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Review

Measurement properties and utility of performance-based outcome measures of physical functioning in individuals with facioscapulohumeral dystrophy – A systematic review and evidence synthesis

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Abstract

Access to reliable, valid, accurate and responsive outcome measures is essential to ensure standards of care and clinical trial readiness in facioscapulohumeral dystrophy. Review aims: 1. identify and provide a descriptive summary of all outcome measures used to measure physical function. 2. systematically appraise the evidence on measurement properties (reliability, construct validity, measurement error and responsiveness) of performance-based outcome measures of physical function in individuals diagnosed with facioscapulohumeral dystrophy. Selected electronic health-related databases were searched from inception - Feb 2019. Two authors independently screened studies for eligibility and extracted data for psychometric evidence. The methodological quality of outcome measure studies was appraised using the consensus-based standards for the selection of health measurement instruments (COSMIN) checklist. Of 12 identified outcome measures, four required high-technology equipment. Only three were FSHD specific. The FSH-clinical score had 'moderate' quality positive evidence for reliability. The remaining measures had 'low' to 'very low' quality evidence supporting properties of reliability, validity, responsiveness and measurement error. Identified studies tended towards low recruitment in middle-aged, ambulant individuals making results hard to generalise across lifespan and levels of severity. There is a paucity of measurement evidence supporting the use of outcome measures in people with facioscapulohumeral dystrophy.

Keywords: Facioscapulohumeral muscular dystrophy; Outcome measure; Motor activity; Systematic review.

1. Introduction

Individuals with facioscapulohumeral dystrophy report altered physical function, such as difficulty lifting objects, impaired walking, reduced balance, and the inability to alter facial expression [4]. Facioscapulohumeral dystrophy, or FSHD, is the third most common of the muscular dystrophies, with an estimated prevalence of 5–13 in 100,000 [5]. It is a slowly progressive condition with an often asymmetrical [6], heterogeneous presentation and variable severity even between affected individuals within the same family [6,7]. Risk of functional impairment is linked to age of symptom onset and underlying genetic factors [7]. Affected individuals commonly present initially with scapulohumeral and facial weakness; the development of truncal, pelvic and lower limb weakness correlates with a 23% risk of wheelchair dependence as the disease progresses [7].

No effective pharmacological or alternative treatments are currently available to alter the clinical course of FSHD. Recent success with genetic-based pharmaceutical treatments for other neuromuscular disorders, provide hope that similar advances will lead to clinical trials of new therapies in FSHD [8], however, until recently progress has been slow due to complex genetics, epigenetic variables and challenges

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in establishing a reliable disease model for FSHD [9]. Disease-specific outcome measures with strong measurement properties, able to accurately quantify functional change as a result of treatment or disease progression, are required not only for clinical trial planning but to ensure best practice in clinical care. In the past five years international FSHD experts have driven the development of new performance-based physical function outcome measures, self-reported health related questionnaires and innovative clinical trial research tools for this purpose [8,10]. Despite the drive to create sensitive disease specific outcome measures to quantify physical functioning in FSHD, to our knowledge there has not been a study summarizing the current status of outcome measures used to assess function in FSHD.

The selection of an outcome measure to quantify clinical progress or measure change from intervention requires careful consideration. Adequate knowledge of the methodological quality of measurement properties, including measurement error, reliability, validity and responsiveness, is required. Measurement constructs need to align with known impairments, activity limitations or participation restrictions quantified by the outcome measure, and the utility of the measure should suit the setting of intended use. The analysis of outcome measures under the International Classification of Functioning, Disability and Health (ICF) framework helps to identity the impairments, activity limitations and participation restrictions being quantified by a given measure [11].

The aim of this review was two-fold: 1) to identify and provide a descriptive summary of all outcome measures used to measure physical function performance and physical function related quality of life in FSHD; 2) to systematically appraise the evidence on measurement properties (reliability, construct validity, measurement error and responsiveness) of performance-based outcome measures of physical function in individuals diagnosed with FSHD. By outlining the levels of evidence for measurement properties and clinical utility (cost, time taken and interpretability) we hope to provide clinicians and researchers with valuable information to assist their choice of outcome measure when assessing physical functioning in individuals with FSHD.

2. Materials and methods

This systematic review was registered with the international prospective register of systematic reviews, PROSPERO https://www.crd.york.ac.uk/prospero/ (reference number: CRD42018092163) and reported according to the preferred reporting items for systematic reviews and meta-analysis (PRISMA) principles [12].

2.1. Search strategy

A comprehensive search strategy was generated by multiple authors in conjunction with a Medical Librarian using the PICO: Patient, Intervention, Comparison, Outcome format [13]. The search strategy was translated in the listed health-related electronic databases from inception until 8 February 2019: MEDLINE (OVID) 1946-present, MEDLINE (PubMed), CINAHL (EBSCO) 1937-present, Embase (OVID) 1947-present and reference lists of reviews and articles. Searches were restricted to English, human (not animal) studies and full text articles in peer-reviewed journals. Supplementary searches of the reference lists of relevant articles were also conducted. An example of the search strategy is provided in Appendix A. An initial search of electronic databases was undertaken by one reviewer (KdV), exported to a systematic review platform (Covidence 2018) and duplicates removed.

Table 1
Eligibility criteria of full text studies.

Inclusion criteria:	Exclusion criteria:
- Genetic diagnosis of FSHD - Mixed participant, data for a subgroup of FSHD is reported separately - The use or reporting of outcome measure/s assessing physical function (either performance-based or self-reported measures) - Identified outcome measure/s assess within the activity domain of ICF - Primary study - Full text published in a peer-reviewed journal	- Population not FSHD or <10% FSHD - FSHD data not reported separately in mixed cohort - No performance-based or self-reported outcome measure/s assessing physical function within the activity domain of ICF *(Performance-based measures should not be solely impairment measures example; joint range, strength, muscle length. Self-report measures should include ability to perform tasks/activities or ADLs and should not be measures of impairments {example; pain or depression})* - Not a primary study - No full text available - Not published in a peer-reviewed journal

ICF - International Classification of Functioning, Disability and Health framework, ADLs - activities of daily living.

