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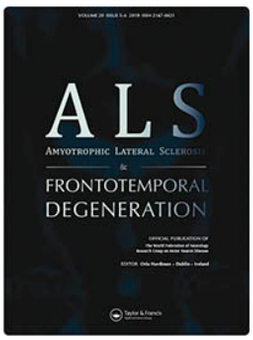

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ORIGINAL ARTICLE

The relationships between symptoms, disability, perceived health and quality of life in amyotrophic lateral sclerosis/motor neuron disease

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Abstract

Objectives: Using the Wilson and Cleary model linking clinical variables to quality of life, we explored the associations between physical and psychological factors, disability, perceived health and quality of life in ALS/MND. *Methods*: The ongoing UK study of Trajectories of Outcomes in Neurological Conditions (TONiC) recruited participants with ALS/MND to complete a questionnaire pack including demographic factors and several patient reported outcome measures (PROMs); a clinician provided data on disease onset type and duration since diagnosis. All PROMs were transformed from ordinal raw scores to interval-scaled latent estimates via the Rasch measurement model. *Results*: Data from 636 patients were analyzed; mean age 65.1 years (SD 10.7), 61.3% male. Median duration since diagnosis was 11.2 months (IQR 4.6–29.9; range 0.4–295.9 months); 67.3% had limb and 27.3% bulbar onset disease. Symptoms such as breathlessness and fatigue, along with most domains of activity limitations, were shown to vary by onset type. A series of models illustrated the importance of physical functioning and anxiety upon quality of life, with breathlessness and fatigue having indirect effects. The models were invariant for gender and onset type. *Conclusions*: This large study highlights the importance of functional status and anxiety as key variables influencing quality of life in ALS/MND. The nature and diversity of factors, both physical and psychological, which have been shown to influence the quality of life of people with ALS/MND provide strong evidence in support of the widespread implementation of multidisciplinary care.

Keywords: *Amyotrophic lateral sclerosis*, *Wilson and Cleary model*, *TONiC*; *quality of life*, *multidisciplinary care*

Introduction

Amyotrophic lateral sclerosis/motor neuron disease (ALS/MND) is a progressive, adult-onset, neurodegenerative disease which causes profound physical disability, including paralysis, loss of verbal communication, and inability to swallow; death is usually related to respiratory failure. Treatments are palliative and interventions may extend life without stopping disease progression. Faced with this bleak prognosis, prevalence rates for depression in ALS/MND patients are up to 44% and for anxiety up to 30% (1), worsening as the disease progresses (2).

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Given our current inability to cure ALS/MND or to halt its progression, the focus of care is the optimization of the patient's quality of life. Health-related quality of life in ALS/MND can be severely compromised; on an EQ-5D derived single index score where full health is 1 and values lower than 0 represent states considered to be worse than death (3), patients scored a mean of 0.63 for initial stage 1 disease severity to a mean of –0.01 for more disabled stage 4 disease severity (2,4). Quality of life in ALS/MND is influenced by a variety of psychological as well as physical factors (5,6), and the clinical challenge is to understand how to intervene regarding the complex interplay of these physical and psychological factors. Conceptual models can help us clarify such relationships, enhancing our understanding of the network of factors and the effects of mediators and moderators, thereby potentially improving clinical care.

One such model was proposed by Wilson and Cleary (7,8). This model proposes a causal pathway beginning with "physiological and biological" factors, which influence symptoms. Symptoms are defined as a patient's perception of an abnormal physical, emotional, or cognitive state, and these in turn may affect functioning. Following from these are health perceptions, a subjective rating which integrates the previous three health concepts of biology, symptoms, and functioning, along with others such as personal and environmental situation. At the end of the continuum is quality of life (8) (see Figure 1). The authors hoped that "a clear understanding of these causal relationships will facilitate the design of optimally effective clinical interventions" (8). While the model has been validated in several chronic conditions, it has never before been studied in ALS/MND (9). The current study uses the Wilson and Cleary model to explore the associations between onset type, physical and psychological factors, perceived health and quality of life in a large cohort of people with ALS/MND, who are part of the ongoing UK longitudinal study of Trajectories of Outcomes in Neurological Conditions (TONiC) (https://tonic.thewaltoncentre.nhs.uk/).

Methods

Data collection

The TONiC study recruited participants with ALS/MND across many UK centers, asking them to complete a questionnaire pack including demographic factors and a variety of patient reported outcome measures (PROMs). As well as quality of life, these PROMs assessed factors deemed important for quality of life in earlier qualitative work conducted with a range of people with ALS/MND (10,11). In addition, a clinician provided data on disease onset type and duration since diagnosis. All participants received written information and informed consent was obtained prior to enrollment into the study. Ethical approval was granted from the relevant local research committees (reference 11/NW/0743).

