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ORIGINAL RESEARCH

Health-Related Quality of Life in Patients with Friedreich Ataxia Using Mobility Assistive Technologies: Limited Fit of the EQ-5D-3L Mobility Dimension

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ABSTRACT

Introduction: Friedreich Ataxia (FA) is a multisystem neurodegenerative disease. Affected individuals rely on mobility assistive technologies (MAT) (e.g. wheelchairs) and require long-term treatments and care. To analyse the patients' health-related quality of life (HRQoL), the EuroQol 5 Dimension 3 Level survey (EQ-5D-3L)—a widely used and recommended generic measure—is used in clinical and in health economic studies. Concerns about using the instrument in mobility-impaired individuals who might have difficulties finding appropriate response options for mobility-related items led us to investigate how the 3L dimensions perform in patients with FA using or not using MAT.
Methods: Using longitudinal data from 607 patients with FA of the EFACTS study (from baseline to the 3-year follow-up), we analysed the acceptability, distribution properties, validity, and responsiveness of the EQ-5D-3L, focusing on the mobility item. Analyses were stratified for patients without and with different MAT-usage.
Results: We identified that n = 177 patients used no MAT, n = 299 a wheelchair and n = 131 walking aids. The mobility item non-response

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was highest in wheelchair users (6.8%) and lowest in patients without MAT. Walking aid users showed the least variability, all selecting the mid-response option “some problems” for mobility. The mobility item correlated moderately with disease severity (r_{sp} = 0.35) and the activities of daily living scale (r_{sp} = 0.36) in wheelchair users. No correlation exists for walking aid users. The strongest health changes occurred for wheelchair users, the weakest for walking aid users. The mobility dimensions showed the highest amount of no changes.

Conclusion: The EQ-5D-3L’s mobility item has limitations in MAT users, particularly in walking aid users, due to a tendency towards mid-responses. These limitations may affect the efficacy and (cost)effectiveness conclusions drawn from interventions and clinical trials with mobility-impaired individuals. Further research is needed to explore the understanding and interpretation of responses of the EQ-5D in patients with FA with mobility support.

Trial Registration: ClinicalTrials.gov identifier NCT02069509.

PLAIN LANGUAGE SUMMARY

Friedreich Ataxia is a rare neurodegenerative multisystem disorder that affects movement and coordination. Many people with Friedreich Ataxia rely on mobility aids like walking sticks or wheelchairs to get around. In studies that measure quality of life, such as with the EQ-5D questionnaire, people with mobility issues often struggle with the questions related to “walking”. This is because the questionnaire does not include options for people using mobility aids, making it difficult for them to answer accurately. Our research found limitations with the EQ-5D-3L’s mobility question in patients with Friedreich Ataxia, using various mobility aids. Many wheelchair users did not answer to the mobility question, while those using walking aids tended to choose the middle option, “some problems”. Poor wording and limited response options could affect the accuracy of health-related quality of life measures, leading to biased conclusions about treatment effectiveness and costs. Therefore, it is essential to rethink how mobility-related questions are structured and formulated to ensure health-related quality of life questionnaires are valid and responsive, particularly for people using mobility aids.

Keywords: Friedreich Ataxia; Health-related quality of life; Mobility assistive technology; EQ-5D-3L

Key Summary Points

Why carry out this study?

Friedreich Ataxia (FA) is a multisystem neurodegenerative disease with no curative treatment, making the measurement of health-related quality of life (HRQoL) in patients with FA a crucial parameter in clinical research and economic evaluations for healthcare resource allocation.

Studies reported that preference-based HRQoL measures, such as the widely and from health technology assessment organisations recommend EQ-5D-3L, raised concerns in mobility-impaired individuals—such as patients with FA—who had difficulties finding appropriate response options for mobility-related items, resulting in biased interpretations of efficacy and (cost)-effectiveness conclusions drawn from interventions and clinical trials.

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The study investigated how the EQ-5D-3L dimensions performed in patients with and without mobility assistive technologies (MAT) to determine the instrument's applicability in patients with FA.

What was learned from the study?

A noticeable number of non-responses in the mobility item in wheelchair users and a tendency towards the mid-response level "some problems" among individuals with FA using walking aids was detected, possibly caused by inappropriate item wording and/ or response options.

Conceptual considerations about the questionnaire's content and structure are crucial, especially in mobility-related items, to avoid potentially biasing efficacy and cost effectiveness conclusions drawn from FA studies.

INTRODUCTION

Friedreich ataxia (FA) is a rare progressive neurodegenerative disease with a prevalence in Europe of approximately one in 50,000 [1]. The first symptoms of FA often appear around puberty and include imbalance and poor coordination [1, 2]. The disease progression is characterised by deep sensory loss and distal weakness, which is why individuals require mobility assistive technology (MAT) support (e.g. walking sticks, wheelchair). Further signs are dysarthria as well as visual and hearing impairments [1].

FA often requires long-term treatment and care, which makes it crucial to understand the balance between costs of therapies and benefits for the patients. To guide such healthcare resource allocation, economic evaluations are used to compare the costs and benefits of different interventions, with a growing emphasis on quality-adjusted life years (QALYs) [3]. QALYs combine life expectancy and health-related quality of life (HRQoL) into a single measure using utilities [3]. Generic preference-based measures, like the EQ-5D-3L [4], are commonly used to generate such utilities due to their broad applicability across diseases, ensuring consistency in decision-making. Additionally, the EQ-5D-3L is one of the most widely used tools, consisting of five items (mobility, self-care, usual activity, pain/discomfort, anxiety/depression) with three response options for each item and is highly recommended by the National Institute of Health and Care Excellence (NICE) for economic evaluations [5].

