

**Psychosocial factors associated with Quality of Life in
Motor Neuron Disease**

**Thesis submitted in accordance with the requirements of
the University of Liverpool for the degree of Master in
Philosophy by Noah John Granger.**

June 2017

Acknowledgements

I would like to thank The Walton Centre NHS Foundation Trust, The National Institute for Health Research, The Motor Neuron Disease Association, Biogen, Novartis, Merck, Roche, Teva pharmaceutical industries, and Genzyme for funding the TONiC study, from which this data is drawn. I would like to thank the TONiC team, and in particular the team at the Walton Centre, for graciously allowing me to join their study.

My sincere thanks to both Professor Carolyn Young and Mr Michael Jenkinson for supervising and supporting me and for putting up with a slow start with some early difficulties. Thank you to Rhiannon Edge and Daniela Schlueter for helping me to understand better the world of biostatistics, guiding my thinking and my method of analysis. Thank you to Claire for our many discussions that helped turn my ramblings into coherent sentences and ultimately a sensible piece of work. Thanks of course to my family for advice and love and care when times were hard but also for support throughout. Finally, thanks to my friends for keeping me sane during day to day life.

Abstract

Psychosocial factors affecting Quality of Life in Motor Neuron Disease

Noah John Granger

Motor neuron disease is a neurodegenerative condition that disrupts the motor system, causing progressive disability and ultimately resulting in death. Death is usually caused by respiratory paralysis within 2-4 years from symptom onset, and within this time quality of life is of the utmost concern. Despite the intuitive idea that the main driver for a decline in quality of life would be the decline in patients' physical function and the ensuing loss of independence, studies do not support this – indeed, the evidence indicates that psychosocial factors may be of more importance when it comes to global quality of life. The most examined factors are depression, anxiety, and social factors, but due to the multiple scales used to measure these factors and to measure quality of life, a consensus has not been reached on their significance.

This study aimed to examine psychosocial factors and quality of life in the TONiC cohort. The study found significant associations between disability and depression, hope and anxiety, physical function and social withdrawal, and quality of life subdomains and social withdrawal. Non-significant associations were found between demographics, time from diagnosis and depression, and locus of control subscales and anxiety. The three main factors - depression, anxiety and social withdrawal - were all found to have significant associations with global quality of life in this cohort.

The importance of these findings lies in creating a greater awareness of the importance of these factors in motor neuron disease, as well as using the associations to identify individuals at risk of depression, anxiety, withdrawal or poor quality of life. Additionally, the findings can be used to prompt investigation into possible interventions for these factors. Due to the cross-sectional nature of this data the direction of effect between factors cannot be identified; accordingly, longitudinal studies are required to identify the direction of effect, and also to identify change in the relative importance of various psychosocial factors over time.

Contents

Contents

Acknowledgements.....	2
Abstract.....	3
Contents.....	4
List of abbreviations.....	5
List of tables.....	10
List of figures.....	11
Systematic review of psychosocial factors affecting quality of life in motor neuron disease.....	13
TONiC study, the TONiC cohort and selected factors.....	51
Investigating Depression in Motor Neuron Disease.....	66
Investigating Anxiety in Motor Neuron Disease.....	84
Investigating Social Withdrawal in Motor Neuron Disease.....	96
Investigating Global Quality of Life in Motor Neuron Disease.....	105
Conclusions.....	125
Bibliography.....	136

List of abbreviations

.RIS	Research Information Systems
.txt	Text Filetype
AAC	Augmentative and Alternative Communication
ADI-12	ALS Depression Inventory-12
ADL	Activities of Daily Living subscale of ALSAQ-40
AKA	Also Known As
ALS	Amyotrophic Lateral Sclerosis
ALSAQ-40	Amyotrophic Lateral Sclerosis Assessment Questionnaire
ALSFRS(-R)	Amyotrophic Lateral Sclerosis Functional Rating Score (-Revised)
ALSSS	Amyotrophic Lateral Sclerosis Severity Score
AMED	The Allied and Complementary Medicine Database
BDI	Beck Depression Inventory
BMJ	British Medical Journal
BNI	British Nursing Index
Brief COPE	Abbreviated Coping Inventory
BSSS	Berlin Social Support Scales
CASP	Critical Appraisal Skills Programme
CBT	Cognitive Behavioural Therapy
CENTRAL	Cochrane Central Register of Controlled Trials
CES-D	Center for Epidemiologic Studies Depression Scale

CINAHL	Cumulative Index to Nursing and Allied Health Literature
COM	Communication subscale of ALSAQ-40
COPD	Chronic Obstructive Pulmonary Disease
COPE index	Carers of Older People in Europe Index
CPQ	Close Persons Questionnaire
D8	Item D8 "I feel slowed down" of the HADS-D
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders 4
DSM-V	Diagnostic and Statistical Manual of Mental Disorders 5
EAT	Eating and drinking subscale of ALSAQ-40
EMBASE	Excerpta Medica dataBASE
EMO	Emotional functioning subscale of ALSAQ-40
EQ-5D	EuroQOL Five Dimensions Questionnaire
EQ-VAS	EuroQOL-Visual Analogue Scale
F-SozU K-14 Questionnaire	Fragebogen zur sozialen unterstützung - Perceived Social Support
FTD	Frontotemporal Dementia
GDS	Geriatric Depression Scale
GQOL	Global Quality of Life
HADS(-D/-A) subscale)	Hospital Anxiety and Depression Scale (-Depression subscale/-Anxiety
HbA1c	Glycated Haemoglobin
HDAS	Healthcare Databases Advanced Search
HHI	Herth Hope Index
HIV	Human Immunodeficiency Virus

HRQOL	Health-Related Quality of Life
ICD 10	International Classification of Diseases 10
IFVR	Individualized Feedback-based Virtual Reality
IQR	Inter-Quartile Range
LIS	Locked In Syndrome
LOC	Locus of Control
MCS	Mental Component Summary
MEDLINE	Medical Literature Analysis and Retrieval System Online
MHLC	Multidimensional Health Locus of Control
MND	Motor Neuron Disease
MNDCS	Motor Neuron Disease Coping Scale
MOB	Mobility subscale of ALSAQ-40
MP	Member of Parliament
MQOL	McGill Quality of Life Questionnaire
MQOL-SIS	MQOL Single Item Scale
MS	Multiple sclerosis
NHP-1	Nottingham Health Profile-Part 1
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMO	Neuromyelitis Optica
PALS	Patients with ALS
PBA	Pseudobulbar Affect
PBP	Progressive Bulbar Palsy

PEG	Percutaneous Endoscopic Gastrostomy
PHQ-9	Patient Health Questionnaire-9
PICO	Population Intervention Comparator Outcome
PLS	Primary Lateral Sclerosis
PMA	Progressive Muscular Atrophy
POMS-SF	Profile of Mood States-Short Form
PPV	Positive Predictive Value
QOL	Quality of Life
SCID-1	Structured Clinical Interview for DSM disorders
SD	Standard Deviation
SEIQOL-DW	Schedule for Evaluation of Individual Quality of Life-Direct Weighting
SEM	Structural Equation Model
SF-36	Short Form-36
SIP	Sickness Impact Profile
SPSS	Statistical Package for the Social Sciences
SSQ	Social Support Questionnaire
SSRIs	Selective Serotonin Reuptake Inhibitors
STAI	State-Trait Anxiety Inventory
STROBE	Strengthening the Reporting of Observational studies in Epidemiology
SURE	Specialist Unit for Review Evidence
SWS	Social Withdrawal Scale
SWSMND	Social Withdrawal Scale – Motor Neuron Disease version
T1	Time 1

T2	Time 2
TBI	Traumatic Brain Injury
TCAs	Tricyclic Antidepressants
TONIC	Trajectories of Outcome in Neurological Conditions
UK	United Kingdom
UNC	University of North Carolina
US	United States
WHODAS 2.0	WHO Disability Assessment Schedule 2.0
WHOQOL-BREF 100	Abbreviated version of the World Health Organisation Quality of Life-
ZDS	Zung Depression Scale

List of tables

Table 1.1 Table to show the different search strategies for each database.

Table 1.2 Factors identified in thematic or narrative studies.

Table 1.3 table to show an evaluation of the qualitative studies identified by this review using the CASP checklist for qualitative studies.

Table 1.4 Table to show measures used when a factor was studied more than once.

Table 2.1 Table to show demographics and disease characteristics of the various multifactor models. Green = value within 5% of the original sample population. Orange = value greater than 5% but less than 10% from the original sample population. Red = Value greater than 10% from the original sample population.

Table 2.2 Table to show, for the descriptives in the depression model, the number of missing entries.

Table 2.3 Table to show, for the disability domains in the depression model, the number of missing entries.

Table 2.4 Table to show, for each factor in the anxiety model, the number of missing entries.

Table 2.5 Table to show, for each factor in the SW-QOL model, the number of missing entries.

Table 2.6 Table to show, for each factor in the SW-ALSFRS model, the number of missing entries.

Table 2.7 Table to show, for each factor in the GQOL model, the number of missing entries.

Table 3.1 Table to show the domains examined by the WHODAS 2.0

Table 3.2 Table to show significant and non-significant single factor models.

Table 4.1 Table to show significant and non-significant single factor models.

Table 6.1 Table to show the results of studies examining depression with participant numbers of 40 or under.

Table 6.2 Table to show the results of studies examining depression with participant numbers of 100 or over.

Table 6.3 Table to show the results of studies comparing anxiety and quality of life in order of increasing participant numbers.

Table 6.4 Table to show the results of studies comparing social withdrawal and quality of life.

List of figures

Figure 1.1 Flowchart showing breakdown of results and exclusion.

Figure 1.2 Graph showing the number of studies that investigated a particular factor.

Figure 1.3 Graph showing for each factor the number of QOL measures with which a significant positive, significant negative or non-significant relationship was found.

Figure 1.4 Graph showing for factors measured more than once the proportions of studies (out of 100%) that demonstrated significant positive or significant negative versus non-significant relationships.

Figure 1.5 Graph showing factors relationship to QOL as measured with SEIQOL.

Figure 1.6 Graph showing factors relationship to QOL as measured with SEIQOL-DW/Index.

Figure 1.7 Graph showing factors relationship to QOL as measured with MQOL.

Figure 1.8 Graph showing factors relationship to QOL as measured with MQOL-SIS.

Figure 1.9 Graph showing factors relationship to QOL as measured with WHOQOL-BREF.

Figure 1.10 Graph showing factors relationship to QOL as measured with EQ-5D.

Figure 1.11 Graph showing depression's relationship to QOL as measured with SF-36 subscales.

Figure 1.12 Graph showing factors relationship to QOL as measured with subscales of the ALSAQ-40.

Figure 2.1 Map of sites involved in the MND aspect of the TONiC study.

Figure 2.2 Image to show demographic and disease-specific data of this sample.

Figure 2.3 Figure to show factors of interest in this thesis.

Figure 6.1 Chart to show depression's association with global quality of life measures.

Figure 6.2 Graph of the interaction term with all data points and anxiety grouped into equal sized groups.

Figure 6.3 Graph of the interaction term without 4 highest social withdrawal values and anxiety grouped into equal sized groups.

Figure 6.4 Graph of the interaction term with all data points and anxiety grouped using the modified cut-offs.

Figure 6.5 Graph of the interaction term without 4 highest social withdrawal values and anxiety grouped using the modified cut-offs.

Figure 7.1 Diagram to show factors with significant associations (green) and non-significant associations (orange).

Systematic review of psychosocial factors affecting quality of life in motor neuron disease

Introduction

Motor neuron disease (MND) is a chronic degenerative neurological condition. Estimates of incidence vary, with a commonly quoted paper reporting it at around 1.5-2.5 per 100,000 per year in Europe and the US¹ whereas a UK based study found it to be higher at 2.6 per 100,000 per year in women and 3.9 per 100,000 per year in men². It occurs at any age in adulthood and the lifetime risk in the UK is estimated at 1 in 350 in men and 1 in 472 in women², although the male preponderance decreases with increasing age, and above 70 the male to female ratio approaches 1.³

MND has several subtypes, depending on the pattern of disease. These include Amyotrophic Lateral Sclerosis (ALS), Progressive Muscular Atrophy (PMA), Progressive Bulbar Palsy (PBP) and Primary Lateral Sclerosis (PLS).⁴ It can also be divided into sporadic and familial cases which make up 90-95% and 5-10% of cases respectively.⁵

Increasing loss of cortical, bulbar and ventral cord motor neurons means that these diseases are progressively disabling and ultimately fatal, usually due to respiratory failure. Average survival is 2-4 years from symptom onset, although a small proportion of the population survives for more than a decade.⁶

Previously considered a purely motor disease, non-motor aspects of MND are increasingly recognised and being researched.⁷ Cognitive deficits and a link with frontotemporal dementia (FTD) were first suggested decades ago.^{8,9,10,11} However, due to the nature of these complaints, patients may not have insight^{12,13} regarding cognitive symptoms, such that screening is required.¹⁴ A more recent paper gives a description of an ALS-plus syndrome, and in its definition gives the possible additional features of “dementia, geographic clustering, extrapyramidal signs, objective sensory loss, autonomic dysfunction, cerebellar degeneration, or ocular motility disturbance.”¹⁵

Unfortunately, only one disease modifying treatment is available, riluzole, and this is described as exerting only a modest neuroprotective effect.⁴ This disease’s characteristics and lack of treatment options means that Quality of Life (QOL) is a significant concern for patients, carers and healthcare staff. QOL is a complicated area for these patients; due to the heterogeneity of presentation, uncertain aetiology and poor prognosis of the disease, a wide variety of factors could impact on QOL in MND, and discovering these factors has been the focus of some research in recent years.

Simmons¹⁶ originally concluded that there was no consensus on which measures to use when looking at MND. They stated that historically “SIP and SF36 etc” were used, but as health-related quality of life (HRQOL) measures they are heavily skewed towards physical function, and would decline with disease progression regardless. More global QOL (GQOL) measures were then developed, including the WHOQOL instruments, as well as the McGill QOL questionnaire, SEIQOL and SEIQOL-DW measures.

Despite the intuitive idea that the drastic decline in physical function would be the driver for reducing QOL there is some evidence to the contrary. In 2000, Simmons et al¹⁷ showed in a prospective study that QOL as perceived by the patient did not correlate with measures of physical function. The finding that QOL may relate to factors other than physical function led to the suggestion that the McGill QOL (MQOL) scale may be more appropriate for measuring QOL than other scales (SIP/ALS-19) as it considers both physical and mental health-related factors, as well as non-health-related factors including existential and spiritual factors. Another prospective study a year later reached a similar conclusion regarding physical function's non-relatedness.¹⁸ In 2002 a cross-sectional study looked at an abbreviated, self-generated measure of QOL (the Schedule for Evaluation of Individual Quality of Life-Direct Weighting (SEIQOL-DW)) and found that, despite 64.5% of the sample nominating health as an important QOL-related category, there was no correlation between SEIQOL-DW and either the ALS severity score (ALSSS) or SIP scores.¹⁹ There was, however, evidence for correlation with emotional support and cognitive difficulties. Another cross-sectional study looked at both the SEIQOL-DW and MQOL and again found that physical status was not significant for QOL and that self-perceived quality of social support was the most important explicatory variable for both QOL scales.²⁰

Neudert, Wasner and Borasio, showed that HRQOL is not necessarily correlated with GQOL.²¹ In their study the SIP and SF-36 (health-related measures) had no correlation with the SEIQOL-DW (a GQOL measure).²¹ In an earlier study of theirs, the validity, as rated by 42 ALS patients, of the SEIQOL-DW was rated higher than that of the SIP ($p < 0.001$) and that of the SF-36 ($p < 0.001$), suggesting that patients may find GQOL measures more representative of their experience than HRQOL measures.²²

The suggestion by Simmons et al that GQOL measures should be adopted in preference to HRQOL measures has not been universally conformed to. However, this idea is key; as the above studies show that not only does a decline in physical function not cause the expected reduction in QOL but, further to this, QOL relates to how an individual experiences their life, not how they experience their health. GQOL measures are required for an accurate representation of the lived experience of MND patients.

In 2013, Gibbons et al²³ aimed to create a Structural Equation Model (SEM) that could explain a large degree of the variance seen in QOL and in depression when looking at a cross-sectional sample of 147 MND patients. It was found that functional status, as measured by the Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS), did not correlate with QOL or with fatigue, but it did mildly correlate with depression. However, QOL was found to correlate most strongly with depression, meaning that an indirect link could be made between functional status and QOL, through its effects on depression.

As well as discovery that MND patient's QOL may not always decline with physical deterioration, it also seems that their QOL may in fact be better than the general population and even caregivers would think.^{24,25} These findings are in line with another study examining multiple conditions across multiple cultures, suggesting that society may have a flawed perspective when it comes to ill health and QOL.²⁶ This has required a change in professional and caregivers' perceptions of how patients respond to their condition. To try to explain these findings, the idea of response shift has been proposed, wherein the changing circumstances of the patient may force re-evaluation of values and a shift in attitudes and internal standards which impact on QOL.²⁷ This is seen in various ways in MND. For example a patient's meaning in life becomes found more in "family and friends, the act of giving and receiving help, the feeling of having a life of their own and accepting the present" as well as their perspective being such that "material things and quarrels were no longer in focus".²⁸ When MND patients were asked to identify the factors affecting their QOL, one study found the most common and most important cues chosen were family/significant other as well as religion, recreation, hobbies, friends, entertainment, leisure activities, and social life.¹⁶ A qualitative study, looking at coping, identified "cognitive reappraisal, reframing, and intellectual stimulation as coping mechanisms; the development of wisdom; and the vital importance of interpersonal relationships" as key themes.²⁹ A study of biographical disruption and repair identified emphasis on "finding new meaning and restoring normality."³⁰ These overlapping and related concepts in the above studies support the notion of a 'response shift' in MND patients and how this may limit the disease's impact on their QOL.

As to whether there is unmet need for psychosocial intervention in the MND population, a team in Oslo investigated patient satisfaction with their treatment and found that patients were least content with the psychological help they received, and with the information given to their relatives.³¹ The qualitative papers mentioned above are by no means an exhaustive survey, but do give us an idea of why psychosocial factors are of such importance in MND, and the relevance of further evaluating these to guide clinical care.

Better understanding of the experience of MND patients also has a more general relevance. Noel Conway is a 67-year-old gentleman with MND who is the most recent person to challenge the law in England and Wales on assisted suicide.³² The High Court case, the first after MPs rejected a change in the law in 2015, demonstrates some of the arguments for and against. The subject is an emotive one, and this is demonstrated by the passionate arguments made by each side. Baroness Jane Campbell, a prominent disability equality advocate, is of the opinion that a change in the law could change perspective such that disabled individuals are devalued in society. Mr Conway's argument relates to his decline in QOL in as much that he feels he has been condemned to "unimaginable suffering." He wishes to have a medically assisted death at a time of his choosing. The key issue, that may be considered as somewhat separate, is that he believes in his right to die and in having control over the manner of his death, thus it may not be a loss of QOL that drives this desire but a loss of autonomy.

This is supported by Ganzini et al who found that physicians' opinions of patients with a wish for hastened death were that they were determined, independent individuals who were concerned with becoming a burden, and with loss of control.³³ The physicians assessed these patients for a mood disorder but did not find that they were depressed and suggested that these patients "viewed living as purposeless and too effortful, and that they were ready for death."

In their study, Albert et al found that, after requesting a hastened death, patients' suffering decreased and their ratings of control increased, reinforcing the notion that wish to die is predominantly an issue of autonomy and avoiding future suffering, and not necessarily an indication of depression or of a drastically poor QOL at that time.³⁴

This should remind the reader that despite the surprisingly positive findings about the QOL of MND patients as a cohort, individuals can still suffer greatly, and the impact of the disease should not be underestimated.

Method:

Aim: Identify psychosocial factors which have been studied regarding their effect on QOL in MND.

Identification of studies

Databases: Medline, Scopus, Web of Science, CINAHL, The Cochrane library, PsycINFO,

AMED, BNI, EMBASE

Types of study: Journal article

Time span: No limit

Languages: Full article must be available in English

Title/Abstract search for:

"Motor neuron disease" OR "Motor Neurone Disease" OR "MND" OR "M.N.D." OR

"Amyotrophic Lateral Sclerosis" OR "ALS" OR "A.L.S." OR "Lou Gehrig's" OR "Lou Gehrig" OR

"Lou Gehrigs" OR "motor neuron diseases" OR "motor neurone diseases" OR "Anterior horn cell disease" OR "Charcot disease" OR "Charcot's disease" OR "Charcots disease" OR "Primary Lateral

Sclerosis" OR "PLS" OR "P.L.S." OR "progressive muscular atrophy" OR "PMA" OR "P.M.A." OR

"Progressive Bulbar Palsy" OR "PBP" OR "P.B.P."

AND

"Quality of life" OR "QOL" OR "Q.O.L." OR "Life quality"

A Population Intervention Comparator Outcome (PICO) system was used initially to generate the domains to be used. Population was considered as MND/ALS, intervention was psychosocial factors but this was only considered later, no comparator was used and the outcome was QOL. The population and outcome keywords were searched in the various databases to retrieve studies for short listing. The choice of databases was based on what investigators thought would give the most relevant and comprehensive yield for the research question as well as MEDLINE and EMBASE being recommended by the Cochrane handbook on systematic reviews³⁵ (although this is aimed more towards clinical trials). The National Institute for Health and Care Excellence (NICE) Healthcare Databases Advanced Search (HDAS) was used to search AMED, BNI, CINAHL, EMBASE, MEDLINE and PSYCHinfo. These databases were searched individually through NICE HDAS as it was discovered by the researchers that combining results with boolean operators does not work when using multiple databases, and that using the thesaurus to 'explode' search terms is not the same across the respective databases. Therefore, for the population parameter a fixed set of keyword phrases was searched for in title and abstracts or equivalent fields in each database with the addition of 'motor neuron disease' and 'amyotrophic lateral sclerosis' being 'exploded' in each database to include 'narrower terms'. For the outcome parameter, the same method was applied with fixed keywords searched across all databases with 'quality of life' being 'exploded' in each database individually. Using AND to connect the population and outcome for each database then generated results that could be exported to the referencing software.

Search keywords were changed or removed if errors occurred when combining results. This seemed to happen with the keywords which contained periods e.g. "A.L.S." or those that produced zero results. Between the original search and a later re-run to identify new results the NICE HDAS website was updated. The performance of the search engine was much improved and the issues detailed above requiring removal of search terms were no longer apparent.

The Cochrane database (Reviews and CENTRAL) only allows a limited number of keywords so “Quality of Life” AND “Motor Neuron disease” OR “Amyotrophic Lateral Sclerosis” were searched in title, abstract and keywords. For MND and ALS there were dropdown options to select when searching, in order to ensure word variations are searched, although it remains uncertain what these variations were. The resulting papers could not be exported en masse as a .RIS file compatible with the referencing software (only as a .txt) so the shortlisting of papers was done on the database with only those selected being exported to the referencing software.

In SCOPUS ‘Articles and reviews’ were searched using the previous terms as a string using the advanced search functions. In Web of Science the search terms were also entered as a string.

Databases	NICE HDAS						Cochrane		SCOPUS	Web of Science	
	AMED	BNI	CINAHL	EMBASE	MEDLINE	PSYCH info	Reviews	CENTRAL			
Fields searched	Titles and Abstracts						Title, Abstracts and Keywords		Title, Abstracts and Keywords	Topic	
Problem/Population											
Motor Neuron Disease	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Motor Neurone Disease	✓	✓	✓	✓	✓	✓	✗	✗	✓	✓	
MND	✓	✓	✓	✓	✓	✓	✗	✗	✓	✓	
M.N.D.	✓	✓	✓	✓	✓	✓	✗	✗	✓	✓	
Amyotrophic Lateral Sclerosis	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
ALS	✓	✓	✓	✓	✓	✓	✗	✗	✓	✓	
A.L.S.	✓	✓	✓	✓	✓	✓	✗	✗	✓	✓	
Lou Gehrig's	✓	✓	✓	✓	✓	✓	✗	✗	✓	✓	
Lou Gehrig	✓	✓	✓	✓	✓	✓	✗	✗	✓	✓	
Lou Gehrigs	✓	✓	✓	✓	✓	✓	✗	✗	✓	✓	
Motor Neuron Diseases	✓	✓	✓	✓	✓	✓	✗	✗	✓	✓	
Motor Neurone Diseases	✓	✓	✓	✓	✓	✓	✗	✗	✓	✓	
Anterior Horn Cell Disease	✓	✓	✓	✓	✓	✓	✗	✗	✓	✓	
Charcot Disease	✓	✓	✓	✓	✓	✓	✗	✗	✓	✓	
Charcot's Disease	✓	✓	✓	✓	✓	✓	✗	✗	✓	✓	
Primary Lateral Sclerosis	✓	✓	✓	✓	✓	✓	✗	✗	✓	✓	
PLS	✓	✓	✓	✓	✓	✓	✗	✗	✓	✓	
P.L.S.	✓	✓	✓	✓	✓	✓	✗	✗	✓	✓	
Progressive Muscular Atrophy	✓	✓	✓	✓	✓	✓	✗	✗	✓	✓	
PMA	✓	✓	✓	✓	✓	✓	✗	✗	✓	✓	
P.M.A.	✓	✓	✓	✓	✓	✓	✗	✗	✓	✓	
Progressive Bulbar Palsy	✓	✓	✓	✓	✓	✓	✗	✗	✓	✓	
PBP	✓	✓	✓	✓	✓	✓	✗	✗	✓	✓	
P.B.P.	✓	✓	✓	✓	✓	✓	✗	✗	✓	✓	
Additional Info	Thesaurus terms for 'motor neuron disease' and 'amyotrophic lateral sclerosis' exploded	Thesaurus term for 'motor neuron' disease was instead 'motor neurone disease' which was exploded, no thesaurus terms found for 'amyotrophic lateral sclerosis'	Thesaurus terms for 'motor neuron disease' and 'amyotrophic lateral sclerosis' exploded	Thesaurus terms for 'motor neuron disease' and 'amyotrophic lateral sclerosis' exploded	Thesaurus terms for 'motor neuron disease' and 'amyotrophic lateral sclerosis' exploded	Thesaurus terms for 'motor neuron disease' and 'amyotrophic lateral sclerosis' exploded	No thesaurus term for 'motor neuron disease' Thesaurus term 'amyotrophic lateral sclerosis' was exploded	"Motor neuron disease" and "Amyotrophic Lateral Sclerosis" looked up as MESH terms and exploded	"Motor neuron disease" and "Amyotrophic Lateral Sclerosis" looked up as MESH terms and exploded	Entered as string*	Entered as string**
Population results	1053	309	6523	119982	92398	105053	22 cochrane reviews + 16 other	354	183,507	88802	
Outcome											
Quality of Life	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
QOL	✓	✓	✓	✓	✓	✓	✗	✗	✓	✓	
Q.O.L.	✓	✓	✓	✓	✓	✓	✗	✗	✓	✓	

Life quality	✓	✓	✓	✓	✓	✓	✗	✗	✓	✓
Additional info	thesaurus term for 'Quality of life' exploded	Health and Quality of Life exploded	thesaurus term for 'Quality of life' exploded	"Quality of life" looked up as MESH term and exploded	"Quality of life" looked up as MESH term and exploded	Entered as string*	Entered as string**			
Outcome results	11445	92512	74813	436757	242921	52565	242 cochrane reviews + 912 other	16214	309139	266249
Population AND Outcome										
Overall results	82	106	375	2398	1255	781	2 cochrane reviews + 2 other	24 trials	1547	1174
*Entered as string TITLE-ABS-KEY(("Motor neuron disease" OR "Motor Neurone Disease" OR MND OR "M.N.D." OR "Amyotrophic Lateral Sclerosis" OR ALS OR "A.L.S." OR "Lou Gehrig's" OR "Lou Gehrig" OR "Lou Gehrigs" OR "motor neuron diseases" OR "motor neurone diseases" OR "Anterior horn cell disease" OR "Charcot disease" OR "Charcot's disease" OR "Charcots disease" OR "Primary Lateral Sclerosis" OR PLS OR "P.L.S." OR "progressive muscular atrophy" OR PMA OR "P.M.A." OR "Progressive Bulbar Palsy" OR PBP OR "P.B.P.") AND ("Quality of life" OR QOL OR "Q.O.L." OR "Life quality"))										
**TS=("Motor neuron disease" OR "Motor Neurone Disease" OR MND OR M.N.D. OR "Amyotrophic Lateral Sclerosis" OR ALS OR A.L.S. OR "Lou Gehrigs" OR "Lou Gehrig" OR "Lou Gehrigs" OR "motor neuron diseases" OR "motor neurone diseases" OR "Anterior horn cell disease" OR "Charcot disease" OR "Charcot's disease" OR "Charcots disease" OR "Primary Lateral Sclerosis" OR PLS OR P.L.S. OR "progressive muscular atrophy" OR PMA OR P.M.A. OR "Progressive Bulbar Palsy" OR PBP OR P.B.P.) AND ("Quality of life" OR QOL OR "Q.O.L." OR "Life quality"))										

Table 1.1 Table to show the different search strategies for each database.

Screening and eligibility

Screening:

Results were evaluated by title and abstract for exclusion of irrelevant results and assessed for quality by the primary researcher. Those of uncertain value had the full article read. Those still of uncertain value were read by a second researcher. Any studies selected for inclusion by the primary researcher were also read by a second researcher. Disagreement resulted in discussion between the two researchers. Reference lists of any review articles were checked to look for studies missed by the literature search.

Eligibility:

Peer reviewed papers (conference abstracts, editorials and letters not eligible) on psychosocial factors which can be defined and measured in patients, for example by published outcome measures, available in English were included. Studies analysing factors which cannot be altered by clinical care, such as personality or economic hardship were excluded. Qualitative papers describing patient effects that could not be defined in a reproducible way were excluded, such as 'the pervasive impact of an awkward and unreliable body' (Brott et al. 2007)³⁶. Papers linking psychosocial factors with QOL according to opinion rather than patient-derived data were excluded. Treatment modalities, eg music therapy, CBT, meditation, and trial protocols were excluded. Studies where participants with MND could not be separated for analysis or were not commented on distinctly from other conditions were excluded.

In sorting, reviews on MND were classified as wrong study type, as they may have had findings related to psychosocial factors, but would only be citing studies which should have been identified by the literature search. Of the final selection of promising results some were found to be conference abstracts with no full paper available and these again were classified as wrong study type.

During shortlisting in Microsoft Excel, six results were lost on 6/10/16 due to the programme crashing, but as these had already been sorted in the referencing program no included results were lost.



Figure 1.1 Flowchart showing breakdown of results and exclusion.

Results of the systematic search ^{14,17,20,23,37-64}

Factors identified by quantitative studies included:

- Mental-health factors: Depression, anxiety.
- Social factors: Social support, social withdrawal, social isolation, speech disturbance/communication issues, sense of burden, satisfaction with relationships, dyadic cohesion, less social anxiety, the support subscore of MQOL.

- Coping strategies: Coping, confiding/emotional support, problem management coping strategy, emotional avoidance coping strategy, cognitive appraisal, protective buffering, emotional role functioning, venting, positive reframing, disengagement, mindfulness.
- Mood/feeling states: Feelings of worthlessness or helplessness, happiness, positive self-perception, hopelessness, confusion-bewilderment, loneliness, boredom, embarrassment, wondering why to keep going, anger, worry, less rumination.
- Other: Religiosity, conservation values (security, conformity, tradition), lack of freedom, psychological and existential subscores of MQOL.

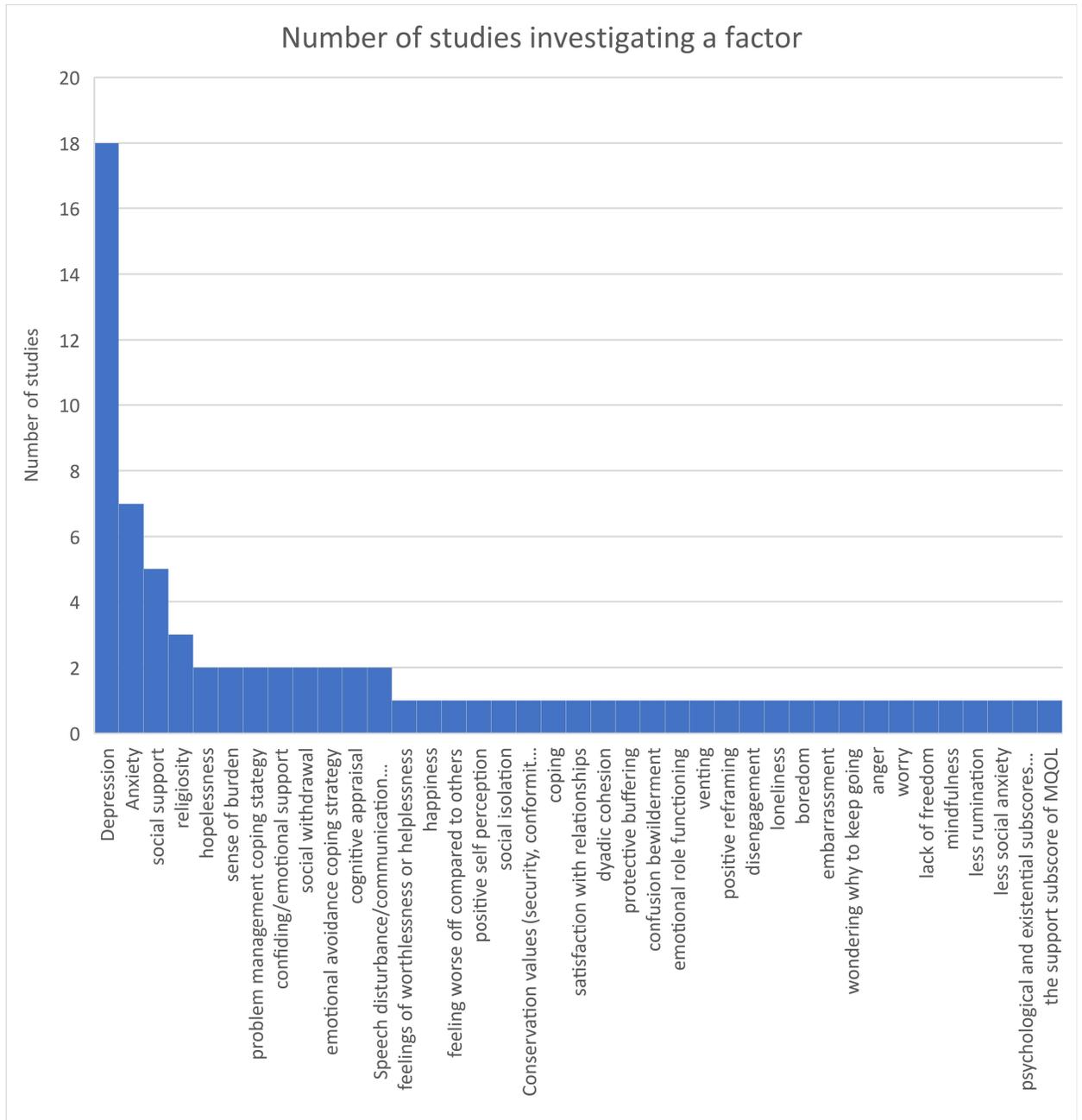


Figure 1.2 Graph showing the number of studies that investigated a particular factor.