Outcome measures included in current analysis

1. Neurological Fatigue Index-MND (NFI-MND) (12)—13 items generating weakness, energy and summary scales, each capable of interval level measurement. Summary scale used in path models.
2. Dyspnoea-12 (13)—12 items measuring severity of breathlessness, incorporating physical and affective aspects.
3. Hospital Anxiety and Depression Scale adapted for MND (HADS-MND) (14,15)—one item from each of anxiety and depression scales required removal due to misfit on the Rasch analysis and cutoff points for probable depression and anxiety were revised to account for the reduced number of items.

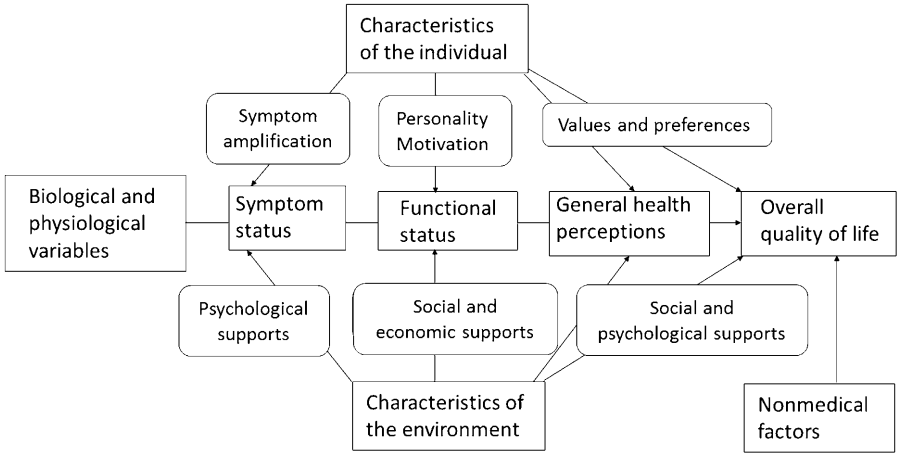

Figure 1. The Wilson and Cleary conceptual model of health-related quality of life.

4. Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised (ALSFRS-R) (16,17)—12 items providing estimates of disability in bulbar (three items), motor (six items), and respiratory (three items) domains.
5. World Health Organization's Disability Assessment Schedule-2.0 (WHODAS-2.0) (18)—seven domains covering: Understanding and Communicating (six items), Getting around (five items), Self-care (four items), Getting along with others (five items), Life activities: household (four items), and Participation in society (eight items), total score without the four work-related items used in path models.
6. Numeric rating scales (NRSs) for perceived health and quality of life—where a high score is better.
7. World Health Organization Quality of Life Scale-BREF (WHOQOL-BREF) (19)—26 items, covering four domains: physical, psychological, social and environment, and two summary items. Ten items are prefaced with "How satisfied are you … ?" and provide a "life satisfaction" operationalization of quality of life for use in the path models.

Rasch analyses

These variables were intended to provide a relevant disease-specific interpretation of the Wilson and Cleary model of health related quality of life, as outlined in Figure 1 (8). The ordinal scores from all PROMs were first transformed to interval-scaled latent estimates via fit of their data to the Rasch measurement model (20,21). The iterative process of the Rasch analysis is designed to verify the underlying assumptions of stochastic ordering of items; local independence, including response and trait dependence, and group invariance (e.g. for age or gender) (22–24). Full details of this process are given elsewhere (25,26). Where the assumption of local response dependence is breached, "testlets" or "super items" are formed by adding the dependent items together (27). Given two testlets absorbing all items, a latent estimate based upon a bi-factor equivalent solution with a conditional test of fit becomes available (28). The explained common variance (ECV) is reported where a value of 1 indicates that all non-error variance is contained within the latent estimate. An ECV value >0.9 is considered sufficient to indicate that the first common factor is unidimensional (29). Values above 1 can be obtained, indicating that some local dependency remains across the two testlets.

Path models

Given fit of data to the Rasch model, the resulting interval-scaled estimates become available to be entered into a path model, together with the directly observed variable of age, an NRS of perceived health; disease onset type, gender, and disease duration were used as grouping variables (moderators) (30). Comparison of onset type is restricted to bulbar versus limb onset, due to low numbers in the unknown and respiratory groups. Each model is tested by a Wald statistic for invariance by gender, disease duration, and onset type, to examine whether the same model holds irrespective of group membership. Given the sample size, indication that the data provide an accurate representation of the model is indicated by a non-significant chi-square statistic (31).

