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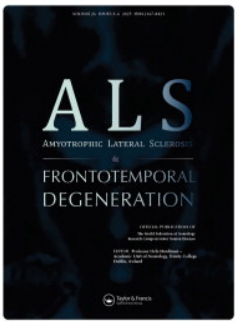
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RESEARCH ARTICLE

Fatigue in amyotrophic lateral sclerosis/motor neuron disease: prevalence, influences and trajectories

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Abstract

Objective: In a large cohort of people with amyotrophic lateral sclerosis/motor neuron disease (pwALS), we examined the age-sex prevalence of fatigue, its relationship to other symptoms and functioning, and trajectories over time. **Methods:** Data from the Trajectories of Outcome in Neurological Conditions study were analyzed by Rasch analysis, structural equation and group-based trajectory models. **Results:** Fatigue was reported by 97.8% on Neurological Fatigue Index-MND (NFI-MND) and 96.4% on Numeric Rating Scale Fatigue among 1058 pwALS: mean age 65 (range 20–90); mean duration 23 months (range 0–301); 60.7% male; onset 26.5% Bulbar, 71.5% Limb and 2.0% Respiratory. Mean (metric) level on NFI-MND was 12.8 (SD 5.3; range 0–24). Cut-points on the NFI-MND of 10 and 15 divided fatigue into mild (27.3%); moderate (36.1%) and severe (36.2%). Structural equation modeling showed that function, cognition, spasticity, dyspnea and pain have descending order of effect. Over average 11.6 months follow-up, 60.5% had stable fatigue, 23.8% increased fatigue level, while 15.8% showed declining fatigue. Trajectory analysis showed three groups, low, average and high fatigue. Those with low trajectories had less spasticity, worry, cognitive problems, as well as better functioning, longer duration and were less likely to be male. High fatigue trajectory was associated with worse spasticity, cognition and anxiety. **Conclusions:** Fatigue is extremely common among pwALS, thus more work is required on fatigue management. In addition to treating fatigue itself, the current study shows that targeting cognition, spasticity, dyspnea and pain might be fruitful.


Keywords: Fatigue, amyotrophic lateral sclerosis, motor neuron disease, trajectories, Rasch, Neurological Fatigue Index-MND, Trajectories of Outcome in Neurological Conditions study

Introduction

Non-motor symptoms such as fatigue are common in amyotrophic lateral sclerosis/motor neuron disease (ALS/MND) (1–5). A recent meta-analysis using 11 studies and 1072 patients found a fatigue prevalence of 48% (CI: 40%–57%) (6). Fatigue

appears to be experienced both as an inability to sustain motor function and as a pervasive tiredness (7). One study showed that although the “physical” component of fatigue may be influenced by the disease itself, in ALS the “mental” component of fatigue correlated with cognitive and

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behavioral impairment, as well as with alterations of functional connectivity in extra-motor networks (8).

However, fatigue is just one symptom, albeit very frequent, among many symptoms experienced by people with ALS (pwALS) (9,10). Fatigue, helplessness and functional mobility have been shown to be independently associated with participation restrictions (11). Dyspneic patients had significantly higher fatigue scores than non-dyspneic patients, and dyspnea alone explained up to 24% of the variance in fatigue (12). Furthermore, fatigue may not be constant, as one longitudinal study reporting 113 patients found that 25% who were fatigued at baseline were not fatigued 3 months later (2).

The complexity of fatigue among other symptoms, and the variability of its presence over time, suggests that it should be examined within comprehensive conceptual frameworks such as those provided by the International Classification of Functioning, Disability and Health (ICF), and the Wilson and Cleary model “linking clinical variables to health related quality of life,” applied in a longitudinal setting (13,14). The latter specifies the relationships as biological/physiological→symptoms→functioning→perceived health→quality of life, while the former omits the last two domains, comprising body functions/structures→impairment (symptoms)→activity limitation (functioning). Both models include individual and environmental influences. However, despite the unidirectional flow of the latter model, it has been shown that there are both adjacent and non-adjacent linkages, for example symptoms directly affecting quality of life (15). In addition, in the model proposed below, consistent with ICF two-way interaction, functioning (activity limitation) is seen as an influence upon fatigue (impairment), consistent with the reported inability to sustain motor function as one of the two key aspects of fatigue (7).

The current longitudinal study examines the extent of fatigue in a large sample of pwALS, to understand its relationship with other symptoms and functioning, and to examine its trajectory over time.

Methods

Samples

Participants with ALS/MND, diagnosed according to El Escorial World Federation of Neurology criteria (16), were recruited into the Trajectories of Outcome in Neurological Conditions (TONiC) study from 36 centers across the United Kingdom between 2013 and 2019. PwALS with a family history of ALS were eligible as were those with only lower motor neuron (LMN) signs in two or more

regions, or with primary lateral sclerosis without spinal LMN signs, provided a consultant neurologist specializing in ALS had confirmed the diagnosis. Participants were excluded if they were unable to give informed consent or unable to complete the self-report questionnaire pack even with writing assistance from a scribe. Age, sex, onset type and duration since diagnosis were recorded from the clinical notes, as was the King’s stage (17). Ethical approval was granted from the relevant local research committees (reference 11/NW/0743).

