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The Dutch registry for facioscapulohumeral muscular dystrophy: Cohort profile and longitudinal patient reported outcomes

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ABSTRACT

Facioscapulohumeral dystrophy (FSHD) is the second most prevalent inherited muscular disorder and currently lacks a pharmaceutical treatment. The Dutch FSHD Registry was initiated in 2015 as a result of an international collaboration on trial readiness. This paper presents the cohort profile and six years of follow-up data of the registered FSHD patients. At the time of self-registration and every six months thereafter, participants were invited to complete a digital survey of patient and disease characteristics and the Dutch versions of the Checklist Individual Strength (CIS20R), the Individualised Neuromuscular Quality of Life Questionnaire (INQoL), the Beck Depression Index – Primary Care and the McGill Pain Questionnaire. From March 2015 to March 2021, 373 participants completed at least one survey. At baseline, fatigue and muscle weakness were the most frequently reported symptoms (median CIS20R sumscore 77 [IQR 60-92], median INQoL Fatigue score 58 [IQR 42-68] and median INQoL weakness score 58 [IQR 42-68]). Pain was experienced most often in the head and shoulder region (193, 52%). Nineteen of the 23 (sub)sections of questionnaires showed no significant changes over time. We conclude that the Dutch FSHD Registry was successfully set up, enabling collection of longitudinal data and facilitating recruitment in several studies.

1. Introduction

Facioscapulohumeral dystrophy (FSHD) is a muscular disorder with a wide variability in clinical symptoms, disease progression and functional impairments. Usually, the first symptoms develop in the second decade of life. Approximately 10% of patients present with an infantile onset, where the disease manifests before age 10 [1]. In general, patients experience weakness of facial, shoulder and upper extremity muscles and gradually weakness of the trunk and leg muscles will develop. In late adulthood, approximately 20% of the FSHD patients use a wheelchair in daily life (this is 40% in infantile-onset patients) [1,2]. Although FSHD is one of the most common inherited myopathies in western countries, it is still classified as a rare disease with a prevalence of <1/5,000 and an estimated incidence of 0.3/100,000 person-years [3–5].

Currently, no curative treatment for FSHD is available. Management of the disease consists of symptomatic therapy such as cognitive behavioural therapy, physical, occupational and speech therapy, aerobic training and adequate pain medication [6,7]. The increase in pathophysiological knowledge of the disease enables the development of novel therapies for FSHD. A surge of new potential medications has arrived of which the first one reached a phase III trial. It is expected that the number of clinical trials will increase quickly in the near future [8–10]. FSHD registries were set-up across various countries to support these upcoming clinical trials [11,12].

Fast and selective recruitment of patients with FSHD is crucial in order to run successful and well-powered trials in this small patient population. Registries are of great value in this process as they provide access to a large number of FSHD patients. Furthermore, the prospective, longitudinal data collected within these registries are valuable to gain insight in the natural history of FSHD, clinical subtypes and genotype-phenotype associations, and may be helpful in selecting outcome measures that are sensitive to change [13].

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This study describes the cohort profile of the Dutch FSHD Registry participants registered between March 2015 and March 2021. Furthermore, longitudinal patient reported outcome measures on fatigue, quality of life, mental status and pain were analysed. Lastly, the studies that made use of the Dutch FSHD registry were reported.

2. Methods

2.1. Registration and recruitment

The Dutch FSHD Registry started in the spring of 2015 by launching the website www.FSHDregistratie.nl. Registration of patients has continued ever since. Patients with FSHD can register themselves or their child by following the guidelines on the website. All forms and questionnaires are in the Dutch language. Foreign/non-Dutch-speaking patients are encouraged to find a registry in their country of residence and/or in a language they master. Genetic confirmation is not obligatory.

Treating physicians and/or the genetic lab are requested to provide the genetic test result of registered patients if permission is provided. Gathering data on genetic information is an ongoing process. Physicians, researchers, nurses and other health care professionals involved, repeatedly encourage FSHD patients to take part in the FSHD Registry. In addition, starting from 2019 onwards, information about the FSHD Registry is provided as standard practice when patients receive genetical confirmation of the disease. Patient advocacy group representatives also play an important role by informing FSHD patients about the FSHD Registry and its significance.

2.2. Governance and data access

The FSHD Registry is a collaboration of four parties: The Dutch Association of Neuromuscular Diseases (a nationwide patients association), the Dutch FSHD Foundation (fundraising organisation), Leiden University Medical Center, and Radboud University Medical Center (Radboudumc). The latter two are academic referral centres for FSHD and form the FSHD Expertise Center in the Netherlands. The ownership of the registry is delegated by these parties to Radboudumc. Its daily management and maintenance is carried out by a registry curator (JCWD). A steering committee for the FSHD Registry was installed by the four collaborating parties and consists of delegates from the parties and a fifth independent rehabilitation physician. The committee decides on requests for data access and study recruitment. Requests can be made by filling in a form available on the website. Contact information and pseudonyms of registered patients are stored in a separate secured location accessible only by the registry manager and a backup manager. Research data are stored in Castor, a secured electronic data capture system operated by Radboudumc.

