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Reliability and validity of the FSHD-composite outcome measure in childhood facioscapulohumeral dystrophy

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Abstract

This study aims to investigate intra-rater reliability and construct validity of the Facioscapulohumeral Dystrophy Composite Outcome Measure (FSHD-COM), in childhood FSHD. Participants included eighteen children with FSHD, and matched healthy controls. Reliability data were collected from 15 participants with FSHD over two testing sessions. Validity data were collected from all participants. Participants with FSHD completed; the FSHD-COM (and modified pediatric version), Motor Function Measure-32 (MFM-32), FSHD Severity Scales, Performance of the Upper Limb 2.0, Pediatric Quality of Life^{TM} Neuromuscular Module and pediatric FSHD Health-Index Questionnaire. Both versions of the FSHD-COM showed excellent intra-rater reliability ($ICC_{1,2} > 0.99$, lower 95%CI > 0.98) with a Minimal Detectable Change (MDC95%) of $\leq$14.5%. The FSHD-COM had robust and widespread correlations with other related outcome measures. The FSHD-COM versions and 6 min walk test effectively discriminated between children with and without FSHD; the MFM-32 and 10 m walk/run test did not. Ceiling effects were not observed on either version of the FSHD-COM. Reliability and validity findings in this childhood FSHD study concord with estimates in adults. Both versions of the FSHD-COM were effective in discriminating disease in children with mild FSHD symptoms. The FSHD-COM has the potential to be a useful measure of function across the life span.

Keywords: Facioscapulohumeral dystrophy (FSHD); Outcome measure; Pediatric; Measurement properties.

1. Introduction

Facioscapulohumeral dystrophy (FSHD) is characterized by distinctive facial and periscapular weakness progressing to include the trunk and lower limbs over time. Variable severity and heterogeneous clinical presentation, even within affected families [1], is common. Recent estimates report a prevalence of 1/8300 in adults [2,3], with lower prevalence in children (0.7–1/100,000) [4]. Presentation in childhood is often associated with increased disease severity and a greater risk of wheelchair dependence, scoliosis and respiratory insufficiency [2].

Improved understanding of disease genetics and pathophysiology is paving the way for pharmaceutical developments to treat FSHD. Reliable, valid, and responsive measures of performance-based and self-reported function are essential to optimize clinical trial readiness and assess response to therapeutic interventions [5,6]. A recent systematic review highlighted the paucity of robust FSHD-specific instruments in adults, with even fewer options available for children [7]. The Facioscapulohumeral Composite Outcome Measure (FSHD-COM) was developed to address this need [6,8]. Measuring multiple constructs (strength, exercise capacity, balance), the FSHD-COM

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assesses functional domains and body regions (excluding face) commonly affected in FSHD. Evidence is available to support its use in adults (22–70 years) [8], but its reliability and validity in a pediatric population is unknown.

As some components of the FSHD-COM already have strong clinometric evidence supporting their use in children with neuromuscular disease [9–12], it appeared feasible that FSHD-COM has potential to be a useful measure in childhood FSHD. The purpose of this study was to estimate the reliability and construct (convergent, discriminant) validity of the FSHD-COM when evaluating physical function in children with FSHD.

2. Methods

This prospective cross-sectional, matched cohort study was embedded within a randomized controlled trial investigating the effect of creatine monohydrate on strength and muscle mass in children with FSHD (ClinicalTrials.gov ID: NCT02948244).

2.1. Participants

Participants with FSHD were recruited between October 2018 and January 2020 through neuromuscular clinic databases at the Royal Children's Hospital (RCH), Melbourne and Queensland Children's Hospital, Brisbane, (Australia), pediatric neurologists within Australia and New Zealand, and via advertisements through patient advocacy groups (FSHD Global, muscular dystrophy associations within Australia and New Zealand). FSHD participants were eligible if they: (i) were aged 5–18 years; (ii) had a confirmed genetic diagnosis of FSHD or clinical symptoms and a first degree relative with a confirmed genetic diagnosis of FSHD; (iii) were able to comply with testing procedures. No restriction was placed on ambulatory status.

A non-FSHD, typically developing (TD) cohort of children was recruited at RCH, identified through family, friends and colleagues. TD children were matched with a 1:1 ratio to children with FSHD for age (+/- 6 months) and sex and excluded only if any condition which would inhibit their performance on functional tests was reported.

2.2. Procedures

Participants with FSHD attended two testing sessions 2–4 weeks apart; TD participants attended a single testing session.

Baseline characteristics (sex, height, weight, typical mobility over 5, 50 and 500 m using the Functional Mobility Scale) [13] were collected for all participants at the initial testing session. Genetic data including FSHD type +/- repeat length were collected (where available). Participants with FSHD completed the tested measures (the FSHD-COM and FSHD-COM Peds) and comparator measures at each testing session. To establish stability of disease symptoms between the first and second testing sessions participants were asked to rate their perceived function (range −4 = very much *worse*, 0 = the *same,* 4 = very much *better),* on a global rating of change scale at the second testing session. TD participants were only required to complete FSHD-COM, FSHD-COM Peds and the Motor Function Measure (MFM-32). All participants were assessed by the same research physiotherapist (KdV) with 20+ years of clinical experience.

