Health utilities and costs for Motor Neurone Disease

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Value in Health

DOI:
10.1016/j.jval.2019.05.011

Published: 01/11/2019

Peer reviewed version

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Running title: Health utilities and costs for MND

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Funding:

We thank the Motor Neurone Disease Association UK (Ref Young/Jan15/929-794), the Walton Neurological Disability Fund and the NIHR CLRN for research support for funding.

Acknowledgement:

The authors would like to thank the participants for their invaluable contribution and the clinical and research staff involved in the TONiC study.

Conflict of Interest:

AM, CAY and DAH declare that they have no conflict of interest.

Contributions:

AM, CAY and DAH contributed substantially to the conception and design of the work. All authors made contributions to the acquisition, analysis, or interpretation of data. AM drafted the paper and all authors revised it critically for important intellectual content, and gave their final approval of the version to be published. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Key words:

Motor Neurone Disease, Amyotrophic Lateral Sclerosis, utility, costs, EQ-5D, ALSFRS-R

Highlights

What is already known about this topic?

- Costs within a UK healthcare context and health utilities for Motor Neurone Disease (MND) are not well documented; neither are their association with well-defined health states.

What does the paper add to existing knowledge?

- This paper uses two well established health staging systems – Kings and MiToS – on a large, representative cohort of patients with MND, to characterise the health state utilities and costs associated with MND.

What insights does the paper provide for informing health care related decision making?

- The results demonstrate the discriminatory value of MND staging systems in relation to health utilities and healthcare costs. Mean EQ-5D-5L utilities decreased and costs increased with worsening patient disability and function.

Abstract

Background: Motor Neurone Disease (MND) places a significant burden on patients, their carers and healthcare systems. However, there is limited information on health utilities and costs within a United Kingdom setting.

Methods: Patients with MND, recruited via 22 regional clinics, completed a postal questionnaire of a cost and quality of life survey. Health outcome assessment included the EQ-5D-5L, EQ-VAS, ALS Utility Index and the Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised. Clinical staging was based on the Kings and MiToS systems. The questionnaire asked about patients' use of primary, secondary and community care services in the previous 3-months. Variability in total costs was examined using regression models.

Results: 595 patients were included in the health utility analysis, of whom 584 patients also completed a resource use questionnaire. Mean health utility decreased and costs increased between consecutive Kings stages, from 0.76 (95%CI 0.71, 0.80) and £1,096 (£757, £1,240) in Kings stage 1, to 0.50 (0.45, 0.54) and £3,311 (£2,666, £4,151) in stage 4, respectively. The changes by MiToS stages, were from 0.71 (0.69, 0.73) and £1,115 (£937, £1,130) in MiToS stage 0, to 0.25 (0.07, 0.42) and £2,899 (£2,190, £3,840) in stage 2. Kings stages 3 and 4, and MiToS Stages 1 and 2, respectively, were significant in explaining variability in total costs.

Conclusions: The impact of MND on health utilities and costs differs by disease severity. The data provided here can be used in cost-effectiveness analyses and to inform decision-making regarding healthcare provision for people with MND.

Introduction

Motor Neurone Disease (MND) (or amyotrophic lateral sclerosis) is a neurodegenerative condition associated with extensive impairment of patients' mobility, communication and breathing which results in large reductions in their health-related quality of life [1]. The average life expectancy is only 3 -5 years from disease onset [2], and treatment is focused on symptom management, slowing disease progression and providing palliative care. MND incurs significant financial burden on patients, caregivers and health-care providers [3].

Economic studies in MND, including cost analyses, preference elicitation and economic evaluations, both in the UK and internationally, have a limited evidence base. The extent of these limitations has been described in our systematic review of economic studies in MND [4]. These studies are restricted in terms of cost measurement, and small samples for estimating health utility. There is limited experience of the EuroQoL (EQ)-5D in MND populations [5,6], with possible flooring effects in the EQ-5D-3L. In one study [6], EQ-5D-3L health utility values decreased as disease severity increased, whereas in the other, health states were not mutually exclusive [5].

The costs of MND to the National Health Service (NHS) in the UK are believed to be high, owing to the nature of the disease, but are not well documented within the health economic literature [4]. A study published in 1998, using expert opinion to estimate resource use, provided cost estimates for some less severe health stages which were higher than the most severe stage [7]. In international studies, reported costs have increased as severity worsened [4].

Previous studies in MND have involved attempts to describe and model disease progression using clinical staging systems [8-11]. These facilitate analyses of costs and benefits using clearly defined clinical health states, and provide a structure for simulation models, such as Markov models [12], for estimating cost-effectiveness. The two most commonly used clinical staging systems in MND are the Kings [10] and the Milano-Torino (MiToS) staging systems [11]. The Kings system is structured around clinical involvement of bulbar and limb areas and nutritional or respiratory failure, whereas the MiToS system is focused on loss of

independence across the domains of bulbar, gross motor, fine motor and respiratory function.

The Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised (ALSFRS-R) [13] is the most commonly used disability measure in MND clinical research and is recommended for capturing changes in functionality along the disease course [14,15]. The Kings system was developed for patients to be staged by clinicians but it can also be derived from the ALSFRS-R with good accuracy [16], whereas the MiToS staging system is based directly on ALSFRS-R responses. The fact that both of these staging systems can be used with ALSFRS-R data makes them particularly useful in the analysis of clinical trials, which routinely use the ALSFRS-R as a primary outcome measure.

We aimed to contribute to the evidence-base of economic studies in MND by presenting costs, and health state utilities based on the EQ-5D-5L [17] and the ALS utility index [18], defined by both Kings and MiToS staging. This study provides evidence for future economic evaluations in MND to inform health technology assessment and decision making within the UK National Health Service. , We provide valuable information on how MND impacts upon patients' quality of life and NHS costs at various clinical stages, by using a range of health measures, and two clinical staging models.

