		
	Stable High Functioning Class (Ref = Slow Functioning Improvement Class)	Early Functioning Improvement Class (Ref = Slow Functioning Improvement Class)	Moderate Functioning Improvement Class (Ref = Slow Functioning Improvement Class)
Intercept	2.15* (0.51-3.78)	−2.64 (−5.65 to 0.37)	2.24† (0.80-3.67)
Age	−0.06‡ (−0.08 to −0.04)	−0.04† (−0.07 to −0.01)	−0.02* (−0.04 to −0.00)
Female (Ref = Male)	−0.48 (−1.08 to 0.12)	−0.13 (−1.01 to 0.74)	−0.47 (−1.02 to 0.09)
Language of correspondence, French (Ref = German)§	−0.64 (−1.34 to 0.07)	−0.56 (−1.58 to 0.46)	−0.07 (−0.70 to 0.56)
Traumatic etiology (Ref = Nontraumatic)	−0.43 (−1.16 to 0.30)	0.86 (−0.19 to 1.92)	−0.63 (−1.30 to 0.04)
Level of injury, paraplegia (Ref = Tetraplegia)‖	1.79‡ (1.18-2.40)	2.03‡ (1.13-2.94)	1.26‡ (0.71-1.81)
Severity of injury, incomplete (Ref = Complete)¶	3.56‡ (2.74-4.39)	4.34‡ (2.25-6.43)	0.87† (0.28-1.46)
Comorbidities before SCI, yes (Ref = No)	−0.18 (−1.04 to 0.68)	−0.04 (−1.29 to 1.20)	−0.43 (−1.19 to 0.34)
Cardiovascular conditions and complications, yes (Ref = No)	0.04 (−0.59 to 0.67)	0.61 (−0.34 to 1.56)	0.07 (−0.49 to 0.63)
Pulmonary conditions and complications, yes (Ref = No)	−1.50‡ (−2.13 to −0.87)	−1.12* (−2.05 to −0.18)	−0.63* (−1.18 to −0.08)
Insurance type, accident (Ref = Health)#	−0.57 (−1.40 to 0.26)	−0.25 (−1.41 to 0.90)	0.33 (−0.41 to 1.06)
Ward type, private (Ref = Basic)**	−0.53 (−1.12 to 0.06)	−1.46† (−2.44 to −0.49)	−0.24 (−0.77 to 0.28)
Ventilation assistance, yes (Ref = No)	−2.20‡ (−3.31 to −1.08)	−1.26 (−2.91 to 0.40)	−0.83* (−1.51 to −0.15)

* $P<.05$.
† $P<.01$.
‡ $P<.001$.
§ Participants with observations in the response categories "Italian" or "other" were excluded from the analysis.
‖ Participants with observations in the response category "intact" were excluded from the analysis.
¶ Participants with observations in the response category "normal" were excluded from the analysis.
# Participants with observations in the response categories "disability" or "self-pay" were excluded from the analysis.
** Response categories "semiprivate" and "private" were collapsed.

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CHAPTER 4
The potential of prediction models of functioning remains to be fully exploited: A scoping review in the field of spinal cord injury rehabilitation

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REVIEW

The potential of prediction models of functioning remains to be fully exploited: A scoping review in the field of spinal cord injury rehabilitation

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Abstract

Objective: The study aimed to explore existing prediction models of functioning in spinal cord injury (SCI).

Study Design and Setting: The databases *PubMed, EBSCOhost CINAHL Complete*, and *IEEE Xplore* were searched for relevant literature. The search strategy included published search filters for prediction model and impact studies, index terms and keywords for SCI, and relevant outcome measures able to assess functioning as reflected in the International Classification of Functioning, Disability and Health (ICF). The search was completed in October 2020.

Results: We identified seven prediction model studies reporting twelve prediction models of functioning. The identified prediction models were mainly envisioned to be used for rehabilitation planning, however, also other possible applications were stated. The method predominantly used was regression analysis and the investigated predictors covered mainly the ICF components of *body functions* and *activities and participation*, next to characteristics of the health condition and health interventions.

Conclusion: Findings suggest that the development of prediction models of functioning for use in clinical practice remains to be fully exploited. By providing a comprehensive overview of what has been done, this review informs future research on prediction models of functioning in SCI and contributes to an efficient use of research evidence.

Keywords: Spinal Cord Injuries; Rehabilitation; Prognosis; Diagnosis; Clinical Decision Rules; Forecasting

1. Introduction

Spinal cord injury (SCI) is a chronic health condition devastatingly affecting a person's life in a variety of ways. The structural damage to the spinal cord and the resulting loss of neurologic functions adversely affects the ability of a person to perform simple and complex activities and to participate in community and major life areas [1]. After the injury, persons with SCI go through an extensive rehabilitation process to live independently with the health condition: from intensive care and inpatient rehabilitation to outpatient specialized care after returning to the community. The World Health Organization (WHO) refers to the lived experience of a health condition as 'functioning' [2]. The concept of functioning, as described in WHO's International Classification of Functioning, Disability and

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Health (ICF), includes different components – *body functions* and *body structures* as well as *activities and participation* – which interact with each other and are outcomes of the interaction between a health condition and *environmental* and *personal contextual factors*. Against this background, the objective of rehabilitation after SCI can be formulated as the optimization and maintenance of a person's functioning [3]. In order to achieve this objective, comprehensive and relevant functioning information is essential to guide rehabilitation planning and management, individual clinical care and decision making.

Prediction research aims to enhance individual health and health care practice by investigating and improving the diagnosis or prognosis of a specific health condition [4-6]. For the purpose of this review, roughly three types of prediction research can be distinguished: [4,7] (1) predictor finding studies, (2) prediction model studies, and (3) impact studies. Predictor finding studies generally aim to explore or identify which variables within a set of candidate predictors are independently associated with a specific outcome. Prediction model studies aim to develop and/or externally validate (with or without updating) a multivariable prediction model for use in medical or clinical practice. Impact studies build on a developed and validated prediction model and aim to assess the impact of the use of such a model in a specific context or setting compared to not using it. Prediction model development, validation and impact studies correspond with the phases, which prediction models for use in practice usually have to undergo in their development process [8-11]. The development of prediction models has gained increasing attention by the recognition of evidence-based health care and the uptake of new statistical methods in the health sciences and clinical epidemiology.

In rehabilitation research, the role of functioning as key health indicator complementing mortality and morbidity [12] poses the question of how prediction research, and specifically prediction models, can improve the use of functioning information for practice. In SCI literature, various efforts have been undertaken to develop and/or validate prediction models for outcomes related to specific aspects of functioning, such as ambulation, [13-20] or bladder and bowel outcomes [21-23]. Predictor finding studies for several functioning outcomes have already been reviewed and synthesized [24-27]. What remains to be investigated is how functioning, as a multidimensional concept is reflected in current prediction models across the corresponding development phases depicted by development, validation and impact studies in the field of SCI rehabilitation. Therefore, the objective of this scoping review is to explore existing prediction models of functioning in SCI. Specifically, the review aims to (1) identify prediction models of functioning in SCI, (2) examine their content by using the ICF as a reference language, (3) examine their use from a systems perspective, and (4) document which methods were used to develop them. The scoping review will shed light on current research gaps as well as on promising directions for future developments and improvements of prediction models of functioning for SCI.

What is new?

Key findings

- Identification of seven prediction model studies reporting twelve prediction models of functioning in SCI; no impact study was identified.

What this adds to what is known?

- The development of prediction models of functioning in SCI is still in its infancy. This review highlights potential future directions in the development of prediction models in the field of SCI rehabilitation with regards to content, use and methods.

What is the implication, what should change now?

- Functioning, as outcome of the identified models, was measured with the FIM™ or the SCIM. The investigated predictors covered mainly body functions, activities and participation, characteristics of the health condition or health interventions. The integration of a broad range of potential predictors including imaging, biomarkers, and genetics, as well as predictors covering body structures and contextual factors remains to be investigated.
- The method predominantly used was linear regression analysis. The application and usefulness of other methods such as machine learning techniques need to be further investigated and its potential merit compared to current methods.
- The identified prediction models were intended to be used for guidance in rehabilitation planning, patient counselling, financial aspects related to the reduction of costs by guided management strategies, and improvements in clinical trial designs. To delineate the value of prediction models for the field of SCI rehabilitation in detail, further research is needed related to validation and impact assessment of prediction models.

2. Methods

The scoping review followed the methodological framework of Arksey and O'Malley [28] and incorporate recent experiences of the application of the framework [29-31] as well as the guidance for the conduction of systematic scoping reviews developed by Peters *et al.* [32]. An unpublished review protocol was developed and agreed upon by all authors prior to conducting the review and is avail-

able from the authors on request. The reporting followed the *Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews* [33] and the corresponding checklist can be found in the Supplemental Table 1.

2.1. Searching for relevant literature

The following three databases were searched for relevant literature: *PubMed*, [34] *EBSCOhost CINAHL Complete*,[35] and *IEEE Xplore* [36]. The databases were chosen to cover literature from a broad spectrum of rehabilitation research topics including clinical and biomedical sciences, nursing and allied health, as well as biomechanical and engineering sciences. We did not explicitly search for grey literature.

The search strategy was defined in an iterative fashion [37] and included the following components: 1) The *Haynes Broad Search Strategy* for prediction studies, [38] which is available on PubMed via the search filters for "Clinical Queries", 2) an update to the strategy in step one in the form of the *Teljeur/Murphy Inclusion Filter* introduced by Keogh *et al.* [39] and adapted by the authors of this study, 3) index terms and keywords for SCI, and 4) relevant outcome measures able to assess the lived experience of health in persons with SCI as operationalized by functioning. The latter were identified by the development of an initial list based on literature [40-50] and feedback by scholars in the field about the most important measures to consider, given the scope of this study. Included languages were German and English, no limits were chosen with regards to the publication date. The search strategy was developed using PubMed and afterwards translated and adapted to the particularities of the identified other databases. The full search strategy for all databases can be found in the Supplemental Table 2. The search was completed on October 12th 2020.

2.2. Study selection

Eligibility was formulated according to in- and exclusion criteria for title/abstract and full-text screening separately (see Table 1). Underlying the eligibility criteria are the different types of prediction research explained in the introduction. Prediction models are thereby understood as “tools that combine multiple predictors by assigning relative weights to each predictor to obtain a risk or probability’’ [5]. Other notions include (clinical) prediction rules, probability assessments, decision rules or risk scores. In accordance with the objective of this review, only models were included that predicted functioning: Outcome variables included in the studies had to reflect different domains of functioning (classified as chapters in the ICF), but at least two chapters of *activities and participation*. Published conference proceedings in the biomechanical and engineering sciences were considered as original publications.

After database searching and removing of duplicates, [51] we followed the approach applied by Maritz *et al.* [52,53] for screening of titles and abstracts. A random sample incorporating 50 articles of the records were screened independently by two reviewers (JH, BP) in light of the eligibility criteria to determine whether an article is relevant. If the agreement in decisions for article in- or exclusion of the reviewers was acceptable (>90%), one reviewer continued to screen the remaining articles (JH). Otherwise, a new random sample of the same size was screened independently by the two reviewers. Disagreement was solved by discussions and the procedure was repeated until an acceptable agreement was reached.

Before starting the full-text screening, the eligibility criteria were revisited and further detailed by the study team. Subsequently, full-texts were screened by one reviewer (JH) and in the case of ambiguity, discussed with a second reviewer (BP). After full-text screening, an additional hand search was conducted. The database findings, screening and references were organized with EndNote [54].

2.3. Data extraction and results charting

The extraction fields presented by Peters *et al.* [32] were entered into a Microsoft Excel sheet and complemented by elements of the checklists for *Critical Appraisal and Data Extraction for Systematic Reviews of Prediction Modelling Studies* (CHARMS) [55] and *Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis* (TRIPOD) [5] in order to document the identified prediction models of functioning in SCI (see Supplemental Table 3).

To examine the content of identified prediction models, the established linking method developed by Cieza *et al.* [56] was applied. This method allows to link the content of outcomes or predictors included in the respective prediction models to the ICF as a reference model, and thus enables the comparison of outcomes and predictors contained in different prediction models. The linking process entails the linking at the conceptual and the classification level. For the purpose of this review, outcomes and predictors reported in the identified studies were extracted and linked if possible at chapter-level of the ICF. The ICF Research Branch (https://www.icf-research-branch.org) was contacted to request existing linking results of specific outcomes and predictors. To examine the envisioned use and implications of the identified prediction models, micro (patient-provider interaction), meso (service provision and payment) and macro (policies and programs) system levels were used as framework of reference. To document the methods used to develop the identified prediction models, the respective author’s description used within the article were extracted together with the stated

Table 1. Eligibility criteria according to title/abstract screening and full-text screening

Inclusion and exclusion criteria for title/abstract screening

Inclusion criteria:

- Primary study
- Prediction model study or impact study
- Study includes at least one variable (predictor and/or outcome) assessed with a measure of the lived experience of health as operationalised by functioning, which reflects two or more chapters of activities and participation as described in the ICF
- Study population includes males and/or females with SCI (traumatic and/or non-traumatic)
- Publication language is English or German

Exclusion criteria:

- Animal study
- Paediatric study
- Predictor finding study
- Prediction model study or impact study with mixed-diagnosis populations
- Study population includes SCI as a complication
- Study includes mortality as solely outcome

Inclusion and exclusion criteria for full-text screening

Inclusion criteria:

- Study includes measure of functioning as outcome variable

Exclusion criteria:

- Study includes measure of functioning as predictor variable only
- Study includes as outcome variable only single items or subscales of a measure of functioning, which no longer reflect two or more chapters of activities and participation as described in the ICF
- Study with outcome assessed/evaluated within the acute rehabilitation setting

Abbreviations. ICF, International Classification of Functioning, Disability and Health; SCI, spinal cord injury.

argumentation for its use, as well as stated advantages and disadvantages.

The data extraction was performed by one reviewer (JH) and cross-checked by a second reviewer (BP). The results of the scoping review were arranged in tabular format and discussed narratively.

3. Results

3.1. Study identification

In total, 2378 articles were retrieved through database searching and after screening the titles and abstracts of 1851 articles and the full-texts of 234 articles, seven eligible studies were identified for inclusion in the scoping review [57-63]. The corresponding flow diagram of the screening process is presented in Figure 1.

3.2. Screening and study selection process

For the title and abstract screening, in total three random samples were screened independently by the two reviewers until acceptable agreement was reached. The specific agreement levels reached for each sample were 78%, 86%, and 94%, respectively. Main reason for disagreement was the challenging distinction between predictor finding studies and prediction model studies. Following the framework of Kent *et al.* [7] the distinction should be based on the study aim. However, often authors did not clearly state the study aim, which was also reported by authors who conducted reviews on prediction models previously [4]. If a study aim was not clearly stated or unsure, studies were nevertheless included for full-text screening if they described a functioning outcome, or mentioned some form of model performance or accuracy assessment.

As the eligibility criteria for the full-text screening were revisited, for prediction model development studies the criteria, that studies need to include an internal validation of the prediction models to be eligible for this review, was decided. This decision was based on the recommendation of the TRIPOD statement for prediction model development studies to include some form of internal validation. In addition, this decision enhanced the consistency in the distinction between prediction model and predictor finding studies.