2.3. Outcome measures

To evaluate construct validity the FSHD-COM and FSHD-COM Peds (tested measures) were compared to performance-based measures; the MFM-32, FSH-clinical (Lamperti) score (FCS), FSH-clinical severity (Ricci) scale (CSS), Performance of the Upper Limb (PUL) 2.0 and self-reported measures Pediatric Quality of Life Inventory™ Neuromuscular Module (PedsQL™NMM) and FSHD-Health Index pediatric version (FSHD-HI Peds).

2.3.1. Tested measures

Facioscapulohumeral Dystrophy Composite Outcome Measure (FSHD-COM) and FSHD-COM Pediatric version (FSHD-COM Peds)

A disease specific performance-based instrument, the FSHD-COM includes 18 items grouped into 5 body regions (leg function, arm/shoulder function, trunk function, hand function, and balance). Scoring is based on a 5-point ordinal scale (range 0 = unaffected/normal performance, 4 = severely affected). The FSHD-COM is scored out of 72 and lower scores correlate with better function [8]. Seven items grade function based on task performance according to pre-set criteria. Eleven items, including timed function tests, the six-minute walk test and grip strength dynamometry require conversion of a raw score into a scaled score. A pediatric version, the FSHD-COM Peds was developed in collaboration with one of the original FSHD-COM instrument developers (Dr. Kate Eichinger) prior to study commencement. To accommodate motor development and lower strength levels expected in childhood items 6–8 in the arm/shoulder region on the FSHD-COM Peds were modified. Two smaller weights (500 g and 1 kg) were added in the shoulder abduction and shoulder flexion and (1 kg and 2 kg) in the elbow flexion strength items. The scale for these items increased from 5 to 7-points, thereby increasing the FSHD-COM Peds total score to 84. Items 6–8 were scored with both the original criteria and the amended weight items, allowing scores for both the adult and pediatric versions to be calculated (Supplementary Table 1).

2.3.2. Comparator measures

2.3.2.1. Motor function measure-32 (MFM-32). Developed and validated to evaluate motor function in children and adults with neuromuscular diseases including FSHD [14], this 32-item instrument is divided into three hierarchical dimensions (D1 standing/transfers, D2 axial and proximal limb, D3 distal motor function) and scored using a 4-point ordinal scale (range 0 = unable to initiate task, 3 = able to perform task without compensation) [15]. Item scores are summed out of

96 with lower scores indicative of poorer function. Time taken to complete MFM-32 item 30 – barefoot 10 m walk/run, was also recorded for each participant.

2.3.2.2. Severity scales. Disease severity was assessed using the CSS scale [16] and FCS score [17]. The CSS classifies the functional effect of disease symptoms using a 10-point ordinal scale (range 0.5 = facial weakness, 5 = wheelchair bound) which has undergone further adaptation to correct for participant age using the formula (CSS= [(CSSx2)/age at assessment]) [16,18]. The FCS quantifies the effect of weakness of facial, scapular, upper limb, leg, pelvic and trunk muscles on functional performance and strength. It is scored using 0–15 ordinal scale (range 0 = unaffected, 15 = severely affected) [17].

2.3.2.3. Facioscapulohumeral dystrophy health index (FSHD-HI Peds). The FSHD-HI is a disease specific patient reported outcome measure designed to measure changes in disease burden in clinical trials and support drug labeling claims. The FSHD-HI measures 14 areas of disease specific health with each use and was developed and validated using interviews with 20 FSHD adults and with a cross-sectional study including over 300 adults with FSHD [19,20]. A pediatric version 'the FSHD-HI Peds' was formulated by the original scale developers for this study. Utilizing expert review, pediatric appropriate questions for the original FSHD-HI were selected for inclusion in the FSHD-HI Peds. All but seven FSHD-HI questions, were retained. The FSHD-HI Peds includes 109 items, divided into 14 subscales assessing a child's perception of their shoulder and arm function, mobility and ambulation, fatigue, cognitive function, activity limitation, trunk strength and function, gastrointestinal function, social performance, body image, hand/finger function, social satisfaction, pain, emotional health and communication [19,21]. Each time the instrument is completed a patient receives a score (0–100) for each of the subscales, with a higher score representing a higher burden of disease. The FSHD-HI Peds was pilot tested with two typically developing children prior to use and further minor modifications were made to the wording, in consultation with the instrument developers and a plain language advisor. The purpose of these alterations was to adapt the language to further suit a pediatric cohort and to remove or adjust any culturally unfamiliar terms for the Australian context e.g. 'milk gallon'. Modifications were again piloted with an additional four typically developing children aged 9–13 years.