The focal relationship in the initial model is between symptoms and quality of life, and all other variables are defined in this context (32,33). The initial model hypothesizes that the effects of breathlessness and fatigue (symptoms) upon perceived health are fully mediated by functional status (summarized by the WHODAS-2.0); that is their effect passes fully through functional status rather than directly (or both ways) to perceived health. Likewise, the impact of functional status upon quality of life is fully mediated by perceived health.

Subsequent analyses explore the role of anxiety to test how it contributes to the overall understanding of the lived experience of those with ALS/MND in the context of impact upon their quality of life. Anxiety in ALS/MND may be considered a consequence of the increasing levels of symptoms and activity limitations, and in turn anxiety may affect perceived health and quality of life.

The same underlying concept can be measured by different PROMs, such as measuring functional status by the WHODAS-2.0 or ALSFRS-R. The final model is re-specified to be based upon the ALSFRS-R, to show how different PROMs can be used to operationalize the Wilson and Cleary model.

The descriptive analysis was undertaken in SPSS24 (SPSS Inc., Chicago, IL), the path analysis in STATA15 (StataCorp LLC, College Station, TX), and the Rasch analysis in RUMM2030 (Perth, Australia) (34–36).

Results

Patients and descriptive characteristics of domains

This analysis used data from the first 636 patients with ALS/MND to join the study and return the baseline questionnaire. Mean age was 65.1 years (SD 10.7), 61.3% were male, and median duration since diagnosis was 11.2 months (IQR 4.6–29.9;

range 0.4–295.9 months). According to onset type, 428 (67.3%) had limb onset, 174 (27.4%) had bulbar onset, and 11 (1.7%) were recorded as having a respiratory onset; 23 (3.6%) had unknown onset. Disease duration differed between people with bulbar and limb onset, with those with bulbar onset having the shortest average duration at 20.1 months compared with limb onset at 28.5 months ($t = 2.837$; $p = 0.005$). Most were married (78.6%), and were able to complete the questionnaire independently (61%). Just 12.9% were employed, either full time or part time.

The median and inter-quartile ranges for each onset type and in total, for all the above scales where reporting takes the form of ordinal scores, along with mean values for age and duration, are given in Table 1. The bulbar, motor, and respiratory domains of the ALSFRS-R all showed a significant difference mostly consistent with onset type; bulbar onset having the lowest rank (worst) for the ALSFRS-R bulbar domain, and respiratory onset for the ALSFRS-R respiratory domain (all domains Kruskal–Wallis $p \leq 0.001$) (Table 1). The Dyspnoea-12 showed strong discrimination

Table 1. Demographics and descriptive statistics of PROMs by onset type.

		Onset type				
	Score range	Bulbar	Limb	Respiratory	Total	p Value from appropriate test
Demographics						
Age	16–90 years	67.0 [10.2]	64.2 [10.8]	67.5 [6.8]	65.0 [10.7]	0.011
Duration	0–296 months	20.1 [28.9]	28.5 [41.3]	24.2 [31.0]	26.0 [38.1]	0.049
PROMs						
ALSFRS-R						
Bulbar	0–12	5 [2–7]	11 [9–12]	12 [10–12]	9 [6–12]	<0.001
Motor	0–24	17 [12–21]	14 [10–17]	11 [6–20]	14 [10–18]	<0.001
Respiratory	0–12	10 [8–12]	11 [9–12]	4 [3–10]	11 [9–12]	<0.001
Dyspnoea-12						
Total	0–36	5 [0–12]	2 [0–9]	13 [7–15]	3 [0–11]	<0.001
Physical	0–21	3 [0–9]	0 [2–7]	10 [5–14]	3 [0–8]	<0.001
Affective	0–15	0 [0–1]	0 [0–0]	1 [0–5]	0 [0–2]	<0.001
HADS-MND						
Anxiety	0–18	5 [2–7]	4 [2–7]	3 [1–7]	4 [2–7]	0.319
Depression	0–18	3 [1–5]	3 [1–6]	4 [3–7]	3 [1–5]	0.209
NFI-MND						
Weakness	0–21	12]8–14]	13 [10–16]	16 [10–18]	13 [10–16]	0.001
Energy	0–21	10 [7–13]	11 [8–13]	11 [6–13]	11 [8–13]	0.375
Summary	0–24	13 [9–16]	14 [11–17]	15 [9–19]	14 [11–17]	0.009
WHODAS-2.0 (32 items excluding work)						
Communication	0–24	3 [1–6]	1 [0–4]	1 [0–1]	1 [0–4]	<0.001
Mobility	0–20	9 [2–14]	12 [7–16]	16 [8–17]	12 [6–16]	0.001
Self care	0–16	5 [2–8]	7 [3–12]	10 [1–14]	7 [3–11]	<0.001
Getting along	0–20	5 [2–8]	3 [1–5]	4 [4–4]	4 [1–6]	<0.001
Life activities	0–16	8 [2–12]	11 [6–16]	16 [12–16]	10 [5–15]	<0.001
Participation	0–32	9 [6–14]	10 [6–14]	13 [8–17]	6 [10–14]	0.402
Summary (32)	0–128	40 [21–62]	48 [31–64]	67 [45–69]	46 [27–64]	0.016
WHOQoL—Bref						
Physical	7–35	23 [20–28]	22 [19–25]	20 [18–27]	22 [19–26]	0.009
Psychological	6–30	23 [19–25]	22 [19–24]	23 [17–26]	22 [19–25]	0.818
Social	3–15	12 [10–13]	12 [10–13]	11 [10–12]	12 [10–13]	0.468
Environmental	8–40	32 [30–35]	30 [28–33]	31 [30–36]	31 [28–34]	<0.001
Life satisfaction	10–50	37 [32–41]	35 [31–39]	36 [32–38]	35 [31–40]	0.012
Numeric rating scales						
Perceived health	0–10	6 [4–8]	5 [4–7]	7 [4–8]	6 [4–7]	0.250
QoL	0–10	7 [5–8]	6 [5–8]	6 [5–8]	6 [5–8]	0.535
N	–	174	429	11	614	–