Methods

Data

Data were obtained from the Trajectories of Outcomes in Neurological Conditions (TONiC) study conducted in the UK. TONiC is an ongoing longitudinal cohort study which, at the time of this study, had recruited patients from 22 MND clinics within the UK. The TONiC study is primarily aimed at assessing factors affecting patients' quality of life and their experience of MND [19]. Patients attending MND clinics are given questionnaires at various time points for postal return; at 0, 4, 9, 14, 18, 27 and 60 months from their inclusion in the TONiC study. The health economic components include a resource use questionnaire, which was a modified version of a questionnaire used in epilepsy [20] (available from the Database of Instruments for Resource Use Measurement [21]) and the EQ-5D-5L questionnaire. Baseline responses were used in the present study as longitudinal data had not matured sufficiently at the time of analysis, which resulted in this study being cross-sectional in nature.

The TONiC study was approved in the UK by NRES Committee North West – Greater Manchester West (reference number 11/NW/0743) and informed consent was obtained from the patients involved.

Demographic and clinical characteristics

Respondents reported their age and gender. MND onset type (limb, bulbar, respiratory or unknown) was determined by a clinician familiar with each patient's case.

Disease-specific measure

The ALSFRS-R, which was completed by study participants, comprises of 12 items, each scored from 0 (worse state) to 4 (best state with less disability) [13]. These items are commonly divided to 3 distinct domains; bulbar (items 1-3), motor (items 4-9) and respiratory (items 10-12) [22]. We used the ALSFRS-R to assign patients to Kings and MiToS states [10,11].

Health utility

Patents completed the EQ-5D-5L which comprises of five domains; mobility, self-care, usual activities, pain/discomfort, and anxiety/depression [17]. Each of these domains has five

levels indicating worsening health, from having no problems, to having severe problems. Responses to the EQ-5D-5L were used to calculate health utilities. Each possible combination of responses to the five questions of the EQ-D5-5L is associated with a health utility value, based on time trade-off valuations from a representative sample of the general public in England [17]. We also present results from the EQ-5D-visual analogue scale (EQ-5D VAS), which complements the main EQ-5D-5L questionnaire and measures self-reported health values as indicated on a vertical scale.

The ALS Utility Index (ALSUI) was calculated from responses to the ALSFRS-R [18]. This measure is the first such to present a disease-specific, preference-based index in MND, based on scoring determined from a standard gamble experiment taken by members of the general public in the United States. The ALSUI algorithm attaches a preference weighting to ALSFRS-R items 1, 6, 8, 10 and 12, to obtain a single index value ranging from 0 (worse possible state) to 1 (best possible state) [18].

Clinical staging

As Kings staging is based on clinical observation, we used a mapping algorithm which estimates Kings stages with 92% accuracy [16]. Kings stages 1,2,3 are allocated by counting the number of times a patient shows any loss (any score below 4 on relevant items) in the domains of bulbar, upper limbs and lower limbs; involvement of any one region leads to stage 1, two regions stage 2 and so on. Patients with respiratory or swallowing failure are allocated to stage 4.

We also allocated patients in this study to MiToS system stages [11]. This was done using the ALSFRS-R, from which the MiToS system was developed. All MiToS stages are allocated on counts of losses in independence in domains of bulbar, gross motor, fine motor and respiratory function. Loss of independence in one domain is stage 1, in two domains stage 2 and so on. If no loss of independence has occurred, patients are allocated to stage 0.

Resource use and cost

The resource use questionnaire asked respondents about their use of NHS resources, including medicines, primary and community care, hospital clinic visits and inpatient stays,

tests and investigations, within the previous 3 months. Unit costs were sourced from NHS reference costs [23] and the Personal Social Services Research Unit (PSSRU) [24,25]. All costs were inflated to 2017 values, where applicable, using the hospital and community health services (HCHS) index PSSRU [24]. The full disaggregated data on items and unit costs are presented in the Supplementary Appendix.

Missing data

Patients were omitted from the analysis of health utility if they had not completed the EQ-5D-5L in full, and from the cost analysis if they had not answered all required questions on the resource use questionnaire. Further to this, patients who did not complete the ALSFRS-R in full were also excluded from the analysis, as they could not be staged according to the Kings or MiToS staging systems.

Statistical analysis

95% Confidence intervals (CI) were estimated using non-parametric bootstrapping, with 2000 replications with replacement to account for the skewed nature of cost and health utility data. Generalized Linear Models (GLM) with a Gamma log link were used to estimate the influence of certain variables, including disease staging, on total patient costs. Data management was undertaken in Excel 2016 (Microsoft, Washington, United States) and all analyses were carried out in R (Vienna, Austria) [26].

Results

Description of data

958 patients received posted questionnaires, of which 636 (66.4%) were returned. Forty-one of the questionnaires returned were not sufficiently completed. Health utility data were therefore available from 595 patients, and of these 584 patients also provided cost information, meaning cost data were available for 98.1% of patients who were staged. Table 1 presents the characteristics of the participants for both health utility and cost analyses. The 11 patients who had completed EQ-5D-5L and ALSFRS-R questionnaires, but had failed to complete the resource use questionnaire, had comparable characteristics to those who had completed all three questionnaires. Patients in the sample were of similar age, gender distribution and MND onset type, to those previously reported in MND populations [27].

Health utility by MND stage and disease onset type

Table 2 shows the distributions of EQ-5D-5L domains by model and health state. The "usual activities" EQ-5D-5L domain was most affected by MND, as it had the highest proportion of severe (level 5) responses and any problems (levels 2-5) across all clinical stages. Conversely, the least affected domain on the EQ-5D-5L questionnaire was "anxiety/depression" across all clinical stages, based on the same metrics, with the exception of patients in MiToS stage 3.