In the hand search we applied the following criteria: 1) publications based on identified SCI cohorts, trials or research projects (European Multicenter Study about Spinal Cord Injury, Rick Hansen Spinal Cord Injury Registry, Spinal Cord Injury Model System, SCIRehab) were specifically searched for in *PubMed*, and 2) the identified eligible studies were checked for updates using the 'Cited-by'-function of *PubMed*.

3.3. Characteristics of the included studies

The basic characteristics of the seven included prediction model studies are shown in Table 2. Six studies [57-60,62,63] described model development and included inter-

Table 2. Overview of included prediction model studies.

Study	Population												Location	Data handling	Modelling		
Authors	Sample size	Mean age (SD) in years	Sex (%)		Aetiology (%)		Level of injury (%)		Severity of injury according to AIS grade (%)[a]				Country, centres	Approaches to handle missing observations	Methods	Predictor selection procedure	Validation approach
			Male	Female	Traumatic	Non-traumatic	Paraplegia (T1-S5)	Tetraplegia (C1-C8)	A	B	C	D					
Ariji et al.	137	60 (16)	80	20	100	0	17	83	36	14	32	18	Japan, singe-centre	complete case analysis	linear regression	backward stepwise	internal, bootstrap
Facchinello et al.	172	49 (18)	NA	NA	100	0	34[b]	66[c]	40	10	15	36	Canada, single-centre	complete case analysis	machine learning	literature	internal, cross-validation
Harrington et al.	417	56 ±28[d]	66	31	75	NA	40	57	25	11	35	26	UK, single-centre	median imputation, LOCF, NOCB	linear regression, generalized linear regression	significance, elastic net penalization	internal, cross-validation
Kaminski et al.	76	43 (18)	76	24	100	0	54	46	53	11	9	27	Canada, single-centre	multiple imputation analysis	linear regression	forward stepwise	internal, bootstrap
Tomioka et al.	31	59 (19)	87	13	100	0	16	84	19	3	52	26	Japan, single-centre	no missing observations reported	logarithmic equation	not applicable	external, extrapolation
Wilson et al.	376	43 (17)	78	NA	100	0	NA	NA	36	17	15	32	Canada/USA, multi-centre	multiple imputation analysis	linear regression, logistic regression	no selection procedure performed	internal, bootstrap
Zariffa et al.	14	44 (18)	93	7	100	0	0	100	NA	NA	NA	NA	Canada/ Switzerland, multi-centre	no missing observations reported	linear regression	cross-validation	internal, cross-validation

Abbreviations. AIS, American Spinal Injury Association Impairment Scale; LOCF, last observation carried forwards; NA, not available; NOCB, next observation carried backwards; SD, standard deviation; UK, United Kingdom; USA, United States of America.

Note. Estimates and percentages have been rounded to zero decimal places for the purpose of this review.

[a] If AIS grade was reported at several time points, the earliest was chosen for this overview;

[b] Paraplegia: T2-L2;

[c] Tetraplegia: C1-T1;

[d] Median ± interquartile range.

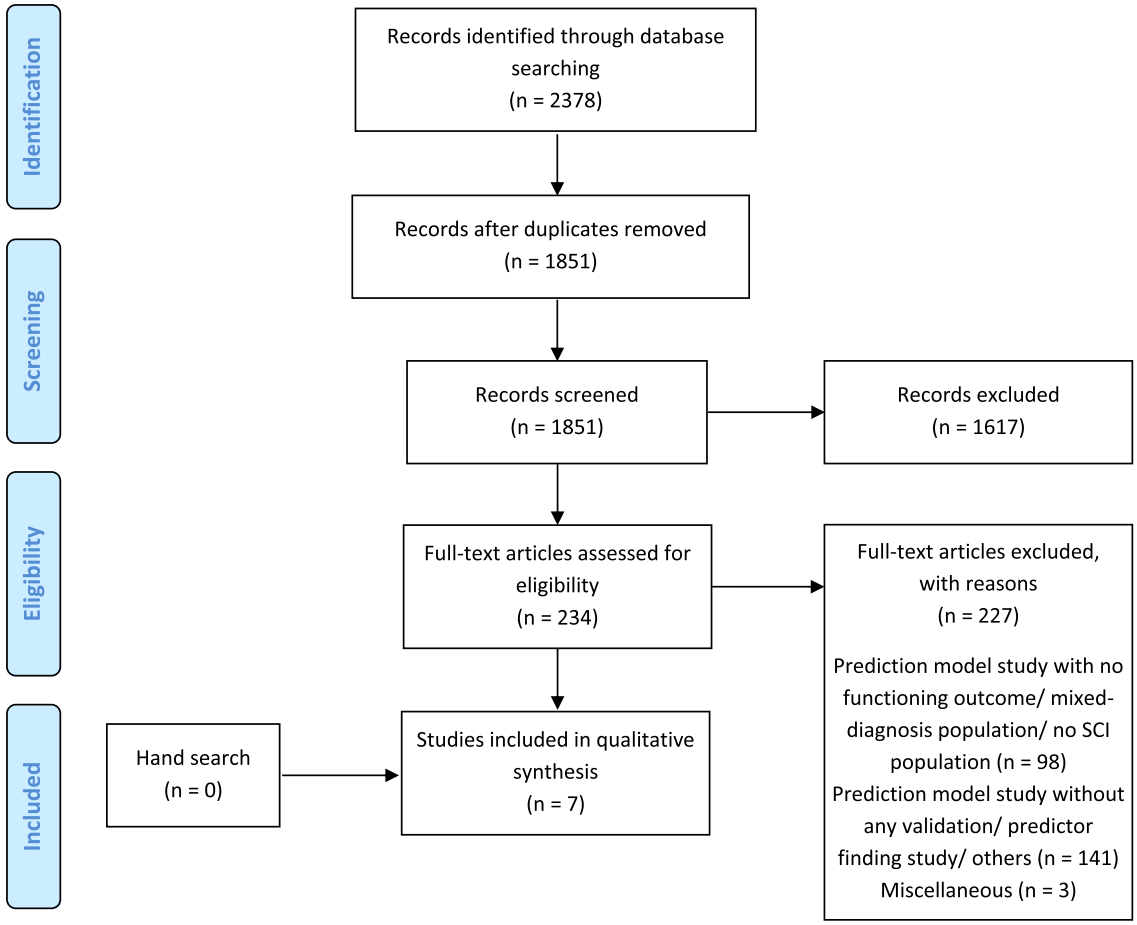

Figure 1. Flow diagram of the scoping review. Note that the reasons for full-text exclusion are not mutually exclusive. Figure adapted from Moher *et al.* 2009 [64].

nal validation approaches either based on cross-validation or bootstrap procedure, one study [61] described an external validation of a prediction model originally developed in stroke [65] and extrapolated to SCI. Only two studies included data from multiple institutions [62,63]. The mean age of the study populations under investigation ranged from 43 (SD=18) to 60 (SD=16) years and the population samples focused on traumatic aetiology and tend to include predominantly men and persons with tetraplegia. No impact studies were found.

In total, the seven included articles described 12 prediction models of functioning. Table 3 shows the identified models, their specific outcomes, investigated predictors and the corresponding linking to the ICF. The functioning outcome variables used in the prediction models all related to the two instruments Spinal Cord Independence Measure (SCIM) and Functional Independence Measure (FIM^{TM}), which both are assessing functional independence of a person in daily life, specifically focusing on self-care, mobility, and bladder and bowel management. The time scope for prediction ranged up to one year after injury. Predictors were assessed during early acute phase and up to one month after injury. Investigated predictor variables described concepts covered by the ICF components *body functions*, and *activities and participation*. Predictors that could not be linked to the ICF mainly described characteristics of the health condition or health interventions. With regards to their intended or envisioned use, all prediction models were assigned to the micro system level (e.g. guidance in rehabilitation planning, goal setting and patient care) [57-63] and some also to the meso system level (e.g. determination of appropriate length of stay, diminishing costs by guided management strategies) [60,61]. Some studies explicitly stated in addition a potential application for research purposes (e.g. improving clinical trial designs) [62,63] and for patient counselling (e.g. informing patients and relatives about expectations and relieving from psychological uncertainty) [58-60,62]. The reported statistical methods for the development of the prediction models were mostly regression analyses (linear and logistic), one study reported the use of machine learning methods, specifically regression tree analysis [58].

Table 3. Overview of outcome and predictor variables of included prediction model studies

Study	Final model(s)							Linking to ICF components					
Authors	**No.**	**Variable specification**						**b**	**s**	**d**	**e**	**pf**	**nc/nd**
		***Outcome /*Predictors**	***Prediction time frame /*Measurement time point**	**Included in final model?**									
				1	**2**	**3**	**4**						
Ariji et al.	1	***SCIM III, total score***	***6 months after injury***	**X**	**-**	**-**	**-**	**X**		**X**			
		Age at injury	NA	X									nd
		ASIA key motor muscle items[a]	1 month after injury	X				X					
		ASIA key sensory point items[b]	1 month after injury					X					
		SCIM III items[c]	1 month after injury	X				X		X			
		WISCI II	1 month after injury	X						X			
Facchinello et al.	2	***SCIM III, total score***	***6/12 MT after injury***	**X**	**X**	**-**	**-**	**X**		**X**			
		Age at injury	Acute care hospitalization	X	X								nd
		ASIA impairment scale	Acute care hospitalization	X	X			X					nc_hc
		Delay from the injury to surgery	Acute care hospitalization	X									nc_ICHI
		Early spasticity	Acute care hospitalization	X				X					
		Energy associated with injury	Acute care hospitalization	X	X								nc_hc
		ISS	Acute care hospitalization	X									nc_hc
		Mechanism of injury	Acute care hospitalization	X									nc_hc
		Neurological level of the injury	Acute care hospitalization	X	X								nc_hc
		Pneumonia	Acute care hospitalization	X									nc_hc
		Pressure ulcers	Acute care hospitalization	X									nc_hc
		Urinary tract infection	Acute care hospitalization	X									nc_hc
Harrington et al.	4[d,i]	***SCIM III, total score***	***Discharge***	**X**		**X**		**X**		**X**			
		SCIM III, total score	***12 months after injury***		**X**		**X**	**X**		**X**			
		Age at injury	NA			X	X						nd
		ASIA impairment scale, grade B	Rehabilitation admission			X		X					nc_hc
		ASIA impairment scale, grade C	Rehabilitation admission					X					nc_hc
		ASIA impairment scale, grade D	Rehabilitation admission			X		X					nc_hc
		ASIA light touch score	Rehabilitation admission					X					
		ASIA motor score	Rehabilitation admission	X	X	X	X	X					
		ASIA pin prick score	Rehabilitation admission	X	X			X					

(*continued on next page*)

Table 3 (*continued*)

Study	Final model(s)							Linking to ICF components					
Authors	No.	Variable specification						b	s	d	e	pf	nc/nd
		***Outcome* /Predictors**	***Prediction time frame* /Measurement time point**	Included in final model?									
				1	2	3	4						
		Alanine transaminase	Time of blood test[e]	X	X			X					
		Albumin	Time of blood test	X				X					
		Alkaline phosphatase	Time of blood test	X				X					
		C-reactive protein	Time of blood test					X					
		Creatinine	Time of blood test	X		X		X					
		Drinking status	NA	X								X	
		Fracture	NA	X									nc_hc
		Gamma glutamyl transferase	Time of blood test	X				X					
		Hematocrit	Time of blood test					X					
		Hemoglobin	Time of blood test					X					
		Lumbar injury	NA										nc_hc
		Mean cell hemoglobin	Time of blood test					X					
		Mean cell volume	Time of blood test	X	X			X					
		Monocytes	Time of blood test	X				X					
		Neurological level of injury, traumatic	NA	X									nc_hc
		Platelets	Time of blood test	X				X					
		Potassium	Time of blood test					X					
		SCIM III, total score	Rehabilitation admission	X	X	X	X	X		X			
		Sex	NA	X	X		X						nd
		Smoker status known	NA									X	
		Smoker status unknown	NA			X						X	
		Surgery	NA	X									nc_ICHI
		Time to first blood test	Time of blood test			X	X						nc_ICHI
		Total bilirubin	Time of blood test					X					
		Total protein	Time of blood test	X				X					
		Type 1 diabetes	NA	X									nc_hc
		Type 2 diabetes	NA			X							nc_hc
		Urea	Time of blood test			X		X					
		White blood count	Time of blood test	X				X					
Kaminski et al.	1	***SCIM III, total score***	***12 months follow-up***	**X**	**-**	**-**	**-**	**X**		**X**			
		Age	Acute phase after injury										nd
		ASIA impairment scale	Acute phase after injury	X				X					nc_hc
		ASIA light touch score	Acute phase after injury	X				X					
		ASIA motor score	Acute phase after injury	X				X					

(*continued on next page*)

Table 3 (*continued*)

Study	Final model(s)							Linking to ICF components					
Authors	**No.**	**Variable specification**						**b**	**s**	**d**	**e**	**pf**	**nc/nd**
		***Outcome /*Predictors**	***Prediction time frame /*Measurement time point**	**Included in final model?**									
				1	**2**	**3**	**4**						
		ASIA pin prick score	Acute phase after injury					X					
		Comorbidity	Acute phase after injury										nc_hc
		Delay to surgery	Acute phase after injury										nc_ICHI
		ISS	Acute phase after injury	X									nc_hc
		Level of injury	Acute phase after injury										nc_hc
		Sex	Acute phase after injury										nd
		TBI	Acute phase after injury										nc_hc
		Type of injury	Acute phase after injury										nc_hc
Tomioka et al.	1	***SCIM III, total score***	***Day X after injury***	**X**	**-**	**-**	**-**	**X**		**X**			
		SCIM III, total score at day A	First assessment of SCIM III in days after injury[f]	X				X		X			
		SCIM III, total score at day B	Third assessment of SCIM III in days after injury[g]	X				X		X			
		Day A	First assessment of SCIM III in days after injury	X									nc_ICHI
		Day B	Third assessment of SCIM III in days after injury	X									nc_ICHI
		Day X	Assessment of SCIM X days after injury	X									nc_ICHI
Wilson et al.	2[h]	***FIM™, motor score***	***6/12 months follow-up***	**X**	**X**	**-**	**-**	**X**		**X**			
		Age at injury	NA	X	X								nd
		ASIA impairment scale	Within 3 days after injury	X	X			X					nc_hc
		ASIA motor score	Within 3 days after injury	X	X			X					
		MRI intramedullary signal characteristics	Within 3 days after injury	X	X								nc_hc
Zariffa et al.	1[d]	***SCIM III, total score***	***Inpatient rehabilitation***	**X**	**-**	**-**	**-**	**X**		**X**			
		Hand range of motion, x direction	All predictor variables were assessed within two weeks of the SCIM III assessment (before or after)	X						X			

(*continued on next page*)

Table 3 (*continued*)

Study	Final model(s)							Linking to ICF components					
Authors	No.	Variable specification						b	s	d	e	pf	nc/nd
		Outcome /Predictors	*Prediction time frame* /Measurement time point	Included in final model?									
				1	2	3	4						
		Hand range of motion, y direction								X			
		Hand range of motion, z direction		X						X			
		Joint range of motion, angle 1								X			
		Joint range of motion, angle 2								X			
		Joint range of motion, angle 3								X			
		Joint range of motion, angle 4								X			
		Joint range of motion, angle 5								X			
		Movement mean jerk over task duration								X			
		Movement mean velocity over task duration								X			
		Number of changes in hand's trajectory direction, normalized by task length								X			
		Range of grip pressure		X						X			
		Ratio of mean to maximum velocity over task duration								X			
		Skewness of grip pressure		X						X			

Abbreviations. ASIA, American Spinal Injury Association examination according to the International Standards for Neurological Classification of Spinal Cord Injury; b, body functions; d, activities and participation; e, environmental factors; FIM™, Functional Independence Measure; ICF, International Classification of Functioning, Disability and Health; ISS, Injury Severity Score; MRI, magnetic resonance imaging; nc, not covered in the ICF; nc_hc, not covered in the ICF, health condition; nc_ICHI, not covered in the ICF, health intervention (International Classification of Health Interventions); NA, not available; nd, not defined; pf, personal factors (not classified in the ICF); s, body structures; SCIM III, Spinal Cord Independence Measure version three; TBI, traumatic brain injury; WISCI II, Walking Index for Spinal Cord Injury version two.