After re-consenting for entry into the longitudinal cohort, follow-up was initially at 11 months, and thereafter at 6-monthly intervals. The timeline from baseline to those who completed the third follow-up (i.e. fourth questionnaire) was 29.6 months (SD 15.7).

Patient reported outcome measures (PROMs)

The TONiC study includes a wide variety of PROMs intended to measure the key domains experienced by those with ALS/MND. In the current analysis these predominately focus on symptoms and psychological factors. They include:

1. **Fatigue:** Neurological Fatigue Index-MND (NFI-MND): 8-item summary scale ranging from 0-24 with higher numbers meaning worse fatigue (18);
2. **Fatigue:** Numeric Rating Scale (NRS) Fatigue: categorized 0-10 for magnitude of overall fatigue, ranged from “0:Lively and alert” to “10:Absolutely no energy to do anything at all;”
3. **Pain:** Numeric Rating Scale (NRS) Pain: categorized 0-10 for magnitude of overall pain, ranged from “0:No pain” to “10:Severe pain;”
4. **Spasticity:** Spasticity Index-Amyotrophic Lateral Sclerosis (SI-ALS) (19);
5. **Breathlessness:** Dyspnea-12 (20);
6. **Cognition:** World Health Organization Disability Assessment Schedule 2.0 understanding and communication subscale (WHODAS Cog) (21), validated in ALS (22);
7. **Functioning:** Amyotrophic Lateral Sclerosis Rating Scale-revised (ALSFRRS-R) (23,24);
8. **Self-Efficacy:** General Perceived Self-Efficacy Scale (GPSE) (25);
9. **Worry:** Penn State Worry Questionnaire (26);
10. **Anxiety:** Modified Hospital Anxiety and Depression Questionnaire (27).

In addition, a number of indicator variables were included. These include an ALS-related symptom inventory, comprising fasciculations, cramps, head drop, drooling, choking and emotional control.

Statistical analysis

Attrition. Attrition was examined by a comparison of baseline variables to those at each succeeding follow-up. Given the progressive nature of the condition, it was expected that certain variables, such as baseline King's stage, would show significant association with the likelihood of engaging with subsequent follow-ups.

Prevalence and consistency of reported fatigue. The age-sex specific prevalence is reported by severity group, derived from a combination of the NRS for fatigue, and the NFI-MND. The Wilson Score interval is used to provide the 95% confidence intervals, suitable for small numbers found in age-sex specific rates. The consistency of the reported levels over time is presented from the longitudinal data.

Rasch analysis. All summative PROMs were transformed to interval scaling via their original publication, subsequent publications, or *de novo* analysis (18,19,24,27–29). Full details of the Rasch methodology are given in the [Supplementary material](#).

Structural equation models (SEM). Conceptually driven models using Rasch transformed estimates from PROMs were entered as single indicator latent variables with predefined errors and regression weights, together with various symptom indicators (30). Acceptable model fit was determined by the Chi-Square χ^2 statistic, which should not be significant. Acceptable values for approximate fit indices are presented including the Root Mean Square Error of Approximation (RMSEA), whose value should be ≤ 0.6 ; details are in the [Supplementary material](#).

For this analysis the data were randomly split into equal sized “training” and “validation” samples. After adjustments in the training sample, the result was validated before pooling data to reaffirm fit with greater precision. The sample size for such analyses varies by model structure (31); details are in the [Supplementary material](#). Sample size was sufficient to detect effect for both training and validation samples, and to determine model fit structure in the total sample. Magnitude of the overall effect was evaluated by the R^2 upon fatigue (32).

Trajectory analysis. Trajectory analysis, a finite mixture model, was applied by an “add-on” in STATA, the *traj.ado* (33,34). The time metric was median month since the baseline questionnaire at each follow-up. Fatigue was assessed at baseline and up to three further follow-ups, details in the [Supplementary material](#).

Classification and regression Tree analysis (CART). In order to provide insights into risk factors for severe fatigue which may be of use in

routine clinical management, a STATA module for Classification and Regression Tree (CART) analysis was used with failure specified as severe fatigue (35). Full details of the methodology are given in the [Supplementary material](#).

All statistical analysis was undertaken with STATA18³⁴.