Participants with FSHD completed the FSHD-HI Peds independently according to a standardized protocol. For participants 8 years or younger and those who had difficulty reading or understanding the questionnaire, the same parent was asked to assist them or to complete the questionnaire on their behalf.

2.3.2.4. Pediatric quality of life™ neuromuscular module (PedsQL™NMM). The PedsQL™NMM self-reported questionnaire developed for and previously validated in children with neuromuscular disease was used to measure health related quality of life [22,23]. Problems experienced in the past month in relation to neuromuscular disease symptoms, ability to communicate and family resources are rated. Scoring is based on a 0–4 ordinal scale (range 0 = never and 4 = almost always). Scores are then linearly transformed into a 0–100 scale where higher scores indicate better health related quality of life. Both the participant and parent versions were administered at each visit. If the child had difficulty reading the questions a staff member read the questions to the child.

2.3.2.5. Performance of the upper limb (PUL 2.0). The PUL 2.0 was developed to assess upper limb function in boys with Duchenne muscular dystrophy [24]. The instrument's 22 items are divided into: high (shoulder); mid (elbow); distal (wrist/hand) activity-levels. An entry item identifies at which level the assessment should commence. Item scores are based on dominant limb performance using pre-set criteria and an ordinal scale. Total scores are calculated out of 44 with larger scores correlating with better upper limb function [25]. These PUL 2.0 data were collected for a subset of subjects ($n = 13$), participating in the creatine monohydrate study referred to above (ClinicalTrials.gov ID: NCT02948244).

2.4. Data and statistical considerations

To estimate sample size requirements, calculations were based on hypothesized ICC values and 95% confidence intervals (95% CI). Based on the results of a prior study of FSHD-COM reliability (ICC = 0.96) [8] and prior correlations of FSHD-COM and FCS ($r > 0.89$, $p < 0.0001$) [8], $ICC_{2,1}$ values were hypothesized to be ≥ 0.90 with a 95% CI of 0.2 (ICC 0.8–1.0) [26,27] with moderate to very strong correlations with disease severity. Using these values, a desired sample size of 18 was calculated.

Participant characteristics were described using means, standard deviations (SD), ranges and percentages as appropriate. Reliability measurements in children with FSHD were collected at two time points and the average number of days between testing sessions was calculated. Intraclass correlations (ICC2,1) using two-way random effects with absolute agreement and single-rater measurements were calculated for intra-rater reliability estimates and were described according to the criteria: ICC < 0.75 poor to moderate, > 0.75 good, > 0.90 excellent [28]. Using Standard Errors of Measurement (SEM) Minimal Detectable Change (MDC90 and MDC95) scores were calculated to express 90% and 95% certainty of true change. Bland-Altman plots were generated to examine systematic bias between repeated measurements. Floor and ceiling effects were calculated from the proportion of participants who achieved maximum or minimum total scores. Construct validity was evaluated using Spearman rank correlation coefficients by examining correlation between dependant variables (the FSHD-COM and FSHD-COM Peds scores) and comparator tests (MFM-32, FSHD severity scales, FSHD-HI Peds, PedsQL™NMM

and PUL 2.0). Where possible, comparator tests were broken down into dimensions and correlations examined. Strength of correlations were considered according to the criteria: $r = 0.3–0.59$ fair, $r = 0.6–0.79$ moderate, $r = 0.8–0.99$ very strong [29,30]. Discriminant validity of the FSHD-COM and FSHD-COM Peds was examined by comparing differences between groups using unpaired t-tests. $P<0.05$ was considered significant.

All data were analyzed using (IBM SPSS 22 statistical package for Windows USA) or Stata®(Version 15) software. Study data were collected and managed using REDCap© electronic data capture tools hosted at the Murdoch Children's Research Institute.

2.5. Standard protocol approvals, registrations and patient consents

This study received multi-site human research ethics approval through the Royal Children's Hospital (HREC36298), Queensland Children's Hospital (ERM35351) and was registered with University of Melbourne Ethics Committee (ID 1,750,318). Written informed consent was obtained from all participants/guardians.

2.6. Data availability

De-identified data will be made available on reasonable request.

3. Results

3.1. Participant characteristics

Eighteen of 25 eligible children aged 7–18 years consented to participate in the study (Fig. 1), of which 56% were male. One participant without a confirmed genetic diagnosis had clinical signs of disease and a first degree relative with FSHD 1. One participant had FSHD 2 (Table 1). Two participants used a wheelchair for all mobility and two for community mobility only (defined as 500 m or more on the Functional Mobility Scale) (Table 2). Disease severity ranged from mild to severe with 83% of participants classified with mild to moderate (FCS 0–6) disease [31].