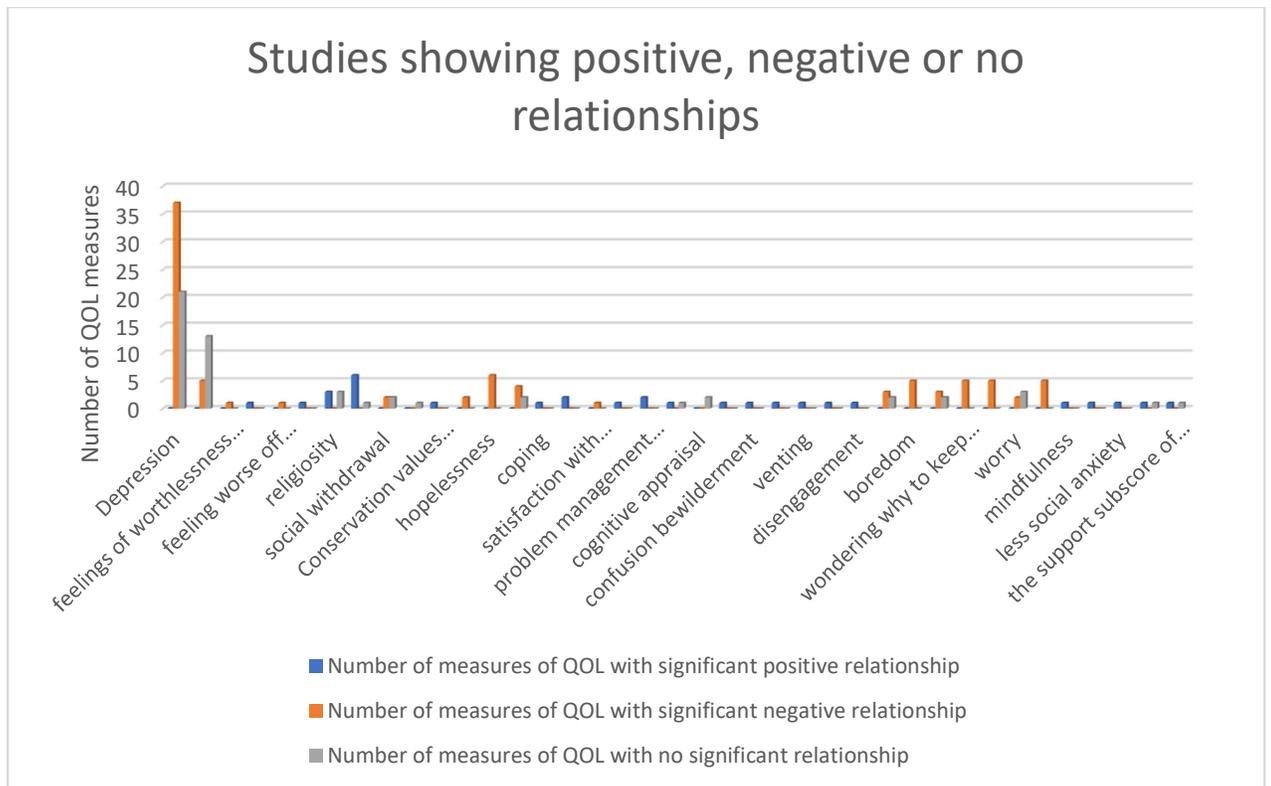


Figure 1.3 Graph showing, for each factor, the number of QOL measures with which a significant positive, significant negative or non-significant relationship was found.

Those factors related to more than one measure of QOL have been represented in the graph below. This shows the proportion of the studies for each factor showing significance versus non-significance.

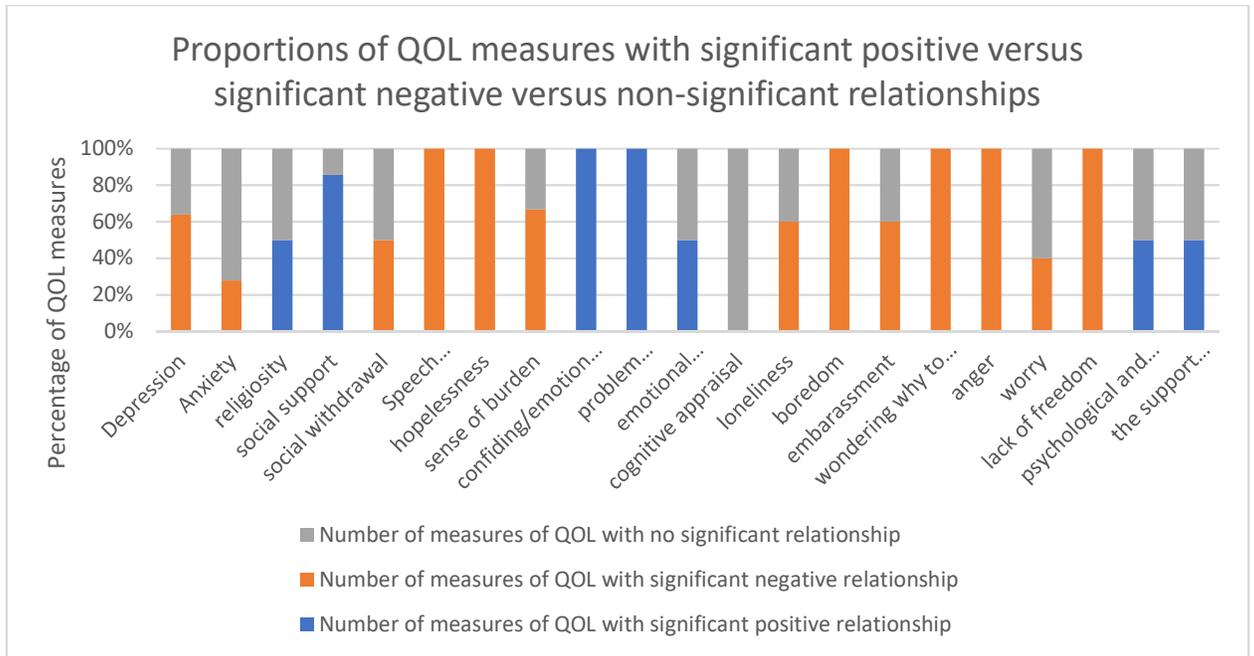


Figure 1.4 Graph showing, for factors measured more than once, the proportions of studies (out of 100%) that demonstrated significant positive or significant negative versus non-significant relationships.

QOL measures used more than once were turned into the following graphs:

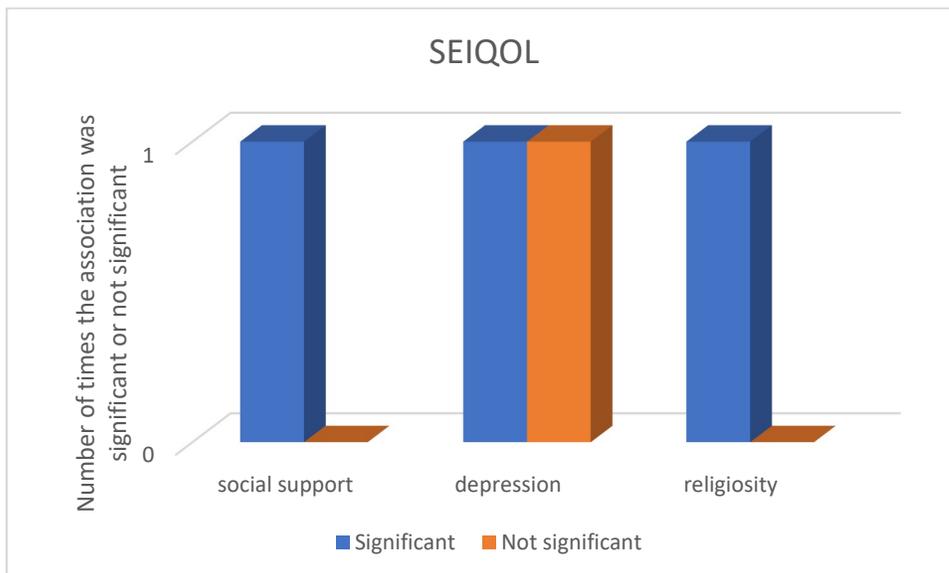


Figure 1.5 Graph showing factors' relationships to QOL as measured with SEIQOL.

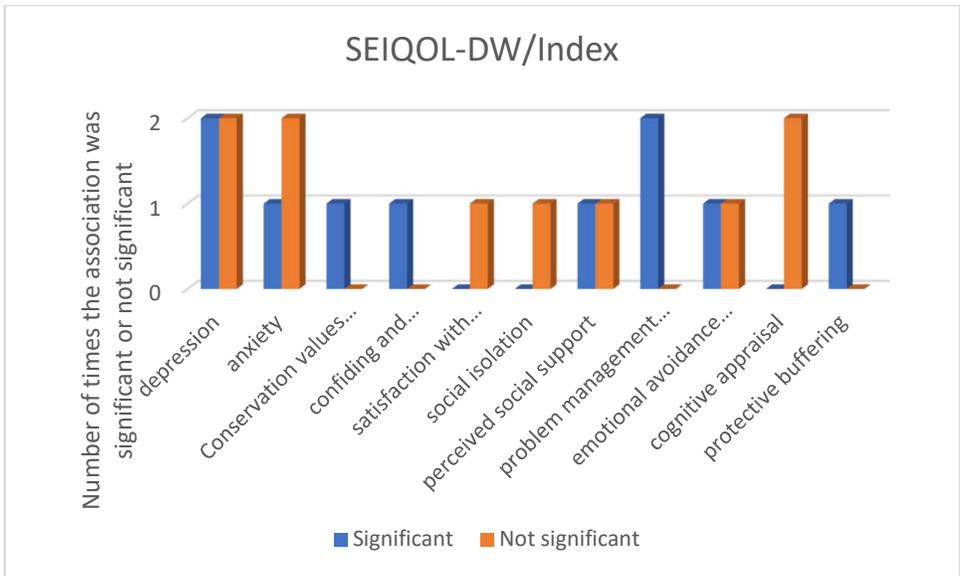


Figure 1.6 Graph showing factors' relationships to QOL as measured with SEIQOL-DW/Index.

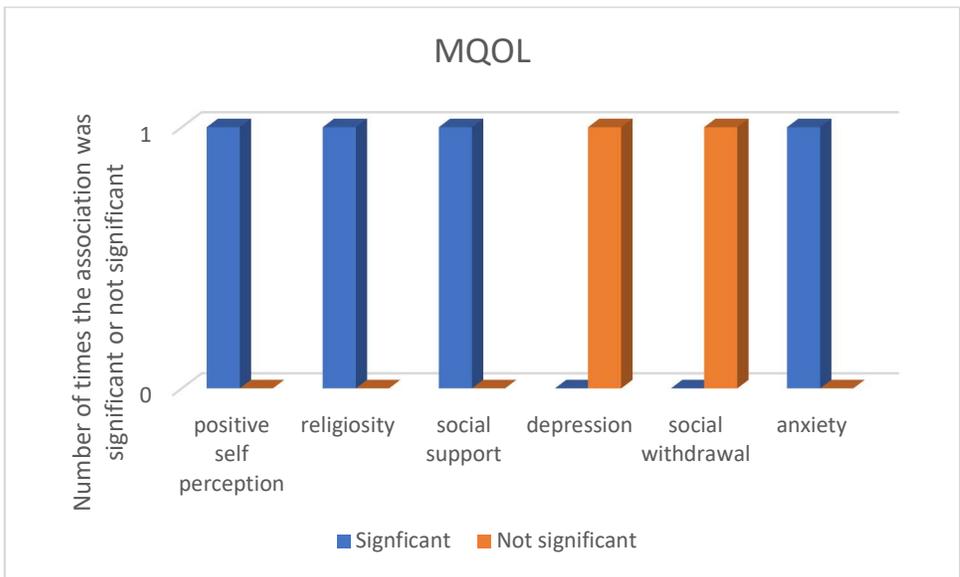


Figure 1.7 Graph showing factors' relationships to QOL as measured with MQOL.

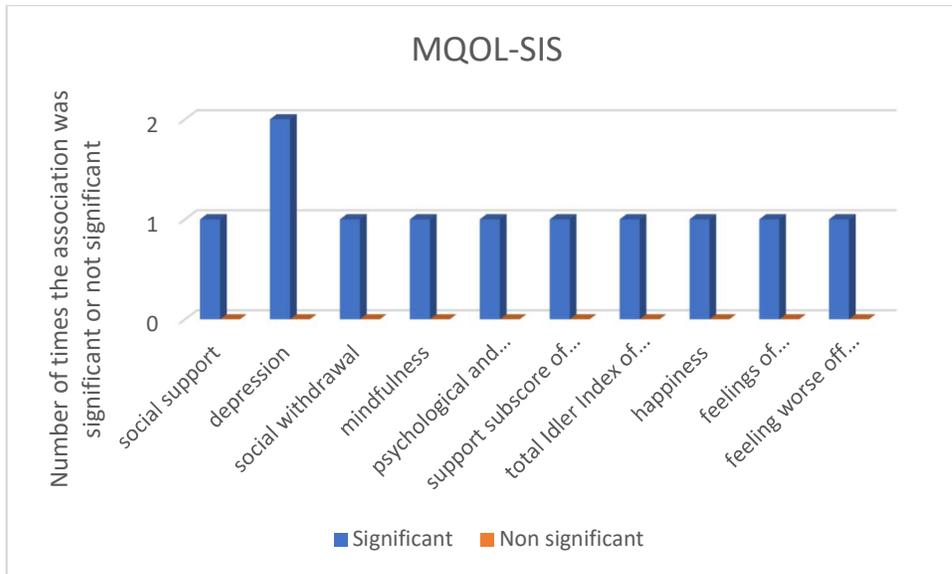


Figure 1.8 Graph showing factors' relationships to QOL as measured with MQOL-SIS.

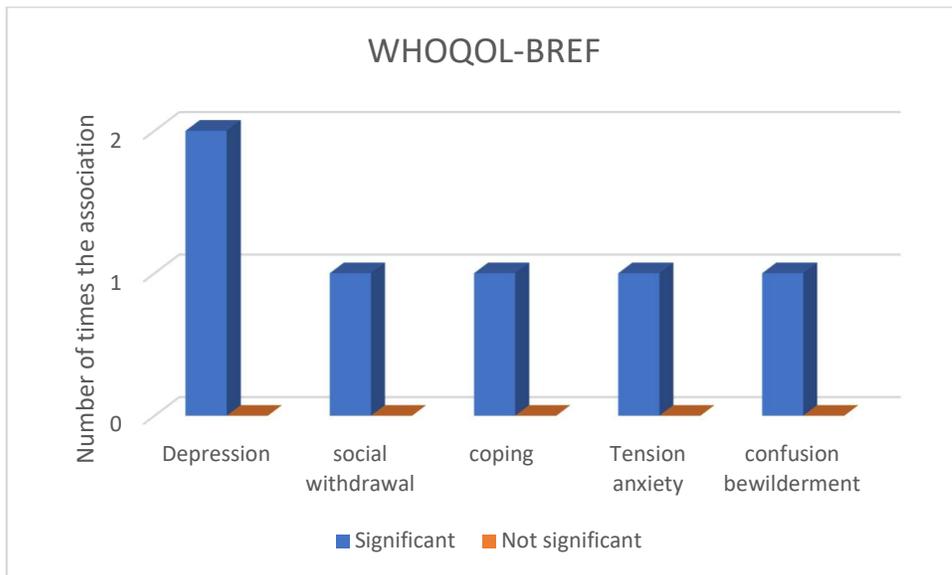


Figure 1.9 Graph showing factors' relationships to QOL as measured with WHOQOL-BREF.

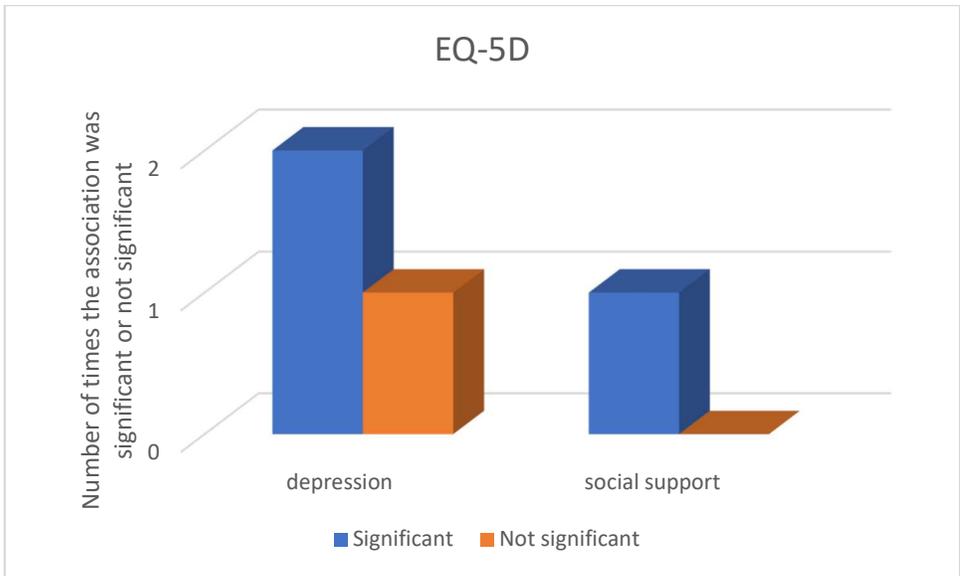


Figure 1.10 Graph showing factors' relationships to QOL as measured with EQ-5D.

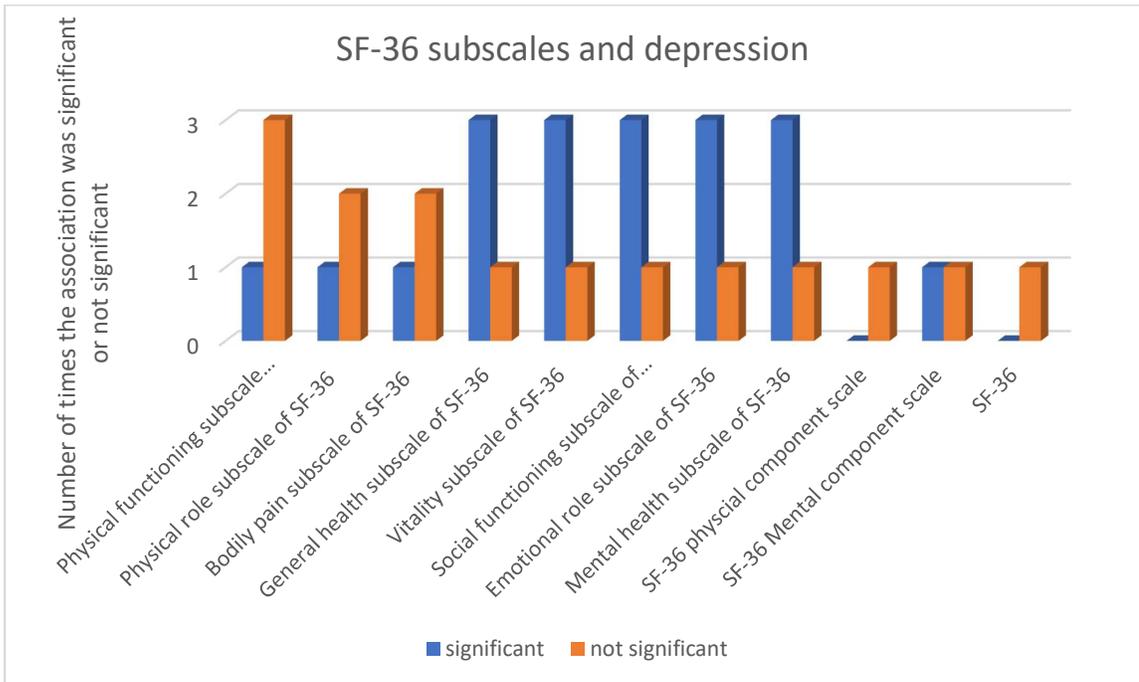


Figure 1.11 Graph showing depression's relationships to QOL as measured with SF-36 subscales.

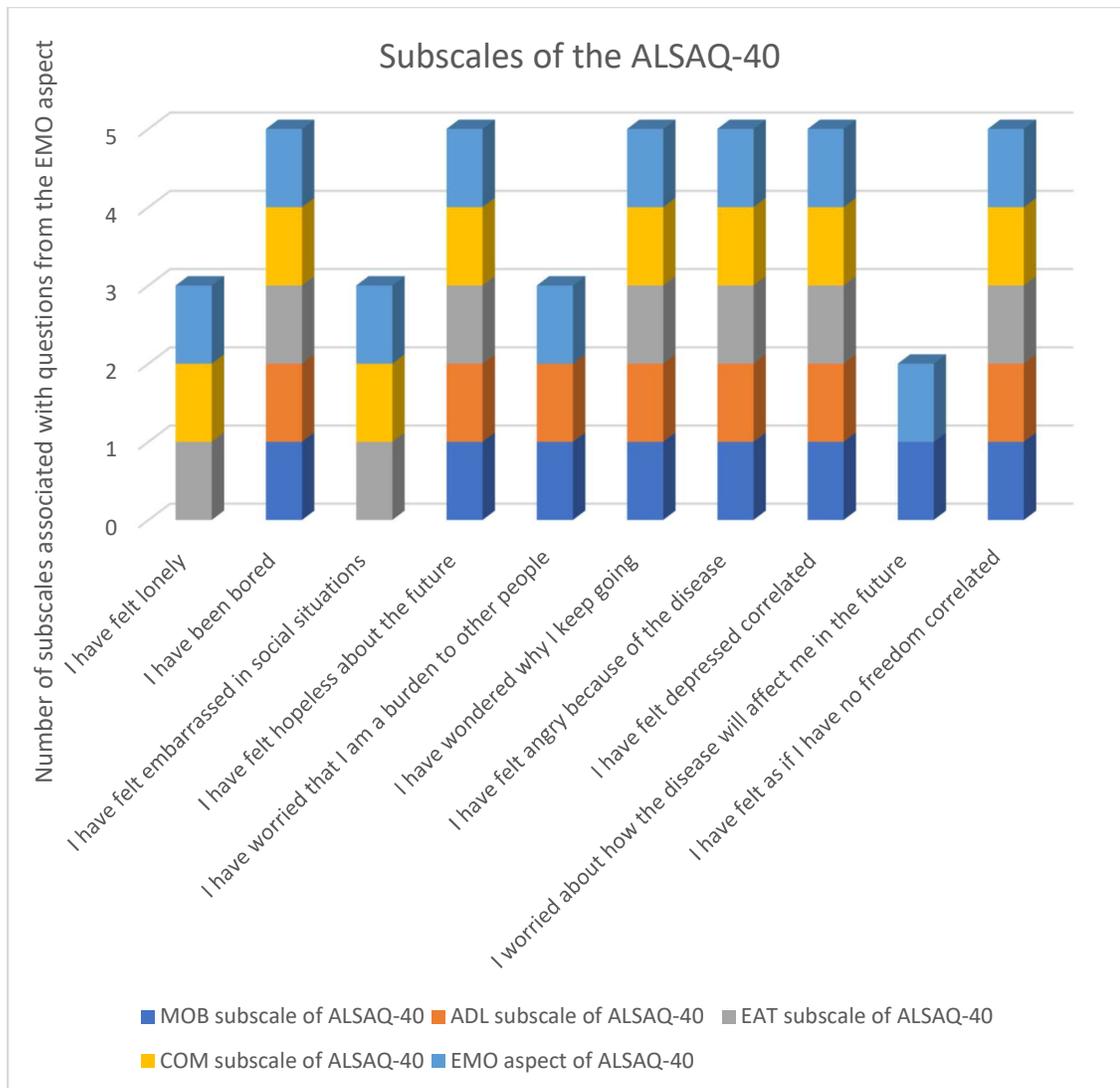


Figure 1.12 Graph based on the data from Mora et al, showing factors' relationships to QOL as measured with subscales of the ALSAQ-40.⁵³

The study by Mora et al⁵³ examined factors that were statements from the emotional reactions (EMO) subscale of the ALSAQ-40 and compared these with all subscales of the ALSAQ-40 – physical mobility (MOB), activities of daily living and independence (ADL), eating and drinking (EAT), Communication (COM), and emotional reactions (EMO).

The results from thematic or narrative studies were:

Study	Themes identified as related to QOL
Foley et al - Perceptions of quality of life in people with ALS: effects of coping and health care. ⁴¹	Importance of faith Search for control Importance of dignity Desire to maintain identity Importance of family A sense of loss Importance of altruism and support Fighting amyotrophic lateral sclerosis Appreciation of life
Trail et al - Major stressors facing patients with amyotrophic lateral sclerosis (ALS): a survey to identify their concerns and to compare with those of their caregivers. ⁶¹	Existential concerns Worry about illness progression Worry about dependency Worry about loved ones' well-being
Lule et al - Depression and quality of life in patients with amyotrophic lateral sclerosis. ⁴⁸	"ALS patients were significantly more likely to name friends and social environment as determinants of their quality of life than were the normal control subjects"
Hecht et al - Subjective experience and coping in ALS. ⁴⁴	At T1 psychosocial factors named as most important were: "reduction of speech" "knowledge of poor prognosis" "becoming dependent on other persons" At T2 these were the unchanged with the addition of "social isolation"

Table 1.2 Factors identified in thematic or narrative studies.

Discussion

The findings of the systematic review indicated that the majority of the studies were quantitative. Of the 28 quantitative studies, the most studies focussed on depression, anxiety and social support. Some other factors were examined more than once, such as religiosity, sense of burden, social withdrawal and hopelessness, but many factors were only examined once. The four qualitative studies reinforced the importance of existential, spiritual, psychological and social factors.

Overarching critical appraisal of the studies

Many checklists are available for critically appraising quantitative observational studies identified by a systematic review such as the CASP (Critical Appraisal Skills Programme) checklist for cohort studies, CASP checklist for case control studies⁶⁵, Newcastle-Ottawa scale⁶⁶, and STROBE (Strengthening the Reporting of Observational studies in Epidemiology) checklist⁶⁷.

Out of these options, the quantitative studies identified in this review could have been evaluated using the STROBE checklist, as it is the checklist recommended by the British Medical Journal (BMJ).⁶⁷

Due to time restrictions (on corrections), it was not possible to formally check all 28 quantitative studies using the STROBE criteria, however, 10 studies were checked (first ten when ordered alphabetically by authors) and the general patterns seen in those studies were that:

The ten studies appraised were good at providing an informative and balanced summary in the abstract, explaining the scientific background and rationale for the study, and presenting key elements of the study design early in the paper. As much of the research was considered to be exploratory by the authors, specific objectives were not always given past investigating the relationship between a given variable/variables and QOL, and, even when more specific objectives were given, there may not have been “prespecified hypotheses”. Some may feel that this is adequate for these types of studies, considering the scarcity of previous studies, but the papers by Ganzini et al⁴² and Fegg et al³⁹ are good examples of specific objectives, and the study by Bremer et al³⁷ is a good example of both specific objectives and prespecified hypotheses, which future authors may wish to consult in order to emulate their clarity.

Study design was not always indicated in the title or abstract and this is something that could easily become uniformly conformed to as awareness and use of checklists (such as STROBE) becomes more commonplace when designing/reporting studies as opposed to only when critically appraising them.

The studies explained the sources of data and methods of assessment well, including the handling of quantitative variables in the analyses. Eligibility criteria was often brief “definite or probable ALS according to the El Escorial revised criteria”, sometimes precluding those with cognitive deficit or overt FTD. The latter point is important as it may impact on patient reported outcomes and so whether these patients were included or not should be clarified. That is not to say that those with cognitive impairment should not be investigated – as they make up a substantial minority of MND patients – but this should be specified in the method to aid interpretation.

Some of the studies provided detailed description of the setting, locations, and relevant dates, including periods of recruitment but many only commented that a certain number of patients were recruited from a neurology centre without including the dates. This also meant that numbers of participants at each stage (potentially eligible, examined for eligibility, confirmed eligible, agreed to participate) were not always reported although with some of the methods – consecutive patients at MND clinic or a retrospective study using a previously acquired cohort – this may not have been entirely appropriate. Where numbers of participants at the different stages were reported, reasons for non-participation were only given as far as ‘not eligible’, and ‘declined to participate’, but, reasons for declining participation were not given. This is understandable, as it can be difficult to elicit these responses within the ethical framework of research.

Gibbons et al²³ is a paper that clearly showed how they had arrived at the study size using statistical methods to achieve a desired power, unfortunately this was not common to other papers in the review as they appeared to use more ‘opportunistic’ sampling. For the same reason, analytic techniques for taking account of the sampling strategy were not considered. However, the statistical methods to examine the desired variables were usually described well.

Most of the ten studies did not undertake sensitivity analysis so item 12e “describe any sensitivity analysis” was not applicable but the study by Bock et al¹⁴ did use sensitivity analysis in order to determine whether there were any differences between those with complete data for forced vital capacity (FVC) and those without complete data for FVC. However, it does not appear that this was reported in the results.

Aside from the example given above, missing data was rarely touched on and this is an area that could be improved upon using tables to indicate the numbers of participants with missing data, as well as whether and how missing data were addressed.

Demographic and clinical characteristics were described well, allowing an understanding of the types of cohorts that were reported on.

Results were mostly well reported with regards to Pearson product moment correlation coefficients, *F* - statistics, *t* - values, beta coefficients, and *p* – values. Reporting of precision, in the form of confidence intervals was less common. A good example of conforming to item 16a “give unadjusted estimates and, if applicable, confounder adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included” would be the study by Bock et al¹⁴ which included tables with all of these details.

The studies were good at giving “a cautious overall interpretation of results” and summarised their key results. Whether results were summarised in reference to study objectives mostly depended on whether the study had given specific objectives and/or hypotheses. In terms of generalizability, Clarke et al³⁸ and Felgoise et al⁴⁰ are good examples of studies that mentioned it specifically – cautioning against premature generalization – but most others either commented on and compared their results to previous studies or didn’t explicitly mention generalizability at all.

The limitations of the studies were often not discussed (although Bock et al¹⁴ is a good example of discussion of limitations) and, related to this, item 9 “describe any efforts to address potential sources of bias” was often ignored aside from some studies comparing the descriptives of their cohort when considering selection bias. Similarly, sources of funding were difficult to comment on in some papers as they was not mentioned, and so it may have been that they received no funding or that the information was simply omitted.

To surmise, improvements could have been made by: clarifying the study design in the title or abstract; providing more detailed description of the setting of the studies, dates between which recruitment took place, and numbers of participants at each stage; describing how sample sizes were arrived at; and discussing the limitations of the studies and how potential bias may have affected the results. However, whilst this incomplete analysis gives an idea of some of the problems that may have been found in the studies included in this systematic review, it should be treated with caution as not all studies have been assessed this way.