2.3. Ethical Approval

The Registry, and the analysis of longitudinal patient reported outcome measures, involve medical research that do not fall within the scope of the Medical Research Involving Human Subjects Act, as declared by the local Medical Ethics Review Committee of the Radboudumc (amendment of file 2015-1812 on April 15th 2020). All participants of the FSHD registry provided their written informed consent before they entered the registry. The registry and its databases are in concordance with the General Data Protection Regulation and all other acting laws.

2.4. Study design

This study was a prospective cohort study. At the time of registration and every subsequent six months, participants received a digital survey invitation. Data collection ran from March 2015 to March 2021. Participants $<$16 years old could be registered, either by or with consent of their parents. However, the number of registered minors was limited, and they completed a different set of questionnaires. Therefore, these data were not included in this study. All registered Dutch FSHD patients aged $\geq$16 years old who completed at least one survey were included in this study.

2.5. Questionnaires

The surveys consisted of five Dutch questionnaires: a questionnaire on FSHD disease characteristics in accordance with the global FSHD registry framework, the Checklist Individual Strength (CIS20R), the Individualised Neuromuscular Quality of Life Questionnaire version 1 (INQoL), the Beck Depression Inventory for Primary Care (BDI-PC), and the McGill Pain Questionnaire – Dutch Language Version (MPQ-DLV) [14–18].

The global FSHD registry framework items included questions about demographics, diagnosis, muscle weakness and its time of onset, best motor function, presence of specific comorbidities like retinal vascular disease, hearing loss, retardation and epilepsy, use of (non-)invasive ventilation and FSHD family history.

The CIS20R measures four dimensions of fatigue and consists of 20 questions with a seven-point Likert scale answer option (1-7). The total CIS20R score ranges from 20-140 points with 20 meaning no symptoms and 140 meaning severe symptoms. The CIS20R can be divided into four subsections: ‘Fatigue’ containing eight items (score range 8-56), ‘Concentration’ with five items (score range 5-35), ‘Motivation’ with four items (score range 4-28) and ‘Activity’ with three items (score range 3-21).

The INQoL measures quality of life and consists of ten subsections with questions on a seven-point Likert scale (0-6 or 1-7). The answers of the subsections are combined and converted to a 0-100% score, with 0% meaning no symptoms and 100% severe symptoms. In total, the INQoL consists of twelve different subscores.

The BDI-PC measures the severity of depression symptoms, consisting of seven questions with four answer options ranging from zero to three points for a possible total of 21 points. A value of $\geq$4 on the BDI-PC has a sensitivity and specificity of 82% for identifying patients with a major depressive disorder [16].

The MPQ-DLV measures pain symptoms and is divided in three subsections. In the first part, participants are asked to indicate where they experience pain and characterize the pain in more detail. In the second part, participants are asked to enter their current, minimum and maximum pain on a visual analogue scale (VAS), which is converted to a 0-10 score. The third part consists of a list of words that describe pain in increasing severity divided in 20 categories. Participants need to indicate which words describe their pain experience best. The third part results in the number of words chosen (NWC-T) ranging from 0-20, and the severity of the pain expressed as the Pain Rating Index (PRI-T), ranging from 0-36. Generally, a high NWC-T or PRI-T means a high burden of pain.

2.6. Data availability and statistical analysis

Incomplete surveys were excluded from analysis. The first completed survey was considered the baseline survey. Baseline data were reported as the median [IQR] value because some questionnaires did not show normally distributed data. Normality of data was determined via visual evaluation of the data. Means (SD) were presented in the tables to make comparisons with other

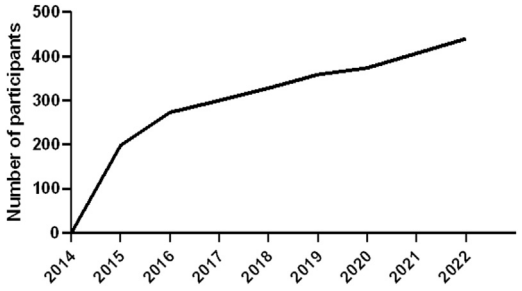

Fig. 1. Number of participants in the registry.

studies more convenient and underpin the mixed models. For the INQoL and MPQ-DLV subsections, the median [IQR] and mean (SD) were calculated using the scores of patients who experienced the concerned symptoms (i.e. subsections with a score of zero were not used for these calculations). The reported percentages of experienced pain and analgesic use were based on the total number of included participants.

