Health-related quality of life and participation of adult patients with spinal muscular atrophy and patients with amyotrophic lateral sclerosis

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The studies on SMA patients presented in this dissertation are based on data retrieved from the Dutch SMA database. This study was registered in the Dutch registry for clinical trials (study no. NL29692.041.09/29692). The studies on ALS patients presented in this dissertation are based on data retrieved in the FACTS-2-ALS trial. The FACTS-2-ALS trial is part of the FACTS-2-NMD project.

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Gezondheidgerelateerde kwaliteit van leven en participatie van volwassen patiënten met spinale musculaire atrofie en patiënten met amyotrofe laterale sclerose

(met een samenvatting in het Nederlands)

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Voor Georg, Tom en Lobke

Contents

Chapter 1

Introduction and thesis outline

GENERAL INTRODUCTION

Motor neurone disorders are a diverse group of neurological disorders, which are associated with progressive muscle weakness. These patients often experience severe limitations in activities and participation. Spinal muscular atrophy (SMA) and Amyotrophic Lateral Sclerosis (ALS) are 2 examples of a motor neurone disorder. Despite the great differences between the diseases, rehabilitation care has the same primary goal, namely helping patients to stay in control of their situation and optimising participation in daily activities, despite often severe, progressive limitations. At the start of this thesis, there was limited knowledge about the quality of life and participation of adults with SMA and patients with ALS. Therefore, the objective of this dissertation was to gain a better understanding of these important topics for daily care.

SPINAL MUSCULAR ATROPHY, SMA

SMA is considered to be an umbrella term for a group of disorders characterized by loss of spinal cord and bulbar α-motor neurones.[1-3] Hereditary proximal spinal muscular atrophy, further described as 'SMA', is the most common hereditary variant. It is a severe neuromuscular disease and an important genetic cause of disability in childhood and adult life. The incidence is estimated at around 1: 12,000 live births. Despite the fact that all patients have the same genetic defect, disease severity varies remarkably. Age at onset and acquired motor milestones are used to define 4 types (1–4) and several subtypes (1a–1c; 2a, 2b, 3a, 3b).[4,5]

Onset in patients with SMA type 1 is before the age of 6 months; they never learn to sit. SMA type 2 is characterized by onset between 6 and 18 months; patients learn to sit but not to walk. Patients with SMA type 3 experience onset of symptoms after 18 months and learn to walk, but they may lose ambulation during life. Onset after the age of 30 years is classified as SMA type 4. SMA is associated with significant disability. Many patients will require non-invasive ventilation, scoliosis surgery, or placement of feeding tubes at a young age, and natural history studies have shown that slow progression of weakness occurs in all patients.[6]

At the time of writing, new treatment strategies have emerged, including nusinersen and SMN1 gene therapy. With a view to accessing these therapies most adult patients with SMA visit the outpatient clinic of the departments of neurology and rehabilitation medicine of the UMCU. Data for our study were, however, collected before these treatments were available. To receive supportive care, patients can rely on a specialized neuromuscular rehabilitation clinic in their region together with local therapists, such as a physiotherapist.

AMYOTROPHIC LATERAL SCLEROSIS, ALS

ALS is a disease characterized by the progressive loss of upper and lower motor neurones, leading to weakness and spasticity of voluntary muscles involved in movement as well as those necessary for swallowing, speech and respiration. Additionally, there are non-motor symptoms, including cognitive and behavioural changes in the frontotemporal spectrum.[7] There is a great variability in prognosis of survival, but also in the course of the disease. The incidence of ALS is estimated to be 2.35/100,000.[8] Previous research showed that multidisciplinary care can improve Health-Related Quality of Life (HRQOL) and participation, prolong survival, and support ALS patients and their families.[9] Previous research has shown that multidisciplinary care from an ALS team is associated with higher HRQOL.[10]

HRQOL

Quality of life (QOL) is a broad concept. The World Health Organization has defined QOL as follows: "The individual's perception of their position in life in the context of the culture and values in which they live and in relation to their goals, expectations, standards and concern".[11] QOL is subjective, includes both positive and negative facets of life and is multidimensional.[12] HRQOL or Health Status is about the patients' experienced (or self-reported) consequences of a health condition in the physical, psychological and social domains.

PARTICIPATION

Wade described the following outcomes of Rehabilitation: social integration and participation, optimisation of a patient's functional autonomy, freedom from pain and distress and ability to adapt to changes.[13] According to the International Classification of Functioning, Disability and Health, participation refers to "a multidimensional concept, that can be defined as the person's involvement in life situation and covers an individual's experience in life activities and social roles, for example, work, leisure activities, and involvement in the community".[14] It is a broad concept that can be evaluated from different perspectives, such as experienced restrictions in daily and social activities, or in terms of (loss of) experienced autonomy and control.

This thesis can be divided in two parts:

In **Part 1**, we describe the outcomes of our studies on HRQOL and participation in adult patients with SMA. We performed two cross-sectional studies. For both studies, all patients were recruited through the Dutch national SMA database (www.treat-nmd.eu/resources/

patient registries/SMA-national-registries/) and were seen in the outpatient clinic of the Department of Neurology at the University Medical Centre, Utrecht. In our study on HRQOL (Chapter 2), we used the Short Form 36–item Health Survey (SF-36) as an outcome measurement. In our study concerning participation (Chapter 3), the outcome measurement was the USER-P, the Utrecht Scale for Evaluation Rehabilitation–Participation (USER-P), a generic instrument which consists of 3 subscales: frequency of participation, restrictions in participation and satisfaction about participation.

Part 2 of this thesis consists of the studies we performed on HRQOL and participation in patients with ALS.

We performed a review, studying associations between psychological factors and HRQOL and global QOL in patients with ALS (Chapter 4). In Chapter 5, we present the results of a longitudinal study on HRQOL and the association with Illness cognitions. Outcome measurement was the ALS Assessment Questionnaire (ALSAQ). In Chapter 6, the results are presented of a cross-sectional study on the prevalence of participation restriction in ambulatory patients with ALS. Perceived participation restrictions were assessed using the social health status dimension of the Sickness Impact Profile (SIP-68), the (SIPSOC), which is the sum of the subscales Mobility Range and Social Behaviour. A second longitudinal study is described in Chapter 7. This concerns participation of patients with ALS during the first 10 months after diagnosis and the association with progression of disease. Outcome measures were the SIPSOC (as described above) and the IPA, the Impact on Participation and Autonomy Questionnaire. Both are generic instruments.

Studies described in Chapters 5, 6 and 7 were part of the FACTS-2-ALS trial, a multicentre trial.

GENERAL AIMS OF THIS THESIS

As there was a lack of knowledge about determinants of HRPOl and participation, the aim of this thesis was/is to gain greater insight into these factors in 2 groups of patients with a neuromuscular, motor neurone disease: adult patients with SMA and ALS patients. There was a particular need for longitudinal studies, during which patients are followed in their adaptation process. Additionally, there is an increasing awareness that psychological and behavioural determinants are associated with HRQoL and participation in patients with a neuromuscular disease like SMA and ALS (15). We aimed to study the association of psychological factors with HRQOL and participation of these patients.

THESIS OUTLINE

Part 1	**Quality of life and participation in adult patients with SMA**
Chapter 2	Correlates of health-related quality of life in adult patients with spinal muscular atrophy
Chapter 3	Social participation of adult patients with spinal muscular atrophy: Frequency, restrictions, satisfaction and correlates
Part 2	**Quality of life and participation in patients with ALS**
Chapter 4	Associations between psychological factors and health-related quality of life and global quality of life in patients with ALS: a systematic review
Chapter 5	Associations between illness cognitions and health-related quality of life in the first year after diagnosis of amyotrophic lateral sclerosis
Chapter 6	Participation restrictions in ambulatory amyotrophic lateral sclerosis patients: Physical and psychological factors
Chapter 7	Participation and autonomy in the first 10 months after diagnosis of ALS, a longitudinal study
Chapter 8	General discussion

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Part one

Quality of life and participation in adult patients with SMA

Chapter 2

Correlates of health related quality of life in adult patients with spinal muscular atrophy

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ABSTRACT

Introduction: To improve care for patients with spinal muscular atrophy (SMA), we assessed the physical and mental quality of life (QoL) in 62 adult patients with SMA.

Methods: Physical component scores (PCS) and mental component scores (MCS) of the Short Form -36 Health Survey (SF-36) were obtained. Correlations with demographics, disease severity, and emotional distress were assessed. We used hierarchical multiple regression analysis to identify determinants of QoL.

Results: PCS scores were lower, and MCS scores higher than in the healthy reference population. Patients with milder SMA types reported lower scores on several MCS domains. Motor skills scores and emotional distress explained 16% of the variance in PCS. SMA type and emotional distress explained 10% and 45% of the variance of MCS.

Discussion: Patients with milder forms of SMA tend to have a reduced mental QoL. Psychological intervention to reduce emotional distress may improve both mental and physical QoL.

INTRODUCTION

Hereditary proximal spinal muscular atrophy (SMA) is caused by homozygous deletions of the survival motor neuron (*SMN*) 1 gene.[1,2] It has a broad range of severity, which is reflected in the distinction of 4 SMA types based on age at onset and acquired motor milestones.[3,4] Onset in patients with SMA type 1 is before age 6 months, and they never learn to sit. SMA type 2 is characterized by onset between 6 and 18 months, and patients learn to sit but not to walk. Patients with SMA type 3 experience onset of symptoms after 18 months and learn to walk, but they may lose ambulation during life. Onset after age 30 years is classified as SMA type 4.[5] SMA is associated with significant disability. Many patients will need non-invasive ventilation, scoliosis surgery, or placement of feeding tubes at a young age, and natural history studies have shown that slow progression of weakness occurs in patients with SMA types 2–3.[6,7] A guideline for standards of care for SMA has been published, but it focuses on physical complications in childhood and does not address health related quality of life (HRQoL).[8]

The previous studies on HRQoL in adult patients with SMA were limited in scope or sample size and did not identify possible determinants.[9-12] The aim of this study was to assess HRQoL in adult patients with the full spectrum of SMA and to investigate its correlates. To this end, we used the physical component score (PCS; reflecting physical quality of life) and mental component score (MCS; reflecting mental quality of life) of the Short Form-36 questionnaire (SF-36). We studied the impact of sociodemographic factors, emotional distress, and disease severity, which were previously found to influence HRQoL in patients with other neuromuscular diseases.[13,14]

MATERIALS AND METHODS

Participants

Adult (age > 18 years) patients with genetically confirmed SMA were included in the study between September 2010 and December 2012. The only exclusion criterion was inability to read Dutch. All patients were recruited through the Dutch national SMA database (www.treat-nmd.eu/resources/patient-registries/SMA-national-registries/) and were seen in the outpatient clinic of the Department of Neurology at the University Medical Center, Utrecht. We documented demographics with a standardized questionnaire. One author (RIW) documented muscle strength bilaterally in 17 muscle groups of arms and legs (arm abduction, external rotation of the shoulder, flexion and extension of the elbow, extension and flexion of the wrist, finger extension and flexion, finger abduction, flexion and extension of the hips, adduction and abduction of upper legs, flexion and extension of the knees,

dorsal and plantar flexion of the ankles) using the 5-point Medical Research Council (MRC) scale and motor skills using the validated Expanded Hammersmith Functional Motor Scale (HFMSE).[15] This study was registered at the Central Committee on Research involving Human Subjects, the Dutch registry for clinical trials. The Medical Ethical Committee of the University Medical Center Utrecht approved the research protocol. All patients gave informed consent prior to inclusion.

Health Related Quality of Life assessment

HRQoL was assessed using the validated Dutch version of the Short Form 36–item Health Survey (SF-36).[16,17] The SF-36 is a generic HRQoL questionnaire, and is composed of 36 items organized into 8 domains. For each domain the item scores are coded, summed, and transformed into a scale ranging from 0–100, where 100 is the best possible rating. Four domains (physical functioning, role limitations due to physical problems, bodily pain, and general health perception) are summarized in the physical health component score (PCS), a measure for physical QoL.[18] Social functioning, role limitations due to emotional problems, mental health, and vitality are summarized in the mental health component score (MCS), a measure for mental QoL. PCS and MCS were calculated according to guidelines as described by Ware, using age-correlated means and standard deviations of a healthy Dutch population.[17]

Determinants of HRQoL

We selected gender, SMA severity (i.e. SMA type), motor skills, muscle strength, and emotional distress as possible determinants of HRQoL.[13] SMA type was defined according to previously published criteria. The subdivision into SMA types 3a and 3b with age at onset before and after 18 months was used, because it reflects differences in prognosis for remaining ambulatory later in life.[4,5] The HFMSE consists of 33 items with a total score ranging from 0 to 66 points. We calculated MRC sum scores for arms and legs by adding MRC scores of individual muscle groups. The presence of emotional distress was assessed with the Dutch version of the Hospital Anxiety and Depression Scale (HADS).[19,20] The HADS is designed to assess feelings of distress without contamination of scores by reports of physical symptomatology and has been used in several studies involving patients with neuromuscular diseases.[21,22] It consists of 14 questions, 7 items focusing on feelings of anxiety and 7 on feelings of depression. Scores for each question range between 0 and 3. The total score is the sum of the anxiety and depression scores and ranges from 0 to 42. A score of 11 or higher suggests symptoms of emotional distress.[23]

Data analysis

To compare the scores of the sub-domains of the SF-36 of the study population with the reference population, we calculated standard scores by dividing the differences between the study population and the reference population (mean score by age group) by the standard deviation of the reference population. These standardized scores indicate the difference in terms of standard deviations. We used 1.5 SD as the cut-off for normal values in line with previous findings.[24] MCS and PCS scores were calculated and compared to the Dutch reference population. The mean reference score is 50 with an SD of 10; scores below 40 and above 60 are considered lower and higher than the reference population.[14] Where non-normal distributions were observed, correlations between variables were investigated using Spearman rank order analysis. Significance level was set at 0.05. Factors that showed significant correlations with the PCS and the MCS were entered into a hierarchical linear regression model (Multi-step entry method). If the assumptions for linear regression were not met, robust regression procedures (bootstrapping) were employed.[25] SPSS version 20 for Windows was used for analysis.

RESULTS

Participants

Sixty-two of 80 (78%) invited patients participated. Patient characteristics are summarized in Table 2.1. Four patients had an early onset and had never been able to sit independently. By definition, these patients have SMA type 1 despite an unusually long survival.[26] All patients with type 1, 90% of patients with type 2, and 46 % of patients with type 3a had undergone scoliosis surgery. Two patients with SMA type 1, 1 patient with SMA type 2, and 1 patient with SMA type 3a used daytime ventilation.

Health related quality of life scores

SF-36 scores are summarized in Table 2.2. Mean PCS (physical QoL) for the total population was 30. The MCS scores were distributed non-normally, and the median score was 62 (range 24–72).

The differences between the study population and the general population in the domains of the SF-36 expressed as standard mean scores corrected for age are depicted in Figure 2.1.

All patients scored low in the SF-36 domain "physical functioning". Scores in the other domains of the SF-36 were within the limit of 1.5 SD, although patients with SMA types 3b/4 scored markedly lower than patients with SMA types 1–3a in the domains "role emotional" and "mental health".

Table 2.1. Patient characteristics

SMA type	Total (n = 62)	Type 1 (n = 4)	Type 2 (n = 21)	Type 3a (n = 13)	Type 3b (n = 20)	Type 4 (n = 4)
Demographics						
Gender, n (%)‡	36 (55%)	3 (75%)	13 (62%)	8 (62%)	9 (45%)	3 (60%)
Age (Y)*	41.7 (14.5)	39.0 (11.5)	33.8 (13.9)	47.3 (14.2)	44.3 (13.2)	54.5 (10.9)
Disease severity						
Motor skills (HFMSE)†	3.5 (0–66)	0	2.0 (0–20)	4.0 (0–35)	29.0 (0–66)	48.0 (43–53)
Strength arms* (MRC score)	54.8 (18.0)	20.3 (4.0)	42.9 (11.8)	52.4 (14.2)	68.6 (10.6)	72.0 (10.9)
Strength legs† (MRC score)	32.5 (16–78)	17.0 (16–24)	22.0 (16–54)	32.0 (16–65)	62.0 (25–78)	66.0 (57–72)
Wheelchair§	46 (74%)	4 (100%)	20 (95%)	12 (92%)	9 (45%)	1 (25%)
Emotional distress						
Total HADS†	6.0 (0–33)	7.0 (4–12)	7.0 (0–16)	5.0 (1–23)	6.5 (2–33)	5.0 (3–7)
% HADS > 11#	13%	25%	19%	15%	5%	0

* Mean (SD); † Median (range); ‡ Gender (% women); § Wheelchair, percentage of patients using a wheelchair during activities at any time of the day; # Percentage of patients with HADS-score > 11. SMA, spinal muscular atrophy; HFMSE, Expanded Hammersmith Functional Motor Scale; MRC, Medical Research Council scale; HADS, Hospital Anxiety and Depression Scale.

Table 2.2. SF-36 domain scores per SMA type

SMA type	Total (n = 62)	Type 1 (n = 4)	Type 2 (n = 21)	Type 3a (n = 13)	Type 3b (n = 20)	Type 4 (n = 4)
SF-36 domains*						
PF (n = 61)	12.9 (24.2)	0	5.0 (21.8)	11.5 (29.0)	17.8 (18.2)	47.5 (31.2)
RF (n = 60)	59.6 (40.9)	43.8 (51.5)	64.3 (40.8)	60.4 (41.9)	52.6 (42.4)	81.3 (23.9)
BP	72.1 (26.4)	72.8 (13.0)	80.6 (23.4)	76.3 (25.6)	60.5 (29.9)	71.8 (25.7)
GH	55.4 (23.2)	51.5 (20.0)	55.3 (23.2)	64.0 (18.3)	51.2 (27.9)	52.8 (13.7)
VIT	62.9 (22.4)	65.0 (13.5)	71.7 (18.9)	71.5 (27.2)	47.5 (16.7)	63.8 (21.7)
SF (n = 61)	72.5 (29.8)	81.3 (21.7)	77.4 (26.7)	72.9 (28.6)	63.1 (36.2)	84.4 (15.7)
RE (n = 59)	91.0 (24.6)	100.0	92.1 (23.3)	88.9 (29.6)	88.9 (28.0)	91.7 (16.7)
MH	82.0 (14.3)	79.0 (3.8)	82.9 (12.5)	82.7 (17.4)	80.4 (16.8)	86.0 (8.3)
PCS (n = 58)	30.4 (9.3)					
MCS (n = 58)	60.4 (8.1)					

* SF-36 scores and PCS and MCS are expressed as mean score (SD). PCS scores and MCS scores are calculated only for the total population. SF-36 domains: PF, physical functioning; RP, Role functioning-physical; BP, bodily pain; GH, general health, VIT, vitality; SF, social functioning; RE, role functioning- emotional; MH, mental health; PCS, physical component scale (SF-36); MCS, mental component scale (SF-36).

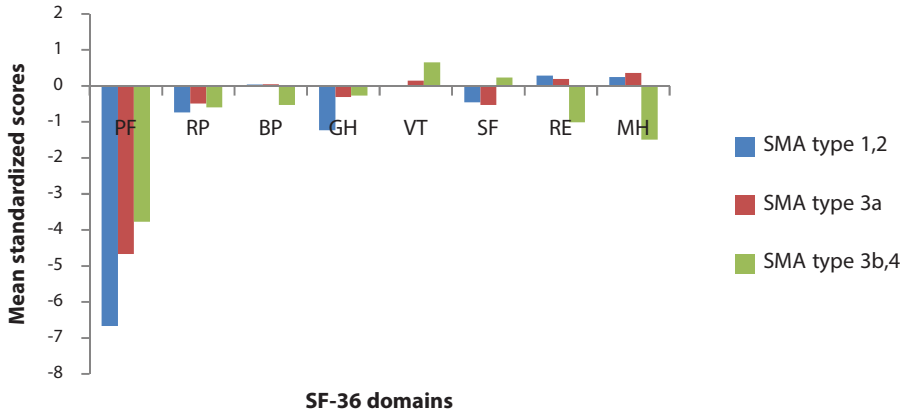

Figure 2.1. SF-36 profile of the patient population.
Note: deviations of the patient population from the reference population are expressed as mean standardized scores. Zero = reference level. More negative scores indicate lower SF-36 scores in the specific domain. Accepted deviation from normal value is between 1.5 and -1.5 SD. SMA, spinal muscular atrophy. SF-36 domains: PF, physical functioning; RP, Role functioning-physical; BP, bodily pain; GH, general health, VIT, vitality; SF, social functioning; RE, role functioning-emotional; MH, mental health.

Determinants of QoL

Correlations of demographics, disease severity, and emotional distress with physical and mental QoL are summarized in Table 2.3. PCS scores of patients with SMA correlated significantly with HFMSE scores and inversely with emotional distress (HADS) scores. MCS scores of patients with SMA correlated inversely with SMA type [patients with severe physical limitations report better MCS scores (mental health) than patients with less physical limitations], arm strength, and emotional distress.

Table 2.3. Spearman rank order correlations with PCS and MCS

n = 62	PCS rho	p	MCS rho	p
Gender	0.151	NS	0.247	NS
SMA type	0.137	NS	-0.321	0.014
Total strength, arms (n = 57)	0.198	NS	-0.318	0.020
Total strength, legs (n = 49)	0.198	NS	-0.187	NS
Motor skills (HFMSE) (n = 60)	0.309	0.020	-0.168	NS
Emotional distress (Total HADS)	-0.394	0.002	-0.462	0.000

NS = p > 0.05. PCS, physical component scale (SF-36); MCS, mental component scale (SF-36); HFMSE, Expanded Hammersmith Functional Motor Scale; HADS, Hospital Anxiety and Depression Scale.

Results of bootstrap linear hierarchical regression analysis of both PCS and MCS are shown in Table 2.4. Motor skills (HFMSE scores) and emotional distress together explained 16% of the variance in physical QoL, with emotional distress accounting for 9%. SMA type and emotional distress explained 10% and 45% of the variance in mental QoL, together explaining 55% of the variance in mental QoL.

Table 2.4. Hierarchical linear regression (Multi-step entry method)

PCS			MCS		
	$\Delta R^{2\ddagger}$	β		ΔR^2	β
Step 1	0.064		**Step 1**	0.102	
HFMSE		0.252	SMA type		-0.320*
Step 2	0.092		**Step 2**	0.005	
HFMSE		0.240	Type		-0.232
Emotional distress		-0.303*	Strength arms		-0.114
			Step 3	0.469	
			Type		-0.248
			Strength arms		-0.036
			Emotional distress		-0.688*
$R^{2\dagger}$ = 15.6%			R^2 = 57.7%		

* $p < 0.05$; † R^2, explained variance; ΔR^2, change in R^2 between 2 equations.
PCS, physical component scale (SF-36); MCS, mental component scale (SF-36); HFMSE, Expanded Hammersmith Functional Motor Scale; HADS, Hospital Anxiety and Depression Scale.

DISCUSSION

Adult patients with SMA, on average, experience a low physical QoL but normal mental QoL in comparison with a reference population from the Netherlands. However, several MCS domain scores, in particular "role limitations due to emotional problems" and "mental health", showed a high degree of variation and were markedly lower in patients with SMA types 3b and 4 (i.e. those with relatively mild disease and late onset) than in patients with SMA types 1–3a. Disease severity (inverse correlation) and emotional distress as reflected by higher HADS scores were determinants of HRQoL. These findings suggest that patients with milder disease and later onset and those who reported feelings of anxiety and depression are at risk to experience a reduced mental QoL (i.e. low MCS score). We used the generic HRQoL instrument SF-36 in the absence of a specific HRQoL instrument for adults with SMA. Although its validity and reliability have not been investigated formally in patients with SMA, the SF-36 has been used in a large number of studies, including patients with other neuromuscular diseases.[27-31] Previous studies on HRQoL in children and adults with SMA showed that they generally report an acceptable QoL despite their physical limitations.[11]

Previous HRQoL studies all had methodological limitations, since they were performed before the era of genetic testing,[9] were limited in sample size,[10-12] or were restricted to a particular SMA type.[10,32] Moreover, none of these studies analyzed possible determinants of HRQoL in adult patients.

Comparison of HRQoL of patients with the full spectrum of SMA, ranging from those with an extraordinarily mild SMA type 1 phenotype to those with SMA type 4, suggests important differences in experienced mental QoL between patients with early and late onset. This may be explained by differences in the adaptation process between early and late onset patients. In patients with SMA types 1–3a, physical limitations are present from a very early age, which allows patients to adapt to their situation, adjust expectations, and redefine concepts related to mental health.[32] Patients with SMA types 3b–4 initially have normal gross motor development with later onset of muscle weakness, and serious limitations due to disease progression may occur as late as middle-age.[5,6] Their adaptation process thus occurs at a later stage in life. Lower mental QoL scores in these patients may therefore reflect a response to an experience of functional deterioration and continuous distress during adaptation attempts, as has also been observed in patients with spina bifida.[12,34] Patients with relatively mild impairment might also be accustomed to comparing themselves with healthy people, which would raise the bar of expectations about functioning. Alternatively, the relatively high mental QoL in patients with more severe SMA may also be explained by the fact that they make a distinction between the concepts of "health" and "disability", resulting in inflated HRQoL scores. For example, patients with early onset SMA may not experience common complications as a sign of impaired health and report next-to-normal physical HRQoL scores.[35] These are examples of the phenomenon known as response shift that refers to a change in QoL as a result of either a change in a person's internal standards of measurement (recalibration), a change in values (reprioritization), or a redefinition of QoL (reconceptualization).[36,37] As a result of these shifts, individuals can sustain a high QoL despite negative changes in physical health.

We aimed at identifying correlates of mental and physical QoL in order to design interventions that could improve care for patients with SMA. Emotional distress emerged as the most important determinant of both physical and mental QoL, despite the fact that only 13% of the SMA patients had total HADS scores higher than 11, which is an indicator of the existence of an anxiety or depressive disorder.[23] We did not formally exclude the possibility that mental health disorders may have confounded the findings, but this was not suggested by patients' medical history or clinical impression. We can also not exclude the possibility that factors such as ethnicity, socioeconomic status, and educational level or other unmeasured demographic characteristics may have accounted for differences in mental QoL scores. Nevertheless, the effect of mood on both physical and mental QoL has been reported previously in patients with other neuromuscular disorders, such as inclusion body myositis.[21,29]

Other potential determinants that were not included in this study are the types of support services or medications patients were receiving for their physical or mental well-being. We cannot exclude the possibility that higher mental QoL scores in a subset of patients could reflect better access to, or at least more frequent use of effective mental health treatments, such as counselling and medication. Although we did not have the impression that there were important differences in the availability of assistive devices and durable medical equipment, unrecorded differences in their use may have varied between those with different types of SMA and have influenced physical QoL. It is possible that conceptual overlap in questionnaire items of the SF-36 and HADS may have led to an overestimation of the correlation level between emotional distress and the MCS.

Moreover, we cannot exclude the possibility that this study reflects HRQoL of a particular population of patients with SMA. Nevertheless, exploring feelings of anxiety and depression might help at least a subgroup of patients to cope with functional deterioration and changing perspectives in life.[38]

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Chapter 3

Social participation of adult patients with spinal muscular atrophy: Frequency, restrictions, satisfaction, and correlates

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ABSTRACT

Introduction: We assessed social participation in 62 adults with Spinal muscular atrophy (SMA) types 1c–4.

Methods: Outcome measure: Utrecht Scale of Evaluation Rehabilitation-Participation (USER-P) with Frequency, Restrictions and Satisfaction scores. Hierarchical regression analysis.

Results: Early (type 1, 2, 3a) and late onset (type 3b, 4) SMA patients reported similar frequency and satisfaction scores. 'Age', 'motor skills', 'pain' and 'feelings of depression' correlated with frequency; 'motor skills' and 'feelings of depression' correlated with restrictions and 'level of education', 'fatigue' and 'feelings of depression' correlated with satisfaction. Motor skills and feelings of depression explained 33% of variance in *frequency* of participation. Motor skills explained 26% of variance of *restrictions* in participation. Fatigue and feelings of depression explained 50% of variance in *satisfaction* with participation.

Discussion: Motor skills, feelings of depression and fatigue are correlates of participation in daily life. This knowledge can be used to optimize care for SMA patients.

INTRODUCTION

Hereditary proximal spinal muscular atrophy (SMA) is an important genetic cause of disability in childhood and adult life.[1] The antisense oligonucleotide nusinersen has been approved and has shown efficacy in altering the natural history of the disease.[2] Other gene therapy trials are ongoing. However, there is currently no cure for SMA.[3-5]

The variety and severity of impairments and disabilities that accompany SMA have been described extensively.[6-10] The consensus guidelines for supportive care outlines management for the most common medical complications (e.g. pulmonary problems, scoliosis) that occur primarily in childhood, but focus strongly on symptom management.[11] Irrespective of SMA type, all patients will encounter moderate to severe disability in life. There is, however, a striking lack of literature on how adult patients participate in daily life activities and how multidisciplinary care can optimize their participation. The few existing studies on participation among adult patients with a broad range of neuromuscular disorders have focused mainly on work, and the results of SMA patients were not reported separately.[12-15] In another qualitative study, SMA patients rated their quality of life as 'fine', but experienced the serious impact of progressive functional limitations on their daily activities.[16] Patients emphasized their need to live a normal life and fully participate in social activities, including an active family role, work and maintaining optimism.[17] Increasing our knowledge of participation among adult patients with SMA and factors associated with participation may help to optimize supportive care.