2.2. Eligibility and exclusion criteria

Title and abstract screening for eligibility was performed by two independent reviewers (IW) and (KdV); full text screening for eligibility was performed by two independent reviewers (KdV and FD) using the criteria outlined in Table 1.

To address the two aims of the review, included studies were classified as those that: a) described any self-reported or performance-based outcome measures of physical function or aspect of quality of life reported in individuals with FSHD; b) described performance-based outcome measures with reported psychometric properties of reliability, validity, measurement error or responsiveness.

2.3. Collection of descriptive evidence and extraction and evaluation of psychometric evidence of outcome measure use

Descriptive data of outcome measures were extracted from identified studies into a customised form. Extracted data

included: the type of measure, scaling and scoring and clinical utility.

Psychometric data including reliability, validity, measurement error or responsiveness of performance-based outcome measures were identified and extracted into a customised, pre-piloted form. Two authors (KdV and FD) extracted data independently and any identified discrepancies were all resolved through discussion. Extracted information included: a) study characteristics; b) evidence supporting: reliability, internal consistency, independence of measure and measurement error; and c) evidence supporting: construct validity, interpretability and responsiveness.

2.4. Risk of bias assessment

Two authors (KdV and FD) independently appraised the methodological quality (risk of bias) of selected outcome measure studies using the consensus-based standards for the selection of health measurement instruments (COSMIN) checklist [14]. The COSMIN checklist is a standardised and validated tool designed to assess the quality of measurement properties including reliability, measurement error, validity and responsiveness. Each measurement property was rated on a number of items in a standardized manner, with the 'worst score counts' rating of an item within each measurement domain determining the overall score for that domain. The level of measurement evidence was also rated against predetermined criteria for 'good measurement properties' outlined in the COSMIN manual [15–17]. An overall rating of the level of evidence according to the categories of: sufficient (+), insufficient (-), inconsistent (±) or indeterminate (?) was determined for each outcome measure. Finally, the overall measurement evidence quality for an outcome measure was assessed using COSMIN's modified GRADE system, in which the quality of the body of evidence is assumed high and is then down-graded as defined by specific criteria (outlined in Appendix B and C) [15]. During this process any discrepancies were resolved by consensus.

3. Results

The search generated 857 studies after duplicate removal (Fig. 1). Of these studies, 29 met the criteria for extraction of descriptive data and 12 for data extraction of measurement property evidence [2,3,18–43].

3.1. Descriptive evidence of performance-based and self-reported outcome measures

Table 2 provides a summary of the 29 performance-based and 12 self-reported measures of physical function used to assess individuals with FSHD reported in the searched literature. Three FSHD disease-specific performance-based measures were identified (FSH-clinical severity score (CSS) or Ricci score, FSH-clinical score (FCS) or Lamperti score, FSH-composite outcome measure (FSH–COM)). No disease-specific self-reported measures were identified. The CSS, FCS [1,27,30,33,44–46], 6-minute walk test (6MWT) [19,20,22,26,28,30,33,41,44,45,47,48] and manual muscle testing (MMT) using modified medical research council (MRC) grading [1,26,27,30,33,35,41,42,44–46,49–51] were the most commonly reported performance-based measures. The short form health survey (SF-36) the most commonly used self-reported measure [20–22,26,29,37,43,44,47].

3.2. Measurement property evidence of performance-based outcome measures

3.2.1. Sample characteristics

Twelve studies investigated measurement properties of 14 different performance-based outcome measures used in an exclusive FSHD or mixed neuromuscular disease population (Table 3). Participant numbers per study were generally small (range 9–86). Ten of the 12 studies had less than 50 participants [1,45]. Nine studies reported participant age ranges spanning 6–89 years. Five studies included some children and adolescents (< 18 years) [1,50,52,53] and three included some older adults (>65 years) [1,45,54]. Eight studies included only ambulant individuals, two both ambulant and non-ambulant individuals [1,53] while functional status was not reported in two studies [52,55]. Four outcome measures- reachable workspace relative surface area analysis (RSA), the instrumented timed-up and go test (iTUG), biomechanical analysis (BA) and upper body movement analysis (UBMA) [46,49,51,55] - required high-technology equipment. The remainder were low-technology clinical measures. The Motor Function Measure (MFM) was the only measure to be examined in multiple studies [1,50,52,53].

3.2.2. Measurement property evidence

Eleven of the 12 studies were rated for evidence quality using the COSMIN risk of bias grading system. The study by Lue [56] was excluded, as COSMIN no longer includes interpretability in the risk of bias checklist. Of the 14 identified outcome measures, reliability was evaluated for 12 measures, measurement error for two, construct validity for six, discriminant validity, internal consistency and responsiveness for one measure. Tables 4 and 5 summarise the measurement properties of performance-based measures and the related COSMIN scores. The quality of evidence supporting the measurement properties assessed ranged from 'inadequate' to 'very good' with responsiveness of the MFM the only measurement property to receive an 'inadequate' rating using the COSMIN 'worst score counts' method. There was good agreement (85%) between reviewers when COSMIN items were rated independently for risk of bias, and any disagreements were easily resolved by discussion.

The level and overall methodological quality of evidence for each outcome measure has been summarised in Table 6. When rating the outcome measures for good measurement properties using COSMIN, the reliability of BA (step-up and level walking items) [49] and the responsiveness of the MFM [53] could not be determined from available