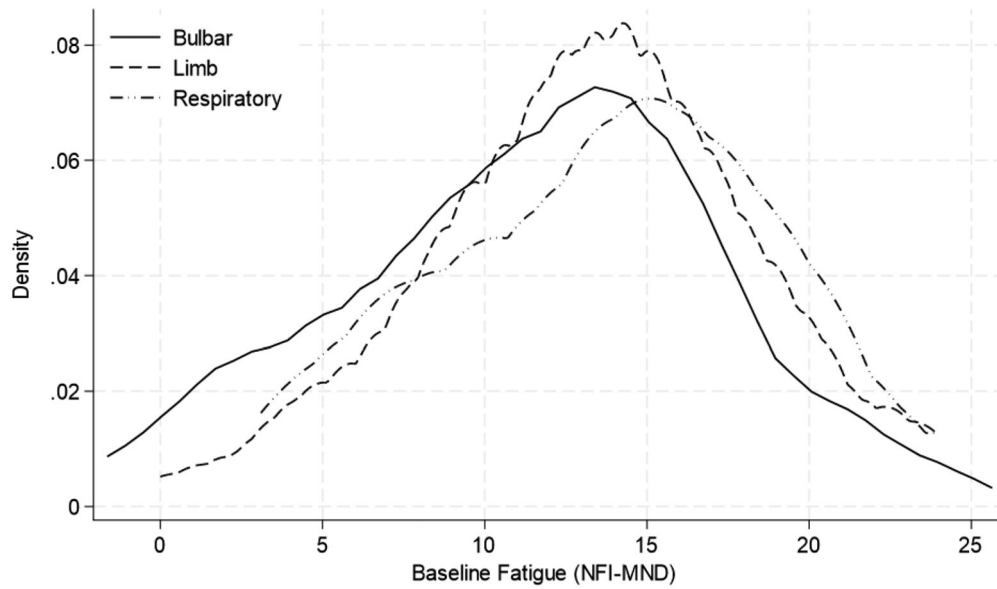
Results

Baseline analysis

The mean age of 1058 pwALS was 65.0 years (SD 10.5; range 20–90). The mean duration since diagnosis was 23.0 months (SD 38.2; range 0–301), while the median duration was 9.0 months (IQR 3.0–24.0). Just over three-fifths (60.7%) were male. Onset types were 26.5% Bulbar onset, 71.5% Limb onset, and 2.0% Respiratory onset. Young-onset, with motor symptoms starting before age 45 affected 6.52% and juvenile onset with symptoms below age 25 occurred in 0.28%. Most were King's stage 2–3 (60.7%), King's stage 0–1 accounted for 19.2% and stages 4a and 4b 20.1%. Virtually all (97.8%) reported some level of fatigue on the NFI-MND, with a mean (metric) level of 12.8 (SD 5.3; range 0–24). Similarly, 96.4% reported a score greater than zero on the NRS Fatigue. A significant difference in the level of metric fatigue was found for onset type where the difference was driven between Bulbar (11.5) and Limb (13.3) (F 12.4; df (2, 1055); $p < 0.001$). Given similar standard deviations, but very different sample sizes, the effect size (Hedges's G) of that difference was 0.343, considered small.

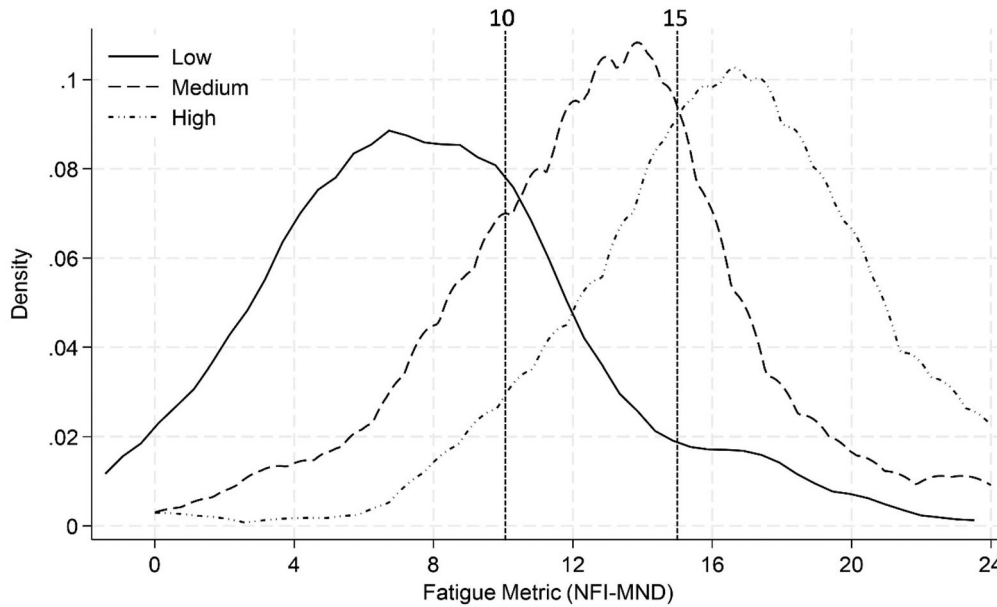
The distribution of fatigue for the three onset types was similar ([Figure 1](#)). When the distribution was compared by grouped categories of the NRS Fatigue, potential cut-points at 10 and 15 emerged to differentiate levels on the NFI-MND, such that it was possible to infer severity groups ([Figure 2](#)). Thus, cut points on the NFI-MND ≤ 9 , including the few with a score of zero (2.2%), give rise to “mild” fatigue with a prevalence of 27.3% (95% CI: 22.2–32.4); “moderate” fatigue (at NFI-MND 10–14) with a prevalence of 36.1% (95% CI: 31.7–41.3), and “severe” fatigue (at NFI-MND ≥ 15) for 36.2% (95% CI: 31.4–41.0). Age-sex specific estimates for moderate fatigue, severe fatigue, and moderate and severe combined are shown in [Table 1](#).

To understand the influences on these severity groups, an exploratory multinomial logistic regression with “mild” as baseline found that being male, cognitive problems, spasticity, pain, functioning and worry all increased the relative risk of “moderate” fatigue compared to mild, and that Bulbar onset (as opposed to Limb) and longer duration decreased that risk ([Supplementary material: Table S2](#)). For comparisons of “severe”



NFI-MND: Neurological Fatigue Index-Motor Neuron Disease

Figure 1. Kernel density graph of baseline fatigue by onset type.