[a] In total, 20 variables were tested, of which 3 entered the final model;

[b] In total, 112 variables were tested, of which none entered the final model;

[c] In total, 19 variables were tested, of which 1 entered the final model;

[d] Only prediction models of functioning outcomes are reported for the purpose of this review;

[e] Mean time of blood test was 31 days (SD = 30 days) post-injury;

[f] Mean assessment time of SCIM III was 69.8 days (SD = 55.6 days) from admission, and mean time between injury and admission was 45.2 days (SD = 60.8);

[g] Mean assessment time of SCIM III was 123.4 days (SD = 58.2 days) from admission, and mean time between injury and admission was 45.2 days (SD = 60.8);

[h] The two models differ according to the used coding scheme of FIM™ and corresponding regression method (discrete score and linear regression model vs. dichotomization according to the achievement of a score of at least 6 in all FIM™ motor score items and logistic regression model);

[i] The respective models differ according to the used regression method and predictor selection (linear regression and significance criteria used for models 3 and 4 vs. generalized linear regression and elastic net penalization used for models 1 and 2).

4. Discussion

We identified seven prediction model studies reporting twelve prediction models of functioning. No corresponding impact studies were found. This suggests that the development of prediction models of functioning and their use in practice is not fully exploited. In order to improve prediction models in SCI, it might be helpful to contrast current models with recent suggestions and examples from other health conditions.

All functioning outcome variables used in the identified prediction models related either to SCIM or FIM™. Predictor variables covered the ICF components *body functions* (e.g. assessed by the American Spinal Injury Association examination), and *activities and participation* (e.g. assessed by SCIM). Other predictors described characteristics of the health condition (e.g. level of injury, complications) or of health interventions (e.g. delay to surgery). Only few studies investigated predictors such as blood measures, [59] magnetic resonance imaging, [62] and sensor data [63]. These findings are in line with Wingbermühle *et al.* [66] and Wartenberg *et al.*, [67] which both identified gaps in the investigation of a broad range of possible predictors including biological and physical, as well as psychosocial measures, and especially in the use of directly observable predictors such as imaging, biomarkers, and genetics. In terms of covered ICF components, the integration of *body structures* and *contextual factors* in prediction models remains scarce. Despite the use of the ICF as a frame of reference in the study and the consistency of using FIM™ and SCIM as outcomes, the comparability of the findings with regards to selected predictors is limited due to the application of different variable coding schemes such as dichotomized, discrete, or interval scores. Moreover, the comparability of the identified prediction models is further hampered by the heterogeneity of the study populations and settings, as well as by the different time points of predictor and outcome measurements. Further information standards are needed to enhance the interoperability of functioning outcomes or existing standards, such as the ICF or the SCI Data Set actually used in research and practice.

The method most often used in these identified prediction models was linear regression analysis. Only two identified studies were multi-centre studies and the respective population samples focused on traumatic aetiology and tend to include predominantly men and persons with tetraplegia, which limits the generalizability of the developed prediction models. Due to the complex and multidimensional nature of functioning in SCI, prediction models based on new methods such as machine learning techniques are promising and may allow a dynamic and real time modelling of interactions among a variety of predictors [66]. Beyond the findings of our review, also other methods are deployed in SCI prediction research, such as artificial neural network analysis [68] or individual growth curve models [69]. However, the applicability and usefulness of these methods needs to be further investigated [70]. To do so, large data sets, ideally designed specifically for prediction research, including a broad variety of predictors and appropriately reflecting the population under study are needed [66].

The identified prediction models were intended for clinical purposes including guidance in individual rehabilitation planning, financial aspects related to the reduction of costs by guided management strategies, patient counselling, as well as for research purposes including the improvement of clinical trial designs, which are in line with other prediction research studies in SCI [13,14,22,23,69]. To delineate the value of prediction models for the field of SCI rehabilitation in detail, validation and impact assessment of prediction models require further research.

4.1. Limitations

There are some limitations to this review. Firstly, scoping reviews aim to give an overview of existing evidence on a given topic, regardless of the quality of the reviewed literature [32]. Since we did not assess the quality of the included studies, we are not able to make any statement about the performances, the usefulness or applicability of the presented prediction models for practice. Secondly, the search strategy specifically included common instruments assessing functioning and used in SCI. We do no claim this list to be complete and it might be the case that prediction model studies were missed because their instruments were not included in our search strategy. Thirdly, although our search strategy based on published search filters for prediction model and impact studies, these filters have been shown to low perform for the search of impact studies [71]. Furthermore, despite the absence of relevant impact studies, prediction models of functioning might be developed and implemented locally and not published internationally. Fourthly, the eligibility criteria understand functioning outcomes as variables covering at least two chapters of the ICF component *activities and participation*. Fifthly, the present review only includes prediction model studies which performed at least some kind of internal validation. Although internal validation is strongly recommended in prediction model development, this eligibility criterion lead to the exclusion of studies [69,72,73] about prediction model development which did not intend or failed for some reason to perform an internal validation. Such studies might also include valuable details to inform the development of prediction models in the future. For example, they might include information on potentially important predictor variables to consider in the development of prediction models of functioning, such as different neurophysiological variables as investigated by Hupp *et al.* [72]. Sixthly, we considered conference proceedings from the engineering sciences as original publications. However, these proceedings were often shorter than ordinary journal

articles and thus, provided less information for the full-text screening and the categorization of excluded articles. Lastly, the authors had primarily expertise in the field of health sciences and less so in biomechanical and engineering sciences.

5. Conclusion

This scoping review sheds light on existing prediction models of functioning in SCI and highlights their content, use cases, and development methods. Findings suggest that the development of prediction models of functioning for use in clinical practice remains to be fully exploited. However, we believe that SCI with its many different functioning aspects concerned and its life-long perspective and requirement for health and social services across the entire continuum of care is an excellent learning example for the development of prediction models of functioning. By providing a comprehensive overview of what has been done, we hope to inform future research on prediction models of functioning in SCI, including the development of new prediction models for specific purposes or the external validation and improvement of existing ones, and contribute to an efficient and meaningful synthesis and use of research evidence.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jclinepi.2021.07.015.

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CHAPTER 5
Discussion

In order to inform the development of future prediction models of functioning in SCI, this doctoral thesis investigated the complexity of functioning and its predictors in persons with SCI attending first rehabilitation in Switzerland (studies 1 and 2) as well as the current state of prediction research in the field of SCI rehabilitation (study 3).

The following chapter summarizes the main findings of the three doctoral studies and discusses them in light of current literature and presents the strengths and limitations of the doctoral thesis. Moreover, potential implications for practice, research and policy are examined.

MAIN FINDINGS

In this section, the main findings of the doctoral thesis are summarized according to its three specific aims and corresponding research studies.

Study 1: Examination of functioning in persons with SCI

The first study aimed to examine the associations between components of functioning and their relationship with age, gender and aetiology in persons with SCI attending first rehabilitation, while considering potential indirect effects and group differences. The cross-sectional study addressed the understanding of functioning and its complexity as well as potential predictor variables related to the examined relationship structures. Using the ICF as a conceptual framework and SEM as methodology, four structural models were developed and tested. All four models examined the associative linkages between body structures and functions with independence in the performance of ADL, which was operationalized using interval-based SCIM III sum scores. Specifically, potential indirect effects of body structures and functions on the independence in the performance of ADL through different mental functions (i.e. anxiety, depression, optimism, self-esteem) were tested. In addition, the structural models were investigated for differences in age, sex and aetiology.

The results illustrate the merit of using the ICF as a framework for the development of multivariable models of functioning, incorporating complex association structures. The study results showed significant direct effects of level of injury, urinary, bowel or skin complications and conditions on SCIM III outcomes at discharge from first rehabilitation. While pain in combination with depression, optimism or self-esteem showed significant indirect effects on SCIM III outcomes. Furthermore, one of the investigated models showed group differences

for aetiology groups. Overall, the tentative results of this exploratory study provide a starting point for further hypothesis development and statistical investigations on the complexity of functioning aiming to enhance empirical evidence for the comprehensive understanding of functioning as operationalized with the ICF.

Study 2: Functioning trajectories in persons with SCI

The second study aimed to identify different classes of functioning trajectories in persons with SCI attending first rehabilitation and to examine potential predictors of class membership. Accordingly, the study approached the description and understanding of functioning and its complexity from a longitudinal perspective. Using the methodology of LPMMs, the number of unobserved, underlying classes of functioning trajectories in persons with SCI undergoing first rehabilitation according to interval-based SCIM III sum scores was examined. Potential predictors of class membership were investigated using multinomial logistic regression.

The results revealed four distinct classes of functioning trajectories that indicate patterns of *stable high functioning*, *early functioning improvement*, *moderate functioning improvement* and *slow functioning improvement*. Among the investigated predictor variables, age, injury level and severity as well as ventilator assistance were found to be robust predictors in distinguishing between the identified classes of functioning trajectories. This explorative study sets the basis for a more detailed examination of the course of functioning of persons with SCI during first rehabilitation, including important corresponding predictor variables. Thus, the study results can serve as the basis for future prediction models of functioning trajectory classes.

Study 3: Prediction models of functioning in the field of SCI rehabilitation

The third study aimed to examine content, context and methods of existing prediction models of functioning in SCI. Using a scoping review approach, literature was searched and identified that focused on the development, validation, or impact assessment of prediction models of functioning in the field of SCI rehabilitation. For prediction models to be considered as prediction models of functioning, the respective outcome variables had to reflect different functioning domains as outlined by the chapters of the ICF, including at least two chapters of the ICF component activities and participation. In addition, for prediction studies with focus on the development phase to be eligible, they had to include at least some form of internal

validation. Subsequently, information on the content and context, as well as on the methods used, was extracted for the identified prediction models of functioning in SCI.

The scoping review identified seven studies describing twelve prediction models of functioning [1-7]. The majority of the seven studies described prediction model development. Only one study described the external validation of a prediction model that was originally developed for use in stroke [5]. Studies were mostly based on regression analyses, with one study using machine learning methods [2]. The identified prediction models incorporated either the SCIM III [1-5, 7] or the Functional Independence Measure (FIM™) [6] as outcome measures. Furthermore, the most frequently investigated predictors included aspects of body functions, activities and participation, or characteristics of the health condition and health interventions. Moreover, reported intended use cases for prediction models included rehabilitation planning, goal setting and patient counselling as well as clinical trial design improvement and reduction of financial costs. This study not only revealed potential research gaps in prediction models of functioning in SCI rehabilitation, it moreover paves the way for future research on prediction models of functioning with the ultimate goal of enhancing clinical practice.

GENERAL DISCUSSION

Building on the assumption that functioning information is essential for individual rehabilitation planning and clinical decision making and that prediction research with respect to functioning is promising in supporting health professionals in different tasks during a Rehab-Cycle, this doctoral thesis investigated the complexity of functioning and its predictors in persons with SCI attending first rehabilitation in Switzerland as well as the current state of prediction research in the field of SCI rehabilitation. With regard to the overall objective of the thesis to inform the development of future prediction models of functioning in SCI, the discussion section focuses specifically on the potential of the presented findings to support the development process and highlights general considerations in the development, validation and impact assessment of prediction models. Note, however, that the indication and value of prediction models of functioning for clinical decision making as such, is a separate topic and goes beyond the scope of this dissertation.

Possible application of functioning trajectory-based prediction models in clinical practice

Altogether, the findings of this doctoral thesis can provide a basis for discussions on developing prediction models of functioning for use in clinical practice, and specifically in first rehabilitation for SCI in Switzerland, as the research studies 1 and 2 build on the SwiSCI Inception Cohort Study. For example, the results of studies 2 and 3 can inform the development of prediction models of functioning trajectory classes for persons with SCI undergoing first rehabilitation. Such prediction models could be envisioned as part of the clinical workflow. That is, health professionals could enter information of individual patients (values of the predictor variables) into the model. This would, in turn, assign the patient with a certain probability to one of the identified classes of functioning trajectories (class membership outcome variable). Such a prediction model could also be integrated into a hospital's clinical documentation system, in which corresponding information is automatically processed and displayed in a meaningful manner for clinical use by health professionals. Patient information could be displayed, for example, as a graphical visualization of the expected class-specific mean functioning trajectory and the actual functioning course of a patient according to repeated routine measurements. This application of a prediction model would enable health professionals to monitor and evaluate the patient's individual functioning course with reference to the expected mean trajectory for similar patients. Employing the expected functioning trajectory in this way has already been described by Stucki et al. [8]. Similar applications with respect to individual growth curve models in SCI rehabilitation have also been described by Kozlowski et al. [9] and Pretz et al. [10]. Prediction models for trajectory classes have been developed, for example, for classes of functional decline in elderly persons [11] or for classes of severe exacerbations in persons with problematic asthma [12]. These studies highlight the potential for the early identification of a person's risk for unfavourable outcomes. Generally, the discussed examples show that different applications of prediction models using classes of functioning trajectories are possible. However, for a prediction model to be meaningful in clinical practice, it's development should be guided by the intended purpose and specific needs of the target clinical context [13].

As shown by this doctoral thesis, a starting point for developing a functioning trajectory-based prediction model for SCI rehabilitation can be the SwiSCI Inception Cohort Study, with its ICF-based data model and longitudinal design. Study 2 demonstrated that the identification of homogeneous classes of functioning trajectories based on SwiSCI Inception Cohort data and

the examination of corresponding predictors is possible. However, further research is needed to clarify whether the currently available potential predictor variables and the number of measurement time points for SCIM III in the SwiSCI Inception Cohort Study support the development of meaningful and useful prediction models of functioning trajectory classes for routine rehabilitation practice.

General considerations in developing prediction models of functioning in the future

Regarding potential future directions in developing prediction models of functioning, the results of study 3 can provide valuable input for discussions and future development activities by shedding light on current research gaps and promising future research directions. For example, the study revealed a current dominance of regression analyses as a methodology in the development of functioning-based prediction models, while the full potential of modern statistical methods, such as machine learning or artificial intelligence, remains to be explored. According to Wingbermühle et al. [14], prognostic modelling for spinal disorders comes with several methodological challenges, including the complexity in predicting recovery outcomes in the long-term. Furthermore, Wingbermühle and colleagues promote modern statistical methods as a way to dynamically depict complex association structures and model interactions between predictors and outcomes also in real-time. Considering the complexity of functioning in SCI, such methods may also have utility in the development of prediction models of functioning. However, applying modern statistical methods is ideally based on large data sets and is best when investigating various different predictors, e.g. genomics information or information from wearables [14]. For example, Gravesteijn et al. [15] found that machine learning algorithms may not outperform traditional methods in specific traumatic brain injury settings, specifically when the number of available predictor variables for model development is small. Considering this example, the decision to apply modern statistical methods needs to be carefully assessed; this includes comparing the proposed methods with other methods, e.g. regression analyses, across the different phases of prediction model development. However, although currently available best practice guidelines for developing prediction models also support the application of modern methods, they provide insufficient guidance on the reporting and assessment of prediction models based on modern methods with respect to transparency, replicability, ethics, and

effectiveness (TREE) [13]. The development of a corresponding consensus-based TREE framework for health-related research has been put for discussion [13].