Mean (95% CI) health utility scores for the entire sample were EQ-5D-5L 0.57 (0.55, 0.59), EQ-5D VAS score 60 (58, 62), and ALS utility Index 0.40 (0.38, 0.42). EQ-5D-5L health utility decreased with increasing clinical severity across both the Kings and MiToS systems. For Kings staging, health utility reduced from 0.76 (95% CI 0.71, 0.80) in stage 1, to 0.50 (0.45, 0.54) in stage 4 (Table 3). In the MiToS staging, mean health utility of stage 0 was 0.71 (95% CI 0.69, 0.73) but reduced to 0.25 (0.07, 0.42) in stage 4. The measures of ALSFRS-R total score, ALSFRS-R domains, ALSUI and EQ-5D VAS all reduced through progressively worse clinical stages. ALS utility index values were much lower for all stages across both systems than the values for EQ-5D-5L. This result was more prominent for the most severe states in both models, with Kings stage 4 mean EQ-5D-5L health utility at 0.50 (0.45, 0.54) and ALSUI at 0.24 (0.21, 0.27); and MiToS stage 4 EQ-5D-5L health utility of 0.25 (0.07, 0.42) and ALSUI utility of 0.07 (0.07, 0.08).

EQ-5D-5L health utility tended to be higher with bulbar onset MND at 0.68 (95% CI 0.64, 0.72), compared to either limb 0.53 (0.49, 0.57) or respiratory onset, 0.53 (0.35, 0.71) (Supplementary Appendix). This was despite the mean ALSFRS-R total score being higher in patients with limb onset MND in our study than in patients with bulbar onset.

Resource use and costs by MND stage and disease onset type

Seventy-seven (13.2%) patients experienced at least one inpatient stay during a 3-month period (Table 4). Inpatient stays were most frequent in Kings stage 4 (0.45) and MiToS stage 1 (0.40). Kings stage 4 was associated with more resource use in all categories compared with other stages, except tests and investigations. The mean number of home visits by doctors and nurses was higher for Kings stage 4 (0.68 and 4.35, respectively) than other Kings stages; higher levels of home care were also evident in patients in MiToS stage 4 (15.2 nurse home visits and 2.2 doctor home visits) than in less severe MiToS stages (ranging between 0.61 and 5.38 nurse home visits, and 0.43 and 1.17 doctor home visits).

The total costs per patient over a 3-month period were £1,889 (95% CI £1,596, £2,214), ranging from £53 to £39,884 (Table 5; Figure 1). Overnight inpatient stays made up 35.8% of total costs, making it the single largest cost category, while community costs contributed 14.2% of total costs.

Kings stages showed progressively higher mean costs with advancing disease, ranging from £1,096 (95% CI £757, £1,240) in stage 1 to £3,311 (£2,666, £4,151) in stage 4 (Figure 1). The association of MiToS staging with costs was less clear, with patients categorised in stage 0 having the lowest cost of £1,115 (£937, £1,130) and stages 1 to 4 having higher costs, with the highest cost occurred in stage 2 at £2,889 (£2,190, £3,810). Drug costs were also higher for Kings stage 4 than other Kings stages; and lower for stage 0 than other stages based on MiToS stages. Secondary care costs were higher than primary care costs for patients in all states, with the exception of those in MiToS stage 4. Bulbar onset patients had higher costs in every cost category compared to other onset types.

Generalized Linear Model regressions indicated that Kings stages 3 and 4, and MiToS Stages 1 and 2, respectively, were significant in explaining variability in total costs (Table 6). Bulbar onset was associated with higher costs in the MiToS system, but neither age nor gender contributed significantly to costs in either model.

Comparison of Kings and MiToS staging

There was moderate correlation (Spearman's rank coefficient of 0.58), in patient categorisation between the Kings and MiToS staging systems (Supplementary Appendix). Within any given Kings stage, health utility scores decreased with increasing MiToS stage. For example, patients in Kings stage 4 had mean health utility scores ranging from 0.25 (MiToS stage 4) to 0.67 (MiToS Stage 1).

Discussion

This analysis of health utility and costs by clinically defined health stages provides empirical evidence of the impact of the progressive nature of MND, and data to support future economic evaluations in MND. This study benefitted from using two commonly used health staging systems, Kings and MiToS staging, and represents the most comprehensive health utility and cost study in MND.

The mean, 3-month NHS costs of £1,889 is significantly higher than estimates for some other neurodegenerative conditions (e.g. £529 for patients with Parkinson's disease [28]) and comparable to others (e.g. £1,880 for patients with Huntington's disease [29]). The comparison between our study and earlier estimates of the costs of MND in the UK is difficult because of difference in methodology and staging systems used. However, our study appears to have a higher cost for the most severe Kings state, (£3,311 over 3 months) compared to the most severe state in Munsat et al [7] (£5,825 over 12 months), after accounting for inflation. This could be attributed to our study accounting for a wider scope of costs such as home-based care, and using resource use information from patient survey questions rather than relying on expert opinion, which is less reliable [7]. A substantial portion of costs (40%) in our study population related to hospital admissions, which occurred at a rate of 92 per 100 patient-years. This reflects the gravity of MND, and the frequent need of patients for specialist medical care.

The Kings staging system showed that patients incurred increased costs with more severe health stages: Kings stage 4 had significantly higher costs than other Kings stages, which is likely a result of this stage being defined by nutritional and respiratory failure, and survival requiring gastrostomy feeding or respiratory support such as non-invasive ventilation. Patients in Kings stages 1 to 3 also show increasing costs, which was expected as these stages reflect an increasing number of body regions affected by the condition. Higher costs in MiToS stage 1 compared to 0 may be explained by this involving the first loss of independence. MiToS stages 2 to 4 were associated was smaller marginal increased costs, as once independence has been lost in one domain, other losses may not result in increased healthcare costs, although it should be noted that the number of patients in these categories were relatively low.