PROMs: patient reported outcome measures; ALSFRS-R: Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised; HADs-MND: Hospital Anxiety and Depression Scale adapted for MND; NFI-MND: Neurological Fatigue Index-MND; WHODAS-2.0: World Health Organization's Disability Assessment Schedule-2.0; WHOQoL-Bref: World Health Organization Quality of Life Scale-Bref.

Mean and [SD] for age and duration, median, and [inter-quartile range] for PROMs. High score is good; ~22 cases omitted where onset type is unknown.

between respiratory onset, and other types, while both the Weakness and Summary domains of the NFI-MND showed a significant difference across onset type (Kruskal–Wallis $p \leq 0.01$), but not the Energy domain. The Communication, Self-care, Mobility, Getting Along with People and Life Activities domains of the WHODAS-2.0 differed by onset type (Kruskal–Wallis $p \leq 0.001$), whereas the Participation domain showed no such difference. The total score of the WHODAS-2.0 (minus the four work items) also differed by onset type.

Overall, from the HADS-MND, 11.1% had "probable" depression, and 13.8% "probable" anxiety. Neither differed by onset type (chi-square $p \geq 0.05$), and nor did their ordinal scores. Despite the observed differences across onset type for many PROMs, perceived health, as represented by an NRS, did not show any difference by onset type (Kruskal–Wallis $p = 0.250$). Finally, while the Physical, Environmental, and Life Satisfaction domains of the WHOQOL-BREF differed by onset type, the Psychological domain and Social domain did not (Kruskal–Wallis $p \geq 0.05$), and neither did the summary NRS item for quality of life (Kruskal–Wallis $p \geq 0.05$). Using the interquartile range to define duration groups, one-quarter of the sample had a duration of 4.6 months or less, and overall an expected increasing gradient was observed for the WHODAS-2.0 across duration groups (Kruskal–Wallis $p = 0.0001$). Within the WHODAS-2.0, the Life Activities domain showed an increase in limitations as duration increased (Kruskal–Wallis $p = 0.00001$), and the Participation domain also showed an increase in restriction (Kruskal–Wallis $p = 0.001$).

Rasch analysis

Fit of the data from the various PROMs is shown in Table 2. After adjusting for local response dependency where necessary, all PROMs showed fit to the Rasch model with the exception of the ALSFRS-R respiratory domain and the WHOQOL-BREF Social domain, both of which also showed low reliability. The 10 "life satisfaction" items from the WHOQOL-BREF met all the requirements of the Rasch model.

Table 2. Fit of scales to the Rasch model.