Longitudinal changes were analysed using linear mixed effect models with compound symmetry matrices and the restricted maximum likelihood as estimation method. The sum scores were the dependent variables. Survey round was a repeated variable and fixed factor. A p-value <0.05 was considered statistically significant.

Current and upcoming trials usually select moderately affected patients (e.g. Ricci-score between 4-8 on a scale from 0-10), as these patients supposedly have the highest chance of rapid disease progression [8-10,19,20]. To simulate this while lacking actual clinical data, a sub-analysis was performed based on the responders' baseline mobility: ambulant, ambulant with assisting device(s) (e.g. brace, walker, or cane) and wheelchair dependent. For this subgroup analysis correction for multiple testing by the Bonferroni method was applied (statistical significance at $p<0.017$).

Data were collected in CastorEDC [21]. Analysis of the data was done in R (R Foundation for Statistical Computing, Vienna, Austria) and SPSS (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.). Graphs were created using GraphPad Prism version 9.0.0 for Windows (GraphPad Software, San Diego, California USA). The data are not publicly available due to privacy or ethical restrictions, but can be requested using the registry's website.

3. Results

3.1. Demographics

From March 2015 until March 2021, a total of 373 participants joined the Dutch FSHD Registry and completed at least one survey. During the first two years the annual number of new registered patients was high: 198 patients in 2015, 75 patients in 2016 and from 2017 onwards an average of 25 (Fig. 1). During the six years of follow-up, thirteen participants were reported to be deceased, nine left the registry, and eighteen reported they did not want to receive the questionnaires anymore but remained in the registry. The response rate of the survey was 97% at baseline and gradually diminished to 65% at survey round twelve, with a mean response rate of 80%.

3.2. Baseline survey data

At baseline, the median age was 51 [39-63] years and 212 participants (57%) were female (Table 1). A genetically confirmed diagnosis was available for 111 participants (30%). Regarding mobility, 224 participants (60%) were ambulant, 109 (29%) were ambulant with assisting device and 40 (11%) were non-ambulant. The country of residence was the Netherlands for 344 participants (92%), 21 (6%) participants were living in Belgium and the remaining seven (2%) in other countries.

Table 1
Characteristics of the FSHD patients in the registry at baseline

	n (%*)
n	373 (100%)
Age (Median [IQR])	51 [39-62]
Female	212 (57%)
Age of onset (Median [IQR])	18 [10-30]
Family history with FSHD	91 (25%)
Country of residence	
The Netherlands	344 (92%)
Belgium	22 (6%)
Other	7 (2%)
Self-reported FSHD diagnosis	363 (97%)[a]
Type 1	113 (30%)
Type 2	16 (4%)
Unknown	233 (62%)
Mosaicism	1 (<1%)
Mobility	
Ambulant	224 (60%)
Ambulant with assisting device	109 (29%)
Non-ambulant	40 (11%)
Wheelchair / scooter use	
None	225 (60%)
Part-time use	106 (28%)
Full-time	42 (11%)
Weakness	
Face	227 (61%)
Neck	129 (35%)
Shoulder girdle	344 (92%)
Trunk	267 (72%)
Lower arm	191 (51%)
Hand	129 (35%)
Hip girdle	268 (72%)
Foot extensor	225 (60%)
Ventilation status	
No assistance	360 (96%)
Non-invasive part-time	11 (3%)
Invasive part-time	0 (0%)
Invasive fulltime	2 (1%)
Comorbidities	
Hearing loss	246 (66%)
Coats (retinal vascular disease)	0 (0%)

* unless stated otherwise
[a] remaining responders reported to be undiagnosed at baseline.

The baseline median total score of the CIS20R was 76 [59-92], mainly caused by a high score on the fatigue scale (38 [29-46]), indicating severe fatigue symptoms (Table 2). According to the INQoL scores, muscle weakness and fatigue were the most pronounced symptoms (median scores 63 [47-74] and 58 [42-68] respectively), yet social relations were barely affected (12 [0-33]). The BDI-PC median score was 1 [0-3] with 117 (23.6%) participants scoring ≥ 4. According to the MPQ-DLV, pain was most often experienced in the head-shoulder area (52% of the participants) (Fig. 2). Furthermore, a large difference between the minimum and maximum pain was reported on the VAS (1.8 [1.0-3.0] vs. 7.3 [5.6-8.5]). Analgesics were used by 149 participants (40%), of which paracetamol (N=91, 24%) and nonsteroidal anti-inflammatory drugs (NSAIDs) (N=65, 17.5%) were the most common (Fig. 3).