The mean health utility of patients in the sample was 0.57, with individual responses across the full range of the EQ-5D-5L index. The largest health utility decrement between consecutive states was from Kings stage 1 to stage 2, indicating that losing functioning in a second domain may impact health-related quality of life more than subsequent additional losses, and suggesting a diminishing marginal negative impact on health utility with disease severity. Health utility was lower for people in more severe stages compared to less severe stages in both the Kings and MiToS systems, reflecting the higher percentages of more severe responses across the 5 domains of the EQ-5D-5L in more advanced stages. It should be noted, however, that as the data are based on a cross-sectional analysis, inferences on longitudinal effects are speculative. Bulbar onset patients in our study tended to have higher EQ-5D-5L health utility than patients with limb or respiratory onset. This result may be in part due to the domains featured in the EQ-5D-5L, which could be expected to capture losses in mobility, which is impacted more in limb onset, than symptoms that are more prominent in bulbar onset.

Health state utilities by Kings staging have been reported previously using the EQ-5D-3L [6]. Our reporting of EQ-5D-5L utilities may mitigate ceiling/floor effects, although insufficient data has been presented in previous studies to evaluate this. Health utilities reported using the EQ-5D-3L are considerably lower across all King's health states (1 to 4) when compared

to our study (0.65, 0.53, 0.41 and 0.27 using EQ-5D-3L, compared to 0.71, 0.60, 0.53 and 0.50, using EQ-5D-5L). This could be attributed to the revised tariffs used in our study, but also to the easing of flooring effects. EQ-5D VAS scores showed better agreement between our study and Jones et al. [6], with the two studies having comparable values for all Kings states. This highlights the differences in structure between the EQ-5D-3L and 5L questionnaires and could provide evidence to suggest the 5 level questionnaire is more sensitive to changes in quality of life in people with MND as the disease progresses.

Differences between the Kings and MiToS staging systems in terms of patient distribution, costs and health utility can be explained by their construct [30]. In the Kings staging system, the focus is on disease spread through upper and lower limbs as well as bulbar regions. Disability in these regions is defined as any loss (any score below 4) in certain ALSFRS-R items. Stages 1, 2 and 3 are assigned by counts of these disabilities. The model also has a mechanism which assigns patients with swallowing or respiratory failure to the most severe stage 4. In contrast, the MiToS system is structured around loss of independence in domains of bulbar, gross motor, fine motor and respiratory loss. Loss of independence in these domains requires respondents to score a 0 or 1 on certain ALSFRS-R items. These scores are low as all items cover a range from 0 to 4. Patients are assigned stages based on a count of affected domains. No mechanism within the MiToS system allocates patients to the most severe stage in the MiToS model if nutritional or respiratory failure occurs.

Limitations of our study include the low number of patients in stages 3 and 4 of the MiToS staging system, and no estimates for caregiver and other indirect costs which are likely to be high [31,32]. Further to this, our study presented cross-sectional results rather than longitudinal and used episode costs for inpatient admissions as the length of hospital stay of patients was unknown.

In conclusion, while it is well understood that MND lowers patients' health-related quality of life and is associated with substantial costs to health care systems, the evidence presented herein provides a basis for future health economic analyses of interventions for MND. Our use of two well established health staging systems, Kings and MiToS, allows for costs and utilities to be assigned to MND health states for use in health economic models.

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Table 1 Characteristics of samples used for the health utility and cost analysis

		Health utility sample	**Cost sample ***
Sample size		595	584
Age in years	Mean (SD)	65.07 (10.89)	65.05 (10.91)
Female	n (%)	232 (39.0)	230 (39.21)
Months since diagnosis	Mean (SD)	26.54 (38.8)	26.59 (38.9)
MND Onset Type	n (%)		
Limb		404 (69.9)	400 (68.5)
Bulbar		159 (26.7)	155 (26.5)
Respiratory		11 (2.5)	11 (1.9)
EQ-5D-5L Utility	Mean (95% CI) Median (IQR)	0.57 (0.55, 0.59) 0.61 (0.38, 0.78)	0.57 (0.55, 0.59) 0.62 (0.38, 0.79)
EQ-5D VAS	Mean (95% CI) Median (IQR)	60 (58, 62) 60 (45, 75)	60 (58, 62) 61 (45, 75)
ALSFRS-R Index	Mean (95% CI) Median (IQR)	31.95 (31.19, 32.55) 33 (27, 38)	31.96 (31.16, 32.58) 33 (27, 38)
ALS Utility Index	Mean (95% CI) Median (IQR)	0.40 (0.38, 0.42) 0.36 (0.27, 0.58)	0.40 (0.38, 0.42) 0.36 (0.27, 0.59)
Kings Staging	n (%)		
Stage 1		89 (15.0)	86 (14.7)
Stage 2		135 (22.7)	131 (22.4)
Stage 3		206 (34.6)	201 (34.4)
Stage 4		162 (27.3)	160 (27.4)
MiToS Staging	n (%)		
Stage 0		301 (50.59)	296 (50.69)
Stage 1		198 (33.28)	195 (33.39)
Stage 2		73 (12.69)	72 (12.33)
Stage 3		18 (3.03)	16 (2.74)
Stage 4		5 (0.84)	5 (0.86)

*Cost analysis cohort was a subset of the health utility study cohort.
*SD = standard deviation, CI = confidence interval, IQR = interquartile range.

