RESEARCH ARTICLE

Friedreich's Ataxia-Health Index

Development and Validation of a Novel Disease-Specific Patient-Reported Outcome Measure

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Neurology: Clinical Practice 2023;13:e200180. doi:10.1212/CPJ.0000000000200180

Abstract

Background and Objectives

To develop a valid, disease-specific, patient-reported outcome (PRO) measure for adolescents and adults with Friedreich ataxia (FA) for use in therapeutic trials.

Methods

We conducted semistructured qualitative interviews and a national cross-sectional study of individuals with FA to determine the most prevalent and burdensome symptoms and symptomatic themes to this population. These symptoms and symptomatic themes were included as questions in the first version of the Friedreich's Ataxia-Health Index (FA-HI). We subsequently used factor analysis, beta interviews with 17 individuals with FA, and test-retest reliability assessments with 20 individuals with FA to evaluate, refine, and optimize the FA-HI. Finally, we determined the capability of the FA-HI to differentiate between subgroups of FA participants with varying levels of disease severity.

Results

Participants with FA identified 18 symptomatic themes of importance to be included as subscales in the FA-HI. The FA-HI demonstrates high internal consistency and test-retest reliability, and it was identified by participants as highly relevant, comprehensive, and easy to complete. FA-HI total and subscale scores statistically differentiated between subgroups of participants with varying levels of disease burden.

Discussion

Initial evaluation of the FA-HI supports its validity and reliability as a PRO for assessing how individuals with FA feel and function.

Introduction

Friedreich ataxia (FA) is an autosomal recessive neurodegenerative disorder historically characterized by a diverse array of clinical features, including impaired coordination (ataxia), muscle weakness, fatigue, vision impairment, hearing loss, speech impairment, scoliosis, diabetes, and cardiac dysfunction.[1] In preparation for future FA clinical trials, it is important to have valid instruments capable of quantifying how a patient feels and/or functions in response to therapeutic intervention. The US Food and Drug Administration (FDA) has identified patient-reported outcome (PRO) measures as valid tools to measure patient health during clinical trials and to support drug labeling claims.[2] The FA research and clinical care

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Funding information and disclosures are provided at the end of the article. Full disclosure form information provided by the authors is available with the full text of this article at Neurology.org/cp.

communities currently do not have access to a fully validated disease-specific PRO that complies with FDA guidance and standards regarding the creation and validation of PROs. We applied a participant-centered approach using published FDA guidance to develop and validate a novel, disease-specific PRO for use in clinical trials involving individuals with FA.

In previous work, we performed qualitative interviews with individuals with FA and conducted a cross-sectional study of 153 individuals with FA to identify the symptoms and symptomatic themes that have the highest prevalence and relative importance to the FA population.[3] In accordance with the FDA guidelines, we used these data in conjunction with beta interviews, test-retest reliability assessment, and known groups analysis to develop the Friedreich's Ataxia-Health Index (FA-HI). The FA-HI and its subscales were designed for use in clinical trials and as a disease-specific tool to support the merit of FA therapeutics. This study details the development of the FA-HI, its content validity, construct validity, test-retest reliability, and ability to differentiate between groups of FA participants with different levels of disease severity.

Methods

Study Participants

Cross-sectional study participants included individuals aged 8 years or older with a self-reported diagnosis of FA. Beta interview and test-retest reliability participants included individuals aged 11 years or older with a self-reported diagnosis of FA. Participants were recruited through the Friedreich's Ataxia Research Alliance (FARA) patient registry. The demographic characteristics and research roles of each sample cohort are provided in Table 1.

Table 1 Demographic Characteristics of Research Participants

	Cross-sectional study[a], known groups analysis	Beta interviews	Test-retest reliability
Total no. of participants	153	17	20
Sex, n (%)			
Female	96 (62.8)	11 (64.7)	11 (55.0)
Male	56 (36.6)	6 (35.3)	8 (40.0)
Prefer not to answer	1 (0.7)	0	1 (5.0)
Age, y			
Mean (SD)	30.8 (12.7)	24.9 (11.0)	25.7 (10.2)
Range	10–65	11–41	12–47
Adults/minors, no. (%)			
Adults	124 (81.0)	11 (64.7)	15 (75.0)
Minors	22 (14.4)	6 (35.3)	5 (25.0)
Omitted	7 (4.6)	0	0
Employment status, n (%)			
Employed full-time	22 (14.4)	2 (11.8)	3 (15.0)
Employed part-time	15 (9.8)	1 (5.9)	1 (5.0)
On disability	59 (38.6)	5 (29.4)	2 (10.0)
Not working/not on disability	15 (9.8)	2 (11.8)	6 (30.0)
Retired	2 (1.31)	0	0
Stay-at-home parent	8 (5.2)	0	0
Student	31 (20.3)	7 (41.2)	6 (30.0)
Other	1 (0.7)	0	2 (10.0)
GAA repeat number (mean, SD)			
Smaller GAA allele	621.1 (209.2)	N/A	N/A
Larger GAA allele	922.1 (226.3)	N/A	N/A
Mean GAA allele	771.6 (169.1)	N/A	N/A
US states represented	20	12	13