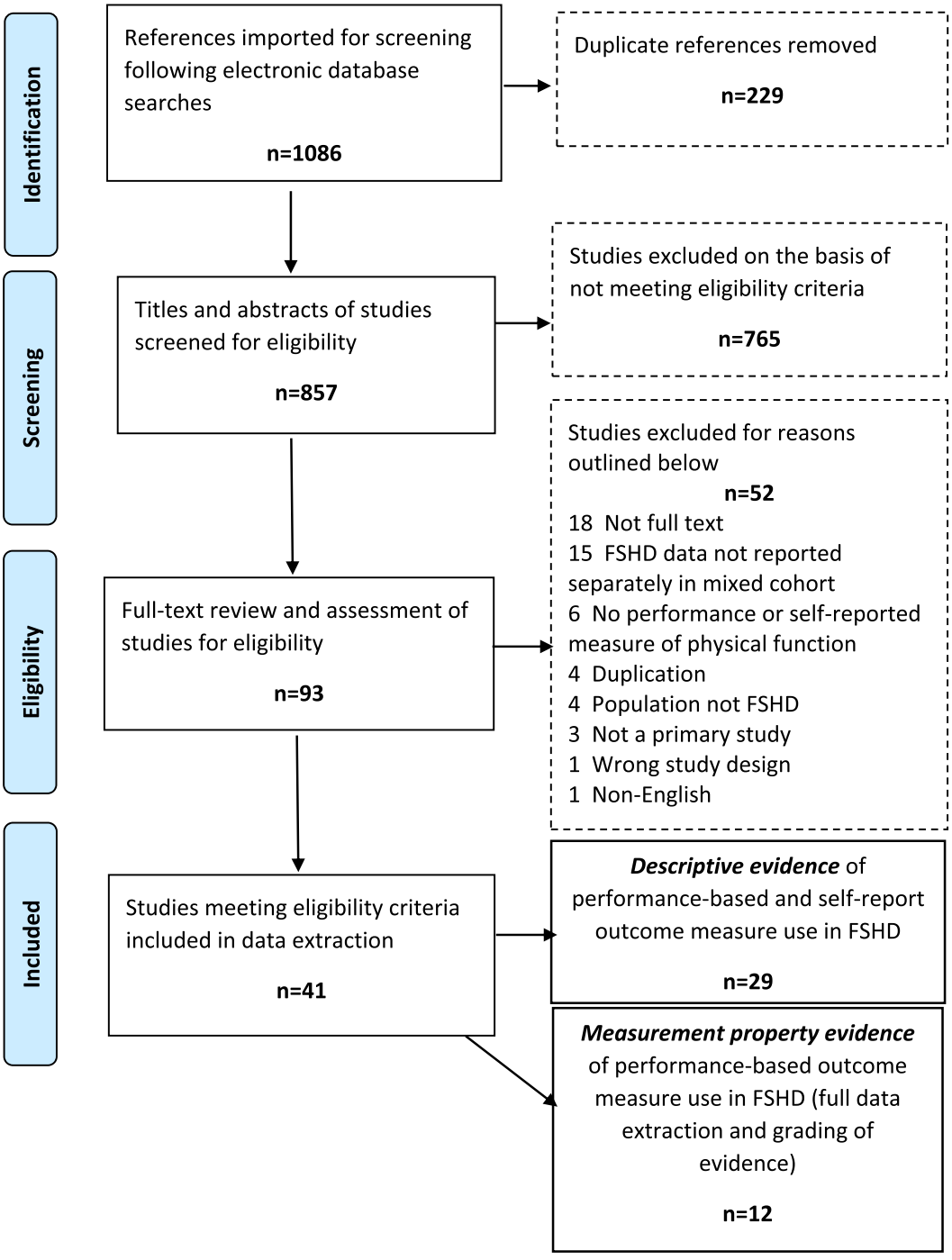

Fig. 1. PRISMA flow chart indicating results of search and screening process.

Table 2
Performance based and self-reported measures summary table.

Outcome measure	Times reported	Scoring	Time to complete (minutes)	No. of test items	Cost/equipment
Performance based measures					
Severity/ classification activity-based measures					
FSHD Clinical Severity Scale (CSS)	11	Ordinal (0–5) age correction	5 min	1 item scored	Free
FSHD Clinical Score (FCS)	8	Ordinal	5–10 min	6 items scored	Free
Brooke (upper extremity)	7	Ordinal (1–6)	5min	1 item scored	Free/minimal, easy to access equipment
Vignos (lower extremity)	5	Ordinal (1–10)	5 min	1 item scored	Free/minimal, easy to access equipment
Timed performance activity-based measures					
14 step stair test (14SST)	2	Time (sec)	2–3 min	1 timed test	Free/minimal, easy to access equipment
5 times sit to stand test (5TSTST)	2	Time (sec)	2–3 min	1 timed test	Free/minimal, easy to access equipment
6 min Walk Test (6MWT)	12	Distance (m)	6 −10 min	1 distance measured	Free/minimal, easy to access equipment
2 min Walk Test (2MWT)	2	Distance (m)	2–5 min	1 distance measured	Free/minimal, easy to access equipment
Walk Run Test (10MWRT/Go'30)	7	Time(sec)	1 min	1 timed test	Free/minimal, easy to access equipment
4 Stair Climb (4SC)	4	Time (sec)	1 min	1 timed test	Free/minimal, easy to access equipment
Timed up and go (TUG)	1	Time (sec)	1 min	1 timed test	Free/minimal, easy to access equipment
Stand from supine (SS)	1	Time (sec)	1 min	1 timed test	Free/minimal, easy to access equipment
Graded activity-based measures					
FSH-composite outcome measure (FSH–COM)	1	Ordinal (0–4) Timed components	35 min	18 items	Free/manual not available/some costly equipment
Motor Function Measure (MFM)	5	Ordinal (0–3)	8–75 min (average of 36 min)	32 items	Free score sheet & manual/ fee for training DVD/easy to access equipment
Antigravity tests (AGT)	1	Ordinal (0–4)	NR	4 items	Free/minimal, easy to access equipment/clinical experience
Functional tests (FT)	1	Mixed ordinal/ continuous	Total time NR	9 items	Some expensive equipment required/some training
Berg Balance Scale (BBS)	1	Ordinal (0–4)	10–20 min	14 items	Free/ minimal, easy to access equipment
Impairment-based measures					
Manual Muscle Testing (MMT)	14	Ordinal (0–5+)	–	–	Free/no equipment
Range of Motion (ROM)	2	Degrees (^{o})	–	–	Free/minimal easy to access equipment
Muscle testing (QMT/MVIC/HHM)*	6	Newton (N)/ kilogram(kgs)	–	–	Costly equipment/ training required
Higher technology activity-based measures					
Reachable workspace (RSA)	2	Meters^2 (m^2)	–	–	Costly equipment/training required
Actometer	1	Accelerations	–	–	Equipment required
Instrumented timed up and go test (iTUG)	1	Tim (sec)	Time NR	1 item	Costly equipment/ training required
Biomechanical analysis (BA)	1	Varied continuous	60 min	4 items	Costly equipment/ training required
Upper body movement analysis (UBMA)	1	ROM analysis Coefficient of attenuation	Time NR	1 item	Costly equipment/ training required
Upper Limb activity-based measures					
Performance of the upper limb (PUL)	1	Ordinal	10–20 min	23 items	Free score sheet & manual/standardised equipment required