Beyond addressing gaps identified in current research on functioning-based prediction models in SCI rehabilitation, various other points will be important to consider before embarking on the development of prediction models of functioning for use in clinical practice. In general, generating a prediction model with the completion of all development phases can be a long and expensive process [16]. There are, however, guidelines available that can support the development process [16-22]. With regard to the completion of the development phases, the findings from study 3 align with reports in other health conditions that prediction model validation and impact studies are rather scarce [16]. These results indicate that most prediction models neither reach the external validation phase nor the stage of impact assessment in practice. Nevertheless, prediction models can be understood as interventions; for them to be useful and effective, their impact on patient care, for example, in terms of outcomes or cost-effectiveness, should be investigated. Since prediction models are ultimately developed to support clinicians and health professionals [16], it is critical how the implementation of a prediction model and impact assessment is presented to the end-users. Involving key stakeholders, for example in questions regarding the presentation format of a prediction model, can facilitate the implementation and impact assessment process [21, 22]. As stakeholder involvement was an important part of the overall NRP74 StARS project, selected results of this doctoral thesis were discussed with relevant stakeholders in the Swiss health system during a stakeholder dialog that took place in November 2019 [23]. Focus group interviews with health professionals in SCI rehabilitation had also been planned in order to gather input on how to best present functioning information in clinical practice. Unfortunately, these interviews had to be cancelled due to restrictions posed by the COVID-19 pandemic. Nevertheless, the results of this thesis will be informative for future discussions with health professionals on the use of functioning information in SCI rehabilitation practice, specifically in the form of functioning-based prediction models.

LIMITATIONS AND STRENGTHS

The following section discusses the limitations as well as strengths of this doctoral thesis.

Due to the design of the SwiSCI Inception Cohort Study, there may be some risk of bias associated with the data collected. Fekete and colleagues have shown that the SwiSCI

Inception Cohort is less likely to include females, persons of older age, persons with lower independence in functioning, and non-traumatic SCI [24]. Thus, the data collected might be prone to a potential non-response bias. To address this issue, they suggest calculating inverse probability weights in order to overcome the underrepresentation of specific patient characteristics. However, such inverse probability weights have not yet been developed, thus were not considered for the present doctoral thesis. Another possible source of bias, i.e. selection bias, may be due to the participant selection procedure implemented for studies 1 and 2. Moreover, the design of the SwiSCI Inception Cohort Study in terms of its measurement time points and form of data collection (clinical examinations, patient questionnaires) poses methodological challenges related to overlapping measurement time points and missing observations [24]. Despite these challenges, a methodological strength of this doctoral thesis is the use of sophisticated methodologies, such as LPMMs [25]. Specifically, LPMMs can be employed to handle study samples in which persons show different numbers of assessments, as it is the case in the SwiSCI Inception Cohort Study. Another methodological strength is that the prospective design of SwiSCI holds the promise of improving existing models of functioning and identifying new trajectory classes by collecting more data. The possibility of confirming, improving and updating existing models is especially relevant in further developing prediction models.

Another limitation pertains to the SCIM III [26], which was chosen as outcome measure in studies 1 and 2. The SCIM III only represents activity-related functioning aspects, but does not assess any participation-related restrictions of persons with SCI, thus neglecting an important aspect of functioning. Nevertheless, this probably poses no major problems during first rehabilitation, since it is assumed that restrictions in participation play out primarily in the community setting. The SCIM measurement itself, however, has several limitations, such as potential ceiling and floor effects [27]. Despite its weaknesses, the SCIM has been shown to outperform other functioning-based measures, and is especially sensitive to change, thus providing a good basis for studying functioning not only from a cross-sectional but also from a longitudinal perspective [27]. In addition, a methodological strength of this doctoral thesis is the incorporation of interval-based SCIM III sum scores. These scores were derived by using Rasch-analysis [28, 29] and to ensure that the comparison of SCIM III sum scores between two or more persons and in the assessment of change over time is valid and accurate.

The cross-sectional design of study 1 and the explorative nature of both studies 1 and 2 allow only tentative results on potentially important predictors; these need to be confirmed with further research. Moreover, it is important to emphasize that both studies do not imply any causality between potential predictors and outcome variables. Instead, they aim to explore the associations between predictors and outcomes in a multivariable fashion in order to identify candidate predictor variables that have promising utility for future prediction studies or studies that explore causation [30]. Thus, in the context of this doctoral thesis, both research studies 1 and 2 were considered as explorative predictor finding studies, even if the distinction between different types of prediction research in practice is not always straightforward. This may be the case for studies 1 and 2. Using the recently published conceptual framework of Kent et al. for prognostic research [30], study 1 might not be fully consistent with the understanding of association and predictor finding studies, since it incorporated statistical methods involving hypothesis testing. In consideration of the Kent et al. conceptual framework, study 2 could also additionally be understood as a descriptive prognostic study. Irrespective of which type of prediction research studies 1 and 2 are considered, both studies provide first indications of outcomes and potentially important predictors towards predictive modelling of functioning in SCI, and can serve as starting point for future generations of empirical evidence on the complexity of functioning in SCI.

Lastly, scoping reviews do not generally assess the quality of included studies. This was the case in the scoping review performed in study 3; the results give no information on the quality of the identified prediction model studies. The scoping review was intended to give an overview of the current state of prediction studies in SCI with regard to their content, context and methods in order to provide a foundation for planning future prediction models of functioning as well as for improving and updating existing ones.

IMPLICATIONS AND FUTURE RESEARCH DIRECTIONS

Implications for practice

This doctoral thesis aimed to inform the future development of prediction models of functioning in SCI. As discussed, to ensure the usefulness and relevance of prediction models in SCI rehabilitation practice, stakeholder involvement is key [16, 21, 22]. The presented findings specifically illustrate currently available SwiSCI data with respect to SCIM III outcomes and potentially important predictors. In addition, they summarize the current state of

prediction studies on functioning in SCI. These findings can serve as basis for discussions with health professionals about the development of prediction models of functioning for use in clinical practice, and specifically for use in first SCI rehabilitation in Switzerland. Such discussions could explore how and when specific functioning information should be presented to health professionals for the information to be meaningful and useful in specified clinical processes. Furthermore, the exchange with health professionals could help identify concrete ideas for using prediction models of functioning in clinical rehabilitation management and planning. A continuous dialogue between researchers and rehabilitation health professionals could foster research initiatives out of practice for practice and has the potential to develop prediction models which are able to meaningfully support, inform and optimize clinical practice.

Implications for research

The research studies conducted within this doctoral thesis highlight the importance of studying functioning in its complexity as reflected in the ICF. They also show that using suitable statistical methods help to account for complex association structures and longitudinal changes and improve our understanding of relevant predictors. Accordingly, this thesis presents several statistical models that can be tested and further developed in future studies. For example, the models developed in study 1 could be translated into longitudinal models to clarify which predictors play out at which time point during first rehabilitation. The model developed in study 2 may be expanded to incorporate interactions among predictors as well as longitudinally varying predictors, which could in turn enhance the understanding of the impact of predictors at specific time points. In addition, classes of functioning trajectories need not be restricted to first rehabilitation. In order to continuously monitor functioning throughout the entire continuum of care, classes of functioning trajectories beyond first rehabilitation of SCI should also be investigated.

Findings of study 3 revealed that current prediction models of functioning specifically focus on regression analysis techniques and that investigated predictors mainly covered aspects of body functions, activities and participation, or characteristics of the health condition and health interventions. In addition to investigating modern statistical methods for use in developing functioning-based prediction models, the study also underscored the investigation of predictors that cover aspects of body structures and contextual factors. Moreover, study 3

showed that identified prediction models lack external validation and impact assessment in practice. Thus, regardless of which ideas are developed or realized in future prediction models of functioning, it will be important that future research attempts also incorporate external validation and impact assessment phases.

Implications for policy

Building on the assumption that functioning information is essential for individual rehabilitation planning and clinical decision making, this doctoral thesis highlights the use of the ICF as a standard reference for describing functioning in persons with SCI. This is in line with WHO's initiative *Rehabilitation 2030* [31] and WHO's *Rehabilitation in health systems: guide for action* [32]. In light of the increasing need for rehabilitation [33, 34], Rehabilitation 2030 calls for action that strengthen the rehabilitation strategy in health systems around the globe. As part of this call for action, the WHO emphasizes the need to include functioning information in health information systems and underscores the relevance of functioning information for decision making not only for clinical care at the micro-level but also for management at the meso-level and for health policy at the macro health systems level. This thesis brings further light on the value of comprehensive functioning information, using SCI as a case in point.

CONCLUSION

This doctoral thesis focused on prediction research as a promising field of study to investigate and understand functioning and its complexity in persons with SCI. Furthermore, prediction research can lay the groundwork for developing prediction models that support health professionals in rehabilitation planning and clinical decision making. The presented research illustrated the use of sophisticated methodologies to investigate comprehensive association structures across functioning components and the longitudinal course of functioning outcomes by means of predictor finding studies. In addition to these explorative statistical approaches, the thesis included a summary of the current literature on prediction models of functioning in the field of SCI rehabilitation. Altogether, the findings of this doctoral thesis lay the basis for further discussions and future research on prediction models of functioning in SCI with the ultimate goal of informing and supporting clinical practice.

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APPENDIX A
Supplementary material study 1

Supplementary Table 1 Analysis relevant variables and number of missing observations before data imputation

Variable	Present study before imputation (N=390)
Body structures	
Level of injury at discharge	
Paraplegia (%)	152 (38.97)
Tetraplegia (%)	235 (60.26)
Missing (%)	3 (0.77)
Severity of injury at discharge	
Complete (%)	63 (16.15)
Incomplete (%)	324 (83.08)
Missing (%)	3 (0.77)
Body functions	
Bowel function	
No (%)	189 (48.46)
Yes (%)	181 (46.41)
Missing (%)	20 (5.13)
Cardiovascular function	
No (%)	303 (77.69)
Yes (%)	85 (21.79)
Missing (%)	2 (0.51)
Pain	
No (%)	135 (34.62)
Yes (%)	244 (62.56)
Missing (%)	11 (2.82)
Pulmonary function	
No (%)	346 (88.72)
Yes (%)	41 (10.51)
Missing (%)	3 (0.77)
Skin function	
No (%)	343 (87.95)
Yes (%)	42 (10.77)
Missing (%)	5 (1.28)
Urinary function	
No (%)	286 (73.33)
Yes (%)	103 (26.41)
Missing (%)	1 (0.26)
Mental functions	
Anxiety: Stressed	
0 (%)	133 (34.10)
1 (%)	188 (48.21)
2 (%)	47 (12.05)
3 (%)	14 (3.59)
Missing (%)	8 (2.05)
Anxiety: Scared	
0 (%)	207 (53.08)
1 (%)	103 (26.41)
2 (%)	51 (13.08)
3 (%)	20 (5.13)
Missing (%)	9 (2.31)

Abbreviations: ADL, activities of daily living; AIS, American Spinal Injury Association Impairment Scale; SCI, spinal cord injury; SwiSCI, Swiss Spinal Cord Injury Cohort Study; NA, not applicable.

Supplementary Table 1 Continued

Variable	Present study before imputation (N=390)
Anxiety: Worried	
0 (%)	174 (44.62)
1 (%)	140 (35.90)
2 (%)	53 (13.59)
3 (%)	15 (3.85)
Missing (%)	8 (2.05)
Anxiety: Relaxed	
0 (%)	142 (36.41)
1 (%)	166 (42.56)
2 (%)	65 (16.67)
3 (%)	9 (2.31)
Missing (%)	8 (2.05)
Anxiety: Fearing	
0 (%)	198 (50.77)
1 (%)	154 (39.49)
2 (%)	21 (5.38)
3 (%)	8 (2.05)
Missing (%)	9 (2.31)
Anxiety: Restless	
0 (%)	159 (40.77)
1 (%)	133 (34.10)
2 (%)	76 (19.49)
3 (%)	14 (3.59)
Missing (%)	8 (2.05)
Anxiety: Panicked	
0 (%)	267 (68.46)
1 (%)	93 (23.85)
2 (%)	14 (3.59)
3 (%)	6 (1.54)
Missing (%)	10 (2.56)
Depression: Enjoying as before	
0 (%)	127 (32.56)
1 (%)	176 (45.13)
2 (%)	61 (15.64)
3 (%)	14 (3.59)
Missing (%)	12 (3.08)
Depression: Laughing	
0 (%)	225 (57.69)
1 (%)	121 (31.03)
2 (%)	30 (7.69)
3 (%)	6 (1.54)
Missing (%)	8 (2.05)
Depression: Being cheerful	
0 (%)	205 (52.56)
1 (%)	128 (32.82)
2 (%)	37 (9.49)
3 (%)	11 (2.82)
Missing (%)	9 (2.31)

Abbreviations: ADL, activities of daily living; AIS, American Spinal Injury Association Impairment Scale; SCI, spinal cord injury; SwiSCI, Swiss Spinal Cord Injury Cohort Study; NA, not applicable.

Supplementary Table 1 Continued

Variable	Present study before imputation (N=390)
Depression: Slowed down	
0 (%)	74 (18.97)
1 (%)	200 (51.28)
2 (%)	65 (16.67)
3 (%)	42 (10.77)
Missing (%)	9 (2.31)
Depression: Interested in appearance	
0 (%)	264 (67.69)
1 (%)	68 (17.44)
2 (%)	38 (9.74)
3 (%)	11 (2.82)
Missing (%)	9 (2.31)
Depression: Looking forward	
0 (%)	181 (46.41)
1 (%)	134 (34.36)
2 (%)	51 (13.08)
3 (%)	15 (3.85)
Missing (%)	9 (2.31)
Depression: Enjoying a book	
0 (%)	250 (64.10)
1 (%)	90 (23.08)
2 (%)	19 (4.87)
3 (%)	19 (4.87)
Missing (%)	12 (3.08)
Optimism: Expecting the best	
0 (%)	4 (1.03)
1 (%)	21 (5.38)
2 (%)	69 (17.69)
3 (%)	116 (29.74)
4 (%)	159 (40.77)
Missing (%)	21 (5.38)
Optimism: Things go wrong if they can	
0 (%)	22 (5.64)
1 (%)	54 (13.85)
2 (%)	79 (20.26)
3 (%)	113 (28.97)
4 (%)	97 (24.87)
Missing (%)	25 (6.41)
Optimism: Optimistic about future	
0 (%)	8 (2.05)
1 (%)	22 (5.64)
2 (%)	68 (17.44)
3 (%)	124 (31.79)
4 (%)	147 (37.69)
Missing (%)	21 (5.38)
Optimism: Expecting things to go wrong	
0 (%)	20 (5.13)
1 (%)	56 (14.36)
2 (%)	61 (15.64)
3 (%)	127 (32.56)
4 (%)	104 (26.67)
Missing (%)	22 (5.64)

Abbreviations: ADL, activities of daily living; AIS, American Spinal Injury Association Impairment Scale; SCI, spinal cord injury; SwiSCI, Swiss Spinal Cord Injury Cohort Study; NA, not applicable.