3.3. Follow-up survey data

Including all participants, nineteen out of the 23 (sub)scores showed no significant changes over time as presented in Fig. 4 and Appendix A (CIS20R Sumsore, Fatigue, Concentration and Motivation; INQoL Weakness, Muscle Locking, Pain, Fatigue,

Table 2
Median scores of the CIS20R, INQoL, BDI-PC and MPQ-DLV at baseline.

Questionnaire (sub)score	Baseline Median [IQR] score[c]	Baseline Mean (SD) score[d]	Possible scoring range[b]	Symptoms experienced by n (%)[a]
CIS20R				
Sumscore	76 [59-92]	76 (24)[N]	20-140	373 (100%)
Fatigue	38 [29-46]	37 (12)[S]	8-56	373 (100%)
Concentration	13 [8-20]	15 (8)[S]	5-35	373 (100%)
Motivation	13 [9-17]	14 (6)[S]	4-28	373 (100%)
Activity	10 [6-14.5]	11 (5)[N]	3-21	373 (100%)
INQoL				
Weakness	63 [47-74]	61 (19)[N]	0-100	351 (94%)
Muscle Locking	47 [32-63]	49 (20)[N]	0-100	138 (37%)
Pain	47 [37-63]	50 (20)[N]	0-100	262 (70%)
Fatigue	58 [42-68]	56 (19)[S]	0-100	314 (84%)
Activities	50 [30-64]	46 (23)[S]	0-100	373 (100%)
Independence	39 [19-56]	38 (26)[S]	0-100	373 (100%)
Social Relations	12 [0-33]	19 (21)[S]	0-100	316 (85%)
Emotions	25 [11-43]	29 (22)[S]	0-100	373 (100%)
Body Image	44 [19-64]	43 (27)[S]	0-100	373 (100%)
Quality of Life	42 [24-56]	40 (20)[N]	0-100	373 (100%)
Perceived Effect of Treatment	33 [17-44]	30 (25)[N]	0-100	190 (51%)
Expected Effect of Treatment	25 [8-42]	26 (25)[N]	0-100	190 (51%)
BDI-PC				
Sumscore	1 [0-3]	2 (3)[S]	0-21	373 (100%)
MPQ-DLV				
VAS current pain	4.0 [2.0-5.5]	4 (2)[N]	0-10	149 (40%)
VAS Minimal pain	1.8 [1.0-3.0]	2 (2)[S]	0-10	149 (40%)
VAS Maximal pain	7.3 [5.6-8.5]	7 (2)[S]	0-10	149 (40%)
NWC-T	12 [9-15]	12 (4)[N]	0-20	259 (69%)
PRI-T	62 [43-83]	63 (26)[N]	0-36	259 (69%)

[a] Number of participants (percentage of total responders) who experienced the symptoms of the concerned subsections of the questionnaires.
[b] Possible scoring range for each subscore, a low score correlating to mild symptoms and a high score indicating severe symptoms in all scores.
[c] The median and interquartile range [IQR] and
[d] mean and standard deviation (SD) were calculated based on the scores of the number of participants in ([a]).
[N] Data were normally distributed.
[S] Data were skewed.CIS20R = The Checklist Individual Strength, INQoL = Individualized Neuromuscular Quality of Life Questionnaire, BDI-PC = Beck Depression Inventory - Primary Care, MPQ-DLV = McGill Pain Questionnaire – Dutch Language Version, VAS = Visual Analogue Scale, NWC-T = Number of Words Chosen – Total, PRI-T = Pain Rating Index – Total.