(*continued on next page*)

Table 2 (*continued*)

Outcome measure	Times reported	Scoring	Time to complete (minutes)	No. of test items	Cost/equipment
Self-reported measures					
Upper limb function					
ABILHAND (plus)	3	Ordinal		27 items	Freely available
Activity limitations measure (ACTIVLIM)	1	Ordinal	5–10 min	18 items	Freely available
Capabilities of the Upper Extremity (CUE)	2	Ordinal	5–10 min	17 items	Freely available
Health and well being					
Short form health survey (SF-36)	9	Ordinal	5–10 min	36 questions (8 domains)	Freely available
Patient reported outcome measurement information system (PROMIS–57)	3	Ordinal	–	8 questions/ domain (7 domains)	Freely available
Individualized Neuromuscular QoL questionnaire (INQoL)	1	Ordinal	–	12 questions (3 domains)	Licence required
Quality of Life in Neurological Disorders (NeuroQoL)	1	Ordinal	–	45 questions	Licence required
EuroQoL	1	Ordinal/visual analogue	5–10 min	5 domains	Licence required
Sickness impact profile (SIP-136)	1	Ordinal	NR	136 questions (12 domains)	New version SIP-68 freely available
Kidscreen (52, 27, 10)	1	Ordinal	5–20 min	Up to 10 domains	Licence required/free for non-commercial use
Barthel Index (BI)	1	Ordinal	5 min	10 items	Freely available
Functional Independence Measure (FIM)	1	Ordinal	–	18 items	Costs associated with training

* QMT= quantitative muscle testing; MVIC= maximal voluntary isometric contraction; HHM= hand held myometry.

evidence. Measurement evidence did not support test re-test reliability of reachable workspace RSA [55], inter-rater reliability of MMT [1,50] and antigravity test (AGT) step-up and step-down items in individuals with FSHD. All remaining measures had positive evidence to support the measurement properties examined. The FCS was the only measure to receive a 'moderate' grade, with remaining measures receiving a 'low' to 'very low' grade for quality. Evidence was down-graded due to serious risk of bias (Appendix B) and imprecision (Appendix C). The COSMIN grading of evidence quality is affected by the risk of bias assessment, imprecision (relating to sample size), inconsistency (where multiple studies per outcome are reported) and indirectness of evidence (where studies are performed in mixed cohorts) [15–17]. The grading of inconsistency and indirectness was not considered, as data included single studies and FSHD cohort data was considered independently in mixed groups.

4. Discussion

To our knowledge this is the first review providing a descriptive summary of both performance-based and self-reported outcome measures assessing elements of physical function in individuals with FSHD. It is also the first to systematically synthesize the measurement property evidence of performance-based physical function outcome measures used in the FSHD population.

While FSHD is one of the more common muscular dystrophies, it remains a rare disease. This review reveals a paucity of quality evidence examining the measurement properties of performance-based outcome measures for this condition, with minimal reporting of measurement error or responsiveness. Low incidence rates of FSHD may compound adequate recruitment for measurement studies, influencing the low participant numbers and mixed participant cohorts found in this review. FSHD prevalence in children is estimated between 3–21% of the total FSHD population [5]. The 12 studies in this review included 364 individuals with FSHD, of which less than 5% of participants were under 18 years or above 70 years of age. Measurement property evidence for outcomes in children and older adults is currently not available. This review has identified a large gap in the literature supporting the use of physical function outcome measures across the life span of FSHD.

Although disease-specific outcome measures are used in other neuromuscular disorders such as Duchenne muscular dystrophy [57–61] and spinal muscular atrophy [62–65], only three performance-based disease specific measures were identified in this review. These included, the FCS, CSS and FSH–COM, all of which assess known activity limitations of individuals with FSHD. The CSS and FCS are most commonly reported and are consistently used to characterise function and disease severity. The CSS has the benefit of being able to correct for age at time of examination [3] however measurement property evidence supporting its use is unknown. The FCS has moderate quality evidence supporting its reliability but has limited evidence of validity, responsiveness and measurement error. The FSH–COM is a

Table 3
Study characteristics.