Therefore, the first objective of this study was to describe the frequency of, and perceived restrictions in, participation and the related satisfaction levels of adult patients with SMA. The second objective was to determine whether selected subjective complaints (pain, fatigue, anxiety, feelings of depression) and coping style are associated with participation in adult patients with SMA, adjusting for demographic factors and disease severity. These possible correlates were selected based on studies showing associations between pain and fatigue, emotional distress, mood and coping strategies with participation and quality of life among patients with neuromuscular diseases.[18-21]

METHODS

Subjects and procedures

Adult patients with genetically confirmed SMA, regardless of type of SMA, aged 18 years or older at inclusion, were recruited for this study between September 2010 and December 2012. Patients were informed about the study and recruited through the Dutch patient organization for neuromuscular diseases (www.spierziekten.nl), through patient communities

on the internet, through pediatricians, (pediatric) neurologists, rehabilitation physicians and the four Dutch Centers for Chronic Respiratory Ventilation. The only exclusion criterion was the inability to read Dutch. All patients were retrieved from the Dutch SMA database.[22] For the purpose of this study, all patients were seen at the outpatient clinic of the Department of Neurology and Neurosurgery at the University Medical Center Utrecht for a structured interview and neurological examination. They were asked to complete questionnaires.

This study was registered in the Dutch registry for clinical trials (study no. NL29692.041.09/29692). The Medical Ethics Committee of the University Medical Center Utrecht approved the research protocol. All patients gave informed consent prior to inclusion.

Measures

The SMA classification system was used to define SMA types 1–4.[6,23,24]

Participation was measured using the Utrecht Scale for Evaluation Rehabilitation-Participation (USER-P), a self-report instrument with 32 items. Validity and reproducibility of the USER-P scale are good.[25-29] Sum scores are calculated for the Frequency, Restrictions and Satisfaction scales, and each sum score is converted to a score on a scale ranging from 0 to 100. Higher scores indicate more favourable levels of participation (higher frequency of activities, fewer restrictions, greater satisfaction). An example question for the Frequency scale is as follows: "How many hours do you spend on household activities?"

An example question for the Restrictions scale is: "Does your illness or condition currently limit your daily life concerning outdoor mobility?". An example question for the Satisfaction scale is as follows: How satisfied are you with your current daily life concerning 'going out' (eating out, visiting a cafe, the cinema, a concert, alone or with others).

Correlates

We used a standardized questionnaire to document disease characteristics (age at diagnosis, age at loss of ambulation) and demographic characteristics (sex, age, relationship status, job status, level of education, whether living independently).

To document motor skills we used the Expanded Hammersmith Functional Motor Scale (HFMSE), a validated test consisting of 33 items to assess motor skills of patients with SMA.[30,31] The maximum score is 66 points. Higher scores indicate better motor skills.

To assess pain and fatigue we used the sub-domain scores 'pain' (two items) and 'vitality' (four items) of the Short Form 36-item Health Survey (SF-36).[32,33] The vitality score is a valid instrument to measure fatigue, as shown by a high correlation between the SF-36 vitality score and scores on the Fatigue Symptom Inventory.[34] Higher scores in domain 'pain indicate that patients experience less pain; higher scores in domain 'vitality' indicate that patients experience less fatigue, feel more vital.

Feelings of depression and anxiety were assessed using the Hospital Anxiety and Depression Scale (HADS).[35-37] Seven items assess feelings of anxiety (HADS-A) and seven items assess feelings of depression (HADS-D), with a maximum of 21 points for the HADS-A and HADS-D scales. A score of 8 or more on the HADS-A or HADS-D is an indication of anxiety or depressed mood.

Coping strategies were assessed using the short version of the Coping Inventory for Stressful Situations (CISS-21).[38,39] The CISS-21 has 21 items divided into three categories: problem-targeted strategies (CISS-P), emotion-focused strategies (CISS-E) and avoidance strategies (CISS-A). Response options range from 'not at all' (1) to 'very applicable' (5). A higher score indicates a preference to use this particular coping strategy.

Statistical analyses

Descriptive statistics were used to describe characteristics of the study population and participation scores. Comparisons between all SMA types were not performed because of the small sample size. Since differences in quality of life were found between patients with a relatively early onset (i.e. SMA types 1–3a) and those with onset later in life (i.e. SMA types 3b–4),[40] we dichotomized the variable SMA types to early onset SMA (types 1–3a) versus late onset SMA (types 3–4) to compare outcomes between these two subgroups.

In addition to the total scores on the USER-P, individual items of the Restrictions and Satisfaction subscales were dichotomized to quantify the presence of restrictions in and dissatisfaction with specific aspects of participation. The options "with difficulty", "with assistance" and "not possible" on the restrictions subscale were defined as "restrictions". The option "without difficulty" was defined as "no restrictions". The answer options "satisfied" and "very satisfied" on the satisfaction subscale were defined as "satisfaction". The answer options "very dissatisfied", "dissatisfied" and "neutral" were defined as "dissatisfaction". The answer option 'not applicable' was defined as a missing variable.

To detect differences in determinants of participation between early and late-onset SMA patients, we used the independent samples Mann Whitney U test. Spearman correlations were computed to determine relationships between potential determinants and participation of the total sample. Using Cohen's rule of thumb, a correlation of 0.10 was considered 'small', of 0.30 'medium' and of 0.50 'large'.[41]

Determinants that showed a p-value < 0.1 in the bivariate correlation analysis were entered into a hierarchical linear regression model (Multi-step enter method). Variables were always entered in the same order: step 1: disease severity variables and demographics; step 2: subjective complaints. Residual analyses were performed and multi-collinearity was tested to search for violations of necessary assumptions in multiple regression.[42] SPSS version 24 for Windows was used for analysis.

Table 3.1. Demographics in the total population and in 2 subgroups, early versus late onset SMA

	Total	Type 1	Type 2	Type 3a	Type 3b	Type 4	Early onset	Late onset
N	62	4	21	13	20	4	38	24
Sex, female	55%	75%	62%	62%	45%	60%	63%	50%
Age in years	43.0 (20–70)	40.5 (24–51)	31.0 (20–68)	51.0 (20–66)	48.0 (20–70)	53.0 (43–69)	37.0 (20–68)	48.0 (20–70)
Partner	61%	25%	38%	69%	80%	100%	47%*	83%
Paid job	39%	25%	29%	31%	55%	50%	30%	54%
Education								
No / Secondary school	66%	50%	72%	54%	65%	100%	64%	71%
Higher education	34%	50%	29%	46%	35%	0	37%	29%
Living independent	68%	75%	38%	85%	80%	100%	58%	83%

Note: values are median (range). * Results differ significantly between groups (SMA types or early versus late onset) with $p < 0.05$. NA, not applicable. Education, highest grade level completed; Partner: living separate or together = yes; Living independent: independent with/without self-coordinated care = yes; Paid employment: frequency scale USER-P, Yes/No.

RESULTS

Sixty-two of 80 (78%) invited patients participated. Descriptive statistics are displayed in Table 3.1. We included four patients with SMA type 1c and onset before 6 months of age who never learned to sit independently but survived into adulthood. Median HADS-A and HADS-D scores were low (Table 3.2). Patients with early onset SMA had significantly lower motor skills (HFMSE-scores) than those with late onset SMA. Significantly fewer patients with early onset SMA had a partner than patients with late onset SMA. Late onset patients reported more pain and more fatigue than early onset patients.

Frequency (level) of participation

Median participation scores are displayed in Table 3.3. There were no significant differences between patients with early and late onset SMA in the frequency of participation (Table 3.3). SMA patients spent most hours on unpaid work and household activities (Table 3.4). Only 39% of them had paid work and only 16% had a full-time job (36 hours a week or more). A detailed description of all participation activities performed by all patients is given in Table 3.4.

Restrictions and satisfaction

Patients with early onset SMA experienced significantly more participation restrictions compared to patients with late onset SMA (Table 3.3). Table 3.5 shows that 16–97% of patients felt restricted in daily activities. They felt most restricted in work/education, household chores, mobility outdoor (by car, public transport or bike to e.g. work), going out (going out to e.g. cinema or pub; outdoor activities like going to church, shopping), physical exercise and visit to family and friends. There were no significant differences between patients with early and late onset SMA in satisfaction with participation (Table 3.3). Table 3.5 shows that 8–58% of patients were dissatisfied about daily activities. They were most dissatisfied about performing household chores and physical exercise.

Correlates of participation

Bi-variable analysis showed a medium correlation between lower frequency of participation and older age, reduced motor skills and pain. We found a medium correlation between lower frequency of participation and more feelings of depression. Participation restrictions were largely correlated with reduced motor skills. There was a medium correlation between satisfaction with participation and level of education, fatigue and a large correlation with fewer feelings of depression.

Table 3.2. Disease severity and psychological factors in the total population and in 2 subgroups, early versus late onset SMA

	Total	Type 1	Type 2	Type 3a	Type 3b	Type 4	Early onset	Late onset
N	62	4	21	13	20	4	38	24
Disease severity								
Motor skills (HFMSE)	3.5 (0–66)	0	2.0 (0–20)	4.0 (0–35)	29.0 (0–66)	48.0 (43–53)	2.0* (0–35)	32.5 (0–66) n = 22
Age at diagnosis	1.5 (0–44)	0.42 (0.33–0.5)	0.75 (0–2)	1.5 (0.5–3)	6.5 (3.5–25)	40.3 (31–44)	0.95 (0–3)*	9.5 (4–44)
Loss ambulation	18.5 (2–59)	NA	NA	17.6 (4–46)	35.1 (9–59)	NA	13.9* (1–45)	34.5 (9–59)
Subjective complaints								
Pain (SF-36)	84.0 (0–100)	73.0 (61–84)	84.0 (20–100)	84.0 (31–100)	57.0 (0–100)	73.0 (41–100)	84.0* (20–100)	62.0 (0–100)
Vitality (SF-36)	62.5 (5–100)	70.0 (45–75)	70.0 (30–100)	80.0 (5–100)	55.0 (15–70)	57.5 (45–95)	75.0* (5–100)	55.0 (15–95)
HADS-A	3.5 (0–21)	4.5 (3–9)	4.0 (0–10)	3.0 (0–9)	3.0 (0–21)	2.5 (2–3)	4.0 (0–10)	3.0 (0–21)
HADS-D	2.0 (0–15)	2.0 (1–4)	1.0 (0–9)	2.0 (0–15)	3.5 (10–12)	2.0 (1–5)	1.5 (0–15)*	3.0 (1–12)
Psychological factors								
CISS								
Task-oriented	26.6 (12–33)	25.5 (19–32)	26.4 (12–33)	25.7 (12–33)	27.8 (20–33)	24.7 (19–28)	27.0 (12–33)	28.0 (19–33)
Emotional	14.6 (7–32)	12.5 (8–15)	15.3 (7–25)	12.5 (7–19)	15.7 (7–32)	14.7 (11–18)	14.1 (7–25)	15.5 (7–32)
Avoidance	19.3 (7–31)	22.0 (16–27)	18.9 (12–28)	19.1 (7–31)	18.7 (9–27)	21.3 (11–28)	19.5 (7–31)	19.1 (9–28)

Note: values are median (range). * Results differ significantly between groups (SMA types or early versus late onset) with $p < 0.05$. NA, not applicable.
Loss of ambulation: stop walking with aid, in years.
Abbreviations: SMA, Spinal muscular Atrophy; HFMSE, Expanded Hammersmith Functional Motor Scale; MRC, Medical Research Council; SF-36, Short Form 36–item Health Survey; HADS, Hospital Anxiety and Depression Scale; HADS-A, Hospital Anxiety and Depression Scale; anxiety subscale; HADS-D, Hospital Anxiety and Depression Scale; depression subscale; CISS-21, Short Form of the Coping Inventory for Stressful Situations.

Table 3.3. USER-P scores for the total population, and early versus late onset SMA

		SMA type					Onset	
USER-P	Total (n = 62)	Type 1 (n = 4)	Type 2 (n = 21)	Type 3a (n = 13)	Type 3b (n = 20)	Type 4 (n = 4)	Early (n = 38)	Late (n = 24)
Frequencies total	34.5 (7–66)	32.1 (21–43)	36.7 (17–49)	30.9 (7–50)	33.5 (18–48)	42.2 (23–66)	35.4 (7–50)	35.4 (18–66)
Frequency: work/education	20.0 (0–45)	17.5 (10–40)	25.0 (0–40)	10.0 (0–30)	22.5 (0–45)	15.0 (5–35)	20.0 (0–40)	20.0 (0–45)
Frequency: leisure activities	48.6 (14–74)	42.9 (31–54)	54.3 (31–71)	48.6 (14–74)	44.3 (26–74)	55.7 (40–65)	50.0 (14–74)	47.1 (25–74)
Restrictions	61.9 (18–100)	40.6 (33–59)	58.2 (36–93)	61.1 (18–89)	67.1 (30–97)	79.4 (59–100)	57.6 (18–93)*	73.3 (30–100)
Satisfaction	72.5 (32–100)	71.9 (47–86)	72.5 (50–100)	77.8 (32–100)	71.0 (33–89)	74.3 (58–98)	75.0 (32–100)	71.0 (33–98)

Note: values are median (range).
* Results differ significant between groups (SMA types or early versus late onset) with $p < 0.05$.
SMA type, SMA types 1-4; Onset, early versus late onset SMA.
Abbreviations: SMA, Spinal Muscular atrophy; USER-P, Utrecht Scale for Evaluation Rehabilitation-Participation.
Frequency, work/education: hours/ week; Frequency, leisure activities: times/month.

Table 3.4. USER-P, Frequency scale: hours per week (work/education) and times per month (leisure activities) spent per item, for the total population, n = 62

	Hours/week		
Domains	Not at all	1–24 hrs	≥ 25 hrs
Paid work	61%	18%	21%
Unpaid work	44%	42%	15%
Education	71%	18%	12%
Household	34%	60%	7%
	Times/month		
	Not at all	1–10 times	> 10 times
Sports and physical exercise	44%	42%	15%
Going out	10%	87%	2%
Daytrips	11%	81%	8%
Leisure activities at home	5%	39%	57%
Visiting family or friends	3%	86%	11%
Receiving visitors	3%	87%	10%
Contact phone, computer	0	16%	84%

Note: Education: only activities in the course of work, or in order to get work.
Abbreviations: USER-P, Utrecht Scale for Evaluation Rehabilitation-Participation.

Table 3.5. Percentage of patients with perceived restrictions and dissatisfaction, for the total population, n = 62

Persisting problems			
Restrictions	%	Dissatisfaction	%
Work/education	67% (n = 52)	Work/education	15% (n = 39)
Household chores	97% (n = 59)	Household chores	43% (n = 56)
Mobility outdoor	82%	Mobility outdoors	31% (n = 61)
Physical exercise	95% (n = 57)	Physical exercise	58% (n = 50)
Going out	71%	Going out	31% (n = 61)
Outdoor activities	79%	Outdoor activities	31% (n = 61)
Leisure indoors	41% (n = 61)	Leisure indoors	12% (n = 61)
Relationship partner	33% (n = 40)	Partner relationship	7% (n = 39)
Visit to family/friends	66%	Family relationships	10%
Visit from family/friends	20% (n = 61)	Friends and acquaintances	8%
Telephone/computer contact	16%		

(n..): n per item NB: Not all items were scored by all patients.

Table 3.6 summarizes results of the multivariable analysis. 33% of the variance in frequency of participation was explained by motor skills in combination with feelings of depression; 26% of the variance in restrictions in participation was explained by motor skills and 50% of the variance in satisfaction with participation was explained by fatigue together with feelings of depression.

Table 3.6. Bivariate and multivariable linear regression analyses for USER-P frequency, restrictions and satisfaction. Stepwise regression.

	Frequency of participation			Participation restrictions			Satisfaction with participation		
	Bivariable	Multivariable		Bivariable	Multivariable		Bivariable	Multivariable	
		Step 1	Step 2		Step 1	Step 2		Step 1	Step 2
Characteristics	ρ	β	β	ρ	β	β	ρ	β	β
Sex, female	0.08	N.E.	N.E.	0.05	N.E.	N.E.	-0.03	N.E.	N.E.
Age in years	-0.28*	-0.24	-0.05	-0.10	N.E.	N.E.	-0.01	N.E.	N.E.
Partner	0.03	N.E.	N.E.	0.11	N.E.	N.E.	0.06	N.E.	N.E.
Education, High	0.05	N.E.	N.E.	0.06	N.E.	N.E.	0.32*	-0.37	-0.20
Living independent	-0.13	N.E.	N.E.	-0.01	N.E.	N.E.	-0.13	N.E.	N.E.
Motor skills (HFMSE)	0.26*	0.27*	0.32*	0.59*	0.45*	0.47*	-0.04	N.E.	N.E.
Pain (SF-36)	0.28*	N.E.	0.06	0.04	N.E.	N.E.	0.21	N.E.	N.E.
Fatigue (SF-36)	0.19	N.E.	N.E.	-0.01	N.E.	N.E.	0.42*	N.E.	0.30*
HADS-A	0.01	N.E.	N.E.	-0.05	N.E.	N.E.	-0.29	N.E.	N.E.
HADS-D	-0.41*	N.E.	-0.44*	-0.24*	N.E.	-0.23	-0.49*	N.E.	-0.41*
CISS									
Task-oriented	-0.06	N.E.	N.E.	-0.14	N.E.	N.E.	-0.03	N.E.	N.E.
Emotional	0.21	N.E.	N.E.	-0.11	N.E.	N.E.	-0.00	N.E.	N.E.
Avoidance	-0.09	N.E.	N.E.	-0.05	N.E.	N.E.	0.02	N.E.	N.E.
ΔR^2		0.14*	0.19*		0.21*	0.05		0.14*	0.36*
R^2		**0.33**			**0.26**			**0.50**	

Note: ΔR^2, change in R^2 between two equations; R^2, explained variance.

* All included variables significant correlation with outcome measure $p < 0.1$.

Abbreviations: USER-P, Utrecht Scale for Evaluation Rehabilitation-Participation; HFMSE, Expanded Hammersmith Functional Motor Scale; SF-36, Short Form 36–item Health Survey; HADS-A, Hospital Anxiety and Depression Scale; anxiety subscale; HADS-D, Hospital Anxiety and Depression Scale; depression subscale; CISS-21, Short Form of the Coping Inventory for Stressful Situations.

DISCUSSION

Patients with early onset SMA (type 1, 2, 3a) experienced more participation restrictions than patients with later onset SMA, but reported similar levels of frequency of participation and resulting satisfaction. Motor skills were independently associated with the frequency of and restrictions in participation. In addition, subjective complaints, namely fatigue, pain and particularly feelings of depression, were associated with participation scores in bivariate analyses. Coping styles were not associated with participation scores. In the multiple regression analyses, having feelings of depression proved to be the only subjective complaint independently related to participation (frequency and satisfaction).

This study identifies the participation activities that pose most problems for adult patients with SMA. There are a few studies on specific domains of participation that enrolled patients with a broader range of neuromuscular diseases. Employment rates of 40–57% were, for example, found in a mixed sample of patients with neuromuscular disorders.[12-14] This percentage is not only similar to our findings, but also comparable to that of patients with spinal cord injury.[28] Our data, therefore, seem to be in line with previous reports on participation in work activities of patients with moderate to severe motor impairments. Satisfaction scores of patients with SMA were also similar to those previously reported by patients with spinal cord injury and patients after stroke.[28,29] It reflects the fact that patients in different situations are able to reorganize their social activities on average, in a satisfactory way, regardless of their restrictions and type of condition.

Age at onset of SMA may also be relevant for satisfaction with participation, since patients with SMA type 1c–3a experienced more restrictions but similar levels of satisfaction as patients with a later onset. A possible explanation for this finding is that patients with early onset SMA might have adapted more successfully to living with severe physical limitations from a very early age onwards.[43] Patients with late onset SMA initially have normal motor development. Relevant physical limitations due to disease progression occur in adulthood. Continuous adaptation attempts might lead to enduring distress as these patients have to redefine their goals and concepts about their daily functioning.

Although the incidence of feelings of depression among patients with SMA is not higher than in those with other neuromuscular diseases,[18,20,21] the presence of feelings of depression was inversely associated with both frequency of participation activities and satisfaction with participation. This suggests that it is important to monitor whether feelings of depression are present in adult patients with SMA, and if so, to consider psychological interventions in order to reduce these feelings that might be the result of impaired emotional adaptation to disease progression.[43,44]

Coping style was not associated with any aspect of participation. To the best of our knowledge, there are no studies on the relationship between coping style and social

participation in patients with neuromuscular disorders. Studies have, however, been carried out on MS patients and spinal cord injury patients, and these also failed to find a relationship between coping styles and participation.[45,46] The fact that healthy individuals exhibit higher levels of coping variability than patients with chronic disease may play a role in this.[47] We cannot, however, exclude the possibility that coping styles are relevant for participation (satisfaction) in a subgroup of patients, in particular among patients with SMA type 3–4 who may face challenges of adaptation in later life.

As in other studies, pain was reported frequently, in particular by late onset patients.[18,48] Causes of pain are multiple, and include spinal deformities, muscle cramps or neurogenic pain. Univariable analysis showed that pain is associated with the frequency of participation activities in patients with SMA, but when feelings of depression was entered into the model, pain did not add significantly to the model (see Table 3.6).

The limited sample size is an important limitation of this study. It allowed the (pre) selection of a limited number of possible correlates. We made this preselection based on the existing literature and clinical experience. In our study we included adult patients with SMA over the whole spectrum (type 1c–4) and assessed participation in more detail than before. This gave us the opportunity to assess the relevance of already known variables in a broader group of patients with SMA, thus expanding the clinical relevance of our study. Follow-up studies should aim at a larger sample size to address the importance of other factors including endurance and stamina for motor activities, social support, upper extremity function and personal factors such as self-efficacy or illness perceptions, in particular since the largest portion of the variance in participation remains unexplained. Larger sample sizes would also allow more detailed subgroup analysis, for example, of subgroups with early and later onset. Although almost 80% of invited patients participated in this population-based study, we cannot fully exclude the possibility of inclusion bias, i.e., the selection of patients in a relatively good condition or of patients who experienced increasing problems (e.g. patients with SMA type 3b), which may have influenced the results of this study.

In conclusion, this study showed that although less restricted, patients with late onset SMA do not feel greater satisfaction with their participation in daily life than patients with early onset SMA. Compared to other diagnoses (e.g. spinal cord injury), SMA patients appear to be as satisfied with their participation in daily activities. Late onset patients reported more fatigue and experienced more pain than patients with early onset SMA. Motor skills, fatigue and feelings of depression in particularly are correlates of participation in daily life. Although these findings do not fully explain variation in participation, addressing these problems may be helpful in optimizing and personalising rehabilitation care for adult patients with SMA.

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Part two

Quality of life and participation in patients with ALS

Chapter 4

Associations between psychological factors and health-related quality of life and global quality of life in patients with ALS: A systematic review

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ABSTRACT

Objective: To systematically identify and appraise evidence on associations between psychological factors (moods, beliefs, personality) and Health-related QoL (HRQoL) and/or global QoL in patients with Amyotrophic Lateral Sclerosis (ALS).

Methods: A systematic review was conducted in several online databases (PsycINFO, EMBASE, PubMed and CINAHL) up to October 2015. Articles were included if they reported associations between psychological factors (moods, beliefs and personality) and HRQoL and/or global QoL in an ALS population. The search was limited to empirical studies, published in English, which provided quantitative data. The methodological quality of the included articles was assessed.

Results: In total, 22 studies were included. Mood was investigated in 14 studies, beliefs in 11 studies and personality in one study. Fifteen different psychological factors were extracted and assessed using 24 different measures. Twelve different QoL measures were used in the selected studies, subdivided into seven different HRQoL measures and five different global QoL measures. Higher levels of anxiety and depression appeared to be related to a poorer HRQoL, whereas a higher level of religiosity seemed to be associated with better global QoL. No conclusive associations were found for confusion-bewilderment (mood), spirituality, mindfulness, coping styles, hopelessness, perception of burden, cognitive appraisal (beliefs), neuroticism, extraversion, openness, agreeableness and conscientiousness (personality), due to insufficient or inconsistent evidence. Religiosity and spirituality appeared to become more positively associated over time.

Conclusions: Our results suggest that higher levels of anxiety and depression are related to a poorer HRQoL, whereas higher levels of religiosity appeared to be related to better global QoL. Associations might change during the disease course. This review supports the importance of psychological factors with regard to ALS care. Further research is needed to supplement the available evidence and to investigate how psychological factors can be modified to improve QoL.

Review registration number: PROSPERO 2015:CRD42015027303.

INTRODUCTION

Amyotrophic Lateral Sclerosis (ALS) is a fatal, progressive, neurodegenerative disorder affecting motor neurons in the spinal cord, brainstem and motor cortex. Patients suffer progressive wasting and weakness of limb, bulbar and respiratory muscles, leading to inability to speak and swallow, respiratory failure and complete paralysis.[1,2] Currently, there is increasing awareness that ALS is also associated with non-motor findings, including behavioral and cognitive deficits.[3,4] Patients eventually die due to respiratory failure within three to five years after symptom onset.[1] The incidence of ALS shows little variation in Western countries, ranging from 1.5 to 2.7 per 100,000 person-years,[5] with an estimated lifetime risk of 1 in 400.[6] To date, no curative treatment is available. Therefore, optimal treatment is based on symptom management and optimizing Quality of Life (QoL).

There is, as yet, no agreed-upon definition of QoL. The World Health Organization (WHO) defines QoL as 'a broad ranging concept affected in a complex way by the person's physical health, psychological state, level of independence, social relationships and their relationship to salient features of their environment' .[7] Burns et al.[8] have suggested that a distinction can be made between Health-related QoL (HRQoL) and global QoL in patients with ALS. Health-related QoL (HRQoL) is more narrowly defined than global QoL and seeks to address those aspects of self-perceived well-being that are related to or affected by the presence of disease or treatment.[8] Assessment of HRQoL typically includes physical, psychological and social domains. Each domain may include measures that assess the patient's perception of symptoms, ability to function and disability.[9] Global QoL reflects overall QoL as judged by the patient and takes into account other, non-medical concepts, such as family, support system and friends.[8] Assessing global QoL generally provides a broader picture of the impact of disease on an individual's life.[9]

HRQoL declines during the course of the disease.[10] This is expected as HRQoL instruments are heavily weighted toward physical function, and thus inevitably decline over time as patients with ALS lose their abilities. In contrast, there is growing evidence that global QoL seems to remain at a stable level, even in patients with advanced ALS. Psychological processes like coping, reframing expectations and spiritual practice might contribute to a change in internal standards and values of QoL, ultimately resulting in unexpectedly high QoL, even in later disease stages.[11,12] QoL in patients with ALS seems to be determined more by psychological, existential and support factors than by physical health,[13-16] implying that a broad range of factors is involved in adjusting to illness. Psychological factors in patients with ALS may be modifiable targets for interventions to improve QoL.

The impact of psychological factors such as neuroticism, coping, cognitive appraisals and mood on QoL has already been demonstrated in other chronic diseases[17,18] and in other progressive neurological illnesses, such as Huntington's disease, Parkinson's disease and

multiple sclerosis.[19] Differences have, however, been reported between these progressive neurological illnesses and ALS concerning the contribution of psychological factors to QoL,[19] suggesting that the rapidly progressive disabling process of ALS requires a different psychological adaptation process.

Over the last decade, interest has grown in the relationships between psychological factors and QoL in patients with ALS and to date, three narrative reviews on this subject have appeared.[20-22] The authors summarized associations between QoL and depression,[20,21] anxiety,[20] spiritual and existential issues,[20-22] sense of burden[22] and hope/hopelessness[20,22] in patients with ALS, but as they did not quantify or appraise them, the relationships remain unclear.

The present study aims to collect and appraise the available evidence on the associations between psychological factors and HRQoL and/or global QoL. Understanding the relationships between QoL and psychological factors and the contribution of these factors to either HRQoL or global QoL might help health professionals to develop adequate interventions in order to optimize QoL in patients with ALS.

METHODS

Procedure

A search of online databases EMBASE, PsychINFO, PubMed and CINAHL was carried out up to October, 2015. No constraint was placed on the year of publication. The following MeSH headings and key words were used: 'amyotrophic lateral sclerosis' or 'motor neuron disease' in combination with 'psychological factors' (and synonyms including related terms, e.g. anxiety, depression, coping, religiosity and neuroticism) and 'quality of life' (and synonyms including related terms, e.g. well-being, value of life and perceived health). Appendix 4.2 provides an overview of the search strategy used in PubMed. Two authors (AvG, CS) independently checked the titles and abstracts on the selection criteria shown below, and compared their results. Concurrence between both researchers was calculated using Cohen's kappa.[23] At each step of the process, disagreement regarding selection was discussed and settled with reference to the explicit inclusion criteria. If, after discussion, no agreement could be reached, another author (JV) was consulted for a final judgment. The same procedure was followed for final in- or exclusion after reading full text articles. The reference sections of retrieved articles were searched to identify further studies suitable for inclusion.

Quality assessment

After the study selection, methodological quality was assessed independently by two researchers (AvG, EK) according to an 8-point checklist, resulting in a score that ranged from

lowest quality (1) to highest quality (8).[17] The level of agreement between the researchers' ratings was established using the Intraclass Correlation Coefficient (ICC).

Eligibility criteria and operationalization of concepts

The current review is restricted to empirical studies which provided quantitative data, thus excluding qualitative studies, reviews and case reports. Only studies of patients with ALS or providing separate data from patients with ALS were included, in which standardized measures were used to assess direct relationships between psychological factors (determinant) and a total QoL construct (outcome). Studies using a total score for HRQoL and global QoL, or a mental or physical component score of the HRQOL and / or a single-item score representing global QoL, were included. Thus studies describing associations between psychological factors and one subscale of a QoL measure were not taken into account. Furthermore, the review was limited to studies written in the English language that were published in peer-reviewed journals.