Similar to the quantitative studies, there are multiple checklists for use in evaluating qualitative studies, such as the CASP checklist for qualitative studies⁶⁵ and SURE (Specialist Unit for Review Evidence) checklist⁶⁸. The four qualitative studies in this review were examined using the CASP checklist⁶⁵ for qualitative studies and performed moderately well. All four studies had a “clear statement of the aims”, although the study by Lule et al⁴⁸ could have been more explicit when compared to the others. Qualitative methodology was appropriate considering the aims. Design, recruitment and data collection mostly seemed appropriate to the aims but were not justified clearly in the text by the studies’ respective authors. In terms of recruitment the study by Trail et al⁶¹ acknowledged that it was limited by its cohort being restricted to those with the “‘motivation, means, and family support to attend an ALS specialty clinic’ - typically not ventilator dependent and strong enough to travel, although they may need mechanical assistance for ambulation.”. With respect to data collection, saturation was not discussed by any of the studies. Similarly, it was not clear whether “the relationship between the researcher and participants” had been adequately considered as it was not mentioned in any of the four studies. All studies except that by Hecht et al⁴⁴ stated their approval from an ethics committee. Analysis was rigorous but there could be greater examination of the role of the researcher, potential bias, and how this may have affected the results of the study. There was a “clear statement of the findings” for all four studies but they did not appear to discuss the “credibility of their findings (e.g. triangulation, respondent validation, more than one analyst)”. Due to the scarcity of studies in this area, these studies were valuable in exploring the subjective experience of some patients, with MND with both Foley et al⁴¹ and Hecht et al⁴⁴ doing well to consider their findings in the context of previous studies.

CASP item	Foley et al - Perceptions of quality of life in people with ALS: effects of coping and health care. ⁴¹	Trail et al - Major stressors facing patients with amyotrophic lateral sclerosis (ALS): a survey to identify their concerns and to compare with those of their caregivers. ⁶¹	Lule et al - Depression and quality of life in patients with amyotrophic lateral sclerosis. ⁴⁸	Hecht et al - Subjective experience and coping in ALS. ⁴⁴
Clear statement of the aims	Yes	Yes	Yes	Yes
Was qualitative method appropriate	Yes	Yes	Yes	Yes
Was the design appropriate to address the aims	Yes- not justified	Yes - not justified	Can't tell	Yes - not justified

Was the recruitment strategy appropriate to the aims	Yes – Not justified	Yes	Yes – Not justified	Yes – Not justified
Was data collected in a way that addressed the research issue	Yes	Can't tell	Yes	Yes
Has the relationship between the researcher and participants been adequately considered	No	No	No	No
Have ethical issues been taken into consideration	Yes	Yes	Yes	Can't tell
Was data analysis sufficiently rigorous	Yes	Can't tell	Yes	Yes
Is there a clear statement of the findings	Yes	Yes	Yes	Yes

How valuable is the research	Valuable	Valuable	Valuable	Valuable
------------------------------	----------	----------	----------	----------

Table 1.3 table to show an evaluation of the qualitative studies identified by this review using the CASP checklist for qualitative studies.

Quality of Life

An overarching limitation of the studies pertinent to this review is how QOL is measured.

When looking at the results of the literature search, it was worth considering whether HRQOL had been used as opposed to GQOL, as HRQOL measures are limited in the ways described earlier. The contradictory findings identified by the systematic review may be due to whether HRQOL or GQOL measures were used, as HRQOL measures are not a comprehensive assessment of MND patients’ experience and Neudert, Wasner and Borasio explain that there may be no association between HRQOL and GQOL measures.²¹ For example, depression was seen to correlate with the WHOQOL-BREF (a global measure) but not with the SIP (a health-related measure).

Nonetheless, GQOL measures have limitations too, for example the MQOL is not disease specific so may not be sensitive to ALS specific factors such as loss of communication. Additionally, Felgoise et al found that the SEIQOL-DW is “of great value in identifying those factors which contribute to the psychosocial well-being of an individual with ALS”, but that it may not be as appropriate for measuring aggregate QOL in a group of ALS patients.⁶⁹

Scales used for psychosocial factors

As well as multiple measures being used for QOL, multiple measures were used for many of the psychosocial factors. Again, this could cause confusion due to the different properties of the scales, as discussed later for depression specifically.

Meta-analysis

Different measures used in the various studies for both QOL and psychosocial factors, as shown in the table below, mean that, despite multiple papers on certain factors, any useful meta-analysis is not possible.

Factor	Measured with	Quality of life measure compared to
Depression	GDS, ZDS, HADS, HADS modified for MND, DSM-IV, BDI, BDI with somatic components removed, CES-D, ADI-12, Depression-Dejection subscale of POMS-SF, 'I have felt depressed' statement from emotional subscale of ALSAQ-40, Hamilton depression score, PHQ-9, MCS of SF-36.	MQOL, MQOL-SIS, SEIQOL, SEIQOL-DW, SIP (possibly 6 point Likert scale instead), WHOQOL-BREF, Subscales of SF-36, Psychological wellbeing subscale of MQOL, SF-12 MCS, SF-36 MCS, Subscales of ALSAQ-40g Endicott QOL enjoyment and satisfaction questionnaire, EQ-5D, EQ-VAS.
Anxiety	HADS, STAI, Tension-Anxiety subscale of POMS-SF.	SEIQOL-DW, WHOQOL-BREF, SF-12 MCS, Endicott enjoyment and satisfaction questionnaire, MQOL.
Social support	SSQ, The Duke UNC functional social support questionnaire, F-SozU K-14, BSSS.	SEIQOL-DW, MQOL, MQOL-SIS, SIP (possibly 6 point Likert scale instead, EQ-5D.
Religiosity	Idler Index of religiosity.	MQOL, MQOL-SIS, SEIQOL-DW, SIP/ALS19.
Hopelessness	The hopelessness scale by Beck and Weissman, 'I have felt hopeless about the future' statement from emotional subscale of ALSAQ-40.	SIP (possibly 6 point Likert scale instead, Subscales of ALSAQ-40.

Sense of burden	Three items from the Zarit Burden Inventory, 'I have worried I am a burden to other people' statement from emotional subscale of ALSAQ-40.	SIP (possibly 6 point Likert scale instead, Subscales of ALSAQ-40.
Social withdrawal	SWS, SWSMND.	MQOL-SIS, WHOQOL-BREF.
Confiding/emotional support.	CPQ, Brief COPE.	SEIQOL-DW, SF-36.
Problem management coping strategy	MNDCS.	SEIQOL-DW.
Emotional avoidance coping strategy	MNDCS.	SEIQOL-DW.
Cognitive appraisal	MNDCS.	SEIQOL-DW.
Speech disturbance/communication.	Speech item of ALSFRS, communication subscale of ALSAQ-40.	ALSSQOL, emotional subscale of ALSAQ-40.

Table 1.4 Table to show measures used when a factor was studied more than once.

Specific papers

The study on pseudobulbar affect (PBA)⁷⁰ met the inclusion criteria at screening but was excluded after review of the full-text due to quality, as it had a low number of MND participants for both their PBA (n=19) and control (n=4) groups and stated that, when using their planned method of a *t*-test, these sample sizes were too low to produce a reliable result.

The paper by Cardol et al met the inclusion criteria at screening but was excluded after review of the full-text due to the low sample number of fifteen patients and the use of a general question with a 5-point scale for experienced QOL.

Sexual relationships and behaviour

In the literature search, there were some studies focusing on sexual relationships/behaviour and MND and these found some dysfunction and dissatisfaction.^{71,72,73} Unfortunately, no studies investigated the direct effect of sexual issues on QOL. It is to be hoped that it is not the socially taboo nature of this topic that has resulted in the scarcity of articles, and that this factor will be examined more closely in future.

Issues to consider when investigating some psychosocial factors in MND

Temporal relationships

Before discussing some of the psychosocial factors identified in this review, it is worth mentioning the finding that different factors vary their influence over time. Some factors may not be important soon after diagnosis, but become a strongly influential factor later in the disease course.^{50,53} This is a theme that is touched on again later in various chapters.

Depression

A large proportion of the studies reviewed examine depression in MND and its effect on QOL. These studies use ordinal scales, some of which distinguish 'caseness'. However, in the case of inferential statistics the results will not distinguish between depressive symptoms and depressive illness. This is not without merit but readers should be aware that conclusions from these studies cannot be applied without consideration. As these findings will relate to both depressive illness and 'sub-threshold' depression, the research will not guide clinicians as to what level of depressive symptoms would benefit from interventions.

Multiple scales are used to measure depression, and, depending on which is used, a different prevalence rate is identified in MND patients. There is a prevalence in the range of 9-11% when using the DSM-IV criteria but up to 44% when using other criteria.⁷⁴

Some frequently used depression measures have limitations in an MND population. The study by Koerner et al, for example, uses the Beck depression inventory but notes its disadvantages in a physically disabled group such as MND, due to the somatic items in the measure. They measured the BDI's correlation with subscales of the SF-36 both with and without these somatic items, but unfortunately only give the p-values for their findings with the unchanged BDI.⁴⁶ In MND patients there may be very different findings when investigating depression depending on whether measures are self-reported or completed by another person. Depression is overestimated by healthy subjects asked to comment on virtual patients and by caregivers compared to what patients report.^{24,25,75} Caregiver's perspectives were not considered in this review, but these findings do indicate a skewed social perspective in comparison to how individuals with MND perceive themselves.

One of Lule et al's papers acknowledges that the DSM-IV clinical interview looks at both the momentary affective state and any history of earlier depressive episodes whereas the measure they used, the ADI-12, only looked at self-reported momentary affective state. They commented that this may have made the ADI-12 less specific and may have found markedly higher rates of depression.⁴⁸ One study uses the Geriatric depression scale; it could be questioned as to whether this is appropriate for an MND cohort.¹⁴

Interventions for depression, such as medication and psychotherapy, which may be implemented early, due to general recommendations of early recognition and intervention in chronic diseases such as this, may affect findings.

Depression and anxiety and QOL worsening over time was shown in a repeated measures study⁷⁶ of 40 patients with ALS (PALS) and their caregivers over a year. The authors postulated that due to the progressive nature of the illness, it was advancement of the physical illness that caused the decrease in all their analysed constructs. They did however state that it is important to offer psychological and sometimes psychiatric support.

There are however many studies that have found no increase in depression over time^{58,77}, or as death approaches⁷⁸. In fact in Salas T et al's study the "Deepest feeling of depression" was found to occur more frequently close to the time of diagnosis.⁷⁹ Therefore this could be a time for increased vigilance and intervention. To fully understand the relationship between depression and time, several confounding factors would need analysis. One may hypothesise whether speed of progression over time affects levels of depression, or whether it is changes in coping styles that affect when depression is most prevalent in certain cohorts.

Studies recognised factors found to affect depression in MND such as delayed diagnosis⁸⁰, physical function (as measured by the ALSFRS-R and Norris scale)⁸¹, anxiety⁶³, mindfulness⁵⁵, negative social support⁸², and certain coping strategies^{83,84,49,44}. These additional factors should be further investigated as they may be targeted to reduce depression and improve QOL.

Similar to this is the idea that other predictive factors for depression could be investigated in order to identify individuals at greatest risk. Some factors found to be associated with depression include gender, employment status, perceived health status and ALS type⁸⁵ as well as educational status⁴⁸.

Social isolation/support

The importance of social support is mentioned in multiple studies, and the related factors of social isolation and withdrawal were also identified by the review. At least one study suggests that there can be a difference between perceived social support and received social support⁴⁹, and therefore the interventions for these may be different, as simply providing more support may not necessarily increase perceived support. There are likely to be many factors influencing social support, withdrawal and isolation. These include depression⁸⁶ as well as relationships with older age (reduced social functioning)⁴⁶ and, as discussed later, communication (more sources of support)⁸⁷ and religiosity (increased support)³⁷. This emphasises the need to examine multiple factors at a time if possible, as focusing on one factor's direct effect on QOL leaves the vast interplay of a multitude of factors unexamined.

As was stated for depression, non-modifiable factors (such as age) may help predict who is likely to require more social support, and modifiable factors (such as communication) can be targeted for improvement by healthcare teams.

Communication

Two quantitative studies^{40,5340} examined the 'direct' effect of communication loss and many more examined interventions to improve communication including eye tracking and Augmentative and Alternative Communication (AAC)^{88-96, 97}. In the study included in this review it was shown that a decline in communication ability was associated with decrease QOL⁴⁰, but it remains to be seen whether this is an independent factor or whether a plethora of associated psychosocial factors such as social isolation⁹², self-esteem, self-image, anxiety, autonomy⁹³ are affected by communication, and whether it is these factors that mediate the effect on QOL.

On this note, one narrative study found that "Users of computer communication reported more sources of support and happiness and less frustration from difficulty expressing themselves."⁸⁷ In terms of both communication and social support a developing field of increasing significance is the use of social media for and with patients, and it will be interesting to see how this develops.⁹⁸

Religiosity/spirituality

Religiosity and religion was identified as a factor in this review and it is worth mentioning some difficulties when investigating this factor. There is a diversity of definitions, which includes deciding whether to separate it from spirituality (sometimes defined as an existential awareness and belief in a higher force without the doctrine of organized religion).

Due to these definitional issues, it is difficult to assess whether one study is comparable to another. Aside from this is the issue as to whether to consider it a trait or a coping mechanism^{99,100}. Additionally, the location of the study must always be borne in mind, as the cultural significance of religion will vary depending on geography, and thus the results are not generalizable to the global MND population. Bremer et al acknowledge that in areas with other religious individuals the social relations that come with public religiosity may provide additional support.³⁷ These authors found that religiosity showed a trend to strengthen its relationship with QOL over time.

Pseudobulbar affect

Aside from the study on Pseudobulbar affect (PBA) mentioned earlier in this review and excluded due to quality there were additional studies investigating how interventions for PBA increased QOL. However, some of these interventions may have affected other factors, such as the use of antidepressants affecting the key factors of depression and anxiety, such that we cannot be certain whether it is the decrease in PBA symptoms that causes the increase in QOL. Nonetheless, it is important to acknowledge that this is a factor that can be influenced with pharmacological management.^{101–104}

An interesting finding with pseudobulbar affect was that it was not always reported to clinicians depending on which emotions were present. The combination of crying and anger was far less likely to be reported than the combination of labile laughing and anger.¹⁰⁵ Neither of these combinations were reported 100% of the time and future work may focus on encouraging patients to feel comfortable reporting pseudobulbar affect, although some may simply not find it troubling.

A finding that may support pseudobulbar affect impacting patients negatively was that emotional lability may increase anxiety¹⁰⁶, however it should be acknowledged that the evidence for anxiety affecting QOL is conflicting.

Limitations of the systematic review

Gold-standard

It was required from a time and resource perspective that the full article must be in English. This is less than the gold standard for systematic reviews and resulted in some studies not being included in the review.

Another limitation of the method was that the grey literature was not searched and again this is less than the gold standard for systematic reviews. For example, a study on locked in syndrome (LIS) by Lule et al¹⁰⁷ commented on unpublished data by Zickler which found that LIS MND patients named family, friends, social contact and social environment as determinants of their QOL more frequently than controls. It also commented on unpublished data by Häcker finding that patients perceiving social support rated their QOL as significantly higher when compared to those not perceiving social support. This highlights that unpublished literature may have further informed this review.

Critical appraisal

It is unfortunate that, due to limited time during corrections it was not possible to assess each quantitative study using the STROBE checklist. Therefore, the findings of the limited analysis of ten studies should be interpreted with caution.

Structure

Upon reflection, it is clear that the structure and overall quality of this systematic review would have been improved by using a tool such as the PRISMA 2009 checklist¹⁰⁸ to ensure accurate and uniform reporting, particularly with respect to statement of principal summary measures, risk of bias in individual studies, risk of bias across studies, describing study selection, and describing study characteristics.

Factors not reviewed

It is worth mentioning, as part of the overall limitations of this review, some other factors which were not included in the scope of this review.

Physical

The improvement in QOL seen with some interventions for physical factors may be due in part to improving psychosocial factors, for example the embarrassment associated with sialorrhea.^{109,110} Without examining physical factors in this review, the full extent of the effect of psychosocial factors may go underestimated.

Conversely psychological factors may influence physical factors such as depression increasing pain interference with daily life¹¹¹ and fatigue being influenced by psychology and personality type¹¹². Clearly a holistic approach to MND patients, as is already advocated, is warranted.

Caregivers

A lot of literature which discusses the interplay between various patient factors and caregiver burden, with particular focus on the significant effects of the behavioural and cognitive symptoms of MND.^{113,114} Some studies look at the association between caregiver's experience of burden and QOL¹¹⁵ and between caregiver burden and patient's desire for euthanasia¹¹⁶.

Despite the obvious importance of these factors, to adequately cover psychosocial factors from the perspective of the carer would be beyond the scope of this review; accordingly results of this study only included patient-rated relationship factors such as 'sense of burden' and 'satisfaction with relationships'. However, it is important to acknowledge that without considering the caregiver's perspective, the interplay of patient-caregiver factors is significant.

Other areas

Concepts related to QOL, such as meaning in life and wish to die, are obviously important to consider, particularly in this patient group, however they are not considered in this review.

Conclusion

Despite many studies, evidence regarding the exact relationship of psychosocial factors to QOL remains limited. This is predominantly due to:

- Lack of agreement on the definition of psychosocial factors.
- Multiple measures used for measurement of psychosocial factors.
- Multiple measures used to assess QOL.
- Studies not using GQOL measures.

However, available evidence indicates that psychosocial factors do impact on patients' experience of MND and their QOL. Thus, it is essential that further research continues to explore psychosocial factors as this will have implications for therapeutic intervention.

TONiC study, the TONiC cohort and selected factors

The TONiC study

The TONiC (Trajectories of Outcome in Neurological Conditions) study began in 2012 with the aim of capturing the experience of patients with long term neurological disability, namely multiple sclerosis, MND, traumatic brain injury (TBI), spinal conditions, first stroke and neuromyelitis optica (NMO). For the purpose of this chapter the following information will be specific to the MND aspect of the study.

TONiC is a multi-centre study, currently with 27 sites for MND. These are co-ordinated by the TONiC team at The Walton Centre NHS Foundation Trust. The TONiC lead/Chief Investigator is Professor Carolyn Young.



Figure 2.1 Map of sites involved in the MND aspect of the TONiC study.

Funding

TONiC has been supported financially by a number of organisations, including:

- The Walton Centre NHS Foundation Trust
- The National Institute for Health Research
- The Motor Neuron Disease Association
- Biogen Inc.
- Novartis International AG
- Merck & Co., Inc.
- Roche Holding AG
- Teva Pharmaceutical Industries Ltd.
- Genzyme Corporation.

Objectives

The objectives, as identified in the research protocol, are:

- To develop a biopsychosocial model of factors affecting QOL in different neurological conditions.
- To examine the validity of the model over time.
- To develop scales that measure different aspects of QOL in neurological illnesses, where generic scales are not available.
- To test the validity of some existing generic measures.

Phases

The first phase of the study began with in-depth interviews with patients to identify themes and items to be used in the measures. The themes and items were appraised by an expert panel which included both clinicians with expertise in the relevant fields and patient representatives.

The protocol stated that items that were reasonable and had face validity were then considered by two focus groups. One composed of professionals and one of patients.

Cognitive debriefing was used in a small trial group of patients invited to face to face interviews. This identified gross problems with wording or item dysfunction as well as assessing for the applicability, relevance, comprehensibility, and completeness of the draft questionnaire (including all the draft scales). A separate group of patients were asked about the ease of use of the scales and any other difficulties when using them. There were additional specific questions about measures anticipated by the researchers to be problematic.

For the MND aspect of the study 26 participants took part in individual interviews and 14 participants took part in focus groups. The groups had mean ages of 63.4 (range 37-84) and 62 (range 37-74), gender proportions of 61% male and 64% male, and illness duration ranges of 1 month - 141 months and 5 months – 141 months respectively. For the interviews 50% of participants had limb onset MND and a mean ALSFRS-R score of 29.9, the remaining half had bulbar onset MND with a mean ALSFRS-R of 38.6. The ALSFRS-R is a revised version of the ALSFRS, a tool for evaluating functional status. It has 12-items that make up three domains: 'motor function', 'bulbar function' and 'respiratory function'. Overall, it can be said that a wide range of participants was consulted to inform this qualitative phase.

The results suggested that four core factors for QOL emerged:

1. Perceived illness prognosis
2. Sense of self
3. Significant others
4. Life to enjoy

As well as three influential factors for people to maintain their QOL post-diagnosis:

1. Influential others
2. Cognitive attitude
3. Flexibility

The following phases (two, three and four) are running concurrently (to facilitate consenting for all phases), and are all ongoing.

In phase two, demographic data is collected. Clinical care and research teams identify potential participants, provide information and obtain informed consent. Demographic data is taken from the clinical notes and includes data such as diagnosis, year of diagnosis, type of onset (limb, bulbar, respiratory) and ALSFRS-R.

Phase three is the cross-sectional phase of the study. A large sample of consenting participants are recruited to complete the questionnaire pack, which contains the chosen disease specific scales and comparison generic scales. A pre-paid envelope is supplied with the questionnaire pack for its return, and the option of a secure web-based questionnaire pack is available. A small number of participants complete a smaller questionnaire 2-4 weeks later to assess the test-retest reliability of several questions from the original pack.

Phase four is the longitudinal phase of the study, it requires participants to have completed phases two and three. Following new consent, participants will receive a shortened questionnaire pack and pre-paid envelope at months 4, 9, 14, 18, 27, 36 and 60 with a ± 2 months window. In keeping with the idea of 'responsive autonomy'¹¹⁷, participants will be asked at each of these points if they wish to continue to take part in the study. Fortunately, if only three or four data points are complete these can still be used for some form of statistical analysis. Newsletters will be sent to participants to inform them of the progress of the study.

Initially phase four was only open to participants who had been diagnosed within the last year. This was to ensure that there were robust systems in place to conduct the longitudinal aspect of the study. However, investigators and participants were of the opinion that more could be gained if this restriction was lifted and as of substantial amendment 8, phase four is now offered to all participants who have completed phase three.

Scales

Many of the scales used have been assessed psychometrically with classical test theory, but as part of the TONiC study some instruments have been subjected to Rasch psychometric analysis to assess their scaling properties and internal construct validity.¹¹⁸⁻¹²⁰ Analysis of differential Item Functioning, within the framework of the Rasch measurement model, was used to test invariance of the scales for variables such as age, gender and clinical subtypes of MND. Spearman's rho was used to assess external construct validity. Test-retest reliability was also assessed using Spearman's rho as well as Rasch analysis and Cohen's kappa.

The TONiC cohort

For the following chapters of this thesis the statistical analysis will be derived from a patient sample of 465 participants.

Demographic and Disease-specific data	
Number of respondents 465	Disease duration Mean duration 11 months (IQR: 39)
Age Mean age 64.9 (S.D.)	ALSFERS-R Domains (Mean & SD)* Bulbar(Range 0-12) 8.3 (3.6) Motor (Range 0-24) 13.5 (5.9) Respirate (Range 0-12) 9.8 (2.7) * Where high score is good
Gender Female 182 (39.4%) Male 280 (60.6%)	Disease Pattern No pattern * 181 (38.9%) Bulbar 66 (14.2%) Respiratory 18 (3.9%) Motor Function 89 (19.1%) Mixed 111 (23.8%) * Not scoring in worst half of any domain.
Marital Status Single 23 (5.1%) Married 358 (78.9%) Divorced 40 (8.8%) Widowed 33 (7.3%)	
Currently Working Yes 66 (14.2%) No 399 (87.6%)	

Figure 2.2 Image to show demographic and disease-specific data of this sample.

It is important to consider what selection biases may be present in a questionnaire based study. In terms of the psychosocial factors to be examined, one may hypothesise whether those with high levels of depression, anxiety or social withdrawal – particularly if impairing daily functioning – are less likely to attend clinics and if they do whether they are less likely to agree to be part of research. Answering these questions would require investigation of non-attendance at clinics as well as reasons for research refusal (within ethical approval). The measures of depression, anxiety, and social withdrawal had low numbers of missing data at 15, 15 and 0 respectively, showing that, for those who agreed to take part in the research, participants were likely to find the scales acceptable.

One may also consider whether patients with low levels of hope would consider research such as this futile and decline engagement. In this thesis, hope had the largest number of missing data entries out of all the factors examined, at 214 entries. This suggests that for those who agreed to participate in the research, there were difficulties in completing this scale. Qualitative research would be required to investigate the reasons for this, which are likely to be scale design or difficulties with the concept.

Of the demographic factors considered, perhaps those still in employment are likely to be under-represented as they may not attend clinic as much as those no longer in employment. Those who are not married or cohabiting may be under-represented as they may find it harder to access the assistance required to visit clinics and to complete the questionnaire. Those with preserved functioning and thus high ALSFRS-R scores may be less likely to attend clinic as they have fewer problems but equally those who are severely disabled, with low ALSFRS-R scores, may find it difficult to complete the questionnaire and may not deem it a priority for them when they need to be considering how to manage their energy levels and time. However, during data entry there were comments more than once that disabled individuals valued this research in terms of exploring their concerns and wished to encourage further research to continue to interact with them. Those of older age or longer disease duration may similarly feel that their time is better spent in other ways.

Without an obligatory census of the MND population with complete data the best we can hope for is a good spread of demographics and disease characteristics to capture a wide-ranging sample and then compare this to previous studies.

The number of respondents is of an adequate size to be a wide-ranging sample of the UK MND population which is estimated to be around 5000 individuals at any one time.¹²¹ The mean age of 64.9 is similar to a mean age of 65.2 found in a Italian study of 377 patients.¹²²

As previously mentioned a male preponderance is to be expected in MND populations and this sample's proportions of male and female gender participants are close to a 2011 UK based study (56.6% male: 43.4% female) of 830 patients² as well as being similar to a number of other European studies.^{122,123,124}

Disease duration is difficult to compare to other studies as they often record symptom duration from diagnosis or disease duration until death. With the latter, the results are longer than the mean disease duration given here as many of our sample are still alive. However, the interquartile range for disease duration in the study population is adequate to represent a range of those with the condition.

The proportion of patients in whom bulbar, respiratory or limb function is affected may differ slightly from other studies, as these figures look at the onset type as estimated at the time of diagnosis. Disease that has evolved to affect more than one domain may be described as mixed, and there is also the inclusion of a category for no disease pattern. A study by Chio et al claims that in most clinical and retrospective epidemiological studies bulbar onset is around 20-25%, limb is 75-80 and respiratory is <1%. It does, however, add the warning that respiratory onset may be under-represented as it may be more easily misdiagnosed.¹²⁵ The mean scores for the ALSFRS-R domains in our population show that our patients are moderately disabled, with motor function being the most impaired domain.

Marriage status could have a possible indirect link to QOL through the possibility of greater social support. An Irish study, by Clarke et al, found their rates to be: married 73.1%, single 15.4%, widowed 7.7%, and separated 3.8%.³⁸ A London based study found their rates to be: married 71.0%, single 12.9%, widowed 9.6% and divorced 6.5%.⁴³ It should be noted that these rates and the significance attached to them will depend upon the local cultural and religious context.

As discussed in chapter one it appears that patients' focus moves away from occupation as a driver for QOL.^{16,28} Nonetheless a German study found that 91.9% of their MND population sample were unemployed (n=36), a rate similar to this sample population.⁶⁴

Overall the above comparisons confirm that this study population is an adequate one to investigate the desired psychosocial factors. Analysis of a large UK population will benefit overall understanding and contribute to the current literature.

Factors

For this thesis, the factors that will be evaluated in this population are as follows:

- Depression
- Anxiety
- Social withdrawal

These factors have widely accepted, agreed definitions with well validated tools to measure them, including those used in the TONiC study. They are some of the most investigated factors in the systematic review, but the evidence is still inconclusive and requires further study.

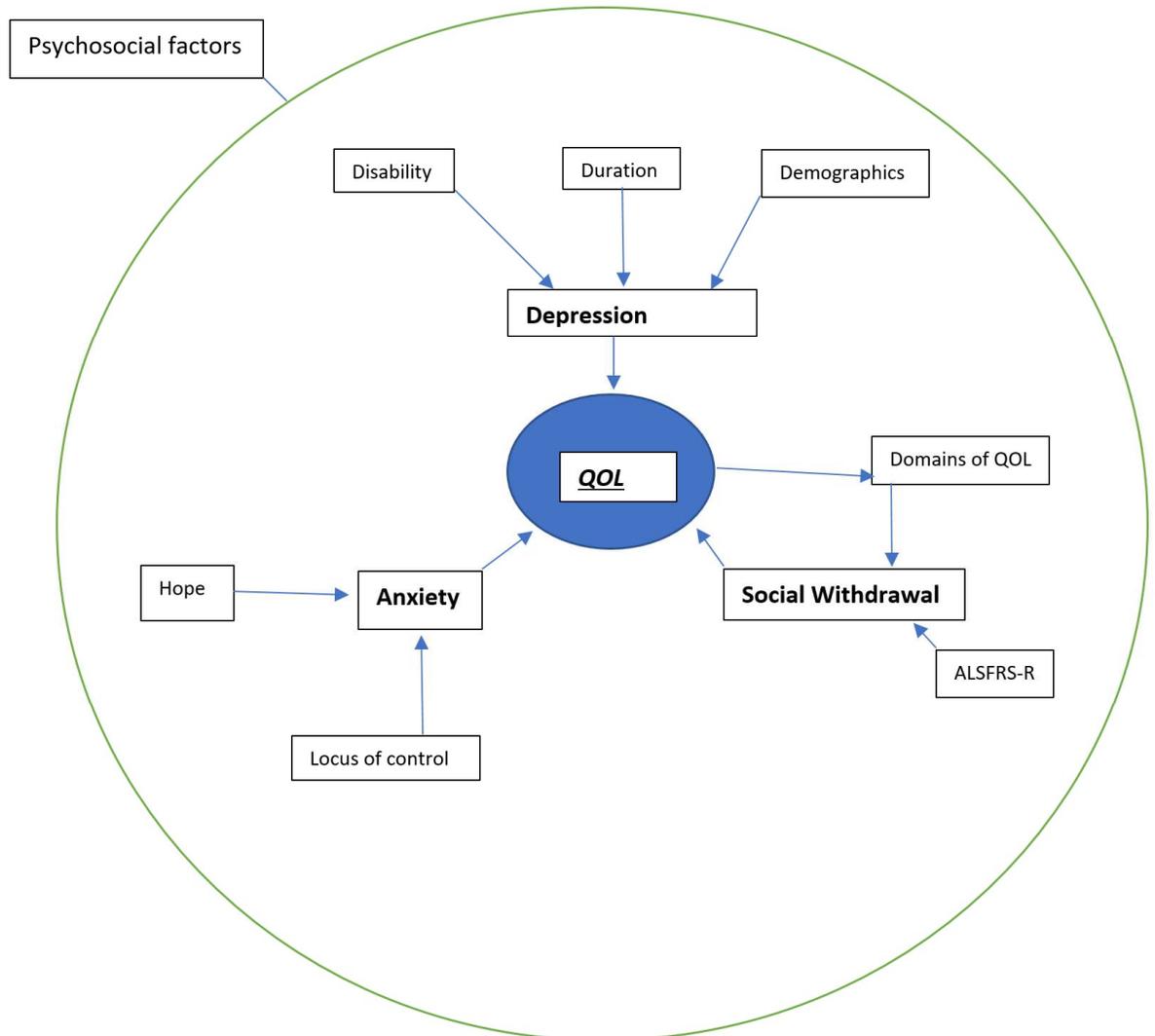


Figure 2.3 Figure to show factors of interest in this thesis.

All statistical analysis will be done in SPSS.

Regression analysis will be used to investigate the significance of the proposed associations and will examine the relative importance of these variables for explaining variance in the outcome measure for each chapter.

The thesis will examine 5 multifactor models. The data set was modified such that participants who were missing data for any of the factors to be examined in a particular model were excluded from all analysis for that model. This ensures uniformity of the population between the initial single factor models, allowing direct comparison so that factors can be assessed by p value and F statistic to order the entry of these factors into the multifactor model.

Total number of MND participants = **465**

- No missing data for depression, disability, duration and demographics = **286**
- No missing data for anxiety, hope or locus of control subscales = **224**
- No missing data for social withdrawal and QOL domains = **417**
- No missing data for social withdrawal and ALSFRS domains = **429**
- No missing data for Overall QOL, depression, anxiety and social withdrawal = **409**

Models that are significant at the $p \leq 0.05$ level will be ranked by p value (smallest to largest) and then F statistic (largest to smallest). Factors will be added in this order using a ‘forwards’ method for building a regression model.

Outliers will be determined by the residuals from the final model rather than the raw values. This is because all values from the scales are realistically possible, such that it would be disingenuous to remove data points as the data would no longer reflect TONiC’s real world MND cohort. Residuals of the final model will be assessed by Cook’s distance to determine whether a data point is having undue influence on the result of the model. These will be assessed graphically by the investigator and models will be tested again excluding data with high Cook’s distances. If no change in significance is found for any factors then the data is still included when reporting the final model.

Non-centred interaction terms will be tested between all the factors in the final, most parsimonious multifactor model. In the event of a significant interaction term, this will be reported in the final model and the interaction will be analysed graphically. This will be done by plotting one of the independent variables against the dependent variable, but whilst grouping the aforementioned independent variable by the second independent variable. This will produce multiple regression lines, which can then be compared. For example, if there were to be a significant interaction term for depression and anxiety when QOL is the outcome, then depression would be plotted against QOL with the data points for depression being grouped by anxiety level, either in even numbered groups or using specific cut-offs.

When considering the multifactor models, it is worth considering how close they are to the original sample population (n=465) in terms of demographics. The table below shows values that were greater than 5% of the original value from the original value as orange and values greater than 10% from the original value in red. In the table below, it can be seen that the multifactor model with the greatest differences from the original sample population is the depression model; the most similar was the social withdrawal – ALSFRSR model. The table below shows that for most models there were moderate, and in the case of the depression model stark, differences when compared to the original sample population. These differences are unfortunate but cannot be avoided when using the chosen methodology of this study at the researcher's skill level. Because of the differences demonstrated below, caution should be taken when interpreting the findings of this thesis.