3.2. Intra-rater test-retest reliability

Intra-rater test re-test reliability was evaluated over two test occasions with an average test interval of 14.9 days (range 4–26). Eighty seven percent of participants reported the 'same' or 'little' change in function since the previous visit, one participant reported 'better' function, and another did not provide a response. Test re-test reliability estimates (Table 3) for FSHD-COM Peds and FSHD-COM were excellent ($ICC_{2,1}$ 0.99, 95% CI 0.99–1.0). SEMs for both versions were low, ranging from 1.25 to 1.31 points and MDC between 2.9 and 3.6 points (Table 3).

3.3. Construct (convergent) validity

Both versions of the FSHD-COM demonstrated strong to moderate correlations with total scores on the MFM-32, CSS, FCS, PUL 2.0 and PedsQL^{TM}NMM, and fair correlation with the FSHD-HI Peds total score (Table 4). Strong to moderate correlation of both FSHD-COM Peds and FSHD-COM were also observed with dimensions D1 (standing/transfers) and D2 (proximal/axial) on the MFM-32; the high (shoulder) and mid (elbow) dimensions of the PUL 2.0; dimensions D1 (NMD symptoms) and D2 (communication) of the participant and dimensions D1 of the proxy PedsQL^{TM}NMM (Table 4). Scores of both versions of the FSHD-COM were associated with the total FSHD-HI Peds score and subscale scores related to groups 1 (shoulder/arm function), 2 (mobility/ambulation), 3 (fatigue), 5 (activity limitation), 10 (hand and finger function), 12 (pain), and 14 (communication) (Table 4).

The distal/hand dimensions of the MFM-32 and PUL 2.0 demonstrated fair correlations with both versions of the FSHD-COM, as did D3 (family resources) on the PedsQL^{TM}NMM proxy version (Table 4).

Scores for the FSHD-COM Peds ranged from 5 to 79 (out of a possible 84) with a mean of 31.3 (SD 19.1) points. Scores for the FSHD-COM ranged from 5 to 64 (out of a possible 72) with a mean of 23.7 (SD 16.5) points (Table 1). The low mean scores reflect the mild to moderate clinical severity of the cohort assessed using CSS and FCS. Floor and/or ceiling effects were not seen with the FSHD-COM Peds or FSHD-COM but were evident with the MFM-32 and PUL 2.0 (Fig. 2).

3.4. Construct (discriminant) validity

Between-group data analysis indicated that participant and TD control groups were very well matched, with no significant differences in age, weight, or height (Table 1). Large significant differences were observed in mean total scores between groups for FSHD-COM Peds (21 points, 95% CI 10–32) and FSHD-COM (14.8 points, 95%CI 6.4–23.3). A statistical and clinically meaningful difference of (−81.3 m, 95%CI −152.5 - −10.2) was observed in 6 min walk distance [32]. The between group difference on the MFM-32 did not reach pre-set $p<0.05$ statistical significance (Table 1). Due to COVID-19 restrictions only 14 TD participants could be recruited. Between group statistical data is presented for $n = 14$ matched participants.

4. Discussion

The impetus for investigation of the FSHD-COM in children is the need for standardized physical function outcome measures for clinical trials and best-practice care. The low incidence of childhood FSHD, in conjunction with its marked clinical heterogeneity, has possibly resulted in a reduced focus on outcome measure development in children. Other pediatric neuromuscular disorders such as Duchenne muscular dystrophy and spinal muscular atrophy, have mature