Psychological factors are part of the contextual factors (personal and environmental factors) defined by the International Classification of Disability, Functioning and Health (ICF).[24] Psychological factors, such as coping styles, may play a role in disability at any level, but are not part of a health condition or health states.[24] In order to gain more insight into their association with HRQoL and/or global QoL, we have clustered the psychological factors into three main groups: mood, beliefs and personality. Mood is a generalized, internal state of feeling (e.g. anxiety, depression and anger) and is closely related to the concepts of affect and emotion. Beliefs refer to people's perceptions of reality including perceptions of health or illness and one's ability to cope with illness (e.g. attitudes, appraisals, religiosity, coping strategies). Personality can be defined as a dynamic and organized set of characteristics which a person possesses and which uniquely influence his or her beliefs, motivations and behaviour in various situations.[25]

Data extraction and analysis

We collected information on study characteristics: author, country, sample size and study design, and patient characteristics: age at inclusion, the time of assessment since ALS onset, the functional status of patients (using the Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS)), the diagnostic criteria and the type of ALS onset (spinal vs. bulbar). Furthermore, measures of global QoL and HRQoL and of psychological factors, as well as associations between psychological factors and QoL (Health-related and global) were extracted.

Bivariate and multivariate associations were described separately in terms of correlation coefficients (r), standardized β-coefficients (β) and the explained variance of the psychological

factors (R^2). The strength of correlation was described as follows: "weak" correlation = 0 < | r | < 0.3; "moderate" correlation 0.3 < | r | < 0.5; "strong" correlation | r | > 0.5.[23] We classified the methodological quality of the studies to be "high" if they were above 5.5, "adequate" between 3.5 and 5.5, and "poor" below 3.5.

Psychological factors were considered "consistent related" if (1) the majority (> 50%) of all studies reported statistically significant bivariate and/or multivariate associations; (2) the majority of the bivariate associations were moderate or strong; and (3) the methodological quality of these studies was adequate or high.

RESULTS

Description of studies included

The search strategy produced a total of 1,040 articles (Figure 4.1). After removing 153 duplicates, a further 887 articles were removed after screening title and abstract. Agreement on selection of titles and abstracts between the two raters was high (Cohen's kappa 0.82). A total of 57 articles remained for full-text screening; 22 articles met all inclusion criteria. The screening of reference lists produced one additional article.[10] In two studies,[16,26] the same cohort data was used; we included the study by Bremer because of a higher quality assessment.

The characteristics of the 22 included studies are presented in Table 4.1. Studies were published between 1999 and 2015; most were cross-sectional (n = 16); six used Long data.[16,27-31] The median sample size was n = 49 (range 26–197). Studies concerned patients with a mean time of ALS onset between 11.7 months and 5.7 years; the disease severity ranged from 17.4 (severely impaired) to 35.1 points (moderately impaired). The mean age at inclusion varied between 55.3 and 64.0 years; a minority of the patients (7–33%) had a bulbar onset of ALS, and there was a slight male prevalence (M:F ratio~1.5:1). These findings were consistent with those of the general ALS population (mean age 58–63 years; bulbar onset of 30% and M:F ratio~1.2–1.5:1).[32,33]

Across the studies, fifteen different psychological factors were assessed using 24 different measures. The various instruments for assessing psychological factors are described in Table 4.2. Mood was investigated in 14 studies, beliefs in 11 and personality in one study. Two ALS-specific questionnaires, the ALS Depression Inventory (ADI-12)[34] and the Motor Neuron Disease Coping Scale (MNDCS)[35] were applied in one[28] and three[30,36,38] studies, respectively. The modified versions of the Hospital Anxiety and Depression Scale (HADS), which were intended not to rely on measuring the physical components of depression, were used in two studies[37,38] (Table 4.2).

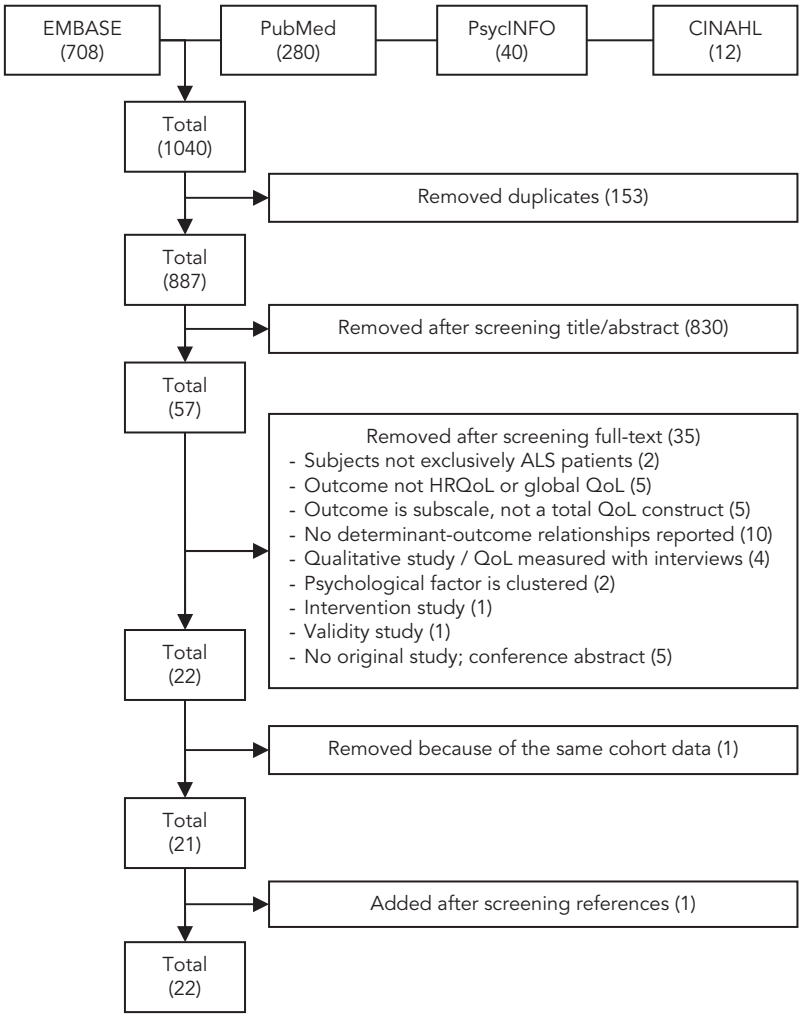

Figure 4.1. Search flowchart.

A total of 12 different QoL measures were used in the selected studies, including five different Global QoL measures and seven different Health-related QoL measures (Table 4.3a and Table 4.3b, resp.). One ALS-specific HRQoL questionnaire, the Sickness Impact Profile ALS (SIP/ALS-19),[39] was used in two studies.[14,31]

The average methodological quality score of the studies was 5.3 and ranged from 3 to 8 out of a maximum 8 points (Table 4.4). Seven studies (32%) achieved a "high quality" score (≥ 6/8). Inter-rater agreement on quality of the individual studies was high (ICC = 0.90).

Table 4.1. Patient and study characteristics

	Study characteristics			Patient characteristics				
Author (date)	Country of research	Sample size n (male n)	Design	Age in years	Time since onset (O) / Time since diagnosis (D)	ALSFRS	Diagnostic criteria	Onset bulbar (%)
Bremer [T0] (2004)[16]	USA	49 (29)	Longitudinal	57.8 (13.0)	34.9 (13.2) mo[O]	27.9 (6.3)	El Escorial	n.m
Chio (2004)[13]	Italy	80 (49)	Cross sectional	59.8 (12.6; 26–81)	2.1 (1.7; 1–7.8) yr[O]	26.6 (9.5; 3–38)	El Escorial	n.m
Clarke (2001)[15]	Ireland	26 (18)	Cross sectional	63[M] (34–86)	31.5 (4–156)[M] mo[D]	22.5[M] (11–36)	El Escorial	n.m
Dal Bello-Haas (2000)[47]	USA	60 (38)	Cross sectional	56.2 (12.2)	n.m	n.m	El Escorial	n.m
Ganzini (1999)[45]	USA	100 (61)	Cross sectional	54[M] (51.6–56.8)	2.8 (2.0–3.6)[M] yr[D]	n.m	n.m	n.m
Gibbons (2013)[38]	UK	147 (90)	Cross sectional	61 (11; 35–81)	n.m	22.3 (9.5; 4–48)	'confirmed diagnosis'	n.m
Goldstein (2002)[37]	UK	31 (19)	Cross sectional	64.0 (11.9)	15.9 (5.2) mo[D]	n.m	El Escorial	n.m
Ilse (2015)[10]	Germany	49 (25)	Cross sectional	63.8 (10.0)	35.1 (36.3) mo[O]	32.6 (9.2)[R]	El Escorial	33%
Krampe [T0] (2008)[27]	Germany	31 (19)	Longitudinal	60.3 (10.4; 32.9–79.7)	96.3 (70.5; 22.4–330.4) wk[O]	27.0 (6.6; 12–38)	El Escorial	19%
Lule [T0] (2008)[28]	Germany	39 (19)	Longitudinal	n.m	43.9 (37.5; 0–170) mo[D]	19.9 (21.1; 0–39)	El Escorial	n.m
Matuz (2010)[36]	Germany	27 (15)	Cross sectional	55.3 (11.1; 35–73)	36 (4–129) mo[D]	17.4 (9.8; 0–36)	'by a neurologist'	7%

Table 4.1. ***Continued***

	Study characteristics			Patient characteristics				
Author (date)	Country of research	Sample size n (male n)	Design	Age in years	Time since onset (O) / Time since diagnosis (D)	ALSFRS	Diagnostic criteria	Onset bulbar (%)
Matuz[T0] (2015)[30]	Germany	27 (15)	Longitudinal	55.3 (11.1; 35–73)	43.2 (30.5; 4–129) mo[D]	17.4 (9.8; 0–36)	El Escorial	7%
McCabe (2009)[19]	Spain	120 (72)	Cross sectional	63.2 (12.4)	5.7 (5.8)[O] yr	n.m	n.m	n.m
Montel (2012)[46]	France	49 (26)	Cross sectional	63 (12)	45 (28) mo[O]	28.2 (9.0)[R]	El Escorial	22%
Pagnini[T0] (2015)[29]	Italy USA	197 (115)	Longitudinal	*	*	30.6(9.9)[SA]	'self-declared'	n.m
Peric (2010)[40]	Serbia	74 (45)	Cross sectional	57 (11)	29 (27) mo[O]	34 (8)[R]	El Escorial	n.m
Pizzimenti (2013)[43]	Italy	36 (22)	Cross sectional	63.7 (10.9)	22 (14) mo[O]	35.1 (8.7)	El Escorial	22%
Robbins [T0] (2001)[31]	USA	60 (32)	Longitudinal	58.5 (13.5; 27–83)	n.m	28.1 (6.3; 12–39)	El Escorial	n.m
Simmons (2000)[14]	USA	96 (52)	Cross sectional	57.8 (23–80)	31.8 (2 mo–10 yr) mo[O]	26.6 (9–39)	'met the criteria'	n.m
Tramonti (2012)[42]	Italy	40 (30)	Cross sectional	59.1 (10.9; 34–84)	n.m	20.8 (8.3; 7–36)	n.m	n.m
Vignola [TD] (2008)[41]	Italy	29 (20)	Cross sectional	63.6 (7.8; 44–78)	11.7 (23.7; 2–43) mo[O]	33.1 (4.8; 22–39)	El Escorial	n.m
Winter (2010)[44]	Germany	37 (21)	Cross sectional	59.6 (11.0)	2.3 (1.9) yr[O]	n.m	El Escorial	n.m

Numbers are presented as means (SD; range), unless stated otherwise. Abbreviations: n.m = not mentioned; M = median instead of mean; yr = year; mo = months; wk = weeks; ALSFRS = Amyotrophic Lateral Sclerosis Functional Rating Scale; R = ALSFRS-Revised; SA = self-administered ALSFRS; T0 = data from baseline measurement; TD = data from diagnostic phase; O = onset; D = diagnosis; * = time since diagnosis and age were reported in categories.

Table 4.2. Psychological factor measurements

Psychological factors	Measurement and references	Number of items	Description	Scoring system	Generic / ALS-specific measure	References in this review
Anxiety	Hamilton rating scale for anxiety (HAM-A) Hamilton (1959)[63]	14	To assess the severity of symptoms of anxiety. Each of the items contains a number of symptoms, and each group of symptoms is rated on a scale.	5-point scale. Total scores for anxiety range from 0 to 56. Score interpretation: < 17: mild severity 18–24: mild to moderate severity 25–30: moderate to severe	Generic	[40]
	Hospital Anxiety and Depression Scale subscale anxiety (HADS-a) Zigmond (1983)[54]	7	To assess psychological distress in medically ill patients. The instrument concentrates on the psychic rather than the somatic symptoms of mood disorder in order to provide an assessment of mood independent of levels of physical disability in patients with medical illnesses.	4-point scale. Total scores for anxiety range from 0 to 21 Score interpretation: ≤ 7: non-cases 8–10: possible clinical levels of distress 11–21: clinical levels of distress	Generic	[15, 37]
	Hospital Anxiety and Depression Scale subscale anxiety (HADS-a) - modified version 1 Gibbons (2011)[56]	6	To assess psychological distress in medically ill patients. The original HADS was modified with removal of question 11 of the original HADS "I feel restless as if I have to be on the move".	4-point scale. Total scores for anxiety range from 0 to 18. Score interpretation: Scores of 9–18: case level anxiety	ALS	[38]
	State and Trait Anxiety Inventory (STAI) Spielberger (1968)[64]	40	To assess trait and state anxiety. STAIs: 20 items assess trait anxiety. STAIs is defined as an unpleasant emotional arousal in face of threatening demands or dangers; STAIt: 20 items assess state anxiety. STAIt reflects the existence of stable individual differences in the tendency to respond with state anxiety in the anticipation of treating situations. These two parts differ in the item wording, in the response format (intensity versus frequency), and in the instructions given for responses.	4-point scale. Total scores for anxiety (STAIs and STAIt) range from 20 to 80. Score interpretation: 20–39: low anxiety 40–59: medium anxiety 60–80: high anxiety	Generic	[41]

Table 4.2. ***Continued***

Psychological factors	Measurement and references	Number of items	Description	Scoring system	Generic / ALS-specific measure	References in this review
Depression	Beck Depression Inventory (BDI) Beck (1961)[53]	21	To assess severity of depressive symptoms.	4-point scale. Total scores for depression range from 0 to 63. Score interpretation: 0–9: no depressive symptoms 10–18: mild to moderate depressive symptoms 19–29: moderate to severe depression 30–63: severe depression	Generic	[10, 27, 44]
	Hamilton rating scale for depression (HAM-D) Hamilton (1960)[63]	21	To assess patient's level of depression. The first 17 of the 21 items contribute to the total score and items 18–21 give additional information, not part of the scale, such as paranoia and diurnal variation	8 items 5-point scale; 9 items 3-point scale. Total scores for depression range from 0 to 50. Score interpretation: 0–7 = normal 8–13 = mild depression 14–18 = moderate depression 19–22 = severe depression 23–50 = very severe depression	Generic	[40]
	Hospital Anxiety and Depression Scale subscale depression (HADS-d) Zigmond (1983)[65]	7	To assess psychological distress in medically ill patients. The instrument concentrates on the psychic rather than the somatic symptoms of mood disorder in order to provide an assessment of mood independent of levels of physical disability in patients with medical illnesses.	4-point scale. Total scores for depression range from 0 to 21. Score interpretation: ≤ 7: non-cases 8–10: possible clinical levels of distress 11–21: clinical levels of distress	Generic	[15]

Table 4.2 continues on next page.

Table 4.2. ***Continued***

Psychological factors	Measurement and references	Number of items	Description	Scoring system	Generic / ALS-specific measure	References in this review
	Hospital Anxiety and Depression Scale subscale depression (HADS-d) - modified version 2 Abrahams (1997)[66]	6	To assess psychological distress in medically ill patients. The original HADS was modified with removal of question 8: "I feel slowed down", as it was felt likely that this would falsely exaggerate the measure of depression due to the physical symptoms of ALS.	4-point scale. Total scores for depression range from 0 to 18. Score interpretation: ≤ 7: non-cases 8–10: possible clinical levels of distress 11–21: clinical levels of distress	ALS	[37]
	Hospital Anxiety and Depression Scale subscale depression (HADS-d) - modified version 1 Gibbons (2011)[56]	6	To assess psychological distress in medically ill patients. The original HADS was modified with removal of question 8: "I feel slowed down".	4-point scale. Total scores for depression range from 0 to 16 (Two items in the depression subscale were recorded 0-1-1-2). Score interpretation: Scores of 8–16: case level depression.	ALS	[38]
	Depressive disorders: DSM-IV. American Psychiatric Association (2000)[67]	9	To assess a major depressive disorder.	Score interpretation: 5 out of 9 symptoms have to be present and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure.	Generic	[45]
	ALS-Depression-Inventory (ADI-12) Kubler (2005)[34]	12	To assess depressive symptoms, specifically developed for ALS patients and addresses depressive symptoms excluding increasing physical impairments commensurate with ALS.	4-point scale. Total scores for depression range from 12 to 48. Score interpretation: < 22: absence of depression 22–28: mild depression > 28: clinically relevant depression	ALS	[28]

Table 4.2. ***Continued***

Psychological factors	Measurement and references	Number of items	Description	Scoring system	Generic / ALS-specific measure	References in this review
	Zung Depression Scale (ZDS); Zung (1965)[68] also called Zung Self-Rating Depression Scale (SDS) (1965)	20	To assess depression	4-point scale. Total scores for depression range from 20 to 80 Score interpretation: 50–59: mild depression 60–69: moderate depression 70–80: severe depression	Generic	[13, 41-43]
Mood	Profile of Mood State short-form (POMS-SF) McNair (1992)[69]	37	To assess six states of mood: tension-anxiety, depression-dejection, anger-hostility, vigour-activity, fatigue-inertia, and confusion-bewilderment.	Abbreviated 37-item version of the original scale using the 5-point Likert Scale; 0 (not at all) to 4 (extremely). Total mood disturbance (TMD): sum of the subscales. Score interpretation: Higher scores reflect higher presence of the mood state.	Generic	[19]
Religiosity	Idler Index of Religiosity (IRR) Idler (1987)[70]	4	To assess the level of religiosity. It addresses both public and private aspects of religiosity: Public religiosity (IIR-Pu) (2 items): frequency of church attendance and number of church members known personally Private religiosity (IIR-Pr) (2 items) how religious they perceived themselves to be and the amount of strength and comfort obtained from religious practices.	Public religiousness: 1-item, 6-point scale; 1-item, 4-point scale Private religiousness: 1-item, 4- point scale; 1-item, 3-point scale The religiosity scores are summed to produce public, private, and total religiosity; scores range from 2–10, 2–7 and 4–17, respectively. Score interpretation: Higher scores indicate higher level of religiosity.	Generic	[13, 14, 16, 31]
Spirituality	Spiritual Well-being Scale (SWBS) (1) Reed (1987)[71]	10	To assess the level of spiritual well-being.	6-point scale. Total scores of spiritual well-being range from 6 to 36. Score interpretation: Higher scores indicate higher spiritual well-being.	Generic	[16]

Table 4.2 continues on next page.

Table 4.2. ***Continued***

Psychological factors	Measurement and references	Number of items	Description	Scoring system	Generic / ALS-specific measure	References in this review
	Spiritual Well-being Scale (SWBS) (2) Ellison (1983)[72]	20	The scale consists of 10 religious well-being items (RWB) and 10 existential well-being items (EWB); spiritual well-being.	6-point scale. Total scores (RWB + EWB) of spiritual well-being range from 20 to 120. Score interpretation: Higher scores indicate higher spiritual well-being.	Generic	[47]
Mindfulness	Langer mindfulness scale (LMS) Pirson (2012)[73]	14	Three domains associated with mindful thinking: novelty seeking, engagement and novelty producing.	Total scores range from 14–98, Score interpretation: Higher scores reflect higher mindfulness	Generic	[29]
Hopelessness	Becks Hopelessness Scale (BHS) Beck (1974)[74]	20	To assess three major aspects of hopelessness: feelings about the future, loss of motivation, and expectations.	2-point scale. Total scores of hopelessness range from 0 to 20. 8–13: moderate hopelessness > 14: severe hopelessness Score interpretation: Higher scores reflect higher levels of hopelessness.	Generic	[45]
Perception of burden to others	Zarit Burden Inventory (ZBI) – revised Zarit (1980)[75]	3	Three items of the original ZBI were revised to measure patient beliefs that their medical condition stressed, burdened, or caused financial hardship to their family.	5-point scale. Total score of perception of burden to others (1 item) range from 0 to 4. Score interpretation: Higher score indicates higher perception of burden to their family.	ALS	[45]
Cognitive appraisal	Appraisal scale Smith (1993)[76]	4	To assess patients' primary (motivational relevance, motivational congruence) and secondary appraisal (problem-focused and emotion-focused coping potential)	9-point scale. Scores per item range from 1 to 9. Total scores are not mentioned. Score interpretation: The larger the difference between the two items of primary appraisal (motivational relevance and motivational congruence), the more patients feel threatened by the disease.	Generic	[30, 36]

Table 4.2. ***Continued***

Psychological factors	Measurement and references	Number of items	Description	Scoring system	Generic / ALS-specific measure	References in this review
Coping	Motor Neuron Disease Coping Scale (MNDCS) – adapted version 1 Lee (2001)[35]	18	To assess extent to which patients relied on the coping strategies. 18 questions of the original 22-item scale were assigned to 6 subscales.	6-point scale. Total score for each type of coping was obtained by generating the mean score of the grouped scales. Ranges of total scores are not mentioned. Score interpretation: Higher score reflects greater use of the coping strategy.	ALS	[30, 36]
	Motor Neuron Disease Coping Scale (MNDCS / Cope-MND) – adapted version 2 Lee (2001)[35]	9	To assess extent to which patients relied on the coping strategies. The original MNDCS was reduced to a 9-item scale.	6-point scale. Ranges of total scores are not mentioned. Score interpretation: Higher scores reflect greater use of the coping strategy.	ALS	[38]
	The Brief COPE Carver (1997)[77]	28	Measures 14 dimensions of coping: distraction; active coping; denial; emotional support; instrumental support; disengagement; venting; positive reframing; planning; acceptance; humour; religion; self-blame; substance use. Each dimension consists of 2 items.	4-point scale. No overall score. Score range per dimension ranges from 2 to 8, per item from 1 to 4. Score interpretation: Higher score reflects greater use of the coping strategy.	Generic	[46]
Personality traits	NEO Five Factor Inventory (NEO-FFI) Costa (1992)[78]	60	To assess the five dimensions of personality, postulated by the five-factor model of personality: neuroticism, extraversion, openness, agreeableness, and conscientiousness.	5-point scale. Each of the five-factor subscales consists of 12 items, resulting in mean factor scores ranging from 0 to 4. Score interpretation: Higher score reflects a type of personality.	Generic	[27]

Table 4.2 continues on next page.

Table 4.3a. Global Quality of Life measurements

Global QoL Measurement and reference	Number of items	Description	References in this review
The Schedule for the Evaluation of Quality of Life (SEIQoL) McGee (1991)[79] O'Boyle (1992)[80]	46	SEIQoL assesses overall subjective QoL as judged by the patient in healthy or ill individuals. It is derived from a decision analysis technique known as judgement analysis, administered through a semi-structured interview. Patients rate their satisfaction with areas of their life by assessing three aspects of QoL. The patients have to 1) nominate the life areas (cues) which are important to their QoL; 2) rate their current level of functioning in each of these salient areas; and 3) rate the relative importance of each of their chosen cues. SEIQoL index score: the SEIQoL scores are entirely person-specific, for the purpose of group analyses an overall global or index QoL score (also referred to as a total QoL score) is calculated. The resulting SEIQoL index ranges from 0 (worst possible QoL) to 100 (best possible QoL).	[15, 42]
The Schedule for the evaluation of Quality of Life-Direct Weighting (SEIQoL-DW) Hickey (1996)[81]	15	SEIQoL-DW is a shorter, direct-weight (DW) version of the SEIQoL, employs an alternative method of deriving cue weights using a colored disk. SEIQoL-DW index score: The SEIQoL-DW scores are entirely person-specific; for the purpose of group analyses an overall global or index QoL score (also referred to as a total QoL score) is calculated. The resulting SEIQoL index ranges from 0 (worst possible QoL) to 100 (best possible QoL).	[13, 28, 30, 37]

Table 4.3a. ***Continued***

Global QoL Measurement and reference	Number of items	Description	References in this review
The McGill Quality of Life Questionnaire (MQOL) Cohen SR (1995/1996)[82,83]	17	MQOL assesses overall subjective QoL as judged by the patient. Subjects evaluate their lives over the past 2 days on five subscales using a 10-point semantic-differential format. Originally designed for cancer and HIV patients. It is not heavily weighted toward physical function and it includes an existential element. MQOL includes five domains, two of which are health-related: Physical Symptoms (MQOL-Ph) (3 items) and Physical Well-being (MQOL-PW) (1 item); and three are non-health-related: Psychological symptoms (MQOL-Ps) (4 item); Existential Well-being (MQOL-EW) (6 items) and Social Support (MQOL-Su) (2 items). Scores on the subscales range from 0 (worst) to 10 (best). The MQOL total score is the mean of the 5 subscales, score ranges from 0 (worst QoL) to 10 (best QoL). MQOL-SIS: besides the subscales there is also a Single-Item Score (SIS): the patient is asked to indicate his/her self-perceived overall QoL in the past two days in a single-item scale (SIS) measuring overall subjective QoL, rated from 0 (very bad) to 10 (excellent).	[13, 14, 16, 27, 29, 41]
QoL-single-item question Self-developed by Ganzini (1999)[45]	1	A single-item question to assess patients self-perceived overall QoL. End-points labelled 1 = "my quality of life is as good as it can be" and 6 = "my quality of life is very bad, horrible".	[45]
QoL-single-item question Self-developed by Krampe (2008)[27]	1	A single-item question to assess patients self-perceived overall QoL. "Over the past seven days, the quality of my life has been": very poor (0) – excellent (10).	[27]

Table 4.3b. Global Quality of Life measurements

Health-related QoL Measurement and reference	Number of items	Description	References in this review
The 36-items Short Form of the Medical Outcomes Study questionnaire (SF-36) Ware (1993) [52]	36	SF-36 is a standardised, generic health-related quality of life measure. It consists of 36 items covering 8 dimensions. Each dimension is transformed into a 0-100 scale on the assumption that each question carries equal weight. High scores indicate good QoL. Four of these dimensions (limitations in physical functioning (PF); role limitations due to physical health problems (RP), bodily pain (BP), and general health perceptions (GH)) are summarized in the Physical Component Score (PCS), and four others (vitality (VT); social functioning (SF), role limitations due to emotional problems (ER), general mental health (MH)), in the Mental Component Score (MCS).	[44, 46]
Sickness Impact Profile (SIP) Bergner (1981) [84]	136	SIP measures physical, mental and social aspects of health-related functioning; it contains statements regarding behaviour "sickness impact" and the individual is asked to respond by checking items that describe their health status. SIP contains 136 items in 12 categories and two dimensions (physical and psychosocial). Overall, category and dimension scores may be calculated from 0 – 100 (best).	[47]
Sickness Impact Profile (SIP/ ALS-19) McQuire (1997) [39]	19	SIP/ALS-19 assess health-related QoL. It is a questionnaire consisting of 19 items from the full SIP (Sickness Impact Profile) believed to have the greatest impact on QoL, based on opinions of ALS clinical specialists. Extracted from the full SIP total score range from 0 – 100 (best).	[14, 31]
EuroQoL-5D Brazier (1993) [85]	5	EuroQoL-5D assess health-related QoL. It consists of five questions that relate to five dimensions of health: mobility, self-care. usual activities, pain/discomfort, anxiety/depression. Each dimension is divided into three levels of severity (1, no problem; 3 severe problem). The EQ-5D-index score can be calculated.	[10, 44]

Table 4.3b. ***Continued***

Health-related QoL Measurement and reference	Number of items	Description	References in this review
EQ VAS Konig (2005) [86]	1	EQ VAS assess health-related QoL. It is a visual analogue scale (VAS thermometer type) to rate patients current HRQoL ranging from 0 (worse imaginable health state) to 100 (best imaginable health state).	[44]
World Health Organization Quality of Life brief questionnaire (WHOQoL-BREF) Skevington (2004) [87]	26	WHOQoL-BREF assesses quality of life within the context of an individual's culture, value systems, personal goals, standards and concerns. Generic instrument, measures QoL of life across 4 domains: physical health (7 items), psychological health (6 items), social relationships (3 items) and environment (8 items). Domain scores can be transformed to total scores from 0 (worse imaginable health state) to 100 (best imaginable health state). Two other items measure overall QoL and general health. Items are rated on a 5-point scale (low score of 1 to high score of 5) to determine a raw item score. Subsequently, the mean score for each domain is calculated, resulting in a mean score per domain that is between 4 and 20. Finally, this mean domain score is then multiplied by 4 in order to transform the domain score into a scaled score, with a higher score indicating a higher QoL.	[19, 38]
Quality of Life Index (QL-Index) Spitzer 1981 [88]	5	The Spitzer Qol Index (SQLI/ QLI/ QL-Index) assesses health-related QoL in palliative care populations. It covers five dimensions of quality of life: activity, daily living, health, support of family and friends, and outlook on life. Each dimension is rated on a three-point Likert scale (0 to 2), with the range of scores from 0 to 10. Lower scores reflect a higher QoL.	[43]

Table 4.4. Methodologic quality assessment

Reference	Year	Internal validity	Control of drop out	External validity	Statistical validity	Proportion Sample size vs determinants	Multi-collinearity	Confounding bias	Reporting	Total (max 8 points)
Bremer[16]	2004	1	1	1	1	0	0	0	1	5.0
Chio[13]	2004	1	0.5	1	1	0	0	1	1	5.5
Clarke[15]	2001	1	1	1	1	0	0	0	1	5.0
Dal-Bello-Haas[47]	2000	1	0	0.5	1	0	0	0	1	3.5
Ganzini[45]	1999	0	1	0.5	1	1	0	1	1	5.5
Gibbons[38]	2013	1	0	1	1	1	1	1	1	7.0
Goldstein[37]	2002	1	0	1	1	0	0	0	0	3.0
Ilse[10]	2015	1	0	1	1	0	0	0	1	4.0
Krampe[27]	2008	0	0	1	1	0	0	1	1	4.0
Lule[28]	2008	1	0	0.5	1	0	0	1	1	4.5
Matuz[36]	2010	1	0	1	1	0	1	1	1	6.0
Matuz[30]	2015	1	1	1	1	0	0	1	1	6.0
McCabe[19]	2009	1	0	0.5	1	1	0	1	1	5.5
Montel[46]	2012	1	0	1	1	0	0	0	1	4.0

Table 4.4. ***Continued***

Reference	Year	Internal validity	Control of drop out	External validity	Statistical validity	Proportion Sample size vs determinants	Multi-collinearity	Confounding bias	Reporting	Total (max 8 points)
Pagnini[29]	2015	1	0.5	0.5	1	1	0	1	1	6.5
Peric[40]	2010	1	0.5	1	1	0	1	1	1	6.5
Pizzimenti[43]	2013	1	1	1	1	1	1	1	1	8.0
Robbins[31]	2001	1	0.5	0.5	1	1	0	1	1	6.0
Simmons[14]	2000	1	0.5	1	1	0	0	0	1	4.5
Tramtoni[42]	2012	1	0	0.5	1	0	0	1	1	4.5
Vignola[41]	2008	1	0.5	1	1	0	0	1	1	5.5
Winter[44]	2010	1	0.5	0.5	1	0	0	1	1	5.0

1 = internal validity: use of validated and reliable measures, 2 = control of patient drop-out: including nonresponse analysis and describing executive patients, 3 = external validity: specifying in/exclusion criteria and demographic and disease characteristics (diagnosis, age, gender, site of ALS onset, time since diagnosis, severity), 4 = statistical validity: testing for statistical significance, 5 = adequate sample size in relation to the number of determinants (univariate ratio 20:1 and multivariate ratio 10:1), 6 = control for multicollinearity, 7 = control for potential confounding variables, 8 = clear description of main finding.[17]

Psychological factors associated with QoL in ALS

An overview of the bivariate and multivariate associations between psychological factors and QoL is presented in Table 4.5. Due to the heterogeneity of instruments used in assessing both psychological factors (n = 24) and QoL (n = 12), a meta-analysis was not possible.