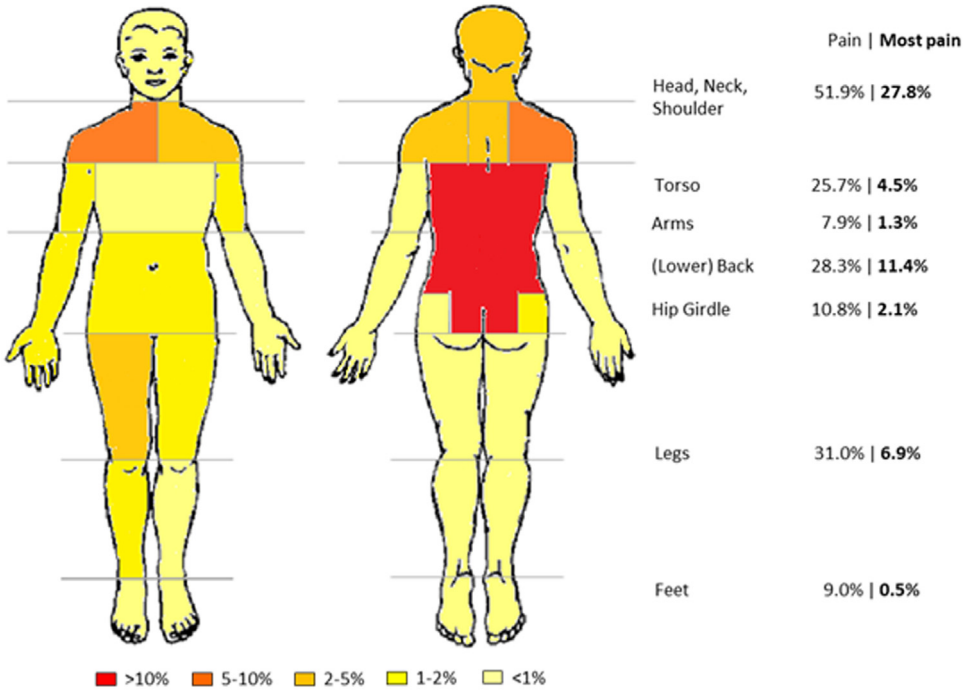

Fig. 2. Pain experienced by FSHD participants at baseline.
The body areas are colored based on where participants experienced the most pain. Smaller body areas were combined into larger body areas, corresponding participant numbers are given in the right column. The left column shows the percentage of the total number of participants (N=373) that reported to experience pain in that body area. The right column shows where the most pain was experienced as a percentage of the total number of participants.

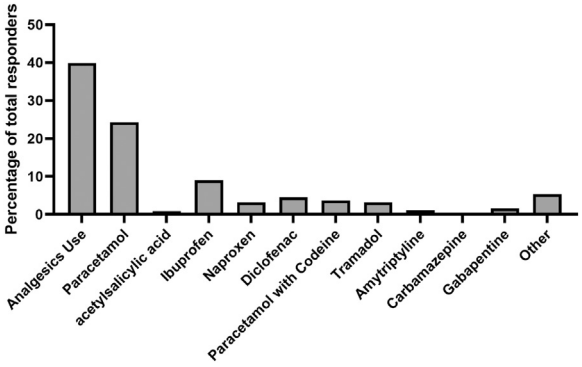

Fig. 3. Analgesic usage in the Dutch FSHD registry participants at baseline. Percentages are calculated based on the number of participants reporting usage of analgesics and the total number of participants (n=373). Paracetamol is also known as acetaminophen.

Activities, Emotions, Quality of Life, Perceived Effect of Treatment and Expected Effect of Treatment; BDI-PC; MPQ-DLV VAS Current, VAS Minimum, VAS Maximum, NWC-T and PRI-T).

The mean CIS Activity score at baseline was 10.6 (SD=5.0, N=373) slowly increasing to 11.6 (SD=3.9, N=46) at survey round 12, indicating slightly more difficulty doing activities. The mean INQoL Independence score increased from 38.2 (SD=25.9, N=373) to 47.3 (SD=24.5, N=46), reflecting loss of independency over time. Unexpectedly, the mean INQoL Social Relations improved from 18.65 (SD=20.7, N=373) to 15.22 (SD=15.9, N=46). Lastly, the mean INQoL Body Image remained mostly stable from the mean baseline score of 43.2 (SD=26.8, N=373), but increased to 45.0 at survey round 11 (SD=23.5, N=121) and 12 (SD=22.6, N=46).

3.4. Mobility sub-analysis

At baseline, the mobility subgroup-analysis showed between-group differences in scores on the CIS Fatigue (p=0.044), CIS Activity (p<0.001), INQoL Weakness, Muscle Locking, Activity, Independence, Social Relations, Body Image, and QoL (p<0.001 for all INQoL sub scores) (Fig. 4). The wheelchair-dependent group showed the highest variability, most likely caused by a small number of participants (N=40 at visit 1, N=5 at visit 12) (Supplementary Table 2).

Within the ambulant participants group, 21 out of 23 (sub)scores showed no significant changes over time. The INQoL Social Relations improved from 15.5 (SD=18.4, N=173) at baseline to 11.6 (SD=14.6, N=19) at round 12. However, the INQoL Quality of Life worsened from 35.3 (SD=19.9, N=173) to 39.0 (SD=19.6, N=58) at round 11. It seemed to improve again at round 12 to 36.5 (SD=19.1, N=19), but this might have been caused by the relatively big drop in the number of participants.

In the subgroup of participants ambulant with assisting device, 22 out of 23 (sub)sections showed no changes over time. Only the INQoL Body Image improved from 54.4 (SD=23.6, N=92) to 44.2 (SD=23.8, N=22).