	Conditional chi-square fit			Reliability		ECV
	Value	df	*p*	PSI	α	% common variance
Ideal values			>0.05*	>0.7	>0.7	>0.90
PROMs						
ALSFRS-R						
Bulbar	4.27	4	0.371	0.67	0.81	1.03
Motor	29.11	16	0.023	0.85	0.84	1.05
Respiratory	19.56	4	***<0.001***	0.37	0.58	0.96
Dyspnoea-12						
Total	28.18	23	0.209	0.85	0.98	1.07
Physical	26.59	12	0.009	0.85	0.95	1.07
Affective	3.32	7	0.854	0.65	0.92	1.39
HADS-MND						
Anxiety	13.96	10	0.175	0.77	0.84	0.99
Depression	10.92	7	0.142	0.67	0.74	1.01
NFI-MND						
Weakness	18.51	13	0.139	0.85	0.89	1.03
Energy	19.08	10	0.039	0.87	0.92	1.03
Summary	13.86	16	0.609	0.87	0.89	1.00
WHODAS-2.0 (32 items excluding work)						
Summary	100.02	92	0.266	0.94	0.97	1.03
WHOQOL—BREF						
Physical	20.36	19	0.373	0.80	0.79	1.01
Psychological	19.49	14	0.147	0.79	0.77	0.93
Social	9.14	3	0.027	***0.57***	***0.45***	***0.65***
Environmental	25.9	18	0.102	0.77	0.76	0.93
Life satisfaction	30.3	25	0.214	0.81	0.81	1.01
Ideal values	–	–	>0.05	>0.7	>0.7	>0.9

PROMs: patient reported outcome measures; ALSFRS-R: Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised; HADs-MND: Hospital Anxiety and Depression Scale adapted for MND; NFI-MND: Neurological Fatigue Index-MND; WHODAS-2.0: World Health Organization's Disability Assessment Schedule-2.0; WHOQOL-BREF: World Health Organization Quality of Life Scale-BREF; PSI: Person Separation Index; ECV: explained common variance; α: Cronbach's alpha.

Embolden and italicized values indicative of misfit.

*Bonferroni's correction $p = 0.003$.

Path analysis

A hypothesized representation of the Wilson and Cleary model was tested, using the various PROMs listed above (Figure 2). The initial model hypothesizes that the effects of breathlessness and fatigue (symptoms) upon perceived health are fully mediated by functional status (summarized by the WHODAS-2.0) and the impact of functional status upon quality of life is fully mediated by perceived health. The initial model, essentially a linear representation of effects, is not supported by the observed data. The model as a whole, while all paths are significant, did not satisfy the chi-square goodness of fit test (chi-square 70.3; $p < 0.001$). The principal problem was mis-specification, in that the modification indices showed that fatigue should have a direct effect on perceived health, making its impact partially mediated, and functional status should have a direct effect on quality of life, thus partially mediated by perceived health. Adjusting for this, the data become an accurate representation of the hypothesized model (chi-square 2.37; df 3; $p = 0.499$) (Figure 3). Furthermore, the model is invariant for gender,

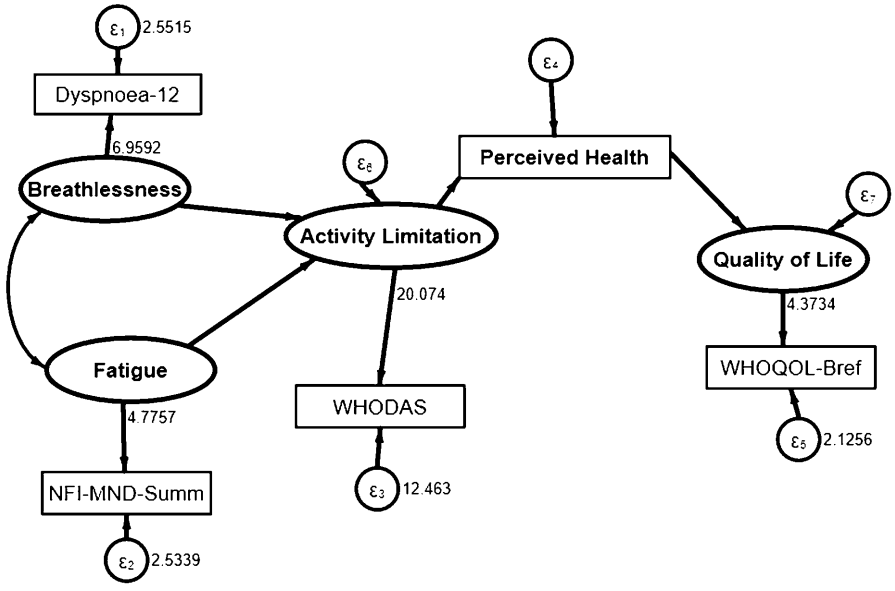

Figure 2. Initial representation of an ALS/MND Wilson and Cleary model. Standardized estimates. NFI-MND-Summ: Neurological Fatigue Index-MND-summary scale; WHODAS: World Health Organization Disability Assessment Schedule–2.0; WHOQOL-Bref: World Health Organization Quality of Life Scale-BREF.