Mood associated with QoL

Concerning mood, relationships between QoL and anxiety, depression and confusion-bewilderment were found.

Anxiety

Six studies assessed the relationship between anxiety and QoL;[15,19,37,38,40,41] three studies reported HRQoL and 3 global QoL.

Two out of three studies, including one high quality study[38] which used a modified HADS, showed significant relationships with HRQoL; anxiety was strongly (-0.53) negatively associated with HRQoL. A similar contribution was obtained from multivariate analyses.[19] In contrast, one high quality study failed to find any relationship between anxiety and HRQoL.[40]

Significant negative associations with global QoL were found in one out of three studies.[41] More specifically, low trait and state anxiety was associated with higher global QoL and was found in the diagnostic as well as the follow-up phase.[41] Two studies, of which one used a modified HADS, did not find any significant associations with global QoL.[15,19]

Depression

In total, fourteen studies assessed depression in relation to QoL.[10,13,15,19,27,28,37,38,40-45] Eight studies reported associations with HRQoL and eight studies with global QoL. Two studies reported both HRQoL and global QoL outcomes.

A significantly negative association with depression and HRQoL was reported in seven out of eight studies, including two of high quality, of which one used a modified HADS. Depression was moderately to strongly (-0.430; -0.60; -0.617)[10,38,42] correlated with HRQoL[10,27,42-44] The contribution of depressive symptoms to HRQoL was also endorsed in regression analysis.[19,27,38,43,44] A single study of high quality failed, however, to find a significant association with depression and HRQoL in bivariate correlations.[40] Another study used four different HRQoL measures and found two out of four significant associations between depression and HRQoL in bivariate and multivariate analysis.[44]

A significantly negative association with depression and Global QoL was reported in four out of eight studies, in both bivariate and multivariate analysis.[13,27,28,41] Depression was moderately (-0.36)[28] negatively associated with global QoL. In four other studies, however, including 2 which used ALS-specific questionnaires, no significant correlations between depression and global QoL were demonstrated.[15,37,42,45]

Table 4.5. Results of the bivariate and multivariate associations between psychological factors and QoL in patients with ALS

	Psychological factor	Measure psychological factor		Measure QoL	Time-points of assessment / F.U. / trajectory	Bivariate association r	Multivariate association β / R^2	Ref.	Quality Score (max. 8)
MOOD	Anxiety								
	Anxiety	HAM-A	HRQoL	SF-36 total		ns / nr		[40]	6.5
		HAM-A		SF-36 PCS		ns / nr			
		HAM-A		SF-36 MCS		ns / nr			
		HADS-a[1]		WHOQoL-BREF total		-0.53**		[38]	7.0
	Anxiety - Tension	POMS		WHOQoL-BREF total		nr	β = -0.47*	[19]	5.5
	Anxiety	HADS-a	Global QoL	SEIQoL index score		ns / nr		[15]	5.0
		HADS-a		SEIQoL-DW index score		ns / nr		[37]	3.0
	State anxiety	STAIs[O]		MQOL total		nr	s**/ nr	[41]	5.5
		STAIs		MQOL total	<1 mo after D.	nr	s**/ nr		
		STAIs		MQOL total	>1 mo after D.	nr	s* / nr		
	Trait anxiety	STAIt		MQOL total	<1 mo after D.	nr	s** / nr		
		STAIt		MQOL total	>1 mo after D.	nr	s* / nr		
	Depression								
	Depression – Dejection	POMS	HRQoL	WHOQoL-BREF total		nr	β = -0.24*	[19]	5.5
	Depression	HADS-d[1]		WHOQoL-BREF total		-0.60**	β = -0.41*	[38]	7.0
		HAM-D		SF-36 total		ns / nr		[40]	6.5
		HAM-D		SF-36 PCS		ns / nr			
		HAM-D		SF-36 MCS		ns / nr			
		ZDS		SF-36 total		-0.617**		[42]	4.5
		ZDS		QL-Index		s / nr*	β = -0.08*	[43]	8.0
		BDI		EQ-5D index score		-0.430**		[10]	4.0
		BDI[A]		SF-36 MCS		nr	β = -0.391**	[44]	5.0
		BDI[A]		SF-36 PCS		ns / nr			
		BDI[A]		EQ-5D index score		nr	β = -0.272		
		BDI[A]		EQ VAS		nr	β = -0.381*		

Table 4.5 continues on next page.

Table 4.5. ***Continued***

	Psychological factor	Measure psychological factor		Measure QoL	Time-points of assessment / F.U. / trajectory	Bivariate association r		Multivariate association β / R^2	Ref.	Quality Score (max. 8)
MOOD		BDI		HRCS	1 mo F.U.	nr		s / nr	[27]	4.0
		BDI		HRCS	12 mo F.U.	nr		s** / nr		
	Depression x time	BDI		HRCS	over 12 mo	nr		ns		
	Depression	ADI-12	Global QoL	SEIQoL index score		-0.36*			[28]	4.5
		DSM-IV		Single-item-question[3]		ns / nr		ns / nr	[45]	5.5
		ZDS		SEIQoL-DW index score		nr		s* / nr	[13]	5.5
		ZDS		MQOL Single Item Score		nr		s* / nr		
		ZDS		SEIQoL index score		-0.205			[42]	4.5
		ZDS°		MQOL total		nr		s**/ nr	[41]	5.5
		HADS-d		SEIQoL index score		ns / nr			[15]	5.0
		HADS-d[2]		SEIQoL-DW index score		ns / nr			[37]	3.0
		BDI		Single-item-question[4]	1 mo F.U.	nr		s* / nr	[27]	4.0
		BDI		Single-item-question[4]	12 mo F.U.	nr		s* / nr		
	Depression x time	BDI		Single item question[4]	over 12 mo	nr		ns		
	Confusion - Bewilderment	POMS	Global QoL	WHOQoL-BREF total		nr		β = 0.33*	[19]	5.5
BELIEFS	Religiosity									
		IIR-tot	HRQoL	SIP/ALS-19 total		0.169			[14]	4.5
		IIR-tot		SIP/ALS-19 total	3 mo F.U.	nr		ns / nr	[31]	6.0
		IIR-tot		SIP/ALS-19 total	6 mo F.U.	nr		s*** / nr		
	Religion - coping	Brief COPE		SF-36 PCS / SF-36 MCS		-0.26[P]	-0.01[M]		[46]	4.0
	Religiosity	IIR-tot	Global QoL	MQOL total		0.15			[16]	5.0
		IIR-tot		MQOL total	3–4 mo F.U.	0.28				
		IIR-tot		MQOL total	6–8 mo F.U.	0.37**				
		IIR-tot		MQOL total	9–12 mo F.U.	0.33*				

Table 4.5. ***Continued***

	Psychological factor	Measure psychological factor		Measure QoL	Time-points of assessment / F.U. / trajectory	Bivariate association r	Multivariate association β / R^2	Ref.	Quality Score (max. 8)
BELIEFS		IIR-tot		MQOL total	12–16 mo F.U.	0.46**			
		IIR-tot		MQOL total	3 mo F.U.	nr	ns / nr	[31]	6.0
		IIR-tot		MQOL total	6 mo F.U.	nr	ns / nr		
		IIR-tot		MQOL total		0.221		[14]	4.5
		IIR-tot		MQOL Single Item Score		0.331**			
	Religiosity Private	IIR-Pr		MQOL total		0.13	β = 0.05; R^2=0	[16]	5.0
		IIR-Pr		MQOL total	3–4 mo F.U.	0.42**	β = 0.31**		
		IIR-Pr		MQOL total	6–8 mo F.U.	0.49**	β = 0.35**		
		IIR-Pr		MQOL total	9–12 mo F.U.	0.34*	β = 0.21		
		IIR-Pr		MQOL total	12–16 mo F.U.	0.50**	β = 0.41***; R^2 = 16***		
		IIR-Pr		SEIQoL-DW index score		s* / nr		[13]	5.5
	Spirituality							[16]	5.0
	Existential well-being	SWBS[6] - EWB	HRQoL	SIP total		ns / nr		[47]	3.5
	Religious well-being	SWBS[6] - RWB		SIP total		-0.996**			
	Spiritual well-being	SWBS[5] total	Global QoL	MQOL total		0.08		[16]	5.0
		SWBS[5] total		MQOL total	3–4 mo F.U.	0.08			
		SWBS[5] total		MQOL total	6–8 mo F.U.	0.17			
		SWBS[5] total		MQOL total	9–12 mo F.U.	-0.12			
		SWBS[5] total		MQOL total	12–16 mo F.U.	0.54**			

Table 4.5 continues on next page.

Table 4.5. ***Continued***

	Psychological factor	Measure psychological factor		Measure QoL	Time-points of assessment / F.U. / trajectory	Bivariate association r		Multivariate association β / R^2	Ref.	Quality Score (max. 8)
	Mindfulness									
	Mindfulness	LMS	Global QoL	MQOL Single Item Score		nr		β = 0.06***	[29]	6.5
	Mindfulness x time	LMS		MQOL Single Item Score	over 4 mo	nr		β = 0.009		
	Coping									
	Positive coping strategies	MNDCS[1]	HRQoL	WHOQoL-BREF total		0.46**		β = 0.35***	[38]	7.0
	Distraction	Brief COPE		SF-36 PCS / SF-36 MCS		0.08[P]	-0.11[M]		[46]	4.0
	Active coping	Brief COPE		SF-36 PCS / SF-36 MCS		-0.16[P]	0.11[M]			
	Denial	Brief COPE		SF-36 PCS / SF-36 MCS		-0.15[P]	0.23[M]			
	Emotional support	Brief COPE		SF-36 PCS / SF-36 MCS		0.38[P]*	0.10[M]			
	Instrumental support	Brief COPE		SF-36 PCS / SF-36 MCS		-0.31[P]	-0.02[M]			
	Disengagement	Brief COPE		SF-36 PCS / SF-36 MCS		0.16[P]	0.33[M]			
BELIEFS	Venting	Brief COPE		SF-36 PCS / SF-36 MCS		-0.10[P]	-0.38*[M]			
	Positive reframing	Brief COPE		SF-36 PCS / SF-36 MCS		-0.22[P]	0.32[M]			
	Planning	Brief COPE		SF-36 PCS / SF-36 MCS		-0.23[P]	0.11[M]			
	Acceptance	Brief COPE		SF-36 PCS / SF-36 MCS		-0.18[P]	0.23[M]			
	Humor	Brief COPE		SF-36 PCS / SF-36 MCS		-0.15[P]	0.25[M]			
	Self-blame	Brief COPE		SF-36 PCS / SF-36 MCS		0.11[P]	-0.24[M]			
	Substance use	Brief COPE		SF-36 PCS / SF-36 MCS		0.26[P]	-0.44*[M]			
	Problem management	MNDCS[2]	Global QoL	SEIQoL index score				β = 0.44**	[36]	6.0
	Problem management	MNDCS[2]		SEIQoL index score	3–6 mo F.U.	nr		β = 0.42**	[30]	6.0
	Problem appraisal	MNDCS[2]		SEIQoL index score		nr		β = 0.15	[36]	6.0
	Emotion management	MNDCS[2]		SEIQoL index score		nr		β = -0.26		
	Emotional avoidance	MNDCS[2]		SEIQoL index score		nr		β = 0.39*		
	Emotional avoidance	MNDCS[2]		SEIQoL index score	3–6 mo F.U.	nr		β = 0.28	[30]	6.0

Table 4.5. ***Continued***

	Psychological factor	Measure psychological factor		Measure QoL	Time-points of assessment / F.U. / trajectory	Bivariate association r	Multivariate association β / R^2	Ref.	Quality Score (max. 8)
BELIEFS	Hopelessness	BHS	Global QoL	Single-item-question[3]		0.43***	s** / nr	[45]	5.5
	Perception of burden to others	ZBI - revised	Global QoL	Single-item-question[3]		0.45***	s* / nr	[45]	5.5
	Cognitive appraisal								
	Appraisal total	Appraisal scale	Global QoL	SEIQoL index score		nr	R^2 = 2%	[36]	6.0
	Primary appraisal	Appraisal scale		SEIQoL index score		nr	β = -0.004		
	Appraisal of coping potential	Appraisal scale		SEIQoL index score		nr	β = 0.15		
PERSONALITY	Agreeableness	NEO-FFI	Global QoL	Single-item-question[4]		nr	β = 1.88*	[27]	4.0
	Agreeableness	NEO-FFI	HRQoL	HRCS		nr	β = 0.69*		
	Agreeableness x time	NEO-FFI	Global QoL	Single-item-question[4]	over 12 mo	nr	β = -0.28*		
	Agreeableness x time	NEO-FFI	HRQoL	HRCS	over 12 mo	nr	β = -0.09*		
	Neuroticism	NEO-FFI	Global QoL	Single-item-question[4]		nr	ns / nr		
	Extraversion	NEO-FFI		Single-item-question[4]		nr	ns / nr		
	Openness	NEO-FFI		Single-item-question[4]		nr	ns / nr		
	Conscientiousness	NEO-FFI		Single-item-question[4]		nr	ns / nr		

Significance levels: * $p < 0.1$; ** $p < 0.01$; *** $p < 0.001$. Abbreviations: ns = not significant; nr = not reported; r = correlation; β = standardized regression coefficient; R^2 = explained variance of the determinant; D = diagnosis; A = obtained from the author; F.U. = follow-up; 1 = modified version 1; 2 = modified version 2; 3 = self-developed single-item-question by Ganzini; 4 = self-developed single-item-question by Krampe; 5 = SWBS developed by Reed;[51] 6 = SWBS developed by Ellison;[52] HRCS: health-related QoL composite score. PCS = physical component summary (P); MCS = mental component summary (M); T0 = data from baseline measurement; O = overall (both <1 month after diagnosis and >1 month after diagnosis); Abbreviations of measurements: see Table 4.2 and 4.3.

A prospective long-term follow-up study reported the relationship between depression and HRQoL and global QoL during the first year after baseline measurement. Patients who were more depressed had lower HRQoL and global QoL scores at month 1 and during a 12-month follow-up. The results of a linear mixed model analysis showed no interaction effect between depression and time, indicating that more depressed patients did not differ from less depressed patients as far as the trajectories of Global QoL and HRQoL were concerned.[27]

Confusion-Bewilderment

One study examined the relation between 'confusion - bewilderment' and QoL. In regression analysis, this mood state made a significant positive contribution to HRQoL ($\beta = 0.33$).[19]

Beliefs associated with QoL

With regard to beliefs, relationships between QoL and religiosity, spirituality, mindfulness, coping, hopelessness, perception of burden and cognitive appraisal were found.

Religiosity

Five studies assessed the relationship between religiosity and QoL:[13,14,16,31,46] three of these reported HRQoL, 4 global QoL and 2 studies both HRQoL and global QoL outcomes.

Two out of three studies did not find any significant relationships between religiosity and HRQoL.[14,46] Regression analyses of a third study, which was of high quality,[31] revealed that a high level of religiosity made a significant positive contribution to HRQoL at 6 months' follow-up, but not at the earlier assessment (3 months' follow-up).

Three out of four studies[13,14,16] showed that a higher level of religiosity was significantly related to higher global QoL. Both 'religiosity' and 'private religiosity' (how religious patients perceived themselves to be and the amount of strength and comfort obtained from religious practices) developed a significant, moderate to strong association with global QoL over time (3–16 months' and 6–16 months' follow-up, respectively).[16] Regression analysis confirmed this increasing relationship between 'private religiosity' and global QoL with time and showed an increase in explained variance of 16% at 12 months follow-up.[16] On the other hand, one high quality study did not find any significant associations with religiosity and global QoL at 3 or 6 months' follow-up.[31]

Spirituality

Two studies tested the correlation between spirituality and QoL.[16,47] One used an HRQoL measure,[47] whereas the other a global QoL measure.[16]

The first study[47] split spiritual well-being along the dimensions of religious well-being (which refers to a relationship with God or what is understood as a spiritual being) and existential well-being (which involves a sense of purpose and meaning in life as a means of

feeling connected to the world, separate from any specifically religious reference, beliefs and needs). Existential well-being was not associated with HRQoL. In contrast, religious well-being was strongly associated (-0.99) with higher HRQoL, independent of the clinical phase of ALS.

The second study[16] showed that spirituality (which refers to a search for the sacred or divine through any type of life experience) was strongly associated (0.54) with higher global QoL at long-term follow-up (12–16 months) but not at the earlier assessments.

Mindfulness

One recent high quality study found a positive association between mindfulness 'the process of actively making new distinctions about a situation and its environment, or its current context, rather than relying on previous categorizations from the past'[48] and global QoL.[29] The results of a linear mixed model analysis showed that high mindfulness at baseline predicted significantly higher global QoL scores after four months.[29]

Coping

Four studies, including three high quality studies, investigated the associations between coping and QoL,[30,36,38,46] in which two studies reported HRQoL and two studies global QoL measures.

One high quality study out of two showed that 'adoption of positive coping strategies' was moderately positively (0.46) associated with HRQoL.[38] The second study[46] related 14 coping strategies to HRQoL (36-item Short Form (SF36); Mental Component Summary score (MCS) and Physical Component Summary scores (PCS)). Of these 28 bivariate correlations, three were significantly associated: negative, moderate correlations were noted between MCS and substance use (-0.44) and between MCS and venting (an externalizing coping technique, the outward expression of emotions) (-0.38). PCS was positively, moderately associated with emotional support (0.38). The other 11 coping strategies (e.g. acceptance, denial, self-blame) were not associated with HRQoL.[46]

Two high quality studies, analyzing the same cohort, showed that the coping strategy 'problem management' was positively associated with global QoL. The first study[36] with a cross-sectional design, using multivariate regression analysis, revealed positive associations between the coping strategy 'problem management' and 'emotional avoidance' and global QoL at baseline.[30] Analysis of a Long follow-up[30] revealed that only the coping strategy 'problem management' was a significant predictor; patients who searched more frequently for information and support at baseline reported higher global QoL at 3 to 6 months' follow-up.[30]

Hopelessness

One study tested the association of hopelessness and global QoL.[45] It was shown that greater hopelessness was moderately correlated with lower global QoL (0.43). This relationship was still significant in a multivariate regression analysis with control variables.

Perception of burden to others

A single study examined the 'perception of burden to others'. Having the belief of being a burden to others was moderately associated with lower global QoL (0.45). The association remained significant in the regression analyses.[45]

Cognitive appraisal

A single study[36] assessed 'cognitive appraisal', which was split into patient's primary (motivational relevance, motivational congruence) and secondary appraisal (problem focused and emotional focused coping potential) and related to global QoL. Results of the regression analysis showed no associations of cognitive appraisal with global QoL. The variance of the global QoL scores could not be significantly accounted for by any of the appraisals scales.

Personality associated with QoL

Neuroticism, extraversion, openness, agreeableness and conscientiousness

One study[27] investigated the relationship between personality factors and QoL. In the regression analysis, it was shown that among the five personality factors (neuroticism, extraversion, openness, agreeableness and conscientiousness), only agreeableness had a strong positive association with both global QoL and HRQoL. Agreeableness refers to 'a personality trait manifesting itself in individual behavioral characteristics that are perceived as kind, sympathetic, cooperative, warm and considerate'.[49] There was also a significant interaction effect of agreeableness and time, meaning that agreeableness significantly influenced the course of global QoL and HRQoL; patients who scored higher on agreeableness had higher QoL ratings at baseline measurement but their decline in QoL was steeper compared to patients with lower scores in agreeableness.[27]

DISCUSSION

The aim of the present review was to systematically collect and appraise evidence of the relationships between psychological factors (mood, beliefs, personality) and QoL in patients with ALS. This review showed that higher levels of anxiety and depression appeared to be related to a poorer HRQoL, whereas a higher level of religiosity seemed to be related to higher global QoL. Furthermore, associations might change during the disease course.

Mood

Anxiety seemed to be negatively related to HRQoL, because higher levels of anxiety were consistently associated with a poorer HRQoL. In contrast, global QoL showed no associations with anxiety; the association could not, however, be refuted because of one poor quality study. Depression was negatively associated with HRQoL, suggesting that the presence of depressive symptoms is related to a poorer HRQoL. On the other hand, for global QoL, we could not support a relationship with depression, because of inconsistent results.

Mood appeared to be related to HRQoL but not to global QoL. This is in concurrence with cancer studies,[9,50] which also revealed that depression explained a large amount of variation in HRQoL, but not global QoL. Our results might in part be ascribed to conceptual overlap[51] between determinants and outcomes. For example, questions about feelings of anxiety and depression are often also included in a HRQoL measure (e.g. "Have you felt downhearted and blue?" SF-36; question 9f[52]), and so studying anxiety and depression as determinants of HRQoL may result in strong associations between determinants and outcomes. This contamination is less likely between mood and global QoL measures, because global QoL assesses such a wide spectrum of domains that contribute to overall QoL as judged by the patient.

Furthermore, it is important to be aware that there is recent evidence suggesting that depression questionnaires, specifically the Beck Depression Inventory (BDI)[53] and to a lesser degree the Hospital Anxiety and Depression Scale (HADS),[54] tend to overestimate depression in ALS, since these scores are highly influenced by the physical impairment of the patients.[55,56] Consequently, the relationships that have been found between depression and HRQoL is questionable.

Beliefs

There seemed to be no relationship between religiosity and HRQoL, because most studies showed weak and non-significant associations. However, religiosity appeared to be positively associated with global QoL in the majority of the studies, including one high quality study. Consequently, we support the assumption that a high level of religiosity made a significant positive contribution to better global QoL. However, these results might also point out to contamination in concepts between religiosity and global QoL since The McGill Quality of Life Questionnaire (MQOL) total score includes items about existential well-being.

Religiosity might be important for the individual's global QoL because it may create meaning and coherence when an individual's world is devastated by a distressing and progressive disease.[47] These findings are mirrored in other diseases such as Multiple Sclerosis[57] and advanced cancer.[58] It should be taken into account that most of the included studies about religiosity are from North America and the religiosity questionnaire which was used relies predominantly on monotheistic terminology, about belief in God or experience

of God.[59] In current (western) culture, people are more interested in spirituality[60] and mindfulness[55] and are searching for a connection with the divine within themselves, instead of a connection with an external almighty power.[60] The fact that religiosity and spirituality are culture dependent and are defined differently in each country might explain the heterogeneity in findings on association of QoL.

Personality

The search has yielded only one hit concerning personality factors, suggesting that personality factors were not considered to be the most important psychological factors influencing QoL. Only a single study of low quality was included, conclusive associations between HRQoL or global QoL could, therefore, not be established.

Miscellaneous

Several other psychological factors were reported in only a single study or measured twice in the same cohort:[30,36] there was, therefore, insufficient evidence to support associations between HRQoL or global QoL and the following psychological factors: confusion-bewilderment (mood); spirituality, mindfulness, coping styles, hopelessness, perception of burden, cognitive appraisal (beliefs) and neuroticism, extraversion, openness, agreeableness and conscientiousness (personality).

Associations throughout the disease course

Although there was not enough evidence per psychological factor, it is valuable to point out with regard to psychological factors as a whole, that associations might change throughout the course of the disease; religiosity and spirituality appeared to become more positively associated with global QoL over time. This is in accordance with the theory of Waldron[61] who suggested that psychological adaptation to terminal illness may involve a shift in focus of determinants of QoL; in the initial stages of a progressive illness, patients may focus on physical functioning and on decreasing disability, but as the illness progresses, the importance of these issues may be replaced by a focus on the psychosocial and spiritual domains.

Strengths and limitations of this systematic review

This is the first systematic review on associations between psychological factors and QoL in patients with ALS. This review was carried out in accordance with the PRISMA guidelines (see Appendix 4.1). The methodological quality of the studies and the consistency of the associations between psychological factors and HRQoL and global QoL were comprehensively

appraised. A limitation, however, of our study is that only a small number of psychological factors could be compared, because most of the associations with QoL were only reported once. Besides, our review may have missed relevant papers published in non-English journals. Finally, as studies with significant results are more likely to be published than studies without significant results, publication bias has to be taken into account.

Limitations of the literature

First, the heterogeneity of the literature with respect to instruments for assessing psychological factors and QoL may have influenced the associations. Levels of anxiety and depression, for example, were measured using 5 and 7 different questionnaires, respectively, and moreover, with a mix of both generic and ALS-specific questionnaires, or questionnaires modified for ALS. Concerning QoL measures, 7 different HRQoL and 5 different global QoL (mostly generic) measures, were extracted. Second, in order to detect which psychological factors affect HRQoL and global QoL over the course of the disease, it is essential to cluster the data of patients according to the same disease stage (diagnostic stage, rehabilitation stage and terminal stage[62]). In fact, only one study analyzed the determinants of patients in the diagnostic phase separately.[41] Other Long studies only reported changing associations of depression, coping, religiosity and personality factors after baseline measurement, without specific information about the disease stage. Other limitations concern studies with a cross-sectional design and the overrepresentation of small studies, without an adequate sample size in relation to the number of determinants.

Conclusions, clinical implications and further research

Our results suggest that higher levels of anxiety and depression are related to a poorer HRQoL, whereas higher levels of religiosity appeared to be related to better global QoL. Furthermore, associations might change throughout the disease course.

Therefore it is important for health professionals to become aware of the relationships between psychological factors and QoL, as these relationships identify possible targets for interventions to improve QoL. It seems relevant for health professionals in ALS care, to focus on influencing mood and beliefs in order to improve HRQOL and global QoL. Furthermore, it is relevant to make a distinction between HRQoL and global QoL, because HRQoL is expected to decline, according to a decrease in mental and physical functioning, whereas global QoL seems more dependent on other factors, such as existential concerns.

More high quality research is needed to confirm the assumed association between anxiety, depression and religiosity and HRQoL and global QoL and to investigate how and when these factors can be targeted in ALS care. Coping, spirituality, mindfulness, hopelessness, perception of burden and agreeableness might be other promising factors

that influence QoL, but warranted further investigation. More Long studies in larger samples are needed because they allow causal relationships and effects of time to be identified. Furthermore, uniformity of measures for QoL and psychological factors, preferably ALS-specific, are required in order to obtain reliable, comparable data. As small sample sizes are inherent to ALS research, the answer may lie in international collaboration and data gathered by online survey.

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Appendix 4.1. PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix 4.2
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	

Appendix 4.1. *Continued*

Section/topic	#	Checklist item	Reported on page #
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	NA
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Figure 4.1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Table 4.1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Table 4.4
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Table 4.5
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	NA
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Table 4.4
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	NA

Appendix 4.1 continues on next page.

Appendix 4.1. ***Continued***

Section/topic	#	Checklist item	Reported on page #
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097
For more information, visit: www.prisma-statement.org.