NFI-MND: Neurological Fatigue Index-Motor Neuron Disease; NRS: Numeric Rating Scale.
 ----- Proposed cut-points

Figure 2. Kernel density graph of metric NFI-MND distribution across NRS Fatigue categories.

to “mild,” Bulbar onset (compared to Limb), significantly reduced the risk of severe fatigue, as did age. Cognitive problems, spasticity, pain, cramps, functioning, worry and possible anxiety were all associated with a higher relative risk of being in the severe fatigue group.

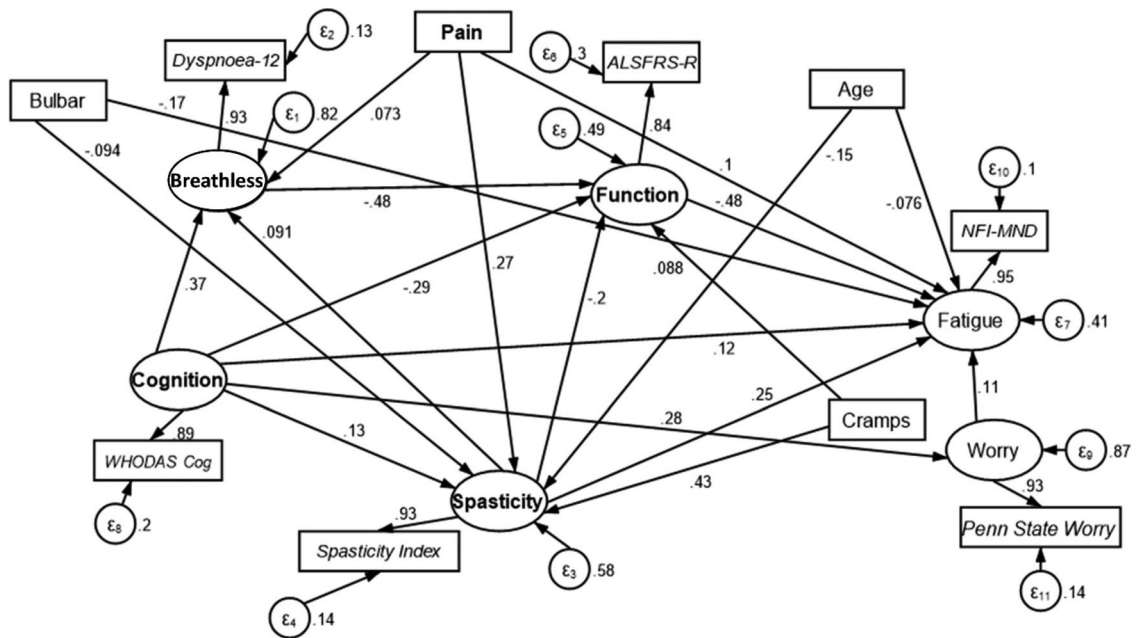
A structural equation model (SEM) then identified the pathways of influence upon fatigue. The variables included were based upon the concept of physiological→symptoms← functioning, the latter

presented as an influence upon fatigue. The model is shown in Figure 3. This model showed acceptable fit in training, validation and total samples (Table 2: model 1). All paths were statistically significant ($p < 0.05$). Direct, indirect and total effects upon fatigue are shown in Table 3. These indicate that in this model function has the greatest total effect, the higher (better) the functional score, the lower the level of fatigue. Cognition has the next highest total effect, largely delivered through its

Table 1. Age-sex specific prevalence of fatigue per 1000 for different severity levels.

Age/severity	Male	CI	Female	CI	Total	CI
<i>Moderate</i>						
Under 50	420.0	293.8–557.7	277.8	158.5–439.9	360.5	267.0–465.9
50–54	403.8	281.6–539.3	294.1	168.3–461.7	360.5	267.0–465.9
55–59	400.0	299.6–509.5	411.8	263.7–577.8	403.5	318.0–495.3
60–64	302.5	227.2–390.2	309.1	202.8–440.3	304.6	241.0–376.6
65–69	393.9	314.7–478.2	250.0	172.8–347.3	334.8	276.3–398.9
70–74	339.6	256.5–434.0	375.0	281.1–479.4	355.7	291.7–425.2
75+	543.7	447.7–636.6	324.7	230.6–435.4	450.0	379.1–523.0
Total	395.6	358.5–433.5	317.3	274.4–363.6	365.0	336.4–394.3
<i>Severe</i>						
Under 50	420.0	283.8–556.8	527.8	370.1–680.1	465.1	363.5–569.8
50–54	365.4	248.0–501.3	470.6	314.5–632.6	407.0	309.3–512.6
55–59	425.0	322.6–534.3	264.7	146.0–431.2	377.2	293.6–468.8
60–64	445.4	359.2–535.0	418.2	297.4–549.7	436.8	265.2–511.1
65–69	348.5	272.5–433.0	358.7	268.2–460.5	352.7	293.1–417.3
70–74	292.5	214.3–385.1	284.1	200.4–385.8	288.7	229.5–356.0
75+	242.7	170.2–333.8	376.6	276.7–488.3	300.0	237.8–370.6
Total	356.7	320.6–394.5	370.2	325.2–417.6	362.0	333.6–391.4
<i>Moderate and severe</i>						
Under 50	840.0	714.9–916.6	805.6	649.7–902.5	825.6	732.0–891.4
50–54	769.2	638.7–862.8	764.7	737.8–875.6	767.4	667.9–844.1
55–59	835.0	727.4–892.8	676.5	508.4–808.7	780.7	696.3–846.8
60–64	747.9	663.0–817.3	727.3	597.7–827.2	741.4	671.6–800.7
65–69	742.4	661.7–809.4	608.7	606.5–702.1	687.5	624.1–744.6
70–74	632.1	537.2–717.8	659.1	555.3–749.6	644.3	574.8–708.3
75+	786.4	697.7–854.5	701.3	591.5–792.0	750.0	682.0–807.6
Total	752.3	717.5–784.2	687.5	641.4–730.2	726.8	699.2–752.8

Abbreviations: CI: Confidence Interval, from Wilson Score Interval.