[a] PRISM-FA cross-sectional study participants (n = 153).[3]

Study Design

Question Selection and Content Validity

In previous research, we used semistructured qualitative interviews to identify the symptoms of FA that have the greatest impact on the lives of those living with this disease.[3] These interviews yielded 1,723 direct quotes regarding the symptomatic burden of FA, which were then used to develop a comprehensive survey to be implemented in a cross-sectional study. The survey included 245 individual symptoms representing 20 symptomatic themes of FA health. This study identified the symptoms with the highest population impact score (a value ranging from 0-4 obtained by multiplying the prevalence of the symptom by the average life impact score) for inclusion in the FA-HI. Symptom questions with a population impact score greater than 0.65 were considered for inclusion in the instrument. Using a research team consensus approach, symptom questions were excluded if they were (1) redundant, (2) vague, (3) not sufficiently responsive to future therapeutic intervention, (4) potentially abrasive, (5) lacking generalizability, or (6) relevant only to a regional location. In addition, symptom questions were excluded if the language was considered above a sixth grade reading level.

Exploratory Factor Analysis

Symptom questions that were selected for the FA-HI were grouped by content into subscales representing the most important symptomatic themes of FA health using a research team consensus approach. Internal consistency was evaluated using factor analysis. A Cronbach alpha score was determined for each

of the subscales in the instrument. Item placement was evaluated using corrected item-total correlations. Symptom questions were moved to alternative subscales as needed to maximize the internal consistency of each subscale. After this analysis, the first version of the FA-HI was developed.

Beta Interviews

Beta interview participants were recruited through the FARA patient registry. Eligible members of the registry received information about the study through email and were directed to contact the study team if they were interested in participating. Participants were asked to complete the first version of the FA-HI and provide feedback on the instrument in an interview with a member of our research team. Participants were asked to comment on the content, relevance, and usability of the instrument and each of the subscales. Participants also described their understanding of the theme addressed in each subscale, provided feedback on the response options, and discussed the time frame they used to recall each symptom. In addition, participants identified any symptoms that were not addressed in the instrument and provided feedback regarding the wording and placement of the symptom questions. All interviews were audio-recorded, transcribed, and analyzed by our research team. Participant feedback obtained through these interviews in combination with a consensus approach with our research team were used to modify the instrument. On completion of beta interview analysis and instrument revision, version 2 of the FA-HI was developed.

Scaling and Scoring of the FA-HI

All subscales were scored on a scale of 0–100 with 0 representing no disease burden and 100 representing the maximum level of disease burden. Symptom questions within each subscale were weighted based on patient-reported relevance as identified through the previous cross-sectional study.[3] Subscale scores were also weighted to generate a total FA-HI score (0–100) representing overall disease burden.

Test-Retest Reliability of the FA-HI

Test-retest reliability participants were recruited through the FARA patient registry. Eligible members of the registry received information about the study through email and were directed to contact the study team if they were interested in participating. This sample cohort was distinct from the beta interview sample cohort; however, we allowed individuals to participate in both studies. Participants were asked to complete the FA-HI at baseline and at 2 weeks to assess the test-retest reliability of the instrument. Both assessments were administered online using REDCap. The time it took each participant to complete the instrument was recorded at baseline and at 2 weeks. Reliability of the individual symptom questions in the instrument was quantified using weighted kappa scores. Symptom questions with a weighted kappa value <0.40 were considered for deletion from the instrument. Reliability of the total FA-HI score and each subscale score was quantified using intraclass correlation coefficients (ICCs). On completion of test-retest analysis and instrument revision, version 3 of the FA-HI was developed.