Appendix 4.2. Literature search
PubMed search strategy d.d. 13.10.2015

ALS domain 25,687
"als"[Title/Abstract] OR "amyotrophic lateral sclerosis"[Title/Abstract] OR "mnd"[Title/Abstract] OR "motor neuron disease"[Title/Abstract] OR "motor neuron diseases"[Title/Abstract] OR Lou Gehrig's disease[Title/Abstract] OR als amyotrophic lateral sclerosis[MeSH Terms] OR amyotrophic lateral sclerosis[MeSH Terms]

Psychological factor determinant 1,923,630
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OR "introversion"[Title/Abstract] OR "extraversion"[Title/Abstract] OR "neuroticism"[Title/Abstract] OR "agreeableness"[Title/Abstract] OR "illness cognition"[Title/Abstract] OR "illness cognitions"[Title/Abstract] OR "acceptance"[Title/Abstract] OR "assertiveness"[Title/Abstract] OR "empathy"[Title/Abstract] OR "emotions"[Title/Abstract] OR "anger"[Title/Abstract] OR "anxiety"[Title/Abstract] OR "depression"[Title/Abstract] OR "fear"[Title/Abstract] OR "mood"[Title/Abstract] OR "grief"[Title/Abstract] OR "loneliness"[Title/Abstract] OR "panic"[Title/Abstract] OR "irritability"[Title/Abstract] OR "rage"[Title/Abstract] OR "catastrophizing"[Title/Abstract] OR "apathy"[Title/Abstract] OR "bereavement"[Title/Abstract] OR "boredom"[Title/Abstract] OR "euphoria"[Title/Abstract] OR "frustration"[Title/Abstract] OR "guilt"[Title/Abstract] OR "shame"[Title/Abstract] OR "happiness"[Title/Abstract] OR "hate"[Title/Abstract] OR "jealousy"[Title/Abstract] OR "laughter"[Title/Abstract] OR "love"[Title/Abstract] OR "pleasure"[Title/Abstract] OR "attitude"[Title/Abstract] OR "attitudes"[Title/Abstract] OR "beliefs"[Title/Abstract] OR "expectation"[Title/Abstract] OR "expectations"[Title/Abstract] OR "hopeless"[Title/Abstract] OR "illness perception"[Title/Abstract] OR "illness perceptions"[Title/Abstract] OR "motivation"[Title/Abstract] OR "motivations"[Title/Abstract] OR "representation"[Title/Abstract] OR "representations"[Title/Abstract] OR "religiosity"[Title/Abstract] OR "spirituality"[Title/Abstract] OR "thoughts"[Title/Abstract] OR "stress"[Title/Abstract] OR "awareness"[Title/Abstract] OR "imagination"[Title/Abstract] OR "intuition"[Title/Abstract]

Quality of life outcome 374,750

"quality of life"[Title/Abstract] OR "qol"[Title/Abstract] OR "life quality"[Title/Abstract] OR "life qualities"[Title/Abstract] OR "hrqol"[Title/Abstract] OR "hql"[Title/Abstract] OR "health related quality of life"[Title/Abstract] OR "well being"[Title/Abstract] OR "value of life"[Title/Abstract] OR "livability"[Title/Abstract] OR "perceived health"[Title/Abstract] OR "sanctity of life"[Title/Abstract] OR "health status"[Title/Abstract] OR "well being"[Title/Abstract] OR "wellbeing"[Title/Abstract] OR "quality of life"[MeSH Terms] OR health status[MeSH Terms]

Domain AND Determinant AND Outcome = 280

Search ((("quality of life"[Title/Abstract] OR "qol"[Title/Abstract] OR "life quality"[Title/Abstract] OR "life qualities"[Title/Abstract] OR "hrqol"[Title/Abstract] OR "hql"[Title/Abstract] OR "health related quality of life"[Title/Abstract] OR "well being"[Title/Abstract] OR "value of life"[Title/Abstract] OR "livability"[Title/Abstract] OR "perceived health"[Title/Abstract] OR "sanctity of life"[Title/Abstract] OR "health status"[Title/Abstract] OR "well being"[Title/Abstract] OR "wellbeing"[Title/Abstract] OR "quality of life"[MeSH Terms] OR health status[MeSH Terms]))) AND (("psychologic factor"[Title/Abstract] OR "psychologic factors"[Title/Abstract] OR "psychological factor"[Title/Abstract] OR "psychological factors"[Title/Abstract] OR

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Chapter 5

Associations between illness cognitions and health-related quality of life in the first year after diagnosis of amyotrophic lateral sclerosis

Kruitwagen-van Reenen ET, Post MWM, van Groenestijn A, van den Berg LH, Visser-Meily JMA

J Psychosom Res. 2020 May;132:109974. doi: 10.1016/j.jpsychores.2020.109974. Epub 2020 Feb 20. Erratum in: J Psychosom Res. 2021 Jan;140:110325. PMID: 32155469.

ABSTRACT

Objective: To describe illness cognitions among patients with amyotrophic lateral sclerosis (ALS), to study cross-sectional associations between illness cognitions and health-related quality of life (HRQoL) and to study the predictive value of illness cognitions measured shortly after the diagnosis for HRQoL at follow-up.

Methods: Prospective longitudinal design. We administered Self-report questionnaires at study onset (n = 72) and follow-up (n = 48). Median follow-up period was 10.0 months. At baseline median ALS Functional Rating Scale-Revised was 43, median time since onset of symptoms was 13.6 months, 79% of patients presented with spinal onset. Illness cognitions Helplessness, Acceptance and Disease Benefits were measured with the Illness Cognitions Questionnaire (ICQ) and HRQoL with the ALS Assessment Questionnaire (ALSAQ-40). Correlational and regression analyses were used.

Results: Patients experienced more Helplessness at follow-up. We found no significant changes in Acceptance or Disease Benefits at follow-up. In cross-sectional analyses, Helplessness was independently related to worse HRQoL at baseline ($\beta = 0.44$; $p = 0.001$) and Acceptance and Disease Benefits were independently related to worse HRQoL at follow-up ($\beta = -0.17$, $p = 0.045$) and $\beta = -0.186$, $p = 0.03$ respectively). Longitudinal analyses showed that, adjusted for disease severity at baseline, Helplessness at baseline was a predictor of worse HRQoL at follow-up ($\beta = 0.43$; $p = 0.006$). None of the illness cognitions were a significant predictor of HRQoL with adjustment for baseline HRQoL.

Conclusion: Helplessness was independently associated with HRQoL in the cross-sectional and longitudinal analyses. These results can help us identify patients shortly after diagnosis who might benefit from psychological interventions.

INTRODUCTION

Amyotrophic Lateral Sclerosis (ALS) is a fatal progressive neurodegenerative disorder. Despite extensive research, there is currently no curative treatment available. Daily care focuses on symptom management and preserving Health-Related Quality of Life (HRQoL).[1] There is an increasing awareness that psychological and behavioural determinants are associated with HRQoL among patients with ALS.[1,2]

The concept of illness cognitions and related concepts such as appraisals, illness beliefs, or illness perceptions refer to the way people think about and perceive their disease.[3-5] The importance of this is increasingly being recognised across a broad range of conditions, including stroke,[6] cancer,[7-10] Huntington,[11] Parkinson's disease,[12] multiple sclerosis,[13] spinal cord injury[14] and muscle disease.[15] One previous study on illness cognitions among ALS patients described two clusters of ALS patients according to their illness representations: adaptors and non-adaptors.[16] The two groups were characterized by different forms of thinking about and perceiving their disease, with impact on their level of health-related quality of life. Additionally, research among other diagnostic groups has suggested that different illness beliefs may be prominent at different disease stages.[17] However, no longitudinal studies among ALS patients have been performed on this subject, and, therefore, we do not have insight in how illness cognitions relate to QoL among patients with ALS during the progression of their disease. For daily practice, having insight in patients at risk of developing a lower QoL shortly after diagnosis, could be helpful in delivering personalized care.

The aims of our study are (1) to describe positive and negative illness cognitions in ALS patients using a validated questionnaire, (2) to study cross-sectional associations between illness cognitions and HRQoL, and (3) to study the longitudinal associations between illness cognitions measured shortly after the diagnosis of ALS with HRQoL at follow-up. Knowledge about illness cognitions and HRQoL could help us identify patients who may benefit from interventions.

PATIENTS AND METHODS

This study used data collected in a multicentre trial (FACTS-2-ALS). The methods have been published elsewhere.[18] Recruitment took place between 2009 and 2015. The Medical Ethics Committees from all participating centres approved the study protocol and informed consent was obtained from all patients.

Inclusion criteria were: age between 18 and 80 years; life-expectancy of more than 1 year; predicted forced vital capacity of at least 80%; diagnosed with probable or definite ALS,[19] at least one month post-diagnosis and able to walk and cycle. Data for the current study were collected at inclusion (T0) and follow-up (after 10 months; T1). Relevant exclusion criteria

were: cognitive impairment (whether or not related to ALS, preventing the intervention from being completed) and psychiatric disorder, both assessed using the Cumulative Illness Rating Scale.[20] Patients could be included for 2 interventions or Usual Care (control group).

The two interventions comprised of cognitive behavioral therapy (CBT) or aerobic exercise therapy (AET). For CBT, an additional inclusion criterium comprised of a Hospital Anxiety and Depression score (HADS)[21] above 8 points. Patients in the control group were not made aware of the possibility of the AET or CBT intervention to avoid a bias relating to negative feelings concerning not participating in the treatment arm.

Measurements

Demographic variables (age, gender), time since onset of first symptoms and site of first symptoms were collected at inclusion. All measurements at follow up were collected in the same way as the first time at T0. Disease severity was assessed using the revised ALS Functional Rating Scale-Revised (ALSFRS-R).[22] The ALSFRS-R, a valid, reliable and sensitive instrument includes 12 items structured on a 5-point scale (0 = unable, 4 = normal). The items assess limb, bulbar and respiratory function.

Forced Vital capacity (FVC) as a determinant of lung-capacity was measured with a spirometer (MicroRPM; PT Medical, Leek, The Netherlands) and the score was expressed as a percentage of the predicted score based on the patient's gender, weight, race and height. In case of insufficient lip closure a face mask was used. Each participant made 2 attempts and the maximum score was recorded.

Illness cognitions were measured using the Illness Cognitions Questionnaire (ICQ).[3,23] This questionnaire consists of 18 items (three 6-item scales), with a 4-point response scale ranging from 'not at all' to 'completely'. The three subscales reflect different illness cognitions: Helplessness as a way of emphasizing the aversive meaning of the disease, Acceptance as a way to diminish the aversive meaning and Disease Benefits as a way of attributing positive meaning to a disease. Scale scores are calculated by summing up the item scores and range from 0 to 24. Higher scores indicate greater presence of the illness cognition in question. The three-factor structure[23] and the clinical usefulness have been studied and supported by various groups.[13,14] In sum, the ICQ showed a strong internal consistency, reliability, and good predictive and construct validity. Intercorrelations between the scales were moderate, which revealed their content validity.

HRQoL was assessed using the Dutch version of the ALS Assessment Questionnaire (ALSAQ-40).[24] The ALSAQ-40 is a disease-specific questionnaire with 40 questions, each with a 5-point response scale. Domains are mobility, independence in mobility and self-care, eating and drinking, communication, emotional functioning. The total score has a range from 0 to 100, with higher scores indicating poorer health status. Validity and reliability of the ALSAQ-40 are reported to be good.[24,25]

Statistical analyses

Descriptive statistics were used to describe characteristics of the study population, ICQ and ALSAQ-40 scores at baseline and at follow-up. At follow-up, it was assessed whether there were differences in the baseline scores of those who continued to participate and those who dropped out. Wilcoxon Signed Rank tests were performed to examine changes in ALSFRS-R, FVC, ALSAQ-40 and ICQ scores between onset and follow-up. Effect sizes were calculated using the formula $r = Z/\sqrt{N}$. Spearman's rank correlation coefficients were computed to assess cross-sectional associations between potential determinants and ALSAQ-40 scores at T0 and at T1. To study the possible correlation between the illness cognition domains and the rate of disease progression evaluated by the difference between ALSFRS-R score at baseline and at follow-up (Δ ALSFRS-R). This allowed us to understand how the level of disease progression may influence the illness cognitions in ALS patients. Using Cohen's rule of thumb, a correlation of 0.10 was considered 'weak', of 0.30 'moderate' and of 0.50 'strong'.[26,27] Hierarchical linear regression was used to study the associations between illness cognitions and ALSAQ-40 scores, controlling for disease severity or HRQoL. Because of the restricted sample size, only determinants that showed a p-value < 0.05 in the correlation analysis (ALSFRS-R and FVC), were entered into the regression models. Variables were entered in the following order: step 1: Illness cognitions; step 2: disease severity variables, and demographics; Step 3: To study the impact of participating in AET or CBT, two dummy variables reflecting participating in either AET or CBT were added to the regression analysis.

Hierarchical linear regression analyses were performed to study the predictive value of illness cognitions at baseline, corrected for CBT or AET intervention, on HRQoL at follow-up, while controlling first for disease severity at baseline and second for HRQoL at baseline.

Residual analyses were performed and multi-collinearity was tested to search for violations of the assumptions underlying multiple regression. For all questionnaires, up to 25% of missing values were permitted. These were replaced by the mean of the missing values of the same scale.

SPSS version 24 for Windows was used for all statistical analyses.

RESULTS

A total of 72 patients were included in the FACTS-ALS trial and 48 patients completed all questionnaires at both baseline and follow-up. Median follow up period was 10.0 months, mean follow up period was 10.1 months (SD 0.57, range 9–12 months). Of these 48 patients, 6 were allocated to the CBT intervention, 16 to the AET intervention (11 of whom completed the module) and 26 to the usual care group. The most frequent reason for dropping out of the trial was death or because they experienced participation as too burdensome. Table 5.1

Table 5.1. Patients' characteristics at baseline (T0) and follow up (T1)

	T0 all patients (n = 72)	T0 patients who completed T1 (n = 48)	T1 (n = 48)	Difference at T0 between participants and dropouts at T1, p
Age in years, mean (SD)	59.9 (10.6)	60.3 (9.4)	60.5 (9.4)	0.91
Sex, male, n (%)	50 (69.4)	31 (64.6)	31 (64.6)	0.21
Time since onset in months, Mdn (IQR)	12.0 (8–21)	13.6 (9–23)	24.0 (20–32)	0.38
Time since diagnosis in months, Mdn (IQR)	3.3 (2–5)	3.3 (2–5)	13.0 (12–15)	0.20
Spinal onset, n (%)	53 (73.6)	38 (79.2)	38 (79.2)	0.13
ALSFRS-R, Mdn (IQR)	43.0 (40–45)	43.0 (40–46)	34 (26–39)	0.11
Severe (≤ 27)	1 (1.4%)	1 (2.1%)	13 (27.1%)	
Moderate (28–37)	6 (8.3%)	3 (6.3%)	21 (43.8%)	
Mild (≥ 38)	65 (90.3%)	44 (91.7%)	14 (29.2%)	
FVC%, Mdn (IQR)	94.0 (82.2–104)	97 (85–104)	74 (66.3–82.8)	0.19
ALSAQ#, Mdn (IQR)	26.9 (17.2–35.6)	23.1 (15.6–35.6)	40.9 (26.4–53.8)	0.09
Nr of patients in AET intervention		6		
Nr of patients in CBT intervention		16		

Higher ALSAQ scores indicate lower health related quality of life. ALSFRS-R, revised ALS Functional Rating Scale; FVC, Forced vital capacity; ALSAQ, ALS Assessment Questionnaire.

Table 5.2. Illness cognition scores at baseline and follow-up and change in Illness cognition scores between baseline and follow-up

ICQ	T0 (n = 71) Median (IQR)	Mean (SD)	T0 (n = 48) Median (IQR)	Mean (SD)	T1 (n = 48) Median (IQR)	Mean (SD)	Effect size, r
Helplessness	12.0 (10–16)	13.2 (4.4)	12.0 (10–16)	12.8 (4.5)	15.0 (13–19)	15.7 (4.1)	0.54*
Acceptance	15.0 (12–17)	15.9 (3.8)	15.0 (13–18)	15.3 (3.8)	16.0 (13–20)	16.3 (4.4)	0.23
Disease Benefits	13.0 (10–15)	13.0 (3.7)	13.0 (10–15)	12.9 (3.7)	13.0 (10–16)	13.4 (3.9)	0.09

ICQ, Illness cognition questionnaire; T0 start trial, T1 10.6 months later.
IQR, interquartile range; Wilcoxon signed Rank effect size, $r = Z/\sqrt{N}$.

presents patient characteristics and scores on the primary outcome measures. No significant differences ($p < 0.05$) at base line were found between patients who participated at follow-up and those who dropped out of the study.

Table 5.2, distributions of the ICQ scores. Helplessness scores increased significantly between baseline and follow-up, but no significant changes in Acceptance or Perceived Benefit scores were seen.

Table 5.3 presents the item scores of the ICQ over time. All item scores of the Helplessness domain increased over time. Overall Acceptance scores appeared to be high compared to scores of the Helplessness domain.

Table 5.3. ICQ item scores of Helplessness, Acceptance and Disease Benefits. % of participants scoring Yes on this items.

n = 48	T0 (%)	T1 (%)
Helplessness		
1. Because of my illness, I miss the things I like to do most	41.7	65.9
2. My illness controls my life	50.0	59.6
3. My illness makes me feel useless at times	10.5	27.7
4. My illness prevents me from doing what I would really like to do	41.7	70.2
5. My illness limits me in everything that is important to me	29.2	46.8
6. My illness frequently makes me feel helpless	16.6	36.2
Acceptance		
7. I can handle the problems related to my illness	75.0	76.6
8. I have learned to live with my illness	47.9	66.0
9. I have learned to accept the limitations imposed by my illness	37.5	55.3
10 I can accept my illness well	50.0	59.5
11. I think I can handle the problems related to my illness, even if the illness gets worse	39.6	54.3
12. I can cope effectively with my illness	62.5	61.7
Disease Benefits		
13. Dealing with my illness has made me a stronger person	20.8	34.0
14. I have learned a great deal from my illness	18.8	38.3
15. My illness has made life more precious to me	50.1	34.0
16. Looking back, I can see that my illness has also brought about some positive changes in my life	14.6	26.0
17. My illness has helped me realize what's important in life	50.0	45.7
18. My illness has taught me to enjoy the moment more	60.5	68.1

Table 5.4 displays the Spearman Correlations between Illness cognitions questionnaire (ICQ) with demographic and disease characteristics and quality of life (ALSAQ), at T0 and T1.

At follow-up, more Helplessness was strongly related to less Acceptance and moderately related to less Disease Benefits and more Acceptance was moderately related to Disease Benefits. More Helplessness was strongly related to higher ALSAQ-40 scores,

Table 5.4. Spearman correlations between Illness cognitions questionnaire (ICQ) with demographic and disease characteristics and quality of life (ALSAQ), at T0 and T1

	Cross-sectional T0 (n = 72)				Cross-sectional T1 (n = 48)			
	ALSAQ T0	Helplessness	Acceptance	Disease Benefits	ALSAQ T1	Helplessness	Acceptance	Disease Benefits
Gender, (m)¶	0.09	-0.22	-0.34¶	-0.11	0.11	0.16	-0.25	-0.14
Age	0.05	0.10	-0.25*	-0.09	-0.16	0.18	-0.14	0.06
ALSFRS-R	-0.63**	-0.48**	-0.02	0.09	-0.86**	-0.43**	0.12	0.15
Δ ALSFRS-R					0.81**	0.46**	-0.17	-0.11
FVC	-0.27*	-0.08	0.07	-0.10	-0.52**	-0.31*	0.18	0.16
ICQ-H	0.64**	1.00	-0.10	-0.13	0.51**	1.00	-0.47**	-0.37**
ICQ-A	-0.08	-0.10	1.00	0.18	-0.34*	-0.47**	1.00	0.35*
ICQ-DB	0.07	-0.13	0.18	1.00	-0.32*	-0.37**	0.35*	1.00

T0 start trial, T1 10 months. ALSFRS-R, revised ALS Functional Rating Scale; Δ ALSFRS-R, difference T1–T0 in ALSFRS-R score; FVC, Forced vital capacity. ICQ, Illness cognitions questionnaire; ICQ-H, Illness cognitions questionnaire Helplessness; ICQ-A, Illness cognitions questionnaire-Acceptance; ICQ-DB, Illness cognitions questionnaire-Disease Benefits; Δ ALSFRS-R, difference T1- T0 ALSFRS-R scores. * $p < 0.05$; ** $p < 0.01$; ¶ Point-biserial correlation.

both at baseline and follow-up. The relationship between functioning and HRQoL scores was stronger at follow-up compared to baseline. There is a significant correlation between Δ ALSFRS-R and outcome measure ALSAQ and ICQ-Helplessness.

Table 5.5 summarizes the results of the cross-sectional regression analyses at baseline and follow-up. At baseline, Helplessness was the only ICQ-subscale independently associated with HRQoL, explaining 38% of the ALSAQ-40 score. After adding the other variables, Helplessness was still independently associated with HRQoL (total explained variance 53%). At follow-up, Helplessness was the only ICQ subscale independently associated with HRQoL, explaining 40% of the variance. After adding disease severity and controlling for AET or CBT, Acceptance and Disease Benefit and disease severity (ALSFRS-R) were significantly associated with HRQoL ($R^2 = 0.41$), explaining 81% of the variance in HRQoL at follow up.

Table 5.5. Linear regression analysis of the effects of illness cognitions on health related QoL (ALSAQ Sum score) at T0 and T1

	Cross-sectional T0 (n = 72)		Cross-sectional T1 (n = 48)	
	Step 1, β	Step 2, β	Step 1, β	Step 2, β
ICQ-Helplessness	0.62*	0.44*	0.56*	0.13
ICQ-Acceptance	NA	NA	-0.08	0.17*
ICQ-Disease Benefits	NA	NA	-0.04	0.19*
ALSFRS-R	NA	-0.40*	NA	-0.66*
FVC	NA	-0.20*	NA	-0.16
Dummy CBT			-0.04	-0.08
Dummy AET			0.07	0.09
ΔR^2	0.38	0.15	0.40	0.41
Explained variance		**53%**		**81%**

T0 start trial, T1 10 months. β, standardized coefficient. * $p < 0.05$. NA, not added. ALSAQ, ALS Assessment Questionnaire; ICQ, Illness cognitions questionnaire; ALSFRS-R, revised ALS Functional Rating Scale; FVC, Forced vital capacity; Yes/ no CBT, participation CBT intervention yes/ no; Yes/ no AET, participation AET intervention yes/no.

Table 5.6 summarizes results of the longitudinal analyses. A total of 48% of the variance in HRQoL at follow-up was explained by HRQoL at baseline. Illness cognitions at baseline were not significantly associated with HRQoL at follow-up, when adjusted for baseline HRQoL. When entering ALSFRS-R (baseline) and ICQ scales (baseline) together in the model, 27% of the variance in HRQoL at follow-up was explained by Helplessness scores at baseline.

This model did not change after controlling for CBT or AET.

Table 5.6. Predictive linear regression analysis with ICQ subscales and ALSFRS-R or ALSAQ at T0 as possible correlates of ALSAQ at T1

	Step 1	Step 2 with ALSAQ T0	Step 2 with ALSFRS-R T0
T0	β	β	β
ICQ-Helplessness	0.44*	0.07	0.43*
ICQ-Acceptance	0.03	0.02	0.02
ICQ-Disease Benefits	-0.16	-0.20	-0.17
ALSAQ-T0	NA	0.59*	NA
ALSFRS-R T0	NA	NA	-0.03
ΔR-square	0.27	0.22	0.01
Total R-square	0.27	0.48	0.27

Dependent variable: ALSAQ-T1. β, standardized coefficient. NA, not added in analysis. T0 start trial, T1 10 month.
* $p < 0.05$; NA, not added in the analysis.

DISCUSSION

There is an increasing awareness that psychological factors are associated with HRQoL among patients with ALS. The results of this study showed a significant increase of Helplessness, but no significant changes in Acceptance or Disease Benefits between baseline and follow-up. Despite this, at follow up Acceptance and Disease Benefits measured at follow up were independently related to HRQoL.Helplessness was further independently related to HRQoL at baseline and Helplessness measured at baseline was an independent predictor of HRQoL at follow-up.

The Helplessness score at baseline was equal to scores among patients with Rheumatoid arthritis (RA) and lower compared to scores among breast cancer patients and patients with Multiple Sclerosis (MS), in a latter phase of their disease.[3,10,13] Baseline Acceptance and Disease Benefits scores were lower (= worse) compared to scores among patients with RA, MS and after stroke.[3,6,13] At follow-up Helplessness score were higher (= worse) than the scores found among stroke patients and patients with spinal cord injury.[6,14] Our patients experienced physical deterioration, which is usually not the case among stroke patients and patients with spinal cord injury which can explain the higher scores. Acceptance and Disease Benefits scores at follow-up were lower (= worse) than those found among spinal cord injury patients and stroke patients in a longitudinal study. Again, this could be associated with the physical deterioration our patients experienced. Compared to these patients, ALS patients reported more change in illness cognitions.

The association between the ICQ-helplessness scores and ALSAQ-40 changed over time. Corrected for disease severity, higher Helplessness scores at baseline were associated with lower HRQoL at follow-up. This result implies that we may have found a way to select a subgroup of patients shortly after diagnosis who might need extra attention in daily care.

This group might benefit from a psychological intervention, such as described in studies among patients with muscle disorders (including ALS patients).[28-33] To target helplessness specifically as an unfavourable cognition individual, daily care should focus on 1: physical aspects of helplessness due to physical limitations and ongoing deterioration by providing personalized care, just in time (assistive devices just in time, adequate symptom management and shared decision making during multidisciplinary care). 2: on the feelings of helplessness due to loss of control.

Despite the fact that Acceptance and Disease benefit scores did not increase significantly, these scores were associated with HRQoL at follow up. At that moment patients have had more experience with the impact of the disease. As stated by Evers, Acceptance can be regarded a way to diminish the aversive meaning of disease and Disease Benefits as a way of attributing positive meaning to a disease. This explains the association with HRQoL and gives ground for psychological interventions based on ACT.

Helplessness at T1 was significantly correlated with disease severity (ALSFRS-R) and change in disease severity (ΔALSFRS-R scores). This association between higher Helplessness scores and disease progression was also found in patients with multiple sclerosis.[13] There is a wide variety in disease progression and survival among patients with ALS.[34] Future studies including larger samples could compare the course of illness cognitions between subgroups with different survival prognosis. In our population the correlation between Helplessness and disease severity increased over time, which may be explained by greater physical deterioration at follow-up. However, the questions in the Helplessness scale are not all oriented at physical functioning. Patients apparently experience an overall feeling of Helplessness due to deterioration. As the variety in Helplessness is strongly correlated to HRQoL, it is important to monitor patients frequently. In our study, 22 patients participated in an intervention of the FACTS-2-ALS trial (CBT or AET). We evaluated the impact of these patients who participated in an intervention, on our results. This has not lead to different conclusions, and therefore we included the data of these patients in our calculations.

Based on theories about post-traumatic growth and response shift and results from other studies[2,8,35,36] we expected, but did not find an increase of Acceptance and Disease Benefits scores between baseline and follow-up. Posttraumatic growth is defined as a collection of positive changes following a traumatic event which stimulates the individual to re-evaluate his/ her worldview. Posttraumatic growth has interfaces with another phenomenon called 'response shift'. The response shift theoretical model[36] posits that a health state change (catalyst) causes an individual to utilize cognitive, behavioral, and emotion-focused coping strategies (mechanisms). Baring these phenomena in mind, we expected more acceptance and disease benefits in time. Qualitative research has suggested that different illness beliefs may be prominent at different disease stages.[16] Regarding the ICQ item scores, from onset, 50% of the patients score on the acceptance items. Over time, a

higher percentage of patients score helplessness, simultaneously. One could conclude that these patients have a realistic insight in the consequences of their disease. Additionally, in accordance with the Theory of Waldron about psychological adaptation to terminal illness, there might be a shift in focus of determinants of QoL, physical functioning to psychological and spiritual domains.[37]

This is the first study with a longitudinal focus on illness cognitions in relation to quality of life among ALS patients. Following patients over time has given us more insight into the development of cognitions like Helplessness, Acceptance and Disease Benefits and their associations with change in HRQoL over time.

However, interpretation of our results must take account of the following limitations. First, patients included in the FACTS-2-ALS trial needed to be able to participate in physical exercise, and therefore the less impaired patients were selected. At diagnosis, there are patients who have already severe physical limitations. Patients with a very progressive disease course are probably not included in this study. However, we do not have insight in the amount of people who were not eligible to participate. Second, the impact of cognitive and /or behavioral changes in the frontotemporal spectrum for example the phenomenon of anosognosia, due to ALS, were not studied, but we would expect a negative association of frontotemporal behavioral changes with adaptative psychological processes. Third, we did not include psychological factors such as resilience or coping in our study; these are factors described among e.g. cancer patients as influencing the adaptation process.[38] Fourth, because of the limited sample size, we were able to add only a limited amount of variables in the regression analysis.

In conclusion, Helplessness was independently associated with HRQoL in the cross-sectional and longitudinal analyses. In daily care, we strive to provide personalized care with the aim to optimize QoL despite physical limitations. The results of this study can help us identify patients with ALS who might benefit from possible psychological interventions e.g. acceptance and commitment therapy (ACT) or mindfulness.[32,33,39] As several authors are indicating that psychological interventions are promising, we should be studying their efficacy.

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Chapter 6

Participation restrictions in ambulatory ALS patients: Physical and psychological factors

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ABSTRACT

Introduction: The aim of this study was to assess the prevalence of participation restrictions in ambulatory patients with amyotrophic lateral sclerosis (ALS) and to identify physical and psychological contributory factors.

Methods: In this cross-sectional study, self-reported participation restrictions of 72 ambulatory ALS patients were assessed using the social health status dimension (SIPSOC) of the Sickness Impact Profile (SIP-68). Associations between SIPSOC and physical functioning, psychological factors, and demographic factors were analyzed using hierarchical regression analyses.