Supplementary Table 1 Continued

Variable	Present study before imputation (N=390)
Optimism: Not relying on good things	
0 (%)	14 (3.59)
1 (%)	50 (12.82)
2 (%)	57 (14.62)
3 (%)	114 (29.23)
4 (%)	134 (34.36)
Missing (%)	21 (5.38)
Optimism: Expecting good things	
0 (%)	16 (4.10)
1 (%)	34 (8.72)
2 (%)	70 (17.95)
3 (%)	114 (29.23)
4 (%)	128 (32.82)
Missing (%)	28 (7.18)
Self-esteem: Having good qualities	
0 (%)	0 (0)
1 (%)	8 (2.05)
2 (%)	207 (53.08)
3 (%)	166 (42.56)
Missing (%)	9 (2.31)
Self-esteem: Feeling useless	
0 (%)	17 (4.36)
1 (%)	61 (15.64)
2 (%)	81 (20.77)
3 (%)	218 (55.90)
Missing (%)	13 (3.33)
Self-esteem: Being of worth	
0 (%)	9 (2.31)
1 (%)	20 (5.13)
2 (%)	137 (35.13)
3 (%)	211 (54.10)
Missing (%)	13 (3.33)
Self-esteem: Taking a positive attitude	
0 (%)	9 (2.31)
1 (%)	23 (5.90)
2 (%)	156 (40.00)
3 (%)	193 (49.49)
Missing (%)	9 (2.31)
Activities	
Mean independence in performing ADL (s.d.)	89.46 (11.28)
Missing (%)	0 (0)
Others	
Mean age at SCI diagnosis, years (s.d.)	53.82 (16.47)
Missing (%)	0 (0)
Aetiology	
Traumatic (%)	228 (58.46)
Non-traumatic (%)	162 (41.54)
Missing (%)	0 (0)

Abbreviations: ADL, activities of daily living; AIS, American Spinal Injury Association Impairment Scale; SCI, spinal cord injury; SwiSCI, Swiss Spinal Cord Injury Cohort Study; NA, not applicable.

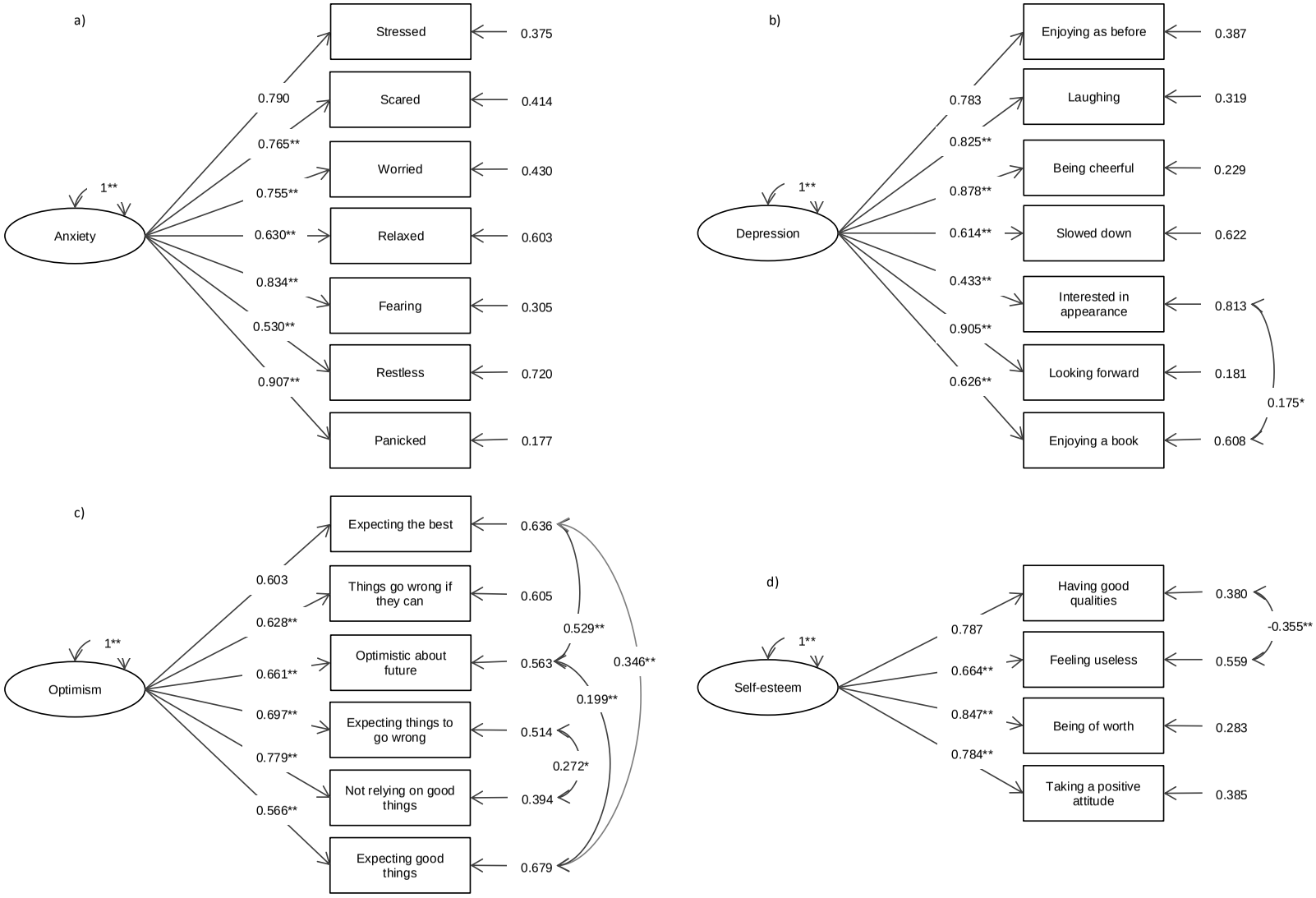
Supplementary Table 1 Continued

Variable	Present study before imputation (N=390)
Sex	
Female (%)	119 (30.51)
Male (%)	271 (69.49)
Missing (%)	0 (0)
Language of correspondence	
German (%)	299 (76.67)
French (%)	78 (20.00)
Italian (%)	11 (2.82)
Other (%)	2 (0.51)
Missing (%)	0 (0)

Abbreviations: ADL, activities of daily living; AIS, American Spinal Injury Association Impairment Scale; SCI, spinal cord injury; SwiSCI, Swiss Spinal Cord Injury Cohort Study; NA, not applicable.

Supplementary Table 2 Observed analysis relevant variance-covariance matrix (N=390)

Variable	1.	2.	3.	4.	5.	6.	7.	8.	9.	10.	11.	12.	13.	14.	15.	16.	17.	18.	19.	20.	21.	22.	23.	24.	25.	26.	27.	28.	29.	30.	31.	32.	33.	34.	35.
1. Age at SCI diagnosis	0.25																																		
2. Sex	0.00	0.21																																	
3. Level of injury	-0.02	0.02	0.24																																
4. Severity of injury	0.03	0.02	-0.02	0.14																															
5. Bowl function	-0.01	-0.02	0.03	-0.08	0.25																														
6. Cardiovascular function	0.05	0.00	0.02	0.02	-0.02	0.17																													
7. Pain	0.01	0.01	-0.03	0.02	0.00	0.02	0.23																												
8. Pulmonary function	0.02	0.00	-0.01	0.01	0.00	0.03	0.01	0.09																											
9. Skin function	0.02	0.00	0.00	-0.03	0.03	0.02	0.00	0.01	0.10																										
10. Urinary function	-0.01	-0.01	0.01	-0.03	0.06	0.01	-0.01	0.00	0.03	0.19																									
11. Stressed											1.00																								
12. Scared											0.55	1.00																							
13. Worried											0.64	0.57	1.00																						
14. Relaxed											0.53	0.44	0.43	1.00																					
15. Fearing											0.61	0.69	0.62	0.53	1.00																				
16. Restless											0.46	0.39	0.39	0.41	0.36	1.00																			
17. Panicked											0.71	0.70	0.68	0.57	0.77	0.46	1.00																		
18. Enjoying as before																		1.00																	
19. Laughing																		0.68	1.00																
20. Being cheerful																		0.65	0.75	1.00															
21. Slowed down																		0.46	0.43	0.53	1.00														
22. Interested in appearance																		0.42	0.33	0.36	0.22	1.00													
23. Looking forward																		0.73	0.72	0.79	0.62	0.38	1.00												
24. Enjoying a book																		0.39	0.54	0.59	0.43	0.39	0.56	1.00											
25. Expecting the best																									1.00										
26. Things go wrong																									0.39	1.00									
27. Optimistic about future																									0.71	0.40	1.00								
28. Expecting things to go wrong																									0.38	0.45	0.50	1.00							
29. Not relying on good things																									0.50	0.48	0.49	0.66	1.00						
30. Expecting good things																									0.57	0.36	0.50	0.38	0.45	1.00					
31. Having good qualities																															1.00				
32. Feeling useless																															0.36	1.00			
33. Being of worth																															0.69	0.51	1.00		
34. Taking positive attitude																															0.59	0.56	0.66	1.00	
35. Independence in performing activities of daily living											-1.59	-1.78	-1.56	-1.79	-1.42	0.17	-2.23	-2.69	-2.57	-2.34	-1.30	-1.70	-2.50	-0.99	2.48	1.95	2.48	2.19	1.91	1.32	1.03	3.47	1.92	1.24	127.01



Supplementary Figure 1 Completely standardized parameter estimates of the measurement models for (a) anxiety, (b) depression, (c) optimism and (d) self-esteem (N=390). Note: Squares indicate observable questionnaire items; Ellipses indicate latent factors; Single-headed arrows indicate direct effects including measurement errors; Double-headed arrows indicate correlations; *P<0.05; **P<0.01.

Supplementary Table 3 Residual correlation matrices of the final measurement models for the mental functions anxiety, depression, optimism and self-esteem (N=390)

Measurement model and item	1.	2.	3.	4.	5.	6.	7.	8.	9.	10.	11.	12.	13.	14.	15.	16.	17.	18.	19.	20.	21.	22.	23.	24.
Anxiety																								
1. Stressed	0.00																							
2. Scared	-0.06	0.00																						
3. Worried	0.04	-0.01	0.00																					
4. Relaxed	0.03	-0.04	-0.05	0.00																				
5. Fearing	-0.05	0.05	-0.01	0.00	0.00																			
6. Restless	0.04	-0.01	-0.01	0.08	-0.08	0.00																		
7. Panicked	-0.01	0.00	0.00	0.00	0.01	-0.02	0.00																	
Depression																								
8. Enjoying as before								0.00																
9. Laughing								0.04	0.00															
10. Being cheerful								-0.03	0.03	0.00														
11. Slowed down								-0.02	-0.08	-0.01	0.00													
12. Interested in appearance								0.08	-0.03	-0.02	-0.04	0.00												
13. Looking forward								0.02	-0.02	-0.01	0.07	-0.02	0.00											
14. Enjoying a book								-0.10	0.02	0.04	0.05	0.00	-0.01	0.00										
Optimism																								
15. Expecting the best															0.00									
16. Things go wrong if they can															0.01	0.00								
17. Optimistic about future															0.00	-0.02	0.00							
18. Expecting things to go wrong															-0.04	0.01	0.04	0.00						
19. Not relying on good things															0.03	-0.01	-0.02	0.00	0.00					
20. Expecting good things															0.00	0.01	0.00	-0.02	0.01	0.00				
Self-esteem																								
21. Having good qualities																					0.00			
22. Feeling useless																					0.00	0.00		
23. Being of worth																					0.02	-0.05	0.00	
24. Taking a positive attitude																					-0.03	0.04	0.00	0.00

Supplementary Table 4 Measurement invariance tests of the measurement models for aetiology, age, sex, level and severity of injury and language (German, French) groups

Measurement model and level of invariance	Invariant?	χ^2_M	df_M	Model comparison	
				χ^2_D	df_D
		Aetiology			
Anxiety					
Configural	Y	26.389	28		
Weak	Y	36.130	34	6.478	6
Depression					
Configural	Y	26.486	26		
Weak	Y	37.071	32	6.664	6
Optimism					
Configural[a]	Y	6.185	10		
Weak[a]	N	25.577	15	20.180**	5
Self-esteem					
Configural	N[c]	-	-		
Weak	-	-	-	-	-
		Age			
Anxiety					
Configural	Y	23.869	28		
Weak	Y	31.491	34	5.139	6
Depression					
Configural	Y	23.256	26		
Weak	Y	27.580	32	3.339	6
Optimism					
Configural	Y	6.065	10		
Weak	Y	12.881	15	6.922	5
Self-esteem					
Configural	Y	5.893	2		
Weak	Y	10.112	5	5.158	3
		Sex			
Anxiety					
Configural	Y	22.071	28		
Weak	Y	33.311	34	6.856	6
Depression					
Configural[a]	Y	20.912	26		
Weak[a]	Y	31.261	32	6.616	6
Optimism					
Configural	Y	5.830	10		
Weak	N	21.025	15	12.035*	5
Self-esteem					
Configural	Y	3.280	2		
Weak	Y	9.258	5	7.138	3
		Language			
Anxiety					
Configural	Y	19.520	28		
Weak	Y	39.290	34	9.605	6
Depression					
Configural	Y	24.813	26		
Weak	Y	29.799	32	4.688	6
Optimism					
Configural	Y	9.786	10		
Weak	N	26.125	15	11.930*	5
Self-esteem					
Configural	Y	4.239	2		
Weak	Y	11.820	5	6.806	3

Abbreviations: M, Model; D, Difference; Y, Yes; N, No.

Note: Configural, no constrains on parameter estimates across groups; Weak, factor loadings constrained to be equal across groups; [a]Collapsing of two response categories needed for one factor indicator due to missing observations; [b]Collapsing of two response categories needed for two factor indicators due to missing observations; [c]Pattern of factor loading not equal across groups in terms of significance (P<0.05); *P<0.05; **P<0.01.

Supplementary Table 4 Continued

Measurement model and level of invariance	Invariant?	χ^2_M	df_M	Model comparison	
				χ^2_D	df_D
		Level of injury			
Anxiety					
Configural	Y	34.231	28		
Weak	N	55.579	34	12.598*	6
Depression					
Configural	Y	29.557	26		
Weak	Y	39.726	32	6.565	6
Optimism					
Configural	Y	6.059	10		
Weak	Y	9.063	15	3.511	5
Self-esteem					
Configural	Y	4.464	2		
Weak	Y	7.138	5	4.011	3
		Severity of injury			
Anxiety					
Configural[b]	N[c]	-	-		
Weak	-	-	-	-	-
Depression					
Configural	Y	30.602	26		
Weak	N	74.565	32	15.219*	6
Optimism					
Configural	N[c]	-	-		
Weak	-	-	-	-	-
Self-esteem					
Configural	N[c]	-	-		
Weak	-	-	-	-	-

Abbreviations: M, Model; D, Difference; Y, Yes; N, No.
Note: Configural, no constrains on parameter estimates across groups; Weak, factor loadings constrained to be equal across groups; [a]Collapsing of two response categories needed for one factor indicator due to missing observations; [b]Collapsing of two response categories needed for two factor indicators due to missing observations; [c]Pattern of factor loading not equal across groups in terms of significance (P<0.05); *P<0.05; **P<0.01.