Mobility function is an essential factor associated with a person's perceived self-rated health. It is also considered a vital core domain in the construct of HRQoL [6] and is included as an item in the EQ-5D-3L. Patients with FA suffer from limitations in their mobility function. Therefore, MAT, such as walking aids or wheelchairs (powered or manual), are commonly used to support these patients' mobility stability [7, 8].

However, previous studies confirmed and raised concerns that mobility-impaired individuals have difficulties finding appropriate response options for mobility-related items and consider such items insulting or irrelevant because of MAT usage [9–11]. The wording "walking about" in HRQoL instruments is criticized as offensive, especially for wheelchair users [12]. A study with 56 patients with FA evaluated the EQ-5D-3Ls' psychometric performance [13], revealing a significantly high amount of non-responses in the mobility item, which could hint at the difficulty of finding a suitable response. Therefore, the inferior fit in answering mobility-related items could affect the validity and responsiveness of the HRQoL measure and bias the intervention and cost effectiveness findings. However, studies investigating the appropriateness of commonly used HRQoL measures in patients with or without different MAT are rare but urgently needed.

Therefore, the aim of this work was to comprehensively analyse how patients with FA without and with MAT (walking sticks, wheelchair) respond to the commonly used EQ-5D-3L in terms of acceptability, distributional properties, validity and responsiveness in health change, with special focus on the mobility dimension.

METHODS

Study Design and Sample

We used data from the prospective cohort study, the European Friedreich's Ataxia Consortium for Translational Studies (EFACTS), conducted in seven European countries (Belgium, England, France, Germany, Italy, Spain and UK). EFACTS started in 2010 and is a longitudinal cohort study of diagnosed patients with FA with annual follow-ups in the respective study center, registered in ClinicalTrials.gov (NCT02069509) [14], designed to enable translational research for the rare autosomal recessive neurological disease [14]. A transition to the worldwide study UNIFAI (Friedreich Ataxia Global Clinical Consortium UNIFIED Natural History study) is in progress (NCT06016946). We considered data from baseline to the 3-year follow-up for the present longitudinal analysis.

Statement of Ethic Compliance

EFACTS was approved by the ethics committees of the participating study centres and have been performed in accordance with the ethical standards laid down in 1964 Declaration of Helsinki. Written informed consent was obtained from all study participants. A detailed description of the EFACTS study design and recruitment procedure has been reported elsewhere [14].

Data Assessment and Outcome Measures

The data was assessed via structured interviews, including a battery of sociodemographic (e.g. age, sex), clinical and patient-reported health-related variables, and performance-based coordination tests at baseline and annual follow-ups. An identical study protocol of assessments was used for all participating centres, confirming data quality [14].

The outcome of interest in our analysis was the self-rated health, measured with the EQ-5D-3L, and compared to ataxia-specific self-rated and clinical-rated outcomes.

Outcomes

Health-Related Quality of Life The preference-based generic EQ-5D-3L consists of a descriptive system and a visual analogue scale (EQ VAS), which is scaled from 0 (worst health) to 100 (best health) to assess a person's current overall health [15]. The descriptive system consists of five health dimensions: mobility, self-care, usual activity, pain/discomfort and anxiety/depression, each with three response levels (no, some and extreme problems), resulting in 3^5 (243) different health profiles. Different from the four other dimensions, the mobility item uses the three response levels "no problems in walking about", "some problems in walking about", and "confined to bed" [15]. We used the European value set to concert the EQ-5D-3L health states into a single index [16].

Activities of Daily Living Activities of Daily Living (ADL) were assessed as part of the validated Friedreich Ataxia rating scale (FARS) [17] developed and evaluated for usage in individuals with FA. The ADL-FARS aims to assess limitations in the ability to perform daily activities (e.g. personal hygiene, speech disturbance, cutting food) resulting in a score range from 0 (no limitations in ADL) to 36 (severe limitations in ADL) [17].

Clinical-Reported Outcome Measures The Scale for the Assessment and Rating of Ataxia (SARA) was used to measure the severity of ataxia based on eight items related to gait, stance, sitting, speech, finger-chase test, nose-finger test, fast alternating movements and heel-shin test [18]. According to functional limitations in the respective item, the SARA sum score ranges between 0 (no ataxia) and 40 (most severe ataxia) [18]. If analytically necessary, we grouped the sum score into three ataxia severity stages: mild < 10, moderate 10–25, and strong > 25 [19].

The Inventory of Non-Ataxia Signs (INAS) provides a checklist of 30 items (e.g. urinary dysfunction, changes in reflexes) categorized into 16 non-ataxia signs assessed by a physician. Based on these categories, the INAS count ranges from 0 (absence of non-ataxia signs) to a maximum of 16 (complex extracerebellar disorder) [20].

Data Analyses

Patients with FA were divided into three groups: (1) individuals without MAT, (2) individuals using walking aids, and (3) individuals using wheelchairs. The grouping was based on a severity index to determine their disability stage [21], including information about the patient's usage of MAT as presented in Supplementary Table S1. The psychometric performance of the EQ-5D with a special focus on the mobility dimension was assessed across these MAT groups.

Acceptability—Item-Non-response Analysis

Non-responses to items were used to indicate difficulties in comprehension or finding suitable answers that fit the individuals' situation. We listed the proportion of missing values for each EQ-5D dimension, expecting a higher mobility-item non-response in MAT users, especially in wheelchair users.