ALSFRS-R: Amyotrophic Lateral Sclerosis Rating Scale-revised; NFI-MND: Neurological Fatigue Index-Motor Neuron Disease; WHODAS Cog: World Health Organization Disability Assessment Schedule 2.0 understanding and communication subscale

Figure 3. Structural equation model for fatigue. Standardized estimates.

indirect effects. The higher the level of cognitive problems, the higher the level of fatigue. Spasticity has a similar total effect, derived from both its

direct effect, and indirect effect through function. The greater the level of spasticity, the greater the level of fatigue. Dyspnea and pain also increase

Table 2. Results of structural equation models.

Model	Sample	Chi-Square			RMSEA	90% CI	CFI	TLI	R ²	N
		Value	df	p						
1	Training	19.92	14	0.210	0.023	0.000–0.050	0.996	0.998	0.62	538
	Validation	14.38	14	0.422	0.007	0.000–0.043	1.000	0.999	0.58	520
	Total	18.77	14	0.174	0.018	0.000–0.037	0.997	0.993	0.59	1058
2	Sex	37.28	26	0.071	0.041	0.000–0.068	0.987	0.966	0.38	520
3	King's	43.57	26	0.017	0.051	0.022–0.077	0.974	0.933	0.31	520
Ideal value				>0.05	<0.6		≥0.95	≥0.95		

Abbreviations: RMSEA: Root Mean Square Error of Approximation; CI: confidence intervals; CFI: Comparative Fit Index; TLI: Tucker–Lewis Index.

Table 3. Structural equation model: direct, indirect and total standardized effects. Full sample.

Model: Onset type→fatigue	Direct effect	Indirect effect	Total effect	R ²
<i>Model 1</i>				0.56
Function	−0.477	−	−0.477	
Cognition	0.115	0.306	0.421	
Spasticity	0.246	0.136	0.382	
Breathlessness	−	0.229	0.229	
Pain	0.102	0.121	0.223	
Bulbar onset	−0.173	−0.036	−0.209	
Age	−0.076	−0.058	−0.134	
Cramps	−	0.121	0.121	
Worry	0.107	−	0.107	

fatigue, but they contribute at a lower level of total effect, and the former indirectly. Bulbar onset is also associated with lower level of fatigue. The model was shown to be invariant by sex (Table 2: model 2) and by King's stage, grouped 0–2, 3+ (Table 2: model 3) with the Score Test indicating that the equal path constraints were valid across groups.

Longitudinal analysis

Baseline and follow-up differences. Of those entered at baseline, 37.5% completed their first follow-up, at an average 11.6 months later (range 0.9–62.0). There was no significant difference regarding those followed up by age (t test 1.36 (df 1056); $p=0.173$), nor duration since diagnosis (t test 0.27 (df 1051); $p=0.788$). Neither was there a difference in onset type (χ^2 3.209 (df 2); $p=0.201$), nor gender (χ^2 1.723 (df 1); $p=0.189$). However, there was a strong statistically significant gradient across King's stages, with 51.3% of those at stage 1 entering the follow-up, compared to 19.7% of those at stage 4 (a and b) (χ^2 52.3 (df 5); $p\leq 0.001$). Likewise, those followed up had a lower level of fatigue at baseline (t test 4.30 (df 1056); $p\leq 0.001$), but the effect size was only small at 0.271. A logistic regression with the dependent variable as follow-up, with 27 independent variables, mostly symptoms, failed to provide any indication of what might have influenced follow-up other than King's stage 4 at baseline (not shown).

At first follow-up, among 387 pwALS, 26.4% had mild fatigue, 38.2% had moderate fatigue and 35.4% had severe fatigue. Three-fifths (60.5%) had maintained the same category of fatigue as at baseline; almost a quarter (23.8%) increased their fatigue level, while 15.8% showed a decline in fatigue. Of those with mild fatigue at baseline 11.9% had moved to a high level of fatigue whereas of those with a baseline high level of fatigue, 2.5% had moved to a mild level.

Almost one-fifth (19.1%) had shown a change in King's staging over the 11.6 months of follow-up. A change from stage 3 to 4 was the most frequent (9.3%) followed by stage 2 to 3 (6.2%). There was no difference in these changes by onset type (χ^2 6.3; (df 10); $p=0.788$). Change in King's stage reflected a change in the level of fatigue with the greatest increase in fatigue associated with the transition from stage 2 to 3 (Table 4) (F2.3; df 5,381; $p=0.44$). However, the magnitude of changes over this period did not impact greatly on the association between the changes in King's staging and the mild-moderate-severe fatigue classification, for example where it would require a change of 5 points to transition across the medium category.