Author (Year) FSHD sample size (m/f) Mean age ± SD (range) Pop type (%FSHD in study)	Disease Severity (FSHD cohort)	Outcome measure (body domain, construct)	Activity	Measurement property assessed
Berard 2005 $n=39$ (f/NR) 87.1% Mixed NMD 12.9% FSHD	Global Clinical Impression 15% mild 54% mod 31% severe	Motor Function Measure - MFM *(Functional whole body strength)*	D1-stand/ transfers D2-axial/ proximal LL D3-distal limb function	Internal consistency Convergent validity Discriminant validity
Eichinger 2018 $n=41$ (f/15) 52.8 ± 11.9(22–70) yrs 100% FSHD	Ambulant Mean FCS: 7.1 ± 2.9(2–13)	FSHD Composite Outcome Measure - FSH–COM *(Functional whole body strength, exercise capacity, balance)*	Sit to stand; 6MWT; Self-select gait; 30′Go/ 10mwrt; 4 stair up/down; UL strength; Don/doff coat; Reach to floor; Sit-up; Spine to sit; Grip HHM; TUG	Intra rater reliability Measurement error Construct validity
Eichinger 2017 $n=86$ (f/36) 49.1 ± 15.2(18–84)yrs 100% FSHD	Ambulant Mean FCS: 6.4 (1–12)	6MWT *(Exercise capacity)*	Walking for 6 min	Test re-test reliability Measurement error Construct validity
Han 2015 FSHD $n=26$(f/12); CG: $n=27$(f/12) FSHD: f 45.9(24.4)yrs; m 51.1(18.0)yrs CG: f 40.5(22.5)yrs; m 45.3(15.0)yrs 49% FSHD	NR	Reachable workspace - RSA *(Functional upper limb strength)*	Reachable workspace relative surface area (RSA)	Test re-test reliability Construct validity
Huisinga 2017 $n=17$(f/10); 53.7 (32–67) yrs 100% FSHD	Ambulant Mean FCS: 6.7 (2–10)	iTUG *(Lower limb function and balance)*	Gait Balance	Test re-test reliability Construct validity
Iosa 2007 FSHD: $n=12$ (f/4); CG: $n=12$ (f/5) FSHD: (26–58) yrs; CG: (23–47) yrs 50% FSHD	Ambulant CSS: $n=5$ no LL weakness $n=7$ LL weakness	Bio-mechanical analysis - BA *(Functional upper/ lower limb strength)*	UL elevation Level walking Step up Squat angle	Inter-trial repeatability Construct validity
Iosa 2010 FSHD: $n=13$ (f/4); CG: $n=13$ (f/4) FSHD: 39±11 yrs; CG: 39±9 yrs 50% FSHD	Ambulant CSS 1–4 CSS>2, $n=8$	UBMA *(Trunk function during gait)*	Barefoot self-selected gait	Test re-test reliability
Lamperti 2010 $n=69$ (f/39) 16–89 yrs 100% FSHD	Ambulant/non-ambulant (56 FSHD sized, 13 normal alleles)	FSHD Clinical Score - FCS *(Functional whole body strength)*	Facial; Shoulder; Elbow/wrist; Leg; Pelvic girdle; Abdominal	Inter rater reliability
Lue 2009 $n=20$ (f/8); 35.5 ± 16.7(13–80) yrs 88.9% Mixed NMD 11.1% FSHD	Ambulant	Brooke Vignos *(Functional upper/ lower limb strength)*	Brooke UL Vignos LL	Interpretability
Personius 1994 FSHD: $n=32$ (f/NR); CG: $n=32$(f/NR) FSHD:36.1 ± 9.6(17–49)yrs CG: 35.8 ± 8.0 (23–50)yrs 50% FSHD	Ambulant	Functional Tests - FT *(Functional and impairment-based whole body strength)*	MMT (Modified MRC); QMT; Grip/pinch HHM; 4 stair-climb; 30′Go; Drink 180 ml; Brooke UL; Vignos LL	Intra rater reliability Inter rater reliability
Rijken 2015 FSHD: $n=9$ (f/2); CG: $n=10$(f/NR) FSHD: 52±8 yrs; CG: 53±9 yrs 47% FSHD	Ambulant CSS range: 3($n=4$); 3.5 ($n=1$); 4 ($n=3$); 4.5 ($n=1$)	Antigravity Tests - AGT *(Functional lower limb strength)*	Step-up Step-down Sit-stance Stance-sit	Inter rater reliability Construct validity
Vuillerot 2012 $n=17$ (f/7); 37(8–59) yrs 88.9% Mixed NMD 11.1% FSHD	Ambulant $n=14$ Non-ambulant $n=3$ Mean: Vignos3.2(2); Brooke2.8(3)	Motor Function Measure - MFM *(Functional whole body strength)*	D1-stand/ transfers D2-axial/ proximal LL D3-distal limb function	Responsiveness

n= sample size; m/*f*= males/females; *f*= number of females; CG= control group; UL= upper limb; HHM= hand held myometry; 6MWT= 6 min walk test; TUG= timed up and go test; 30′Go= 30 foot walk run test; 10MWRT= 10 m walk run test; NR= not reported; iTUG= instrumented timed up and go; NMD= neuromuscular disease; *D*= dimension; LL= lower limb; CSS= clinical severity scale; MMT= manual muscle test; QMT= quantitative muscle testing; ADL= activities of daily living; UBMA= upper body movement analysis; ROM= range of motion.
The expanded version of Table 3 including measurement scale and clinical utility of outcome measures is available, see supplementary table S1.

Table 4
Results of measurement properties of performance-based measures (reliability and measurement error).