Distribution of Data

Distributional properties (frequencies, floor and ceiling effects) were analysed for the EQ-5D dimensions. Based on studies reporting low response variability for the 3L [22, 23], we expected the mid-response category "some" in the mobility item to occur significantly more frequently among MAT users. Therefore, we calculated a response ratio by dividing the number of "some" responses by the combined counts of "no problems" and "severe problems".

Informativity (Discriminatory Power)

To explore the diversity of the EQ-5D-3L and compare it with already existing literature [24, 25], we used the Shannon index (H') and the evenness index (J') to evaluate discriminatory power [24, 26] in each dimension of the EQ-5D-3L across MAT groups.

The Shannon index is defined as:

$$H = \sum\nolimits_{I=1}^{n} p_I log_2 p_I$$

The absolute amount of informativity (H') for each level in the EQ-5D-3L dimensions (n) can be observed by using the proportion (p) of the observed response number and the total sample size. A log—as a base of 2—allows for an interpretation on an individual level [26]. Higher H′ values (with a maximum of 1.58 based on the three levels) correspond to a higher classification efficiency and an even distribution of all item levels [25]. Dividing H' with $H'_{\max}$ yields Shannon's Evenness index (J'), which describes the relative informativity (evenness ranging from 0 to 1), independently of the possible item levels. Consequently, the EQ-5D-3L would show good discriminating powers if Shannon's H' and J reach their maximum values. We expected lower H′ and J′ in the mobility dimension compared to the four other dimensions, particularly present in the group of wheelchair users.

Convergent Validity

We tested the validity between the EQ-5D-3L dimensions and ADL, SARA and INAS to identify differences (divergent) or similarities (convergent) between the measures by using Spearman's correlation coefficients (r_{sp}) with the following interpretation: $r_{sp} < 0.3$ small, $0.3 \geq r_{sp} < 0.5$ moderate and $r_{sp} \geq 0.5$ high/strong [27, 28]. Considering our expectations of a higher frequency of the mid-response "some" in the mobility item, we hypothesized lower correlations for this item compared to the items "self-care" and "usual activity". Further, we expected minimal correlations with the mental items pain/discomfort and anxiety/depression (divergent validity).

Responsiveness

We used the Paretian Classification of Health Change (PCHC) [29] to examine health changes from baseline (BL) to the third follow-up (FU) across all EQ-5D dimensions, categorizing participants into the groups (1) "No change": Responses of two time points are identical; (2) "Improved": Reporting less problems in the respective dimension compared to the BL;

and (3) “Worse”: Reporting more problems in the respective dimensions compared to the BL. Given the 3L’s low variability of possible responses, we expected a high amount of “no changes” in MAT users.

To analyse health changes in the EQ-5D-3L’s indices compared to the SARA and ADL, we additionally reported differences in self-rated and clinician-rated health in patients with FA from BL to the third FU by calculating standardized effect sizes (SES) for dependent samples (paired *t* test) interpreted as follows: 0.2 small, 0.5 medium/moderate and ≥ 0.8 large [27]. We assumed an underrepresentation of health changes with the 3L in wheelchair users.

For the acceptability analysis, distributional properties, informativity and validity, cross-sectional (baseline) data were used; to examine health changes, we used longitudinal data. No imputation was performed to address missing data in our statistical analyses. Data were analysed using RStudio.

RESULTS

Description of the Sample

The sample consisted of 607 patients with FA with a mean age of 33.5 years and a female proportion of 54.0%. The disease onset was at the mean age of 15.5. Slightly more than 80% had a typical disease onset (before the age of 24 years). The majority of patients are grouped in the category of wheelchair usage ($n = 299$), characterized by longer disease duration, higher severity ataxia score (SARA mean 29.85), more limitations in ADL (mean 20.75), and more non-ataxia-signs (INAS mean 5.97) compared to patients with no ($n = 177$) or with walking aid support ($n = 131$) (Table 1).

Item-non Response

The highest number of missing responses was detected for the mobility item. Considering the MAT groups, the proportion of item non-responses was lowest in the group of no MAT users (0.75% in the anxiety/depression dimension) and walking aid users (1.77% in pain/discomfort) and highest in the group of wheelchair users (6.8% in mobility) (Table 2).

Data Distribution and Informativity

Generally, with increased MAT usage (from no MAT to a wheelchair), the proportion of “severe problems” increased. Ceiling effects (overall dimensions) only occurred in 8.4% of no MAT users, with the highest number of no problems reported in self-care (87%). In all individuals, the middle response option “some” was selected approximately five times more often in the mobility dimension (Table 3). Walking aid users selected only the mid-response option for the mobility item (some problems: 100%), while non-MAT users selected two (no problems: 15.3%, some problems 84.7%) and wheelchair users all three response levels (no problems: 0.5%, some problems: 73.5%, confined to bed: 26%) (Table 3).

The EQ-5D-3L mobility item had the lowest informativity compared to the other four dimensions, resulting in lower (H' J') values, ranging from 0.00 (0.00) in walking aid users to 0.87 (0.55) in wheelchair users (Table 3).

Validity

In wheelchair users, the mobility dimension correlated moderately with the clinical rating scale for ataxia SARA (r_{sp} = 0.35) and the ADL scale (r_{sp} = 0.36). Among users of walking aids, no correlation could be calculated due to the absence of response option variability in the EQ-5D mobility item. However, for patients not using MAT, we observed poor and moderate correlations between SARA (r_{sp} = 0.20) and ADL (r_{sp} = 0.36).