Results: Ninety-two percent of the patients reported participation restrictions; 54.9% could be explained by physical functioning; psychological factors accounted for 8.1% of the variance. Lung capacity, functional mobility, fatigue, and helplessness were independently associated with participation restrictions.

Discussion: Ambulatory ALS patients experience participation restrictions, which might be influenced if early ALS care is directed toward lung capacity, functional mobility, fatigue, and feelings of helplessness.

INTRODUCTION

Patients with ALS experience progressive wasting and weakness of limb, bulbar, and respiratory muscles. Death due to respiratory failure occurs within 3 to 5 years after symptom onset.[1] The physical decline can restrict ALS patients in their social roles and everyday functions and activities, including work, leisure, relationships, and household management. These roles, functions, and activities encompass the meaning of the term *participation*.[2] According to the International Classification of Functioning, Disability and Health (ICF), participation refers to a 'multidimensional concept' that can be defined as 'the person's involvement in life situations'.[3] On the other hand, *participation restrictions* can be defined as 'problems an individual may experience in involvement in life situations'.[3] It has been shown that participation by patients with progressive neurological diseases contributes to their well-being and Health-Related Quality of Life (HRQoL).[2,4] The ability to participate decreases as the disease progresses,[5] but those affected still strive to maintain independence and their social roles.[6] Although there is no cure for ALS, ALS care can assist people to continue to function independently and safely, manage their symptoms, and, most importantly, participating in a fulfilling life despite having a disease that is known to shorten lifespan.[7]

The construct of participation has been studied in other progressive neurological conditions such as multiple sclerosis (MS)[8-10] and Parkinson disease.[2,4] Little is known, however, about the prevalence of perception of participation restrictions among ALS patients and the factors that may affect such restrictions. Patient-focused interviews revealed that ALS patients experienced a withdrawal from many social activities during all disease stages.[11] Qualitative data have shown that communication disorders in ALS were associated with participation restrictions.[12] Higher levels of social withdrawal were shown to be associated with increased severity of physical symptoms[11,13] and time since diagnosis,[11] but also with psychological factors. Specifically, higher levels of depression,[11,13,14] anxiety,[13,14] and poorer coping[15] were shown to be related to higher levels of social withdrawal and lower levels of social interaction.

This study focused on participation restrictions in ambulatory patients with ALS. By identifying the factors associated with participation restrictions, clinicians may be better able to address some of the potential, and possibly even modifiable, contributing factors in the early stages of ALS. We studied the contributions of disease severity, bulbar onset, coping, and symptoms of anxiety and depression, factors which were previously found to influence participation restrictions. In addition, the associations between illness cognitions and dissatisfaction with social support and participation restrictions were examined, as these factors have been shown to contribute to participation in other chronic diseases.[16-18]

The aims of this study were: (1) to describe the prevalence of participation restrictions and the participation domains (e.g. social life and relationships) in which ambulatory

ALS patients are restricted; (2) to determine the contribution of physical functioning and psychological factors to participation restrictions.

MATERIALS AND METHODS

Participants and procedures

This study was part of the FACTS-2-ALS trial in which ambulatory ALS patients were followed for 10 months. The methods have already been published elsewhere.[19] Five outpatient rehabilitation clinics in The Netherlands participated, and patients were enrolled between October 2009 and November 2014. The medical Ethics Committee of all participating centers approved the study, and informed consent was obtained from all included patients, according to the Declaration of Helsinki.[20] This study reports cross-sectional data from the first assessment. Inclusion criteria were: (1) age between 18 and 80 years; (2) life-expectancy > 1 year; (3) a forced vital capacity (FVC) of at least 80% of predicted; (4) diagnosis of "probable" or "definite" ALS according to the "revised El Escorial World Federation of Neurology (WFN) criteria"; (5) at least 1 month since the diagnosis of ALS; (6) diagnostic phase is completed; and (7) walking ability with or without an ankle-foot orthosis or stick (> 10 minutes), and cycling ability (> 15 minutes) on a cycle ergometer. Exclusion criteria were: (1) severe cognitive impairment, whether or not related to ALS, preventing the aerobic exercise therapy (AET) from being completed (assessed using the Cumulative Illness Rating Scale (CIRS));[21] (2) insufficient mastery of the Dutch language; (3) disabling co-morbidity (assessed using the CIRS[21]); and (4) psychiatric disorder (assessed using the CIRS[21]).

Eligibility criteria were confirmed by the rehabilitation physician. After informed consent had been given by the patient, the rehabilitation physician filled in demographic variables, a medical chart with ALS-related factors (time since onset and site of onset), the ALS Functional Rating Scale Revised (ALSFRS-R)[22] and the Hospital Anxiety and Depression Scale (HADS).[23] Furthermore, the initial assessment took place within approximately 2 weeks of enrolment and included self-administered questionnaires at home and, within the same week, functional performance tests conducted by trained research assistants in a hospital room. Questionnaires and tests are described in the following section.

Measures

Participation restrictions

Perceived participation restrictions were assessed using the social health status dimension (SIPSOC); the sum of the subscales Mobility Range and Social Behavior of the Sickness Impact Profile (SIP-68),[24-25] which asks patients to check statements about social settings that

apply to their situation and assesses perceived limitations in participation. The SIPSOC is a self-administered 22-item questionnaire. All questions are equally weighted and describe participation restrictions of different ICF domains;[3] domestic life (6 items); interpersonal interactions and relationships (2 items); community, social, and civic life (7 items); mobility (4 items); major life areas (1 item); and self-care (2 items). We treated participation as a continuous variable. A higher SIPSOC score represents poorer participation. The SIPSOC has been proven to be valid and reliable in individuals with disabilities and spinal cord injury.[25] The Cronbach alpha for participation in this study was 0.85.

Physical functioning

Disease severity was assessed using the ALS Functional Rating Scale (Revised) (ALSFRS-R).[22] The ALSFRS-R includes 12 that assess limb, bulbar, and respiratory function. Each item has a 5-point scale: 0 for unable and 4 for normal, thus the total score can range from 0 to 48; a lower score represents a poorer level of physical functioning. The ALSFRS-R includes both items at the ICF level of body functions / impairments such as speech and swallowing and items at the ICF level of activities / activity limitations such as walking, climbing stairs, and performing self-care).[3,26] The ALSFRS-R is a valid, reliable and sensitive instrument.[22]

Lung capacity was assessed by percent-predicted forced vital capacity (FVC%) measured with a spirometer (MicroRPM, Pt Medical, the Netherlands) and adjusted for age, gender, race, weight, and height. In case of insufficient lip closure, a facemask was placed on the flow sensor. Each participant made 2 attempts, and the maximum score was recorded.

Fatigue severity was measured with the subscale of the Checklist Individual Strength (CIS-fatigue).[27] This scale consists of 8 questions about fatigue as experienced during the previous 2 weeks; each question was scored on a 7-point Likert scale A total score ≥ 35 indicates severe fatigue.

Grip strength was assessed using a hydraulic hand-held dynamometer with adjustable grip (Jamar, Biometrics Ltd., USA). When optimal grip span had been determined, each participant performed 2 attempts with each hand, with the arm flexed to form an angle of 90° with respect to the trunk. Supporting the lower arm with the contralateral hand was allowed. The dynamometer was squeezed with as much force as possible, the maximum score in kilograms for each hand was recorded, and the mean sum score of both hands was used in the analyses.

Functional mobility was measured with the Timed Up and Go (TUG) test[28] which measures the time it takes a subject to rise from a seated position in a chair, walk 3 meters, turn around, and return to the same seated position of the same chair without physical assistance. As it predicts falls, the TUG test can prompt the recommendation of mobility aids to prevent falling.[29] The TUG test has been shown to have high intra- and inter-rater reliability.[28]

Psychological factors

The presence of anxiety and depressive symptoms was evaluated using the Hospital Anxiety and Depression Scale (HADS).[23] This instrument concentrates on the psychological rather than the physical symptoms of mood in order to provide an assessment of mood independent of levels of physical disability in patients with medical illness. The HADS has a subscale for symptoms of anxiety (HADS-A) and another for depressive symptoms (HADS-D). Each subscale consists of 7 items (score range: 0–3). Levels of symptoms of anxiety and depression are considered clinically relevant at a cut-off score of ≥ 8 on each subscale.[23] The HADS has been proven to be a valid and reliable instrument for detecting symptoms of anxiety and depression.[30] It is frequently used in ALS populations.[31,32]

Illness cognition was assessed using the Illness Cognition Questionnaire (ICQ).[17] This contains 18 items consisting of 3 6-item scales related to cognitive ways patients ascribe meaning to chronic illness. The following were assessed: helplessness (focusing on the negative consequences of the disease and generalizing them to functioning in daily life); acceptance (acknowledging being chronically ill and perceiving the ability to manage the negative consequences of the disease); and perceived benefits (also perceiving positive, long-term consequences of the disease). Items are scored on a 4-point Likert scale (score range: 1–4). Scale scores for the 3 illness cognitions are calculated by summing the item scores. Higher scores indicate that illness cognition is more strongly present in the respondent. The ICQ has strong internal consistency and reliability and good construct and predictive validity across chronic conditions.[33]

Coping style was assessed by the shortened version of the Coping Inventory for Stressful Situations: Situation Specific Version (CISS:SSC).[34] The CISS:SSC consists of 21 items measuring 3 types of coping: task-oriented; emotion-oriented; and avoidance. Patients were asked to complete the CISS:SSC based on their reaction to the most stressful situation encountered over the past 4 weeks. Each scale consists of 7 items rated on a 5-point Likert scale (score range: 1–5). Scores for all items in each scale are summed to form scale scores; higher scores indicate a greater use of that particular coping style. The CISS has been applied frequently in chronically ill patients with various diseases and has proven to have good psychometric characteristics in adult samples.[35]

Dissatisfaction with social support was measured by the Social Support List-Discrepancies (SSL-D).[36] The subscale SSL-D measures the extent to which the support received from relatives, friends, acquaintances, and colleagues is in accordance with the needs of the respondent. Items are rated on a 4-point scale (score range: 1–4). Scores for the SSL-D range from 8 to 32. A high score reflects greater dissatisfaction with regard to the perceived social support. The reliability of this instrument is good.[36]

Statistical analysis

Descriptive statistics were used to describe characteristics of the patients. Normality was assessed using the Kolmogorov-Smirnov test of normality.

Bivariate analyses were used to examine the strength of the associations between the independent factors (physical functioning, psychological, and demographic factors) and the dependent factor (participation restriction). Spearman rho correlation was calculated, since most of the dependent variables were non-normally distributed. Effect sizes of the correlations were as follows: small (r = 0.1–0.3), medium (r = 0.3–0.5), and large (r > 0.5). Subsequently, hierarchical regression analyses were conducted to study the relative contribution of the independent variables, which were significant in bivariate analyses, to participation restriction. The 0.01 level of significance was used, given the sample size. Due to their skewed distribution, best fit of the residuals was achieved by an inverse transformation of the TUG test and a square-root transformation of the SIPSOC and HADS-D. Subsequently, we standardized these variables. Bulbar onset and gender were included as binary variables. In the first step of the hierarchical regression analysis "physical functioning factors" were entered, followed by "psychological factors" in the second step. Alpha was set at 0.05.

Missing data were treated with pair-wise deletion. For all questionnaires, up to 25% missing values were permitted; these were replaced by the mean of the missing-values within the same (sub)scale. Multicollinearity was verified by analyzing Spearman rho correlations between all variables (r > 0.7). Data were analyzed using SPSS version 20.0 (SPSS Inc, Chicago, IL, USA).

RESULTS

Participants

A total of 72 patients were included. Table 6.1 lists the demographic and ALS characteristics of the patients at baseline. Thirty patients (42%) were severely fatigued. The median (IQR) scores of the levels of symptoms of anxiety and depression were 4.0 (4.0) and 3.0 (5.0), respectively; 6 patients (8.3%) showed definite clinical levels of anxiety, and 12 patients (23.6%) showed clinical levels of depression. Supplementary Table S6.1 lists the measures that were administered during the initial assessment.

Description of reported participation restrictions

The scores of the SIPSOC showed that 92% of the patients reported at least 1 participation restriction. More than two-thirds of the patients reported doing less regular daily work and less heavy work around the house. More than one-third were taking part in fewer community activities and were spending shorter periods of time on hobbies and recreations. Visiting

others, going outside, and taking care of personal and financial business were least often affected in ambulatory patients with ALS (Table 6.2).

Table 6.1. Patients' demographic and ALS-related characteristics (n = 72)

Characteristics	
Age in years	59.9 (10.6)
Men gender, n (%)	50 (69.4)
Time since onset in months	17.1 (12.2)
Spinal onset, n (%)	53 (73.6)
ALS disease severity (ALSFRS-R)	42.1 (3.7)
Severe (≤ 27), n (%)	1 (1.4)
Moderate (28–37), n (%)	6 (8.3)
Mild (≥ 38), n (%)	65 (90.3)
FVC% (n = 65)	92.9 (17.1)

Numbers are presented as means (SDs), unless otherwise specified. ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale Revised; FVC% = Forced Vital Capacity, percent predicted.

Table 6.2. Item scores of the social health status dimension of the 68-item Sickness Impact Profile (SIPSOC), in order of ascending values (n = 72)

SIPSOC items	% "Applies to me"
I am not doing heavy work around the house.	71.8
I am doing less of the regular daily work around the house than I would usually do.	70.4
I do my hobbies and recreation for shorter periods of time.	39.4
I am doing fewer community activities (e.g., community work, associations, or church).	36.6
My sexual activity is decreased.	32.4
I am doing fewer social activities with groups of people.	28.2
I am going out for entertainment less often.	26.8
I am not doing any of the housecleaning that I would usually do.	25.7
I am not doing any of the shopping that I would usually do.	25.7
I am not doing any of the regular daily work around the house that I would usually do.	24.3
I am drinking fewer fluids.	22.5
I stay home most of the time.	18.6
I am cutting down the length of visits with friends.	16.9
I am not going into town.	15.7
I stay away from home only for brief periods of time.	15.5
I am eating much less than usual.	14.1
I am not doing any of the clothes washing that I would usually do.	12.9
I do not get around in the dark or in unlit places without help.	7.1
I am cutting down on some of my usual inactive recreation and pastime (e.g., watching TV, cards, or reading).	7.0
I have given up taking care of personal or household business affairs (e.g., paying bills, banking, or working on a budget).	5.7
I am getting around only within 1 building.	2.9
I am not going out to visit people at all.	2.9

Associations of physical functioning, psychological and demographic factors with perceived participation restrictions

Bivariate analyses (Table 6.3) revealed that more participation restrictions were strongly associated with physical functioning (higher disease severity, higher fatigue severity, and poorer functional mobility) and moderately associated with poorer lung capacity and poorer grip strength. Two psychological factors showed a significant association with more participation restrictions; more depressive symptoms were moderately related, and higher levels of helplessness were strongly associated with participation restrictions (Table 6.3). Demographic factors were not significantly associated with participation restrictions; they were not, therefore, included in the hierarchical regression analyses. There was no collinearity between the independent variables.

Table 6.3. Bivariate and multivariate analysis of the SIPSOC

	Participation restrictions		
	Bivariate	Multivariate (Beta)	
Variables	(Spearman)	Step 1	Step 2
Demographic factors			
Age	0.16	NE	NE
Gender (men/women)	-0.06	NE	NE
Physical functioning			
Disease severity	-0.55**	-0.29*	-0.17
Type of onset (bulbar/spinal)	0.03	NE	NE
Fatigue severity	0.51**	0.37**	0.22*
Lung capacity	-0.33**	-0.22*	-0.26**
Grip strength	-0.35**	-0.04	0.03
Functional mobility	0.52**	-0.25*	-0.26*
Psychological factors			
Symptoms of anxiety	0.06	NE	NE
Depressive symptoms	0.49**	NE	0.15
Illness cognitions			
Helplessness	0.60**	NE	0.29*
Acceptance	-0.06	NE	NE
Perceived benefits	-0.08	NE	NE
Coping			
Task-oriented	-0.13	NE	NE
Emotion-oriented	0.22	NE	NE
Avoidance-oriented	-0.04	NE	NE
Dissatisfaction with social support	0.22	NE	NE
R^2	0.549	0.630	
Adjusted R^2	0.505	0.577	

* $p \leq 0.05$, ** $p \leq 0.01$; NE = not entered.

Multiple regression analysis (Table 6.3) demonstrated that physical functioning (disease severity, lung capacity, fatigue severity, and functional mobility) explained 54.9% of the variance in participation restrictions (step 1). Psychological factors (depressive symptoms and helplessness) together explained an additional 8.1% of the variance in self-reported participation restrictions (step 2). The final model showed that poorer lung capacity, greater fatigue severity, poorer functional mobility, and more helplessness were independently associated with more reported participation restrictions (Table 6.3).

DISCUSSION

This study showed that participation restrictions are common in a representative sample of ambulatory patients with ALS. This applied to not only activities which require physical strength, such as 'doing heavy household tasks', but also activities that rely less on physical ability, such as 'doing community activities', were restricted.

Although physical functioning contributed most to the variation in self-reported participation restrictions, psychological factors contributed a relatively small, but substantial amount. Our findings suggest that patients with poorer lung capacity, poorer functional mobility, or who experience fatigue and feelings of helplessness, are at risk for participation restrictions.

Physical functioning

The association between FVC and SIPSOC found in our study was in agreement with previous studies in chronic disease.[37] Furthermore, although our patients were able to walk for > 10 minutes at the time of the study inclusion, the level of functional mobility does explain participation restrictions. This indicates that the TUG test measures enough dispersion in functional mobility to explain variance in participation restrictions, suggesting that functional mobility is complex, requiring coordination, balance, and strength. Fatigue independently contributed to participation restrictions and warrants attention in ALS clinical practice, as 42% of our cohort reported fatigue using the (self-reported) CIS-fatigue.

Bulbar onset did not contribute to the explanation of participation restrictions. This was in contrast to a qualitative study in which ALS patients reported restrictions in participation, because they were unable to speak loudly enough to make themselves heard in social situations.[12] In the early stages of ALS, however, initial symptoms might be limited to a reduction in speaking rate, a change in voice quality, or imprecise articulation[38] and might not yet interfere with participation. This might explain why we did not find associations between bulbar onset and participation restrictions.

Consistent with literature concerning MS patients, grip strength showed no independent correlation with participation restrictions.[39] Also disease severity, as measured with the ALSFRS-R, did not contribute to the explanation of variance in participation restrictions, suggesting that the ALSFRS-R, which captures the whole spectrum of ALS symptoms, was not sufficiently specific to explain variance in participation restrictions in this particular group of ALS patients.

Demographic factors

Neither gender nor age provided a significant contribution to the explained variance in participation restrictions. This was in line with other studies in chronic disease.[40,41]

Psychological factors

Helplessness was the only psychological factor that was associated independently with participation restrictions. This was consistent with a previous study on helplessness and participation among visually impaired adults.[16] The fact that the patient cannot influence the neurological decline in ALS might contribute to helplessness. In cases of high levels of helplessness, patients emphasize the negative aspects of their chronic condition as an uncontrollable, unpredictable, and unchangeable consequence of their disease and generalize these negative aspects to functioning in daily life.[17] In accordance with a study among MS patients,[42] higher levels of helplessness were associated with more fatigue and depressive symptoms in bivariate analysis.

The low prevalence of dissatisfaction with social support in our sample may explain the lack of association between dissatisfaction with social support and participation restrictions. Also, coping style did not contribute to participation restrictions. This was in contrast to a study in patients with traumatic brain injury which found that a passive coping style was a significant predictor of more participation restrictions.[43] Furthermore, although symptoms of anxiety and depression have been associated with social withdrawal in ALS patients,[13,14] they were not related to participation restrictions in our sample. A possible explanation might be that our sample was characterized by low levels of anxiety and depressive symptoms (Supplementary Table S6.1).

Strengths and limitations

An important strength of this study was the simultaneous assessment of performance-based measures and self-reported questionnaires. Moreover, most of our performance-based instruments, such as TUG and FVC% are already standard instruments in ALS clinical practice. In the absence of a specific instrument to measure participation in ALS patients, we introduced the SIPSOC, which has proved to be reliable in this study. A limitation of this

study was the fact that we did not examine ALS-related cognitive functions, while there is evidence that disease-related cognitive functions could be associated with participation restrictions in other progressive neurological conditions.[44] In addition, the cross-sectional nature of our study did not allow us to see how associations change over time. As the disease severity of ALS progresses, the physical and psychological contributory factors may change as well. Furthermore, we did not examine work and employment, which is also an important domain of participation.[3]

Clinical implications

Clinicians might underestimate participation restrictions and contributory factors when evaluating patients who are in the early stages of their disease. They should be aware of early restrictions in participation in ambulatory ALS patients and screen regularly for functional mobility, lung capacity, fatigue, and helplessness in clinical practice. Functional mobility might be targeted by providing appropriate mobility aids, such as canes, crutches, and walkers.[7,29] Lung capacity might be improved by inspiratory muscle training (IMT) and lung volume recruitment training (LRVT).[45] Furthermore, helplessness and fatigue might be modified by teaching patients how to exert more control over the consequences of their disease by implementing a psychological intervention, such as cognitive behavioral therapy (CBT). CBT has already shown to improve helplessness and fatigue in patients with other motor neuron disease and other chronic diseases.[46,47] Further research is needed to investigate whether psychological interventions could also modify feelings of helplessness and fatigue in ambulatory ALS patients. Longitudinal studies are required to further explore physical and psychological contributory factors on participation restrictions over time.

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Supplementary Table S6.1. Characteristics of independent and dependent variables and measures applied

Characteristics	Measure	Score used (range)	n	Median	IQR	Range
Independent variables						
Physical functioning						
Disease severity	ALSFRS-R	Total score (0–48)	67	43.0	5.0	21.0
Lung capacity (FVC%)	Spirometer	Total score (0–∞)	60	96.5	20.5	96.0
Fatigue severity	CIS-fatigue	Total score (0–56)	63	32.0	23.0	46.0
Grip strength (kilograms)	Handheld dynamometer	Total score (0–∞)	67	39.0	32.0	111.00
Functional mobility (seconds)	TUG test	Total score (0–∞)	67	9.2	4.2	52.1
Psychological factors						
Symptoms of anxiety	HADS-A	Total score (0–21)	66	4.0	4.0	12
Depressive symptoms	HADS-D	Total score (0–21)	66	3.0	5.0	12
Illness cognitions						
Helplessness	ICQ	Total score (6–24)	66	12.0	5.3	18.0
Acceptance	ICQ	Total score (6–24)	66	15.0	4.3	17.0
Disease benefits	ICQ	Total score (6–24)	66	13.0	5.0	17.0
Coping						
Task-Oriented Coping	CISS:SSC	Total score (7–35)	63	26.5	5.5	23.0
Emotion-Oriented Coping	CISS:SSC	Total score (7–35)	62	15.5	9.0	24.0
Avoidance-Oriented Coping	CISS:SSC	Total score (7–35)	62	19.5	9.3	28.0
Dissatisfaction with social support	SSL-D	Discrepancy score (8–24)	65	8.0	2.0	8.0
Dependent variable						
Participation						
Participation Restrictions	SIPSOC	Total score (0–22)	67	4.0	7.0	17.0

SIPSOC = Social health status dimension of the Sickness Impact Profile; ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale Revised; FVC% = Forced Vital Capacity, percent predicted; CIS-fatigue = subscale fatigue of the Checklist Individual Strength; TUG test = Timed Up and Go test; HADS-A = Hospital Anxiety and Depression Scale, subscale anxiety; HADS-D = Hospital Anxiety and Depression Scale, subscale depression; ICQ: Illness Cognition Questionnaire; CISS:SSC: Coping Inventory for Stressful Situations: Situation Specific Coping; SSLD = Social Support List-Discrepancies.

Chapter 7

Participation and autonomy in the first 10 months after diagnosis of ALS: A longitudinal study

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ABSTRACT

Introduction: More insight is needed into participation in daily activities and autonomy among patients with ALS. Aims of this study were 1: to describe the course of participation restrictions and autonomy in participation during the first 10 months after diagnosis; 2: to study the influence of the rate of ALS progression on the course of participation.

Methods: Secondary analysis of data from the longitudinal multicentre FACTS-2-ALS study. Self-report questionnaires were administered at inclusion (T0; n = 71), at 4 months (T1), 7 months (T2), 10 months (T3) after inclusion. Median duration of follow-up was 10.0 months. Participation restrictions were assessed using the sum of the Mobility Range and Social Behaviour subscales of the Sickness Impact profile-68 (SIPSOC). Autonomy in participation was assessed using the Impact on Participation and Autonomy questionnaire (IPA). Fast disease progression was defined as an increase of 1.1 points per month or more on the ALS-Functional Rating Scale.

Results: Patients reported participation restrictions in all subscales while having mild physical limitations. There was a decrease of participation over time (restrictions and autonomy). This decrease was greatest in patients with fast disease progression. Disease progression negatively influenced movement -related participation more than social interaction domains. Rate of disease progression was more strongly related to SIPSOC scores compared to IPA scores.

Discussion: Preserving participation may be an important determinant of quality of care for patients with ALS. Rate of progression of the disease should be taken into account as it was found to be significantly associated with the level of participation.

Key words: Amyotrophic lateral sclerosis, motor neuron disease, social participation, autonomy, progression.

INTRODUCTION

Amyotrophic Lateral Sclerosis (ALS) is a fatal, progressive, neurodegenerative disorder. Despite extensive research, no curative treatment is currently available. Daily care focuses on symptom management and preserving participation and health-related quality of life (HRQOL).[1] In the International Classification of Functioning, Disability and Participation (ICF),[2] participation is defined as involvement in a life situation and covers an individual's experience in life activities and social roles, for example, work, leisure activities, and involvement in the community. It is a broad concept that can be evaluated from different perspectives, such as experienced restrictions in daily and social activities, or in terms of (loss of) experienced autonomy and control.[3,4]

The variety and severity of impairments and disabilities that accompany ALS in relation to HRQOL have been described extensively.[5-7] There has, however, been less focus on preserving participation among ALS patients or on how multidisciplinary care might help optimize their participation during disease progression. Previous studies revealed that ALS patients experienced a withdrawal from many social activities during all disease stages and that physical decline, psychological factors and communication disorders were associated with participation restrictions in ALS.[8,9] Previous studies also demonstrated that restrictions in participation are associated with decreased HRQOL among patients with progressive neurological diseases, including ALS.[10-12] However, no longitudinal data about the impact of ALS on participation are available.

It is, therefore, important to know more about the course of participation restrictions, the way autonomy in participation is upheld in relation to disease progression, and whether participation restrictions increase in parallel with physical decline, or follow a different pattern. This knowledge may help optimize supportive care for patients with ALS. The aims of this study were 1: to determine the course of participation restrictions and autonomy in participation in the first 10 months after diagnosis of ALS, and 2: to investigate the influence of the rate of ALS progression on the course of participation.

MATERIALS AND METHODS

Patients

This study concerns a secondary analysis of data from the longitudinal multicentre FACTS-2-ALS study.[13] Recruitment took place between 2009 and 2015. Patients could be included for 2 interventions, cognitive behavioural therapy (CBT) and aerobic exercise therapy (AET), or Usual Care (control group). As neither intervention proved effective, we studied these patients as one group.[14,15] Inclusion criteria were: aged between 18 and 80 years; diagnosis

of probable or definite ALS; life-expectancy of more than 1 year (estimate based on the clinical view of the rehabilitation physician), predicted forced vital capacity (FVC) of at least 80%; at least one month post-diagnosis; and able to walk and cycle. Exclusion criteria were: cognitive impairment (whether or not related to ALS, sufficiently serious to prevent the study from being completed) and psychiatric disorder, both assessed using the Cumulative Illness Rating Scale (CIRS).[16] Eligibility criteria were confirmed by the rehabilitation physician. All participants who filled in questionnaires at T0 (N=71) were included in the analyses.

Methods

Data for the current study were collected at inclusion (T0), and 4 months (T1), 7 months (T2) and 10 months (T3) thereafter. The initial assessment took place within approximately two weeks of enrolment and included self-administered questionnaires to be completed at home. Within the same week, Forced Vital capacity was measured by trained research assistants. The same procedure was followed at T1, T2 and T3. The Medical Ethics Committees from all participating centres approved the study protocol and informed consent was obtained from all patients.

Instruments

Experienced participation restrictions were assessed using the 68-item Sickness Impact profile (SIP68).[17] The questionnaire comprises six subscales, two of which measure participation restrictions: Mobility Range (10 questions; range of actions to which a person has (limited) capabilities given his or her health status, such as shopping, house-cleaning, and taking care of personal business affairs) and Social Behaviour (12 items; possible consequences of a health disorder in a person's functioning in relation to other people involving sexual activity, visiting friends, and activities in groups of people). We used the sum of these two subscales, the SIPSOC, to measure participation restrictions.[18] The SIPSOC asks patients to confirm or deny 22 statements about possible restrictions in participation. A higher score indicates more participation restrictions. The SIPSOC has been proven to be valid and reliable in individuals with disabilities and SCI.[19,20]

The Impact on Participation and Autonomy Questionnaire (IPA) assesses autonomy in participation.[21] This measure consists of 32 items in six subscales: Autonomy indoors (7 items, mobility indoors and self-care), Family Role (7 items, responsibilities and performing tasks at home), Autonomy outdoors (5 items, visiting friends/ neighbours, engaging in social activities outdoors), Social life (7 items, personal interaction with loved ones and friends), and Work/ education (6 items). All items are graded on a 5-point rating scale with discrete responses, ranging from 0 (very good) to 4 (very poor). For each domain the participation score is calculated by summing the item scores. Higher scores denote more limitations

in participation and autonomy. The validity, consistency and reliability of the instrument are good. This has been tested in patients with a wide range of conditions, in particular neuromuscular disease, spinal cord injuries, traumatic head injuries, multiple sclerosis, stroke and rheumatoid arthritis.[22-24]

Demographic variables (age, gender), time since symptom onset and site of onset were collected at inclusion. Disease severity was assessed using the revised ALS Functional Rating Scale-Revised (ALSFRS-R).[25] The ALSFRS-R is a valid, reliable and sensitive instrument for assessing physical functioning. It consists of 12 items to evaluate bulbar function, gross and fine motor function and respiratory function; each item is scored on a scale of 0 to 4. Higher scores indicate better physical functioning.