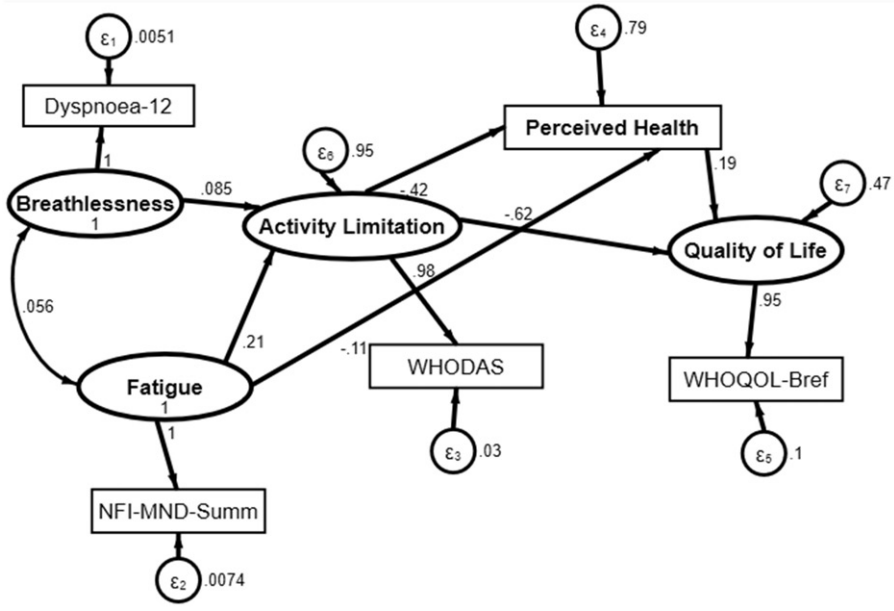

Figure 3. ALS/MND and the Wilson and Cleary Model. Standardized estimates. NFI-MND-Summ: Neurological Fatigue Index-MND-summary scale; WHODAS: World Health Organization Disability Assessment Schedule–2.0; WHOQOL-Bref: World Health Organization Quality of Life Scale-BREF.

Table 3. Standardized direct, indirect and total effects upon quality of life.

Model Variable	Scale	Effect			Chi-square model fit
		Direct	Indirect	Total	
Figure 3 → *QoL*					$p = 0.499$
Function	WHODAS-2.0	–0.623	–0.081	–0.704	
Perceived health	NRS	0.192	–	0.192	
Fatigue	NFI-MND	–	–0.169	–0.169	
Breathlessness	Dyspnoea-12	–	–0.060	–0.060	
Figure 4 → *QoL*					$p = 0.480$
Function	WHODAS-2.0	–0.549	–0.154	–0.703	
Anxiety	HADS-MND-A	–0.221	–0.018	–0.239	
Perceived health	NRS	0.167	–	0.167	
Fatigue	NFI-MND	–	–0.167	–0.167	
Breathlessness	Dyspnoea-12	–	–0.082	–0.082	
Figure 5 → *QoL*					$p = 0.603$
Motor	ALSFRS-Motor	0.442	0.061	0.503	
Respiratory	ALSFRS-Respiratory	–	0.409	0.409	
Anxiety	HADS-MND-A	–0.349	–0.038	–0.387	
Perceived health	NRS	0.215	–	0.215	
Bulbar	ALSFRS-Bulbar	–	–0.075	–0.075	

QoL: quality of life; NRS: numeric rating scale; ALSFRS: Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised; HADs-MND-A: Anxiety domain from Hospital Anxiety and Depression Scale adapted for MND; NFI-MND: Neurological Fatigue Index-MND; WHODAS-2.0: World Health Organization's Disability Assessment Schedule-2.0.