Known Groups and Area Under the Curve Analysis

Average FA-HI total and subscale scores were determined for predefined subgroups from the cross-sectional study sample population (n = 153). Participant scores were grouped by age (above vs below the mean age), sex (male vs female), employment status (on disability vs not on disability), age of symptom onset (above vs below the mean), speech status (no changes to speech vs experiences speech impairment), functional staging for ataxia (0–4.0 vs > 4.0, where 0–4.0 represents a lower level of disability and >4.0 represents a higher level of disability), heart problems (has cardiomyopathy vs does not have cardiomyopathy), and minimum GAA repeat length (above vs below the mean).[4] Wilcoxon rank-sum scores were used for group comparisons of the mean total scores. For comparing between 2 groups, we used the Wilcoxon two-sample test and t approximation 2-sided *p*-values. In addition, we performed area under the curve (AUC) analysis of total FA-HI scores against functional staging for ataxia for 153 cross-sectional study participants.

Confirmatory Factor Analysis of the FA-HI

On completion of the final FA-HI, we conducted confirmatory factor analysis and used Cronbach alpha scores to quantify the internal consistency of the total instrument and each of the subscales. Cronbach alpha scores for the total FA-HI, short form, and subscales are provided in Table 2.

This same methodology has been used and described in studies of other neurologic disease populations.[5-8]

Standard Protocol Approvals, Registrations, and Patient Consents

All aspects of this research were approved by the University of Rochester Research Subjects Review Board.

Data Availability

Additional anonymized data not included in the article can be obtained through request to the corresponding author.

Results

Question Selection and Content Validity

The initial survey implemented in the PRISM-FA cross-sectional study consisted of 245 symptom questions representing 20 symptomatic themes.[3] We removed 24 symptom questions and 2 symptomatic themes because of a low population impact score (<0.65). We removed 106 symptom questions deemed by the research team to be redundant, vague, not sufficiently responsive to future therapeutic intervention, potentially abrasive, not generalizable, regional, or worded at above a sixth grade reading level. We reworded 3 symptom questions for clarity. Figure 1 provides an overview of the process used to select, remove, and modify questions during each phase of FA-HI development.

Exploratory Factor Analysis

After exploratory factor analysis, version 1.0 of the FA-HI was developed which consisted of 115 symptom questions grouped into 18 symptomatic themes of FA health.

Table 2 Test-Retest Reliability and Internal Consistency of Final FA-HI Full Form, Short Form, and Subscales

FA-HI subscales	No. of questions in final subscale	Internal consistency, Cronbach alpha	Intraclass correlation coefficient (ICC)
Total FA-HI score	113	0.99	0.96
Short form	18	0.91	0.86
Mobility and ambulation	15	0.96	0.96
Coordination	9	0.90	0.90
Fatigue	4	0.90	0.86
Lower extremity strength	4	0.89	0.86
Social performance	6	0.87	0.91
Activity participation	15	0.96	0.96
Emotional health	7	0.92	0.95
Shoulder and arm function	4	0.87	0.65
Hand and finger function	7	0.92	0.86
Communication	6	0.92	0.76
Sleep and daytime sleepiness	6	0.86	0.92
Pain	8	0.91	0.79
Sensation	7	0.89	0.82
Vision	4	0.92	0.80
Gastrointestinal function	4	0.68	0.74
Swallowing function	5	0.95	0.85
Heart function	1	N/A	0.88
Breathing function	1	N/A	0.64

Beta Interviews

Seventeen individuals with FA participated in beta interviews (11 adults, 6 minors). All interviews conducted were 30–60 minutes in length. Overall, beta interview participants (n = 17) commented that the instrument was easy to use and comprehensively covered the symptoms that had the greatest impact on their lives. Participants provided feedback that they felt the instrument was capable of capturing how they feel and function, and they also stated that the instrument was a reasonable way to gauge their disease severity. When asked to identify the themes addressed by each subscale, participant responses were consistent with the intended symptomatic theme. Participants also provided constructive criticism regarding the wording, placement, and inclusion of specific questions, all of which led to instrument modifications. The symptom questions "difficulty moving small objects," "difficulty brushing teeth," "difficulty catching things," and "difficulty playing sports" were identified by participants as vague, so all were deleted from the instrument. The symptom question "difficulty holding a pen or pencil" was identified as redundant to other questions in the instrument pertaining to hand and finger function and was also deleted from the instrument. The question, "difficulty standing when your eyes are closed" was identified as not generalizable and was deleted from the instrument. The question "difficulty drinking from a cup" was reworded for clarity to "difficulty drinking from a cup without a straw." The question, "difficulty getting to the bathroom" was reworded to "difficulty getting to the bathroom in time" for clarity. Some symptom questions were added back to the instrument because participants identified the symptoms as highly impactful and important to include in the instrument. These included "difficulty getting to the bathroom in time," "difficulty typing," "frustration," "shaky eyes," and "loss of sensation of hot or cold."