Table 2 EQ-5D-5L domain responses by health stage and system

	EQ-5D-5L domain				
Response Level	**Mobility**	**Self-Care**	**Usual Activities**	**Pain/Discomfort**	**Anxiety/Depression**
Full sample (N= 595)	n (%)	n (%)	n (%)	n (%)	n (%)
Level 1	99 (16.6)	118 (19.8)	53 (8.9)	179 (30.1)	268 (45.0)
Level 2	81 (13.6)	152 (25.6)	117 (19.7)	213 (35.8)	203 (34.1)
Level 3	157 (26.4)	162 (27.2)	174 (29.2)	161 (27.1)	98 (16.5)
Level 4	152 (25.5)	71 (11.9)	118 (19.8)	37 (6.2)	20 (3.4)
Level 5	106 (17.8)	92 (15.5)	133 (22.4)	5 (0.9)	6 (1.0)
Some Problems	496 (83.3)	477 (80.2)	542 (91.1)	416 (69.9)	327 (55.0)
Kings stage 1 (N= 89)					
Level 1	49 (55.1)	42 (47.2)	25 (28.1)	46 (51.7)	53 (59.5)
Level 2	7 (7.9)	23 (25.8)	27 (30.3)	26 (29.2)	29 (32.6)
Level 3	12 (13.5)	16 (17.98)	16 (18.0)	16 (18.0)	6 (6.7)
Level 4	15 (16.9)	6 (6.4)	11 (12.4)	1 (1.1)	1 (1.1)
Level 5	6 (6.7)	2 (2.2)	10 (11.3)	0 (0)	0 (0)
Some Problems	40 (44.9)	63 (52.8)	64 (72.0)	43 (48.3)	36 (40.4)
Kings stage 2 (N= 135)					
Level 1	22 (16.3)	28 (20.7)	11 (8.2)	43 (31.9)	66 (48.9)
Level 2	28 (20.7)	40 (29.6)	33 (24.4)	47 (34.8)	45 (33.3)
Level 3	37 (27.4)	34 (25.2)	44 (32.6)	33 (24.4)	16 (11.9)
Level 4	26 (19.3)	16 (11.9)	28 (20.7)	10 (7.4)	5 (3.7)
Level 5	21 (15.6)	16 (11.9)	18 (13.3)	1 (0.74)	2 (1.5)
Some Problems	113 (83.7)	107 (79.3)	124 (91.9)	92 (68.1)	69 (51.1)
Kings stage 3 (N= 206)					
Level 1	6 (2.9)	22 (10.7)	6 (2.9)	43 (20.9)	86 (41.7)
Level 2	30 (14.6)	57 (27.7)	36 (17.5)	76 (36.9)	75 (36.4)
Level 3	66 (32.0)	65 (31.6)	66 (32.0)	72 (35.0)	39 (18.9)
Level 4	63 (30.6)	31 (15.0)	47 (22.8)	11 (5.4)	3 (1.5)
Level 5	40 (19.5)	30 (14.6)	50 (24.3)	3 (1.5)	2 (1.0)
Some Problems	200 (97.1)	184 (89.3)	200 (97.1)	163 (79.06)	120 (58.3)
Kings stage 4 (N= 162)					
Level 1	19 (11.7)	24 (14.8)	9 (5.6)	45 (27.8)	61 (37.7)
Level 2	17 (10.5)	31 (19.1)	21 (13.0)	61 (37.7)	53 (32.7)
Level 3	40 (24.7)	46 (28.4)	48 (29.6)	40 (24.7)	35 (21.6)
Level 4	48 (29.6)	18 (11.1)	31 (19.1)	15 (9.3)	11 (6.8)
Level 5	38 (23.5)	43 (26.5)	53 (32.7)	1 (0.6)	2 (1.2)
Some Problems	143 (88.3)	138 (85.2)	153 (94.4)	117 (72.2)	101 (62.4)
MiToS stage 0 (N= 301)					
Level 1	79 (26.3)	94 (31.2)	46 (15.3)	113 (37.5)	154 (51.2)
Level 2	54 (17.9)	119 (39.5)	96 (31.9)	102 (33.8)	107 (35.6)
Level 3	96 (31.9)	75 (24.9)	101 (33.6)	71 (23.6)	35 (11.6)
Level 4	88 (29.2)	13 (4.3)	39 (13.0)	14 (4.6)	5 (1.7)
Level 5	6 (2.0)	0 (0)	22 (7.3)	1 (0.3)	0 (0)
Some Problems	222 (73.4)	207 (68.8)	255 (84.7)	188 (62.5)	147 (48.8)
MiToS stage 1 (N=198)					
Level 1	16 (8.9)	22 (11.1)	9 (4.6)	40 (20.2)	84 (42.4)
Level 2	22 (11.1)	26 (13.1)	16 (8.1)	75 (37.9)	63 (31.8)
Level 3	44 (22.2)	60 (30.3)	60 (30.3)	66 (33.3)	37 (18.7)
Level 4	60 (30.3)	41 (20.7)	57 (28.8)	14 (7.1)	7 (3.5)
Level 5	54 (27.3)	47 (23.7)	54 (27.3)	1 (0.5)	3 (1.5)
Some Problems	182 (91.9)	176 (88.9)	189 (95.5)	158 (80.0)	114 (57.6)