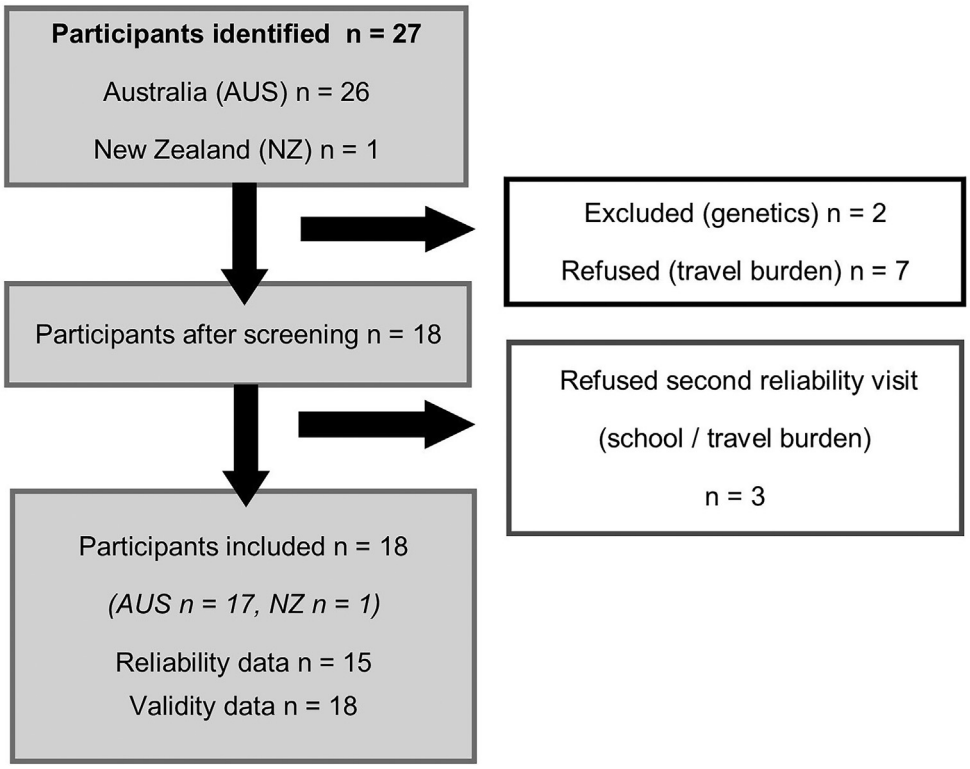

Fig. 1. Participant recruitment.

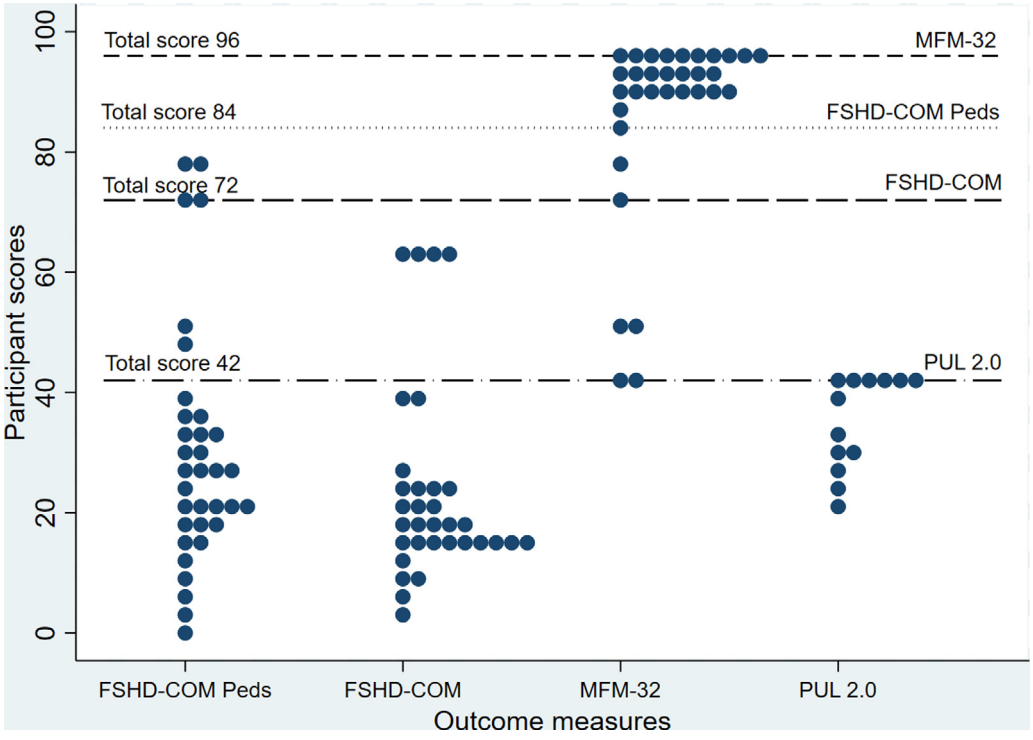

Fig. 2. Distribution of outcome measure data showing ceiling effects
Abbreviations: FSHD-COM – facioscapulohumeral dystrophy composite outcome measure, MFM – motor function measure, PUL (2.0) – performance of the upper limb.
FSHD-COM, FSHD-COM Peds and MFM-32 visits 1 and 2 data displayed ($n = 18$), PUL 2.0 visit 2 data only ($n = 13$).

Table 1
Baseline FSHD and typically developing control demographics and physical function characteristics.