FVC, as a determinant of lung-capacity, was measured with a spirometer (MicroRPM; PT Medical, Leek, The Netherlands) and the score was expressed as a percentage of the predicted score based on the patient's gender, weight, race and height. In case of insufficient lip closure, a face mask was used. Each participant made 2 attempts and the highest score was recorded.

Analyses

Descriptive statistics were used to describe characteristics of the study population. Rate of disease progression per month was calculated as the difference between two ALSFRS-R scores at T0 and a second measurement (the last available measurement in time) divided by the time between these measurements in months. The median of the difference score was calculated and used as cut-off to define two subgroups: 'slow' progression and 'fast' progression. Mann Whitney tests were performed at T0 to describe differences in participant characteristics between these two subgroups.

To provide greater insight into changes in participation, scores were calculated for individual items, subscales of the SIPSOC and the subscales of the IPA. To analyse the course of participation between T0 and T3, random coefficient analysis (multi-level analysis) was applied. With this technique, all available data could be used. SIPSOC scores, SIPSOC Social Behaviour and Mobility, and all IPA subscales were separately used as the dependent variable, resulting in 8 different models. First, unconditional means models were fitted with a random intercept to account for nested data within individuals (due to the repeated measures). Next, the models were expanded by adding a random intercept to account for nested data within the intervention conditions (CBT, AET or usual care). Likelihood ratio tests were used to assess model fit. For all SIPSOC and IPA subscales, adding a random intercept for intervention condition did not result in a significantly better model. Therefore, in all cases, we used the models with only a random intercept to account for repeated measures within individuals.

Subsequently, Time was entered into the models as a set of 3 dummy variables with T0 as reference. Finally, the dichotomous disease progression variable was added to the

model to study the effect of disease progression and the interaction effect between disease progression rate and participation time. In case the effect was significant, Cohen's effect size was calculated, to determine the impact of progression and (d = difference between scores at T3 / SD of baseline score). Using Cohen's rule of thumb, an effect size of 0.12 was considered 'small', of 0.30 'medium' and of 0.50 'large (26). SPSS version 25 for Windows was used for all statistical analyses.

RESULTS

Study population

Seventy-one patients were included. Of these 71 patients, 10 patients were allocated to CBT, 26 patients were allocated to AET and 35 patients were allocated to the control group. Seven patients died during the course of the study and 14 dropped out because they experienced the study as too burdensome (total 21 patients). Of these 21 patients, we included data of 13 patients, of which there were data of at least 2 measurements in time.

Patient characteristics are displayed in Table 7.1. Progression of disease was calculated for 63 patients who filled in questionnaires, at least at T0 and T1. The median progression rate was 1.1 points per month. We defined slow progression as < 1.1 points per month and fast progression as ≥ 1.1 points per month. Time since onset of ALS was the only variable showing a significant difference between the patients with slow progression versus those with fast progression

Table 7.1. Patient characteristics

	T0 (n = 71)	T0, slow (n = 30)	T0, fast (n = 33)	Difference Slow vs fast; p
Age in years, Mean (SD)	60.1 (10.5)	60.6 (11.7)	58.8 (8.8)	0.21
Sex, male n (%)	49 (69)	19 (63)	26 (79)	0.18
Time since onset in months, Mean (SD)	17.2 (12.8)	22.0 (15.7)	13.1 (7.1)	0.01*
Spinal onset n (%)	52 (73)	25 (83)	21 (64)	0.08
ALSFRS-R at inclusion, Mean (SD)	42.1(3.7)	41.7 (4.4)	43.0 (2.9)	0.34
Severe (≤ 27) (%)	1 (1.4)	1 (3.3)	0	
Moderate (28–37) (%)	6 (8.5)	4 (13.3)	0	
Mild (≥ 38)	64 (90)	25 (83)	33 (100)	
FVC% Mean (SD)	91.3 (16.9)	96.9 (11.1)	88.2 (18.4)	0.08

T0 slow, subgroup with slow progression, < 1.1 point on ALSFRS-R/ month. T0 fast, subgroup with fast progression ≥ 1.1 points on ALSFRS-R / month. Slow vs fast, p = significance of difference between groups (slow vs fast progression at inclusion) by Mann Whitney Test; *, significant (p < 0.05). ALSFRS-R = revised ALS Functional Rating Scale.

SIPSOC item scores over time from the complete case analysis are presented in Table 7.2 and in Supplemental Table S7.1. The proportion of patients who experience participation restrictions over time (affirmative answer to the questions) increases for almost all items. Over time, most patients (40%–72%) reported restrictions in daily work and chores around the house, in participating in social activities, and from onset about 40% of the patients reported restrictions in sexual activity and community activities. Four groups of SIPSOC items can be distinguished: (1) 'Minor restrictions' is a category with items to which hardly any patients report restrictions throughout the study (indoor mobility, taking care of personal business). (2) 'Restrictions from the start of the study' is a category of items with a substantial amount of patients reporting restrictions from onset and which increases over time (sexual activity, community activities, regular daily work around the house, doing heavy work around the house). (3) items showing a strong increase of patients reporting restrictions during the study (activities around the house, household activities, going out at night, visiting friends); and (4) items that were difficult to categorize. Table 7.2 also shows mean IPA scores over time from the complete case analyses. Autonomy indoors scores increase most over time, followed by Autonomy outdoors. Social life and relationships scores are lowest from onset and throughout the course of the study.

Table 7.2. SIPSOC and IPA scores over time

SIPSOC items Mean (SD)	T0 (n = 71)	T1 (n = 63)	T2 (n = 55)	T3 (n = 53)
SIPSOC	5.2 (4.2)	8.0 (5.3)	8.4 (5.1)	10.0 (5.4)
SIPSOC Social Behaviour	3.8 (2.7)	5.2 (3.2)	5.1 (3.1)	5.9 (3.2)
SIPSOC Mobility Range	1.4 (2.3)	2.9 (2.8)	3.3 (2.8)	4.1 (2.9)
IPA Mean (SD)	**T0 (n = 71)**	**T1 (n = 63)**	**T2 (n = 54)**	**T3 (n = 52)**
Autonomy indoors	0.7 (0.7)	1.0 (0.8)	1.1 (0.7)	1.3 (0.9)
Family role	1.5 (0.9)	1.6 (0.9)	1.8 (1.0)	1.8 (1.0)
Autonomy outdoors	1.2 (0.9)	1.4 (0.9)	1.4 (0.8)	1.6 (0.9)
Social life relationships	0.8 (0.7)	0.9 (0.6)	1.0 (0.6)	1.0 (0.6)
Work education	2.0 (0.9) (n = 31)	2.3 (1.1) (n = 34)	2.0 (1.0) (n = 19)	2.2 (0.9) (n = 23)

Note: higher score means more restrictions (SIPSOC) and less autonomy (IPA) in participation.

Rate of change in participation over time (longitudinal models)

Figures 7.1a and 7.1b show the estimated SIPSOC (participation restrictions) and IPA (autonomy in activities) scores, based on estimates of fixed effects. Overall, the SIPSOC and the IPA scores increased significantly over time (Table 7.3, 7.4).

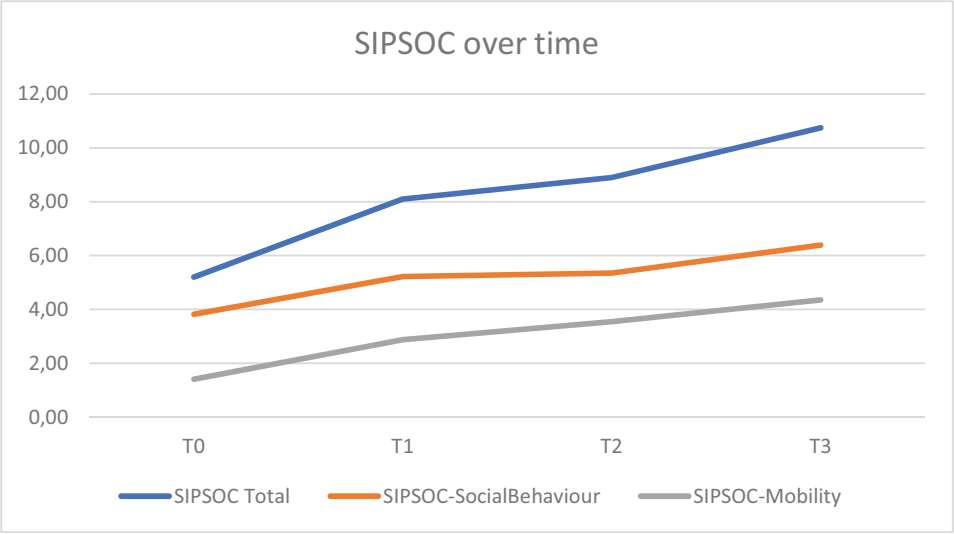

Figure 7.1a. Estimated SIPSOC scores, based on estimates of fixed effect over time.
Note: higher score means more restrictions in participation.

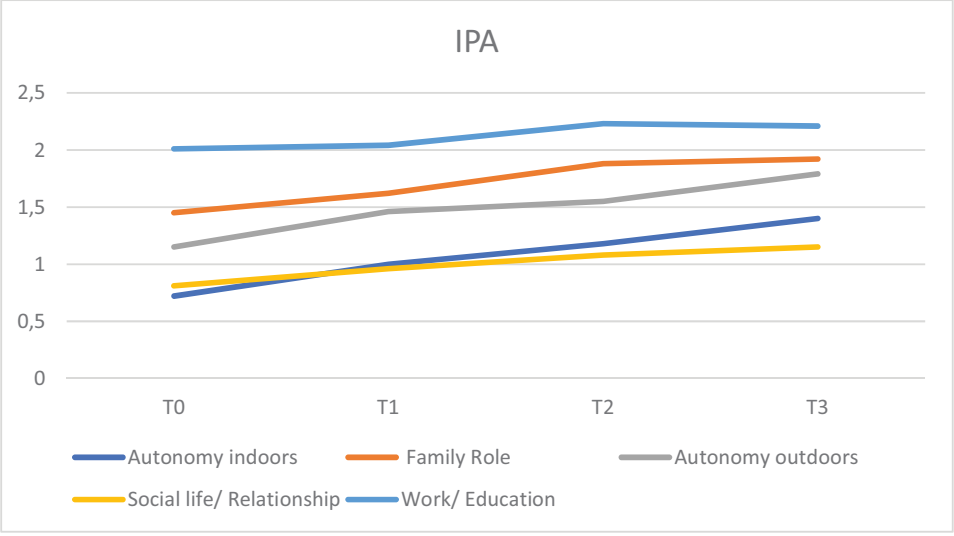

Figure 7.1b. Estimated IPA scores, based on estimates of fixed effect, over time.
Note: higher score implies less autonomy.

Table 7.3. Rate of change in participation (measured by SIPSOC scores, Social Behaviour and Mobility Range) over 10 months after diagnosis of ALS (n = 71) and associations with disease progression (n = 63)

	SIPSOC		SIPSOC Social Behaviour		SIPSOC Mobility Range	
	Time only	Time and ALS progression	Time only	Time and ALS progression	Time only	Time and ALS progression
Intercept	5.21*	4.92*	3.81*	3.38*	1.41*	1.52*
Time factors						
T0-T1	2.88*	1.59*	1.40*	0.82	1.47*	0.86*
T0-T2	3.65*	1.98*	1.53*	1.03*	2.13*	1.06*
T0-T3	5.54*	3.57*	2.57*	1.65*	2.94*	1.99*
Progression		0.01		0.56		-0.43
T0–T1*Progression		2.62*		1.25*		1.28*
T0–T2*Progression		3.53*		1.03		2.36*
T0–T3*Progression		4.08*		1.97*		2.19*

* $p < 0.05$. All 4 models had random intercepts. Total, total population. All figures are regression coefficients from random coefficient analyses.

Associations with disease progression

Disease progression and time by progression interaction effects were calculated in a subgroup of 63 patients. Significant time by progression interaction effects were observed with regard to the total SIPSOC and the subscales Mobility Range and Social Behaviour (the latter only between T0–T1, T0–T3), showing that the number of participation restrictions increased more in patients with faster progression of disease (Table 7.3). We additionally calculated the effect size, regarding the impact of progression. Cohen's effect size was respectively 0.97 for the SIPSOC scale (large effect), 0.93 for subscale Mobility Range (large effect) and 0.77 subscale Social Behaviour (medium effect).

Regarding the IPA, significant time by progression interaction effects were observed for Autonomy Indoors and Autonomy Outdoors (both between T0–T2, T0–T3) (Table 7.4). Cohen's effect size was large, respectively 0.89 and 1.0. No interaction effect of progression of disease was observed for Family Role and Social Life (IPA), meaning that in our population, patients with fast progressive disease do not experience less autonomy in participation with regard to Family Role or Social Life compared to patients with slow progression. We cannot draw conclusions about Work and Education, because of the large number of missing values for this subdomain of the IPA.

Table 7.4. IPA. Results of random coefficient analysis (multi-level analysis). Estimates of fixed effects over 10 months after diagnosis of ALS (n = 71) and associations with disease progression (n = 63).

	Autonomy indoors		Family role		Autonomy outdoors		Social life		Work education	
	Time model	Time and ALS progression	Time model	Time and ALS progression	Time model	Time and ALS progression	Time model	Time and ALS progression	Time model (n = 31)	Time and ALS progression (n = 27)
Intercept	0.72*	0.75*	1.45*	1.40*	1.15*	1.10*	0.81*	0.77*	2.01*	1.54*
Time factors										
T0–T1	0.28*	0.12	0.17	0.02	0.30*	0.18	0.16*	0.09	0.02	-0.11
T0–T2	0.46*	0.15	0.43*	0.34*	0.40*	0.12	0.27*	0.19*	0.22	0.81
T0–T3	0.68*	0.32*	0.47*	0.41*	0.64*	0.34*	0.34*	0.23*	0.198	0.18
Progression		-0.17		-0.02		0.01		0.17		1.01*
T0–T1*Progression		0.26		0.26		0.22		0.13		0.33
T0–T2*Progression		0.64*		0.15		0.57*		0.21		0.30
T0–T3*Progression		0.79*		0.12		0.58*		0.20		-0.04

* $p < 0.05$. All 4 models had random intercepts. Total, total population. All figures are regression coefficients from random coefficient analyses.

DISCUSSION

ALS patients reported participation restrictions in all subscales shortly after diagnosis, while experiencing relatively mild physical limitations. Participation decreased over time (restrictions and autonomy), to the greatest extent in patients with a more rapidly progressive disease course. Over time, rate of disease progression negatively influenced the participation domains related to movement indoors/outdoors more than those related to social interaction domains. Rate of disease progression also negatively influenced experienced restrictions in activities (SIPSOC scores) more than the sense of autonomy (IPA).

As stated before, after onset 34% of the patients were already experiencing restrictions in sexual activity, 36% in community activities and 72% in heavy work around the house. These percentages did not change significantly over time, which could suggest that physical decline is not associated with these factors. On the other hand, it could also suggest that ALS care in The Netherlands is very effective in arranging adequate auxiliary tools during those 10 months. Our results on sexuality are consistent with previous studies, showing that sexuality plays a crucial role in personal well-being.[27] These results imply that dealing with restrictions in sexuality, experienced by ALS patients and their partners, may be an important early topic for multidisciplinary care.

A substantial number of the patients experience restrictions in community activities (church, voluntary work, clubs), indicating that this is an important group to identify to prevent social isolation.[28,29]

In over two-thirds of patients, restrictions in being able to do regular and/or heavy housework were reported, meaning that support from caregivers, family and/ or neighbours was needed. This is also reflected in the IPA subscale 'Family Role'. Throughout the study, participants reported the least autonomy in these activities. Compared to patients with spinal cord injury, mean SIPSOC scores showed that patients with ALS reported fewer participation restrictions shortly after the diagnosis of ALS, but considerably more restrictions 4 and 10 months later.[30] At onset, patients in our study were able to walk and exercise on a home-trainer, but experienced physical decline due to progression of the disease. In contrast, following spinal cord injury (paraplegic and tetraplegic), patients immediately experience severe physical restrictions which do, however, remain stable.

Taking IPA scores over time, mean scores increased most in the subdomain of Autonomy indoors. When we compare our mean IPA scores with results from studies in patients with MS, stroke, spinal cord injury and a mixed group (neuromuscular disease and brain injury), ALS patients experienced less autonomy in participation in all domains, 10 months after diagnosis.[31-36] Shortly after diagnosis, scores of ALS patients were comparable to those of patients with MS, and patients following stroke, spinal cord injury, brain damage.

All this underlines the large impact of ALS on participation and related thereto quality of life of patients, starting shortly after diagnosis.

Rate of progression of the disease seems to influence the motor domains more than the social interaction domains and activities at home. Despite a rapid decline in physical functions, patients can apparently still maintain autonomy in activities and responsibilities at home and in personal interactions with loved ones, friends. They depend heavily on their caregivers who facilitate all aspects of their everyday lives. This means that caregivers must also adapt in order to support the autonomy of a patient, a loved one. There is, therefore, an increasing relevance of seeking support from family members;[37] we must be aware of the burden on caregivers, already in the first 10 months after the diagnosis. When comparing the interaction coefficients, the rate of progression seems to negatively influence experienced restrictions in activities (SIPSOC scores) more than the sense of autonomy (IPA scores). Patients can become overwhelmed by the ongoing decline in function, especially those with rapidly progressive disease, but apparently this has more impact on experienced restrictions. Apparently many patients are successful in maintaining a sense of autonomy, a sense of control, even when it becomes more difficult to perform certain activities. Our study suggests that for those patients with a more progressive disease course, it is harder to find a new equilibrium, but not impossible. We know that QOL in patients with ALS, when considered in its broadest sense, does not correspond well to physical function, and is maintained by psychological, existential, and support factors. Perhaps the relative maintenance of social interaction domains and autonomy is what preserves QOL in these individuals, as described by Mc Caffrey et al.[38-40]

This study has a number of strengths and limitations. Follow-up started directly after diagnosis and has given us insight into the interaction of rate of progression from 1 month after diagnosis. Having insight in rate of progression can help determine which patients are more 'at risk' of restrictions in participation at the beginning of this palliative care process. This would improve the personalized care we aim to give our patients.

As patients included in the FACTS-2-ALS trial needed to be able to participate in physical exercise, less impaired patients were selected at baseline. One could argue, therefore, that participation restrictions were possibly underestimated at baseline. However, slope of disease progression in our patients is comparable to that of patients in other studies.[41] Hence, we do not believe that patients with a fast progressive disease course are under-represented in this study. This is a secondary analysis of data of the FACTS-2-ALS study. Follow-up of this study is 10 months which is relevant but relatively short. Future studies should have a follow up throughout the disease course giving us important knowledge adjuvant to natural course studies on physical complaints.

We used multilevel analysis to deal with the dropouts. All 13 patients who dropped out during the study, but who were included in analysis, were in the fast progression group. Had

we not used multilevel analysis, then data of these patients would not have been included and our results would have been set to high and we would have underestimated the levels of participation restrictions.

We did not focus on possible other determinants of participation, such as communicational problems. This should be the focus of future studies.[42]

We made the assumption of a linear course of disease progression measured by the ALS-FRSR. However, the rate of progression of ALS, based on change in ALSFRS-R, is not necessarily linear. Yet, the rate of progression calculated for our patients is not always calculated over the same interval of time. We choose to follow standard practice for clinical trials where both trial design and the analysis virtually always assume a linear trend in ALSFRS-R rate of decline. Additionally, we conducted a multilevel analysis with progression as the outcome and time as predictor to investigate the course of progression. The results supported our choice to assume a linear trend.

In conclusion, ALS patients in the first 10 months after diagnosis experienced an increase of participation restrictions and loss of autonomy over time, which was highest in patients with rapidly progressive disease. Over time, rate of progression of the disease negatively influenced the participation domains related to movement indoors/outdoors, more than those related to social interaction domains, and negatively influenced experienced restrictions in activities (SIPSOC scores) more than the sense of autonomy (IPA).

Our results indicate that, from day one, focus on participation is an important determinant for optimal multidisciplinary care of ALS patients and their caregivers. Professionals must be aware that even patients with relatively mild physical limitations experience restrictions (in sexuality, community activities) and loss of autonomy in important activities. Prioritizing a patient's participation in social and meaningful activities is one of the characteristics of person-centred care[43] and improves quality of life.

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Supplemental Table S7.1. Item scores on social health status dimension of the 68-item Sickness Impact profile; divided in subgroups

SIPSOC items	T0 (n = 71)	T1 (n = 63)	T2 (n = 55)	T3 (n = 53)
Minor restrictions				
I am getting around only within 1 building	2.8	7.0	8.5	5.6
I am not going out to visit people at all	2.8	4.2	7.0	7.0
I have given up taking care of personal or household business affairs	5.6	8.5	14.1	12.7
I am cutting down on some of my usual inactive recreations and pastimes (e.g. watching TV, cards, or reading)	7.0	8.5	8.5	14.1
I am eating much less than usual	14.1	18.3	15.5	19.7
Restrictions from the start of the study:				
I spend shorter periods of time on my hobbies and recreational activities	39.4	47.9	38.0	39.2
I am doing fewer social activities with groups of people	28.2	36.6	25.4	39.4
I am taking part in fewer community activities	36.6	31.0	40.8	40.8
My sexual activity has decreased	32.4	43.7	38.0	42.3
I am doing less of the regular daily work around the house than I would usually do	70.4	73.2	59.2	62.0
I am not doing heavy work around the house	71.8	78.9	69.0	64.8
Strong increase of patients reporting restrictions:				
I cannot get around in the dark or in unlit places without help	7.0	21.1	22.5	26.8
I am cutting down the length of visits with friends	16.9	32.4	28.2	32.4
I stay home most of the time	18.3	33.8	22.5	42.3
I am not doing any of the clothes washing that I would usually do	12.7	29.6	31.0	42.3
I am not doing any of the shopping that I would usually do	25.4	42.3	42.3	47.9
I am not doing any of the regular work around the house that I would normally do	23.9	36.6	38.8	49.3
I am not doing any of the house-cleaning that I would usually do	25.4	40.8	47.9	50.7
Rest group				
I stay away from home for only brief periods of time	15.5	18.3	18.3	21.1
I am not going into town	15.5	29.6	21.1	29.6
I am drinking fewer fluids	22.5	28.2	18.3	21.1
I go out less often for entertainment	26.8	43.7	35.2	35.2

Note: all figures represent the % of patients that stated 'applies to me' to an item of the SIPSOC.

Chapter 8

General discussion

INTRODUCTION

In this chapter I will first present the main findings of my studies. Next, I will discuss the possible interpretations and explanations of these findings, followed by methodological considerations. Finally, I will discuss the implications for improving care and directions for future research.

MAIN FINDINGS

Quality of life of patients with SMA or ALS

HRQOL of SMA patients (Chapter 2):

HRQOL of SMA patients was investigated in a cross-sectional study involving 62 patients and measured with the SF-36. With the exception of the Physical Functioning domain score, MA patients tend to report average levels of HRQOL, comparable to a healthy reference population. With regard to the Physical and Mental Component scores (PCS and MCS) of the SF-36, PCS scores were lower, and MCS scores were higher than in the healthy reference population. In our study, we merged SMA types into two groups: SMA with an early onset (types 1, 2, 3a, later called SMA-early), and SMA with a relatively late onset (types 3b and 4 later called SMA-late). Patients with milder SMA types (SMA-late) reported lower scores on several MCS domains than patients with early onset SMA. Disease severity (inverse correlation) and emotional distress were determinants of HRQOL.

HRQOL of ALS patients (Chapters 4 and 6):

Our review suggests that higher levels of anxiety and depression are related to poorer HRQOL, whereas higher levels of religiosity appeared to be related to better global HRQOL. These associations might change during the disease course. Additionally, we performed a longitudinal study with 48 patients in which we considered whether illness cognitions are possible determinants of HRQOL. Acceptance and Disease Benefits were independently related to HRQOL ten months after diagnosis (follow-up). Increased Helplessness was independently related to lower HRQOL at baseline and increased Helplessness measured at baseline was an independent predictor of lower HRQOL at follow-up.

Participation of adult patients with SMA (Chapter 3):

A cross-sectional study was performed involving 62 patients. Patients with early-onset SMA (types 1, 2, and 3a) experienced more participation restrictions than those with late-onset SMA, but reported similar levels of frequency of participation and satisfaction with

participation. Compared to patients with other diagnoses (e.g. spinal cord injury), SMA patients appeared to be just as satisfied with their participation in daily activities. Motor skills, fatigue and feelings of depression in particular were correlates of participation in daily life.

Participation of patients with ALS (Chapters 5 and 7):

In a cross-sectional study (72 patients), 92% of the patients reported participation restrictions directly after diagnosis, while indicating, on average, mild physical limitations. Physical functioning explained 54.9% of the variance and psychological factors accounted for 8.1% of the variance. Lung capacity, functional mobility, fatigue and helplessness were independently associated with participation restrictions.

In our longitudinal study (71 patients), we found an increase of participation problems over time (restrictions and autonomy) which was highest in patients with a rapidly progressive disease (**Chapter 7**). Participation domains related to movement indoors/outdoors were more strongly affected over time than domains related to social interaction. Rate of progression also negatively influenced experienced restrictions in activities (SIPSOC scores) more than the sense of autonomy (IPA).

DISCUSSION OF THE MAIN FINDINGS

A common factor in our studies was our description of the impact of living with a very serious, progressive, neuromuscular disease with severe limitations. Despite the considerable differences in e.g. progression rate between ALS and SMA, outcomes of the studies corresponded in several ways.

HRQOL

In both SMA and ALS patients, psychological factors were identified as determinants of HRQOL. One of these was mood, or emotional distress. Higher levels of anxiety and depression, measured with the HADS, seemed to be related to a lower HRQOL. This can partly be explained by the fact that the SF-36 also contains questions about mood. This conceptual overlap in questionnaire items of the SF-36 and HADS may have led to an overestimation of the association between emotional distress and HRQOL, but it is a recognizable phenomenon. Surprisingly, patients with milder SMA types reported lower scores on several MCS domains (poorer HRQOL) than patients with early onset SMA (patients with severe physical limitations). Patients with mild SMA phenotype experience physical problems later in life. They might be accustomed to comparing themselves to healthy individuals, and maintain a high bar for their expectations about functioning. This is a phenomenon well known to rehabilitation

specialists and has been reported before. Patients with relatively mild acquired brain injury, or spina bifida occulta, for example, with mild physical limitations, often report lower HRQOL than expected.[1,2] They tend to receive less attention for their problems and regard themselves as being less impaired; they can, therefore, feel more frustrated at not being able to function as well as their 'healthy' peers. They tend to ask for support at a latter phase and often have trouble finding their way in the health care system. As a psychological factor, we studied the role of *appraisal* in the form of Illness cognitions in relation to HRQOL in ALS patients. Other studies among patients with NMD have also focused on the role of appraisal. Graham, Rose and Fischer found associations between illness perceptions and HRQOL and mood in ALS patients and SMA patients, respectively.[3-5] A later study, with a focus on the role of illness perceptions in dealing with SMA (Cremers et al., unpublished data), illustrated a broad diversity of illness perceptions. Appraisal is very relevant in the process a patient goes through in the search for control over a repeatedly changing situation; also, it is related to participation and HRQOL. Health care professionals must be more aware of the patients' perceptions of a disease and actively question them about their perceptions. This can form the starting point for psychotherapy.

Participation

Participation decreased over time, also in patients with relatively mild restrictions (SMA-late; ALS patients at the start of the study). Again, psychological factors were identified as determinant of participation, both in ALS and SMA patients. Satisfaction with participation may be related to psychological well-being.[5-8] Satisfaction scores of patients with SMA were similar to those previously reported by patients with spinal cord injury and patients after stroke.[8-10] SMA patients often present themselves with the following quote: "I am satisfied with my life, however the struggle to uphold my way of functioning is very hard". Obviously, one patient is better than the other in dealing with the daily challenges, due to personal resources such as resilience and optimism.[11] These results reflect the fact that patients in different situations are, on the whole, able to reorganize their social activities in a satisfactory way, regardless of their restrictions and type of condition.

Adaptation to progression

In ALS patients, the fact that they have to deal with a progressive disease together with the speed of progression greatly influences HRQOL and participation. In our longitudinal study, we found an increase of participation problems over time (restrictions and autonomy) which was highest in patients with a rapidly progressive disease. Interestingly, rate of progression negatively influenced experienced restrictions in activities (SIPSOC scores) more than the sense of autonomy (IPA). We know that HRQOL in patients with ALS, when considered in its

broadest sense, does not correspond well to physical function, and is, as in other palliative diagnoses, maintained by psychological, existential, and support factors.[12,13] According to the self-determination theory[14] about human well-being, three basic psychological needs underlie human motivation, one of them being autonomy. Perhaps it is the relative maintenance of social interaction domains and autonomy that preserves HRQOL in these individuals. The theory of Waldron adds another explanation, namely that in the initial stages patients may focus on physical functioning, but as the disease progresses, focus turns to psychosocial and spiritual domains.[15] We could not study the impact of progression on HRQOL or participation in SMA patients; however, it is clear from daily practice and previous studies that the fact that they have to deal with their progressive disease also greatly influences HRQOL and participation.[16-19] Muscle strength and motor function decline in a fairly linear pattern in SMA patients.[20] Qualitative research has shown that constant readjusting to a small decrease in function influences mood and leads to loss of autonomy.[16,17] Mental health care was highlighted in that study as a major unmet need of SMA patients, particularly during times of fear and frustration in response to loss of function and social isolation.