MiToS stage 2 (N= 73)					
Level 1	4 (5.5)	3 (4.1)	1 (1.4)	21 (28.8)	24 (32.9)
Level 2	5 (6.9)	4 (5.5)	5 (6.9)	26 (35.6)	29 (39.7)
Level 3	11 (15.1)	21 (28.8)	10 (13.7)	15 (20.6)	15 (20.6)
Level 4	17 (23.3)	15 (20.6)	19 (26.0)	8 (11.0)	4 (5.5)
Level 5	36 (49.3)	36 (49.3)	38 (52.1)	3 (4.1)	1 (1.4)
Some Problems	69 (94.5)	70 (95.9)	72 (98.6)	52 (71.2)	49 (67.1)
MiToS stage 3 (N=18)					
Level 1	0 (0)	0 (0)	0 (0)	4 (22.2)	3 (16.7)
Level 2	1 (5.6)	2 (11.1)	1 (5.6)	7 (38.9)	5 (27.8)
Level 3	3 (16.7)	5 (27.8)	2 (11.1)	6 (33.3)	8 (44.4)
Level 4	7 (38.9)	1 (5.6)	2 (11.1)	1 (5.6)	2 (11.1)
Level 5	7 (38.9)	10 (55.6)	13 (72.2)	0 (0)	0 (0)
Some Problems	18 (100)	18 (100)	18 (100)	14 (77.8)	15 (83.3)
MiToS stage 4 (N= 5)					
Level 1	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Level 2	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Level 3	1 (20)	1 (20)	1 (20)	1 (20)	2 (40)
Level 4	2 (40)	0 (0)	0 (0)	1 (20)	1 (20)
Level 5	2 (40)	4 (80)	4 (80)	3 (60)	2 (40)
Some Problems	5 (100)	5 (100)	5 (100)	5 (100)	5 (100)

'Some problems' are defined as any response from level 2 to level 5

Table 3 Mean EQ-5D-5L utility, ALSFRS-R and ALS Utility Index by stage and MND onset type

	EQ-5D-5L Utility	**EQ-5D VAS**	**ALSFRS-R Index**	**ALSFRS-R Bulbar**	**ALSFRS-R Gross Motor**	**ALSFRS-R Respiratory**	**ALS Utility Index**
	Mean (95% CI)						
Full Sample	0.57 (0.55,0.59)	60 (58,62)	31.95 (31.19,32.55)	8.43 (8.13,8.69)	13.67 (13.16,14.07)	9.85 (9.61,32.55)	0.40 (0.38,0.42)
Kings staging							
Stage 1	0.76 (0.71,0.80)	72 (68,76)	40.90 (40.56,41.94)	10.48 (9,63,10.85)	19.98 (18.79,20.81)	11.44 (11.24,11.58)	0.63 (0.60,0.68)
Stage 2	0.60 (0.56,0.64)	63 (59,66)	35.68 (35.25,37.03)	10.33 (10.09,10.79)	14.38 (13.44,15.24)	11.02 (10.92,11.35)	0.50 (0.46,0.54)
Stage 3	0.53 (0.50,0.56)	59 (57,62)	30.54 (29.89,31.58)	8.09 (7.77,8.41)	11.91 (11.56,12.76)	10.49 (10.30,10.69)	0.35 (0.33,0.37)
Stage 4	0.50 (0.45,0.54)	52 (48,56)	24.42 (25.16,25.65)	5.85 (5.21,6.49)	11.53 (10.62,12.48)	7.04 (6.57,7.68)	0.24 (0.21,0.26)
MiToS staging							
Stage 0	0.71 (0.69,0.73)	68 (66,70)	37.39 (36.89,37.98)	9.19 (8.89,9.52)	17.26 (16.85,20.31)	10.97 (10.83,11.11)	0.56 (0.54,0.58)
Stage 1	0.48 (0.44,0.51)	55 (52,58)	29.59 (28.85,30.31)	8.49 (7.98,8.98)	11.21 (10.31,11.94)	9.89 (9.52,10.22)	0.30 (0.28,0.32)
Stage 2	0.36 (0.31,0.42)	49 (43,54)	21.44 (20.21,22.67)	6.75 (5.85,7.60)	8.23 (7.12,9.42)	6.43 (5.74,7.18)	0.16 (0.13,0.18)
Stage 3	0.33 (0.23,0.43)	47 (37,58)	15.17 (13.61,16.83)	3.57 (2.39,4.78)	5.50 (3.83,7.33)	6.11 (4.61,7.61)	0.08 (0.06,0.11)
Stage 4	0.25 (0.07,0.42)	45 (22,70)	9.40 (5.1,12.6)	2.00 (0.6,3.6)	3.40 (1,5.8)	4.00 (2,6)	0.07 (0.03,0.09)

Scale range of included measures (minimum to maximum): EQ-5D-5L -0.21 to 1; EQ-5D VAS 0 to 1; ALSFRS-R Index 0 to 48; ALSFRS-R Bulbar 0 to 12; ALSFRS-R Gross Motor 0 to 24; ALSFRS-R Respiratory 0 to 12; ALS Utility Index 0 to 1.

Table 4 Resource use by health stage and system

			Kings stage				MiToS stage				
Resource Category	**Units; Number of**	**Full Sample**	1	2	3	4	0	1	2	3	4
		Mean, (maximum value) – all min values = 0									
Primary Care											
Nurse GP Surgery	Visits	0.48 (20)	0.39 (4)	0.53 (10)	0.26 (5)	0.77 (20)	0.48 (10)	0.54 (20)	0.30 (6)	0.50 (2)	2.2 (10)
Doctor GP Surgery	Visits	0.88 (10)	0.90 (8)	0.89 (10)	0.75 (8)	1.03 (10)	1.05 (10)	0.83 (10)	0.58 (6)	0.50 2)	1.6 (6)
Nurse at Home	Visits	1.95 (90)	0.53 (10)	0.99 (90)	1.32 (25)	4.35 (90)	0.61 (15)	1.78 (25)	6.25 (90)	5.38 (24)	15.2 (28)
Doctor at Home	Visits	0.30 (12)	0.08 (2)	0.13 (5)	0.20 (12)	0.68 (10)	0.04 (3)	0.43 (12)	0.63 (10)	1.17 (8)	2.2 (8)
Secondary Care											
Casualty Department	Visits	0.24 (10)	0.13 (8)	0.17 (7)	0.28 (10)	0.33 (8)	0.18 (8)	0.31 (10)	0.40 (10)	0.17 (1)	0.00 (0)
Nurse Outpatient	Visits	0.96 (18)	0.65 (4)	0.58 (6)	0.78 (10)	1.68 (18)	0.71 (10)	1.29 (18)	1.10 (12)	1.61 (10)	0.40 (1)
Doctor Outpatient	Visits	2.11 (31)	2.05 (21)	2.32 (21)	2.06 (31)	2.12 (21)	2.17 (31)	2.19 (31)	1.31 (12)	3.00 (12)	1.80 (3)
Ambulance Use	Call outs	0.25 (12)	0.04 (2)	0.23 (6)	0.25 (12)	0.37 (10)	0.1 0 (12)	0.27 (10)	0.60 (6)	0.11 (1)	0.00 (0)
Inpatient Stays	Number of admissions	0.23 (12)	0.08 (2)	0.17 (10)	0.15 (12)	0.45 (10)	0.10 (4)	0.40 (12)	0.34 (5)	0.11 (1)	0.20 (1)
Tests											
Blood	Tests	1.16 (12)	1.11 (6)	0.97 (6)	0.39 (10)	0.75 (10)	1.10 (6)	1.04 (12)	1.54 (18)	1.00 (3)	0.40 (2)