Generally, higher correlation coefficients were observed in the more observable dimensions (mobility, self-care, usual activity) with the self-rated ADL compared to the clinician-rated SARA. Moderate correlations were found in wheelchair users between the EQ-5D-3L (index, self-care and usual activity dimension) and the SARA (3L index r_{sp} = -0.53, self-care r_{sp} = 0.57) and the ADL scale (3L index r_{sp} = – 0.60, self-care r_{sp} = 0.64,

Table 1 Overview of the sample, total and grouped by usage of support

Variables	Total ($n = 607$)	No MAT ($n = 177$)	Usage of walking aids ($n = 131$)	Wheelchair usage ($n = 299$)	p value*
Sociodemographic variables					
Gender, female, n (%)	327 (54.0)	91 (51.4)	83 (63.4)	153 (51.3)	0.051[b]
Age, mean (SD)	33.5 ± 13.8	28.4 ± 14.2	36.5 ± 14.6	35.5 ± 12.4	< 0.001[a]
Disease onset					
Age of onset mean (SD)	15.5 ± 10.30	18.7 ± 11.7	19.9 ± 12.4	11.6 ± 6.2	< 0.001[a]
Typical onset, n (%)	504 (83.9)	129 (74.1)	91 (69.5)	284 (95.9)	
Late onset, n (%)	97 (16.1)	45 (25.9)	40 (30.5)	12 (4.1)	
Ataxia severity					
SARA score, mean (SD)	21.88 ± 9.64	10.41 ± 4.10	19.03 ± 4.85	29.85 ± 4.83	< 0.001[a]
INAS count, mean (SD)	5.04 ± 1.65	3.58 ± 1.38	4.93 ± 1.28	5.97 ± 1.25	< 0.001[a]
ADL score, mean (SD)	14.61 ± 7.77	6.21 ± 3.18	12.22 ± 3.61	20.75 ± 5.37	< 0.001[a]
Health-related quality of life					
EQ-5D-3L index, mean (SD)	0.58 ± 0.2	0.74 ± 0.12	0.62 ± 0.12	0.47 ± 0.19	< 0.001[a]
EQ-VAS, mean (SD)	61.8 ± 20.4	64.5 ± 18.1	59.3 ± 19.2	61.6 ± 22.0	0.300[a]

Typical onset FA symptoms before the age of 24 years[52]

ADL activity of daily living as part of the Friedreich Ataxia Rating Scale (FARS); range from 0 to 36 with higher values indicating more limitations in ADL, *EQ-5D-3L indices/EQ-VAS* higher values indicate better health, *INAS* Inventory of Non-Ataxia Signs; range from 0 to 16 with higher values indicating more non-ataxia signs, *MAT* mobility assistive technology, n number of observations, *SARA* Scale of the Assessment and Rating of Ataxia; range from 0 to 40 with higher values indicating severe FA, *SD* standard deviation

*Differences between the three mobility aids groups

[a] Analysis of variance

[b] Chi square test

Table 2 Overview of non-responses among the EQ-5D-3L dimensions (excluded missing in all dimensions)

EQ-5D dimensions	No MAT % (n) (133)	Walking aid user % (n) (113)	Wheelchair user % (n) (239)
Mobility	0	0	6.83 (20)
Self-care	0	0	0.34 (1)
Usual activity	0	0	0.68 (2)
Pain/discomfort	0	1.77 (2)	3.41 (10)
Anxiety/depression	0.75 (1)	0	0

MAT mobility assistive technology, n number of observations

Table 3 Distribution of responses, response ratio and Shannon Indices for each dimension of the EQ-5D-3L (completely filled out EQ-5D data)

	Total sample *n* = 463	**No MAT** *n* = 131	**Usage of walking aids** *n* = 113	**Wheelchair usage** *n* = 219
Mobility, % (*n*)				
No problems	4.5 (21)	15.3 (20)	0 (0)	0.5 (1)
Some problems	83.2 (385)	84.7 (111)	100.0 (113)	73.5 (161)
Severe problems	12.3 (57)	0 (0)	0 (0)	26.0 (57)
Response ratio	4.94	5.55	All "some"	2.78
Shannon index (H', J')	0.8, 0.5	0.62, 0.39	0.00, 0.00	0.87, 0.55
Self-care, % (*n*)				
No problems	39.3 (182)	87.0 (114)	40.7 (46)	9.7 (22)
Some problems	45.6 (211)	13.0 (17)	58.4 (66)	58.4 (128)
Severe problems	15.1 (70)	0 (0)	0.9 (1)	31.5 (69)
Response ratio	0.84	0.15	1.40	1.41
Shannon index (H', J')	1.46, 0.92	0.56, 0.35	1.04, 0.66	1.31, 0.83
Usual activity, % (*n*)				
No problems	25.7 (119)	52.7 (69)	16.8 (19)	14.2 (31)
Some problems	66.3 (307)	47.3 (62)	79.6 (90)	70.8 (155)
Severe problems	8.0 (37)	0 (0)	3.5 (4)	15.1 (33)
Response ratio	1.98	0.89	3.91	2.42
Shannon Index (H', J')	1.19, 0.75	1.00, 0.63	0.86, 0.55	1.16, 0.73
Pain/discomfort, % (*n*)				
No problems	50.5 (234)	65.6 (86)	40.7 (46)	46.6 (102)
Some problems	47.1 (218)	34.4 (45)	57.5 (65)	49.3 (108)
Severe problems	2.4 (11)	0 (0)	1.8 (2)	4.1 (9)
Response ratio	0.89	0.52	1.35	0.97
Shannon Index (H', J')	1.14, 0.72	0.93, 0.59	1.09, 0.69	1.21, 0.76
Anxiety/depression, % (*n*)				
No problems	56.2 (260)	61.1 (80)	59.3 (67)	51.6 (113)
Some problems	40.4 (187)	36.6 (48)	38.1 (43)	43.8 (96)
Severe problems	3.5 (16)	2.3 (3)	2.7 (3)	4.6 (10)
Response ratio	0.68	0.58	0.61	0.83
Shannon Index (H', J')	1.16, 0.73	1.09, 0.69	1.12, 0.7	1.22, 0.77