Test-Retest Reliability

Twenty individuals with FA participated in test-retest reliability assessment of the FA-HI (15 adults, 5 minors). No participants achieved a maximum or a minimum score on the FA-HI; thus, no floor or ceiling effects were observed. One symptom question, "problems using buttons", was deleted because of a low weighted kappa score (<0.40). The ICC value for the total FA-HI and each of its subscales are provided in Table 2. The average time to complete the FA-HI was 15.6 minutes (one data point was excluded as an outlier).

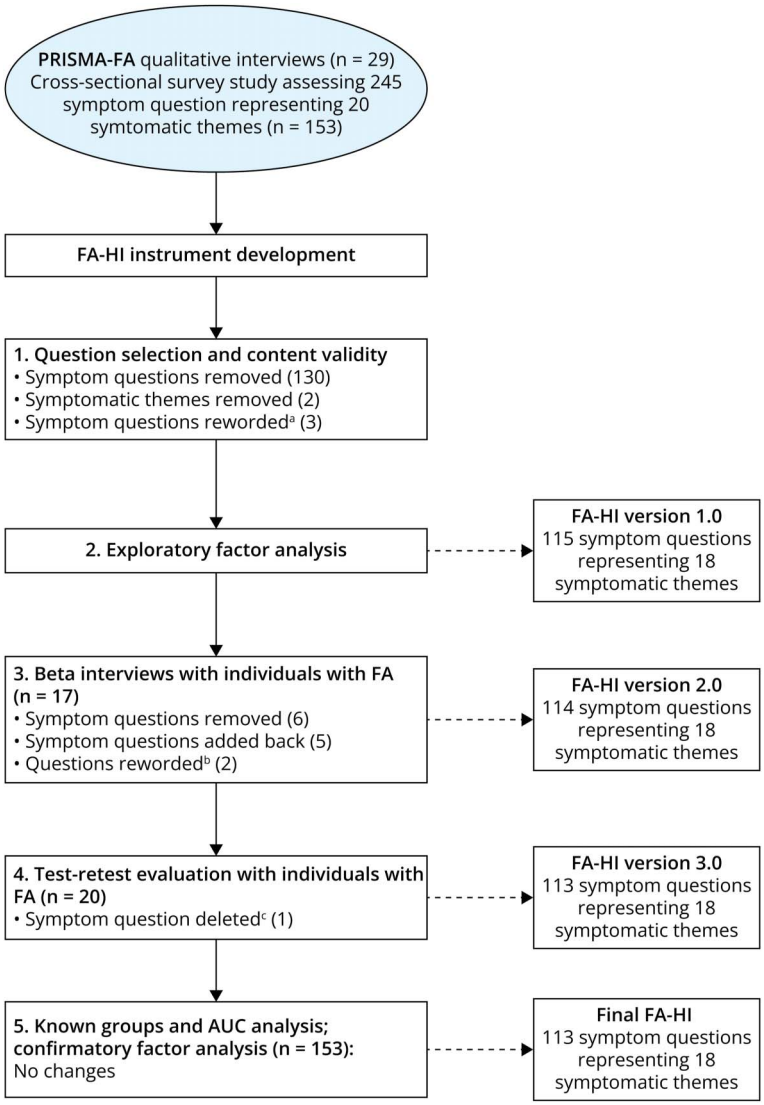
Known Groups and AUC Analysis

Data from 153 participants with FA, who previously had participated in our cross-sectional study, was used for known groups analysis. There were significant differences in FA-HI total and subscale scores among subgroups of the sample cohort believed to differ in their severity of disease. Specifically, higher average FA-HI total scores were found in participants who were above the mean age of 30.1 years, identified their employment status as on disability, experienced speech impairment, had heart problems/cardiomyopathy, had a functional staging for ataxia score of >4.0, or had a minimum GAA repeat length above the mean. There were also widespread differences in FA-HI subscale scores based on predetermined markers of disease severity. The most significant differences in subscale scores among subgroups were demonstrated in those by employment status, speech status, and functional staging for ataxia. FA-HI total, short form, and subscale scores across demographic subgroups and corresponding *p*-values are provided in Table 3, eTable 1, eTable 2 (links.lww.com/CPJ/A453), and Figures 2-4. The AUC value for FA-HI total score against functional staging for ataxia was 0.75. The corresponding AUC graph is provided in Figure 5.