	FSHD ($n=18$)		TD ($n=14$)		Between group difference ($n=14$)[f]	
	Mean (SD)	Range,%	Mean (SD)	Range,%	CI 95%	p value
Baseline characteristics						
Sex, m/f, (male,%)	10/8	56%	9/5	64%	–	–
Age, y	13.3 (3)	7 – 18	13.5 (3)	7 – 19	−2.8 – 2.4	0.88
Height, cm	161 (18)	118 – 187	159 (19)	125 – 188	−13.4 – 17.0	0.81
Weight, kgs	53.5 (14.9)	23.8 – 75.5	52(15.7)	23.8 – 70.0	−12.3 – 14.8	0.85
BMI, kg/m^2	20.3 (3.9)	15.1 – 30.2	19.2 (3.4)	15.2 – 25.5	−1.6 – 3.8	0.4
FSHD type, FSHD1/2, (FSHD1,%)[a]	16/1	94%	–	–	–	–
D4Z4 fragment size, kb [b]	16.9	10 – 30	–	–	–	–
D4Z4 repeat array [c]	4.8	3 – 7	–	–	–	–
FCS (mild–mod 0–6,%)	5.2 (3.2)	2 – 13 (83%)	–	–	–	–
CSS(mild-mod 0–2,%)	2.0 (1.2)	0.5 – 4.5 (72%)	–	–	–	–
Physical function measures						
FSHD-COM Peds	31.3 (19.1)	5 – 79	8.1 (6.7)	2 – 21	10.2 – 32	0.0005 [e]
FSHD-COM	23.7 (16.5)	5 – 64	6.6 (4.3)	2 – 14	6.4 – 23.3	0.001 [e]
MFM–32	85.9 (14.9)	43 – 96	95.5 (0.7)	94 – 96	0.1 – −15	0.05
10MWRT, sec [d]	3.4 (1.2)	2.3 – 7.6	2.8 (0.3)	2.5 – 3.5	−0.2 – 1.3	0.12
6MWT, meters [d]	558 (114)	397 – 787	661 (66)	554 – 808	−152 – −10	0.02 [e]
Self-reported measures						
PedsQL^{TM}NMM Participant Proxy	73.9 (15.7) 73.5 (17.1)	47 – 9542 – 97	–	–	–	–
FSHD-HI Peds	21.9 (22.5)	0.2 – 67.5	–	–	–	–

Abbreviations: TD – typically developing, SD – standard deviation, CI – confidence interval, kb – kilobytes, BMI – body mass index, FSHD – facioscapulohumeral dystrophy, FCS – FSH clinical (Lamperti) score, CSS – FSH clinical severity (Ricci) scale, FSHD-COM – facioscapulohumeral dystrophy composite outcome measure, MFM – motor function measure, 10MWRT – 10 m walk/run test, 6MWT – 6 min walk test

[a] $n=1$ missing
[b] $n=14$ results available.
[c] $n=10$ results available.
[d] $n=16$ performed 6MWT and 10MWRT.
[e] significant $p < 0.05$.
[f] between group differences examined using unpaired t-tests.

disease-specific outcome measures [25,33–36]. This study, along with recent disease-specific FSHD natural history studies contributes to the small but growing body of evidence required to support clinical trials in pediatric FSHD [4,37].

The excellent test re-test reliability results from this study support the ability of the FSHD-COM Peds and FSHD-COM to provide reproducible, consistent measurement results in children as young as 7 years with potential for use in younger children. Despite the obvious differences in growth and development between adults and children, this study mirrors reliability results of FSHD-COM (ICC 0.96) in adults with FSHD [8]. This positive result was not unexpected, as the FSHD-COM is composed of items scored using both timed and graded function which have evidence supporting reliability in TD and children with NMD as young as 4 years [38,39]. The brief instructions, simple technology and the ability to standardize testing have resulted in the use of timed function tests as primary outcome measures in pharmaceutical trials and as part of standard clinical care in pediatric neuromuscular clinics worldwide [40,41].

Floor and ceiling effects are important characteristics to consider when selecting an outcome measure. The FSHD-COM Peds and FSHD-COM demonstrated no floor or ceiling effects in children in this study. In contrast, both the MFM-32 and PUL 2.0 reached ceilings in this study and in the childhood FSHD natural history study conducted in the Netherlands [4]. In our study, three of 18 children achieved a maximum MFM-32 score of 96 points or 100% (mean 89.5%, range 45–100). Scores in Goselink's study ($n=18$) were even higher (mean 99.4%, range 96–100) [4]. Similarly 46% of participants in this study and 66.6% in the Goselink study achieved maximum scores in the high (shoulder) dimension of the PUL 2.0 [4] (Fig. 2.). The lack of ceiling effect of the FSHD-COM Peds and FSHD-COM further supports the usefulness of these measures in both children and adults with FSHD [8]. More than 70% of affected participants in this study had mild-moderate disease severity. Both versions of the FSHD-COM effectively discriminated between TD children and those with FSHD whereas the MFM-32 did not make this distinction.

As in Eichinger's original FSHD-COM study [8], this study was not designed to calculate a minimal clinically important difference (MCID) using a traditional anchor-based approach. We could however estimate this figure based on

Table 2
Distribution of individuals with FSHD according to genetic and clinical features.