Table 3 continued

	Total sample *n* = 463	No MAT *n* = 131	Usage of walking aids *n* = 113	Wheelchair usage *n* = 219
No problems over all dimensions (ceiling effect)	2.4% (11)	8.4% (11)	0 (0)	0 (0)
Severe problems over all dimensions (floor effect)	0 (0)	0 (0)	0 (0)	0 (0)

MAT mobility assistive technology, *n* number of observations

usual activity r_{sp} = 0.50). The INAS correlated weakly to barely with the EQ-5D items, index, or VAS (Table 4).

Responsiveness

In general, patients with FA reported both deteriorations and improvements in the EQ-5D dimensions over all observed periods, as depicted in Fig. 1. Specifically, the mobility dimension indicated the lowest health changes over 3 years among walking aid users (no changes: 93%, worsened: 2.3%) compared to patients without MAT use (no changes: 86.9%, worsened: 6.6%) and wheelchair users (no change: 62%, worsened: 34.2%) (Table 5).

Findings regarding health changes using the EQ-5D index, ADL and SARA scores are presented in Supplementary Table S2. While moderate to large effect sizes were found for SARA and ADL, the 3L showed no relevant (SES < 0.2) to small changes (SES 0.2–0.5). For individuals with walking aids, no significant effect sizes were observed with the EQ-5D-3L compared to the ADL and SARA over 3 years. In wheelchair users, small to moderate effect sizes occurred with the EQ-5D-3L index over 2 and 3 years.

DISCUSSION

We studied the psychometric performance of the EQ-5D-3L mobility item in a large longitudinal sample of patients with FA using or not using MAT. We found limitations in the instrument's descriptive system concerning the mobility item structure in patients with FA with MAT (walking sticks and wheelchairs). Specifically, wheelchair users had a noticeable amount of non-responses in the mobility dimension while patients with walking aids frequently selected the mid-response option "some problems" without changes over time. A high number of missing responses, and a lack of item variability and measurable changes can limit the instrument's ability to detect intervention effects in clinical trials and could also underpin the presence of different conceptual interpretations of the HRQoL construct in MAT users.

Riazi et al. validated the EQ-5D in a smaller sample of individuals with FA [13]. They reported the highest number of non-responses in the mobility item (20%), which is consistent with our findings, having the highest missing responses in the mobility item (6.83%) in wheelchair users. The 3-point response scale of the EQ-5D may not adequately represent the patients' movement impairment. Therefore, patients could have difficulties choosing an answer [9, 11] or find it offensive to do so [30], causing non-responses. Another reason could be that it is unclear whether MAT are considered an alternative or substitute for "walking". A patient in a wheelchair may struggle to answer whether he or she can "walk" or not or if he or she is "confined to bed". Although studies reported lower missing values in the updated version EQ-5D-5L, the wording "walking" is still present without substitutes, supporting the assumption of a persistent issue. The opportunity to consider functional health concerning the usage of MAT, which is considered in the World Health Organization's International Classification of Functioning, Disability, and Health (ICF) concept as

Table 4 Correlations between EQ-5D dimensions with SARA, ADL and INAS by group of support

	SARA			ADL			INAS		
	r_{sp}	*n*	*p* value	r_{sp}	*n*	*p* value	r_{sp}	*n*	*p* value
No MAT									
EQ-5D									
3L index	− 0.10	130	0.249	− 0.23	131	< 0.01	− 0.04	133	0.614
EQ VAS	− 0.13	127	0.146	− 0.09	127	0.300	0.04		0.676
Convergent									
Mobility	0.20	132	< 0.05	0.36	133	< 0.01	0.21	133	< 0.05
Self-care	0.21	132	< 0.05	0.28	133	< 0.01	0.17	133	< 0.05
Usual activity	0.15	132	0.089	0.21	133	< 0.05	0.09	133	0.324
Divergent									
Pain/discomfort	− 0.10	131	0.249	− 0.01	132	0.903	− 0.09	132	0.326
Anxiety/depression	− 0.05	131	0.146	0.03	132	0.702	− 0.12	132	0.183
Walking aids									
EQ-5D									
3L index	− 0.31	111	< 0.05	− 0.41	113	< 0.01	− 0.19	113	< 0.05
EQ VAS	− 0.17	107	0.088	− 0.05	109	0.627	− 0.10	109	0.295
Convergent									
Mobility	n.a.	111	n.a.	n.a.	113	n.a.	n.a.	113	n.a.
Self-care	0.41	111	< 0.01	0.55	113	< 0.01	0.27	113	< 0.01

Table 4 continued

	SARA			ADL			INAS		
	r_{sp}	*n*	*p* value	r_{sp}	*n*	*p* value	r_{sp}	*n*	*p* value
Usual activity	0.11	111	0.240	0.19	113	< 0.05	−0.06	113	0.557
Divergent									
Pain/discomfort	0.10	111	0.316	0.05	113	0.568	0.12	113	0.192
Anxiety/depression	0.08	111	0.390	0.20	113	< 0.05	0.09	113	0.364
Wheelchair usage									
EQ-5D									
3L index	−0.53	218	< 0.01	−0.60	219	< 0.01	−0.25	219	< 0.01
EQ VAS	−0.14	227	< 0.05	−0.19	227	< 0.01	0.03	228	0.637
Convergent									
Mobility	0.35	218	< 0.01	0.36	219	< 0.01	0.23	219	< 0.01
Self-care	0.57	237	< 0.01	0.64	238	< 0.01	0.19	238	< 0.01
Usual activity	0.44	236	< 0.01	0.50	237	< 0.01	0.11	237	0.094
Divergent									
Pain/discomfort	0.10	238	0.136	0.09	238	0.181	−0.04	239	0.509
Anxiety/depression	0.20	238	< 0.01	0.24	238	< 0.01	0.00	239	0.950