Instrument Finalization and Confirmatory Factor Analysis

The final version of the FA-HI contains 113 symptom questions representing 18 symptomatic themes (subscales). An 18-question short form was developed as a surrogate of the total instrument. The short form includes one representative question of each subscale in the instrument. Cronbach alpha scores representing the internal consistency of the

Figure 1 Friedreich's Ataxia-Health Index (FA-HI) Question Selection, Deletion, and Modification



[a]24 Symptom questions & 2 symptomatic themes removed because of low population impact score (<0.65). 106 symptom questions removed because of the following reasons: redundant (45), vague (24), not responsive (19), language (2), potentially abrasive (2), not generalizable (13), regional (1). 3 symptom questions reworded for clarity. [b]6 symptom questions removed because of the following reasons: vague (4), redundant (1), not generalizable (1). 2 symptom questions reworded for clarity. 5 symptom questions added back because of importance. [c]1 symptom question deleted because of a low weighted kappa score (<0.40). AUC = area under the curve analysis; FA-HI = Friedreich's Ataxia-Health Index; PRISM-FA = Patient-Reported Impact of Symptoms in Friedreich's Ataxia 3 FA Friedreich's Ataxia.

final FA-HI instrument, short form, and subscales are provided in Table 2.

Discussion

The FA-HI is a valid, multifactorial, disease-specific PRO developed in accordance with published FDA guidance for use in FA clinical trials.[2] The instrument consists of 18 subscales, each of which represents a unique symptomatic theme of FA health. The FA-HI was designed and validated using extensive input from participants with FA. The instrument, when completed, generates a total score of disease burden and a score in each of the individual subscales based on a patient's own perception of how they feel and function.

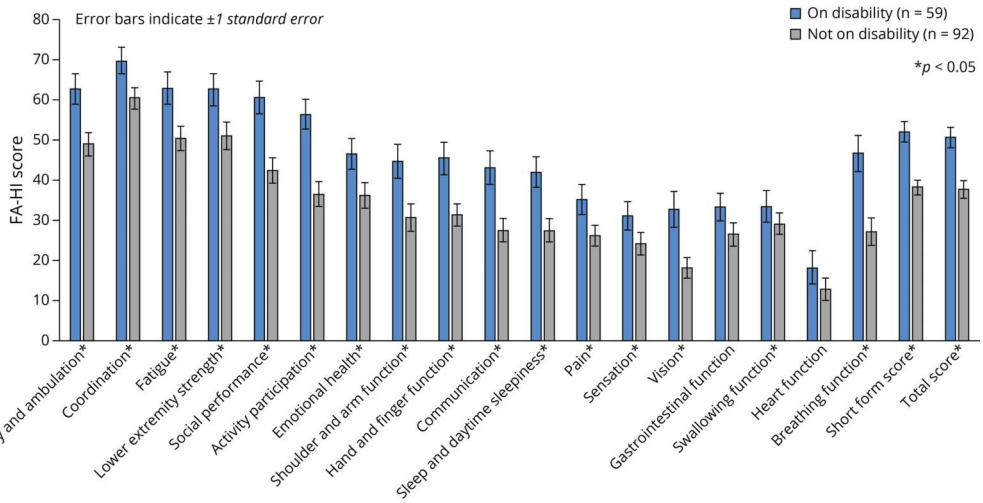
There are existing PROs that were designed for FA and cerebral ataxias, such as the Friedreich Ataxia Impact Scale (FAIS) and the Patient-Reported Outcome Measure of Ataxia (PROM-Ataxia); however, these PROs have distinct limitations.[9-11] Individuals with FA were underrepresented throughout the PROM-Ataxia development process.[9] In addition, the FAIS was developed using a UK participant population, which may limit its clarity and applicability to a US cohort of individuals with FA. Moreover, FAIS subscales previously demonstrated limited responsiveness at both one-year and two-year assessments of individuals with FA during a longitudinal study.[10,11] FA clinical trials have historically implemented generic and semigeneric PROs such as the PROMIS, Activities of Daily Living scales, NeuroQol, and EuroQol. Disease-specific PROs such as the FA-HI have extensive advantages over generic PROs. Disease-specific PROs are more precise, are preferred by participants, display greater sensitivity to changes in disease burden, and have a higher correlation with functional measures of disease.[12,13]