Model	465	DEPRESSION	ANXIETY	SW-QOL	SW-ALSFRSR	WHOQOL
n	465	486	424	417	427 - 429?	409
AGE	64.86	63.72	64.57	63.74	64.84	63.68
DISEASE DURATION	26.17	28.58	31.4	27.23	26.82	27.35
ALSFRS BULBAR	8.34	8.45	8.11	8.53	8.44	8.56
ALSFRS RESP	9.81	9.67	9.84	9.81	9.82	9.8
ALSFRS MOBILITY	13.48	13.62	13.24	13.6	13.54	13.59
MALE %	60.6	63.6	61.9	63.1	60.8	62.9
FEMALE %	39.4	36.4	38.1	36.9	39.2	37.1
ONSET BULBAR	24.7	27.3	24.1	23.3	23.5	23.2
ONSET LIMB	60	67.1	57.6	60.9	60.6	60.9
ONSET UNKNOWN	15.3	5.6	18.3	15.8	15.9	15.9
MS COHABITING	78.9	83.6	78.2	81.7	78.3	81.6
MS SINGLE	5.1	4.5	5.5	4.6	5.3	4.7
MS DIVORCED	7.3	5.6	6.8	7.1	7.4	7.2
MS WIDOWED	8.8	6.3	9.5	6.6	9.1	6.5
EMPL MED RETIRED	23.4	28.3	26.8	24.9	22.8	25.2
EMPL RETIRED	54.6	49.3	54.5	51.6	54.5	51.1
EMPL FULL TIME	9	10.1	6.7	9.6	9.6	9.5
EMPL PART TIME	5.2	6.3	4.9	5.8	5.6	5.9
EMPL OTHER	7.7	5.9	7.1	8.2	7.5	8.3
HADSA	4.7	4.81	4.57	4.68	4.67	4.68
HADSD	3.3	3.28	3.28	3.25	3.32	3.25

Table 2.1 Table to show demographics and disease characteristics of the various multifactor models. Green = value within 5% of the original sample population. Orange = value greater than 5% but less than 10% from the original sample population. Red = Value greater than 10% from the original sample population.

It is also of interest to consider which factors contributed most to missing data in which models, which is shown in the tables below. For the depression model, it was shown that a substantial number of respondents did not have complete data for 'disease duration', domain 4 of the disability score, and domain 6 of the disability score. For the anxiety model, nearly half of respondents had missing data for the hope score.

Model	Age	Disease duration	Gender	Onset Type	Marital status	Employment status	HADS-D modified
Depression	0	64	3	0	11	0	15

Table 2.2 Table to show, for the descriptives in the depression model, the number of missing entries. Green = Less than 5% missing data from the original sample population. Orange = Greater than 5% but less than 10% missing data from the original sample population. Red = Greater than 10% missing data from the original sample population.

Model	WHODAS D1	WHODAS D2	WHODAS D3	WHODAS D4	WHODAS D5	WHODAS D6
Depression	24	14	25	51	17	61

Table 2.3 Table to show, for the disability domains in the depression model, the number of missing entries. Green = Less than 5% missing data from the original sample population. Orange = Greater than 5% but less than 10% missing data from the original sample population. Red = Greater than 10% missing data from the original sample population.

Model	HADS-A modified	Herth Hope Index	Internal LOC	Chance LOC	Others LOC
Anxiety	15	214	25	27	24

Table 2.4 Table to show, for each factor in the anxiety model, the number of missing entries. Green = Less than 5% missing data from the original sample population. Orange = Greater than 5% but less than 10% missing data from the original sample population. Red = Greater than 10% missing data from the original sample population.

Model	Social withdrawal	Physical health	Psychological health	Social relationships	Environment and financial resources
SW - QOL	0	8	8	48	8

Table 2.5 Table to show, for each factor in the SW-QOL model, the number of missing entries. Green = Less than 5% missing data from the original sample population. Orange = Greater than 5% but less than 10% missing data from the original sample population. Red = Greater than 10% missing data from the original sample population.

Model	Social withdrawal	ALFRS-R Bulbar	ALSFRS-R Respiratory	ALSFRS-R Motor
SW - ALSFRSR	0	12	21	20

Table 2.6 Table to show, for each factor in the SW-ALSFRS model, the number of missing entries. Green = Less than 5% missing data from the original sample population. Orange = Greater than 5% but less than 10% missing data from the original sample population. Red = Greater than 10% missing data from the original sample population.

Model	Total QOL	HADS-D modified	HADS-A modified	Social withdrawal
GQOL	48	15	15	0

Table 2.7 Table to show, for each factor in the GQOL model, the number of missing entries. Green = Less than 5% missing data from the original sample population. Orange = Greater than 5% but less than 10% missing data from the original sample population. Red = Greater than 10% missing data from the original sample population.

Investigating Depression in Motor Neuron Disease

Introduction

Factors

The systematic review highlighted that depression is the factor which has been most investigated with respect to QOL in MND. This is possibly because of the healthcare practitioner's familiarity with the concept, given it is a psychiatric diagnosis (ICD 10/DSM-V), and thus there is information regarding aetiology, diagnosis, treatment (National Institute for Health and Clinical Excellence (2009) Depression in adults: recognition and management. NICE guideline (CG90))¹²⁶ and prognosis with available well validated screening measures.

It is also likely to be due to the recognised relationship between long-term physical health conditions and depression¹²⁷, as well as the general attitude that a diagnosis of MND is devastating, and would increase susceptibility to depression.

Previous studies have demonstrated a relationship between depression and some demographic/disease factors such as gender, employment status, ALS type and educational status, but these studies did not use a UK cohort.^{48,85} The effect of these factors may differ between cultures, as different emphasis may be placed on them, and thus the relationship between depression and some demographic factors will be studied in the large UK TONiC cohort.

One factor with conflicting evidence about its relationship to depression is time, specifically whether depression worsens with time. As described in the systematic review, the study by Jones et al found that depression increased over time, and they posited physical decline as a contributing factor.⁷⁶ However, several studies have shown that depression is stable over time.^{58,77,78} It is possible that a relationship between time from diagnosis and depression could be confounded by a number of factors, including physical decline as suggested previously, and it would be valuable to re-examine this relationship.

Physical function has been linked to depression before^{45,46,85} but it would be useful to examine *how* these factors may be linked, by examining whether patients ability to undertake certain activities is associated with depression, thus contextualising their physical function in terms of disability.

Measuring depression

An issue raised in the systematic review is how depression is measured in studies. In the MND population, screening tools are often used both clinically and in research to evaluate levels of depression. Screening tools are not diagnostic and so conclusions reached in research may not be in relation to categories of 'diagnosed depression' vs. 'no depression' per se, but in relation to categories of 'no depression', 'possible depression' and 'probable depression' (labels given depending on cut-off scores defined within the measures).

The Hospital Anxiety and Depression Scale (HADS) is a 14-item screening tool for both anxiety and depression and can be split into two subscales accordingly – the HADS-A and the HADS-D. The HADS-D has 7 items with cut-offs of scores ≥ 11 for 'probable depression', 8-10 for 'possible depression' and ≤ 7 for 'no depression'. In the general and other disease populations, the HADS has been shown to have good sensitivity and specificity when compared with the Structured Clinical Interview for DSM disorders (SCID-1 DSM-IV version) for identifying psychiatric disorder.¹²⁸ A study on breast cancer patients found that the depression subscore had good sensitivity and specificity when compared to a DSM diagnosis of major depression, but a positive predictive value (PPV) of 36%.¹²⁹ The low PPV means that the HADS-D is likely to overestimate the prevalence of depression in this population.

The results of a recent study using Rasch psychometric validation concluded that the HADS-D could be modified for use in the MND population by removing item D8 "I feel slowed down", and revising the cut-off scores to ≥ 8 for 'probable depression', 5-7 for 'possible depression' and ≤ 4 for 'no depression'.¹¹⁹ This adjustment had previously been made by some authors, as it was thought reasonable to assume that item D8 may be confounded by the physical impairment that comes with MND.^{43,130} However, there was not the evidence to support the modified measure at that time.

A benefit of screening scales is that they generate ordinal data which, given appropriate conditions, can allow use of inferential statistical techniques looking at ‘relationships and correlations’, as opposed to categorical data which only allows statistical techniques looking at ‘differences between groups’. The Rasch analysis of the HADS resulted in a modified scale that produces interval level data allowing the use of more simple, conventional, and robust inferential statistical techniques.

Another benefit of screening tools is that the diagnostic interview is particularly resource intensive to administer and interpret when compared to screening tools, which are often patient-reported. This is advantageous as large volumes of data can be collected in a shorter space of time. Thus, the diagnostic interview is the *gold-standard* for identifying depression but, for the reasons above, psychometrically validated screening tools could be regarded as an acceptable proxy for investigating depression in large cohorts.^{131–138}

Method

Aim: To investigate some factors’ association with depression in this TONiC MND cohort.

Research questions:

1. Are certain demographic factors significantly associated with depression in MND?
2. What is the relationship of time from diagnosis and disability to depression in MND and do these factors interact?

Analysis

This study used a regression model, depression being the dependent variable with the factors age, gender, onset type, marital status, employment status, time from diagnosis and disability as the independent variables. Multiple regression analysis allows each factor to be checked on its own for significance, but then also together to examine for confounding.

The use of disability over a measure of pure physical function was intended to allow an examination of specific areas affected by physical decline such as the domains of self-care, mobility and communication. Additionally, there are no interventions available currently to improve a patient's physical function but there is the possibility of intervention aimed at improving a patient's disability, making the study more clinically relevant. Finally, the measure of disability is patient-reported as well as contextualised in terms of activities and patient's ability to participate in them; thus, it has the benefit of being a subjective measure of the patient's 'lived experience' of MND.

Initial plots did not suggest any non-linear relationships between the factors and depression, so multiple linear regression was chosen as an appropriate method.

Participants

The data set was modified such that participants who were missing data for any of the factors to be examined were excluded from all analysis. This ensured uniformity of the population between the initial single factor models.

Total participants: **n = 465**

Participants with complete data for depression, disability, time from diagnosis and demographic: **n = 286**

Scales

- Depression was measured using the HADS-D subscale modified for use in MND as per the paper by Gibbons et al.¹¹⁹
- Disability was measured using the WHODAS 2.0, which is a disability scale by the World Health Organisation examining 6 domains, although domain 5 is split into 2 subdomains.¹³⁹

Domain	Measures
Domain 1	Understanding and Communicating
Domain 2	Getting around
Domain 3	Self-care
Domain 4	Getting along with people
Domain 5a	Life activities – household questions
Domain 5b	Life activities – work and school
Domain 6	Participation in society

Table 3.1 Table to show the domains examined by the WHODAS 2.0

Models

Overall model

To generate an overall multifactor model, single factor models were run for the following factors:

- WHODAS 2.0 domains – domain scores were modified using the item-response-theory based scoring from the WHODAS 2.0 handbook.¹³⁹ Domain 5b, the ‘work and school’ subsection of life-activities, was not included for regression, as it was only rarely completed due to the nature of MND.
- Time from diagnosis – measured in ‘months from diagnosis’.
- Age
- Gender – Scored as ‘male’ or ‘female’.
- Onset type – Scored as ‘limb’, ‘bulbar’ and ‘unknown’. ‘Unknown’ was chosen to be the comparison variable and ‘limb’ and ‘bulbar’ as the dummy variables.
- Marital status – Scored as ‘single’, ‘cohabiting/married’, ‘divorced’, ‘widowed’. ‘Cohabiting/married’ was chosen to be the comparison variable and ‘single’, ‘divorced’ and ‘widowed’ were coded as the dummy variables.
- Employment status – Scored as ‘working full-time’, ‘working part-time’, ‘medically retired’, ‘retired’ (other than medical), and ‘other’. ‘Medically retired’ was chosen as the comparison variable and ‘working full-time’, ‘working part-time’, ‘retired’ and ‘other’ were coded as dummy variables.

Interaction model

To specifically test the interaction between time and disability, a summed score for the disability domains was calculated and multiplied by 'time from diagnosis' to generate the interaction term. Then a multifactor model was tested with the factors 'disability', 'time from diagnosis' and the 'interaction term' being added in that order.

Results

Overall model

Single factor models that were statistically significant:

- WHODAS 2.0 domain 1 (Understanding and Communicating) ($F_{1,284} = 74.046, p < .001$)
- WHODAS 2.0 domain 2 (Getting around) ($F_{1,284} = 47.090, p < .001$)
- WHODAS 2.0 domain 3 (Self-care) ($F_{1,284} = 69.755, p < .001$)
- WHODAS 2.0 domain 4 (Getting along with people) ($F_{1,284} = 85.965, p < .001$)
- WHODAS 2.0 domain 5a (Life activities – household questions) ($F_{1,284} = 72.977, p < .001$)
- WHODAS 2.0 domain 6 (Participation in society) ($F_{1,284} = 128.220, p < .001$)

Single factor models that were not statistically significant:

- Time from diagnosis ($F_{1,284} = 0.460, p = .498$), Logn time from diagnosis ($F_{1,284} = 1.486, p = .224$),
- Age ($F_{1,284} = 0.138, p = .711$)
- Gender ($F_{1,284} = 0.000, p = .997$)
- Onset type ($F_{2,283} = 0.230, p = .795$)
- Marital status ($F_{3,282} = 1.365, p = .254$)
- Employment status ($F_{4,281} = 1.050, p = .382$)

Significant single factor models	Non-significant single factor models
Domain 1 (Understanding and Communicating)	Time from diagnosis
Domain 2 (Getting around)	Age
Domain 3 (Self-care)	Gender
Domain 4 (Getting along with people)	Onset type
Domain 5a (Life activities – household questions)	Marital status
Domain 6 (Participation in society)	Employment status

Table 3.2 Table to show significant and non-significant single factor models.

In order to find the most parsimonious model a ‘forwards’ approach was used which resulted in a model incorporating domains 6, 4, and 1 ($F_{3,282} = 58.071, p < .001$). Interaction terms for these factors were not significant. The final model accounted for 38.2% of the variance in HADSD scores as shown by an R^2 of 0.382.

The final model’s regression equation was as follows:

$$\text{HADSD} = 0.370 + 0.037 * \text{domain 6} + 0.017 * \text{domain 4} + 0.028 * \text{domain 1}$$

Interaction model

In the model testing for an interaction between disability and time from diagnosis, the ‘total disability’ score was significant as a single factor model ($F_{1,284} = 127.646, p < .001$). The addition of ‘time from diagnosis’ did not produce a significant R square change ($p = .119$) and the addition of the interaction term also did not produce a significant R square change ($p = .229$).

Discussion

Demographics

All demographic factors examined in this study were found to be non-significant in terms of association with depression. This is consistent with a previous paper by Tedman, Young, and Williams¹⁴⁰, but is contradicted by Cui et al.¹⁴¹

Relationship of depression with time from diagnosis of MND

This study does not support a significant relationship between depression and time from diagnosis of MND. Nor did it support a significant interaction between time and disability when examining depression. However, whether depression increases over time and as death approaches may be due to a myriad of other confounding factors such as religiosity/spirituality and social support. Other factors important to consider are adjustment and coping; future research could divide sample populations into high and low adjustment or divide them by coping style. Another important factor to consider would be whether patients are receiving effective palliative care, and whether they are satisfied with this care.

Another consideration is whether the magnitude of impact of various psychosocial factors may change over time. For example, a thematic study by Hecht et al found that social isolation was named as being one of the most important psychosocial factors at T2 whereas it was not at T1.⁴⁴ Similarly, the paper by Bremer et al found that, in their sample, private religiosity was not initially related to QOL.³⁷ However, it showed a trend to increase with time and by 1 year the combined effects of private and public religiosity accounted for 53% of the variance in QOL. They suggested that public religiosity may provide additional support through social relations, but the above examples still demonstrate the possibility of change in psychosocial factors' importance over time. Matuz et al commented on how the degenerative course of MND exposes individuals to short and long-term stressors.⁴⁹ They suggested that patients utilise different coping styles, depending on (i) the stage of the disease and (ii) which type of stressor they are attempting to cope with at that time. Following this, they suggested that despite the idea that 'confrontation is good and avoidance is bad', denial or avoidant coping may be helpful in terms of maintaining QOL until later in the disease course, when it becomes maladaptive.

A beneficial factor increasing its effect over time, such as improved coping, may go some way to explaining why, despite decline in other areas such as functional ability, depression is not correlated with time in this cohort.

Disability

Significant single factor models confirm the importance of considering domains one (understanding and communicating), two (getting around), three (self-care), four (getting along with people), five A (life activities – household tasks) and six (Participation in society) of the WHODAS 2.0 questionnaire when considering a patient's mental health.

The most parsimonious model included domains 6, 4 and 1. The coefficients of these scores may seem small but the domain scores could be in the hundreds and so the magnitude of these factors should not be underestimated, as demonstrated by the variance in depression explained by the final model. The final model demonstrates the importance of social disability for patients with MND. Due to the cross-sectional nature of this analysis the direction of effect cannot be determined, and so it may be that social disability is a driver for increased levels of depression – or it could be that higher levels of depression cause patients to struggle to communicate, get along with people and participate in society. Equally, it is just as likely that the interaction is bi-directional.

The results of this study are consistent with previous studies, which have explored the relationship between depression and functional ability in MND.^{142,143} Hogg, Goldstein and Leigh used the Barthel Index, which looks at independence of mobility and speech, and found significant correlation with depression.¹⁴³ Emotion, sleep and eating scores of the sickness impact profile (SIP) were also correlated with depression, showing further links with the disability incurred by physical limitation. They additionally found a significant association between depression and social interaction, further supporting the findings of this study's final model. In Matuz et al's study, they found that the factor in their model that best predicted severity of depressive symptoms was perceived social support, which lends support to the social factors aspect of this study's findings.⁴⁹

Physical function

Physical function's relationship with QOL could be considered confusing; physical impairment has been shown to be a risk factor for depression^{45,46,85}, but, in spite of this this, lower physical function does not appear to be associated with lower QOL^{17,18,20,43}. Considering the strong link between depression and QOL, this is a curious finding and perhaps future studies could seek a mitigating factor. It may be that initially physical function is associated with adjustment, but as a response shift occurs, this link weakens, and there is no impact on QOL.

To reiterate, disability was chosen instead of physical function in this chapter, as it allows physical decline to be contextualised in terms of ability to undertake or participate in activities such as self-care, getting around and communicating with others. Additionally, whilst physical function cannot currently be improved in MND with any of the available pharmaceutical armament, interventions can be aimed at reducing disability. This notwithstanding, it is worth considering that lower physical function may be a separate risk factor for depression, outside of the disability it entails.

It could also be that a patient's limited physical function serves as a reminder of the progressive and ultimately fatal nature of the disease course. A similar sentiment was suggested by Hogg, Goldstein and Leigh¹⁴³. Narrative interviews have reported patient's comments that "the diagnosis is a 'death sentence'" and that "life is already over."³⁰

It would be interesting to explore whether all the variance in depression scores explained by physical function is absorbed by disability, or whether physical function has a significant unique contribution.

It is shown in this study that the disability that results from physical limitation impacts strongly on the patient's mood, and this supports prioritising interventions towards adaptations, devices and services that can reduce the impact of physical limitation on disability. For example, in interviews about the impact of neck weakness, some of the problems described included the social limitations of low eye-level and the lack of freedom as it was more difficult to get around.¹⁴⁴ This was then supported in various ways by physiotherapists and occupational therapists for example with the use of splints and neck supports. This does not of course improve a patients' neck strength, but does reduce their disability.

Depression has been shown in several chronic diseases, including multiple sclerosis¹⁴⁵ and COPD¹⁴⁶ to worsen functional status, or at least perceived disability. Thus, the relationship may be found to be bi- directional.

Perceived health status

Although not examined in this study, it is interesting to consider how impaired physical function or disability may impact on perceived health status. Perceived health status was found to predict depression in South Korean ALS patients⁸⁵, and this demonstrates the importance not only of objective impairment but also of the subjective experience of the patient.

There are a number of interventions which may improve or worsen perceived health status, including those aimed at reducing disability, as well as physical treatments such as P.E.G. or ventilator support. In addition, there may be additional therapeutic potential for improving perceived health status in the form of psychological intervention. It has been shown in many disease groups and in the healthy population that organised programs aimed to improve rates of physical activity and/or nutrition can have significant benefit on self-perceived health status. This includes, but is not limited to, sprint training, yoga, tai-chi, empowerment focussing on physical activity, individualized feedback-based virtual reality (IFVR) exercise, support groups and CBT focussed on exercise and diet, and group exercise coupled with nutrition classes.¹⁴⁷⁻¹⁵³

These examples are of course confounded by the evidence about the benefits of exercise on mental health^{154,155} aside from self-perceived health status and additionally some will be less applicable to MND patients due to their physical limitations.

Benefits to perceived health status from psychoeducational approaches that do not involve physical activity have been seen in different disease groups. Some examples are as follows: structured self-care telephone talks¹⁵⁶, short-term CBT intervention via telephone¹⁵⁷, Psychoeducational Intervention Program¹⁵⁸, therapeutic skill building and support activities including reinforcement with practice and role-playing to reduce stress and burden associated with caregiving¹⁵⁹, counselling sessions led by psychotherapists¹⁶⁰, motivational interview-based health coaching¹⁶¹, acceptance training intervention combined Rational Emotive Behaviour Therapy with music, relaxation, and guided imagery¹⁶². These types of interventions may have a wider merit in terms of their effect on other psychosocial factors e.g. self-esteem, self-efficacy, or depression.

The use of telephone based interventions may be seen as beneficial in terms of resource cost as well as having additional benefit for MND patients with reduced mobility, improving their access to psychological therapies.

Acceptance training intervention may have particular relevance to MND. Meaning or transcendence based coping is related to the idea of response shift, and is defined by some as acceptance of self and others and altruism¹⁶³. There is evidence in a wide range of illnesses that the life-changing impact of an intractable disease can cause an increase in self-transcendence, with an acknowledgment that this can have a wide range of benefits in terms of mental well-being.¹⁶⁴ Some may argue that coping with the existential and psychosocial crises that the diagnosis of a fatal illness brings, accelerates a person's journey through the psychosocial stages as suggested by Erikson¹⁶⁵. If these psychosocial crises are resolved, then the patient may adjust to their terminal diagnosis more readily than expected.

Meaning focused coping is discussed in further detail in the following chapter in relation to both hope and locus of control.

Prevalence of depression

Prevalence of 'probable' depression as per the modified cut-off points given by Gibbons et al¹¹⁹ =7.1% (n=450), and 'possible' depression =22.3%.

Treatment for depression in MND

A 2014 review, "The evidence for symptomatic treatments in amyotrophic lateral sclerosis" concluded that although usual antidepressants and cognitive behavioural therapy (CBT) approaches are used, no randomised controlled trials have studied the treatment of depression in MND.¹⁶⁶ This was reiterated in a 2016 review which recommended multidisciplinary management, psychological support, palliative care, physical therapy as well as the standard drug treatments used in other conditions for the management of psychological symptoms including depression in MND patients.¹⁶⁷ This is consistent with recommendations in the 2009 NICE guidance for "Depression in adults with a chronic physical health problem".¹²⁷

A paper quoting expert opinion states that there is a broad consensus that selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs) are helpful.⁷⁴ The authors add that TCAs treat symptoms of pseudohypersalivation and insomnia due to their anticholinergic effects, which may be an added benefit.

A paper investigating the impact of long-term medical conditions on the outcomes of psychological therapy by Delgado et al concluded that standard stepped-care interventions (in the form of CBT) are “insufficient to support patients with multiple morbidity.”¹⁶⁸ In this study, they investigated the treatment of individuals who were depressed with no long-term condition and compared this with the same treatment in patients with multiple morbidity. They found that using the same intervention style for chronically ill patients who were depressed was not as effective, when compared to depressed patients with no long-term condition. They also noted that in most self-reported long-term conditions, patients were significantly more likely to receive more intensive and costly psychological interventions, but that in some groups higher-intensity therapy was associated with higher average post-treatment distress, compared to low-intensity therapy. They suggested that high-intensity therapy was not necessarily superior to low-intensity therapy in a primary care setting for patients with long-term conditions.

One interpretation of this study is that a particular, evidence based, CBT intervention for psychological symptoms including depression may not be as effective in MND patients. Patients with MND may require different therapeutic interventions for the treatment of any psychological symptoms.

Following on from this, a study examining both MND patients and late-stage cancer patients found similar rates of depression as per the Beck depression inventory, but found that the characteristics or ‘quality’ of the depression differed between the groups.¹⁶⁹ MND patients had higher scores for demoralisation and hopelessness, as well as suicidal ideation. Cancer patients suffered more with anhedonia. If further research corroborates these findings, this could inform both assessment and management approaches in different patient groups.

Future research

Depression and time

A relationship between depression and time would need to take multiple psychosocial factors into account. One idea might be to examine whether there is an association early in the disease course, when patients may not have compensating psychosocial mechanisms.

Disability and social programs

Further research could investigate whether interventions based around disability have a positive impact on individual's mental health or – by extension – QOL. Yet, care should be taken not to simply try to improve these factors via external support without improving how patients feel about these factors. Investing more in support services to help with 'self-care' (washing, eating, dressing) or household activities may not improve patients' outlook in the intended way, as it may be the fact that they cannot accomplish these things *for themselves* that distresses them – any success of the aforementioned services may also have to do with social factors, more so than the impact the service has on their disability or burden.

Social programs including support groups could be beneficial not only in terms of social factors, such as improving support and reducing withdrawal and isolation, but also in terms of WHODAS domains six and four ('participation in society' and 'getting along with people' respectively). However, these programmes may be problematic as people are often reluctant to join initially – for a plethora of reasons, from denial to embarrassment, or to inconvenience – and often only see the benefits after joining. This is coupled with themes from qualitative work, as mentioned in chapter one, indicating that MND patients may switch their focus to consolidating existing relationships as opposed to seeking new friendships.²⁸

Some studies have suggested that patients can be distressed by the content of discussions, the purpose of such groups and by seeing peers who are more advanced in their illness. Some would rather engage in activities unrelated to MND.¹⁷⁰

Locock and Brown examined support groups, social comparison and two key themes of 'valuing camaraderie and comparison' and 'choosing isolation'.¹⁷¹ They noted that groups offered practical and social support and, with respect to the first key theme, an opportunity for social comparison, where seeing others coping well could provide hope, and seeing others worse off could make people feel better about their own situation. This notwithstanding, they also noted that most people were also shocked and saddened by seeing other individuals with the same condition, and that the second key theme, choosing isolation, can be a deliberate defence mechanism to avoid seeing how much worse they could be in future. Choosing isolation could also be used when attending the group caused disruption to a person's identity such that they felt defined as 'a person with MND' rather than 'the person I am that happens to have MND'. Balancing benefits and psychological distress, as well as an individual's 'changing needs and fears', may result in changing levels of involvement over time.

When examining resilience in neurological disease, McCabe et al found that those with high levels of adjustment engaged more in sport, groups, clubs and classes than individuals with low adjustment.¹⁷² It was seen that those with a high level of adjustment intended to use activities to maintain a positive outlook, not focus on the illness more than necessary and remain physically active. However, they did also find that those in the low-adjustment group did report support groups as helping them cope with their illness. A resource effective way of investigating the impact of support groups would be to research the benefits and costs (emotional and monetary) of existing support groups using both qualitative and quantitative methods.

Psychological Interventions to improve psychological wellbeing including depression in MND

There have been previous calls in the literature for research into psychological support for MND and for recommendations and 'best practice' guidelines to be developed. There is the additional suggestion that interventions for other life-threatening disorders could be modified to suit MND patients.¹⁷³

In a 2006 review, a revised model of adjustment for chronic disease, incorporating many psychosocial models, was proposed, and the authors felt that this could be used to guide the improvement of treatment.¹⁷⁴ They argued that most interventions for psychopathology focused on cognitive strategies to challenge unhelpful beliefs about their illness, but did not target other processes such as response shift, meaning-finding and other relevant factors. Consequently, it was argued that the most appropriate strategies for an individual may be underutilised, and that their model could act as a guide to identify, at a particular time point, which strategy would most facilitate adjustment.

Processes which they recommended considering include:

- Schema-enmeshment
- Self-regulation model
- Reality-matching
- Response shift
- Abstraction of meaning
- Benefit finding

Research such as this could be adapted to examine new methods of psychological support for MND patients.

The review also commented on the tendency of depressed individuals to selectively attend to and recall negative information and disability related words. Thus, in the psychological support of individuals with MND the cognitive biases of those with depression should be accounted for. This is relevant for both the direct provider of psycho-supportive therapies (CBT, psychodynamic therapy etc) and the entire healthcare team. Health-messages can be tailored to avoid negative illness words so that recall of the overall message is not affected.

Psychological distress and mortality

Some studies have shown psychological distress to be associated with earlier death.^{175,176} However, a review by Chio et al comments that psychological distress could have been the consequence of more rapidly progressive disease¹⁷⁷, although McDonald et al claimed to control for length of illness, disease severity and age¹⁷⁵. Chio et al also warned that MND patients with florid FTD are known to have shorter survival time, and so psychological disorder could have been due to cognitive impairment, but this could not be distinguished in the studies, as they did not include 'rigorous' frontal lobe assessment.¹⁷⁷

If psychological distress is associated with earlier mortality in MND patients, then there is additional benefit to be gained from studies which explore psychological symptoms in MND aside from understanding the impact on QOL.

Limitations of this study

Limitations include the reduction in cohort size due to elimination of participants with missing data for any of the factors investigated. The validity of this model's findings relating to some of the demographic factors may rightly be questioned due to both the potential biases in the overall TONiC cohort, as well as the findings that the reduced cohort in this model had moderate differences from the original cohort, particularly with respect to marital status, employment status and onset type. Of the other factors examined, disease duration, WHODAS domain 4, and WHODAS domain 6 had greater than 10% missing data so there may be issues with these measures that could have affected the results of this model.

This model is by no means comprehensive and there may be many other factors whose relationships with depression are unappreciated in this model and which may have changed the significance of those factors examined here.

An issue arose with the forward building of the multiple linear regression model, as the results given in SPSS meant that the order of *p* values for the WHODAS 2.0 domains could not be determined. The *p* value was reported to 3 decimal places and as such was reported to equal less than .001 for all the domains. This meant that the order of entry was determined by F statistic.

Conclusion

In conclusion, this study has shown a significant association between disability and depression in MND with particular emphasis on 'participation in society', 'getting along with people' and 'understanding and communicating'. There may be merit in examining physical function separately to disability for any number of distinguishing reasons mentioned in the discussion. Demographic factors, and 'time from diagnosis' were found to be non-significant with respect to any association with depression, but there may be confounding factors to consider. With regards to 'time from diagnosis', an interaction with disability was considered but this was non-significant. The management of depression in MND patients is in accordance with general guidance for treating depression, but as specific research pertinent to MND becomes available this may be improved. Further research should investigate the temporal effects of various psychosocial factors.

Investigating Anxiety in Motor Neuron Disease

Introduction

The systematic review highlighted that anxiety has been the second most investigated factor with respect to QOL in MND. As with depression this is likely to be due to healthcare practitioners' familiarity with the concept as a psychiatric diagnosis, compared to some other less well defined psychosocial constructs, and the availability of validated measures for anxiety. Considering this, it is of interest to investigate the significance of some other factors and their relationship to anxiety.

Hope

Psychosocial factors such as hope are now more readily discussed by traditional medical specialities who care for people with chronic health conditions, both due to the increase in joint care with palliative services, as well as increased adoption of the biopsychosocial model of healthcare. The systematic review identified two papers which investigated hopelessness in relation to QOL in MND. A PubMed search (22/03/17) using the key words ("hope" OR "hopelessness" AND "Motor neuron disease") identified 50 studies. A lot of these studies were talking about hope in relation to a new intervention, but there were a number of studies which examined the role of hope in MND.

Hopelessness is classically associated with depression in the general psychiatric literature, but may be linked to other factors such as anxiety also. A PubMed search (22/03/17) using key words ("anxiety" AND "hope") identified 986 studies commenting on both of these factors in various illness groups. Narrowing this search to neurological illness (using the key words "neurology" OR "Neurological" AND "anxiety" AND "hope") identified 28 studies and narrowing the search to MND (using the key words "motor neuron disease" OR "MND" AND "anxiety" AND "hope") identified 7 studies. Of these seven studies, three focussed on dignity therapy, one was a review, one was investigating non-invasive ventilation, one investigated caregivers and another was looking at Tourette's syndrome. From this it can be said that it would add valuable data to the literature to examine the relationship between hope and anxiety in the TONiC MND cohort.

It may seem paradoxical that people could have hope in a disease such as MND. The limited treatment options and unrelenting progression could be considered a barrier to hope. Progressive weakness and symptom burden strips patients of their independence and leaves no prospect of true improvement of physical function. There is an increased awareness of MND research, particularly after the recent 'ice bucket challenge'¹⁷⁸⁻¹⁸⁰ but the results of disease modifying drug studies are thus far disappointing, so that, depending on an individual's optimism, this may not engender much hope.

However, this is a limited view of hope. A study examining "generalised hopes" in stroke patients by Soundy et al found three key "themes" of: social identity, meaningful activities and experiences, and relief from suffering.¹⁸¹ Fanos et al identified numerous hope "categories" used by MND patients including: 'hope for a cure', 'social support', 'search for information', 'spiritual beliefs', 'limiting the impact', 'adapting to changing capacities', 'living in the moment', and 'self-transcendence'.¹⁸² Understanding that hope is multifaceted demonstrates its potential importance as an area of study, and for consideration in clinical practice.