Urine	Tests	0.11 (5)	0.04 (3)	0.04 (2)	0.13 (4)	0.19 (5)	0.06 (2)	0.14 (4)	0.21 (5)	0.33 (2)	1.20 (1)
Ultrasound	Scans	0.06 (3)	0.08 (3)	0.05 (2)	0.05 (2)	0.08 (2)	0.04 (1)	0.09 (3)	0.10 (3)	0.11 (1)	0.00 (0)
X-ray	Scans	0.18 (6)	0.15 (2)	0.15 (3)	0.19 (5)	0.22 (6)	0.14 (3)	0.21 (5)	0.30 (6)	0.11 (1)	0.00 (0)
CT Scan	Scans	0.12 (10)	0.13 (2)	0.13 (2)	0.10 (2)	0.13 (10)	0.12 (2)	0.16 (3)	0.05 (2)	0.00 (0)	0.00 (0)
MRI Scan	Scans	0.20 (6)	0.21 (2)	0.25 (3)	0.23 (6)	0.11 (2)	0.23 (2)	0.20 (3)	0.15 (6)	0.00 (0)	0.00 (0)
EMG	Scans	0.26 (3)	0.33 (2)	0.33 (3)	0.26 (3)	0.18 (3)	0.25 (3)	0.25 (3)	0.16 (3)	0.06 (1)	0.00 (0)
Community Care											
Health Visitor	Visits	0.83 (46)	0.49 (8)	0.24 (5)	0.85 (46)	1.50 (20)	0.44 (12)	1.25 (46)	1.36 (16)	1.00 (12)	1.00 (3)
Social Worker	Visits	0.41 (14)	0.21 (3)	0.23 (4)	0.46 (10)	0.61 (14)	0.22 (3)	0.52 (10)	0.67 (5)	1.28 (14)	1.20 (2)
Physio-therapist	Visits	2.09 (40)	1.76 (40)	1.74 (12)	2.11 (16)	2.56 (20)	1.72 (40)	2.31 (16)	2.60 (15)	4.94 (20)	2.40 (4)
Psychologist	Visits	0.12 (40)	0.08 (4)	0.13 (6)	0.11 (10)	0.17 (4)	0.07 (10)	0.18 (6)	0.15 (4)	0.33 (3)	0.00 (0)
Counsellor	Visits	0.10 (7)	0.06 (4)	0.04 (2)	0.04 (3)	0.23 (7)	0.04 (3)	0.10 (4)	0.27 (7)	0.22 (2)	0.00 (0)

Abbreviations: CT Computerised Tomography; MRI Magnetic Resonance Imaging; EMG Electromyography

Table 5 Direct healthcare costs by health stage and system, mean, £ sterling (95% CI)