#	Sex, Age (y)	Age at symptom onset (y)	D4Z4[a]	Frag size[b] (kb)	CSS[c] (0–5)	Age CSS	FCS[c] (0–15)	MFM[d] (0–96)	FSHD-COM Peds[c] (0–84)	6MWT (m)	WC use(FT/PT/N)
1	F, 7	5	2	12	1.5	429	6	93	35	525	N
2	M, 7	3	u	u	0.5	143	2	90	20	469	N
3	F, 9	9	u	u	1	222	2	94	18	561	N
4	M, 11	9	u	u	1	182	2	96	13	697	N
5	F, 12	12	6	21	1.5	250	4	95	20	585	N
6	M, 12	9	3	10	1.5	250	6	89	30	567	N
7	F, 12	7	5	17	1	167	3	90	18	422	N
8	M, 13	10	3	16	4	615	8	78	50	397	PT
9	M, 13	10	6	19	1	154	2	91	22	450	N
10	F, 13	4	9	30	1.5	231	5	83	39	402	PT
11	M, 14	11	4	13	2	286	4	95	26	664	N
12	M, 14	2	7	25	4	571	12	43	79	ua	FT
13	M, 14	7	7	23	1	143	2	96	5	787	N
14	M, 15	8	u	u	2	267	5	92	32	578	N
15	F, 15	3	3	10	4.5	600	13	51	72	ua	FT
16	F, 16	8	3	10	3.5	467	6	88	33	521	N
17	F, 16	7	4	14	2	250	5	91	28	627	N
18	M, 18	12	4	17	3	333	6	91	23	676	N

[a] – mean number of units with in D4Z4 repeat.
[b] – residual D4Z4 fragment size.
[c] – larger score indicative of poorer function.
[d] – larger score indicative of better function, # - participant number, F – female, M – male, CSS – FSHD Clinical Severity Scale, Age CSS – age corrected CSS, FCS – FSHD Clinical Score, *u* – unavailable, y – years, m – meters, ua – unable, WC – wheelchair, FT – full-time, PT – part-time, N – never.

the commonly reported 0.5 x standard deviation calculation [42]. The estimated MCID of 10 points (10%) on the FSHD-COM Peds and 8 points (11%) on the FSHD-COM from this study were with the estimated MCID of 10% reported by Eichinger et al. [8]. The calculated MDC of between 3 and 4 points for both measures, along with the estimated MCID, provides promising evidence that both versions of the FSHD-COM could effectively detect meaningful change. While this study provides evidence to support discriminant validity and change detection, it has not addressed the level of responsiveness of the FSHD-COM Peds and the FSHD-COM. The slowly progressive nature of FSHD limits the MFM-32′s ability to detect change over a 12 month period [43]. Further investigation of the responsiveness of the FSHD-COM Peds and the FSHD-COM is prudent to support their use in interventional studies in children and adults with FSHD. Availability of these data will also help determine if both versions of the FSHD-COM are required or if one could be used to measure function across the lifespan of FSHD.

Both versions of the FSHD-COM showed moderate to very strong correlations with other performance-based measures including FSHD severity scales, the PUL 2.0 and the MFM-32. During the administration of the distal hand dimensions of the PUL 2.0 and MFM-32, however, researchers noted that most participants could perform all items without compensation, achieving very high scores. Unlike the MFM-32 and the PUL 2.0, there is little emphasis on hand function assessment in the FSHD-COM measures, which only assess grip strength. Additional analysis also found that distal hand components of both measures correlate poorly with the FSHD-COM Peds and FSHD-COM, while all other dimensions correlated well. These results support the construct validity of both versions of the FSHD-COM as whole-body measures. The development of the FSHD-COM considered the most affected body regions, as reported by individuals with FSHD, and weighted the number of items included to evaluate those regions in the scale accordingly. The moderate correlation of both versions of the FSHD-COM with participant and proxy PedsQL^{TM}NMM, and the FSHD-HI Peds, indicates that these tools can evaluate the impact of physical function on patient perceived disease burden and quality of life. This evidence supports the use of these tools to measure both performance-based and self-reported constructs of physical function in childhood FSHD.

These results provide evidence supporting the reliability and construct (convergent and discriminant) validity of the FSHD-COM Peds and FSHD-COM in children with FSHD. The conversion of a raw score into a standardized

Table 3
Test re-test reliability of FSHD-COM pediatric and adult versions.

Tested Measures($n=15$)	ICC	CI 95%	SEM	CI 95%	MDC 90	CI 95%	MDC%	MDC 95	CI 95%	MDC%
FSHD-COM Peds	0.995	0.987–0.998	1.31	0.96–2.1	3.1	2.2–4.8	9.9	3.6	2.2–4.8	11.8
FSHD-COM	0.995	0.985–0.998	1.25	0.9–2.0	2.9	2.1–4.6	12.1	3.5	2.1–4.6	14.3

Abbreviations: FSHD-COM – facioscapulohumeral dystrophy composite outcome measure, Peds – pediatric, ICC – intraclass correlations, CI – confidence interval, SEM – standard error measurement, MDC – minimal detectable change.

Table 4
Correlation of the FSHD-COM Peds and FSHD-COM with comparator measures.