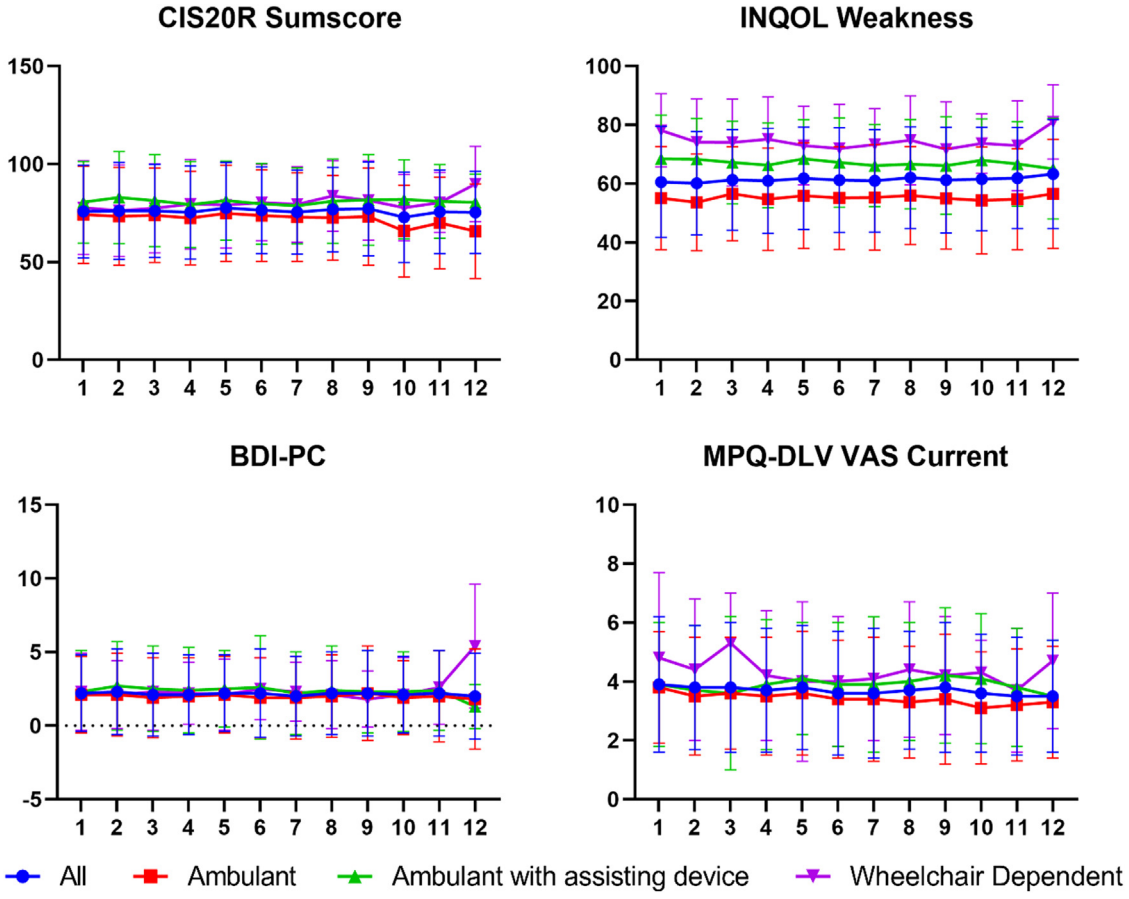

Fig. 4. Change in mean (SD) over time. The graphs show the mean (SD) of the (sub)questionnaires for all responders and for the subgroups 'ambulant', 'ambulant with assisting device' and 'wheelchair dependent'. On the y-axis the score of each (sub)questionnaire is given, on the x-axis the survey rounds.
CIS20R= Checklist Individual Strength, INQoL = Individualized Neuromuscular Quality of Life, QoL = Quality of Life, BDI-PC = Beck Depression Inventory – primary care, MPQ-DLV= McGill Pain Questionnaire – Dutch Language Version, VAS = Visual Analogue Scale

In the wheelchair-dependent group, none of the (sub)scores showed a significant change over time, possibly caused by the small number of participants.

3.5. Studies facilitated

From 2015 until 2023, the registry received fourteen requests so far for either data (3), facilitating recruitment of participants (8) or a combination of both (3). These requests were all reviewed and approved by the steering board. Studies included patient-reported FSHD symptoms and their impact in daily life, a study on the socioeconomic burden of FSHD, and clinical drug trials and a questionnaire study regarding FSHD symptoms and received care during the COVID-19 pandemic was conducted using the registry (publication pending) [10,20,22,23]. In addition, the registry was used to inform all participants about early access to the first COVID-19-vaccination round in the Netherlands in 2021. A (Dutch) layman summary of all approved requests is posted on the website, accompanied by a results summary and link to the paper as soon as this becomes available (www.fshdregistratie.nl/gehonoreerde-verzoeken/).

4. Discussion

In 2015, the Dutch FSHD Registry was set up according to the recommendations discussed in the trial readiness workshop (2015) and workshop of the European Neuromuscular Centre (ENMC) on the global FSHD registry framework (2016) [11,12]. The registry has successfully been used to gather cross-sectional and longitudinal data from self-reported questionnaires. Overall, the results showed barely any longitudinal changes on (self-reported) fatigue, QoL, mental status and pain. Furthermore, the registry facilitated targeted patient recruitment for a number of studies, clinical trials and the collection of longitudinal patient-reported outcome measures.