One study acknowledges that hope in MND patients may be experienced differently from other patient groups due to their certain knowledge of the disease's fatality from the point of diagnosis. In this paper meaning is mentioned again and hope is also considered to include "a peaceful acceptance of life, and its inexplicable beginnings and endings".¹⁸³ This links back to another paper by Soundy et al, who suggested hope can be expressed as either a paradox, a dichotomy or as transcendence.¹⁸⁴ The latter term would fit with other findings in MND with regards to meaning finding, positive reappraisal and response shift. Having no meaning in life has been found to predict hopelessness in MND, and this may be one of the ways in which meaning in life is associated with adjustment and associated outcomes such as mood.¹⁸⁵

Locus of control

Locus of control (LOC) is a way of describing to what extent individuals attribute situations in their life to be controlled by themselves or controlled by something other than themselves.¹⁸⁶ If an individual believes that circumstances are under their control then this is described as an internal locus of control, whereas, if they believe that circumstances are out of their control, this is described as an external locus of control. External locus of control can be broken into the belief that powerful others (e.g. doctors, teachers) control the individual's situation or that chance decides their fate; from this we get the two subscales of external locus of control: 'powerful others' and 'chance'. Individuals can have varying measures of each subscale of locus of control without necessarily identifying with one type of LOC entirely.

Due to MND's relentless disabling progression and lack of cure, it would be interesting to see how ratings of internal and external locus of control affect the level of anxiety experienced by patients. There is a large amount of literature examining the relationship between anxiety and locus of control¹⁸⁷⁻¹⁸⁹, but very few papers look at locus of control or perceived control in MND specifically¹⁹⁰⁻¹⁹³, and none appear to examine the relationship with anxiety.

The reality-matching hypothesis (AKA goodness-of-fit hypothesis) is a hypothesis relating to locus of control, which suggests that the best adjustment occurs when an individual's appraisal of a situation or disease's controllability matches closely with that situation or disease's actual controllability.¹⁹⁴ So if a situation is controllable by the individual then an internal locus of control will benefit them more than an external locus of control and for an uncontrollable situation an external locus of control will benefit them more than an internal locus of control.

Therefore, one could hypothesise that due to MND's uncontrollability a highly rated internal locus of control may be associated with negative outcomes such as mood. However, Matuz et al found the appraisal of emotion and problem-focused coping potential significantly predicted level of depression in MND patients and suggested from this that higher internal locus of control was associated with lower levels of depression.⁴⁹

Method

Aim: To investigate some factors' association with anxiety in this TONiC MND cohort.

Research questions:

1. Are lower levels of hope associated with anxiety in MND.
2. Is a more internal or external locus of control associated with more anxiety in MND.

Analysis

Initial plots did not suggest any non-linear relationships between the factors and anxiety, so multiple linear regression was chosen as an appropriate method.

Participants

The data set was modified such that participants who were missing data for any of the factors to be examined were excluded from all analysis. This ensured uniformity of the population between the initial single factor models.

Total participants: **n = 465**

No missing data for anxiety, hope or locus of control subscales: **n = 224**

Scales

- Anxiety was measured using the HADS-A subscale modified for use in MND as per the paper by Gibbons et al.¹¹⁹ The results of Rasch psychometric validation concluded that the HADS-A could be modified for use in the MND population by removing item A11 “I feel restless as if I have to be on the move”, combining A3 and A5 as a testlet and changing the cut-off points. The cut-offs were changed from ≥ 11 for ‘probable anxiety’, 8-10 for ‘possible anxiety’ and ≤ 7 for ‘no anxiety’ to ≥ 9 for ‘probable anxiety’, 7-8 for ‘possible anxiety’ and ≤ 6 for ‘no anxiety’. The reliability of the modified scale was stated as suitable for both clinical work and research.
- Hope was measured using the Herth Hope Index (HHI), which is a 12-item, abbreviated version of the Herth Hope Scale.¹⁹⁵ It is a multidimensional measure with three subscales: temporality and future, positive readiness and expectancy, and interconnectedness.
- Locus of control was measured using Form C of the Multidimensional Health Locus of Control (MHLC) scale. This 18-item scale is for measuring LOC in chronic health conditions and can be divided into its three subscales ‘internal’, ‘chance’ and ‘powerful others’.¹⁹⁶

Models

Single factor models were run for the following factors:

- Hope
- Internal locus of control
- Chance locus of control
- Powerful others locus of control

Results

Of the single factor models ‘hope’ was found to be significant ($R^2 = .235$, $F_{1,222} = 68.163$, $p < .001$) but none of the MHLC scales (internal, chance, others) were:

- Internal ($F_{1,222} = 2.390$, $p = .123$)
- Chance ($F_{1,222} = 3.022$, $p = .084$)
- Others ($F_{1,222} = 0.151$, $p = .698$)

Significant single factor models	Non-significant single factor models
Hope	Internal locus of control
	Chance locus of control
	Powerful others locus of control

Table 4.1 Table to show significant and non-significant single factor models.

The final model with hope explained 23.5% of variance in HADS-A scores.

The final model’s regression equation was as follows:

$\text{Anxiety (HADS-A modified)} = 12.893 - 0.326 * \text{HHI}$
--

Discussion

Findings

Hope was found to be a significant single factor model, demonstrating its importance with respect to anxiety and supporting its wider relevance as a psychosocial factor. Hope alone explained 23.5% of the variance in anxiety scores.

None of the locus of control subscales were found to have a statistically significant association with anxiety and possible reasons for this are discussed below.

Hope

The role of hope is often discussed in relation to depression, and has been associated with suicidal ideation¹⁹⁷ and desire for assisted death in MND^{34,198}. Averill et al suggested that hopelessness and end-of-life concerns are more common than clinically significant depression in MND patients, and emphasise the importance of assessing a wider range of psychosocial factors, other than just depression.¹⁹⁹

One might suppose that hope would decrease as a MND patient's body deteriorates more and more, as they lose strength and start to find breathing more difficult. However, Fanos et al found no significant relationships between hope and forced vital capacity or between hope and individual as well as total ALSFRS-R scores.¹⁸² This could suggest that physical decline has a minor, if any, role to play in hope compared to other psychosocial factors. In a large group of adolescents, it was found that hope's beneficial relation to anxiety (as well as depression, subjective happiness, and interpersonal difficulties) was mediated by attention to positive information.²⁰⁰ The authors suggested that this highlights both the importance of a hopeful thinking style, and attention to positive information, in the mental health of adolescents. It would be interesting to see whether similar associations could be found in patients with MND.

Hope being significantly associated with anxiety is in accordance with other findings in adult mental health patients. Two measures of hope and one of hopelessness were found to significantly correlate with both state and trait anxiety, ranging from -.44 to -.67.²⁰¹

One study found that there was a significant interaction between loneliness and hope when predicting anxiety. The interaction was stronger for individuals with low hope compared to those with high hope.²⁰² This highlights another way in which social factors may affect mood or psychological distress.

Soundy et al's suggestion that hope can be expressed as either a paradox, a dichotomy or as transcendence may go some way to explaining its effect on anxiety in MND.¹⁸⁴ Transcendence based coping mechanisms such as meaning finding and biographical repair were found in narrative studies to be beneficial for MND patients, as a way of maintaining QOL and mental well-being.^{28,30}

Definition of hope

Studies must take care to be clear how they define hope. Hope can have a broad definition with many aspects to consider. A large survey of the general population found that ‘a religious sense of hope, but not a general sense of hope, reduces feelings of death anxiety across successively older age-groups’.²⁰³ Thus, it must be clear which aspects of hope are being considered, in which studies, to avoid overstating conclusions. Some earlier scales considered hope within the narrow conceptualisation of “an expectation of goal achievement” which is evidently inadequate.

Qualitative work meant that later scales aimed to incorporate themes such as “the interpersonal element, the time-oriented, future focus of hope, and the goal-achievement expectation of hope”.¹⁹⁵ Even further qualitative work meant that the Herth Hope Scale was based on Dufault and Martocchio’s²⁰⁴ model of hope in order to include elements of hope not included in the previous multidimensional measures such as “(a) a more global, non-time-oriented sense of hope, (b) hope despite diminished or absent interpersonal relationships, (c) hope as a sense of 'being' available and engaging in relationships, as opposed to 'doing' for oneself and others, and (d) potential of hope for controlling behavioural or emotional responses as opposed to the control of events or experiences”.¹⁹⁵

Intervention for hopelessness

Ganzini et al found that, in a population of MND patients, whilst hopelessness is a prevalent feature in depression, not all those who are hopeless are depressed.²⁰⁵ They suggested that, in the non-depressed group, it may be more appropriate to provide nonpharmacological interventions such as cognitive therapies, to reduce hopelessness, pessimism and any other form of existential despair. They suggested helping the patient to find meaning in the future, to reduce their fears and to avoid focusing on the worst possible outcomes. The idea of meaning finding being used to soothe existential worries again links to the theme of transcendence.

Intervention for anxiety using hope

The use of hope as an intervention was tested in a group of renal failure patients undergoing haemodialysis. The results showed that ‘hope therapy’ reduced depression and anxiety.²⁰⁶

Another study examined using a hope-based intervention for patients undergoing genetic tests for hereditary colorectal cancer. Paired *t*-tests demonstrated a significant increase in hope post intervention, and a significant decrease in anxiety.²⁰⁷

Locus of Control

A key theme of the reality-matching hypothesis (AKA goodness-of-fit hypothesis) is that of controllability and the appraisal of controllability. This is of interest in MND as its progression is not truly controllable (despite riluzole's moderate effect), and the management of symptoms is similarly unwieldy.

Affleck et al examined a cohort of rheumatoid arthritis sufferers and found that, in patients with moderate and severe disease, perceiving personal control over symptoms was associated with a more positive mood state, but that, in severe disease, perceiving personal control over the disease course was negatively associated with mood.²⁰⁸ This illustrates that a distinction must be drawn between control over symptoms and control over disease course, as these have different levels of controllability, and so perceived control has a different impact depending on which is considered, as per the goodness of fit hypothesis. The second consideration is that illness severity has an impact on the effect of perceiving personal control.

This suggests that the study method used to examine locus of control in this MND cohort was too simplistic, as a relationship with anxiety was searched for without determining illness severity, and without making a distinction between symptoms and overall disease course.

There may also be a substantial difference from the above study, in that rheumatoid arthritis is a chronic disease, as opposed to the inevitably fatal nature of MND.

Multiple sclerosis (MS) is like MND in that treatment (and therefore controllability) is limited, but MS is complicated by its unpredictability, that results in a range from benign to severely disabling MS. It is also not inevitably fatal, as is seen with MND. This notwithstanding, research has found that low levels of controllability in MS moderate the effects of optimism on mood. There is also the suggestion that disability moderates the effect of locus of control on QOL: for less disabled patients, a highly rated internal LOC was beneficial, but in severely disabled patients greater internal LOC was associated with poorer QOL.²⁰⁹ This further supports the consideration of additional factors when examining the effects of LOC, in this case disability.

In their paper on HIV-positive men, Park et al mention earlier work suggesting styles of coping to be a significant co-variable, when assessing controllability and how appraisal of controllability affects adjustment.²¹⁰ They mention that in general, problem-focused coping has been associated with better adjustment than emotion-focused coping, however they point out that better adjustment can be seen with problem-focused coping when faced with *controllable* situations, and better adjustment can be seen with emotion-focused coping in *uncontrollable* situations. Some studies mentioned by Park et al support the first statement but not the latter leading to the suggestion that “coping may be related to adjustment exclusively in controllable situations.” Park et al did in fact find that emotion-focused coping was more useful in situations appraised to be less controllable when compared to emotion-focused coping in controllable situations and so supported both suggestions. They attempt to explain the difference in their findings compared to others, by pointing out the differences in how emotion-focused coping is operationalised – in their case using ‘distancing’, a more neutral term than ‘self-denigration’ or ‘escapism’ as used by other studies. A paper examining coping in MND found that patients rated both emotion-focused and problem-focused coping highly, but that they dealt better with the situation by utilising emotion-focused coping.⁴⁹

Park et al did clearly find support for problem-focused coping being beneficial in controllable situations, but, more relevant to MND, also found that meaning-focused coping (in the form of transcendence) was inversely related to depressed mood *regardless of controllability*.²¹⁰

Future work on LOC in MND should examine the relative use of problem, emotion and meaning-focused coping as part of the analysis.

Some criticism of the MHLC scales is the generality of the scales and the argument that patients may feel that they have different levels of control for different aspects of their disease.²⁰⁹ This is mentioned earlier in terms of the distinction between control over symptoms and control over disease course, but there may also be significant differences in controllability and perceived control between different symptoms, for example between pain and communication. Without asking separately about these specific aspects, the scale may not be nuanced enough, but it should also be noted that some symptoms are disease specific, such that to be comprehensive would require modified scales for each disease. This may not be feasible and so a balance must be struck between generality for applicability’s sake and specificity for accuracy’s sake.

This may go some way to explaining why self-efficacy is considered by some to be a better construct for explaining behavioural differences, as there are not as many distinctions to make, so that its generality is an advantage. The other point made by Luszczynska and Schwarzer is that MHLC is simply an attribution of responsibility, whereas self-efficacy is of prospective and operative nature.²⁰⁹

There may be additional benefit (when examining LOC) in looking at combinations of the three subscores, as well as considering them separately. A paper on diabetes found that 2 combinations, 'pure internal' (high internal score, low powerful others score and low chance score) and 'believers in control' (high internal score, high powerful others score and low chance score), had lower HbA1c values, postulated to be due to better adherence to self-care, than all other combinations of control beliefs.²¹¹ This is of interest because it appears that high 'internal' score may have had a permissive effect on whether a high 'powerful others' score had a significant effect. This makes sense in this example as it related to a *self-care* regime, so an individual who believed it was in *their* control to adhere to their doctor's advice will do better than one who believes that their doctor has control over the disease but they do not. Again, in MND, specific symptoms and treatments would likely need to be considered separately, as some will be purely healthcare administered (e.g. botox injections for spasticity) and others will require input from the patient (e.g. managing a percutaneous endoscopic gastrostomy and diet). Management of MND is complicated and sometimes unreliable, and repeated treatment failures or difficulties may result in a loss of confidence in healthcare professionals' and patients' own ability to control their illness. This may then have further effects on ability to hope, optimism, mood and QOL.

Ultimately all of the above should be taken into consideration when investigating locus of control in MND, but, due to time constraints and lack of skill, the methodology of this study was not able to be revised.

Prevalence

In this TONiC data (n=450) 'probable' anxiety as per the modified cut-offs was 13.5%. When scored in the non-modified HADS-A 'probable' anxiety was 13.8%.

Limitations

Limitations include the reduction in cohort size due to elimination of participants with missing data for any of the factors investigated. Pertaining to this, the greatest number of missing data were from the Herth Hope Index, which, at nearly half of the original cohort, is likely to have had an effect on the results of this model. This may be due to difficulties with the scale itself – requiring a different, or at least modified, scale – or with the concept – requiring qualitative work to examine the issues around this and identify how this could be addressed. The three LOC subscales each had greater than 5% missing data and it seems evident that consideration of other factors alongside LOC would be required to examine this factor properly.

The reduced cohort had greater than 10% differences from the original cohort in terms of ‘time from diagnosis’, onset type and employment status and it is possible that these could have had effects on participants’ experiences of either hope or LOC and so these may require further investigation before the results of this model can be fully interpreted.

Conclusion

This study lends support to hope being an important factor in patient’s experience of MND. Future research should consider further associations alongside transcendent coping mechanisms, such as meaning finding and reappraisal. LOC is worth further investigation, since this analysis did not consider other significant factors such as level of disability and coping styles. If these were considered this could result in subscales of locus of control having a significant relationship with anxiety.

Investigating Social Withdrawal in Motor Neuron Disease

Introduction

Importance of social factors and why?

Social factors were found to be linked to GQOL in the systematic review. Social support was the third most examined factor in quantitative studies, with five quantitative studies, and social withdrawal and social isolation added three studies between them. In particular, Chio et al's study found that, of the variables they measured, the most important explicatory variable for both the SEIQOL-DW and the MQOL was social support.²⁰ Qualitative studies showed MND patient's perspective changed such that "family and friends" drove patient's meaning in life²⁸, "family/significant other... friends... social life" affected their QOL¹⁶, and "the vital importance of interpersonal relationships" was a key theme in coping²⁹.

Investigating the domains of QOL would be of interest as it may be felt that social factors will have a strong relationship with the 'social relationships' domain and perhaps 'psychological health', but how it relates to 'physical health', and 'environment and financial resources' is less certain.

One question might be whether social factors are so important in part due to the nature of MND. As the disease progressively reduces a person's independence by reducing their physical strength, and isolates them by reducing their mobility and ability to communicate, is it better to share their burden and draw support from others rather than struggle and ultimately fail to be independent? Brownlee et al suggest that problems with adjustment may arise when a patient's self-representation, for example as an independent person, conflicts with the disease-representation, for example as severely disabling.²¹² They suggest that patients may create propositional rules (if...then...), such as "if I do not ask for help, then I am still independent", but that these rules can lead to maladjustment, when the reality of the scenario does not allow for the rules to be followed without detriment to the patient's life.

Because of a possible link with mobility, communication and independence, it will be of relevance to investigate the relationship of social withdrawal to ALSFRS-R domains. It is of particular interest as to whether increasing severity of bulbar and respiratory symptoms is associated with greater social withdrawal.

For the above reasons, this thesis will examine social withdrawal in more detail.

Methods

Aim: To investigate Social withdrawal in this TONiC MND cohort.

Research questions:

1. What is the relationship between social withdrawal and the four domains of QOL as measured by the WHOQOL-BREF?
2. Is Social withdrawal significantly associated with severity of ALSFRS-R domains?

Analysis

Initial plots did not suggest any non-linear relationships between the factors and social withdrawal, so multiple linear regression was chosen as an appropriate method. Single factor models were run initially, and then two multifactor models were created to investigate QOL domains and ALSFRS-R domains separately.

Participants

The data set was modified to produce two data sets such that for each multifactor model participants who are missing data for any of the factors to be examined were excluded from analysis for that multifactor model (WHOQOL-BREF domains model or ALSFRS-R domains model). This ensured uniformity of the population between the initial single factor models.

Total participants: **n = 465**

No missing data for social withdrawal and QOL domains: **n = 417**

No missing data for social withdrawal and ALSFRS domains: **n = 429**

Scales

- The WHOQOL-BREF is a 26-item short version of the original WHOQOL scale, which measures four domains of QOL: 'physical health', 'psychological health', 'social relationships', and 'environment and financial resources'.²¹³

- The ALSFRS-R is a revised version of the ALSFRS, a tool for evaluating functional status. It has 12-items that make up three domains: 'motor function', 'bulbar function' and 'respiratory function'. These three domains will be used for analysis rather than a summed score for a number of reasons: By examining the domains, more information will be available about which domains may relate to social withdrawal and their relative importance when compared to each other, allowing for a determination of whether, for example, the severity of motor symptoms has a stronger association than the severity of respiratory symptoms. Additionally, it has been shown that the summed score of the ALSFRS-R does not stand up to rigorous psychometric testing as it is not unidimensional and so is not comparable between individuals with the same overall score.²¹⁴

- Social withdrawal was measured using the 14-item MND-SWS modified for use in MND as per the paper by Gibbons et al.¹²⁰

Models

Single factor models were run for the following factors:

- Physical health domain of WHOQOL-BREF
- Psychological health domain of WHOQOL-BREF
- Social relationships domain of WHOQOL-BREF
- Environment and financial resources domain of WHOQOL-BREF
- Physical health domain of ALSFRS-R
- Psychological health domain of ALSFRS-R
- Social relationships domain of ALSFRS-R
- Environment domain of ALSFRS-R

Results

QOL analysis

All single factor models were significant.

- Physical health ($F_{1,415} = 174.110, p < .001$)
- Psychological health ($F_{1,415} = 95.221, p < .001$)
- Social relationships ($F_{1,415} = 50.589, p < .001$)
- Environment ($F_{1,415} = 100.332, p < .001$)

The final model included the 'physical health' and 'environment' domains. The interaction term was not significant. The final model explained 31.1% of the variance in social withdrawal scores.

$R^2 = .311$ ($F_{2,414} = 93.600, p < .001$)

The final model's regression equation was as follows:

$$\text{MND-SWS} = 66.446 - 1.612 * \text{physical health} - 0.742 * \text{environment}$$

ALSFERS-R analysis

All single factor models were significant.

- Bulbar ($F_{1,427} = 12.144, p = .001$)
- Respiratory ($F_{1,427} = 23.379, p < .001$)
- Motor ($F_{1,427} = 96.759, p < .001$)

All factors were initially significant in the multifactor model but examination and removal of extreme cook's distances ($\text{NOT}(\text{COO}_1 > 0.08000)$) resulted in 'motor' and 'bulbar' being the significant factors of the final model. The addition of the interaction factor motor*bulbar was not significant. The final model explained 30.7% of the variance in social withdrawal scores.

$R^2 = .307$ ($F_{2,423} = 93.744, p < .001$)

The final model's regression equation was as follows:

$$\text{MND-SWS} = 50.459 - 0.957 * \text{motor domain} - 0.339 * \text{bulbar domain}$$

Discussion

Quality of life

With regards to QOL domains, all single factor models were significant, suggesting that social withdrawal has a wider ranging relationship with QOL than just with social relationships and psychological health. When considered in the multi-factor model, the most parsimonious model included 'physical health' and 'environment and financial resources', which suggested that these were the most important domains of QOL with respect to social withdrawal and that together they explained 31.1% of the variance in social withdrawal scores. The order of importance of these domains as determined by their standardized coefficients was 'physical health', and then 'environment' with coefficients of -0.442, -0.162 respectively.

The analysis revealed that the four cases with the highest levels of social withdrawal did not follow the given trend for any of the QOL domains. These cases were not excluded, as to do so would falsely represent social withdrawal in this MND cohort. It is however likely that some additional factor may explain these outliers, and this could be the focus of future research.

It is of note that 'psychological health' was of borderline significance. Considering the WHOQOL group's comments in their psychometric paper using the general population that there was some cross-domain overlap between items in 'physical health' and 'psychological health'²¹⁵, it could be that this overlap was greater in our MND population, and that 'physical health' absorbed the explanatory power of 'psychological health', to the point of 'psychological health' not having a significant unique contribution.

It may be considered surprising that the weakest relationship is between social withdrawal and the QOL domain 'social relationships'. However, the domain 'social relationships' encompasses a wide range of social factors including satisfaction with personal relationships, satisfaction with sex life, and satisfaction with support, whereas the 'social withdrawal' scale focusses on the ability to undertake and participate in social activities, as well as how being with others makes someone feel. Thus, the two measures are exploring different aspects of social relatedness. This may have contributed to the finding in this study that 'social relationships' had the most missing data out of the QOL domains, as a wider range of factors may have made it more difficult to answer all questions, especially considering attitudes to intimate questions around sex life.

In addition, the QOL domain 'social relationships' may be less reliable than other domains such as 'physical health' or 'environment and financial resources'. In the psychometric analysis done by the WHOQOL group using a general population, it was found in 19 out of the 23 regions surveyed to have the lowest internal consistency of the four domains.²¹⁵ When considering their total sample from all regions they reported Cronbach's alpha for 'social relationships' to be 0.68 compared to 0.82, 0.81 and 0.80 for 'physical health', 'psychological health' and 'environment and financial resources' respectively. The WHOQOL group described these findings as expected due to the low number of questions in the 'social relationships' domain, to which Cronbach's alpha is sensitive.

ALSFERS-R

With regards to ALSFRS-R, all single factor models were significant demonstrating a link between physical function and social withdrawal. The most parsimonious multifactor model included the 'motor' domain and 'bulbar' domain, suggesting these to be the most important ALSFRS-R domains when considering social withdrawal. The order of importance for ALSFRS-R domains was motor and then bulbar, as demonstrated by their standardized coefficients, -0.535 and -0.113 respectively. These two domains explained 30.7% of the variance in social withdrawal scores.

The association between motor and bulbar impairment and social withdrawal may be due to psychological distress occurring alongside declining physical function, but may also be to do with how these impairments impede participation in social situations. Declining motor function limiting mobility can impair an individual's ability to leave their house and engage with others, especially without assistance or aids. Worsening bulbar disease can greatly limit communication without aids, as well as drooling and fear of choking possibly affecting patient's decisions to engage in social activities such as eating in public.

Increasing use of social media is an interesting factor that may have increasing relevance with regard to this, allowing easier contact with friends and loved ones.⁹⁸ This contact can be made from afar, bypassing impaired mobility to some degree, although some may question to what degree online interactions can replace face-to-face interactions.

Social support is lauded in the literature but may not always be a good thing in and of itself, it may depend on context. Goldstein et al found that negative social support including negative interactions (as measured using the close persons questionnaire) predicted depression.⁸² Context is also emphasised as important when considering Carver and Scheier's theory of 'scaling back goals' which involves shifting priorities.²¹⁶ It was suggested that neither 'scaling back goals' nor response shift were helpful, if focus was directed at areas of their life that were in fact negative or unhelpful. An example being that emphasis on family would be helpful if the individual's family was considered loving and warm, but that the same emphasis would be counterproductive when there was conflict in the family.

Other factors and future research

In Gibbons et al's paper, fatigue and coping were seen to have significant effects on social withdrawal.²³ Fatigue, as suggested for motor and bulbar symptoms, may exert an effect both psychologically and physically. It may decrease the *desire* to interact with others as well as limit the *ability* to interact with others. Care should be taken with assuming the direction of effect, especially with the measures of physical function, as a paper by Scharloo et al found seeking social support to predict better functioning in patients with psoriasis.²¹⁷ The outcome measure used was however a measure of disability, so would not necessarily have discriminated between the impact of social support on the psychological burden of the illness and the purely physical.

As this study evidences an association between social withdrawal and these symptoms, but via multiple possible mechanisms, it will be important to undertake qualitative studies such as semi-structured interviews to better understand patient's perspectives.

Another link between coping and social withdrawal was found in Hugel et al's paper, which used structured interviews for physicians to independently assess whether they considered patients to be 'copers' or 'non-copers'.²¹⁸ Inter-rater agreement was excellent and 'non-copers' also had significantly lower scores on a self-completed coping scale. In the study, they found that 'Non-copers' were significantly younger, had limb onset of disease, had significantly higher depression and anxiety scores and had significantly higher levels of social withdrawal at time point 1. This finding at time point 1 (T1) may indicate the increased importance of social factors early in the disease course as part of the initial adjustment to the diagnosis, and the importance of identifying these factors early in order to intervene and facilitate adjustment. The study also supports healthcare practitioners to have confidence in their ability to identify those individuals who are struggling to come to terms with their illness, and who may need additional support.

Limitations

Limitations include the reduction in cohort size due to elimination of participants with missing data for any of the factors investigated. In the QOL model, social relationships had greater than 10% missing data. This, in combination with the possible issues with reliability discussed above, may have affected the result of this model. Also in the QOL model, there were greater than 10% differences from the original cohort with respect to marital status and employment status, both factors which could have had an effect on patients' experience of social withdrawal, their rating of social relationships, their rating of their psychological health, or their rating of their 'environment and financial resources'.

Conclusion

The regression analysis reveals a significant relationship between social withdrawal and the four WHOQOL-BREF domains, notably with 'physical health', and 'environment and financial resources'.

Social withdrawal also has a significant relationship with disease severity as demonstrated by significant single factor models for each of the domains 'motor', 'bulbar' and respiratory'. The multifactor model demonstrated the strongest associations with the 'motor' and 'bulbar' domains with multiple possible mechanisms for both of these factors being related to social withdrawal. Qualitative interviews could be used in a future investigation, to understand how social interaction is limited by the psychological and physical impact of increasing motor and bulbar symptom severity.

Investigating Global Quality of Life in Motor Neuron Disease

Introduction

Having examined depression, anxiety, and social withdrawal in more detail, it is worth re-examining the findings of the systematic review for these factors, before evaluating their relationships with GQOL in this TONiC cohort.

The systematic review identified 18 studies, which examined whether there is an association between depression and QOL. Some of these studies used multiple measures of depression and QOL, and so, in total, an association between depression and QOL has been examined 58 times. Depression had a significant negative correlation with QOL 37 times and was non-significant 21 times. The studies used different methodologies, and some had low sample numbers, but overall indicate that there is a likely negative correlation between depression and QOL. For studies with participant numbers of 40 or under, table 1.0 shows their conflicting results.

Study	n	Depression correlated with QOL	Depression scale(s)	QOL scale(s)
Clarke et al - Assessing individual quality of life in amyotrophic lateral sclerosis. ³⁸	21	No	HADS	SEIQOL

Goldstein, Atkins, and Leigh - Correlates of Quality of Life in people with motor neuron disease (MND). ⁴³	31	No	HADS	SEIQOL-DW
Lou et al - Fatigue and depression are associated with poor quality of life in ALS. ⁴⁷	25	Yes	CES-D	Psych wellbeing MQOL
Lule et al - Depression and quality of life in patients with amyotrophic lateral sclerosis. ⁴⁸	T1=39 T2=30	Yes	ADI-12	SEIQOL-DW
Pizzimenti, Aragona, and Onesti - Depression, pain and quality of life in patients with amyotrophic lateral sclerosis: A cross-sectional study. ⁵⁷	36	Yes	Zung self rating dep scale	Spitzer QOL index
Tramonti et al - Quality of life of patients with amyotrophic lateral sclerosis. ⁶²	40	Yes	ZDS	Subscales of SF-36
		No	ZDS	SEIQOL

Winter et al - Health-related quality of life in ALS, myasthenia gravis and facioscapulohumeral muscular dystrophy. ⁶⁴	37	Yes	depression/anxiety domain of EQ-5D	SF-36 Mental component scale, EQ-VAS
		No	depression/anxiety domain of EQ-5D	EQ-5D

Table 6.1 Table to show the results of studies examining depression with participant numbers of 40 or under.

Of studies with over 100 participants, the two studies reporting definite associations were the largest (n = 964) and third largest (n = 147). McCabe et al also reported a definite yes but at a p-value of $p = .08$ which would be considered by some to be non-significant or borderline. The second largest study, by Koerner et al, found mixed results when comparing the BDI, with and without somatic items, to subscales of the SF-36. BDI correlated with all domains except the 'physical functioning' subscale and the BDI with somatic items removed correlated with 'general health', 'vitality', 'social functioning', 'emotional role', and 'mental health' subscales but not with 'physical functioning', 'physical role', or 'bodily pain'. The study reporting a non-significant association was limited by its use of a 6-point scale for QOL. The sample size of the TONiC study is the second largest when compared to the studies identified in the systematic review but it is worth considering that the only study with a larger cohort used the EQ-5D, a HRQOL measure.

Study	n	Depression correlated with QOL	Depression scale(s)	QOL scale(s)
Ganzini, Johnston, and Hoffman - Correlates of suffering in amyotrophic lateral sclerosis. ⁴²	100	No	DSM-IV	6-point scale

Gibbons et al - The impact of fatigue and psychosocial variables on quality of life for patients with motor neuron disease. ²³	147	Yes	HADS-MND	WHOQOL-BREF
Koerner et al - Interaction of physical function, quality of life and depression in Amyotrophic lateral sclerosis: characterization of a large patient cohort. ⁴⁶	159	Mixed	BDI	Subscales of SF-36
		Mixed	BDI without somatic components	Subscales of SF-36
McCabe, Firth, and O'Connor - Mood and quality of life among people with progressive neurological illnesses. ⁵¹	120	Yes (but $p = .08$)	POMS-SF	WHOQOL-BREF
Thakore et al - Depression in ALS in a large self-reporting cohort. ⁶⁰	964	Yes	PHQ-9	EQ5D, EQ5D-VAS

Table 6.2 Table to show the results of studies examining depression with participant numbers of 100 or over.

Of the thirteen studies examining depression that used GQOL measures, nine studies reported significant associations, three reported no significant associations and one study, using three QOL measures, reported mixed results. Interestingly the three studies reporting no association were using the SEIQOL and SEIQOL-DW as their measures of QOL. The SEIQOL has been described as limited in evaluating the QOL of groups and has been posited to measure a construct other than QOL.⁶⁹

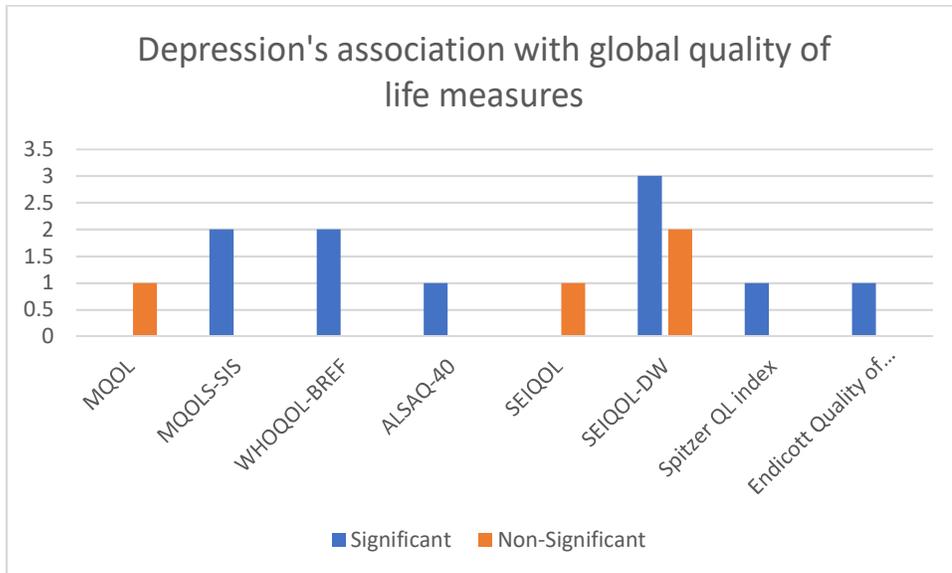


Figure 6.1 Chart to show depression's association with GQOL measures.