At the same time, the fact that progression is slow, makes more room for a 'response shift', which explains high HRQOL and satisfaction about participation.[21] The fact that MCS scores of the SF-36 in SMA patients were higher than in the healthy reference population, can be explained by response shift. For example, patients with early onset SMA may not experience common complications as a sign of impaired health and report next-to-normal physical HRQOL scores. They are fully adapted to the physical limitations to which they have become accustomed throughout their lives. "I am not ill, I have a condition called SMA". Response shift is also likely to be prevalent in participation measurement, because effective coping with disability – whether stable or progressive – would require a regular reappraisal of one's meaning of participation, relevant experiences to sample, relevant standards to apply, and the relative importance one assigns to the various life domains related to participation.[21] In ALS, patients with a slowly progressive disease have more time to adapt; a response shift is likely to occur in this patient group. These issues are summarized in the Stress coping model, introduced by Lazarus and Folkman (Figure 8.1).[22]

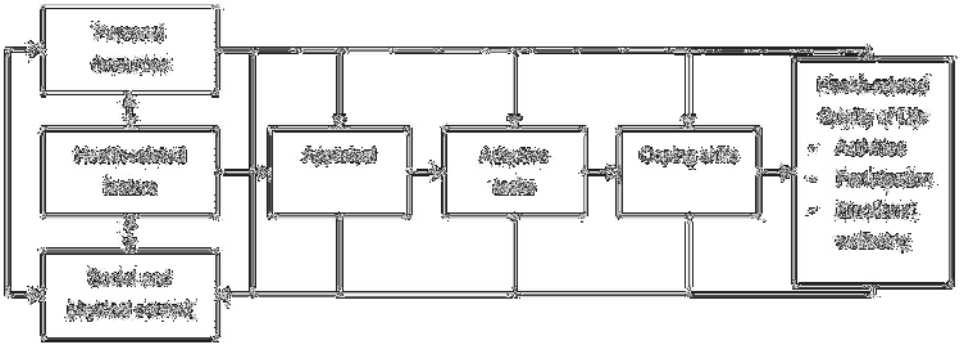

Figure 8.1. Stress coping model Lazarus and Folkman.

METHODOLOGICAL CONSIDERATIONS

Design

SMA studies: these studies were among the first to focus on adult patients with all types of SMA. We studied a unique adult cohort, including all SMA subtypes. The main limitation was due to the cross-sectional design, studying a very diverse population with a limited sample size. This meant that we were not able to study relationships with more possible determinants.

ALS studies: we performed both a cross-sectional and a longitudinal study with different outcome measures. This meant that we could not study possible association of determinants found in the cross-sectional study, in the longitudinal study. Because of the limited sample size, we were able to add only a limited number of variables in the regression analysis. Patients with fast progressive disease were excluded; therefore, we could not study the possibly more difficult adaptation process in these patients.

A natural history study is required, focussing on non-physical symptoms, also among patients with very fast and very slow progressive disease.

Study sample

SMA: the inclusion of all types of SMA was a strength of this study because we gained greater insight into the diversity of physical limitations, disabilities, participation and HRQOL among SMA patients. All patients were recruited through the Dutch national SMA database and were seen in the outpatient clinic of the Department of Neurology at the University Medical Centre, Utrecht. Patients who did not participate may have experienced no problems or possibly too many problems to allow a physical visit. Patients who experienced no problems in daily life

may not have wanted to make the effort, but did not necessarily have a less severe type of SMA. We cannot, therefore, draw conclusions about a possible selection bias.

ALS: there was a selection bias in all our studies. Data were from the FACTS-2-ALS database. Patients were found to be eligible for the FACTS-2-ALS study, if able to use a home trainer or walk a short distance. Also, as was the case in the SMA studies, patients who could not understand the Dutch language were not included. This is true of many studies. The Dutch society is multicultural and in future, maximum effort should be made to include these patients.

Measurements

In our SMA study we used the SF-36 (HRQOL). Our goal was to obtain insight into this population compared to other diagnoses, making this a suitable instrument.

In our ALS studies we used the SF-36 and the ALSAQ. Both the SF-36 and the ALSAQ focus on the general health status of the patient, with a focus on deficits in physical functioning, implying that absence of physical deficits concurs with positive health. In retrospect, the ALSAQ is not the most suitable outcome measure to study illness cognitions as a possible determinant of HRQOL. The Illness cognitions questionnaire asks about the response of a patient to a disease; it reflects the way a patient perceives the situation. A global QOL questionnaire or a questionnaire about general well-being may have been more suitable for studying the impact of illness cognitions. For this purpose, Simmons suggested adding items like religiosity and meaningfulness to a HRQOL instrument to be applied in ALS research.[23]

We used several participation outcome measures: in SMA patients, the USER-P; in ALS patients, the IPA and the SIPSOC. The USER-P gave us the opportunity to compare participation levels, subjectively and objectively, with other Dutch populations. The IPA and SIPSOC gave us complementary information which allowed greater insight into the impact of restrictions on e.g. autonomy, which is a central concept in dealing with a chronic disease.

IMPLICATIONS FOR REHABILITATION CARE

The main goal of rehabilitation care is to optimize HRQOL and participation in daily life activities and to have control over the disease.

- **Screening instruments, when used in daily care, should encompass not only physical factors, but also include questions about participation and psychological issues.** At the moment, applying the USER-P and the HADS in the evaluation of functioning is a very useful and effective way for patients to prepare themselves for

a consultation, and for the rehabilitation specialist to obtain greater insight into the impact of the chronic disease. We would prefer also to include psychological and environmental factors as determinants of participation and HRQOL in daily care that are modifiable (interventions). For the individual patient, we should focus on outcome measurements other than HRQOL in daily care, one reason being the fact that HRQOL instruments typically focus on deficits in functioning, implying that an absence of deficits is synonymous with positive functioning. It has been suggested that well-being, assessing positive psychological variables, should be considered as an important outcome in chronic illness. Well-being can be conceptualised as subjective well-being (evaluations that people make about their life, their body and mind, circumstances in which they live) and psychological well-being. Psychological well-being encompasses concepts such as personal growth, resilience, mastery and acceptance.[5]

- **Health care professionals should focus on delivering personalized care and aim to improve individual outcomes of care.** Together with SMA patients and the Nivel, we developed a tool ,'de gesprekskaart', for patients with SMA. This tool comprises questions about all subjects important to patients regarding their functioning, including daily activities, participation and mood. Patients appreciate tools to e.g. prepare themselves for an outpatient clinic visit. By completing these instruments in advance, patients feel they are better placed during the consultation and that they are more in control of the situation.

- **A recent definition of health by Huber emphasizes positive psychological factors, such as the ability to adapt and self-manage.[24] By focusing on these concepts, like resilience and post-traumatic growth, we would be focusing on well-being.** Not only physical abilities should be stimulated, also mental/ psychological abilities should be the focus of attention in daily care.[25] A recent review reported that positive psychology interventions, with the focus on eliciting positive feelings, cognitions or behaviours, not only have the potential to improve well-being, but can also reduce distress in populations with clinical disorders.[26]

- **We strongly recommend paying more attention to psychological factors and psychological interventions.** A multidisciplinary care team should always offer care from a psychologist, in addition to the other disciplines. Care should comprise a pallet of possible choices, e.g. talking to a peer group, group treatment, individualized care, psychoeducation, focus on meaning in life, at the outpatient clinic, or blended care, a combination with online care. A psychologist can also act as a coach for the other team members, to train them to be attentive to the impact of psychological factors on e.g. treatment goals, and coach them on how to deal with these in their sessions.

Persons with ALS or SMA want to keep or regain a sense of control. Daily care can increase the sense of control by paying attention to important personal psychological goals. As advised by Fischer et al.,[5] clinical assessment and management should focus on optimizing patients' satisfaction with their basic psychological needs (autonomy, competence, relatedness), as this is strongly related to indices of psychological well-being. A study by Weeks describes factors which impede or facilitate engagement in psychological interventions for ALS patients.[27] They concluded that flexibility, interventions tailored to individual needs and encouraging autonomy are key attributes for psychological interventions. Patients with ALS are often reluctant to undergo psychological screenings unless they are making an immediate request for help. They do, however, report the benefit of contact with peers or individual interventions. Scholten et al. reported that one's own baseline psychological distress and psychological characteristics were important in the prediction of later psychological distress among both individuals with spinal cord injury (SCI) or acquired brain injury (ABI) and their significant others.[28] Following this, we recommend implementing a form of psychological screening in daily care, for instance with the HADS or a coping scale.

We must be aware that patients possibly regard the rehabilitation physician as a doctor for physical problems only. We must educate our patients about topics which can be raised during consultation; the 'gesprekskaart' or an instrument like the HADS can be helpful here.

We must be aware of individual needs, both in content and the way care is delivered. Patients with a depression, for instance, can benefit from finding alternative activities they enjoy, or tools that enable them to be autonomous in daily activities (wheelchair). This underlines the need for attention to psychological factors, but also the need to focus on personalized care.

DIRECTIONS FOR FUTURE RESEARCH IN SMA AND ALS

- **We should strive to find a screening tool which allows us to easily identify vulnerable patients.** Previous studies showed that the HADS might be suitable,[28] which is also our experience in the UMC Utrecht, where it is implemented in daily care. It would be useful to investigate whether adding a measure of psychological characteristics, such as resilience, would have added value as compared to using only the HADS. However, we do have the 'gesprekskaart' for SMA patients, developed in a co-creation process. We are in the process of applying for SKMS funding, to further implement the gesprekskaart among other NMD. This card mentions psychological/personal factors, such as mood, frustration, being in control. The next step would be to evaluate the 'gesprekskaart' as an instrument to identify vulnerable patients.

- **We should study the efficacy of psychological interventions for patients with neuromuscular disorders.** A review on the impact of possible interventions for QOL and wellbeing reported that there is currently insufficient evidence to recommend psychosocial interventions in patients with a NMD.[29] However, we must be aware of the promise of psychological interventions and the psychological tools that are available. Graham e.g. studied how psychological interventions derived from cognitive behavioural therapy (CBT), in particular Acceptance and Commitment Therapy (ACT), might be applied to address the issues of distress, in people with muscle disorders.[30] Other authors studied the possible impact of psychotherapeutic interventions, mindfulness or meditation for QOL and well-being in ALS patients.[31-34] Sommers highlights stigma as a potential treatment target for psychological interventions aimed at people living with ALS, and proposes the development and testing of a web-based compassion intervention aimed at reducing self-stigma in ALS patients and their family caregivers.[35,36] Obviously, further research is required to study the efficacy of these treatments.
- **Future studies should include interventions to improve well-being of caregivers** of adult patients with SMA. This is missing from our studies and also there is a lack of international studies on this subject.
- **We should aim for longitudinal studies on well-being, participation and its determinants.** Telemonitoring can lower the threshold for participation in such studies and improve compliance. Larger sample sizes would also allow for more detailed subgroup analysis, for example, of subgroups with early and late onset SMA. At this moment, many patients with SMA, and hopefully in due course ALS patients, have the option of receiving new therapeutic strategies. Now that adult patients have started receiving nusinersen in the Netherlands, we should monitor them over a longer period of time, and also their caregivers. Knowledge about the course of the disease and the effect of a new drug on all domains of the ICF, especially well-being, mood and participation is essential to allow proper evaluation of the impact of these new, often very costly therapies.

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Chapter 9

Samenvatting

SAMENVATTING

Motorische voorhoornaandoeningen is een paraplu-term voor een groot aantal uiteenlopende neurologische aandoeningen, welke gepaard gaan met progressieve spierzwakte. Deze patiënten ervaren vaak forse beperkingen in activiteiten en participatie. Spinale Musculaire Atrofie (SMA) en Amyotrofe Laterale Sclerose (ALS) zijn twee voorbeelden van een voorhoornaandoening. Multidisciplinaire revalidatieteams richten zich op het behoud van de kwaliteit van leven (KvL) en participatie van deze patiënten. Bij de start van dit proefschrift was er beperkte kennis over de kwaliteit van leven en participatie van volwassenen met SMA en patiënten met ALS. De doelstelling van dit proefschrift was dan ook om meer inzicht te krijgen in deze belangrijke thema's voor de dagelijkse zorg.

SMA

SMA is een erfelijke aandoening die leidt tot beperkingen op kinderleeftijd en op volwassen leeftijd. In Nederland zijn er ongeveer 300 patiënten met SMA. Jaarlijks worden er ongeveer 20 zuigelingen geboren met SMA. Vijftig procent van deze kinderen heeft SMA type 1, de ernstigste vorm van SMA. Alle patiënten hebben hetzelfde genetische defect, maar de ernst van het beloop van SMA hangt sterk af van de leeftijd waarop de klachten beginnen. In ons onderzoek maken we gebruik van een tweedeling: SMA met een vroeg begin, voor de leeftijd van 18 maanden (types 1, 2, 3a, later genoemd SMA-vroeg), en SMA met een relatief laat begin, na 18 maanden tot op oudere leeftijd (types 3b en 4 later genoemd SMA-laat). Veel patiënten met SMA-vroeg zullen op jonge leeftijd niet-invasieve beademing, scoliose chirurgie of plaatsing van voedingsbuisjes nodig hebben. Studies naar het natuurlijk beloop van SMA hebben aangetoond dat langzame progressie van spierzwakte bij alle typen SMA optreedt.

ALS

ALS is een ziekte die ontstaat op volwassen leeftijd. Deze ziekte wordt gekenmerkt door een progressieve zwakte en spasticiteit van de spieren van de ledematen, evenals die voor slikken, spreken en ademhalen. Daarnaast zijn er niet-motorische symptomen, waaronder cognitieve en gedragsveranderingen in het frontotemporale spectrum. Er is een grote variabiliteit in levensverwachting, maar ook in het verloop van de ziekte. In Nederland zijn er ongeveer 1.500 patiënten met ALS en krijgen ongeveer 500 mensen jaarlijks de diagnose. Eerder onderzoek heeft aangetoond dat multidisciplinaire revalidatiezorg door een ALS team geassocieerd is met een hogere KvL..

Om inzicht te krijgen in de kwaliteit van leven van volwassenen met SMA (met alle types) en beïnvloedende factoren hebben we een cross-sectioneel vragenlijstonderzoek uitgevoerd

(**hoofdstuk 2**). Aan deze studie deden 62 mensen met SMA mee. Zij vulden een kwaliteit van leven vragenlijst (SF-36) in met vragen over fysieke en mentale aspecten van KvL. SMA-patiënten rapporteerden over het algemeen een gemiddeld niveau van kwaliteit van leven en daarmee vergelijkbaar met een gezonde populatie. Op fysieke aspecten van KvL scoorden mensen met SMA lager dan de gezonde referentiepopulatie, maar op mentale aspecten scoorden ze hoger. Patiënten met mildere SMA-types (SMA-laat) rapporteerden daarbij lagere scores op verschillende mentale aspecten dan ernstig aangedane patiënten (SMA-vroeg). Ziekte-ernst (inverse correlatie) en gevoelens van angst en somberheid bleken gecorreleerd met KvL. Deze bevindingen suggereren dat patiënten die relatief mild zijn aangedaan en degenen die gevoelens van angst en depressie ervaren het risico lopen op een lagere KvL. Aandacht en begeleiding bij gevoelens van angst en depressie kan patiënten helpen om te gaan met functionele achteruitgang en veranderende perspectieven in het leven.

De mate van participatie in dagelijkse en maatschappelijke activiteiten (verder: participatie) van volwassenen met SMA en de factoren die hiermee samenhangen is in een cross-sectionele studie onderzocht (**hoofdstuk 3**). Uitkomstmaat was de USER-P, een meetinstrument met drie subschalen: frequentie van uitvoeren van belangrijke activiteiten, beperkingen in activiteiten en tevredenheid over participatie. Patiënten met SMA-vroeg ervoeren meer participatiebeperkingen dan patiënten met SMA-laat, maar rapporteerden vergelijkbare niveaus van frequentie van participatie en tevredenheid met participatie. Patiënten met type 3b en 4 (SMA-laat) ervoeren meer vermoeidheid en pijn dan patiënten met SMA-vroeg. Vergeleken met patiënten met andere diagnoses (bv. ruggenmergletsel), bleken SMA-patiënten even tevreden te zijn met hun participatie. Lagere motorische vaardigheden en gevoelens van depressie waren geassocieerd met *frequentie* van deelname, lagere motorische vaardigheden waren geassocieerd met *beperkingen* in deelname aan dagelijkse activiteiten en meer vermoeidheid en gevoelens van depressie waren geassocieerd met *tevredenheid over* participatie. Dit betekent dat we in de dagelijkse zorg gerichte behandeling moeten aanbieden gericht op gevoelens van angst en depressie en op klachten van vermoeidheid.

De studies naar KvL en participatie van ALS-patiënten staan beschreven in de hoofdstukken 4–7.

Om inzicht te krijgen in de mate waarin psychologische factoren de kwaliteit van leven van patiënten met ALS beïnvloeden hebben we een systematisch literatuuronderzoek uitgevoerd naar de associaties tussen psychologische factoren en KvL (**hoofdstuk 4**). Er werden 22 studies gevonden die deze samenhang hebben onderzocht. De psychologische factoren werden geclusterd in drie groepen: stemming, perceptie van en coping met de realiteit en persoonlijkheid. Resultaten uit de verschillende studies suggereren dat hogere niveaus van angst en depressie gerelateerd zijn aan een slechtere KvL, terwijl een hogere mate van spiritualiteit gerelateerd bleek te zijn aan een betere KvL. Daarbij bleek dat deze

associaties kunnen veranderen tijdens het ziekteverloop, met toename van de associatie van spiritualiteit met KvL. Concluderend kunnen we stellen dat de geïncludeerde artikelen het belang van psychologische factoren voor KvL onderstrepen, maar dat toekomstig onderzoek de gevonden relaties moet bevestigen en zich moet richten op timing en inhoud van de interventies gericht op gevonden psychologische factoren.

Daarnaast voerden we een longitudinale studie uit waarin 48 mensen met ALS vanaf de diagnose tien maanden gevolgd werden. Zij vulden vragenlijsten in over KvL en ziektecognities, waarmee we onderzochten of ziektecognities mogelijke determinanten zijn van KvL bij ALS-patiënten (**hoofdstuk 5**). In deze studie werd de Illness Cognitions Questionnaire (vragenlijst naar ziektecognities) afgenomen, bestaande uit drie subschalen: vragen die gaan over Hulpeloosheid, Acceptatie en Ervaren Ziektewinst. Acceptatie en Ervaren Ziektewinst waren onafhankelijk gerelateerd aan KvL tien maanden na de diagnose (follow-up). Een verhoogd gevoel van Hulpeloosheid was onafhankelijk gerelateerd aan een lagere KvL bij de start van de studie en een verhoogd gevoel van Hulpeloosheid gemeten bij de start van de studie was een onafhankelijke voorspeller van een lagere KvL bij follow-up. De resultaten van deze studie kunnen ons helpen bij het identificeren van patiënten met ALS die baat zouden kunnen hebben bij psychologische begeleiding zoals gedragstherapie of mindfulness.

In **hoofdstuk 6** worden de resultaten beschreven van een studie over het voorkomen van participatieproblemen van ALS-patiënten direct na de diagnose. Daarbij bestudeerden we de invloed van fysieke en psychologische factoren (stemming, copingstijl, ziektecognities en tevredenheid met sociale steun) op participatie. In een cross-sectionele studie (72 patiënten) rapporteerde 92% van de patiënten beperkingen in participatie direct na de diagnose, terwijl zij gemiddeld milde fysieke beperkingen rapporteerden. Longcapaciteit, functionele mobiliteit, vermoeidheid en gevoelens van hulpeloosheid waren onafhankelijk geassocieerd met participatiebeperkingen. Dit betekent dat ook ambulante patiënten met lichte fysieke klachten beperkingen hebben in participatie. Vroege ALS-zorg zou zich niet alleen moeten richten op longcapaciteit en functionele mobiliteit, maar ook op ervaren vermoeidheid en gevoelens van hulpeloosheid.

In onze longitudinale studie (met data van 71 patiënten) vonden we een toename van participatieproblemen in de tijd (beperkingen en autonomie) die het hoogst was bij patiënten met een snel progressieve ziekte (**hoofdstuk 7**). Participatiedomeinen gerelateerd aan mobiliteit binnen- en buitenshuis werden sterker beïnvloed in de tijd dan participatiedomeinen gerelateerd aan sociale interactie met de omgeving. De snelheid van progressie had een grotere negatieve invloed op de ervaren beperkingen in participatie dan op het gevoel van autonomie. Deze resultaten geven aan dat, vanaf de eerste dag, aandacht voor participatie een belangrijk onderdeel is van de multidisciplinaire zorg voor ALS-patiënten en hun verzorgers. Professionals moeten zich ervan bewust zijn dat zelfs patiënten met

relatief milde fysieke klachten beperkingen ervaren (seksualiteit, sociale activiteiten in hun woonomgeving) en verlies van autonomie in belangrijke activiteiten. Prioriteit geven aan deelname van een patiënt aan sociale en zinvolle activiteiten is één van de kenmerken van persoonsgerichte zorg en verbetert de kwaliteit van leven.

In het afsluitende hoofdstuk (**hoofdstuk 8**) worden de belangrijkste bevindingen, de theoretische en methodologische overwegingen en de klinische implicaties bediscussieerd. Aanbevelingen voor toekomstig onderzoek worden gegeven.

De belangrijkste conclusies van dit proefschrift zijn:

- SMA-patiënten rapporteren over het algemeen een vergelijkbare KvL als een gezonde populatie. Daarin is geen onderscheid tussen patiënten met SMA-vroeg met ernstige beperkingen en de relatief mild aangedane groep patiënten met SMA-laat.
- SMA-patiënten die relatief mild zijn aangedaan (SMA-laat) en degenen die angstgevoelens hebben en somber zijn lopen het risico op een lagere KvL.
- In vergelijking met patiënten met andere diagnoses (bijvoorbeeld ruggenmergletsel), zijn SMA-patiënten even tevreden met hun deelname aan dagelijkse activiteiten (participatie). Vooral motorische vaardigheden, vermoeidheid en gevoelens van depressie zijn gecorreleerd met participatie in het dagelijks leven.
- Een verhoogd gevoel van hulpeloosheid bij ALS-patiënten direct na de diagnose is een voorspeller van KvL 10 maanden later.
- Ambulante ALS-patiënten met lichte fysieke klachten direct na de diagnose ervaren ook participatiebeperkingen. In de zorg direct na de diagnose moet ook aandacht zijn voor ervaren vermoeidheid en gevoelens van hulpeloosheid.
- Er is een toename van participatieproblemen in de tijd bij ALS-patiënten (beperkingen en autonomie). Deze is het hoogst bij ALS-patiënten met een snel progressieve ziekte.
- ALS-patiënten rapporteren dat participatiedomeinen gerelateerd aan mobiliteit binnen- en buitenshuis sterker worden beïnvloed in de tijd dan domeinen gerelateerd aan sociale interactie met de omgeving. De snelheid van progressie heeft een grotere negatieve invloed op de ervaren beperkingen in activiteiten dan op het gevoel van autonomie.
- Bij zowel SMA- als ALS-patiënten zijn psychologische factoren (stemming, ziektecognities) geïdentificeerd als determinanten van KvL en participatie.

Implicaties en adviezen voor de dagelijkse zorg:

- Gebruik screeningsinstrumenten die niet alleen over fysieke klachten gaan, maar die ook vragen bevatten over psychologische factoren en participatie. Hierdoor krijgen ook relatief mild aangedane patiënten op tijd de juiste zorg.

- Psychologische begeleiding moet een onderdeel zijn van de dagelijkse zorg voor zowel ALS- als SMA-patiënten. De zorg moet bestaan uit een pallet van mogelijke keuzes, zoals bijvoorbeeld 'praten met een lotgenotengroep', groepsbehandeling, geïndividualiseerde zorg, aandacht voor zingeving in het leven. Alle opties moeten worden aangeboden op een wijze die aansluit bij de behoefte van de patiënt; dit kan op de polikliniek zelf of als blended care (een mix met online zorg op afstand).
- Psychologische interventies als cognitieve gedragstherapie kunnen individuele patiënten helpen regie terug te krijgen en daarmee een hoger welbevinden ondanks vaak ernstige beperkingen.
- Zorgverleners moeten ook positieve eigenschappen van patiënten benadrukken zoals het vermogen tot aanpassing en zelfmanagement. Hierin moeten we patiënten bekrachtigen. Door ons te richten op deze concepten richten we ons op verbetering van hun welzijn.
- Patiënten met lichte beperkingen ervaren al wel participatieproblemen en lopen een risico op een lagere KvL. Zij zijn ook de groep patiënten die mogelijk laat om hulp vragen. Dit versterkt de conclusie dat we laagdrempelige, gepersonaliseerde zorg moeten aanbieden met een duidelijke boodschap waarvoor mensen om hulp kunnen vragen.
- We moeten ons ervan bewust zijn dat patiënten de revalidatiearts mogelijk beschouwen als een arts voor alleen lichamelijke problemen. Wij moeten onze patiënten voorlichten over de onderwerpen waarover zij de revalidatiearts c.q. het revalidatieteam kunnen raadplegen. Een 'gesprekskaart' of vragenlijsten zoals de HADS of een copingschaal kunnen hierbij behulpzaam zijn.

Appendices

Dankwoord
Curriculum vitae
Publications

DANKWOORD

Allereerst wil ik de mensen met ALS en SMA die deelgenomen hebben aan de studies, bedanken voor hun inzet. Heel veel dank ook voor de inspiratie die jullie me gegeven hebben gedurende de jaren. Ik heb met veel plezier met een aantal van jullie gesproken over de uitkomsten van ons onderzoek, en over de essentie waar we ons in de zorg op moeten richten. Daardoor werd ik nog extra gesterkt om dit proefschrift af te ronden en verder te gaan met onderzoeksprojecten en innovaties om de zorg voor mensen met SMA en ALS verder te verbeteren. Want daar gaat het tenslotte allemaal om.

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Prof. dr. W.L. van der Pol, beste Ludo. Je was degene die me ertoe aanzette te starten met revalidatiegeneeskundig onderzoek bij volwassen patiënten met SMA. Veel dank voor je steun gedurende de jaren. Ik kijk uit naar de nieuwe gezamenlijke projecten waarin we verder inzoomen op 'the unknown unknowns' en 'the known unknowns' over het functioneren van volwassenen met SMA.

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CURRICULUM VITAE

Esther Kruitwagen-van Reenen is geboren op 2 november 1967 in Harderwijk. In 1985 behaalde zij haar VWO-diploma aan het Christelijk College Nassau-Veluwe te Harderwijk, waarna zij startte met de opleiding geneeskunde aan de Vrije Universiteit te Amsterdam. In 1993 behaalde zij haar artsendiploma. De daarop volgende jaren werkte zij als assistent niet in opleiding op de afdelingen neurologie van het Slotervaartziekenhuis te Amsterdam en van het Amsterdam Medisch Centrum. Daarna begon haar loopbaan in de revalidatiegeneeskunde, eerst in het Revalidatiecentrum Amsterdam. Vanaf 1997 tot 2001 was zij in opleiding tot revalidatiearts in het netwerk revalidatiegeneeskunde Utrecht (RC De Hoogstraat en UMCU), onder supervisie van Prof. dr. E. Lindeman en Prof. dr. A Prevo. Na haar opleiding heeft zij allereerst gewerkt in revalidatiecentrum De Hoogstraat met als aandachtsgebied neurorevalidatie, waarna zij in 2006 gedetacheerd werd naar de afdeling Revalidatiegeneeskunde van het UMCU. Vanaf 2006 is zij zich gaan specialiseren in de zorg voor volwassen patiënten met neuromusculaire aandoeningen, met allereerst speciale aandacht voor patiënten met ALS en later ook voor volwassenen met SMA. Vanaf 1 januari 2018 is zij volledig in dienst bij het UMCU. Ze is, namens het ALS Centrum Nederland, betrokken bij meerdere onderzoeksprojecten en implementatietrajecten van innovaties voor zorgverbetering. Voorbeelden daarvan zijn implementatie van eHealth (de mantelzorg app, Thuis-ALS-Thuis website, telemonitoring vanuit thuis via ALS Thuismeten en Coachen). Maar ook de ontwikkeling en verspreiding van voorlichtingsmateriaal voor patiënten, hun naasten en hulpverleners over ALS en cognitieve en gedragsproblemen. En meer recent, voor de begeleiding van kinderen van een ouder met ALS. Jaarlijks organiseert zij het landelijk ALS-symposium voor zorgverleners. Dit doet zij als coördinator van het landelijk zorgnetwerk voor ALS. Zij geeft regelmatig lezingen in allerlei settings. Vanuit het SMA expertisecentrum was zij betrokken bij de ontwikkeling van een gesprekskaart voor SMA-patiënten. Op dit moment is zij betrokken bij de ontwikkeling van een landelijk SMA Zorgnetwerk. Zij was voorzitter van de Richtlijn ALS (i.s.m. IKNL) en participeerde in de richtlijnen Duchenne spierdystrofie en Chronische Thuisbeademing. Tenslotte is zij voorzitter van de Werkgroep Ziekenhuisrevalidatie van de Nederlandse Vereniging van Revalidatieartsen.

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