4.1. Cohort profile compared with other FSHD registries

So far, 452 FSHD patients were registered within the Dutch FSHD Registry. As the prevalence of FSHD in the Netherlands is estimated at 2,000 individuals, this represents approximately 23% of the Dutch FSHD population [3]. This finding is similar to the French registry (21%), but lower than in the United Kingdom registry (31%) [24,25]. The Dutch prevalence estimate was based on a capture-recapture calculation, taking into account unobserved persons. Other prevalence estimates were based on observed persons only, resulting in lower prevalence estimates and thus higher registry coverage rates. Therefore, the coverage of the Dutch FSHD registry is probably higher compared to other FSHD registries. Nevertheless, efforts to encourage patients to participate in the registry are ongoing to further improve coverage. Also, we expect a rise of new participants when additional clinical trials will start.

In line with the high level of motivation of the study group, response rates on the half-yearly questionnaires were initially high. Although the response rate did decrease over time, it was still considered relatively high compared to response rates of other surveys [26]. The decrease in response rate was possibly caused by the relatively large time investment for completing all the questionnaires and/or a lack of information about the results. Reducing the number of questionnaires based on usefulness as well as more frequent reporting of the results may be necessary to maintain a high response rate.

4.2. Baseline comparison

The baseline scores on the questionnaires were similar to the scores found in other studies. The high CIS20R scores indicating severe fatigue were also observed in a different Dutch study of 135 FSHD patients, reiterating the high prevalence of fatigue symptoms. We do expect these two cohorts to overlap partly, which may account for the similar outcomes [27]. The different subscores of the INQoL corresponded well with the findings reported by the UK FSHD Registry [28]. Interestingly, the Dutch registry cohort scored lower on the Independent, Emotions, Body Image and QoL subcategories, indicating a lower burden, compared with the UK registry population. This may be caused by the slight difference in disease severity between the two cohorts. The UK cohort seemed to have a higher disease severity with 48% of the cohort being ambulant compared with 60% in the Dutch cohort. Additionally, country-specific cultural and healthcare differences may play a part. For example, a large European survey on chronic pain reported a higher use of analgesics (NSAIDS and opioids as well) in the UK compared with the Netherlands [29]. This corresponds well with the much larger proportion (92%) of UK FSHD patients using analgesics, most commonly NSAIDs or opioids (both roughly 30%), compared with 40% of the Dutch patients using analgesics consisting mostly of paracetamol (24%) or NSAIDs (17.5%) [28].

Lastly, the mean BDI score of the FSHD population corresponds well with the mean score found in screening 120 random outpatient clinic patients (2.15 vs 2.18) [30]. Although we cannot say for certain that the 117 (23.6%) FSHD patients who scored $\geq$4 on the BDI-PC were all affected by a major depressive disorder, this percentage also corresponds well with the outpatient clinic study (24% were diagnosed with a major depressive disorder).

4.3. Minimal clinically important difference

The majority of the questionnaires in this study showed no (sub)score changes in persons with FSHD over the course of six years. Based on the currently accepted view that the strength and functionality of moderately affected patients decline relatively fast, we expected the 'ambulant with assisting device' group to show the largest difference over time. However, even in this subgroup almost all (sub)scores remained stable over the six years follow-up. Of the (sub)scores that did show a small change over time, it is highly unlikely that a clinically important difference was reached within this timeframe. Unfortunately, no data are available on what would be the minimal clinically important difference (MCID) of the questionnaires for FSHD. Barely any data were available on the MCIDs of these questionnaires in other diseases and it is questionable if MCIDs correspond well across diseases. The general MCID of the CIS Fatigue is 10 points, which was not reached in our cohort [31]. The MCID of the pain score (0-10) in chronic pain patients was 0.9-2.7 depending on the calculation method used and could be compared to the VAS scores in the MPQ-DLV questionnaire [32]. However, both scores were stable and no MCID was not reached in our cohort. It is clear that the knowledge base regarding the MCIDs of these questionnaires is small and mostly unavailable for FSHD [33]. A currently ongoing natural history study within this research group will provide more knowledge about the clinical progression of FSHD symptoms over a longer period. Combining the clinical data with the FSHD-registry data may enable us to determine clinically important differences of these questionnaires and provide knowledge about MCIDs in FSHD and the responsiveness of specific PROMS.