The systematic review identified seven studies which looked at the association between anxiety and QOL. Again, studies used different and sometimes multiple measures of anxiety and QOL. Five times there was a significant negative association and thirteen times the association was non-significant. Eleven out of thirteen of the non-significant results for anxiety were obtained when subscales of the SF-36 (HRQOL measure) were used. The five significant associations were found with WHOQOL-BREF, SEIQOL-DW, Endicott Quality of Life Enjoyment and Satisfaction Questionnaire, MQOL and the mental component score of the SF-12. The former four demonstrate anxiety's association with GQOL and the latter is a mental health HRQOL measure. Significantly, when considering only GQOL measures, the ratio of significant to non-significant associations is 4:2. The anxiety measures for the studies with significant results were the POMS-SF, HADS and STAI, the measure for the studies with non-significant results was the HADS. Thus, studies using HADS-A have reported conflicting results for HADS' relationship with GQOL, this may be explained to some degree by the sample sizes. The two studies with non-significant results had the smallest sample sizes at 26 and 31 compared to 120, 75, 50 and 49.

Study	n	Anxiety correlated with GQOL	Anxiety scale(s)	QOL scale(s)
Clarke et al - Assessing individual quality of life in amyotrophic lateral sclerosis. ³⁸	26	No	HADS	SEIQOL-Index
Goldstein, Atkins, and Leigh - Correlates of Quality of Life in people with motor neuron disease (MND). ⁴³	31	No	HADS	SEIQOL-DW

Rabkin, Wagner, and Del Bene - Resilience and distress among amyotrophic lateral sclerosis patients and caregivers. ⁵⁸	49	Yes	STAI	Endicott Quality of Life Enjoyment and Satisfaction Questionnaire
O'Doherty et al - Measuring life quality, physical function and psychological well-being in neurological illness. ⁵⁴	50	Yes	HADS	SEIQOL-DW, MCS SF-12
Peric et al – Health-related quality of life in patients with myotonic dystrophy type 1 and amyotrophic lateral sclerosis. ⁵⁶	74	No	Hamilton anxiety score	Subscales of SF-36
Vignola et al - Anxiety undermines quality of life in ALS patients and caregivers. ⁶³	75	Yes	STAI	MQOL

McCabe, Firth, and O'Connor - Mood and quality of life among people with progressive neurological illnesses. ⁵¹	120	Yes	POMS-SF	WHOQOL-BREF
--	-----	-----	---------	-------------

Table 6.3 Table to show the results of studies comparing anxiety and QOL in order of increasing participant numbers.

Of the previous studies investigating anxiety, the greatest sample size was 120 participants; this study will examine this relationship using a sample size of 409. Investigating the impact of anxiety on a GQOL measure in a cohort of this size will add valuable data to the literature.

Two studies examining the relationship between social withdrawal and QOL in MND were identified in the systematic review. Twice a significant correlation was found and two times the correlation was non-significant. All of the QOL measures were GQOL measures. Chio et al's study examined three different GQOL scales and only found a significant association with the MQOL-SIS, which may be seen as discouraging when considering that the MQOL-SIS was the least nuanced of the GQOL measures. As Simmons suggests, single question evaluations of QOL may not "provide the patient with a platform by which to perform a structured, item-by-item analysis of their QOL".¹⁶ Of the related social factors support and isolation, support had six significant results and one non-significant result and isolation had one non-significant result. The term social isolation may be interchangeable with social withdrawal, but no formal definitions are given, and use of either term seems to be determined only by which measurement scale is used. For example, in the case of the 'Nottingham Health Profile – Part 1' (NHP-1) or the 'Close Persons Questionnaire', the term 'social isolation' is used and in the case of the 'social withdrawal scale' or 'MND – social withdrawal scale', social withdrawal is of course used. Although there appears to be no distinction, it is important that future researchers define what they are measuring clearly.

Study	n	Social Withdrawal correlated with GQOL	Social Withdrawal scale(s)	QOL scale(s)
Gibbons et al - The impact of fatigue and psychosocial variables on quality of life for patients with motor neuron disease. ²³	147	Yes	SWS-MND	WHOQOL-BREF
Chio et al - A cross sectional study on determinants of quality of life in ALS. ²⁰	80	No	SWS-MND	SEIQOL-DW
		No	SWS-MND	MQOL
		Yes	SWS-MND	MQOL-SIS

Table 6.4 Table to show the results of studies comparing social withdrawal and QOL.

The role of social factors in QOL is complex and not fully-understood but qualitative studies suggest that it is a promising avenue for research.

Method

Aim: To investigate the association between the three factors depression, anxiety and social withdrawal and GQOL in this TONiC MND cohort.

Research questions:

1. Does depression have a significant association with GQOL?
2. Does anxiety have a significant association with GQOL?
3. Does social withdrawal have a significant association with GQOL?

Analysis

Initial plots did not suggest any non-linear relationships between the factors and WHOQOL-BREF, so multiple linear regression was chosen as an appropriate method.

Participants

The data set was modified, such that participants who were missing data for any of the factors to be examined were excluded from all analysis. This ensures uniformity of the population between the initial single factor models.

Total number of MND participants: **n = 465**

No missing data for Overall QOL, depression, anxiety and social withdrawal: **n = 409**

Scales

- GQOL was measured using the total score for WHOQOL-BREF 2.0 calculated as described in the WHOQOL 2.0 handbook to be comparable to the WHOQOL-100.²¹³
- Depression was measured using the HADS-D subscale modified for use in MND as per the paper by Gibbons et al.¹¹⁹
- Anxiety was measured using the HADS-A subscale modified for use in MND as per the paper by Gibbons et al.¹¹⁹
- Social withdrawal was measured using the MND Social withdrawal scale (MND-SWS) as per the paper by Gibbons et al.¹²⁰

Models

Single factor models were run for the following factors:

- Depression
- Anxiety
- Social withdrawal

Results

All single factor models were statistically significant when compared to the null model (all $p <$

Depression	$(F_{1,407} = 132.557, p < .001)$
Anxiety	$(F_{1,407} = 146.632, p < .001)$
Social withdrawal	$(F_{1,407} = 158.561, p < .001)$

.001).

A final model including the three factors and an interaction term was significant ($F_{4,404} = 157.090, p < .001$). The interaction term was between anxiety and social withdrawal, which suggests that the effects of anxiety and social withdrawal on QOL do not only depend on their respective coefficients but also on each other and the interaction coefficient. Interaction terms between 'depression and anxiety', and 'depression and social withdrawal' were not significant. The final model accounted for 60.9% of the variance in WHOQOL 2.0 scores as shown by an R^2 of 0.609.

The final model's regression equation was as follows:

$$\text{WHOQOL-BREF} = 76.672 - 1.895 * \text{HADSDmod} - 0.936 * \text{HADSAmod} - 0.335 * \text{SWS} + 0.020 * (\text{HADSA} * \text{SWS})$$

The interaction term was analysed graphically, as described in chapter two, by plotting social withdrawal against QOL, but with the data points for social withdrawal grouped by levels of anxiety.

The findings indicated that greater anxiety at a set level of social withdrawal resulted in lower QOL but with this difference diminishing as social withdrawal increased. There was an intercept within the range of the TONiC data where, at a high level of social withdrawal, individuals with 'non-case' level anxiety have worse predicted QOL compared to 'possible' anxiety. The interaction is commented on further in the discussion below.

Discussion

Significant factors

These results show that for the TONIC cohort of the MND population, depression, anxiety, and social withdrawal are all statistically significant factors that combine to strongly influence a patient's QOL.

This was shown by the single factor models (all $p < .001$) but also the final combined model which showed each factor having a unique contribution when considered alongside each other and with the final model explaining 60.9% of the variance in QOL scores.

Each factor's unique contribution meant that for example, even when a proportion of the variance in QOL has been explained by depression and social withdrawal, the addition of anxiety increases the explanatory power of the model with a significant change in the F statistic. The three factors' order of importance, as determined by their standardised coefficients, was depression (-.554), followed by social withdrawal (-.408), followed by anxiety (-.359).

Strengths of this study

The use of measures which had undergone Rasch validation provided the benefit of robust interval scales for the independent variables. A large sample population meant that multiple factors could be entered into the regression model and be adequately powered, thus lowering the chances of noise (in the form of high standard deviation - σ), obscuring the relationship between variables and producing false negative results.

In future, a comprehensive model considering all biopsychosocial factors and explaining close to all the variance in QOL scores may never be possible or even desirable. However, studies such as this may have separate merit by increasing awareness of factors and their relative contribution to QOL in MND, therefore influencing the thinking around MND and MND patient management.

Generalizability

This study supports the importance of these three factors in the United Kingdom MND population but further research may be required to confirm or deny the generalisability of these results to the global MND population, especially considering the impact cultural variation can have on certain psychosocial factors.²¹⁹ This notwithstanding, it could be considered surprising for these three factors not to have an effect on QOL in other countries and cultures as they are ubiquitous and consistently carry negative connotations in terms of their effects.

Interaction between anxiety and social withdrawal

Analysis of the interaction between social withdrawal and anxiety was done graphically by comparing regression lines for groupings of anxiety on a plot of social withdrawal versus QOL. This was first done by grouping anxiety as three equal sized groups and then repeated using the modified cut-off points as suggested by Gibbons et al¹¹⁹. It was deemed as part of the analysis that the cases with the 4 highest values for social withdrawal were exerting undue effect on the gradient of the regression lines and the differences are demonstrated in the 'equal groups' analysis (figure 6.2 compared to figure 6.3) as well as the 'modified cut-offs' analysis (figure 6.4 compared to figure 6.5). The following discussion comments on the analyses in which those values were excluded (figures 6.3 and 6.5).

'Equal groups'

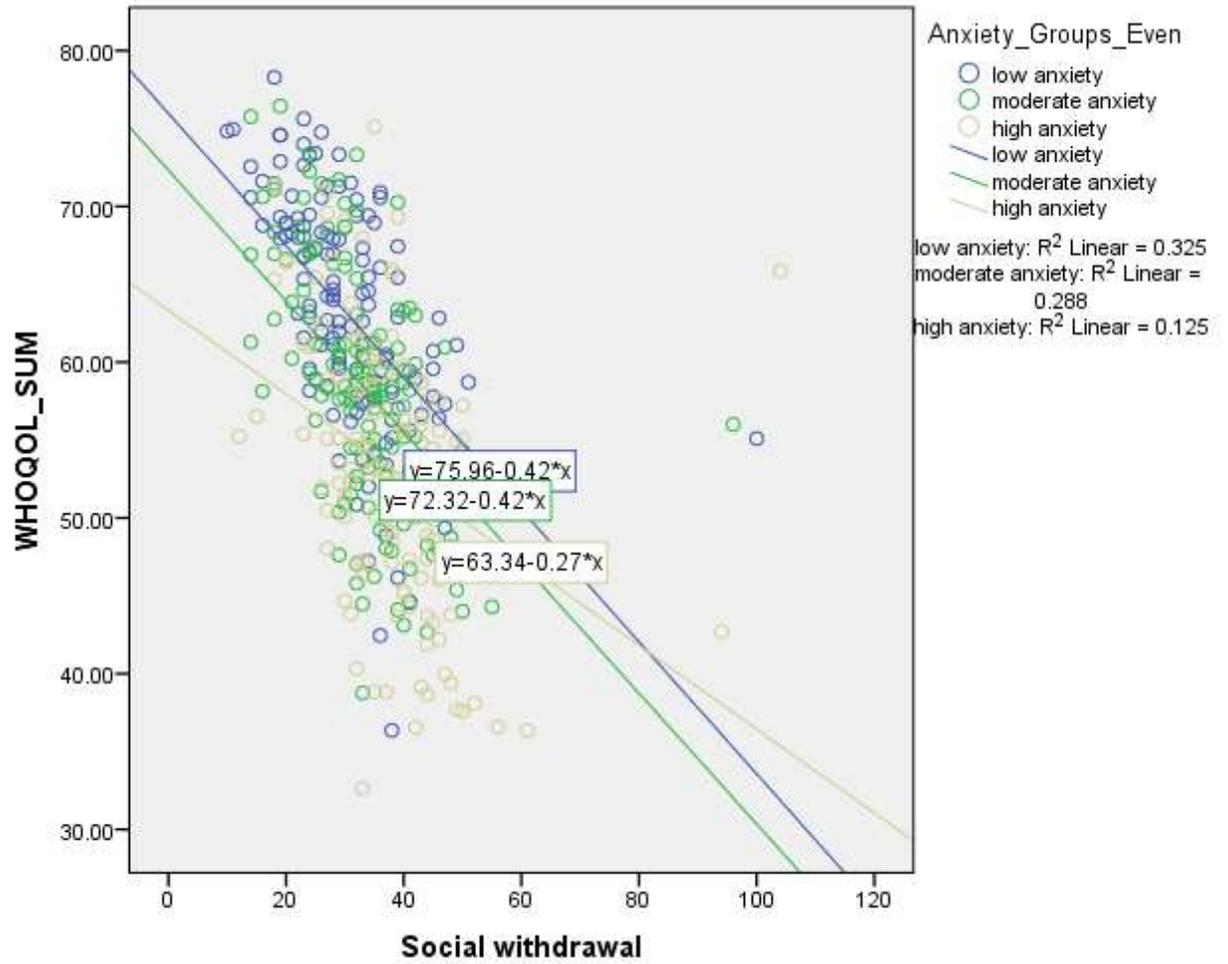


Figure 6.2 Graph of the interaction term with all data points and anxiety grouped into equal sized groups.

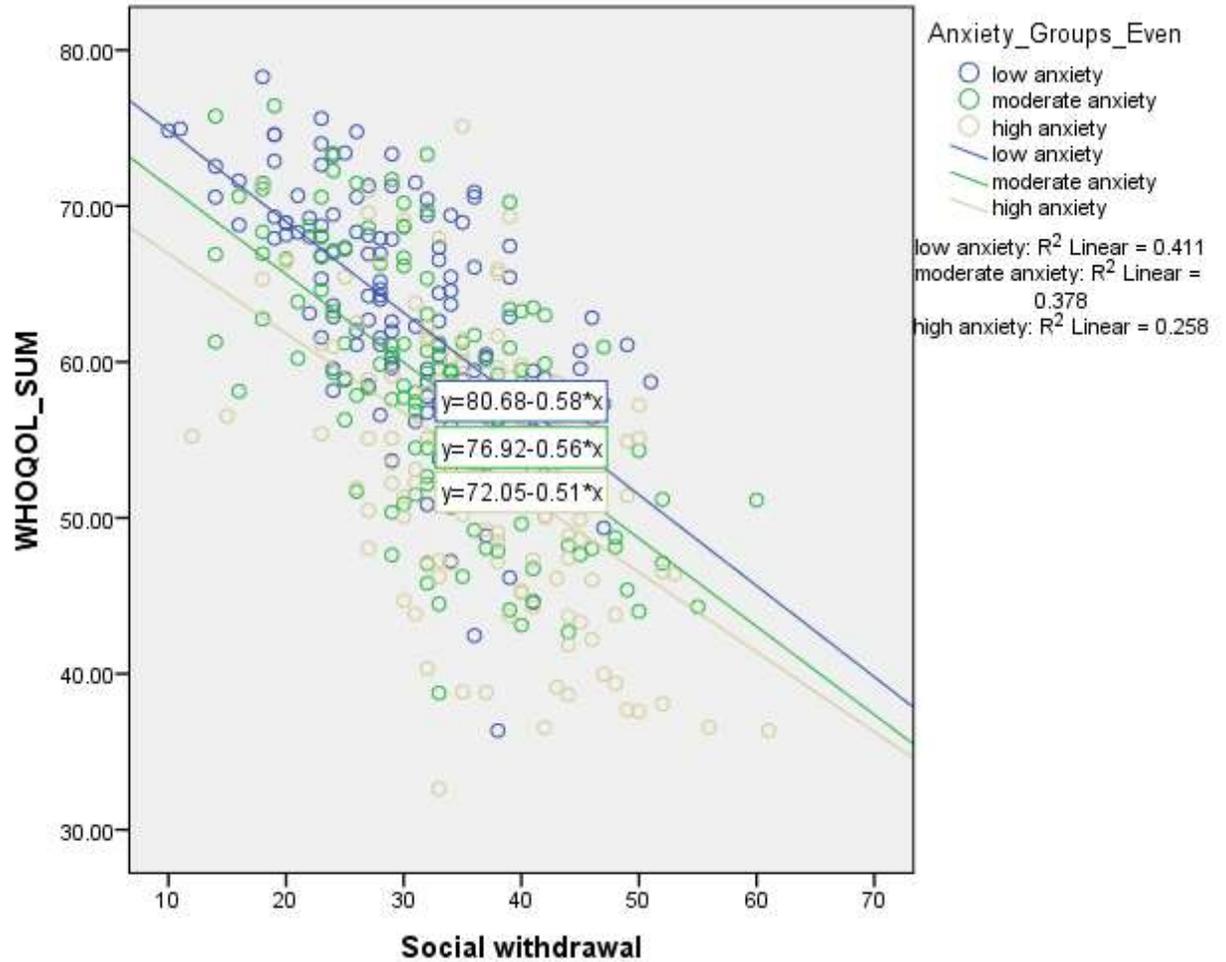


Figure 6.3 Graph of the interaction term without 4 highest social withdrawal values and anxiety grouped into equal sized groups.

Exploring the Interaction of social withdrawal with anxiety using the scatterplot shown in figure 6.2 suggested that: for the range of results available, at a set level of social withdrawal, low anxiety resulted in higher QOL than moderate anxiety. This was also true of the relationship between moderate and high anxiety groups. However, the gradient of the line for low anxiety was steeper than for moderate anxiety which was in turn steeper than for high anxiety. This suggests that, as social withdrawal increases, the additive effect of higher levels of anxiety lessens.

This interpretation is limited by the fact that the groupings of low, moderate and high anxiety are not based on any clinically meaningful cut-offs but were simply an even dividing of the ordered results into three groups.

'Modified cut-offs'

The analysis of the interaction was repeated with the modified cut-off points as suggested by Gibbons et al¹¹⁹ which gave relative frequencies of 56 'probable' cases, 56 'possible' and 293 non-cases.

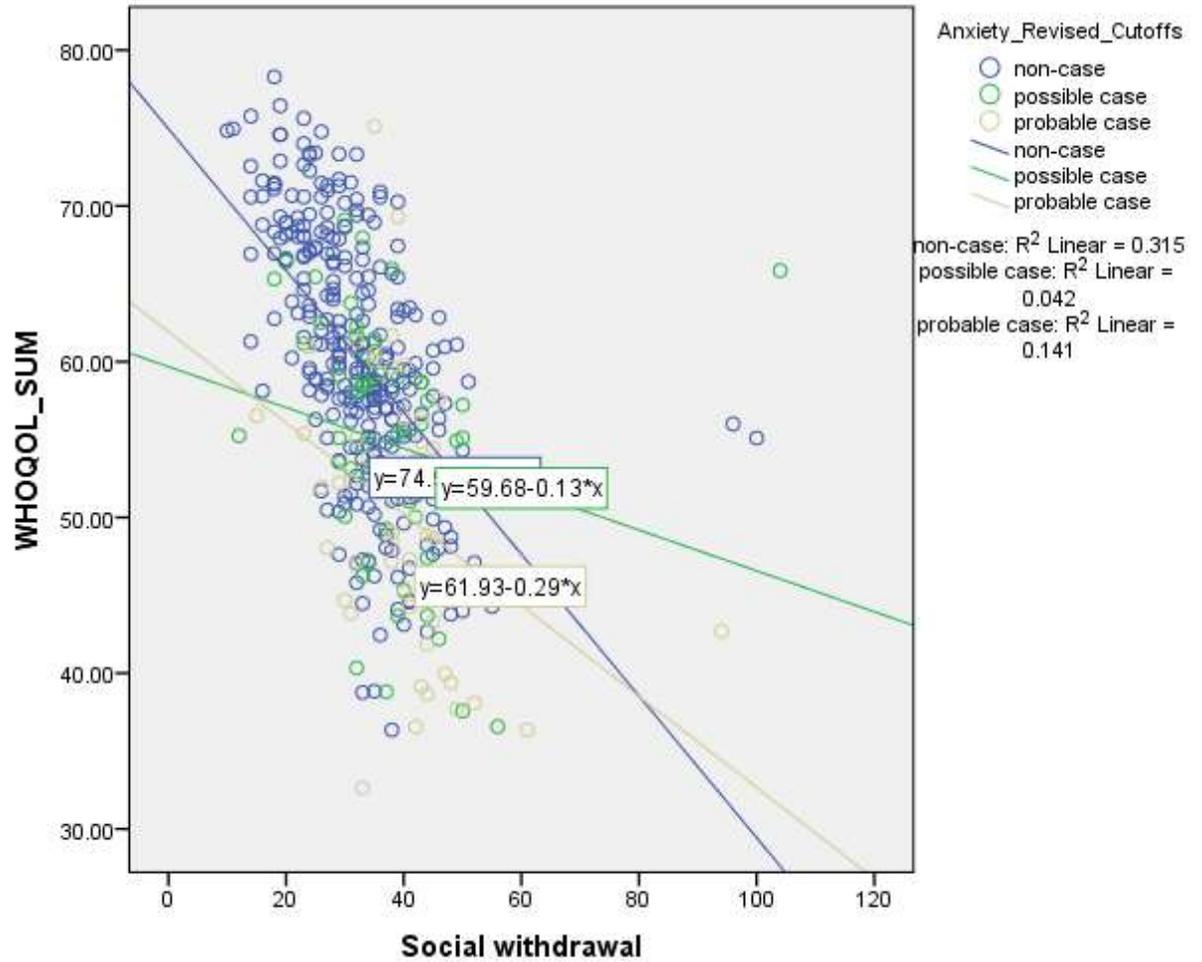


Figure 6.4 Graph of the interaction term with all data points and anxiety grouped using the modified cut-offs.

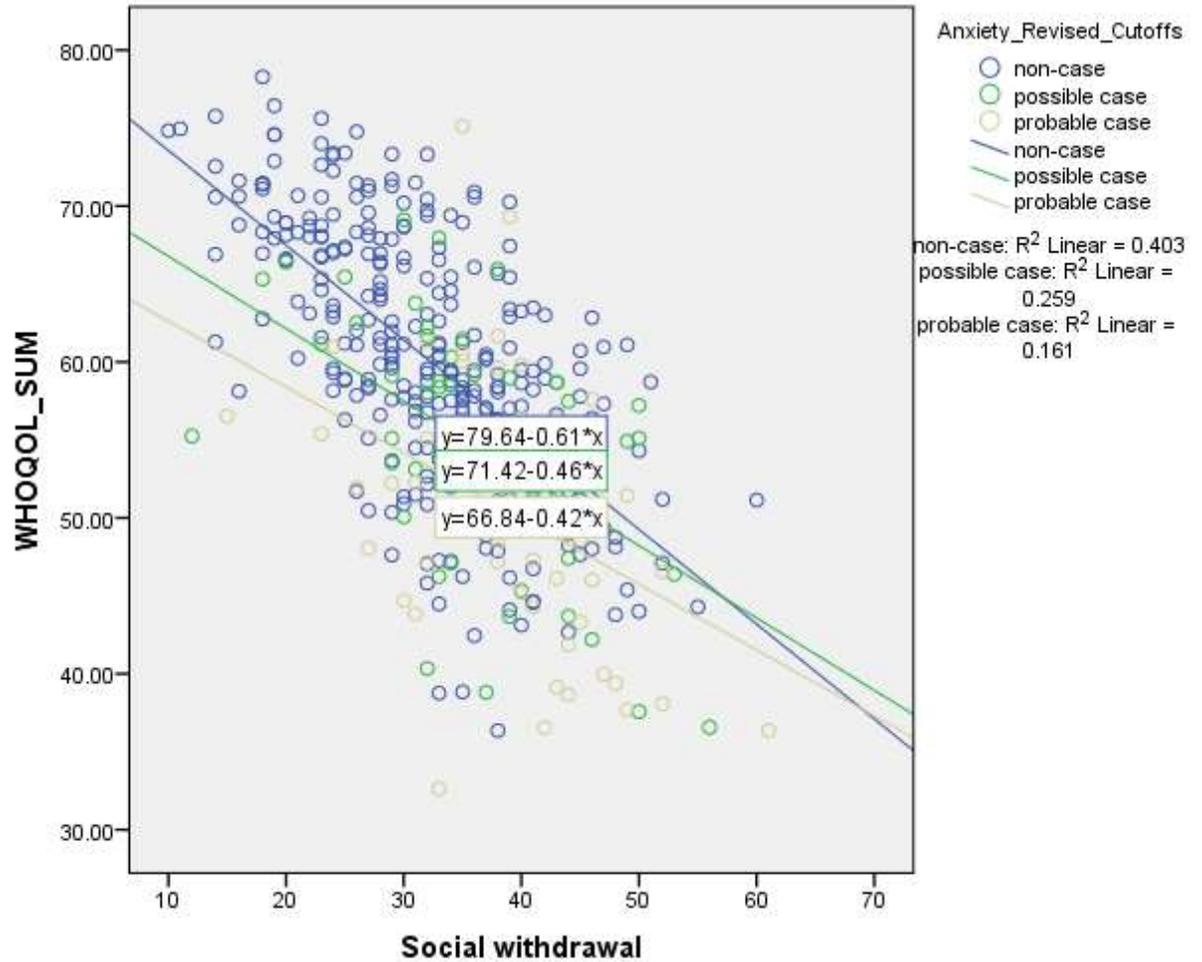


Figure 6.5 Graph of the interaction term without 4 highest social withdrawal values and anxiety grouped using the modified cut-offs.

Examining figure 6.4 reveals similar findings to figure 6.2 with greater anxiety at a set level of social withdrawal resulting in lower QOL, with this difference diminishing as social withdrawal increases. There is an intercept within the range of the TONiC data where, at a high level of social withdrawal, individuals with 'non-case' level anxiety have worse predicted QOL, compared to 'possible' anxiety.

The interaction between anxiety and social withdrawal is difficult to interpret at high levels of withdrawal, and further research may help enlighten the true relationship between the variables. One possibility may be that not all social interaction is beneficial for MND patients, and it may be that in the case of highly anxious patients, increasing social withdrawal has less of an effect due to the lack of negative social experience, which may outweigh positive social experience in terms of effect on this subgroup of patients. Hogg, Goldstein and Leigh suggested that MND patients may find relating to other people anxiety provoking, because of the pattern of physical impairments that characterise MND.¹⁴³

A limitation of the analysis using the modified cut-offs may be that, with these smaller numbers in the 'probable' and 'possible' groups, the regression lines estimated by SPSS for these groups may be less accurate, when compared to the non-case group.

Clinical Implications

This study confirms the utility of healthcare personnel considering these psychosocial factors when managing and interacting with MND patients, and suggests the large benefit that could be gained from interventions aimed towards these three factors. Despite a lower prevalence than perhaps expected of psychiatrically defined anxiety and depression in MND populations⁷⁴, reinforced by this study's findings of low levels of 'probable depression' and 'probable anxiety' using the modified HADS, this analysis shows a significant association with GQOL along a continuum of depression and a continuum of anxiety. It may be that there is a substantial population of 'sub-threshold' depression and anxiety who would not be identified when examining prevalence of 'depressive illness' or 'anxiety disorder', but for whom their depressive and anxious symptoms have a significant impact on their QOL. Thus, a liaison service or increased availability of psychology and psychotherapy services may have a broader impact mitigating moderate levels of anxiety and depression ('possible' depression and anxiety measured via the HADS) and therefore reducing their effect on QOL. Social withdrawal could be targeted with support schemes as well as addressing their mobility and communication needs.

From the successful application of the multiple linear regression model, it may be hoped that in future a multifactor clinical tool, based on regression, may be developed to assist healthcare workers in assessing a patient's QOL. This could increase efficiency with clinicians or other staff entering demographic data as well as information from a preclinic questionnaire to give an estimation of the patient's QOL as well as flagging the relevant areas for discussion.

However, a problem with this approach, as seen from the qualitative studies mentioned in chapter one, is that QOL has a very individual basis. A worry may be that healthcare practitioners over-relying on a tool as described above could limit the range of discussion, and may not accurately cover the issues pertinent to each individual. As a compromise, the use of pre-clinic questionnaires or online forms could help to stratify patient's risk of depression, anxiety, social withdrawal, etc., and this could increase efficiency, by prompting whether it is appropriate to engage in a full clinical interview to investigate these areas.

Limitations

Limitations include the reduction in cohort size due to elimination of participants with missing data for any of the factors investigated. The measure for total QOL had greater than 10% missing data when compared to the original cohort. There was also a greater than 10% difference from the original cohort with respect to marital status and employment status and these could feasibly have had an impact on the factors examined here.

This model sought only to examine these three factors' relationships with GQOL, as directed by results of the systematic review. This is early work that could be improved on, and it is to be acknowledged that there is a plethora of other factors that are likely to have relationships with GQOL and these factors in turn could have affected the strength of the examined factors' relationships with GQOL.

Conclusion

The results of this analysis suggest that the depression, anxiety, and social withdrawal do play a significant role with regards to MND patients' QOL. The burden of depression and anxiety in this cohort in terms of prevalence of 'probable depression' and 'probably anxiety' may not be as high as expected for such a severe illness, but, when considering depression and anxiety on spectrums from symptoms into 'illness', the burden on the individual, in terms of QOL, is high.

This study supports the appropriateness of further in-depth investigation of these psychosocial factors, to understand factors affecting them, and to understand where interventions may be appropriate. The interaction between anxiety and social withdrawal warrants further study, to determine its true nature and what the implications of this may be.

Conclusions

Conclusions of the chapters

Systematic review

The systematic review found that most studies focused on depression and anxiety and social factors relationship with QOL. This may be due to healthcare practitioners' familiarity with these factors, especially depression and anxiety, where there is readily available information about diagnosis and management. This lends to the ease of investigation with regards to these factors, as well as increasing the likelihood that attention will be paid to the results of these studies; both themes increasing the incentive to study these factors compared to a wider range of psychosocial factors.

Multiple tools are available for critical appraisal. Applying the STROBE checklist⁶⁷ to ten quantitative studies suggested that improvements could be made by: clarifying the study design in the title or abstract; providing more detailed description of the setting of the studies, dates between which recruitment took place, and numbers of participants at each stage; describing how sample sizes were arrived at; and discussing the limitations of the studies and how potential bias may have affected the results. However, the findings of the limited analysis of ten studies should be interpreted with caution.

Using the CASP checklist for qualitative studies⁶⁵ it appeared that the qualitative studies identified by the review could be improved by more closely examining the relationship between the researcher and participants and how this may influence their results, as well as explicitly justifying their study design, recruitment strategy, and data collection.

Unfortunately, multiple measures were used for QOL, HRQOL, as well as psychosocial factors. The resulting heterogeneity prevented any useful meta-analysis. This, in combination with the varying quality of the studies, resulted in inconclusive findings with respect to many factors and demonstrates the need for clearly oriented research – with respect to the findings of the current literature and their suggestions for future research – limiting itself to validated measures in order to provide a robust evidence base.

Depression

Demographic factors did not have a significant association with depression in this study, but other studies are not agreed on this, so further investigation could be used to clarify this issue.^{140,141} It should also be considered that the demographics of this multifactor model, with depression as the outcome, were different from the 'original' n=465 cohort (see table 2.1), and this could feasibly have affected the results of this model.

Similarly, time from diagnosis was not found to be significant in this study, but this relationship is compounded by so many possible factors that more sophisticated analysis is required. One possible interaction with time which was examined, was the interaction between time and disability – which was not significant in this cohort.

The results of the single factor models suggested that all the domains of the WHODAS had a significant association with depression. However, the final model emphasised that domains six, four, and one had the strongest associations. These were 'participation in society', 'getting along with people', and 'understanding and communicating', which emphasised that the strongest associations were with social disability.

Physical function may have other mechanisms by which it relates to depression, such as its impact on perceived health⁸⁵, and this may warrant investigation following on from the theme 'the importance of subjectivity' discussed in this thesis.

Reviewing the literature, treatment for depression in MND seems to be based on general guidelines for depression in chronic illness.¹⁶⁷ Some studies suggest that this may not be entirely appropriate¹⁶⁸, and there is a call for MND specific studies, to develop or determine useful interventions.¹⁷³

Anxiety

Hope was found to have a significant association with anxiety. The definition of hope in MND must be considered to be more than just a 'hope for cure', incorporating many other categories including 'social support', 'search for information', 'spiritual beliefs', 'limiting the impact', 'adapting to changing capacities', 'living in the moment', and 'self-transcendence'.¹⁸² This is important because of the links to transcendence, which is an area of study with great potential benefits for MND patients, and because of how it demonstrates that the idea of hope and the act of hoping is very individual and can vary greatly amongst patients. This again challenges preconceived notions of disease and illness and emphasises the disparity between what professionals and laymen alike may think and how patients actually experience their illness.