Table 3 Known Groups Analysis of FA-HI Scores

	Age, y			Functional staging for ataxia			Heart problems		
Subscales	Above mean (30.77) n = 70	Below mean (30.77) n = 76	*p* Value	0–4.0 n = 64	>4.0 n = 89	*p* Value	Yes n = 63	No n = 81	*p* Value
Total Score	46.7	38.6	**0.0204**	32.1	50.2	**<0.0001**	48.0	38.3	**0.0065**
Short Form Score	47.2	40.0	**0.0359**	34.8	49.9	**<0.0001**	48.5	39.4	**0.0045**
Mobility and ambulation	55.6	52.8	0.5394	51.9	55.9	0.2752	56.5	51.8	0.3108
Coordination	69.5	58.4	**0.0074**	54.1	71.1	**<0.0001**	70.3	58.2	**0.0060**
Fatigue	58.2	51.5	0.1436	49.0	59.6	**0.0195**	54.4	56.0	0.9151
Lower extremity strength	59.0	51.8	0.2033	38.3	67.7	**<0.0001**	63.5	49.6	**0.0122**
Social performance	53.6	46.0	0.1847	38.9	57.0	**0.0009**	55.2	45.6	0.0970
Activity participation	51.9	37.7	**0.0045**	21.4	60.5	**<0.0001**	56.9	34.4	**<0.0001**
Emotional health	40.5	39.4	0.9267	38.5	41.3	0.4911	40.0	40.6	0.7891
Shoulder and arm function	41.2	31.3	0.1460	22.8	45.5	**0.0001**	42.5	30.2	**0.0326**
Hand and finger function	44.9	29.9	**0.0032**	19.4	49.2	**<0.0001**	43.3	30.9	**0.0144**
Communication	43.4	24.0	**0.0001**	16.9	45.3	**<0.0001**	42.0	26.1	**0.0057**
Sleep and daytime sleepiness	36.6	28.1	0.0597	26.4	37.8	**0.0185**	32.8	32.3	0.9694
Pain	28.9	29.1	0.9469	23.4	34.1	**0.0081**	34.8	25.2	**0.0158**
Sensation	27.5	25.6	0.6304	14.9	35.2	**<0.0001**	33.9	22.5	**0.0304**
Vision	28.9	18.1	0.0691	11.1	32.8	**0.0001**	30.0	17.8	**0.0260**
Gastrointestinal function	35.9	22.6	**0.0051**	21.9	34.3	**0.0019**	29.9	26.9	0.5524
Swallowing function	28.7	22.1	0.0802	11.6	35.0	**<0.0001**	35.7	16.3	**0.0003**
Heart function	13.2	14.5	0.8078	8.2	19.7	**0.0053**	34.1	0.6	**<0.0001**
Breathing function	38.9	28.6	**0.0454**	26.2	40.7	**0.0096**	34.9	34.6	0.9917

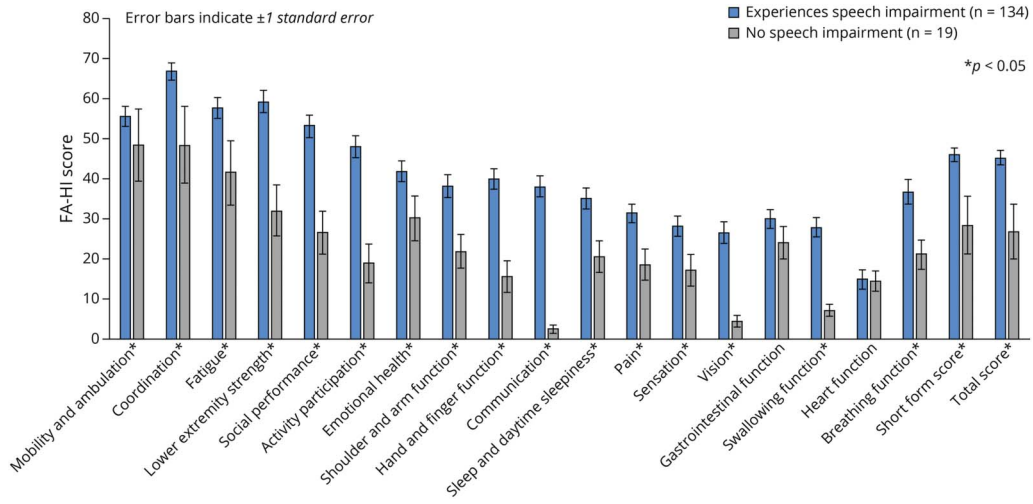
Abbreviation: FA-HI = Friedreich Ataxia-Health Index.
Bolded values indicate $p < 0.05$.

Figure 2 FA-HI Total and Subscale Scores by Employment Status



FA-HI = Friedreich's Ataxia-Health Index.