Outcome measure	Reliability						Measurement error	
	n	Design	Results	C score	Internal consistency	C score	Results	C score
FSH–COM (Eichinger 2018)	32	intra-rater ≤3 weeks	ICC (liner mixed effects): Total: 0.96 (95% LCL 0.92) sub-scale scores: 0.90–0.94 (95% LCL 0.80–0.88)	A	α 0.79 (0.70–0.80)	D	MDC90 9.3%, 6.67pts	A
iTUG (Huisinga 2017)	14	test re-test ≤ 2 weeks	ICC (linear mixed effects): 0.99; 0.84–0.99 (95% LCL not reported)	A	–	–	–	–
BA level walking (Iosa 2007)	12	inter-trial repeatability	CMC hip, knee, ankle joint kinematics - 0.99, 0.98, 0.94 kinetic - 0.58, 0.71, 0.98	V	–	–	–	–
BA step-up (Iosa 2007)	12	inter-trial repeatability	CMC hip, knee, ankle fl/ext angles: 0.95,0.92, 0.82 fl/ext moment:0.43,0.60, 0.72	V	–	–	–	–
FCS (Lamperti 2010)	69	inter-rater same day	ƙ 0.77 (95% LCLM not reported)	V	–	–	–	–
AGT step-up (Rijken 2015)	9	inter-rater same day/time	Fleiss ƙ 0.65 ($P<0.001$); absolute agreement 72%	D	–	–	–	–
AGT step-down (Rijken 2015)	9	inter-rater same day/time	Fleiss ƙ 0.67 ($P<0.001$); absolute agreement 68%	D	–	–	–	–
AGT sit-stance (Rijken 2015)	9	inter-rater same day/time	Fleiss ƙ 0.85 ($P<0.001$); absolute agreement 89%	D	–	–	–	–
AGT stance-sit (Rijken 2015)	9	inter-rater same day/time	Fleiss ƙ 0.81 ($P<0.001$); absolute agreement 84%	D	–	–	–	–
6MWT (Eichinger 2017)	25	test re-test < 3weeks	ICC (model not reported): 0.99; (95% LCL 0.98)	A	–	–	MDC 95 34.3m	A
Reachable work space RSA (Han 2015)	8	test re-test same day, hours later	$r=0.952$ ($P<0.0001$)	D	–	–	–	–
FT MMT (Personius 1994)	32	intra-rater, 3 trials in 3 consec days	wƙ 0.79–0.98 (95% LCL not reported)	A	–	–	–	–
	6	inter-rater, 2 consec days	wƙ 0.50–1.0 (95% LCL not reported)	A	–	–	–	–
FT QMT (Personius 1994)	32	intra-rater, 3 consec days	ICC 1,1: 0.85–0.99 (95% LCL not reported)	A	–	–	–	–
	6	inter-rater, 2 consec days	ICC 2,1: 0.85–0.99 (95% LCL not reported)	A	–	–	–	–
FT grip (Personius 1994)	31	intra-rater, 3 consec days	ICC 1,1: 0.94–0.97 (95% LCL not reported)	A	–	–	–	–
FT pinch grip (Personius 1994)	22	intra-rater, 3 consec days	ICC 1,1: 0.95–0.97 (95% LCL not reported)	A	–	–	–	–
FT straw drink (Personius 1994)	32	intra-rater, 3 consec days	ICC 1,1: 0.63 (95% LCL not reported)	A	–	–	–	–
UBMA range of motion analysis (Iosa 2010)	13	test re-test inter-trial within same session	ICC 2,1: head: AP 0.74, ML 0.94, V 0.66; shoulder: AP 0.77, ML 0.95, V 0.84; pelvis: AP 0.84, ML 0.81, V 0.80 (95% LCL not reported)	A	–	–	–	–
UBMA coefficient of attenuation (Iosa 2010)	13	test re-test inter-trial within same session	ICC 2,1: pelvis to head: AP 93, ML 0.85, V 0.78; shoulder to head: AP 0.80, ML 0.74, V 0.73; pelvis to shoulder: AP 0.95, ML 0.82, V 0.75 (95% LCL not reported)	A	–	–	–	–

n= sample size; - =not reported; COSMIN= consensus-based standards for the selection of health measurement instruments; C score= COSMIN score; *V*=very good, *A*=adequate; *D*=doubtful; *I*=inadequate; ICC= intra class correlation; LCL= lower confidence limit; CMC= co-efficient of multiple correlation; MDC= minimal detectable change; fl/ext= flexion/extension; *w*ƙ= weighted kappa; α = Cronbach's alpha; ƙ= kappa; *r*= pearson correlation co-efficient; iTUG= instrumented timed up and go; FSH–COM= FSH composite outcome measure; MFM= motor function measure; FCS= FSH-clinical score; BA= biomechanical analysis; AGT= anti-gravity tests; RSA= relative surface area; FT= functional tests; MMT= manual muscle tests; 6MWT= 6 min walk test; QMT= quantitative muscle testing; UBMA= upper body movement analysis; AP= antero-posterior; ML= medio-lateral; *V*= vertical.

Table 5
Results of measurement properties of performance-based measures (validity).

Outcome measure	Validity			
	n	Design	Result	C score
FSH–COM (Eichinger 2018)	41	construct validity	+ive corr with years since diagnosis $r=0.63$, $P=0.001$; - ive corr with SF36-P $r=-0.63$, $P<0.0001$; MMT $r=-0.91$, $P<0.0001$; FDI physical $r=-0.43$, $P=0.005$	A convergent/ discriminant
	40	construct validity	+ive corr with FCS $r=0.89$, $P<0.0001$ 1 point increase on FCS=4.3 point increase on FSH–COM, 95% CI [3.5, 5.2]	A convergent/ discriminant
	31	construct validity	+ive corr with PROMIS_57 PF $r=0.75$, $P<0.001$; - ive corr with QMT standard score $r=-0.77$, $P<0.0001$	A convergent/ discriminant
iTUG (Huisinga 2017)	17	construct validity	+ive corr with FCS $r=0.79$, $P<0.01$, MMT $r=-0.72$, $P<0.01$, PROMIS_57 PF $r=-0.58$, $P=0.01$	A convergent/ discriminant
MFM (Berard 2005)	39	discrim-inant validity	Total score and sub-scores: good discrimination between diagnosis groups (ANOVA $F^{7.295}=29.1$, $P<0.0001$), mean scores decreased with increased motor disability	V convergent A discriminant
BA ul elevation (Iosa 2007)	12	construct validity	- ive corr of sh ABD with disease duration $r=-0.65$, $P<0.05$; sh horiz ABD with FCS $p=-0.61$, $P<0.05$ and disease duration: $r<-0.59$, $P<0.05$	V convergent/ discriminant
BA level walking (Iosa 2007)	12	construct validity	Correlation of WS with disease duration $r=-0.77$, $P<0.01$; lower df at foot strike with TA MRI-score $P=-0.47$, $P=0.02$; lower max hip extension angle with hip extensor MRI-score $p=0.41$, $P=0.04$	V construct/ discriminant
BA step-up (Iosa 2007)	12	construct validity	+ive corr of time step-up with disease duration (non- self-selected leg) $r=0.59$, $P=0.05$.; - ive corr of df angles with TA MRI-score $p=-0.63$, $P<0.01$. Peak-to-peak hip & ankle sagittal moments of leading limb and the peak-to-peak ankle moments of trailing limb correlated with trunk A-P ROM $r=0.46$, $r=0.45$, $r=-0.63$, $P<0.05$	V construct/ discriminant
BA squat (Iosa 2007)	12	construct validity	Patient centre of mass vertical displacement correlation with mean MRI knee-score $p=-0.61$, $P<0.01$ and disease duration $r=-0.58$, $P=0.05$	V convergent/ discriminant
AGT step-up (Rijken 2015)	9	construct validity	+ive corr with AGT step-down $p=0.90$; sit-stance $p=0.87$; stance-sit $p=0.89$, $P<0.01$; No corr with: 6MWT $p=0.59$; 10MWRT $p=0.52$; BBS $p=0.61$; TUG $p=-0.62$, $P<0.01$	A convergent/ discriminant
AGT step-down (Rijken 2015)	9	construct validity	+ive corr with AGT step-up $p=0.90$; sit-stance $p=0.89$; stance-sit $p=0.91$, $P<0.01$ No corr with CTs: 6MWT $p=0.53$; 10MWRT $p=0.47$; BBS $p=0.70$; TUG $p=-0.61$, $P<0.01$	A convergent/ discriminant
AGT sit-stance (Rijken 2015)	9	construct validity	+ive corr with AGT: step-up $p=0.87$; step-down $p=0.89$; stance-sit $p=0.83$, $P<0.01$; No corr with: 6MWT $p=0.54$; 10MWRT $p=0.54$; BBS $p=0.67$; TUG $p=-0.59$, $P<0.01$	A convergent/ discriminant
AGT stance-sit (Rijken 2015)	9	construct validity	+ive corr with AGT: step-up $p=0.89$; step-down $p=0.91$; sit-stance $p=0.83$, $P<0.01$; Corr: 6MWT $p=0.81$; 10MWRT $p=0.72$; BBS $p=0.70$; TUG $p=-0.83$, $P<0.01$	A convergent/ discriminant
6MWT (Eichinger 2017)	38	construct validity	- ive corr with FCS $p=-0.57$, $P<0.0001$	A convergent/ discriminant
	48	construct validity	- ive corr with TUG $p=-0.81$, $P<0.0001$	A convergent/ discriminant
	50	construct validity	- ive corr with 30′Go/10MWRT $p=-0.83$, $P<0.0001$	A convergent/ discriminant
	35	construct validity	+ive corr with LL MMT scores $p=0.79$, $P<0.0001$; LL strength accounted for 47% variability in 6MWT distance ($R^2=0.47$, $P<0.0001$)	A convergent/ discriminant
Reachable workspace RSA (Han 2015)	52	construct validity	Corr of normalised% predicted HHM with RSA: FSH group: +ive elb F $r=0.528$, $P<0.0001$; combined elb F/sh ABD $r=0.477$, $P=0.0003$; no correlation for sh ABD $r=0.094$, $P=0.508$; FSH/CGroup: +ive elb F $r=0.664$, $P<0.0001$; sh ABD $r=0.479$, $P<0.0001$, combined elb F/sh ABD $r=0.675$, $P<0.0001$	A convergent V discriminant