Trajectory analysis

Trajectory analysis showed a relatively stable average level of fatigue for the full sample over the follow-up period but this average masked three different groups, each with significant differences in

Table 4. Changes in fatigue and functioning associated with change in King’s stage.

King’s stage change	Fatigue change		Functioning change		N	%
	Mean	SD	Mean	SD		
Reduced stage	-1.26	5.63	4.02	7.06	22	5.7
No change	0.77	4.16	-2.87	4.14	291	75.2
Stage 0/1 → 2	1.70	3.39	-7.00	0.71	2	0.5
Stage 2 → 3	2.68	5.12	-4.54	3.85	24	6.2
Stage 3 → 4	0.99	5.06	-3.96	4.16	36	9.3
Stage 2 → 4	2.65	3.85	-7.59	4.27	12	3.1
Total	0.85	4.43	-2.85	4.73	387	100.0

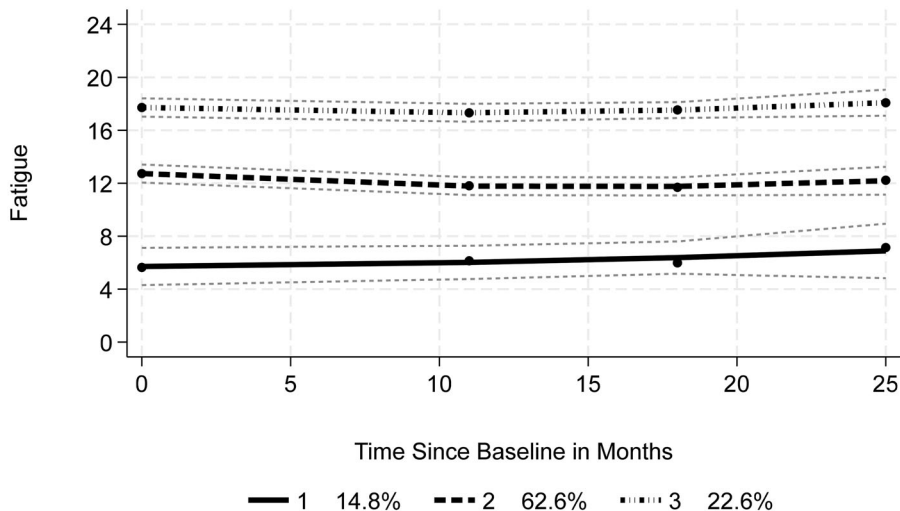


Figure 4. Fatigue trajectories. N= 1056.

the level of fatigue upon entry into the study and then distinct trajectories at different levels of fatigue (Figure 4). In Table 5, group 2 can be considered the “average” trajectory, and so the analysis is focused on how those with lower or higher trajectories of fatigue differ from the average. In contrast to group 2 (average), group 1 (low) showed lower spasticity, cognitive problems and worry, and higher (better) functioning, and a longer disease duration. Being male also had a lower risk of group 1 membership. Group 3, on the other hand, had higher spasticity and cognitive problems, together with possible anxiety. It is of note that the risk associated with function does not differentiate group 3 from group 2.

Classification and regression tree analysis (CART)

The SEM showed that there were many possible interactions between symptoms influencing fatigue. Figure 5 illustrates how these might be useful for routine clinical management: three variables can highlight the probability of being first to reach severe fatigue at follow-up, given a lower level of fatigue at baseline. Without anxiety, but with moderate or high (above median) cognitive problems, together with low (below median) self-efficacy, the probability of that individual in the group developing severe fatigue before other group members is

0.72 (HR 2.57). However, with high (above median) self-efficacy this probability of severe fatigue is reduced to 0.29 (HR 0.41). Possible or probable anxiety, by itself, has a probability of 0.64 (HR 1.73), and no anxiety and low cognitive problems has a probability of 0.42 (HR 0.73) of becoming severely fatigued sooner than others.

A second CART examined the relationship between cognition and functioning and their joint influence upon severe fatigue at follow up (Figure 6). Here a cognitive metric score alone at nine and above gave a probability of reaching severe fatigue first of 0.66; with a score below nine, but with an ALSFRS-R metric at 30 or less a probability of 0.51, and with cognition 0-8 and ALSFRS-R > 30 the probability falls to 0.33.

Discussion

The current study has shown fatigue to be extremely common among those with ALS/MND, affecting over 95% of 1058 participants; clinically it is perhaps unsurprising that the progressive weakness caused by gradual motor neuron loss should be accompanied by the symptom of fatigue. Fatigue in pwALS appears more common than for chronic diseases in general, where fatigue was reported by 50% of a UK general practice cohort

Table 5. Multinomial regression of three group trajectories. Average group (2) as base. $N=984$.