4.4. Disease progression and QoL

The lack of change in scores on the questionnaires could indicate that: 1) FSHD patients remain stable for a long time, 2) the questionnaires are not sensitive enough to detect the probably small occurring changes, and/or 3) fatigue, QoL, depression and pain are influenced by a wide range of factors and do not directly relate to disease progression. As this study currently does not include sufficient clinical data regarding the disease severity and its changes, we cannot rule out nor confirm any of these hypotheses. However, a longitudinal study in myotonic dystrophy type 1 patients did not find longitudinal changes in the INQoL subscores (or even improvements on some subscores) either, despite worsening of the clinical symptoms in the patients [34]. The authors suggested that quality of life was not directly related to disease progression and could increase by changing external factors (e.g. using assisting devices or a wheelchair when necessary) or internal factors (adaptation of the patient's perspective on what relates to quality of life). Their conclusions point towards the second and third hypothesis. In addition, previous studies pointed to at least mild progressiveness of symptoms within a year, and the Italian FSHD Registry found clinical worsening of disease after five years of follow-up, making it unlikely that the Dutch cohort remained stable over (a maximum of) six year follow-up [35,36].

Although we cannot completely rule out the usefulness of the questionnaires in clinical trials because the subgroup analysis displayed the ability to discriminate between specific mobility subgroups, the data collected from this cohort seem to suggest a lack of sensitivity to change for all the questionnaires. We are therefore hesitant to recommend the CIS20R, INQoL, BDI-PC and MPQ-DLV to measure drug efficacy in a clinical trial.

4.5. Future perspectives

Currently, access to longitudinal clinical outcome assessments has been unavailable. Interpretation of the results of the questionnaires will improve with access to longitudinal clinical data and gives the opportunity to calculate the MCID. Furthermore, it will improve the enrolment process by increasing the possibilities for pre-screening (e.g. based on clinical severity scores or muscle strength scores). Lastly, this will enable to start a range of new studies for example about identifying subtypes of FSHD, establishing genotype-phenotype correlations or investigating the relationship between muscle weakness, psychosocial factors, daily functioning and quality of life. We therefore propose that FSHD registries will be expanded to include clinical outcome assessments, either by performing separate study visits, combining registry data with already ongoing natural history studies or by linking the registry to parts of the patient files.

As almost all of the (sub)questionnaires remained stable over the course of six years, we recommend reducing the survey frequency. This will lower the burden on the registered patients and is expected to improve the response rate. Furthermore, recently developed questionnaires such as the FSHD-HI and FSHD-RODS may be more sensitive and specific and be useful to include in the registries as well [37,38]. Together with the Dutch patient advocacy group, we started the process to carefully select which improvements need to be made, what clinical data need to be captured, which questionnaires are to be used and in which frequency, while minimizing the burden on both the participants and clinicians. In this process, we will make sure that the Dutch registry remains harmonised with other national FSHD registries. Additionally, an effort should be made to combine the data of all the national registries as was originally the aim.

4.6. Strengths and limitations

The strengths of this study are the size of the FSHD cohort and the long follow-up period with frequent survey rounds and high response rate, resulting in reliable cross-sectional and longitudinal analysis.

There are several limitations. First, selection bias may be introduced by self-registration, and the registry may therefore not be representative of the entire Dutch FSHD population. However, the demographics of the Dutch Registry population were similar to other studies and FSHD registries. Another limitation of the Registry is the lack of clinical data collection. As mentioned before, clinical data will be useful for interpreting the results of questionnaires, enabling large genotype-phenotype studies, and a more precise preselection of patients for clinical trials. Finally, the process of including the genetical confirmation of the disease was not fully completed at the time of writing. It will become available in the near future to be used for upcoming studies and enable genotype-patient reported phenotype coupling.

5. Conclusion

The Dutch FSHD Registry has been successfully implemented with a still increasing number of participants. It has been used for fast and selective patient recruitment for several studies and for contacting patients on short notice if important information became available. It will prove to be invaluable for recruitment in future trials. Although the CIS20R, INQoL, BDI-PC and MPQ-DLV questionnaires do discriminate between specific subgroups of this FSHD cohort, these scores detected minimal or no longitudinal changes in these FSHD patients over a six-year period. These questionnaires may therefore not be useful to monitor disease progression in prognostic studies or clinical trials in patients with FSHD. The inclusion of clinical outcome assessments in FSHD registries should be considered.

Abbreviations

FSHD	Facioscapulohumeral Muscular Dystrophy
CIS20R	The Checklist Individual Strength
INQoL	Individualized Neuromuscular Quality of Life Questionnaire
BDI-PC	Beck Depression Inventory - Primary Care
MPQ-DLV	McGill Pain Questionnaire – Dutch Language Version
VAS	Visual Analogue Scale
NWC-T	Number of Words Chosen – Total
PRI-T	Pain Rating Index – Total
MCID	Minimal Clinically Important Difference

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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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.2023.10.020.

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