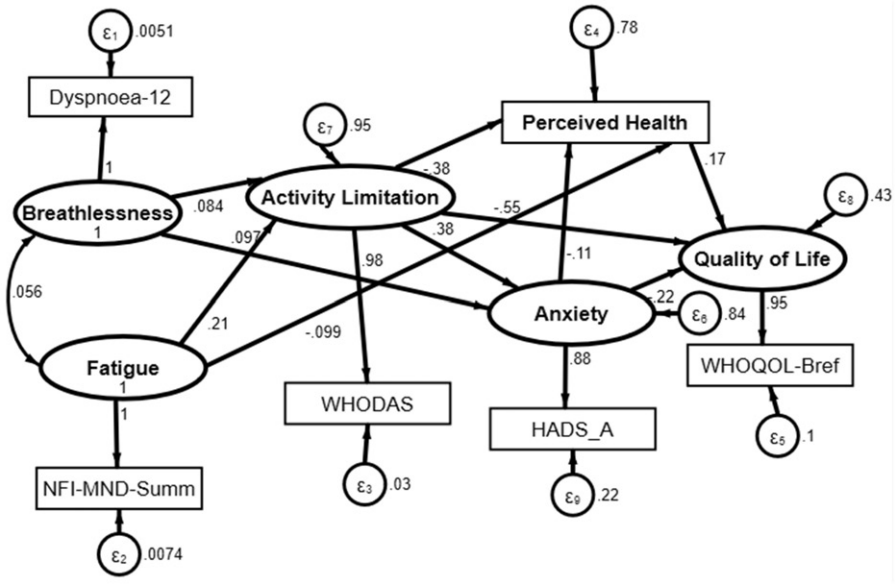

Figure 4. Anxiety as consequent to symptoms and functional status, and its effect upon perceived health and quality of life. Standardized estimates. NFI-MND-Summ: Neurological Fatigue Index-MND-summary scale; WHODAS: World Health Organization Disability Assessment Schedule–2.0; WHOQOL-Bref: World Health Organization Quality of Life Scale-BREF; HADS_A: Hospital Anxiety and Depression Scale adapted for MND-anxiety subscale.

duration and onset type (Wald's test >0.05). Overall, the model for quality of life had R^2 0.53. Including onset type as a moderator (interaction term) into the model resulted in an adjusted R^2 for quality of life ranging from 0.44 for limb onset, through 0.49 for bulbar onset, to 0.58 for respiratory onset. In this model, impaired functional status (activity limitations) is the main contributor to a poorer quality of life (Table 3). Perceived health is next, and both fatigue and breathlessness contribute "behind the scenes" through indirect effects.

Anxiety may be considered a consequence of the increasing levels of symptoms and activity limitations, and in turn may affect perceived health and quality of life (Figure 4). In this model, the focal relationship remains between symptoms and quality of life. The data provided an accurate representation of the model (chi-square 3.48; df 4; $p = 0.480$). The model R^2 for quality of life was 0.57. Once again activity limitations played the major role in influencing quality of life but in this model, anxiety had the second greatest influence

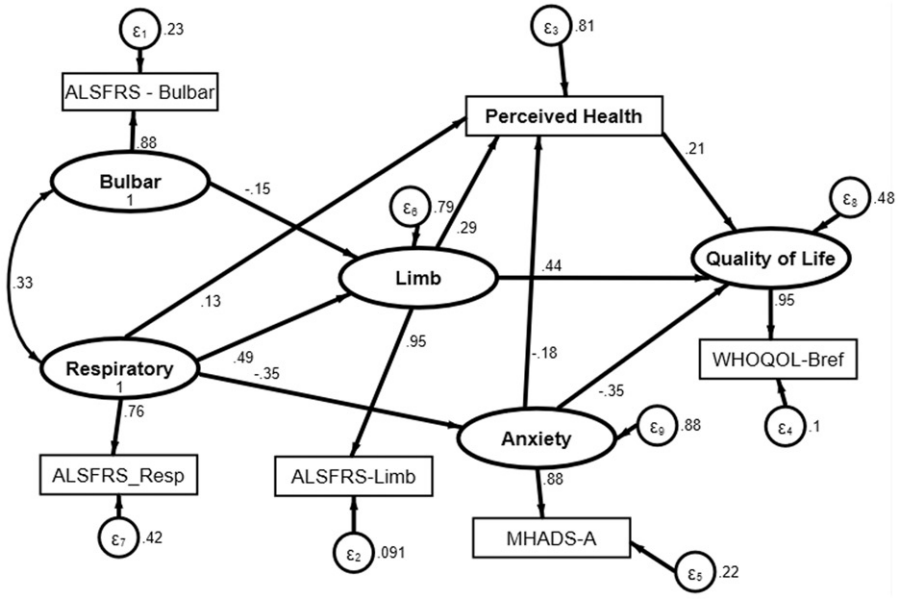

Figure 5. ALS/MND and the Wilson and Cleary Model as specified through ALSFRS-R domains, showing relation with perceived health, anxiety and quality of life. Standardized estimates. ALSFRS-Bulbar: Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised-Bulbar subscale; ALSFRS_Resp: Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised –respiratory subscale; ALSFRS-Limb: Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised-motor subscale; MHADS-A: Hospital Anxiety and Depression Scale adapted for MND-anxiety subscale; WHOQOL-Bref: World Health Organization Quality of Life Scale-BREF.

(Table 3). The model was invariant for gender, duration and onset type (constrained to limb and bulbar).

Figure 5 shows the model as specified through ALSFRS-R domains. The data adequately represent the model (chi-square 2.20; df 5; $p = 0.821$). Once again activity limitations dominate, along with ALSFRS-Motor, with anxiety following in influence. The model R^2 for quality of life was 0.52. Unlike the model using WHODAS-2.0, this model with ALSFRS-R was not invariant for gender, duration, and onset type. There was some difference in path parameters between bulbar and limb by gender, and by duration, but these differences appeared to be one of magnitude as the parameter remained significant across groups (Wald's test).