Supplementary Table 5 Residual correlation matrices of the structural models (N=390)

Structural model and item	1.	2.	3.	4.	5.	6.	7.	8.	9.	10.	11.	12.	13.	14.	15.	16.	17.	18.	19.	20.	21.	22.	23.	24.	25.	26.	27.	28.
Anxiety																												
1. Stressed	0.00																											
2. Scared	-0.05	0.00																										
3. Worried	0.04	0.00	0.00																									
4. Relaxed	0.03	-0.04	-0.05	0.00																								
5. Fearing	-0.05	0.05	0.00	0.00	0.00																							
6. Restless	0.05	-0.01	-0.02	0.09	-0.07	0.00																						
7. Panicked	-0.01	0.00	0.01	-0.01	0.01	-0.01	0.00																					
8. Independence in performing activities of daily living	0.02	-0.02	-0.04	0.00	0.00	0.07	-0.02	0.00																				
Depression																												
9. Enjoying as before									0.00																			
10. Laughing									0.03	0.00																		
11. Being cheerful									-0.03	0.04	0.00																	
12. Slowed down									-0.02	-0.07	-0.02	0.00																
13. Interested in appearance									0.08	-0.06	-0.01	-0.04	0.00															
14. Looking forward									0.02	-0.03	-0.01	0.07	-0.02	0.00														
15. Enjoying a book									-0.10	0.03	0.03	0.05	0.00	0.00	0.00													
16. Independence in performing activities of daily living									-0.02	0.03	-0.01	-0.01	-0.02	0.00	0.03	0.00												
Optimism																												
17. Expecting the best																	0.00											
18. Things go wrong if they can																	0.00	0.00										
19. Optimistic about future																	0.00	0.00	0.00									
20. Expecting things to go wrong																	0.00	-0.03	0.01	0.00								
21. Not relying on good things																	-0.04	0.04	-0.01	0.01	0.00							
22. Expecting good things																	0.02	-0.02	0.00	0.01	0.00	0.00						
23. Independence in performing activities of daily living																	0.03	-0.01	-0.02	0.01	0.00	-0.01	0.00					
Self-esteem																												
24. Having good qualities																								0.00				
25. Feeling useless																								0.00	0.00			
26. Being of worth																								0.03	-0.06	0.00		
27. Taking a positive attitude																								-0.03	0.03	0.00	0.00	
28. Independence in performing activities of daily living																								-0.08	0.12	-0.03	0.00	0.00

Note: The structural models were set up conditional on the variables of the body structures, body functions and personal factors (exogenous covariates). Therefore, the model-implied residual correlation matrices include the variables of the respective mental functions and activities, only.

APPENDIX B
Supplementary material study 2

Supplemental Appendix S1

Within this technical appendix, we describe the latent process mixed model (LPMM) analysis procedure in full detail and present the R syntax of the final LPMM.

A) LPMM analysis procedure

Following Proust-Lima et al.[1] the analysis included two steps:

(1) A set of three LPMMs with different parameterized link functions – linear function and quadratic I-splines functions with two or three knots at percentiles - were fitted to identify the best-fitting link function able to account for non-normal and bounded longitudinal outcomes.[1]

Model specification information: All models followed equal specifications with respect to the number of latent classes (one), the effect for time of assessment (linear random effects including random intercept and slope) and correlated differences in the change of the outcome (unstructured random effects variance-covariance matrix).

(2) Two sets of six LPMMs, each with an increasing number of latent classes (one to six), were fitted to identify the number of classes of functioning trajectories.

Model specification information: The difference between the set of models was the specification of the random effects variance-covariance matrix, which was set to be class-invariant (fixed across classes) in the first, and class-specific (proportionally varying across classes) in the second set of models. The common settings of both model sets included linear random effects for time of assessment, unstructured random effects variance-covariance matrix, class-specific patterns of change on the outcome (linear mixture effects for time of assessment), and the best-fitting link function from step one.

In both steps, all fitted models correspond to unconditional models, i.e. no covariates were integrated.

B) R syntax of the final LPMM

The used R syntax for the estimation of the final LPMM was based on the R Package *lcmm version 1.8.1*[1] and looks as follows:

```
m4spl2q <- gridsearch(rep = 100, maxiter = 50, minit = m1spl2q,
           lcmm(SCIM_rasch~days_SCIM_adm, random=~days_SCIM_adm, mixture=~days_SCIM_adm,
           subject='id_swisci_num', ng=4, nwg = T, idiag = F, data=data_long, link='2-quant-splines'))
```

m4spl2q R object where results of the final model estimation are stored

gridsearch(..) R function to perform a grid of random initial values for model estimation. Used options are:

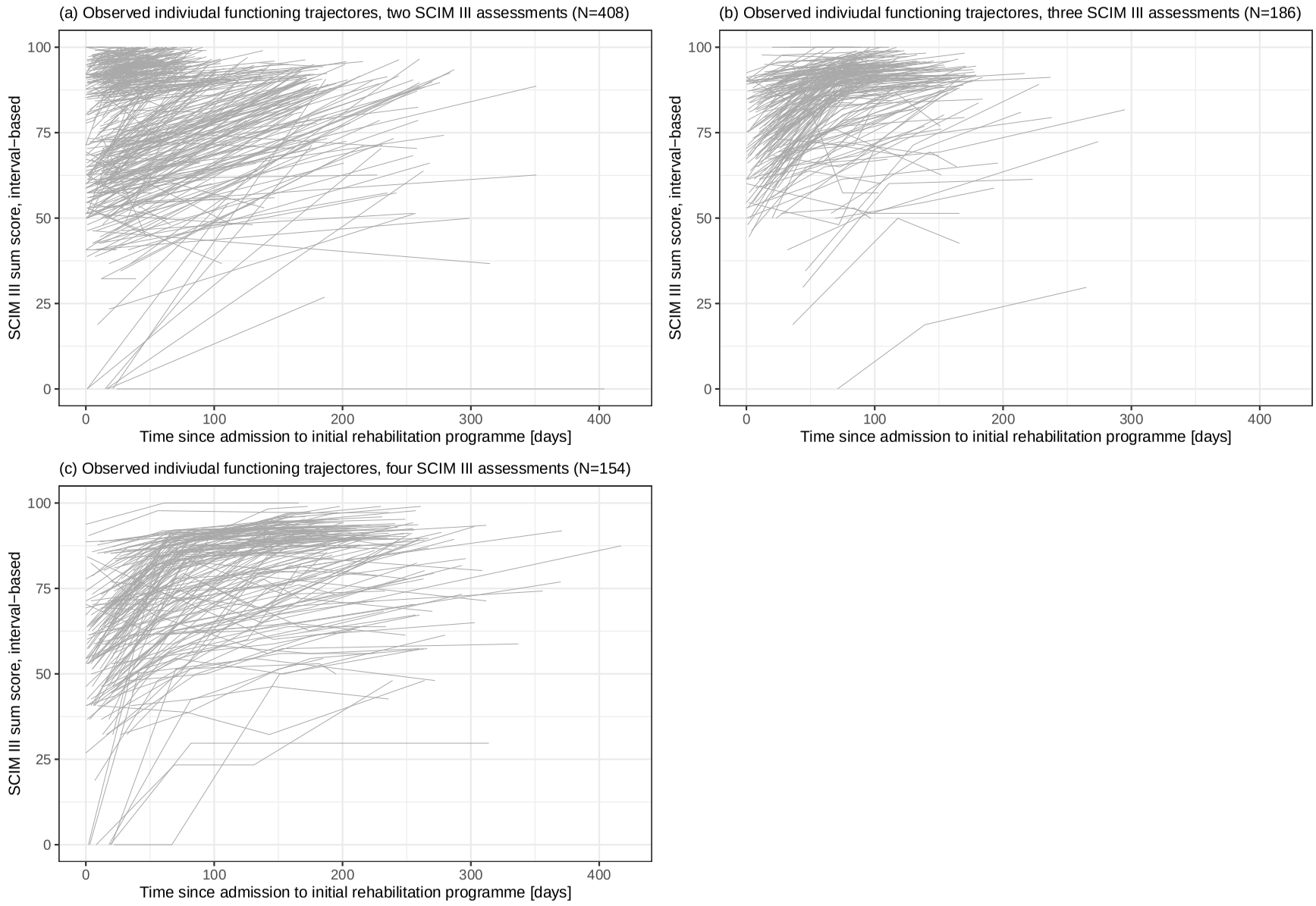
- *rep* Number of random starting values departures, which is set to *100*.
- *maxiter* Number of iterations, which is set to *50*.
- *minit* Random starting values, which is generated based on a previously estimated model (*m1spl2q*) corresponding to *m4spl2q* with one class of functioning trajectories only.

lcmm(..) R function to estimate the final LPMM model. Used options are:

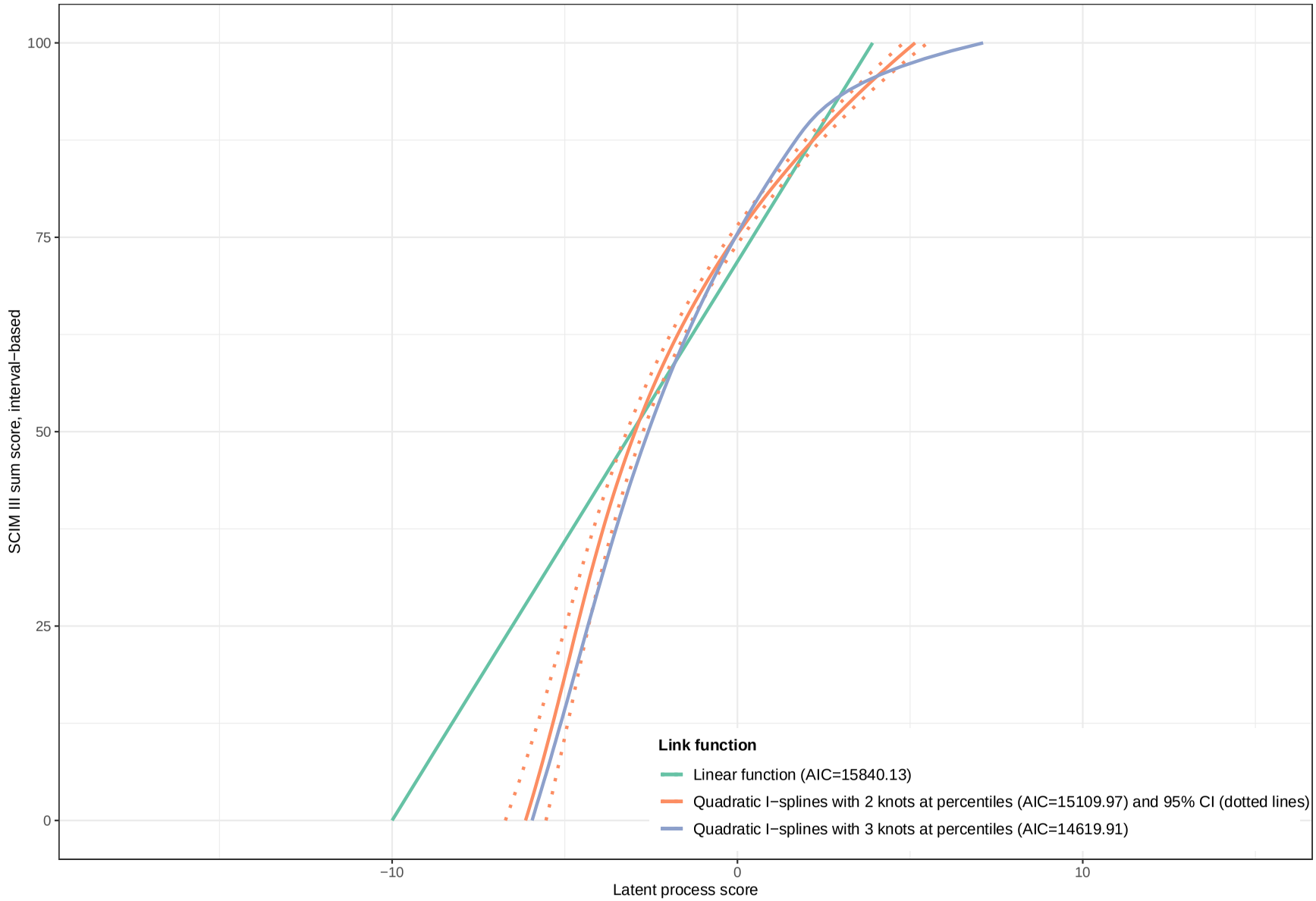
- *SCIM_rasch~days_SCIM_adm* Fixed effects within the estimated model, which are set to linear fixed effects for the time of assessment variable (*days_SCIM_adm*) on the repeated functioning measures (*SCIM_rasch*).
- *random* Random effects within the estimated model, which are set to linear random effects including random intercept and slope for the time of assessment variable (*days_SCIM_adm*).
- *mixture* Mixture effects within the estimated model, which are set to linear mixture effects for the time of assessment variable (*days_SCIM_adm*).
- *subject* Participant identification number, which is set to the respective variable within the prepared SwiSCI Inception Cohort data set (*id_swisci_num*).
- *ng* Number of classes of functioning trajectories used for model estimations, which is set to *4* for the final model.
- *nwg* Setting for the random effects variance-covariance matrix, which was specified to be class-specific (TRUE), i.e. allowing the between-participants variability in trajectories to be different across classes.
- *idiag* Setting for the random effects variance-covariance matrix, which was specified to be unstructured (*FALSE*), i.e. allowing correlated random effects.
- *data* Data set used for model estimations (needs to be in long format), which is set to the prepared SwiSCI Inception Cohort data set (*data_long*).
- *link* Parametrized link function used for model estimation, which is set to the quadratic I-splines functions with two knots at percentiles (*2-quant-splines*).

[1]Proust-Lima C, Philipps V, Liquet B. Estimation of Extended Mixed Models Using Latent Classes and Latent Processes: The R Package lcmm. Journal of Statistical Software 2017;78(2):1-56.