- =not reported; *n*= sample size; COSMIN= consensus-based standards for the selection of health measurement instruments; C score= COSMIN score; *V*= very good, *A*= adequate; *D*= doubtful; *I*= inadequate; +ive corr= positive correlation; - ive corr= negative correlation; SF36-*P*=36 item short form health survey-physical sub-scale; FSH= facioscapulohumeral dystrophy, FCS= FSH-clinical score; FSH–COM= FSH-composite outcome measure; iTUG= instrumented timed up and go; UL= upper limb; MFM= motor function measure; BA= biomechanical analysis; AGT= anti-gravity tests; FT= functional tests; FDI= facial disability index; MMT= manual muscle testing; QMT= quantitative muscle testing; *r*= pearson's correlation; *p*= spearman rank correlations; BA= biomechanical analysis; sh ABD= shoulder abduction; sh horiz ABD= shoulder horizontal abduction; PROMIS_57 PF=patient-reported outcomes measurement information system (physical function sub-scale); WS = weight shift; df= dorsiflexion; TA= tibialis anterior; MRI= magnetic resonance imaging; A-P ROM= antero-posterior range of motion; 10MWRT= 10 m walk run test; 30′Go= 30 foot walk run test; 6MWT= 6 min walk test; LL= lower limb; elb *F*= elbow flexion; HHM= hand held myometry; CGroup= control group; RSA= reachable workspace relative surface area; UBMA= upper body movement analysis; AGT= antigravity tests; CT= conventional tests; BBS= berg balance scale; TUG= timed up and go.
The expanded version of Table 5 containing responsiveness and interpretability data is available, see supplementary table S2.

Table 6
Overall rating and quality of measurement evidence for each outcome measure organised in hierarchy of moderate, low and very low quality evidence.

Outcome Measure	Reliability[1]				Measurement error[2]				Construct validity[3]				Internal consistency[4]				Responsiveness[5]			
	COSMIN	n	Rating	Quality	COSMIN	n	Rating	Quality	COSMIN	n	Rating	Quality	COSMIN	n	Rating	Quality	COSMIN	n	Rating	Quality
Moderate (M) quality																				
FCS	V	69	+	M																
Low (L) quality																				
BA level walk	V	12	?	L					V	12	+	L								
BA step-up	V	12	?	L					V	12	+	L								
BA ul elevate									V	12	+	L								
BA squat									V	12	+	L								
Low (L) / Very Low (VL) quality																				
FSH-COM	A	32	+	VL	A	32	+	VL	A	41	+	VL	D	32	+	VL				
6MWT	A	25	+	VL	A	25	+	VL	A	51	+	L								
RSA	D	8	-	VL					A	52	+	L								
MFM									A	39	+	VL					I	17	?	VL
FT QMT	A	32	+	VL																
FT MMT	A	32	+intra -inter	VL																
FT hand grip	A	31	+	VL																
FT pinch grip	A	22	+	VL																
FT straw-drink	A	32	-	VL																
iTUG	A	14	+	VL					A	17	+	VL								
AGT step-up	D	9	-	VL					A	9	+	VL								
AGT step down	D	9	-	VL					A	9	+	VL								
AGT sit-stance	D	9	+	VL					A	9	+	VL								
AGT stance-sit	D	9	+	VL					A	9	+	VL								

FCS= FSH-clinical score; BA= biomechanical analysis; UL= upper limb; 6MWT= 6 min walk test; RSA= reachable workspace relative surface area; FT= functional tests; MMT= manual muscle tests; QMT= quantitative muscle testing; UBMA= upper body movement analysis; AGT= anti-gravity tests; FSH–COM= FSH-composite outcome measure; MFM= motor function measure; iTUG= instrumented timed up and go; *n*= sample size; ICC= intraclass correlation coefficient; AUC= area under the curve; LoA= limits of agreement; MIC= minimal important change; SDC= smallest detectable change; intra= intra-rater; inter= inter-rater; COSMIN= consensus-based standards for the selection of health measurement instruments. *COSMIN 'risk of bias' score*: *V*= very good; *A*= adequate; *D*= doubtful; *I*= inadequate. *Quality grade: M*= moderate; VL= very low; *L*= low. *Measurement property rating:* (+) sufficient; (-) insufficient; (?) indeterminate.