Trajectory Group: Base "Average"	RRR	St.Err	<i>t</i> -value	<i>p</i> -value	[95% Conf. Interval]	Sig	
Group 1 (low)							
<i>Demographic</i>							
Age	1.01	.013	0.77	.442	.985	1.035	
Male	.557	.131	-2.48	.013	.351	.885	**
<i>Clinical</i>							
Bulbar	1.736	.505	1.90	.058	.982	3.069	*
Respiratory	1.257	1.114	0.26	.796	.221	7.135	
Duration	1.008	.003	3.08	.002	1.003	1.014	***
<i>Symptoms</i>							
Cognition	.88	.045	-2.50	.012	.795	.973	**
Breathlessness	.978	.028	-0.80	.425	.924	1.034	
Spasticity	.941	.01	-5.45	0	.921	.962	***
Pain	.881	.058	-1.94	.052	.775	1.001	*
Fasciculation	.566	.247	-1.30	.193	.24	1.333	
Head drop	.437	.228	-1.58	.113	.157	1.217	
Cramps	.894	.332	-0.30	.763	.432	1.851	
Emotional liability	1.335	.477	0.81	.418	.663	2.688	
Drooling	1.229	.512	0.50	.62	.544	2.781	
Choking	2.154	.842	1.96	.05	1.001	4.635	**
<i>Functioning</i>							
Functioning	.852	.022	-6.09	0	.809	.897	***
<i>Psychological</i>							
Self-efficacy	1.023	.021	1.14	.255	.983	1.065	
Worry	.963	.012	-2.95	.003	.94	.988	***
Anxiety:	1	
Possible	.275	.156	-2.28	.023	.091	.836	**
Probable	.898	.424	-0.23	.819	.356	2.264	
Constant	22.47	26.799	2.61	.009	2.17	232.703	***
Group 3 (High)							
<i>Demographic</i>							
Age	.983	.008	-2.07	.039	.967	.999	**
Male	.864	.163	-0.77	.438	.598	1.25	
<i>Clinical</i>							
Bulbar	.692	.174	-1.46	.144	.422	1.134	
Respiratory	1.216	.787	0.30	.763	.342	4.326	
Duration	1.001	.002	0.49	.622	.997	1.006	
<i>Symptoms</i>							
Cognition	1.064	.027	2.43	.015	1.012	1.118	**
Breathlessness	1.023	.014	1.68	.094	.996	1.05	*
Spasticity	1.032	.01	3.40	.001	1.014	1.051	***
Pain	1.071	.04	1.84	.065	.996	1.152	*
Head drop	1.387	.312	1.45	.146	.892	2.157	
Fasciculation	.831	.199	-0.77	.439	.521	1.328	
Cramps	1.449	.299	1.79	.073	.966	2.172	*
Emotional liability	.92	.206	-0.37	.71	.594	1.426	
Drooling	1.463	.412	1.35	.176	.843	2.541	
Choking	.905	.211	-0.43	.669	.573	1.43	
<i>Functioning</i>							
Functioning	1.044	.023	1.92	.055	.999	1.091	*
<i>Psychological</i>							
Self-efficacy	.965	.016	-2.14	.032	.935	.997	**
Pain	.989	.009	-1.17	.242	.971	1.007	
Anxiety:							
Possible	2.067	.51	2.94	.003	1.275	3.352	***
Probable	1.612	.41	1.87	.061	.979	2.655	*
Constant	.175	.163	-1.88	.061	.028	1.081	*

Note: Cragg & Uhler's R2: 0.447. Chi-square 450.439 Prob > chi² 0.000. *** $p < .01$, ** $p < .05$, * $p < .1$.

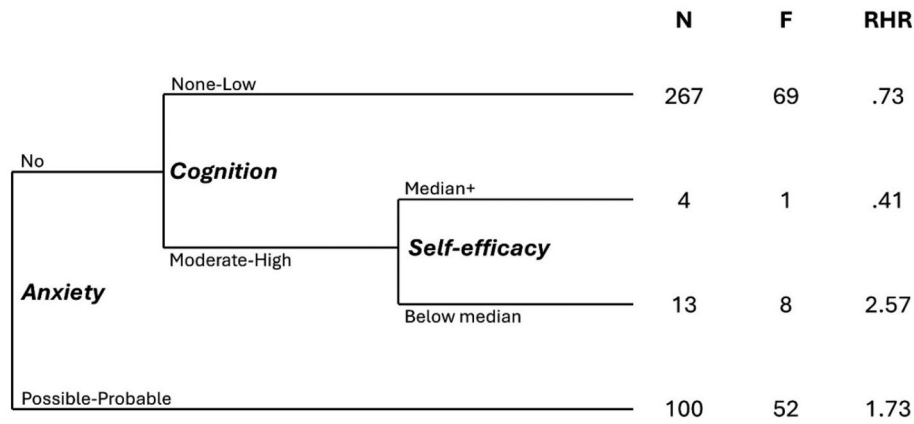
Abbreviations: RRR: relative risk ratio; St.Err: standard error; Conf Interval: confidence interval; Sig: significance.

(36), or compared to population surveys: 18.3% in the UK (37) and 21.9% in Switzerland (38).