Supplemental Figure S1

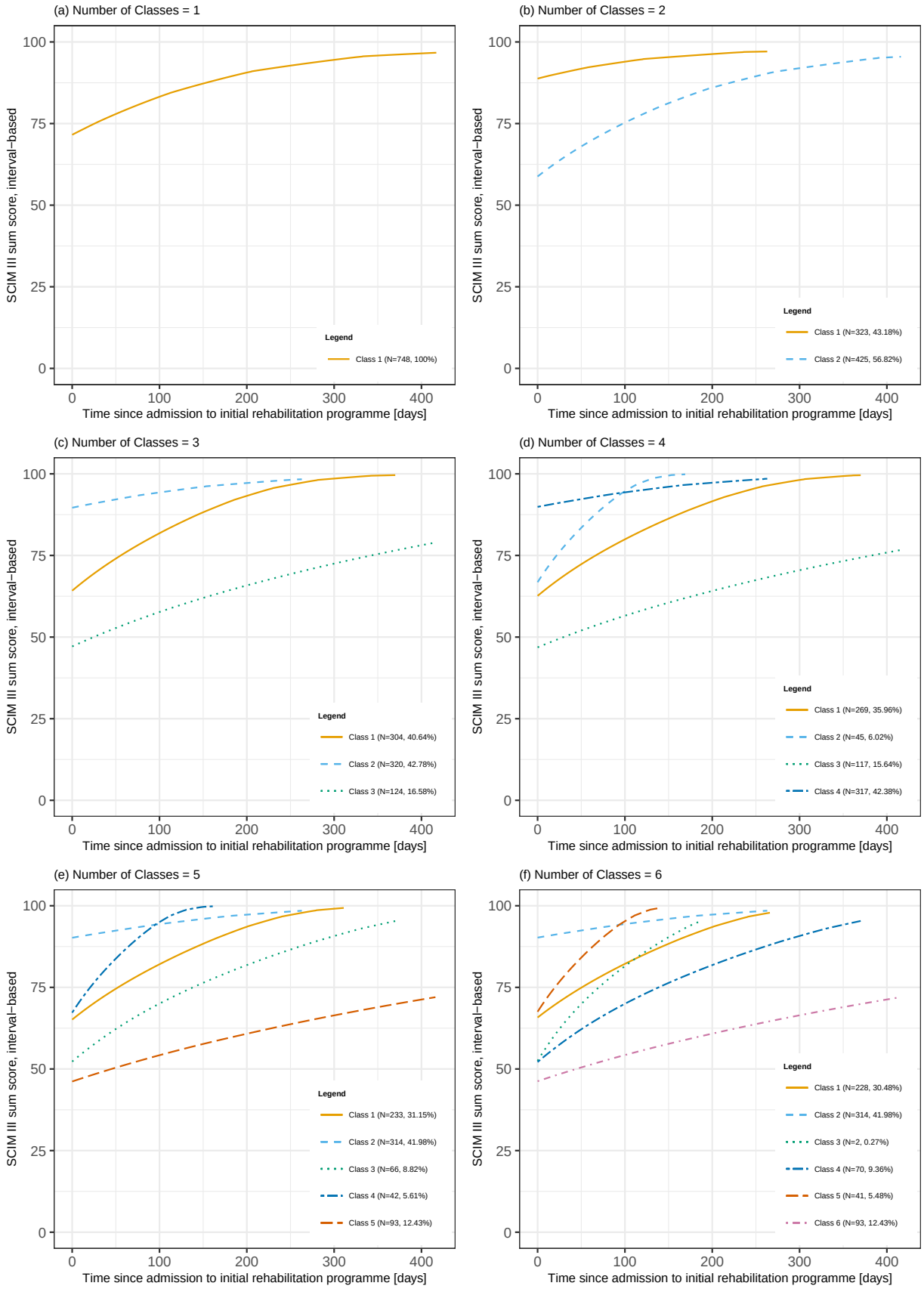


Supplemental Figure S2 Estimated parameterized link functions

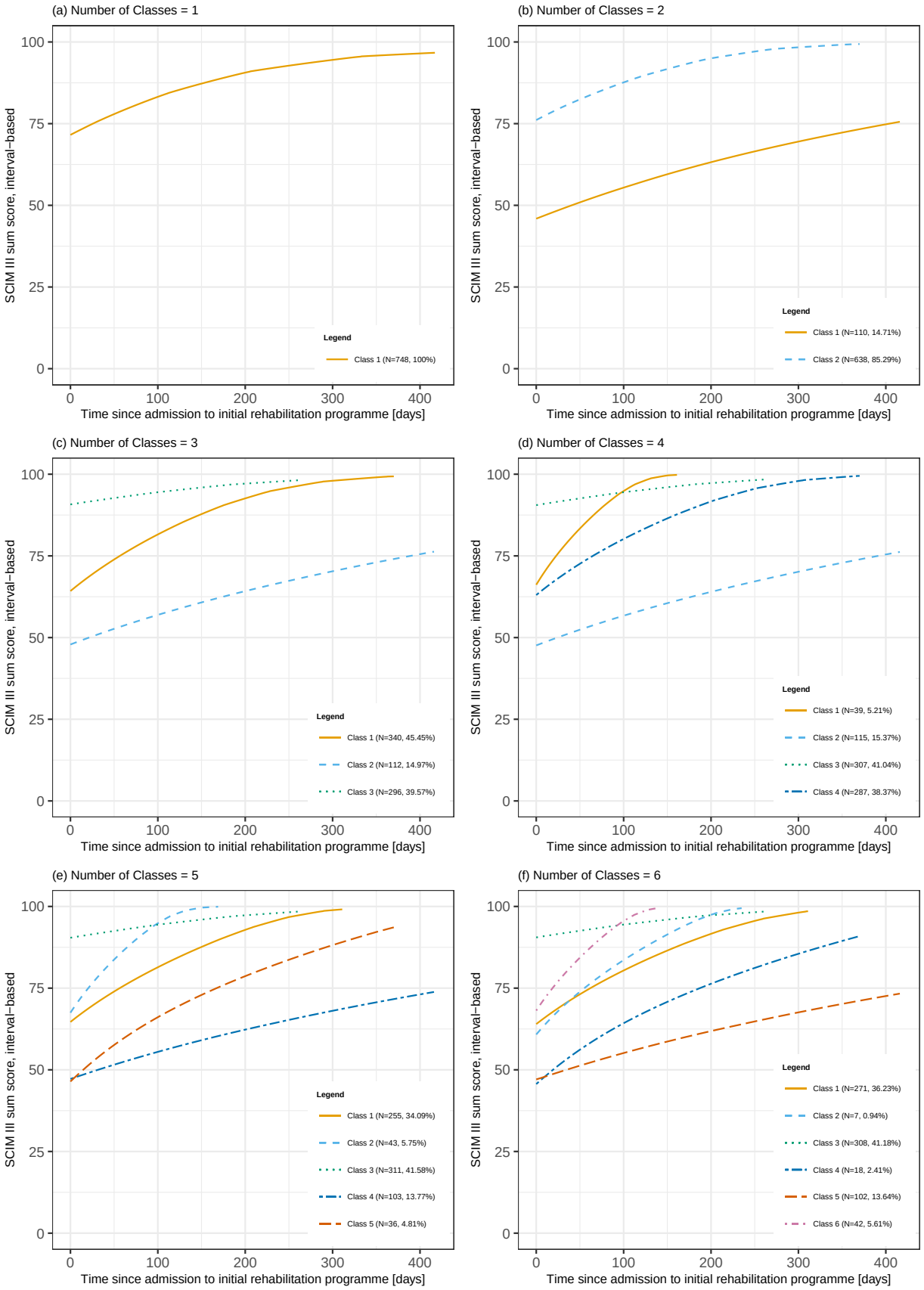


Supplemental Figure S3 Estimated parameterized link functions (sensitivity analysis based on participants with three or four SCIM III assessments)

Supplemental Figure S4 Class−specific mean predicted trajectories of the LPMMs with class−invariant random effects variance−covariance matrix



Supplemental Figure S5 Class−specific mean predicted trajectories of the LPMMs with class−specific random effects variance−covariance matrix



Supplemental Table S1 Estimated parameters and posterior classification table for the best-fitting latent process mixed model

A) Fixed effects in the class-membership model (Ref=class 4)

Parameter	Coefficient	SE	P-value
Intercept class 1	-1.983	0.332	0.000
Intercept class 2	-0.945	0.178	0.000
Intercept class 3	0.008	0.111	0.943

Note. SE, standard error; class 1, early functioning improvement class; class 2, slow functioning improvement class; class 3, stable high functioning class.

B) Fixed effects of the longitudinal model

Parameter	Coefficient	SE	P-value
Intercept class 1 (not estimated)	0.000	-	-
Intercept class 2	-1.752	0.399	0.000
Intercept class 3	4.244	0.383	0.000
Intercept class 4	-0.318	0.393	0.419
Time of assessment Class 1	0.055	0.005	0.000
Time of assessment Class 2	0.008	0.001	0.000
Time of assessment Class 3	0.010	0.001	0.000
Time of assessment Class 4	0.025	0.001	0.000

Note. SE, standard error; class 1, early functioning improvement class; class 2, slow functioning improvement class; class 3, stable high functioning class; class 4, moderate functioning improvement class.

C) Variance-covariance matrix of the random effects for class 4

	Intercept	Time of assessment
Intercept	1.12249	
Time of assessment	0.00228	0.00001

Note. Class 4, moderate functioning improvement class.

D) Proportional coefficients for variance-covariance matrix of the random effects

	Coefficient	SE
Class 1	0.801	0.259
Class 2	0.933	0.147
Class 3	0.680	0.104
Residual SE (not estimated)	1	-

Note. SE, standard error; class 1, early functioning improvement class; class 2, slow functioning improvement class; class 3, stable high functioning class.

E) Parameters of the link function (quadratic I-splines with knots 0 and 100)

Parameter	Coefficient	SE	P-value
I-splines1	-4.305	0.429	0.000
I-splines2	1.188	0.102	0.000
I-splines3	-0.000	0.015	0.992
I-splines4	3.084	0.043	0.000

Note. SE, standard error.

Supplemental Table S2 Sensitivity analysis of multinomial logistic regression of class membership for best-fitting latent process mixed model (N=546).

	Estimates (95% CI)		
	Stable high functioning class (Ref. = Slow functioning improvement class)	Early functioning improvement class (Ref. = Slow functioning improvement class)	Moderate functioning improvement class (Ref. = Slow functioning improvement class)
Intercept	2.47** (0.60, 4.34)	-2.27 (-5.59, 1.06)	2.31** (0.64, 3.97)
Age	-0.06*** (-0.08, -0.04)	-0.04* (-0.07, -0.01)	-0.02* (-0.05, -0.00)
Sex=Female (Ref=Male)	-0.38 (-1.05, 0.29)	0.02 (-0.98, 1.01)	-0.58 (-1.21, 0.04)
Language of correspondence=French (Ref=German)[a]	-0.59 (-1.40, 0.23)	-0.73 (-1.98, 0.52)	-0.07 (-0.81, 0.66)
Aetiology=Traumatic (Ref=Non-traumatic)	-0.67 (-1.48, 0.15)	0.74 (-0.50, 1.97)	-1.01** (-1.77, -0.25)
Level of injury=Paraplegia (Ref.=Tetraplegia)[b]	1.69*** (1.00, 2.38)	1.68** (0.67, 2.69)	1.32*** (0.69, 1.96)
Severity of injury=Incomplete (Ref.=Complete)[c]	3.28*** (2.36, 4.20)	3.77*** (1.63, 5.91)	0.93** (0.25, 1.60)
Comorbidities before SCI=Yes (Ref=No)	0.08 (-0.89, 1.05)	0.07 (-1.33, 1.47)	-0.10 (-0.98, 0.77)
Cardiovascular conditions and complications=Yes (Ref=No)	0.09 (-0.61, 0.79)	0.77 (-0.28, 1.82)	0.04 (-0.59, 0.68)
Pulmonary conditions and complications=Yes (Ref=No)	-1.13** (-1.83, -0.42)	-0.87 (-1.92, 0.18)	-0.42 (-1.04, 0.20)
Insurance type=Accident (Ref.=Health)[d]	-0.49 (-1.42, 0.44)	-0.02 (-1.33, 1.29)	0.58 (-0.24, 1.40)
Ward type=Private (Ref.=Basic)[e]	-0.69* (-1.36, -0.03)	-1.61** (-2.72, -0.51)	-0.28 (-0.88, 0.32)
Ventilation assistance=Yes (Ref=No)	-2.68*** (-4.06, -1.31)	-1.25 (-2.97, 0.46)	-0.92* (-1.69, -0.14)

NOTE. CI, confidence interval; SCI, spinal cord injury; [a]participants with observations in the response categories "Italian" or "other" were excluded from the analysis; [b]participants with observations in the response category "intact" were excluded from the analysis; [c]participants with observations in the response category "normal" were excluded from the analysis; [d]participants with observations in the response categories "disability" or "self-pay" were excluded from the analysis; [e]Response categories "semi-private" and "private" were collapsed; *p<0.05; **p<0.01; ***p<0.001.

APPENDIX C
Supplementary material study 3

Supplemental Table 1 Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) Checklist.

SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE #
TITLE			
Title	1	Identify the report as a scoping review.	Title
ABSTRACT			
Structured summary	2	Provide a structured summary that includes (as applicable): background, objectives, eligibility criteria, sources of evidence, charting methods, results, and conclusions that relate to the review questions and objectives.	Abstract
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known. Explain why the review questions/objectives lend themselves to a scoping review approach.	Section 1
Objectives	4	Provide an explicit statement of the questions and objectives being addressed with reference to their key elements (e.g., population or participants, concepts, and context) or other relevant key elements used to conceptualize the review questions and/or objectives.	Section 1, paragraph 3
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists; state if and where it can be accessed (e.g., a Web address); and if available, provide registration information, including the registration number.	Section 2, paragraph 1
Eligibility criteria	6	Specify characteristics of the sources of evidence used as eligibility criteria (e.g., years considered, language, and publication status), and provide a rationale.	Section 2.2, paragraph 1; Table 1
Information sources*	7	Describe all information sources in the search (e.g., databases with dates of coverage and contact with authors to identify additional sources), as well as the date the most recent search was executed.	Section 2.1
Search	8	Present the full electronic search strategy for at least 1 database, including any limits used, such that it could be repeated.	Supplemental Table 2
Selection of sources of evidence†	9	State the process for selecting sources of evidence (i.e., screening and eligibility) included in the scoping review.	Section 2.2, paragraphs 2-3
Data charting process‡	10	Describe the methods of charting data from the included sources of evidence (e.g., calibrated forms or forms that have been tested by the team before their use, and whether data charting was done independently or in duplicate) and any processes for obtaining and confirming data from investigators.	Section 2.3
Data items	11	List and define all variables for which data were sought and any assumptions and simplifications made.	Supplemental Table 3
Critical appraisal of individual sources of evidence§	12	If done, provide a rationale for conducting a critical appraisal of included sources of evidence; describe the methods used and how this information was used in any data synthesis (if appropriate).	Not applicable
Synthesis of results	13	Describe the methods of handling and summarizing the data that were charted.	Section 2.3, paragraphs 2-3
RESULTS			
Selection of sources of evidence	14	Give numbers of sources of evidence screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally using a flow diagram.	Figure 1
Characteristics of sources of evidence	15	For each source of evidence, present characteristics for which data were charted and provide the citations.	Section 3.1; Section 3.2
Critical appraisal within sources of evidence	16	If done, present data on critical appraisal of included sources of evidence (see item 12).	Not applicable
Results of individual sources of evidence	17	For each included source of evidence, present the relevant data that were charted that relate to the review questions and objectives.	Tables 2 & 3
Synthesis of results	18	Summarize and/or present the charting results as they relate to the review questions and objectives.	Section 3.3

DISCUSSION			
Summary of evidence	19	Summarize the main results (including an overview of concepts, themes, and types of evidence available), link to the review questions and objectives, and consider the relevance to key groups.	Section 4, paragraphs 1-4
Limitations	20	Discuss the limitations of the scoping review process.	Section 4.1
Conclusions	21	Provide a general interpretation of the results with respect to the review questions and objectives, as well as potential implications and/or next steps.	Section 5
FUNDING			
Funding	22	Describe sources of funding for the included sources of evidence, as well as sources of funding for the scoping review. Describe the role of the funders of the scoping review.	Section "Funding"

JBI = Joanna Briggs Institute; PRISMA-ScR = Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews.

* Where *sources of evidence* (see second footnote) are compiled from, such as bibliographic databases, social media platforms, and Web sites.

† A more inclusive/heterogeneous term used to account for the different types of evidence or data sources (e.g., quantitative and/or qualitative research, expert opinion, and policy documents) that may be eligible in a scoping review as opposed to only studies. This is not to be confused with *information sources* (see first footnote).