Figure 3 FA-HI Total and Subscale Scores by Speech Status



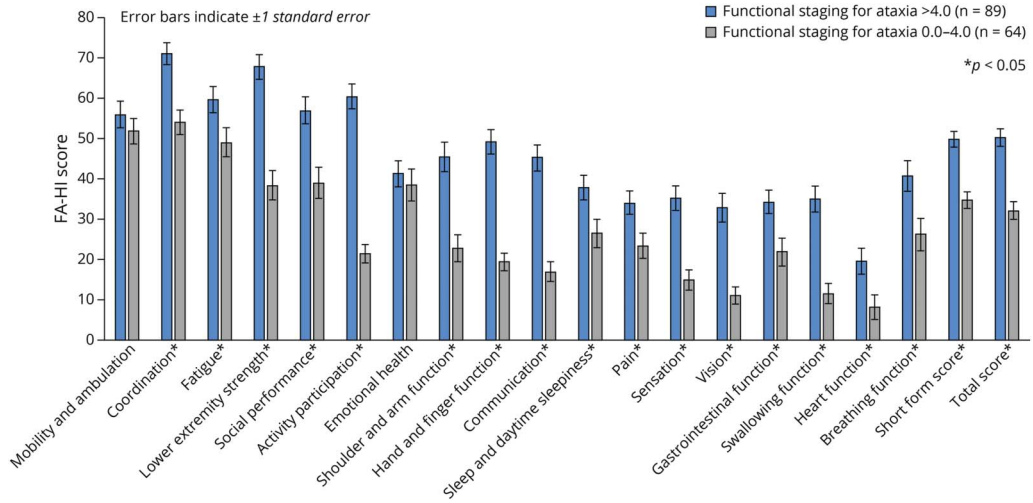
FA-HI = Friedreich's Ataxia-Health Index.

The FA-HI was developed using the same methodology previously used and described for the development of the MDHI, a disease-specific PRO for use in myotonic dystrophy type 1 (DM1) clinical trials.[5,12-14] The MDHI was identified through the NINDS common data elements initiative as the one highly recommended outcome measure to implement in DM1 clinical trials.[15] Like the MDHI, the FA-HI adheres to FDA standards for the development and validation of disease-specific PROs.[2]

The design and utility of the FA-HI offers significant benefit to the FA research community. The instrument is capable of quantifying disease burden in a broad age range of individuals with FA (10 years and older) with diverse functional abilities. The instrument can be completed in approximately 15 minutes by a participant without the need for professional administration. The short form version can be completed in less than one minute. Importantly, the FA-HI offers a unique opportunity to bring the patient perspective to the forefront of clinical trials that are evaluating the effects of a therapeutic intervention in FA.

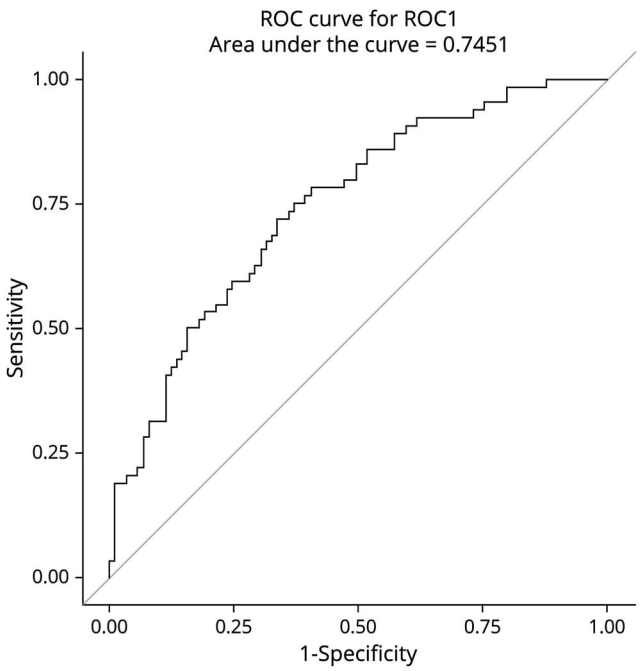
The FA-HI total and subscale scores demonstrated an ability to differentiate between subgroups of participants suspected to differ in their severity of disease. Studies such as Friedreich's Ataxia Clinical Outcome Measure Study (FACOMS) are currently underway and are analyzing the longitudinal metrics of the FA-HI and comparing the sensitivity of its scores to detect

Figure 4 FA-HI Total and Subscale Scores by Functional Staging for Ataxia



FA-HI = Friedreich's Ataxia-Health Index.

Figure 5 AUC Analysis of FA-HI Total Score by Functional Staging for Ataxia (n = 153)



AUC = area under the curve; FA-HI = Friedreich's Ataxia-Health Index.

changes in disease burden with those of functional outcome measures.