None of the locus of control subscales were found to have a significant association with anxiety, but in retrospect the study design was deemed inadequate, as it did not specify whether the locus of control was with respect to overall disease course or symptoms, and did not consider the impact of differing levels of disability, and different coping strategies. Overall, the generality of this study does not consider many nuances that impact on the relationship LOC may have with mood and mental health based outcomes, and so future studies should consider other factors alongside locus of control. Alternatively, one may wish to examine a different construct instead of locus of control, one that is less dependent on as many external factors. One example would be self-efficacy, which is considered by Luszczunski and Schwarzer²⁰⁹ to be a superior construct for explaining behavioural differences. Explaining behavioural differences was not the goal of this study but it could also be considered that self-efficacy more closely relates to the 'self' than LOC and so, as well as being easier to investigate when compared to the context specific nature of LOC, it is also in keeping with the emphasis on the importance of the subjective experience of patients.

Social withdrawal

To examine social withdrawal two multifactor models were created; one to examine associations with the 4 WHOQOL-BREF domains and one to examine associations with ratings of physical function as measured by the ALSFRS-R.

Single factor models found significant relationships between social withdrawal and the four WHOQOL-BREF domains. When considered in the multi-factor model, the most parsimonious model included 'physical health' and 'environment and financial resources'. 'Psychological health' was borderline significant in the multifactor model and one reason for this may have been cross-domain overlap between 'physical health' and 'psychological health', similar to that found by the WHOQOL group in the general population.²¹⁵ The finding that the weakest association was between social withdrawal and the 'social relationships' domain may be explained by the WHOQOL group's finding that Cronbach's alpha, and therefore reliability, was lowest for the 'social relationships' domain²¹⁵, as well as the consideration that 'social relationships' considers a lot of other social aspects compared to just social withdrawal, possibly reducing the level of agreement between the two factors.

With regards to the ALSFRS-R domains, social withdrawal had a significant relationship with each of the 'motor', 'bulbar', and 'respiratory' domains, as demonstrated by significant single factor models.

The multifactor model demonstrated the strongest associations being with the 'motor' and 'bulbar' domains, with possible mechanisms being psychological distress occurring alongside declining physical function, as well as how these impairments may impede participation in social situations. Declining motor function can greatly limit mobility, which therefore reduces an individual's ability to leave their house and engage with others, without assistive devices or without the assistance of others. Declining bulbar function can isolate individuals by limiting communication as well as possibly increasing stigma associated with drooling, and possibly increasing fear of choking preventing "eating out" as a social activity.

It could be considered that these two models may demonstrate how a large proportion of social withdrawal is driven by barriers to participation, in the form of poor health, and then, whether an individual has the financial and environmental resources to overcome the limitations imposed by their health. This may suggest that socioeconomic inequalities have a role to play in how MND patients experience social withdrawal.

Quality of life

The overall QOL model showed that the three factors depression, anxiety and social withdrawal had significant associations with GQOL. These three factors explained 60.9% of the variance in WHOQOL-BREF, demonstrating the importance of psychosocial factors with respect to QOL. The order of importance of the factors, as determined by their standardised coefficients, was: depression, then social withdrawal, then anxiety.

The major benefit of this study's investigation of these factors when compared to the studies identified in the systematic review is the large sample size of 409 with the second largest sample size of studies examining depression, the largest compared to studies examining anxiety and the largest compared to the studies of social withdrawal and social isolation.

A significant interaction term was found to exist between anxiety and social withdrawal, such that, for a set level of social withdrawal, a higher grouping of anxiety (using the modified HADS-A) resulted in higher QOL. However, this difference between groups diminished as social withdrawal increased. The coefficient for this interaction term was small but possible reasons for its significance include the idea that not all social interaction is beneficial for patients with MND.¹⁴³

How these models' methods build on the current literature and their drawbacks

The systematic review identified that previous studies used a multitude of scales, sometimes not validated for use in research, and that this caused difficulty interpreting the results in a cohesive manner. Particularly, previous studies used multiple measures for QOL, including HRQOL measures, despite GQOL measures being shown to be superior for understanding the subjective experiences of MND patients. This thesis attempts to improve on that issue by using validated scales that are thought to be appropriate for the research questions being asked, and, with particular respect to QOL, by using a well-validated measure of GQOL. Additionally, previous work was often in the form of smaller studies for many of the factors to be investigated, whereas this thesis has a large cohort, with the largest multifactor model using data from 429 participants, and the smallest multifactor model using data from 224 participants. With these considerations in mind, it is hoped that this thesis has helped to add clarity with regards to which psychosocial factors are associated with one another and with GQOL.

As part of the model building method of this thesis, participants with missing data for any of the factors to be examined in a multifactor model were excluded from analysis for that model. This was required because it would be disingenuous to rank factors' order of entry into the model using their *F* statistic if those *F* statistics were drawn from different cohorts. This resulted in five unique cohorts of varying sizes, one for each multifactor model.

Each of these models was designed to answer the research questions asked of it without consideration of the factors examined in the other models. Due to the model building approach chosen, a model incorporating all of the factors examined in this thesis would require exclusion of so many participants that it would result in it being under-powered.

Because of the differences in the cohorts outlined in table 2.1, direct comparisons between multifactor models are unlikely to be valid. However, none of the cohorts vary so drastically that the general interpretation of their results, such as social withdrawal possibly being driven by a lack of resources, could not be investigated in conjunction with an interpretation from another model – for example, whether increasing resource provision may be associated with a decrease in social withdrawal, and thereby a decrease in social disability, and a lessening of depressive symptoms.

Overall

The overall findings as described above are shown in figure 7.1.

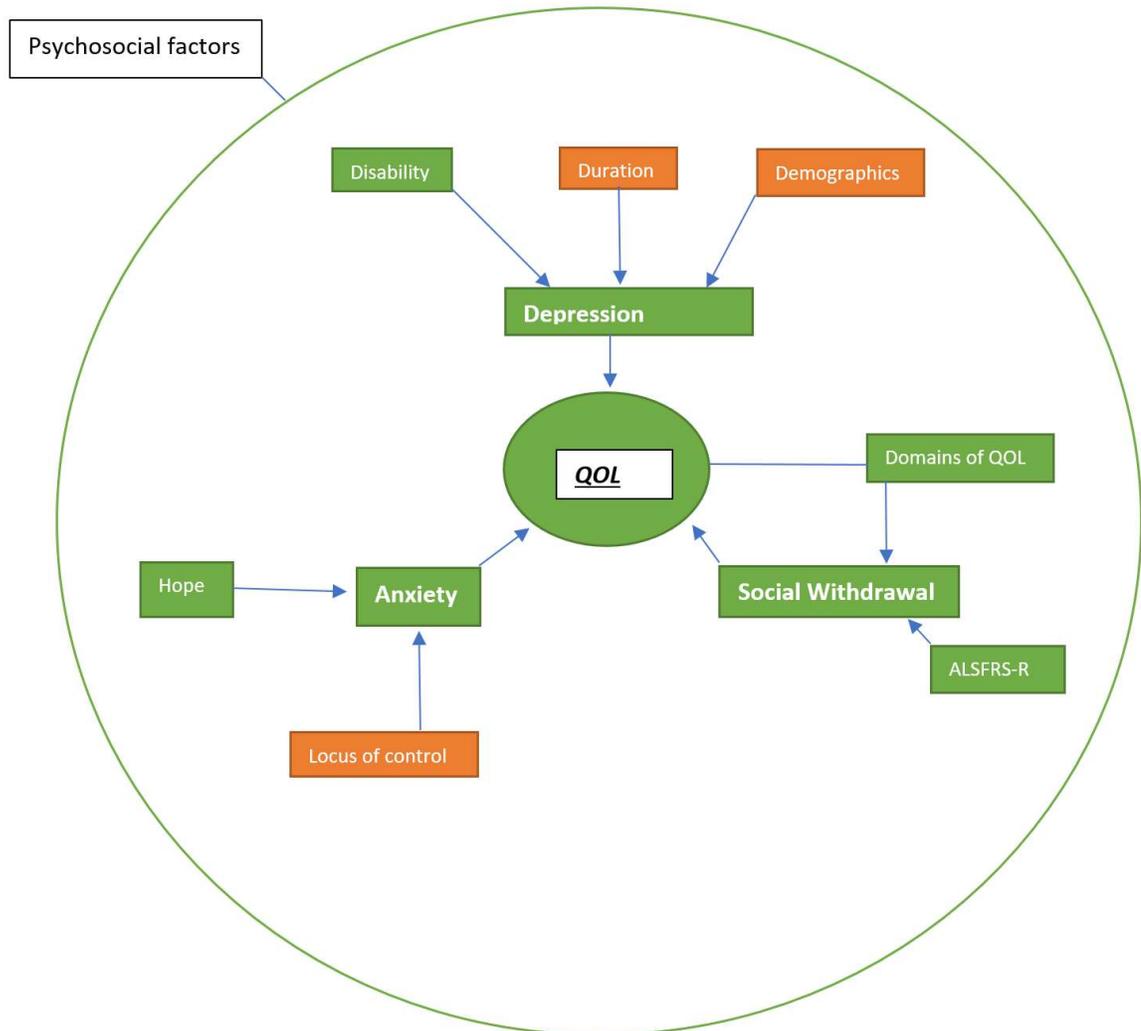


Figure 7.1 Diagram to show factors with significant associations (green) and non-significant associations (orange). Note that the arrows do not denote causality, only which factors were considered in relation to each other.

Clinical implications

These findings are important, because understanding these factors' relationships to each other, and to patients' QOL, will allow targeted interventions as well as early identification of patients at risk for depression, anxiety and social withdrawal. This could mean, for example, targeting social disability to reduce depression or using low motor or bulbar ALSFRS-R scores to prompt questions about social withdrawal.

Using social support groups to improve social disability may be problematic, due to issues with how these groups are perceived, as well as the difficulty of spending time with peers who may be further in their disease progression. Another way of improving patients' ability to participate in social settings may be by improving their mobility, with mobility aids such as power assisted wheelchairs or by improving their communication, with augmentative and alternative communication methods such as alphabet boards, eye gaze technology or 'electronic voice to output typed text' devices. This links to the findings in chapter five which found that social withdrawal was associated with severity of motor and bulbar symptoms as well as finding that, out of the four GQOL domains the strongest associations with social withdrawal were from the 'physical health' domain and the 'environment and financial resources' domain. An interesting avenue of research is the use of online social media, which may help patients remain connected to their close friends and relatives, but could also be adapted for use as a proxy for support groups. This could reduce material costs of running the support groups, due to not requiring a venue to be hired, or other amenities be provided, or someone being present to chair and run the group (someone could instead moderate the group remotely). Additionally, it may also remove the pressure of being directly confronted with one's peers. A drop-out, drop-in style service could then be possible due to the lower material costs which may then allow patients to utilise the support group only when it would be advantageous for them, avoiding the possible negative consequences discussed by Locock and Brown¹⁷¹ in terms of distressing social comparison and disruption to identity. Improving patients' autonomy may increase the value of this support as patients' involvement can reflect their need at a specific point in time.

When considering the findings in relation to depression and anxiety in this study, one must bear in mind that interval scales and inferential statistical techniques were used. This means that depression and anxiety were not considered as groups of 'cases' and 'non-cases', or as 'probable' depression/anxiety, 'possible' depression/anxiety and 'non' depression/anxiety, but were considered along a spectrum. This means that the findings of this study cannot be applied selectively to 'diagnosed' depression and anxiety, rather that they apply to MND patients as a whole. It is worth considering that there may be a substantial population of 'sub-threshold' depression and 'sub-threshold' anxiety, who may benefit from nonpharmacological intervention.

Future research

Considering that MND patients' QOL has been found to be better than some would suspect^{24,25} along with low levels of depression, some may wonder whether these patients are in denial and this is supported to some degree.²²⁰ However, this would ignore the findings suggesting that transcendence and response shift is important for maintaining patients' psychological and existential well-being, which in turn preserves their GQOL.²⁸⁻³⁰

One may also consider biological reasons for the findings of preserved QOL, such as cognitive impairment^{14,221} resulting in better QOL than expected, and relative preservation of the serotonergic system resulting in lower levels of depression²²⁰, but even if these were found to account for some of the picture, the importance of the psychosocial factors described above should not be overlooked.

Another hypothesis for the better than expected QOL in MND could be framed in Carver and Scheier's "scaling back goals" and "self-adjustment" model as they applied it to various diseases.²¹⁶ This could be relevant in MND in that it may be that the daily experience and limitations of the disease – preventing patients from achieving their goals – creates a negative 'affect', via the 'feeling' feedback loop, that then drives an increase in the rate of adjustment in the 'behaviour' loop, an increase in psychological "velocity". Thus, it could be that MND patients may more readily "scale back" their goals when compared to other disease groups, increasing the likelihood of 'success' and allowing them to remain engaged. Qualitative studies may help with understanding the validity of this argument.

Although the adjustment discussed in this thesis is mostly discussed with respect to ‘individual’ factors, a consideration should be made for the attitudes of others, in that, for the most part, society’s attitude toward illness is one that expects care and support to be given - proportional to the severity of the disease. Social support has been found to be an important factor and it may be that these societal attitudes or expectations could result in large support for MND patients (a severe illness) – a motivation which could be examined in qualitative studies with caregivers – and this may aid in the rapidity of adjustment.

From all of the above said the evidence suggests that MND can drive positive growth of an individual. This links to themes explored by Havi Carel in her consideration of the philosophy of medicine and illness.²²²⁻²²⁴ She talks about ‘wellness within illness’ and how severely chronically ill people are not necessarily committed to a life of misery.

An overall limitation of this thesis is that due to the use of cross-sectional data the direction of effect between factors cannot be identified. This prompts the requirement of longitudinal studies. However, repeated measurement of psychosocial factors over time may be complicated by the ideas proposed by Golembiewski et al.²²⁵

Golembiewski et al suggest that one must consider whether changes (or lack of changes) seen with repeated use of a scale is due to ‘true’ change where the meaning of the scale has not changed for the individual between measurements (termed alpha change). Alternatively, a change (or lack of change) can be due to the scale’s intervals no longer having the same psychological anchors as they did before (beta change), or due to an entire reconceptualization of that factor (gamma change). Howard et al link this conceptualisation of change to response shift and QOL, emphasising its relevance in this area.²²⁶ Another complication of longitudinal studies is of course the attrition rate associated with MND, but it is hoped that larger, multi centre studies, similar to the TONiC study, will help to produce robust results. Studies collecting large amounts of data from patients over time must be aware of the burden that can be caused by long, time-consuming questionnaire packs and difficult to use scales. Because of the disability and fatigue associated with MND, it is key to ensure that scales and questionnaires are acceptable to the patients, in order to avoid deterring them from continuing to participate in the study, or in future studies.

Considering the possibility of change in importance of psychosocial factors over time, further research should examine when certain factors are more important than others for maintaining a patient's psychological well-being over time, and whether this compensates for other factors, such as declining physical ability. From this it can be seen that an additional benefit of longitudinal studies will be to plot the disease course with respect to psychosocial factors, exposing times of vulnerability, and times of improvement.

Qualitative methodology should not be overlooked as this may help to suggest *how* and *why* certain factors are related, as well as suggesting which factors should be examined. An example of the former would be that, following this study's findings of significant associations between the domains of ALSFRS-R and social withdrawal, structured interviews could be used to examine the mechanisms by which these relationships exist. An example of using qualitative studies to guide further study would be to focus on themes identified by patients as important, such as control, dignity and identity⁴¹, as well as worries about dependency⁴⁴.

Overall

It is clear that considering psychosocial factors is key when trying to understand the experience of MND patients, what is important for their GQOL, and how to improve their care. Further research should seek to find further associations, using quantitative methods, and to understand how these associations may come about, using qualitative methods. Longitudinal studies are needed to understand the relevance of psychosocial factors throughout the course of the illness.

Bibliography

1. Worms PM. The epidemiology of motor neuron diseases: a review of recent studies. *J Neurol Sci.* 2001;191(1-2):3-9.
2. Alonso A, Logroscino G, Jick SS, Hernán MA. Incidence and lifetime risk of motor neuron disease in the United Kingdom: a population-based study. *Eur J Neurol.* 2009;16(6):745-751.
3. Haverkamp LJ, Appel V, Appel SH. Natural history of amyotrophic lateral sclerosis in a database population Validation of a scoring system and a model for survival prediction. *Brain.* 1995;118(3).
4. Riva N, Agosta F, Lunetta C, Filippi M, Quattrini A. Recent advances in amyotrophic lateral sclerosis. *J Neurol.* 2016;263(6):1241-1254. doi:10.1007/s00415-016-8091-6.
5. Talbott EO, Malek AM, Lacomis D. The epidemiology of amyotrophic lateral sclerosis. In: *Handbook of Clinical Neurology.* Vol 138. ; 2016:225-238. doi:10.1016/B978-0-12-802973-2.00013-6.
6. Forsgren L, Almay BG, Holmgren G, Wall S. Epidemiology of motor neuron disease in northern Sweden. *Acta Neurol Scand.* 1983;68(1):20-29.
7. Guenther R, Richter N, Sauerbier A, et al. Non-Motor Symptoms in Patients Suffering from Motor Neuron Diseases. *Front Neurol.* 2016;7. doi:10.3389/fneur.2016.00117.
8. Mitsuyama Y, Takamiya S. Presenile dementia with motor neuron disease in Japan. A new entity? *Arch Neurol.* 1979;36(9):592-593.
9. Wikström J, Paetau A, Palo J, Sulkava R, Haltia M. Classic amyotrophic lateral sclerosis with dementia. *Arch Neurol.* 1982;39(11):681-683.
10. Ludolph AC, Langen KJ, Regard M, et al. Frontal lobe function in amyotrophic lateral sclerosis: a neuropsychologic and positron emission tomography study. *Acta Neurol Scand.* 1992;85(2):81-89.
11. Kew J, Leigh N. Dementia with motor neurone disease. *Baillieres Clin Neurol.* 1992;1(3):611-626.

12. Flaherty-Craig C V, Brothers A, Yang C, Svoboda R, Simmons Z. Declines in problem solving and anosognosia in amyotrophic lateral sclerosis: Application of Guilford's structure of intellect theory. *Cogn Behav Neurol*. 2011;24(1):26-34.
13. Flaherty-Craig C, Brothers A, Svoboda R, Simmons Z. Impaired insight for cognitive decline in ALS with cognitive impairment. *Amyotroph Lateral Scler*. 2010;11.
14. Bock M, Duong Y-N, Kim A, Allen I, Murphy J, Lomen-Hoerth C. Cognitive-behavioral changes in amyotrophic lateral sclerosis: Screening prevalence and impact on patients and caregivers. *Amyotroph Lateral Scler Frontotemporal Degener*. 2016;17(5):366.
15. McCluskey LF, Elman LB, Martinez-Lage M, et al. Amyotrophic lateral sclerosis-plus syndrome with TAR DNA-binding protein-43 pathology. *Arch Neurol*. 2009;66(1):121-124. doi:10.1001/archneur.66.1.121.
16. Simmons Z. Patient-Perceived Outcomes and Quality of Life in ALS. *Neurotherapeutics*. 2015;12(2):394-402. doi:10.1007/s13311-014-0322-x.
17. Simmons Z, Bremer BA, Robbins RA, Walsh SM, Fischer S. Quality of life in ALS depends on factors other than strength and physical function. *Neurology*. 2000;55(3):388-392.
18. Robbins RA, Simmons Z, Bremer BA, Walsh SM, Fischer S. Quality of life in ALS is maintained as physical function declines. *Neurology*. 2001;56(4):442-444.
19. Goldstein L, Atkins L, Leigh P. Correlates of Quality of Life in people with motor neuron disease (MND). *Amyotroph Lateral Scler Other Mot Neuron Disord*. 2002;3(3):123-129. doi:10.1080/146608202760834120.
20. Chio A, Gauthier A, Montuschi A, et al. A cross sectional study on determinants of quality of life in ALS. *J Neurol Neurosurg Psychiatry*. 2004;75(11):1597. doi:10.1136/jnnp.2003.033100.
21. Neudert C, Wasner M, Borasio GD. Individual Quality of Life is not Correlated with Health-Related Quality of Life or Physical Function in Patients with Amyotrophic Lateral Sclerosis. *J Palliat Med*. 2004;7(4):551-557. doi:10.1089/jpm.2004.7.551.
22. Neudert C, Wasner M, Borasio GD. Patients' assessment of quality of life instruments: a randomised study of SIP, SF-36 and SEIQoL-DW in patients with amyotrophic lateral

- sclerosis. *J Neurol Sci.* 2001;191(1-2):103-109.
23. Gibbons C, Thornton E, Ealing J, et al. The impact of fatigue and psychosocial variables on quality of life for patients with motor neuron disease. *Amyotroph Lateral Scler Frontotemporal Degener.* 2013;14(7):537.
 24. Lulé D, Ehlich B, Lang D, et al. Quality of life in fatal disease: the flawed judgement of the social environment. *J Neurol.* 2013;260(11):2836-2843. doi:10.1007/s00415-013-7068-y.
 25. Adelman EE, Albert SM, Rabkin JG, Del ML, Tider T, O'Sullivan I. Disparities in perceptions of distress and burden in ALS patients and family caregivers. *Neurology.* 2004;62(10):1766.
 26. Crocker TF, Smith JK, Skevington SM. Family and professionals underestimate quality of life across diverse cultures and health conditions: systematic review. *J Clin Epidemiol.* 2015;68(5):584-595. doi:10.1016/j.jclinepi.2014.12.007.
 27. Sprangers MA., Schwartz CE. Integrating response shift into health-related quality of life research: a theoretical model. *Soc Sci Med.* 1999;48(11):1507-1515. doi:10.1016/S0277-9536(99)00045-3.
 28. Ozanne O, Graneheim H, Strang S. Finding meaning despite anxiety over life and death in amyotrophic lateral sclerosis patients. *J Clin Nurs.* 2013;22(15):2141.
 29. Young JM, McNicoll P. Against all odds: positive life experiences of people with advanced amyotrophic lateral sclerosis. *Health Soc Work.* 1998;23(1):35.
 30. Locock L, Ziebland S, Dumelow C. Biographical disruption, abruption and repair in the context of motor neurone disease. *Sociol Heal Illn.* 2009;31(7):1043-1058.
 31. Leirvik A, Liverod M, Holmoy T. Quality of life and content with treatment among patients with amyotrophic lateral sclerosis [Norwegian] Livskvalitet hos pasienter med amyotrofisk lateral sklerose. *Tidsskr den Nor Laegeforening.* 2006;126(19):2520-2522.
 32. "I fear being entombed in my body" - suicide legal challenge - BBC News. <http://www.bbc.co.uk/news/health-38500873>. Accessed June 5, 2017.
 33. Ganzini L, Dobscha SK, Heintz RT, Press N. Oregon Physicians' Perceptions of Patients Who Request Assisted Suicide and Their Families. *J Palliat Med.* 2003;6(3):381-390.

doi:10.1089/109662103322144691.

34. Albert SM, Rabkin JG, Del ML ML, et al. Wish to die in end-stage ALS. *Neurology*. 2005;65(1):68-75.
35. Higgins JPT, Green S (Sally E, Cochrane Collaboration. *Cochrane Handbook for Systematic Reviews of Interventions*. Wiley-Blackwell; 2008.
36. Brott T, Hocking C, Paddy A. Occupational Disruption: Living with Motor Neurone Disease. *Br J Occup Ther*. 2007;70(1):24-31. doi:10.1177/030802260707000107.
37. Bremer A, Simone A-L, Walsh S, Simmons Z, Felgoise H. Factors Supporting Quality of Life Over Time for Individuals With Amyotrophic Lateral Sclerosis: The Role of Positive Self-Perception and Religiosity. *Ann Behav Med*. 2004;28(2):119.
38. Clarke S, Hickey A, O'Boyle C, Hardiman O. Assessing individual quality of life in amyotrophic lateral sclerosis. *Qual Life Res*. 2001;10(2):149-158.
39. Fegg MJ, Wasner M, Neudert C, Borasio GD. Personal values and individual quality of life in palliative care patients. *J Pain Symptom Manage*. 2005;30(2):154-159.
40. Felgoise H, Zaccheo V, Duff J, et al. Verbal communication impacts quality of life in patients with amyotrophic lateral sclerosis. *Amyotroph LATERAL Scler Front Degener*. 2016;17(3):179-183. doi:10.3109/21678421.2015.1125499.
41. Foley G, O'Mahony P, Hardiman O. Perceptions of quality of life in people with ALS: effects of coping and health care. *Amyotroph Lateral Scler*. 2007;8(3):164.
42. Ganzini L, Johnston WS, Hoffman WF. *Correlates of Suffering in Amyotrophic Lateral Sclerosis*. Vol 52.; 1999.
43. Goldstein LH, Atkins L, Leigh PN. Correlates of Quality of Life in people with motor neuron disease (MND). *Amyotroph Lateral Scler Other Motor Neuron Disord*. 2002;3(3):123-129. doi:10.1080/146608202760834120.
44. Hecht M, Hillemacher T, Gräsel E, et al. Subjective experience and coping in ALS. *Amyotroph Lateral Scler Other Motor Neuron Disord*. 2002;3(4):225.
45. Ilse B, Prell T, Walther M, et al. Relationships Between Disease Severity, Social Support

- and Health-Related Quality of Life in Patients with Amyotrophic Lateral Sclerosis. *Soc Indic Res*. 2015;120(3):871-882. doi:10.1007/s11205-014-0621-y.
46. Koerner S, Kollwe K, Abdulla S, et al. Interaction of physical function, quality of life and depression in Amyotrophic lateral sclerosis: characterization of a large patient cohort. *BMC Neurol*. 2015;15:84. doi:10.1186/s12883-015-0340-2.
 47. Lou JS, Reeves A, Benice T, Sexton G. Fatigue and depression are associated with poor quality of life in ALS. *Neurology*. 2003;60(1):122-123.
 48. Lulé D, Häcker S, Ludolph A, Birbaumer N, Kübler A. Depression and quality of life in patients with amyotrophic lateral sclerosis. *Dtsch Arztebl Int*. 2008;105(23):397.
 49. Matuz T, Birbaumer N, Hautzinger M, Kubler A. Coping with amyotrophic lateral sclerosis: An integrative view. *J Neurol Neurosurg Psychiatry*. 2010;81(8):893-898.
 50. Matuz T, Birbaumer N, Hautzinger M, Kübler A. Psychosocial adjustment to ALS: A longitudinal study. *Front Psychol*. 2015;6:1197.
 51. McCabe MP, Firth L, O'Connor E. Mood and quality of life among people with progressive neurological illnesses. *Int J Clin Heal Psychol*. 2009;9(1):21-35.
 52. Montel S, Albertini L, Spitz E. Coping strategies in relation to quality of life in amyotrophic lateral sclerosis. *Muscle Nerve*. 2012;45(1):131.
 53. Mora S, Salas T, Fajardo L, Iváñez L, Rodríguez-Santos F. Self perceived emotional functioning of Spanish patients with amyotrophic lateral sclerosis: A longitudinal study. *Front Psychol*. 2013;3.
 54. O'Doherty Jane L, Hickey A, Hardiman O, O'Doherty LJ, Hickey A, Hardiman O. Measuring life quality, physical function and psychological well-being in neurological illness. *Amyotroph Lateral Scler*. 2010;11(5):461-468.
 55. Pagnini F, Phillips D, Bosma M, et al. Mindfulness, physical impairment and psychological well-being in people with amyotrophic lateral sclerosis. *Psychol Health*. 2015;30(5):503. doi:10.1080/08870446.2014.982652.
 56. Peric S, Rakocevic-Stojanovic V, Stevic Z, et al. Health-related quality of life in patients with myotonic dystrophy type 1 and amyotrophic lateral sclerosis. *Acta Neurol Belg*.

2010;110(1):71-77.

57. Pizzimenti A, Aragona M, Onesti E IM. Depression, pain and quality of life in patients with amyotrophic lateral sclerosis: A cross-sectional study. *Funct Neurol*. 2013;28(2):115-119.
58. Rabkin JG, Wagner GJ, Del Bene M. Resilience and distress among amyotrophic lateral sclerosis patients and caregivers. *Psychosom Med*. 2000;62(2):271-279.
59. Roach R. Executive deficits in amyotrophic lateral sclerosis: Examining the consequences of self-regulatory impairment on quality of life. *Diss Abstr Int Sect B Sci Eng*. 2015;75(9).
60. Thakore NJ, Pioro EP, Thakore J, Pioro P. Depression in ALS in a large self-reporting cohort. *Neurology*. 2016;86(11):1031. doi:10.1212/WNL.0000000000002465.
61. Trail M, Nelson N, Van N, Appel H, Lai C. Major stressors facing patients with amyotrophic lateral sclerosis (ALS): a survey to identify their concerns and to compare with those of their caregivers. *Amyotroph Lateral Scler Other Motor Neuron Disord*. 2004;5(1):40.
62. Tramonti F, Bongioanni P, Di Carolina B, Davitti S, Rossi B. Quality of life of patients with amyotrophic lateral sclerosis. *Psychol Health Med*. 2012;17(5):621.
63. Vignola A, Guzzo A, Calvo A, et al. Anxiety undermines quality of life in ALS patients and caregivers. *Eur J Neurol*. 2008;15(11):1231.
64. Winter Y, Schepelmann K, Spottke AE, et al. Health-related quality of life in ALS, myasthenia gravis and facioscapulohumeral muscular dystrophy. *J Neurol*. 2010;257(9):1473-1481.
65. CASP Tools & Checklists. <http://www.casp-uk.net/casp-tools-checklists>. Accessed September 24, 2017.
66. Ottawa Hospital Research Institute. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp. Accessed September 24, 2017.
67. von Elm E, Altman DG, Egger M, et al. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *BMJ*. 2007;335(7624):806-808. doi:10.1136/bmj.39335.541782.AD.

68. Critical appraisal checklists - Specialist Unit for Review Evidence - Cardiff University. <http://www.cardiff.ac.uk/specialist-unit-for-review-evidence/resources/critical-appraisal-checklists>. Accessed September 24, 2017.
69. Felgoise SH, Stewart JL, Bremer BA, Walsh SM, Bromberg MB, Simmons Z. The SEIQoL-DW for assessing quality of life in ALS: Strengths and limitations. *Amyotroph Lateral Scler*. 2009;10(5-6):456-462. doi:10.3109/17482960802444840.
70. Colamonico J, Formella A, Bradley W. Pseudobulbar Affect: Burden of Illness in the USA. *Adv Ther*. 2012;29(9):775-798. doi:10.1007/s12325-012-0043-7.
71. Taylor B. Sexuality, intimacy and motor neurone disease: Matters of concern. *Br J Neurosci Nurs*. 2014;10(5):242-251.
72. Wasner M, Bold U, Vollmer C, Borasio Domenico G. Sexuality in patients with amyotrophic lateral sclerosis and their partners. *J Neurol*. 2004;251(4):445.
73. Marconi A, Meloni G, Fossati F, et al. Aggressiveness, sexuality, and obsessiveness in late stages of ALS patients and their effects on caregivers. *Amyotroph Lateral Scler*. 2012;13(5):452.
74. Kurt A, Nijboer F, Matuz T, Kubler A. Depression and anxiety in individuals with amyotrophic lateral sclerosis: Epidemiology and management. *CNS Drugs*. 2007;21(4):279-291.
75. Lule D, Ludolph AC. Quality of Life and Depression in ALS - A Matter of Perspective. *Klin Neurophysiol*. 2013;44(2):154-158. doi:10.1055/s-0033-1345200.
76. Jones R, Jivraj N, Balendra R, et al. Health utility decreases with increasing clinical stage in amyotrophic lateral sclerosis. *Amyotroph Lateral Scler Frontotemporal Degener*. 2014;15(3):285.
77. Rabkin JG, Goetz R, Factor-Litvak P, et al. Depression and wish to die in a multicenter cohort of ALS patients. *Amyotroph LATERAL Scler Front Degener*. 2015;16(3):265-273. doi:10.3109/21678421.2014.980428.
78. Rabkin JG, Albert SM, Del ML ML, et al. Prevalence of depressive disorders and change over time in late-stage ALS. *Neurology*. 2005;65(1):62.