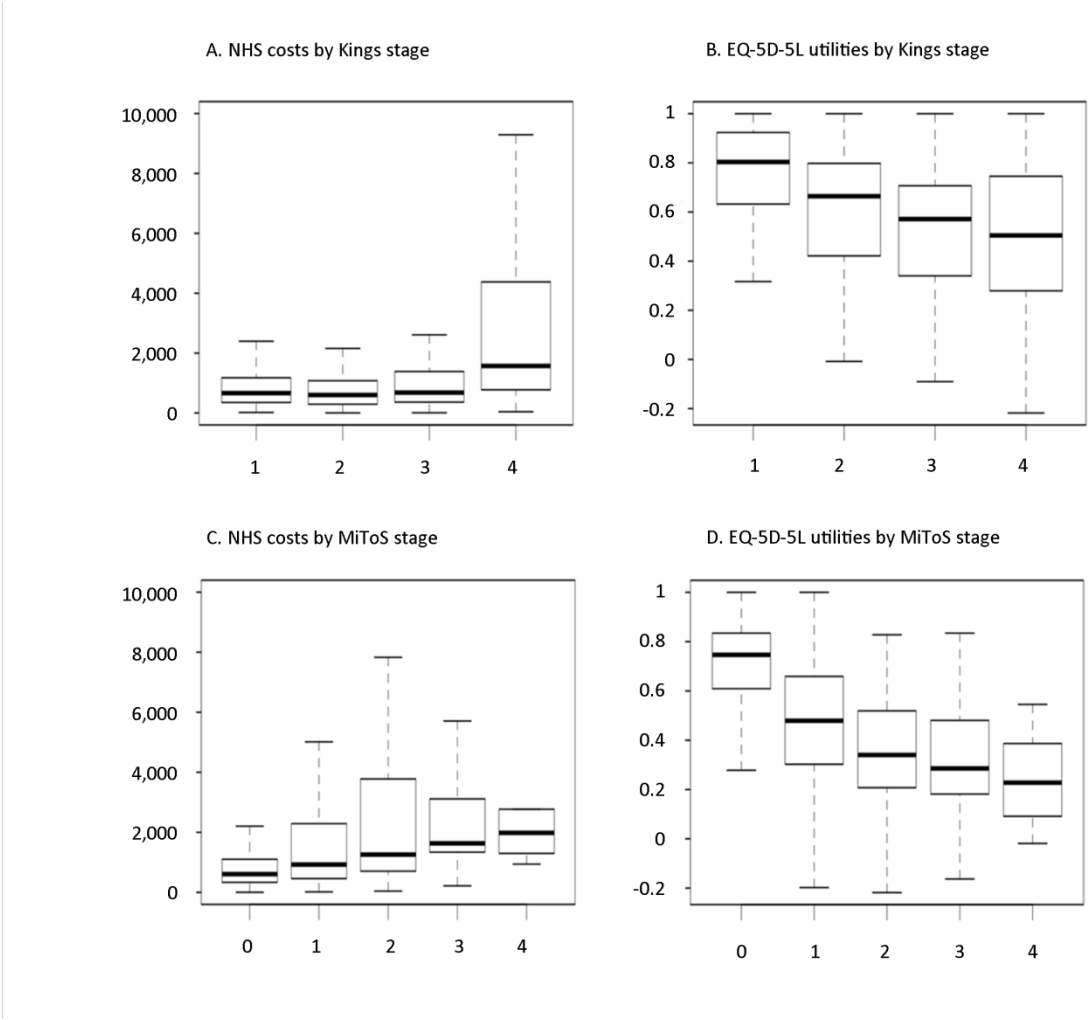
		Kings				MiToS				
Category	Full Sample	Stage 1	Stage 2	Stage 3	Stage 4	Stage 0	Stage 1	Stage 2	Stage 3	Stage 4
Primary Care	164 (132, 196)	74 (50,92)	113 (52,173)	118 (77,154)	329 (237,424)	77 (61,87)	259 (134,384)	392 (186,598)	420 (186,652)	1054 (597,1510)
Secondary Care	1,183 (896,1502)	572 (324,639)	899 (405,1586)	927 (809,1514)	2146 (1507,2930)	642 (449,838)	1668 (1376,1781)	1724 (987,2507)	837 (243,1616)	944 (54,2546)
Of which are inpatient stays	763 (521,1037)	256 (80,281)	575 (150,1199)	523 (186,1028)	1520 (999.2186)	326 (187,489)	1115 (937,1130)	1155 (554,1802)	375 (0,937)	675 (0,2024)
Tests	110 (94,128)	133 (94,172)	129 (92,168)	115 (84,148)	85 (54,122)	575 (150,1199)	113 (81,150)	83 (32,142)	25 (16,55)	2 (1,5)
Community services	250 (222,283)	184 (120,263)	173 (114,226)	262 (211,320)	367 (303,432)	167 (141,197)	308 (254,372)	370 (279,468)	563 (316,913)	377 (262,484)
Drug costs	161 (127,201)	99 (51,188)	76 (58,97)	86 (70,105)	369 (303,432)	94 (73,127)	192 (121,283)	302 (189,441)	386 (160,687)	271 (43,580)
Total Direct Costs	1889 (1596,2214)	1096 (757,1240)	1353 (879,2002)	1534 (1111,2123)	3311 (2666,4151	1329 (532,1700)	2678 (1948,3545)	2899 (2190,3840	2281 (1613,2988)	2666 (1292,4597)

Table 6 Generalized Linear Models, showing influence of disease staging, onset type, and demographic variables on total costs

Variable	Coefficient (SE)	Relative increase in costs associated with variable*	p-value
Kings Staging			
Constant	7.02 (0.53)		<0.01
Kings 2	0.36 (0.26)	1.43 (1.11, 1.86)	0.17
Kings 3	0.50 (0.25)	1.65 (1.28, 2.12)	0.05
Kings 4	1.24 (0.26)	3.45 (2.66, 4.48)	<0.01
Bulbar onset	0.07 (0.19)	1.07 (088, 1.30)	0.25
Respiratory onset	-0.67 (0.57)	0.51 (0.29, 0.90)	0.71
Gender (male = 1)	0.01 (0.16)	1.01 (0.97, 1.05)	0.98
Age (years)	0.001 (0.01)	1.001 (0.999, 1.002)	0.88
Time since diagnosis (months)	-0.01 (0.002)	0.99 (0.98, 1.0)	<0.01
MiToS Staging			
Constant	7.13 (0.45)		<0.01
MiToS 1	0.84 (0.15)	2.32 (1.99, 2.69)	<0.01
MiToS 2	0.98 (0.22)	2.66 (2.14, 3.32)	<0.01
MiToS 3	0.92 (0.41)	2.51 (1.67, 3.78)	0.07
MiToS 4	0.79 (0.75)	2.20 (1.04, 4.66)	0.29
Bulbar onset	0.32 (0.16)	1.38 (1.17, 1.62)	0.04
Respiratory onset	-0.32 (0.51)	0.73 (0.44, 1.12)	0.53
Gender (male = 1)	0.01 (0.04)	1.01 (0.97, 1.05)	0.97
Age	0.001 (0.01)	1.001 (1.0, 1.002)	0.98
Time since diagnosis (months)	-0.01 (0.002)	0.99 (0.98, 1.0)	<0.01

*Increase relative to Kings stage 1 or MiToS stage 0 (e.g. Kings stage 3 is associated with a 65% increase in costs relative to Kings stage 1).

Figure 1 Utilities and costs by health stage system and stages, shown with box plots



Parts A and B show costs and utilities, respectively, by Kings staging system whereas parts C and D show the same information for MiToS staging system