Discussion

This baseline dataset from the TONiC study illustrates the pathways between physical symptoms, and psychological symptoms, through functional status, to perceived health and quality of life, as experienced by people with ALS/MND. We showed that onset type and duration of condition had the greatest influence on breathlessness, fatigue in terms of NFI-MND weakness or summary score, disability as measured by ALSFRS-R, most domains of WHODAS-2.0, and the physical, environmental, and life satisfaction domains of the WHOQOL-BREF. For example, bulbar onset patients had shorter duration with worse symptoms and physical functioning. An earlier smaller study reported that bulbar onset is related to a worse outcome, along with age of onset (37). Another earlier smaller study reported that bulbar compared to limb onset is an important factor in quality of life changes during the disease course (38). In the current study, anxiety, depression, perceived health and psychological and social quality of life showed no differences across onset type.

The chosen set of PROMs showed adequate fit to the Rasch model, so enabling the Wilson and Cleary model to be operationalized by linear transformed values of the PROMs raw scores in the form of a path analysis. These estimates are entered into the model as single indicator latent variables, with their error and regression weights pre-defined. From a conceptual perspective, after some adjustment, the empirical data was shown to provide a good representation of the model, implying a mostly linear trajectory from symptoms through functional status to perceived health and quality of life. A recent review showed that the Wilson and Cleary model was a robust conceptual framework to characterize predictors of quality of life in 26 studies across 13 conditions; however, the single study examining stroke means we currently have little data on the validity of the model in neurological conditions (9).

The symptom status (body functions) and functional status (activities) in the Wilson and Cleary model, together with the characteristics of the individual and the environment, foreshadowed the International Classification of Functioning, Disability and Health (ICF) model from the World Health Organisation (WHO), which was

published some six years later (39). The Wilson and Cleary model is more comprehensive in that it extends the later WHO ICF model to include the antecedents of biological and physiological variables, and the consequent variables of perceived health and quality of life. The linearity of the model, oft criticized in the original WHO ICF model, is nevertheless largely supported in the current study, as well as recent work on the ICF model itself (40). As such, the Wilson and Cleary model provides a general framework to explore the relationships between symptoms (impairments), functional status (activity limitations), and quality of life. These relationships can be operationalized by different PROM instruments, and recent advances in scale co-calibration provide the ability to exchange domain-specific scores from different instruments, so facilitating better comparability across model-related findings (41). In the current study, the alternate models utilizing different PROMs to represent the same domains both gave similar results in that functional status and anxiety were dominant in influencing quality of life.

There are limitations to the current study. Onset type was not available for 23 patients; although, these were modeled explicitly. The current analysis is made upon the baseline data from a longitudinal study, and as such is cross-sectional and can only build the case to infer causality. Nevertheless, the robustness of the path estimates, including their invariance across groups, suggests that the results offer a good foundation for further work to explore these relationships over time. Subsequent measurement by the TONiC longitudinal study will seek to verify the models as the disease progresses within individuals, identify potential different trajectories, and strengthen the inferences of causality.

The study also has a number of strengths. The sample size is substantial in ALS/MND research, making the Rasch analysis of the PROMs robust, and so too the path analysis and group comparisons (42). The PROMs in the TONiC study provide an unusually comprehensive profile of the bio-psychosocial experience of the participants.

The TONiC study offers a unique opportunity to explore the lived experience of those with ALS/MND from a quantitative perspective, revealing potential areas for clinical intervention. The model confirms the importance of multidisciplinary care in maintaining quality of life for those with ALS/MND, as the results presented above show the importance of ameliorating disability, monitoring symptoms and managing anxiety. Multidisciplinary teams must optimize functional status through recurrent interventions, provided in the context of a declining, progressive condition. Symptoms such as breathlessness and fatigue are causative for changes in quality of life and need active clinical management. Managing anxiety may maintain quality of life, so teams need psychology input. Anxiety had strong impact on quality of life, in all onset types, and played a role even when patients did not reach thresholds for possible or probable caseness. The effect of anxiety on quality of life was evident at all durations of the illness, underlining that access to psychology cannot be restricted to the early stage after diagnosis.

In conclusion, the Wilson and Cleary model has been shown to offer a useful platform for understanding the lived experience of those with ALS/MND from a quantitative perspective. It demonstrates the influence of symptoms and functioning upon perceived health and quality of life, and highlights the importance of anxiety and functional status as key variables influencing quality of life in ALS/MND.

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Declaration of interest

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