Using a combination of the NFI-MND and an NRS of fatigue, three levels of fatigue were identified, with prevalences of 27.3%, 36.1% and 36.2% for low, moderate and severe fatigue respectively. Fatigue was also shown to vary across time with

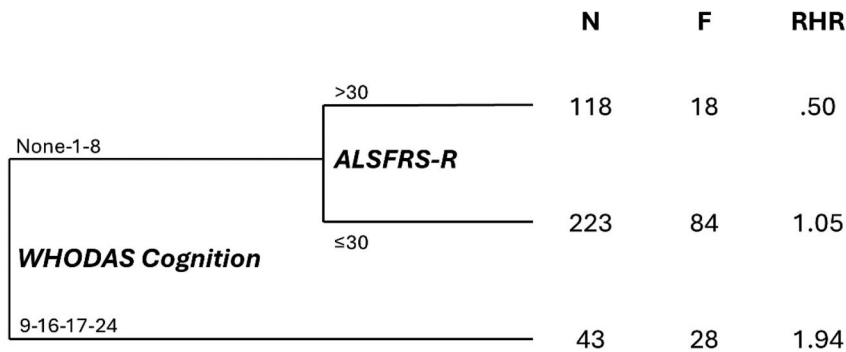
movement across the groups in both directions, consistent with earlier findings (2).

The analyses confirmed a complex interaction of factors, with functioning, cognition, and spasticity showing strong effects upon fatigue in both the multinomial regression and the SEM. Furthermore, in SEM it was rare for any factor to



N: number of pwALS; F: failure; RHR: relative hazard ratio

Figure 5. Classification and regression tree (CART) analysis for severe fatigue at follow.



N: number of pwALS; F: failure; RHR: relative hazard ratio

Figure 6. Classification and regression tree (CART) analysis for influence of cognition and functioning on severe fatigue at follow-up.

have only a direct effect upon fatigue, and some factors, like cognition, had a much stronger indirect effect than direct effect. Trajectory analysis identified three different groups at different levels of fatigue, and re-emphasized the role of spasticity and cognition in differentiating those groups.

The CART analysis showed probabilities of the transition to severe fatigue over a period of 11.6 months using just three factors: anxiety, cognition and self-efficacy. It highlighted the critical influence of self-efficacy to reduce the probability of transition to severe fatigue in the presence of moderate/high cognitive problems, reducing the probability of that transition from 0.72 to 0.29. Previous studies have shown the positive influence of self-efficacy on mitigating pain and maintaining quality of life for pwALS (39,40).

The large variability in reported prevalence of fatigue is likely in part to reflect the different scales used to assess fatigue. One systematic review looking at Minimal Important Differences (MID) for

fatigue scales in ALS identified 28 different scales (41). This multiplicity of PROMs presents a considerable challenge regarding collating evidence of interventions for fatigue because without systematic comparisons between scales, interpretations cannot be standardized. An example of how this might be addressed is found with physical function scales for rheumatoid arthritis, where eleven scales were calibrated onto a “reference metric,” so allowing conversions across all scales (42).

The strengths of the study arise from the sample size, Rasch transformed metrics for SEM and trajectory analysis, a clear indication of how fatigue severity was defined based upon the NFI-MND, and the age-sex specific estimates so derived. The limitations arise from the attrition over time, although apart from King’s stage, this was shown to be unaffected by demographic and other clinical factors. The GPSE was shown to have less than ideal fit to the Rasch model (Supplementary material), suggesting that the development of an

ALS/MND specific scale for self-efficacy should be a priority.

For clinical management, an important result of the CART analysis was that it required just three PROMs to estimate risk of developing severe fatigue, feasible for a screening questionnaire either applied in a paper format or electronically. The NFI-MND summary scale itself is just 8 items, and the metric cut points of 10 and 15 (which equate to the ordinal raw score cut points of 10 and 16), enable a simple categorization into the mild-severe continuum (18). Future work is required on fatigue management; although a variety of treatments have been researched, the evidence base is limited (43). In addition to treating fatigue itself, the current study shows that targeting cognition, spasticity, dyspnea and pain might be fruitful. Improvements in fatigue observed during follow-up refute concerns that fatigue is fixed or inevitably worsening in ALS/MND.

Future work could examine the effect of medications on fatigue levels, whether exacerbating fatigue or by altering symptoms leading to secondary effects on fatigue. Such analyses would benefit the design of future fatigue treatment trials by clarifying guidance regarding concomitant medications. Other factors to be studied include socio-economic status, deprivation, comorbidities and smoking. Work on whether fatigue varies in biologically distinct groups should consider pwALS from different ethnic backgrounds, who may experience, interpret, and report fatigue in different ways due to biological, cultural, or healthcare access differences. Examination of fatigue in those with a family history or known mutation might provide insights into earlier symptom expression and potential care tailoring for genetically at-risk individuals. With a bigger sample size, the profile of fatigue in young-onset or juvenile-onset ALS could be examined.

In conclusion, fatigue is extremely common among pwALS, over 95% of a diverse cohort reported some level of fatigue. The 8-item summary scale of the NFI-MND provides an interval level measurement of fatigue which can be analyzed using parametric statistics, the mean for this cohort was 12.8 (SD 5.3; range 0–24). With cut points of 10 and 15 on the NFI-MND, 27.3% had mild fatigue, 36.1% moderate fatigue and 36.2% severe fatigue. The three factors most influencing fatigue were functioning, cognition and spasticity, with lesser effects from dyspnea and pain. By first year of follow-up, fatigue was stable for 60.5% and worse for 23.8%, but 15.8% had less fatigue. More work is needed on strategies to reduce fatigue in pwALS; results shown here may suggest avenues for developing more effective fatigue management.

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Declaration of interest


The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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Data availability statement

Data supporting this study are not openly available due to reasons of sensitivity and are available from the corresponding author upon reasonable request. Data are located in controlled access data storage at Walton Center NHS Trust.

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