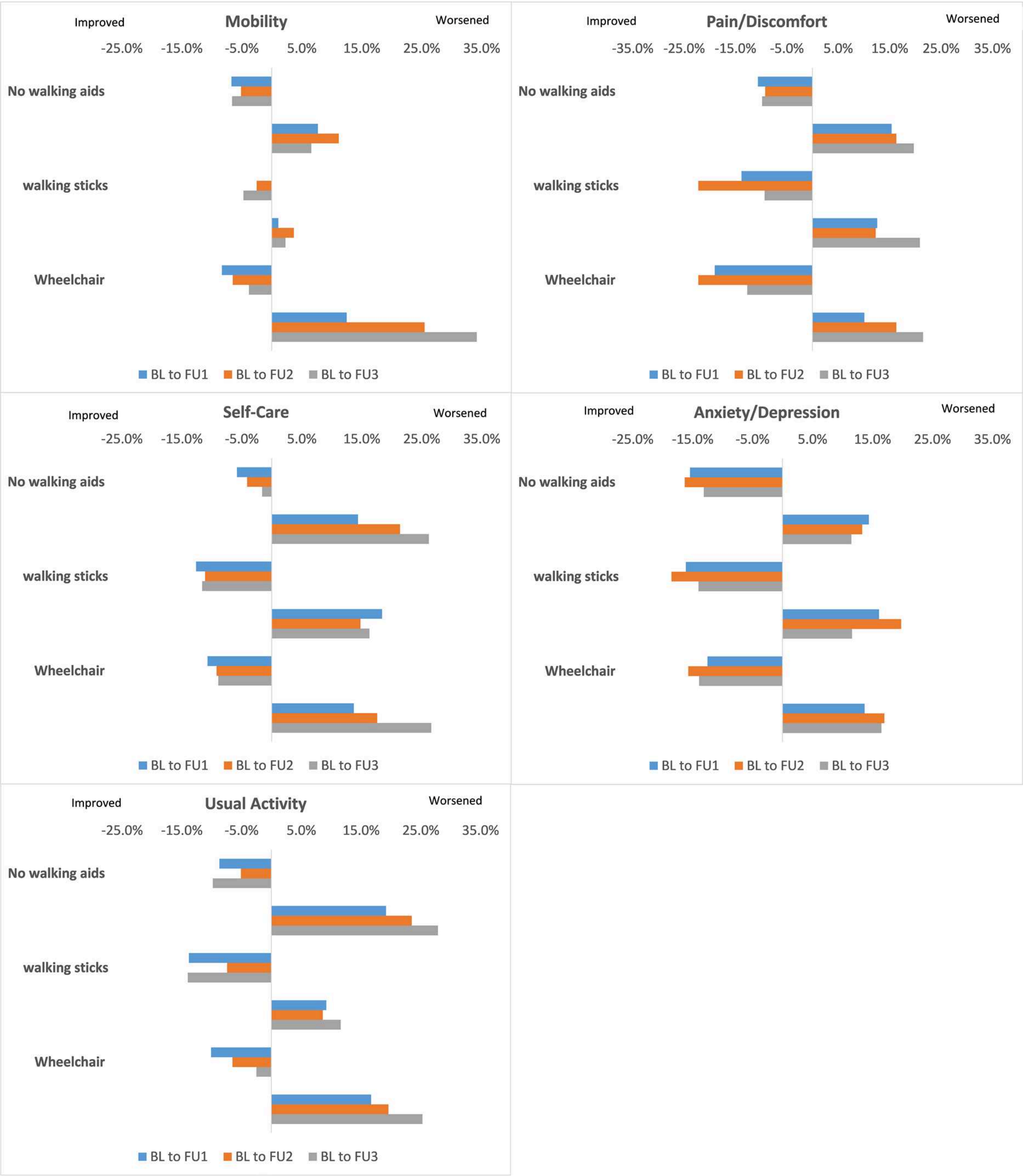

Fig. 1 Proportion (%) of individuals with FA showing improved or deteriorated self-rated health on the EQ-5D-3L dimensions, using PCHC. *BL* baseline, *FU1* follow-up 1, *FU2* follow-up 2, *FU3* follow-up 3, *PCHC* Paretian Classification of Health Change

“performance” [31], could be highly relevant in mobility-impaired people, as a study already explicitly shows using a modified version of the generic HRQoL measure SF-36 [10]. Nevertheless, further research with the same focus and line of inquiry is essential to expand and