Comparator measures	FSHD-COM Peds		FSHD-COM	
	Spearman *r*	*p* - value	Spearman *r*	*p* - value
FCS	0.88	0.0001*	0.82	0.0001*
CSS	0.80	0.0001*	0.70	0.001*
CSS, age correction	0.81	0.0001*	0.73	0.0005*
MFM-32, total score	−0.75	0.0003*	−0.80	0.0001*
D1- stand/transfers	−0.71	0.001*	−0.74	0.0004*
D2 - proximal/axial	−0.78	0.0001*	−0.74	0.0005*
D3 - distal hand	−0.39	0.10	−0.44	0.07
PUL (2.0), total score [c]	−0.96	0.0001*	−0.94	0.0001*
Level 1 - high/shoulder	−0.94	0.0001*	−0.94	0.0001*
Level 2 - mid/elbow	−0.87	0.0001*	−0.87	0.0001*
Level 3 - distal/hand	−0.46	0.11	−0.37	0.22
PedsQL^{TM}NMM participant, total score [a]	−0.66	0.004*	−0.70	0.002*
D1 - NMD symptoms [a]	−0.76	0.0005*	−0.79	0.0002*
D2 - communication [b]	−0.74	0.002*	−0.72	0.003*
D3 - family resources [b]	−0.44	0.1*	−0.40	0.12
PedsQL^{TM}NMM proxy, total score	−0.67	0.003*	−0.63	0.006*
D1 - NMD symptoms	−0.73	0.0005*	−0.68	0.002*
D2 - communication	−0.18	0.48	−0.11	0.67
D3 - family resources	−0.54	0.02*	−0.54	0.01*
FSHD-HI Peds, total score	0.69	0.002*	0.60	0.008*
group 1 (shoulder and arm function)	0.70	0.002*	0.58	0.01*
group 2 (mobility and ambulation)	0.64	0.004*	0.60	0.009*
group 3 (fatigue)	0.60	0.008*	0.50	0.03*
group 4 (cognitive function)	−0.12	0.67	−0.12	0.63
group 5 (activity limitation)	0.66	0.003*	0.59	0.009*
group 6 (core strength and function)	0.46	0.06	0.37	0.13
group 7 (gastrointestinal function)	0.35	0.16	0.39	0.11
group 8 (social performance)	0.53	0.02*	0.45	0.06
group 9 (body image)	0.28	0.27	0.24	0.35
group 10 (hand and finger function)	0.58	0.01*	0.52	0.03*
group 11 (social satisfaction)	0.17	0.50	0.04	0.86
group 12 (pain)	0.58	0.01*	0.60	0.008*
group 13 (emotional health)	0.21	0.41	0.22	0.39
group 14 (communication)	0.66	0.003*	0.60	0.008*

Abbreviations: FSHD-COM – facioscapulohumeral dystrophy composite outcome measure, r – spearman rho, MFM – motor function measure, CSS – FSHD clinical severity (Ricci) scale, FCS – FSHD clinical (Lamperti) score, FSHD-HI Peds – FSHD health index paediatric version, PedsQL^{TM}NMM – pediatric quality of life neuromuscular module, PUL – performance of the upper limb 2.0, NMD – neuromuscular disease
$n = 18$.
[a] $n = 17$ completed D1 PedsQL^{TM}NMM participant.
[b] $n = 15$ completed D2/D3 PedsQL^{TM}NMM participant.
[c] $n = 13$ completed entire PUL, * significant $p < 0.05$.

scaled score in functional measurement instruments is a useful method of comparing participants' functional abilities. Scaled scores in the FSHD-COM are based on normative functional data collected in adults. The lack of sex and age matched data in the FSHD-COM Peds and FSHD-COM currently limits conversion of raw scores to scaled scores in a pediatric cohort. The inclusion of additional weight increments for the arm and shoulder items in the FSHD-COM Peds accommodates strength development expected as children grow. While modifications made to create the FSHD-COM Peds accommodate some age-related growth and maturation, the measure may benefit from further comparison of raw scores to a typically developing pediatric population by means of a *z*-score. Z-scores are used effectively in the CMTPedS, an instrument measuring function in Charcot Marie Tooth disease [44]. Normative data already exists for some items included in the FSHD-COM versions (6 min walk, 10 m walk/run, self-selected gait speed, grip strength, timed-up and go) [38,45–49]; however for other items (sit to stand, ascend/descend stairs, arm/shoulder, trunk function) normative reference values are needed. The availability of age-based reference values for all included items would enable refinement of scoring relating to age and further support validity of the FSHD-COM Peds when used to assess the function of children with FSHD.

While this single site study is one of the largest published cohorts of children with FSHD, the sample size remains small. Results therefore need to be considered with caution. The generalizability of results from this modest, yet fairly representative sample, would be enhanced by inclusion of younger children and those with more severe disease. While this study contributes to available intra-rater reliability,

measurement error and construct validity evidence, further research to support inter-rater reliability, generalizability to other settings and responsiveness is required.

Given the paucity of outcome measure research and development in children with FSHD, this work adds positively to available evidence. While additional testing and refinement is required, the use of the FSHD-COM Peds and FSHD-COM to evaluate physical function in children with FSHD shows significant promise.

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