We acknowledge the potential limitations of this research. While we aimed to recruit a large and diverse sample for our cross-sectional study and subsequent known groups analysis, our sample cohort was likely not a perfect representation of the general FA population. Participants were recruited using an online format through the FARA patient registry, and our sample cohorts had a slightly higher percentage of female participants than male participants. Individuals with FA with more severe disease or those with limited access to the internet were likely underrepresented in our sample cohort. In addition, the subgroup analysis performed using the self-reported functional staging for ataxia scale and FA-HI scores was based on participant-reported data without external validation by a clinician or researcher. While participants themselves are well suited to report on their own functional ability, we acknowledge that there may be discrepancy in participant-reported values and those reported by a clinician or researcher. Ongoing studies such as FACOMS will provide much needed information regarding the correlation between FA-HI scores and functional or clinician-reported assessments of FA health.

This research provides initial evidence of the content validity, construct validity, test-retest reliability, and usability of the FA-HI as a disease-specific PRO to assess how a patient with FA feels and functions during clinical trials. The FA-HI provides FA researchers and clinicians with a mechanism to use the direct perspective of the patient to quantify meaningful changes in disease burden across multiple symptomatic domains. The FA-HI supplements existing clinical trial infrastructure in FA research and offers a valid mechanism to facilitate therapeutic assessment in FA.

Study Funding

This research was funded by the Friedreich's Ataxia Research Alliance (FARA).

Disclosure

J. Seabury reports no disclosures relevant to the manuscript; D. Alexandrou reports no disclosures relevant to the manuscript; C. Engebrecht reports no disclosures relevant to the manuscript; N. Dilek reports no disclosures relevant to the manuscript; B. Greco reports no disclosures relevant to the manuscript; J. Heatwole reports no disclosures relevant to the manuscript; J. Larkindale is a paid employee of PepGen Inc.; D.R. Lynch receives grant support from the NIH, FDA, Friedreichs Ataxia Research Alliance, Reata Pharmaceuticals, Retrotope, PTC Therapeutics, Design Pharmaceuticals; C. Park reports no disclosures relevant to the manuscript; S. Rosero reports no disclosures relevant to the manuscript; S. Subramony receives research support from the NIH, FDA, Wyck, Friedreichs Ataxia Research Alliance, Muscular Dystrophy Association, Facioscapulohumeral Muscular Dystrophy Society, National Ataxia Foundation, Reata, PTC, Retrotope, Biohaven, Takeda, Acceleron, Pharnext, Avidity, and Reneo. He has provided consultation or served on advisory boards for Dyne, Avidity, Reata, and Avexis; A. Varma reports no disclosures relevant to the manuscript; E. Wagner reports no disclosures relevant to the manuscript; S. Walther reports no disclosures relevant to the manuscript; J. Weinstein reports no disclosures relevant to the manuscript; M. Wells reports no disclosures relevant to the manuscript; C. Zizzi has provided consultation to Recursion Pharmaceuticals; C. Heatwole receives royalties for the use of multiple disease-specific instruments. He has provided consultation to Biogen Idec, Ionis Pharmaceuticals, aTyr Pharma, AMO Pharma, Acceleron Pharma, Cytokinetics, Expansion Therapeutics, Harmony Biosciences, Regeneron Pharmaceuticals, Astellas Pharmaceuticals, AveXis, Recursion Pharmaceuticals, IRIS Medicine, Inc., Takeda Pharmaceutical Company, Scholar Rock, Avidity Biosciences, Novartis Pharmaceuticals Corporation, SwanBio Therapeutics, and the Marigold Foundation. He receives grant support from the Department of Defense, Duchenne UK, Parent Project Muscular Dystrophy, Recursion Pharmaceuticals, SwanBio Therapeutics, the National Institute of Neurological Disorders and Stroke, the Muscular Dystrophy Association, the Friedreichs Ataxia Research Alliance, Cure Spinal Muscular Atrophy, and the Amyotrophic Lateral Sclerosis Association. Full disclosure form information provided by the authors is available with the full text of this article at Neurology.org/cp.

Publication History

Received by *Neurology: Clinical Practice* December 23, 2022. Accepted in final form June 2, 2023. Submitted and externally peer reviewed. The handling editor was Associate Editor John P. Ney, MD, MPH.

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How to cite this article: Seabury J, Rosero S, Varma A, et al. Friedreich's Ataxia-Health Index: development and validation of a novel disease-specific patient-reported outcome measure. *Neurol Clin Pract*. 2023;13(5):e200180. doi: 10.1212/CPJ.0000000000200180.