Table 5 Proportion of individuals with FA showing no changed, deteriorated or improved self-rated health on the 3L dimension level (PCHC) by group of support

	n	EQ-5D-3L Dimensions				
		Mobility	Self-care	Usual activity	Pain/discomfort	Anxiety/depression
No MAT						
BL to FU1						
No change	104	**89 (85.6)**	83 (79.8)	75 (72.1)	77 (74.0)	73 (70.2)
Improved		7 (6.5)	6 (5.8)	9 (8.7)	11 (10.6)	**16 (15.4)**
Worsened		8 (7.7)	15 (4.4)	**20 (19.2)**	16 (15.4)	15 (14.4)
BL to FU2						
No change	98	**82 (83.7)**	73 (74.5)	70 (71.4)	73 (74.5)	69 (70.4)
Improved		5 (5.1)	4 (4.1)	5 (5.1)	9 (9.2)	**16 (16.3)**
Worsened		11 (11.2)	21 (21.4)	**23 (23.5)**	16 (16.3)	13 (13.3)
BL to FU3						
No change		**53 (86.9)**	44 (72.1)	38 (62.3)	43 (70.5)	46 (75.4)
Improved		4 (6.6)	1 (1.6)	6 (9.8)	6 (9.8)	**8 (13.1)**
Worsened	61	4 (6.6)	16 (26.2)	**17 (27.9)**	12 (19.7)	7 (11.5)
Walking aids						
BL to FU1						
No change	87	**86 (98.9)**	60 (69.0)	67 (77.0)	64 (73.6)	59 (67.8)
Improved		0 (0.0)	11 (12.6)	12 (13.8)	12 (13.8)	**14 (16.1)**
Worsened		1 (1.1)	**16 (18.4)**	8 (9.2)	11 (12.6)	14 (16.1)
BL to FU2						
No change	81	**76 (93.8)**	60 (74.1)	68 (84.0)	53 (65.4)	50 (61.7)
Improved		2 (2.5)	9 (11.1)	6 (7.4)	**18 (22.2)**	15 (18.5)
Worsened		3 (3.7)	12 (14.8)	7 (8.6)	10 (12.3)	**16 (19.8)**
BL to FU3						
No change	43	**40 (93.0)**	31 (72.1)	32 (74.4)	30 (69.8)	32 (74.4)
Improved		2 (4.7)	5 (11.6)	6 (14.0)	4 (9.3)	**6 (14.0)**
Worsened		1 (2.3)	7 (16.3)	5 (11.6)	**9 (20.9)**	5 (11.6)

Table 5 continued

	n	EQ-5D-3L Dimensions				
		Mobility	**Self-care**	**Usual activity**	**Pain/discomfort**	**Anxiety/depression**
Wheelchair usage						
BL to FU1						
No change	168	**133 (79.2)**	127 (75.6)	123 (73.2)	119 (70.8)	124 (73.8)
Improved		14 (8.3)	18 (10.7)	17 (10.1)	**32 (19.0)**	21 (12.5)
Worsened		21 (12.5)	23 (13.7)	**28 (16.7)**	17 (10.1)	23 (13.7)
BL to FU2						
No change	153	104 (68.0)	112 (73.2)	**113 (73.9)**	94 (61.4)	103 (67.3)
Improved		10 (6.5)	14 (9.2)	10 (6.5)	**34 (22.2)**	24 (15.7)
Worsened		**39 (25.5)**	27 (17.6)	30 (19.6)	25 (16.3)	26 (17.0)
BL to FU3						
No change	79	49 (62.0)	51 (64.6)	**57 (72.2)**	52 (65.8)	55 (69.6)
Improved		3 (3.8)	7 (8.9)	2 (2.5)	10 (12.7)	**11 (13.9)**
Worsened		**27 (34.2)**	21 (26.6)	20 (25.3)	17 (21.5)	13 (16.5)

BL baseline, *FU1* follow-up 1, *FU2* follow-up 2, *FU3* follow-up 3, *MAT* mobility assistive technology, *n* number of observations, *PCHC* Paretian Classification of Health Change, Bolded entries indicate the dimension with the highest proportion of "no change", "improved" and "worsened"

contextualise the hypothesis on FA more comprehensively and in greater depth.

Previous studies evaluating HRQoL of mobility-impaired individuals reported that the upper and lower response options were less often selected [32, 33]. A broad range of studies in different patient populations revealed that most mobility-impaired patients reported some problems [34], avoiding the response choice "no problems in walking" and "confined to bed" [35], which could otherwise lead to an over- or underestimation of the patients' actual state. Our study results align with these observations. The response option "some" was chosen remarkably often, especially in the mobility dimension from 83.2% of the total sample. To our surprise, all (100%) walking aid users have chosen the mid-response category "some" in the mobility dimension. Compared to the 5L version, studies further revealed that the updated EQ-5D-5L showed a significantly better response distribution for all dimensions [24], concluding that the two extra stages provide an improved response range, not forcing the patient to choose between two extremes. This was also stated in the literature by the absolute (H') and relative (J') Shannon indices with higher values for the 5L than the 3L overall dimensions [36]. In our data, the mobility item showed the worst H' and J' indices, underpinning the avoidance of the two extreme responses and choosing the mid-response "some" with up to 100%. Compared to the other dimensions, the highest amount of informativity was gained in pain/discomfort and anxiety/depression, which is also in line with other patient populations [32, 34]. Therefore, future studies should carefully consider questionnaires with only three severity levels, which may hinder finding a suitable response option that fits the patients' situations and, thus, the detection of existing health changes over time. As already done in different population contexts [37], conceptual considerations about a questionnaire's content and structure are required.

Knowing how patients with FA interpret items is crucial, ensuring that the respective instrument measures what it is actually supposed to measure. In the UNIFAI study (NCT06016946) as the successor of the EFACTS study, the EQ-5D-5L and the SF-36 will be used, giving further information about the response behaviour, especially in comparison to the 3L version.