‡ The frameworks by Arksey and O'Malley (6) and Levac and colleagues (7) and the JBI guidance (4, 5) refer to the process of data extraction in a scoping review as data charting.

§ The process of systematically examining research evidence to assess its validity, results, and relevance before using it to inform a decision. This term is used for items 12 and 19 instead of "risk of bias" (which is more applicable to systematic reviews of interventions) to include and acknowledge the various sources of evidence that may be used in a scoping review (e.g., quantitative and/or qualitative research, expert opinion, and policy document).

From: Tricco AC, Lillie E, Zarin W, O'Brien KK, Colquhoun H, Levac D, et al. PRISMA Extension for Scoping Reviews (PRISMAScR): Checklist and Explanation. Ann Intern Med. 2018;169:467–473. doi: 10.7326/M18-0850.

Supplemental Table 2 Used search strategy per data base (the search was performed on the October 12th 2020).

Database	Search strategy
PubMed¶	(predict*[tiab] OR "predictive value of tests"[mh] OR score[tiab] OR scores[tiab] OR scoring system[tiab] OR scoring systems[tiab] OR observ*[tiab] OR "observer variation"[mh]) AND ((diagnos*[tiab] AND model*[tiab]) OR (diagnos*[tiab] AND outcome*[tiab]) OR (diagnos*[tiab] AND validat*[tiab]) OR (diagnos*[tiab] AND risk*[tiab]) OR (predict*[tiab] AND model*[tiab]) OR (predict*[tiab] AND accura*[tiab]) OR (prognos*[tiab] AND model*[tiab]) OR (prognos*[tiab] AND accura*[tiab]) OR (prognos*[tiab] AND outcome*[tiab]) OR (prognos*[tiab] AND rule*[tiab]) OR (prognos*[tiab] AND score*[tiab]) OR (prognos*[tiab] AND validat*[tiab]) OR (prognos*[tiab] AND value*[tiab]) OR (prognos*[tiab] AND risk*[tiab]) OR (clinical[tiab] AND predict*[tiab]) OR (clinical[tiab] AND model*[tiab]) OR (clinical[tiab] AND score*[tiab]) OR (decision[tiab] AND rule*[tiab]) OR (derive*[tiab] AND validat*[tiab]) OR (diagnos*[tiab] AND accura*[tiab]) OR (diagnos*[tiab] AND rule*[tiab]) OR (diagnos*[tiab] AND score*[tiab]) OR (diagnos*[tiab] AND value*[tiab]) OR (predict*[tiab] AND outcome*[tiab]) OR (predict*[tiab] AND rule*[tiab]) OR (predict*[tiab] AND score*[tiab]) OR (predict*[tiab] AND validat*[tiab]) OR (predict*[tiab] AND value*[tiab]) OR (risk*[tiab] AND assessment*[tiab]) OR (risk[tiab] AND score*[tiab]) OR (sensitivity[tiab] AND specificity[tiab]) OR (symptoms[tiab] AND signs[tiab]) OR (validat*[tiab] AND decision*[tiab]) OR (validat*[tiab] AND rule*[tiab]) OR (validat*[tiab] AND score*[tiab]) OR (predict*[tiab] AND risk*[tiab])) AND (("spinal cord injuries"[mh] OR "spinal cord diseases"[mh] OR "paraplegia"[mh] OR "quadriplegia"[mh] OR "spinal injuries"[mh]) OR (spinal cord trauma*[tiab] OR spinal cord injur*[tiab] OR spinal cord transection*[tiab] OR spinal cord laceration*[tiab] OR spinal cord contusion*[tiab] OR spinal cord disease*[tiab] OR spinal cord disorder*[tiab] OR myelopath*[tiab] OR paraplegia*[tiab] OR quadriplegia*[tiab] OR tetraplegia*[tiab] OR quadripares*[tiab] OR spinal injur*[tiab]))

	AND (("Assessment of Life Habits" OR "LIFE-H") OR ("Barthel Index" OR "BI") OR ("Canadian Occupational Performance Measure" OR "COPM") OR ("Community Integration Questionnaire" OR "CIQ") OR ("Craig Handicap Assessment and Reporting Technique" OR "CHART") OR ("Frenchay Activities Index" OR "FAI") OR ("Functional Independence Measure" OR "FIM") OR ("ICF-Measure of Participation and Activities Screener" OR "IMPACT-S") OR ("Needs Assessment Checklist" OR "NAC") OR ("Nottingham Health Profile" OR "NHP") OR ("Participation Survey of Mobility Limited People" OR "Participation Survey/Mobility" OR "PARTS/M") OR ("Physical Activity Recall Assessment for People with Spinal Cord Injury" OR "PARA-SCI") OR ("Physical Activity Scale for Individuals with Physical Disabilities" OR "PASIPD") OR ("Quadriplegia Index of Function" OR "QIF") OR ("Reintegration to Normal Living Index" OR "RNL" OR "RNLI") OR ("Short Form" OR "SF" OR "SF36" OR "SF12") OR ("Sickness Impact Profile" OR "SIP" OR "SIP68") OR ("Spinal Cord Ability Ruler" OR "SCAR") OR ("Spinal Cord Independence Measure" OR "SCIM") OR ("Spinal Cord Injury-Functional Index" OR "SCI-FI") OR ("Spinal Cord Injury Lifestyle Scale" OR "SCILS") OR ("Spinal Functional Abilities Scale" OR "S-FAS") OR ("Utrecht Scale for Evaluation of Rehabilitation-Participation" OR "USER-P" OR "USER-Participation") OR ("Work Rehabilitation Questionnaire" OR "WORQ") OR ("World Health Organization Disability Assessment Schedule" OR "WHODAS"))
EBSCOhost CINAHL Complete¶	((TI predict* OR AB predict*) OR MH "predictive value of tests+" OR (TI score OR AB score) OR (TI scores OR AB scores) OR (TI scoring system OR AB scoring system) OR (TI scoring systems OR AB scoring systems) OR (TI observ* OR AB observ*) OR MH "observer bias+") AND (((TI diagnos* OR AB diagnos*) AND (TI model* OR AB model*)) OR ((TI diagnos* OR AB diagnos*) AND (TI outcome* OR AB outcome*)) OR ((TI diagnos* OR AB diagnos*) AND (TI validat* OR AB validat*)) OR ((TI diagnos* OR AB diagnos*) AND (TI risk* OR AB risk*)) OR ((TI predict* OR AB predict*) AND (TI model* OR AB model*)) OR ((TI predict* OR AB predict*) AND (TI accura* OR AB accura*)) OR ((TI prognos* OR AB prognos*) AND (TI model* OR AB model*)) OR ((TI prognos* OR AB prognos*) AND (TI accura* OR AB accura*)) OR ((TI prognos* OR AB prognos*) AND (TI outcome* OR AB outcome*)) OR ((TI prognos* OR AB prognos*) AND (TI rule* OR AB rule*)) OR ((TI prognos* OR AB prognos*) AND (TI score* OR AB score*)) OR ((TI prognos* OR AB prognos*) AND (TI validat* OR AB validat*)) OR ((TI prognos* OR AB prognos*) AND (TI value* OR AB value*)) OR ((TI prognos* OR AB prognos*) AND (TI risk* OR AB risk*)) OR ((TI clinical OR AB clinical) AND (TI predict* OR AB predict*)) OR ((TI clinical OR AB clinical) AND (TI model* OR AB model*)) OR ((TI clinical OR AB clinical) AND (TI score* OR AB score*)) OR ((TI decision OR AB decision) AND (TI rule* OR AB rule*)) OR ((TI derive* OR AB derive*) AND (TI validat* OR AB validat*)) OR ((TI diagnos* OR AB diagnos*) AND (TI accura* OR AB accura*)) OR ((TI diagnos* OR AB diagnos*) AND (TI rule* OR AB rule*)) OR ((TI diagnos* OR AB diagnos*) AND (TI score* OR AB score*)) OR ((TI diagnos* OR AB diagnos*) AND (TI value* OR AB value*)) OR ((TI predict* OR AB predict*) AND (TI outcome* OR AB outcome*)) OR ((TI predict* OR AB predict*) AND (TI rule* OR AB rule*)) OR ((TI predict* OR AB predict*) AND (TI score* OR AB score*)) OR ((TI predict* OR AB predict*) AND (TI validat* OR AB validat*)) OR ((TI predict* OR AB predict*) AND (TI value* OR AB value*)) OR ((TI risk* OR AB risk*) AND (TI assessment* OR AB assessment*)) OR ((TI risk OR AB risk) AND (TI score* OR AB score*)) OR ((TI sensitivity OR AB sensitivity) AND (TI specificity OR AB specificity)) OR

	((TI symptoms OR AB symptoms) AND (TI signs OR AB signs)) OR ((TI validat* OR AB validat*) AND (TI decision* OR AB decision*)) OR ((TI validat* OR AB validat*) AND (TI rule* OR AB rule*)) OR ((TI validat* OR AB validat*) AND (TI score* OR AB score*)) OR ((TI predict* OR AB predict*) AND (TI risk* OR AB risk*))) AND ((MH "spinal cord injuries+" OR MH "spinal cord diseases+" OR MH "paraplegia+" OR MH "quadriplegia+" OR MH "spinal injuries+") OR ((TI spinal cord trauma* OR AB spinal cord trauma*) OR (TI spinal cord injur* OR AB spinal cord injur*) OR (TI spinal cord transection* OR AB spinal cord transection*) OR (TI spinal cord laceration* OR AB spinal cord laceration*) OR (TI spinal cord contusion* OR AB spinal cord contusion*) OR (TI spinal cord disease* OR AB spinal cord disease*) OR (TI spinal cord disorder* OR AB spinal cord disorder*) OR (TI myelopath* OR AB myelopath*) OR (TI paraplegia* OR AB paraplegia*) OR (TI quadriplegia* OR AB quadriplegia*) OR (TI tetraplegia* OR AB tetraplegia*) OR (TI quadripares* OR AB quadripares*) OR (TI spinal injur* OR AB spinal injur*))) AND (("Assessment of Life Habits" OR "LIFE-H") OR ("Barthel Index" OR "BI") OR ("Canadian Occupational Performance Measure" OR "COPM") OR ("Community Integration Questionnaire" OR "CIQ") OR ("Craig Handicap Assessment and Reporting Technique" OR "CHART") OR ("Frenchay Activities Index" OR "FAI") OR ("Functional Independence Measure" OR "FIM") OR ("ICF-Measure of Participation and Activities Screener" OR "IMPACT-S") OR ("Needs Assessment Checklist" OR "NAC") OR ("Nottingham Health Profile" OR "NHP") OR ("Participation Survey of Mobility Limited People" OR "Participation Survey/Mobility" OR "PARTS/M") OR ("Physical Activity Recall Assessment for People with Spinal Cord Injury" OR "PARA-SCI") OR ("Physical Activity Scale for Individuals with Physical Disabilities" OR "PASIPD") OR ("Quadriplegia Index of Function" OR "QIF") OR ("Reintegration to Normal Living Index" OR "RNL" OR "RNLI") OR ("Short Form" OR "SF" OR "SF36" OR "SF12") OR ("Sickness Impact Profile" OR "SIP" OR "SIP68") OR ("Spinal Cord Ability Ruler" OR "SCAR") OR ("Spinal Cord Independence Measure" OR "SCIM") OR ("Spinal Cord Injury-Functional Index" OR "SCI-FI") OR ("Spinal Cord Injury Lifestyle Scale" OR "SCILS") OR ("Spinal Functional Abilities Scale" OR "S-FAS") OR ("Utrecht Scale for Evaluation of Rehabilitation-Participation" OR "USER-P" OR "USER-Participation") OR ("Work Rehabilitation Questionnaire" OR "WORQ") OR ("World Health Organization Disability Assessment Schedule" OR "WHODAS"))
IEEE Xplore†	(("Document Title":predict* OR "Abstract":predict*) OR "Index Terms":"predictive value of tests" OR ("Document Title":score OR "Abstract":score) OR ("Document Title":scoring system OR "Abstract":scoring system) OR ("Document Title":observ* OR "Abstract":observ*) OR "Index Terms":"observer variation") AND (("Index Terms":"spinal cord injuries" OR "Index Terms":"spinal cord diseases" OR "Index Terms":"paraplegia" OR "Index Terms":"quadriplegia" OR "Index Terms":"spinal injuries") OR (("Document Title":spinal cord OR "Abstract":spinal cord) OR ("Document Title":myelopathy OR "Abstract":myelopathy) OR ("Document Title":paraplegia OR "Abstract":paraplegia) OR ("Document Title":quadriplegia OR "Abstract":quadriplegia) OR

	("Document Title":tetraplegia OR "Abstract":tetraplegia) OR ("Document Title":quadriparesis OR "Abstract":quadriparesis) OR ("Document Title":spinal injury OR "Abstract":spinal injury)))

Note. ¶ Language was manually set to English and German; † No language settings performed, limited number of allowed keywords and wildcards per search.

Color legend. Blue: Haynes Broad Search Strategy for prediction studies[1], available on PubMed via the search filters for "Clinical Queries" (broad "Clinical Prediction Guides" filter); Purple: Teljeur/Murphy Inclusion Filter[2], adapted by the authors of this study; Green: Index terms and keywords for spinal cord injury; Orange: Relevant outcome measures able to assess the lived experience of health in persons with spinal cord injury as operationalized by functioning

[1] Wong SS, Wilczynski NL, Haynes RB, Ramkissoonsingh R, Hedges T. Developing optimal search strategies for detecting sound clinical prediction studies in MEDLINE. AMIA Annu Symp Proc 2003:728-32.

[2] Keogh C, Wallace E, O'Brien KK, Murphy PJ, Teljeur C, McGrath B et al. Optimized retrieval of primary care clinical prediction rules from MEDLINE to establish a Web-based register. J Clin Epidemiol 2011;64(8):848-60.

Supplemental Table 3 Overview of the information extracted from included articles.

Topic	Sub-category
General article information	Authors
	Title
	Year of publication
	Study aim¶
	Type of prediction research (prediction model study, impact study)
Study population and context	Sample size
	Population characteristics (mean age, sex, aetiology, injury level, injury severity)
	Eligibility criteria¶
	Location (country)
	Number of included centres
	Time frame for data collection
	Setting¶
	Envisioned/ intended use of prediction model¶
	Prediction model use from a system perspective (micro, meso, macro system level)
Predicted outcome	Method of measurement/ measurement instrument
	Outcome variable
	Coding strategy
	Prediction time frame
	ICF-Linking
Investigated predictors	Method of measurement/ measurement instrument
	Predictor variable
	Coding strategy
	Measurement time point
	ICF-Linking
	Inclusion in the final model (yes/no)
	Applied selection procedure¶
Missing data handling	Missing data information¶
	Procedure/methods used for missing data handling¶
Model development	Method¶
	Development sample size
Final model performance and validation	Type of performed validation¶
	Validation sample size
	Final model performance¶
	Calibration
	Discrimination
	Classification measures
Results	Presentation of final model (table, equation, nomogram, sum score, etc.)
	Proposed updates (for external validation studies only)
Interpretation and discussion	Strengths and potentials¶
	Weaknesses and challenges¶
	Future directions and next steps¶

Abbreviations. ICF, International Classification of Functioning, Disability and Health; SCI, spinal cord injury.
Note. ¶ As described by the authors.

COLOPHON

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