Criteria for measurement property rating:

[1] (+) ICC > 0.7; (-) ICC < 0.7 (?)ICC not reported.

[2] (+) SDC or LoA < MIC; (-) SDC or LoA > MIC; (?) MIC not defined.

[3] (+) Result is in accordance with the hypothesis; (-) Result is not in accordance with the hypothesis; (?) No hypothesis defined.

[4] (+) At least low evidence for sufficient structural validity AND Cronbach's alpha(s) ≥ 0.70 for each unidimensional scale or subscale; (-) At least low evidence for sufficient structural validity AND Cronbach's alpha(s) <0.70 for each unidimensional scale or subscale; (?) Criteria for "At least low evidence for sufficient structural validity" not met.

[5] (+) The result is in accordance with the hypothesis OR AUC ≥ 0.70; (-) The result is not in accordance with the hypothesis OR AUC <0.70; (?) No hypothesis defined (by the review team).

newly developed measure encompassing most body domains, has multiple constructs, includes items with associated norm reference values (ie. 6MWT, TUG, self-selected gait speed and hand grip myometry) and has one published study examining its measurement properties [44]. Currently, there is a small amount of evidence to support the measurement properties of reliability, construct validity and measurement error and no evidence to support responsiveness. There is limited evidence for use of the FSH–COM in children, older adults and non-ambulant individuals with FSHD. Further research is required to evaluate its place in clinical research. While no FSHD-specific measures of participation were identified, a study by Johnson and colleagues discussed the development process of a FSHD health index (FSH–HI) [4]. The FSH–HI has since been developed as a measure of disease burden. No data reporting its measurement properties are yet available.

Understanding the spectrum of severity in individuals with FSHD is important in appropriate outcome measure selection. Age of symptom onset and genetic factors increase the risk of an individual requiring assisted devices such as a wheelchair [7]. Of the outcome measures examined in this review, the FCS and MFM were the only measures used to assess both ambulant and non-ambulant individuals with FSHD. As it is performed in a seated position, one would assume that the reachable workspace RSA measure outlined by Han and colleagues could be used to evaluate upper limb function in non-ambulant individuals. Disease severity and the mobility status of participants was not reported in this study [55]. Weakness and reduced function of the shoulder girdle are early signs of FSHD which often precede the loss of lower limb function. While reachable workspace RSA may be an appropriate measure of upper limb function in non-ambulant individuals, the utility of the measure may be limited in those with more severe muscle weakness.

When selecting a performance-based outcome measure of physical function, consideration should be paid to the robustness of its psychometric properties, while also ensuring the construct/s and body domain/s being measured match the desired purpose. Clinical utility (time to complete, cost, equipment or training required) and the environment of use are additional considerations. High-technology outcome measures are likely more complex, expensive and have greater utility in a research setting. Low-technology, less complex measures require less equipment and are more clinically appropriate. This review identified a mix of high and low technology measures. Outcome measures with higher technology requirements tended to address single constructs in fewer body domains (reachable workspace RSA, iTUG, BA, UBMA). Low technology measures assessed multiple body domains and constructs within the same measure (MFM, FSH–COM, AGTs, FCS, and FTs). The FSH–COM was the only measure to include all body domains (besides the face) and multiple constructs, including functional strength, impairment-based strength, exercise capacity and balance. The clinical utility of the FSH–COM means it can be completed in 35 min, without specialised training and requires easy to access equipment, apart from a hand grip myometer. High-technology measures require more complex analysis of detailed movement data whereas the MFM, FSH–COM and FCS generate easy-to-interpret results which can be assessed for change over time. There is currently no gold standard outcome measure to measure physical function in FSHD. Clinicians and researchers should consider available evidence, utility and general characteristics when selecting the most appropriate outcome measures to match their purpose.

The strength of this review includes the use of the updated 2018 version of COSMIN, a robust tool designed to grade and rate evidence for outcome measures. However, the use of COSMIN could also act as a limitation in this study. As COSMIN is designed to rate patient-reported outcome measures, there may be a risk of bias rating for performance-based measures. The exclusion of non-English papers, generalisability of search strategy and publication bias could also be limiting factors in this review. The construction of a comprehensive search strategy with a medical librarian and use of a standardised systematic review methodology helped to minimise these limitations.

5. Conclusions

The review used well-established systematic review methodology to provide a comprehensive summary to assist researchers and clinicians in selecting outcome measures to measure physical function in FSHD. This review demonstrates that there are very few studies examining the measurement properties of outcome measures of physical function in individuals with FSHD, with sparse evidence supporting their use in children, adolescents, older adults and those with severe physical function limitations. Despite the lack of measurement property evidence for these outcome measures, they have been used to quantify change in clinical trials in FSHD. This study supports the goal of international experts to evaluate the measurement properties of already established and novel outcome measures and address the gap in measures available to evaluate the spectrum and severity of FSHD across the lifespan [8].

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.nmd.2019.09.003.

Abbreviations

FSHD	facioscapulohumeral dystrophy
FSH-COM	facioscapulohumeral composite outcome measure
FCS	facioscapulohumeral clinical score [1]

CSS	facioscapulohumeral clinical severity scale [2, 3]
MFM	motor function measure
MMT	manual muscle testing
BA	biomechanical analysis
RSA	relative surface area
FT	functional testing
AGT	antigravity tests
TUG	timed up and go
UBMA	upper body movement analysis
COSMIN	consensus-based standards for the selection of health measurement instruments

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