Following the literature, EQ-5D-3L performs well in terms of validity in different settings and patient populations [38–41] and rare ataxia diseases [42]. However, our analysis could not confirm these findings in patients with FA using MAT. Surprisingly, we detected the lowest correlations between HRQoL and the clinical measures in the group of no walking aid usage and the highest in individuals using wheelchairs. In the group of patients with walking aids, no correlation analysis was possible for the mobility dimension, due to the fixed use of the mid-response option “some problems”. Although the usage of walking aids indicates movement limitations, it does not mean being confined to bed, which makes the response behaviour of using the mid-response understandable. Additionally, it has to be considered carefully, that coordination problems in upper limp functions and instability of the trunk may influence the ability to propel the wheelchair or handle walking aids [43], what could also impact the individuals’ response behaviour.

The fixed response pattern observed walking aid users severely limited the detection of health changes. However, enabling the chance to detect health changes is an important measure characteristic. Contrary to our expectations, we observed the most sensitive health changes in patients with FA who used wheelchairs. It is of particular interest that the EQ-5D-3L index outperformed the clinical measure SARA in detecting disease progression in individuals using wheelchairs. Therefore, our findings contribute to the understanding that the EQ-5D-3L is less responsive to health changes in walking aid users but demonstrated acceptable responsiveness in wheelchair users. This underlines that patients with MAT understand, interpret, and respond differently to mobility-related questions, significantly impacting the psychometric properties of HRQoL questionnaires that include mobility-related dimensions. It is especially true for detecting health changes, where patients with FA cannot improve their scoring due to the mobility-related question’s inability to accurately fit the situation of patients with MAT. Considering the used value set, the third level of the mobility item (confined to bed) dramatically decreases the EQ-5D indices. If a health state change is not observable on the item level (mobility), the index value may significantly underestimate the patients’ actual health state. This strongly affects the measurement’s responsiveness in interventional studies, such as randomized controlled trials, where HRQoL is a commonly used and a relevant outcome.

Previous studies [44, 45] already raised awareness that the inability to walk is not necessarily associated with worse HRQoL. Mobility-impaired people can adapt to their situation and interpret limitations in mobility differently from people without functional disabilities. Thus, it is a remark to pay attention to the scoring algorithm used in generic preference-based HRQoL measures derived from the general public, resulting in a biased health state valuation [46]. This further underscores the importance of incorporating disease-specific terminology in the wording of response levels in HRQoL measures.

Strengths and Limitations

FA is a rare disorder, which leads to studies with smaller sample sizes. We, therefore, chose data from the longitudinal observation study EFACTS, which provided a considerably large study population. Patients’ data from different European research centres was collected in a routine healthcare setting with a standardized data collection procedure, supporting data quality. Nevertheless, our analysis is not free of limitations. Previous scientific findings clearly show the inferiority of the 3L compared to the 5L version regarding psychometric properties among different patient populations [24]. It would be beneficial to explore the EQ-5D-5L performance in FA in combination with another generic HRQoL measure (UNIFAI study—continuation of EFACTS) or a self-rated disease-specific HRQoL measure [47], which is missing in the present analysis. Conducting a qualitative interview study to investigate knowledge about how patients with FA understand and interpret items of different HRQoL measures would be urgent. Concerning the reported EQ-5D-3L indices, the European value set used might restrict the preciseness of the study sample. However, the study sample consists of individuals from different European countries, which explained the usage of the value set developed by Greiner et al. [16]. The EFACTS study was not primarily developed for a validation study [14]. Accordingly, it was not possible to gain adequate reliability characteristics due to the 1-year distance between data assessments [48, 49]. Further, the order of the EFACTS baseline and follow-up assessments could influence the participants' response behaviour. In the assessment battery, many functional questions with repetitive characteristics could cause patient burden or a reduced awareness in responding. In addition, a potential limitation of this study is that all data were collected within the context of a non-interventional natural history study. Responses may differ for individuals participating in drug trials, where motivations to answer questions could be influenced by treatment-related factors. However, this limitation is considered minor in the context of the study's overall findings.

CONCLUSION

There are concerns about using HRQoL measures, such as the EQ-5D, in mobility-impaired individuals who had difficulties finding appropriate response options for mobility-related items. Our findings demonstrated limitations of the EQ-5D-3L mobility item in patients with FA using MAT, detecting a noticeable amount of non-responses in the mobility item in wheelchair users and a tendency to the mid-response level "some problems" in individuals using walking aids. The latter caused poor correlations with clinical FA measures and responsiveness to detect health changes over time. The descriptive system's most significant issue lies in the mobility dimension, which could be improved by an adapted version that aligns with the situation of MAT users, especially in individuals diagnosed with the rare multisystem disease, Friedreich Ataxia. In the current version, the wording "walking" is used, and MAT are missed to be considered as an alternative or substitute for it. Since the EQ-5D is of great importance in economic evaluation studies, it is apparent that the consensus of using the instrument as a "fit for all" is not always suitable and could potentially lead to false estimations about the self-assessed health of patients with FA or patients using MAT. Inappropriate item wording and response options could significantly impact the validity and responsiveness of HRQoL measures, potentially biasing efficacy and cost effectiveness conclusions drawn from FA studies. Therefore, conceptual considerations about the HRQoL questionnaire's content and structure are crucial, especially in mobility-related items. This will help us to understand how individuals with FA using MAT interpret, understand and respond to mobility-related items of HRQoL questionnaires, ensuring the validity and responsiveness of HRQoL instruments.

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Declarations

Conflict of Interest. All authors declare that they have no competing interests to declare that are relevant to the content of this article. Michelle Pfaff started a Master Program during the preparation of the manuscript. Therefore, her affiliation changed into School of Public Health, San Diego State University, San Diego, CA, USA. MGE is member of the European Reference Network – Rare Neurological Diseases (ERN-RND).

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