79. Salas T, Mora JS, Fajardo ML, Ivanez L, Rodriguez F. Self-perceived quality of life in the course of the disease in Spanish patients with amyotrophic lateral sclerosis (ALS). *Eur J Neurol*. 2009;16(S3):230.
80. Caga J, Ramsey E, Hogden A, Mioshi E, Kiernan MC. A longer diagnostic interval is a risk for depression in amyotrophic lateral sclerosis. *Palliat Support Care*. 2015;13(4):1019-1024. doi:10.1017/S1478951514000881.
81. Ozanne A, Strang S, Persson L. Quality of life, anxiety and depression in ALS patients and their next of kin. *J Clin Nurs*. 2011;20(1):283.
82. Goldstein LH, Atkins L, Landau S, Brown RG, Leigh PN. Longitudinal predictors of psychological distress and self-esteem in people with ALS. *Neurology*. 2006;67(9):1652-1658. doi:10.1212/01.wnl.0000242886.91786.47.
83. Larsson BJ, Nordin K, Askmark HH, et al. Coping strategies among patients with newly diagnosed amyotrophic lateral sclerosis. *J Clin Nurs*. 2014;23(21-22):3148. doi:10.1111/jocn.12557.
84. Lee JN, Rigby SA, Burchardt F, Thornton EW, Dougan C, Young CA. Quality of life issues in motor neurone disease: the development and validation of a coping strategies questionnaire, the MND Coping Scale. *J Neurol Sci*. 2001;191(1-2):79. doi:10.1016/S0022-510X(01)00619-0.
85. Oh H, Sin M-K, Schepp KG, Choi-Kwon S. Depressive Symptoms and Functional Impairment Among Amyotrophic Lateral Sclerosis Patients in South Korea. *Rehabil Nurs*. 2012;37(3):136-144.
86. Rigby SA, Thornton EW, Tedman S, Burchardt F, Young CA, Dougan C. Quality of life assessment in MND: development of a social withdrawal scale. *J Neurol Sci*. 1999;169(1-2):26. doi:10.1016/S0022-510X(99)00212-9.
87. Hirano YM, Yamazaki Y, Shimizu J, Togari T, Bryce TJ. Ventilator dependence and expressions of need: a study of patients with amyotrophic lateral sclerosis in Japan. *Soc Sci Med*. 2006;62(6):1403-1414.
88. Caligari M, Godi M, Guglielmetti S, Franchignoni F, Nardone A. Eye tracking

- communication devices in amyotrophic lateral sclerosis: impact on disability and quality of life. *Amyotroph Lateral Scler Frontotemporal Degener.* 2013;14(7):546.
89. Calvo A, Pasian V, Moglia C, et al. Eye-tracking communication system: Impact on quality of life and mood in patients with ALS in locked-in syndrome. *Amyotroph Lateral Scler.* 2009;10:201-202.
90. Calvo A, Chio A, Castellina E, et al. Eye tracking impact on quality-of-life of ALS patients. In: Miesenberger, K and Klaus, J and Zagler, W and Karshmer, A, ed. *COMPUTERS HELPING PEOPLE WITH SPECIAL NEEDS, PROCEEDINGS.* Vol 5105. LECTURE NOTES IN COMPUTER SCIENCE. ; 2008:70-77.
91. Giacone S, Ilardi A, Pasian V, et al. Can eye-tracking system communication improve quality of life and mood in ALS patients with locked-in syndrome? *J Neurol.* 2010;257(1):S113.
92. Holmoy T, Worren T. Augmentative and alternative communication in amyotrophic lateral sclerosis [Norwegian] Kommunikasjonshjelpemidler ved amyotrofisk lateral sklerose. *Tidsskr den Nor Laegeforening.* 2006;126(19):2523-2525.
93. Hwang C-S, Weng H-H, Wang L-F, Tsai C-H, Chang H-T. An eye-tracking assistive device improves the quality of life for ALS patients and reduces the caregivers' burden. *J Mot Behav.* 2014;46(4):233.
94. Koerner S, Siniawski M, Kollewe K, et al. Speech therapy and communication device: impact on quality of life and mood in patients with amyotrophic lateral sclerosis. *Amyotroph LATERAL Scler Front Degener.* 2013;14(1):240.
doi:10.3109/21678421.2013.774586.
95. Londral A, Pinto A, Pinto S, Azevedo L, De Mamede C, De Carvalho M. QUALITY OF LIFE IN AMYOTROPHIC LATERAL SCLEROSIS PATIENTS AND CAREGIVERS: IMPACT OF ASSISTIVE COMMUNICATION FROM EARLY STAGES. *Muscle Nerve.* 2015;52(6):933.
doi:10.1002/mus.24659.
96. Schmalbach S, Sieniawski M, Kollewe K, Dengler R, Krampfl K, Petri S. Speech therapy and communication devices: Impact on quality of life in patients with ALS. *Amyotroph Lateral Scler.* 2010;11.

97. Pessia A, Ilardi A, Pasian V, et al. Use of eye-tracking system communication in ALS patients: Positive impact on quality of life and mood. *Eur J Neurol*. 2010;17(3, SI):303.
98. Caron J, Light J. ``My World Has Expanded Even Though I'm Stuck at Home{'}``: Experiences of Individuals With Amyotrophic Lateral Sclerosis Who Use Augmentative and Alternative Communication and Social Media. *Am J Speech Lang Pathol*. 2015;24(4):680-695. doi:10.1044/2015_AJSLP-15-0010.
99. O'Brien M, Clark D. Spirituality and faith: Means for coping with the effects of ALS/MND. *Amyotroph Lateral Scler*. 2009;10.
100. O'brien R, Clark D. Spirituality and/or religious faith: A means for coping with the effects of amyotrophic lateral sclerosis/motor neuron disease? *Palliat Support Care*. 2015;13(6):1603.
101. Piro E, Brooks B, Cummings J, et al. Persistent efficacy of dextromethorphan (DM)/Quinidine (Q) for pseudobulbar affect (PBA): Results from a 12-Week, open-label extension (OLE) study. *Neurology*. 75(4).
102. Pope E. AVP-923 as a novel treatment for pseudobulbar affect in ALS. *Prog Neurother Neuropsychopharmacol*. 2006;91.
103. Rosen H. Dextromethorphan/quinidine sulfate for pseudobulbar affect. *Drugs Today (Barc)*. 2008;44(9):661.
104. Brooks BR, Thisted RA, Appel SH, et al. Treatment of pseudobulbar affect in ALS with dextromethorphan/quinidine: a randomized trial. *Neurology*. 2004;63(8):1364.
105. Wicks P, Kaye R. Pseudobulbar affect: Better understanding through research on a social network. *Amyotroph Lateral Scler*. 2009;10:169-170.
106. Palmieri A, Abrahams S, Soraru G, et al. Emotional Lability in MND: Relationship to cognition and psychopathology and impact on caregivers. *J Neurol Sci*. 2009;278(1-2):16-20. doi:10.1016/j.jns.2008.10.025.
107. Lule D, Zickler C, Hacker S, et al. Life can be worth living in locked-in syndrome. *Prog Brain Res*. 2009;177(C):339-351.
108. Moher D, Liberati A, Tetzlaff J, Altman DG, Group TP. Preferred Reporting Items for

- Systematic Reviews and Meta-Analyses: The PRISMA Statement. *PLoS Med.* 2009;6(7):e1000097. doi:10.1371/journal.pmed.1000097.
109. Kasarskis EJ, Hodskins J, Clair WHS. Unilateral parotid electron beam radiotherapy as palliative treatment for sialorrhea in amyotrophic lateral sclerosis. *J Neurol Sci.* 2011;308(1-2):155-157.
 110. Scully C, Limeres J, Gleeson M, Tomas I, Diz P. Drooling. *J ORAL Pathol Med.* 2009;38(4):321-327. doi:10.1111/j.1600-0714.2008.00727.x.
 111. Stephens HE, Lehman E, Raheja D, et al. The role of mental health and self-efficacy in the pain experience of patients with amyotrophic lateral sclerosis. *Amyotroph LATERAL Scler Front Degener.* 2016;17(3):206. doi:10.3109/21678421.2015.1131832.
 112. Finsterer J, Mahjoub SZ. Fatigue in Healthy and Diseased Individuals. *Am J Hosp Palliat Med.* 2014;31(5):562-575. doi:10.1177/1049909113494748.
 113. Cui L-Y, Liu M-S, Li X-G, et al. Behavioral Symptoms in Motor Neuron Disease and Their Negative Impact on Caregiver Burden. *Chin Med J (Engl).* 2015;128(17):2295. doi:10.4103/0366-6999.163393.
 114. Hsieh S, Leyton CE, Caga J, et al. The Evolution of Caregiver Burden in Frontotemporal Dementia with and without Amyotrophic Lateral Sclerosis. Slachevsky A, ed. *J Alzheimer's Dis.* 2015;49(3):875-885. doi:10.3233/JAD-150475.
 115. Galvin M, Corr B, Madden C, et al. Caregiving in ALS – a mixed methods approach to the study of Burden. *BMC Palliat Care.* 2016;15(1):81. doi:10.1186/s12904-016-0153-0.
 116. Whitehead B, O'Brien MR, Jack BA, Mitchell D. Experiences of dying, death and bereavement in motor neurone disease: A qualitative study. *Palliat Med.* 2012;26(4):368-378. doi:10.1177/0269216311410900.
 117. Wallace SE, Gournas EG, Laurie G, Shoush O, Wright J. Respecting Autonomy Over Time: Policy and Empirical Evidence on Re-Consent in Longitudinal Biomedical Research. *Bioethics.* 2016;30(3):210-217. doi:10.1111/bioe.12165.
 118. Gibbons CJ, Mills RJ, Thornton EW, et al. Development of a patient reported outcome measure for fatigue in motor neurone disease: the Neurological Fatigue Index (NFI-

- MND). *Health Qual Life Outcomes*. 2011;9(1):101. doi:10.1186/1477-7525-9-101.
119. Gibbons CJ, Mills RJ, Thornton EW, et al. Rasch analysis of the hospital anxiety and depression scale (HADS) for use in motor neurone disease. *Health Qual Life Outcomes*. 2011;9:82. doi:10.1186/1477-7525-9-82.
 120. Gibbons CJ, Thornton EW, Ealing J, et al. Assessing social isolation in motor neurone disease: a Rasch analysis of the MND Social Withdrawal Scale. *J Neurol Sci*. 2013;334(1-2):112-118. doi:10.1016/j.jns.2013.08.002.
 121. Motor Neurone Disease (MND) | MIMS online. <http://www.mims.co.uk/motor-neurone-disease-mnd/neurology/article/882300>. Accessed June 5, 2017.
 122. Pupillo E, Messina P, Logroscino G, et al. Trauma and amyotrophic lateral sclerosis: a case-control study from a population-based registry. *Eur J Neurol*. 2012;19(12):1509-1517. doi:10.1111/j.1468-1331.2012.03723.x.
 123. Bonvicini F, Vinceti M, Marcello N, Rodolfi R, Rinaldi M. The epidemiology of amyotrophic lateral sclerosis in Reggio Emilia, Italy. *Amyotroph Lateral Scler*. 2008;9(6):350-353. doi:10.1080/17482960802196150.
 124. Logroscino G, Beghi E, Zoccolella S, et al. Incidence of amyotrophic lateral sclerosis in southern Italy: a population based study. *J Neurol Neurosurg Psychiatry*. 2005;76(8):1094-1098. doi:10.1136/jnnp.2004.039180.
 125. Chiò A. Risk factors in the early diagnosis of ALS: European epidemiological studies. *Amyotroph Lateral Scler Other Motor Neuron Disord*. 2000;1 Suppl 1:S13-8.
 126. Depression in adults: recognition and management | Guidance and guidelines | NICE.
 127. Depression in adults with a chronic physical health problem: recognition and management | Guidance and guidelines | NICE.
 128. Herrero MJ, Blanch J, Peri JM, De Pablo J, Pintor L, Bulbena A. A validation study of the hospital anxiety and depression scale (HADS) in a Spanish population. *Gen Hosp Psychiatry*. 25(4):277-283.
 129. Krespi Boothby MR, Hill J, Holcombe C, Clark L, Fisher J, Salmon P. [The accuracy of HADS and GHQ-12 in detecting psychiatric morbidity in breast cancer patients]. *Turk Psikiyatri*

Derg. 2010;21(1):49-59.

130. Abrahams S, Goldstein LH, Al-Chalabi A, et al. Relation between cognitive dysfunction and pseudobulbar palsy in amyotrophic lateral sclerosis. *J Neurol Neurosurg Psychiatry.* 1997;62(5):464-472.
131. Wang Y-P, Gorenstein C. Assessment of depression in medical patients: a systematic review of the utility of the Beck Depression Inventory-II. *Clinics (Sao Paulo).* 2013;68(9):1274-1287. doi:10.6061/clinics/2013(09)15.
132. Bjelland I, Dahl AA, Haug TT, Neckelmann D. The validity of the Hospital Anxiety and Depression Scale. An updated literature review. *J Psychosom Res.* 2002;52(2):69-77.
133. Porter E, Chambless DL, McCarthy KS, et al. Psychometric Properties of the Reconstructed Hamilton Depression and Anxiety Scales. *J Nerv Ment Dis.* February 2017;1. doi:10.1097/NMD.0000000000000666.
134. Segal DL, Coolidge FL, Cahill BS, O'Riley AA. Psychometric Properties of the Beck Depression Inventory II (BDI-II) Among Community-Dwelling Older Adults. *Behav Modif.* 2008;32(1):3-20. doi:10.1177/0145445507303833.
135. Kjaergaard M, Arfwedson Wang CE, Waterloo K, Jorde R. A study of the psychometric properties of the Beck Depression Inventory-II, the Montgomery and Åsberg Depression Rating Scale, and the Hospital Anxiety and Depression Scale in a sample from a healthy population. *Scand J Psychol.* 2014;55(1):83-89. doi:10.1111/sjop.12090.
136. Nilges P, Essau C. Die Depressions-Angst-Stress-Skalen. *Der Schmerz.* 2015;29(6):649-657. doi:10.1007/s00482-015-0019-z.
137. Hopko DR, Bell JL, Armento MEA, et al. The phenomenology and screening of clinical depression in cancer patients. *J Psychosoc Oncol.* 2008;26(1):31-51.
138. Osório FL, Carvalho ACF, Fracalossi TA, Crippa JAS, Loureiro ESR. Are Two Items Sufficient to Screen for Depression within the Hospital Context? *Int J Psychiatry Med.* 2012;44(2):141-148. doi:10.2190/PM.44.2.e.
139. WHO | WHO Disability Assessment Schedule 2.0 (WHODAS 2.0). *WHO.* 2017.
140. Tedman BM, Young CA, Williams IR. Assessment of depression in patients with motor

- neuron disease and other neurologically disabling illness. *J Neurol Sci*. October 1997:S75-9.
141. Huang X, Cui F, Zhu W, et al. Frequency and risk factor analysis of cognitive and anxiety-depressive disorders in patients with amyotrophic lateral sclerosis/motor neuron disease. *Neuropsychiatr Dis Treat*. 2015;11:2847. doi:10.2147/NDT.S90520.
 142. Goldstein LH, Adamson M, Jeffrey L, et al. The psychological impact of MND on patients and carers. *J Neurol Sci*. October 1998:S114-21.
 143. Hogg KE, Goldstein H, Leigh PN. The psychological impact of motor neurone disease. *Psychol Med*. 1994;24(3):625.
 144. Baxter S, Reed H, Clarke Z, et al. Evaluating a novel cervical orthosis, the Sheffield Support Snood, in patients with amyotrophic lateral sclerosis/motor neuron disease with neck weakness. *Amyotroph Lateral Scler Front Degener*. 2016;17(5-6):436-442. doi:10.3109/21678421.2016.1148170.
 145. Smith SJ, Young CA. The role of affect on the perception of disability in multiple sclerosis. *Clin Rehabil*. 2000;14(1):50-54. doi:10.1191/026921500676724210.
 146. Kim HFS, Kunik ME, Molinari VA, et al. Functional Impairment in COPD Patients: The Impact of Anxiety and Depression. *Psychosomatics*. 2000;41(6):465-471. doi:10.1176/appi.psy.41.6.465.
 147. Freese EC, Acitelli RM, Gist NH, Cureton KJ, Evans EM, O'Connor PJ. Effect of Six Weeks of Sprint Interval Training on Mood and Perceived Health in Women at Risk for Metabolic Syndrome. *J Sport Exerc Psychol*. 2014;36(6):610-618. doi:10.1123/jsep.2014-0083.
 148. Takai I. [Influence of comprehensive intervention composed of nutrition and exercise on the development of exercise habits and self-perceived health among community-dwelling elderly individuals]. *Nihon Ronen Igakkai Zasshi*. 2013;50(4):522-527.
 149. Van Puymbroeck M, Burk BN, Shinew KJ, Kuhlenschmidt MC, Schmid AA. Perceived Health Benefits From Yoga Among Breast Cancer Survivors. *Am J Heal Promot*. 2013;27(5):308-315. doi:10.4278/ajhp.110316-QUAL-119.
 150. Nguyen MH, Kruse A. The effects of Tai Chi training on physical fitness, perceived health,

and blood pressure in elderly Vietnamese. *Open Access J Sport Med.* 2012;3:7.
doi:10.2147/OAJSM.S27329.

151. Chang AK, Fritschi C, Kim MJ. Sedentary Behavior, Physical Activity, and Psychological Health of Korean Older Adults with Hypertension: Effect of an Empowerment Intervention. *Res Gerontol Nurs.* 2013;6(2):81-88. doi:10.3928/19404921-20121219-01.
152. Lee M, Son J, Kim J, Yoon B. Individualized feedback-based virtual reality exercise improves older women's self-perceived health: A randomized controlled trial. *Arch Gerontol Geriatr.* 2015;61(2):154-160. doi:10.1016/j.archger.2015.06.010.
153. Yarborough BJH, Leo MC, Yarborough MT, et al. Improvement in Body Image, Perceived Health, and Health-Related Self-Efficacy Among People With Serious Mental Illness: The STRIDE Study. *Psychiatr Serv.* 2016;67(3):296-301. doi:10.1176/appi.ps.201400535.
154. Ensari I, Motl RW, Pilutti LA. Exercise training improves depressive symptoms in people with multiple sclerosis: Results of a meta-analysis. *J Psychosom Res.* 2014;76(6):465-471. doi:10.1016/j.jpsychores.2014.03.014.
155. Kelley GA, Kelley KS, Hootman JM. Effects of exercise on depression in adults with arthritis: a systematic review with meta-analysis of randomized controlled trials. *Arthritis Res Ther.* 2015;17(1):21. doi:10.1186/s13075-015-0533-5.
156. Sundsli K, Söderhamn U, Espnes GA, Söderhamn O. Self-care telephone talks as a health-promotion intervention in urban home-living persons 75+ years of age: a randomized controlled study. *Clin Interv Aging.* 2014;9:95. doi:10.2147/CIA.S55925.
157. Wilz G, Meichsner F, Soellner R. Are psychotherapeutic effects on family caregivers of people with dementia sustainable? Two-year long-term effects of a telephone-based cognitive behavioral intervention. *Aging Ment Health.* 2017;21(7):774-781. doi:10.1080/13607863.2016.1156646.
158. Martín-Carrasco M, Martín MF, Valero CP, et al. Effectiveness of a psychoeducational intervention program in the reduction of caregiver burden in alzheimer's disease patients' caregivers. *Int J Geriatr Psychiatry.* 2009;24(5):489-499. doi:10.1002/gps.2142.
159. Basu R, Hochhalter AK, Stevens AB. The Impact of the REACH II Intervention on

- Caregivers' Perceived Health. *J Appl Gerontol*. 2015;34(5):590-608.
doi:10.1177/0733464813499640.
160. Winzer R, Brucefors AB. Does a short-term intervention promote mental and general health among young adults? – An evaluation of counselling. *BMC Public Health*. 2007;7(1):319. doi:10.1186/1471-2458-7-319.
161. Linden A, Butterworth SW, Prochaska JO. Motivational interviewing-based health coaching as a chronic care intervention. *J Eval Clin Pract*. 2010;16(1):166-174. doi:10.1111/j.1365-2753.2009.01300.x.
162. McDonald PE, Zauszniewski JA, Bekhet AK, DeHelian L, Morris DL. The effect of acceptance training on psychological and physical health outcomes in elders with chronic conditions. *J Natl Black Nurses Assoc*. 2011;22(2):11-19.
163. Fanos JH, Gelinas DF, Foster RS, Postone N, Miller RG. Hope in Palliative Care: From Narcissism to Self-Transcendence in Amyotrophic Lateral Sclerosis. *J Palliat Med*. 2008;11(3):470-475. doi:10.1089/jpm.2007.0098.
164. Iwamoto R, Yamawaki N, Sato T. Increased self-transcendence in patients with intractable diseases. *Psychiatry Clin Neurosci*. 2011;65(7):638-647. doi:10.1111/j.1440-1819.2011.02256.x.
165. Erik Erikson | Psychosocial Stages | Simply Psychology.
<https://www.simplypsychology.org/Erik-Erikson.html>. Accessed June 5, 2017.
166. Jenkins M, Hollinger H, McDermott J. The evidence for symptomatic treatments in amyotrophic lateral sclerosis. *Curr Opin Neurol*. 2014;27(5):524-532.
167. Hobson E V, McDermott CJ, Hobson V, McDermott J. Supportive and symptomatic management of amyotrophic lateral sclerosis. *Nat Rev Neurol*. 2016;12(9):526. doi:10.1038/nrneurol.2016.111.
168. Delgadillo J, Dawson A, Gilbody S, Böhnke JR. Impact of long-term medical conditions on the outcomes of psychological therapy for depression and anxiety. *Br J Psychiatry*. 2016.
169. Clarke DM, McLeod JE, Smith GC, Trauer T, Kissane DW. A comparison of psychosocial and physical functioning in patients with motor neurone disease and metastatic cancer. *J*

- Palliat Care*. 2005;21(3):173-179.
170. Soundy A, Condon N. Patients experiences of maintaining mental well-being and hope within motor neuron disease: a thematic synthesis. *Front Psychol*. 2015;6:606. doi:10.3389/fpsyg.2015.00606.
 171. Locock L, Brown JB. "All in the same boat"? Patient and carer attitudes to peer support and social comparison in Motor Neurone Disease (MND). *Soc Sci Med*. 2010;71(8):1498-1505. doi:10.1016/j.socscimed.2010.06.043.
 172. McCabe P, O'Connor J. Why are some people with neurological illness more resilient than others? *Psychol Health Med*. 2012;17(1):17.
 173. Pagnini F, Simmons Z, Corbo M, Molinari E. Amyotrophic lateral sclerosis: Time for research on psychological intervention? *Amyotroph Lateral Scler*. 2012;13(5):416-417. doi:10.3109/17482968.2011.653572.
 174. Sharpe L, Curran L. Understanding the process of adjustment to illness. *Soc Sci Med*. 2006;62(5):1153-1166. doi:10.1016/j.socscimed.2005.07.010.
 175. McDonald ER, Wiedenfeld SA, Hillel A, Carpenter CL, Walter RA. Survival in amyotrophic lateral sclerosis. The role of psychological factors. *Arch Neurol*. 1994;51(1):17-23.
 176. Johnston M, Earll L, Giles M, McClenahan R, Stevens D, Morrison V. Mood as a predictor of disability and survival in patients newly diagnosed ...: University of Liverpool Library. *Br J Health Psychol*. 1999;4:p127-p136.
 177. Chio A, Logroscino G, Hardiman O, et al. Prognostic factors in ALS: A critical review. *Amyotroph Lateral Scler*. 2009;10(5-6):310-323.
 178. Learn | A Life Story Foundation. <https://www.alifestoryfoundation.org/learn/?gclid=CPyz87n2qNICFS4W0wodwTIFQQ>. Accessed June 5, 2017.
 179. Remember the ice bucket challenge? It just funded an ALS breakthrough | Society | The Guardian. <https://www.theguardian.com/society/2016/jul/26/ice-bucket-challenge-als-charity-gene-discovery>. Accessed June 5, 2017.
 180. Ice Bucket Challenge | ALS Therapy Development Institute.

<https://www.als.net/icebucketchallenge/?gclid=CN6Pwrf2qNICFS4W0wodwTIFQQ>.
Accessed June 5, 2017.

181. Soundy A, Liles C, Stubbs B, Roskell C. Identifying a Framework for Hope in Order to Establish the Importance of Generalised Hopes for Individuals Who Have Suffered a Stroke. *Adv Med*. 2014;2014:1-8. doi:10.1155/2014/471874.
182. Fanos JH, Gelinis DF, Foster RS, Postone N, Miller RG. Hope in palliative care: From narcissism to self-transcendence in amyotrophic lateral sclerosis. *J Palliat Med*. 2008;11(3):470-475. doi:10.1089/jpm.2007.0098.
183. Centers LC. Beyond denial and despair: ALS and our heroic potential for hope. *J Palliat Care*. 2001;17(4):259-264.
184. Soundy A, Smith B, Dawes H, Pall H, Gimbrere K, Ramsay J. Patient's expression of hope and illness narratives in three neurological conditions: a meta-ethnography. *Health Psychol Rev*. 2013;7(2):177-201. doi:10.1080/17437199.2011.568856.
185. Plahuta M, McCulloch Jan B, Kasarskis J, Ross A, Walter A, McDonald R. Amyotrophic lateral sclerosis and hopelessness: psychosocial factors. *Soc Sci Med*. 2002;55(12):2131.
186. Rotter JB. Generalized expectancies for internal versus external control of reinforcement. *Psychol Monogr*. 1966;80(1):1-28.
187. Pahlevan Sharif S. Locus of control, quality of life, anxiety, and depression among Malaysian breast cancer patients: The mediating role of uncertainty. *Eur J Oncol Nurs*. 2017;27:28-35. doi:10.1016/j.ejon.2017.01.005.
188. Brown AJ, Sun CC, Urbauer DL, Bodurka DC, Thaker PH, Ramondetta LM. Feeling powerless: Locus of control as a potential target for supportive care interventions to increase quality of life and decrease anxiety in ovarian cancer patients. *Gynecol Oncol*. 2015;138(2):388-393. doi:10.1016/j.ygyno.2015.05.005.
189. Omani Samani R, Maroufizadeh S, Navid B, Amini P. Locus of control, anxiety, and depression in infertile patients. *Psychol Health Med*. 2017;22(1):44-50. doi:10.1080/13548506.2016.1231923.
190. Eccles FJR, Simpson J. A review of the demographic, clinical and psychosocial correlates

- of perceived control in three chronic motor illnesses. *Disabil Rehabil.* 2011;33(13-14):1065-1088. doi:10.3109/09638288.2010.525287.
191. Goldstein LH, Atkins L, Leigh PN. Health-related locus of control: does it change in motor neurone disease (MND)? *Amyotroph Lateral Scler Other Motor Neuron Disord.* 2003;4(1):27-30.
192. McDonald ER, Hillel A, Wiedenfeld SA. Evaluation of the psychological status of ventilatory-supported patients with ALS/MND. *Palliat Med.* 1996;10(1):35-41. doi:10.1177/026921639601000106.
193. Ando H, Williams C, Angus RM, et al. Why don't they accept non-invasive ventilation?: Insight into the interpersonal perspectives of patients with motor neurone disease. *Br J Health Psychol.* 2015;20(2):341-359. doi:10.1111/bjhp.12104.
194. Lazarus RS, Folkman S. *Stress, Appraisal, and Coping.*; 1984.
195. Herth K. Abbreviated instrument to measure hope: development and psychometric evaluation. *J Adv Nurs.* 1992;17(10):1251-1259.
196. Wallston KA, Stein MJ, Smith CA. Form C of the MHLC Scales: A Condition-Specific Measure of Locus of Control. *J Pers Assess.* 1994;63(3):534-553. doi:10.1207/s15327752jpa6303_10.
197. McLeod E, Clarke M. A review of psychosocial aspects of motor neurone disease. *J Neurol Sci.* 2007;258(1):4.
198. Ganzini L, Block S. Physician-Assisted Death — A Last Resort? *N Engl J Med.* 2002;346(21):1663-1665. doi:10.1056/NEJM200205233462113.
199. Averill AJ, Kasarskis EJ, Segerstrom SC. Psychological health in patients with amyotrophic lateral sclerosis. *Amyotroph LATERAL Scler.* 2007;8(4):243-254. doi:10.1080/17482960701374643.
200. Yeung DY, Ho SMY, Mak CWY. Brief report: Attention to positive information mediates the relationship between hope and psychosocial well-being of adolescents. *J Adolesc.* 2015;42:98-102. doi:10.1016/j.adolescence.2015.04.004.
201. Carretta CM, Ridner SH, Dietrich MS. Hope, Hopelessness, and Anxiety: A Pilot

- Instrument Comparison Study. *Arch Psychiatr Nurs*. 2014;28(4):230-234.
doi:10.1016/j.apnu.2014.05.005.
202. Muyan M, Chang EC, Jilani Z, Yu T, Lin J, Hirsch JK. Loneliness and Negative Affective Conditions in Adults: Is There Any Room for Hope in Predicting Anxiety and Depressive Symptoms? *J Psychol*. 2016;150(3):333-341. doi:10.1080/00223980.2015.1039474.
203. Krause N, Pargament KI, Ironson G. In the Shadow of Death: Religious Hope as a Moderator of the Effects of Age on Death Anxiety. *Journals Gerontol Ser B Psychol Sci Soc Sci*. April 2016:gbw039. doi:10.1093/geronb/gbw039.
204. Dufault K, Martocchio BC. Symposium on compassionate care and the dying experience. Hope: its spheres and dimensions. *Nurs Clin North Am*. 1985;20(2):379-391.
205. Ganzini L, Johnston WS, McFarland BH, Tolle SW, Lee MA. Attitudes of Patients with Amyotrophic Lateral Sclerosis and Their Care Givers toward Assisted Suicide. *N Engl J Med*. 1998;339(14):967-973. doi:10.1056/NEJM199810013391406.
206. Rahimipour M, Shahgholian N, Yazdani M. Effect of hope therapy on depression, anxiety, and stress among the patients undergoing hemodialysis. *Iran J Nurs Midwifery Res*. 2015;20(6):694. doi:10.4103/1735-9066.170007.
207. Ho SM, Ho JW, Pau BK, Hui BP, Wong RS, Chu AT. Hope-based intervention for individuals susceptible to colorectal cancer: a pilot study. *Fam Cancer*. 2012;11(4):545-551. doi:10.1007/s10689-012-9545-3.
208. Affleck G, Tennen H, Pfeiffer C, Fifield J. Appraisals of control and predictability in adapting to a chronic disease. *J Pers Soc Psychol*. 1987;53(2):273-279.
209. Luszczynska A, Schwarzer R. Multidimensional Health Locus of Control: Comments on the Construct and its Measurement. *J Health Psychol*. 2005;10(5):633-642. doi:10.1177/1359105305055307.
210. Park CL, Folkman S, Bostrom A. Appraisals of controllability and coping in caregivers and HIV+ men: testing the goodness-of-fit hypothesis. *J Consult Clin Psychol*. 2001;69(3):481-488.
211. Stenström U, Wikby A, Andersson P-O, Rydén O. Relationship between locus of control

- beliefs and metabolic control in insulin-dependent diabetes mellitus. *Br J Health Psychol.* 1998;3(1):15-25. doi:10.1111/j.2044-8287.1998.tb00552.x.
212. Brownlee S, Leventhal H, Leventhal EA. Chapter12 – Regulation, Self-Regulation, and Construction of the Self in the Maintenance of Physical Health. In: *Handbook of Self-Regulation.* ; 2000:369-416. doi:10.1016/B978-012109890-2/50041-X.
213. WHO | WHO Quality of Life-BREF (WHOQOL-BREF). *WHO.* 2013.
214. Rooney J, Burke T, Vajda A, Heverin M, Hardiman O. What does the ALSFRS-R really measure? A longitudinal and survival analysis of functional dimension subscores in amyotrophic lateral sclerosis. *J Neurol Neurosurg Psychiatry.* 2017;88(5):381-385. doi:10.1136/jnnp-2016-314661.
215. Skevington SM, Lotfy M, O’Connell KA, WHOQOL Group. The World Health Organization’s WHOQOL-BREF quality of life assessment: Psychometric properties and results of the international field trial. A Report from the WHOQOL Group. *Qual Life Res.* 2004;13(2):299-310. doi:10.1023/B:QURE.0000018486.91360.00.
216. Carver CS, Scheier MF. Scaling back goals and recalibration of the affect system are processes in normal adaptive self-regulation: understanding “response shift” phenomena. *Soc Sci Med.* 2000;50(12):1715-1722. doi:10.1016/S0277-9536(99)00412-8.
217. Scharloo M, Kaptein A., Weinman J, et al. Illness perceptions, coping and functioning in patients with rheumatoid arthritis, chronic obstructive pulmonary disease and psoriasis. *J Psychosom Res.* 1998;44(5):573-585. doi:10.1016/S0022-3999(97)00254-7.
218. Hugel H, Pih N, Dougan CP, Rigby S, Young CA. Identifying poor adaptation to a new diagnosis of motor neuron disease: A pilot study into the value of an early patient-led interview. *Amyotroph Lateral Scler.* 2010;11(1-2):104-109. doi:10.3109/17482960902829205.
219. Albert SM, Wasner M, Tider T, Drory VE, Borasio GD. Cross-cultural variation in mental health at end of life in patients with ALS. *Neurology.* 2007;68(13):1058-1061. doi:10.1212/01.wnl.0000257820.96756.ea.
220. Moore MJ, Moore PB, Shaw PJ. Mood disturbances in motor neurone disease. *J Neurol*

Sci. October 1998:S53-6.

221. Irwin D, Lippa CF, Swearer JM. Cognition and Amyotrophic Lateral Sclerosis (ALS). *Am J Alzheimers Dis Other Demen.* 2007;22(4):300-312. doi:10.1177/1533317507301613.
222. Carel H. *Phenomenology of Illness.* Oxford University Press; 2016. doi:10.1093/acprof:oso/9780199669653.001.0001.
223. Havi Carel: Illness & philosophy - YouTube. <https://www.youtube.com/watch?v=QQ12Bp93nhU&feature=youtu.be%5D>. Accessed June 6, 2017.
224. Carel H. *Illness : The Cry of the Flesh.*
225. Golembiewski RT, Billingsley K, Yeager S. Measuring Change and Persistence in Human Affairs: Types of Change Generated by OD Designs. *J Appl Behav Sci.* 1976;12(2):133-157. doi:10.1177/002188637601200201.
226. Howard JS, Mattacola CG, Howell DM, Lattermann C. Response shift theory: an application for health-related quality of life in rehabilitation research and practice. *J Allied Health.* 2011;40(1):31-38.