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Fatigue and associated factors in 172 patients with McArdle disease: An international web-based survey

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ABSTRACT

McArdle disease is an autosomal recessive inherited disease caused by pathogenic variants in the *PYGM* gene, resulting in virtual absence of the myophosphorylase enzyme in skeletal muscle. Patients experience physical activity intolerance, muscle pain, and muscle fatigue. This study aimed to investigate other fatigue domains with the Multidimensional Fatigue Inventory (MFI-20) along with an investigation of potential contributing factors, including relevant disease and lifestyle-related factors. We conducted a survey in an international cohort of patients with McArdle disease. The survey included questions on demographics and McArdle disease-related symptoms, and the questionnaires: MFI-20, Insomnia Severity Index (ISI), and International Physical Activity Questionnaire Short-Form (IPAQ-SF). One hundred seventy-four responses were included in the data analyses. We found relatively high fatigue scores in all five domains (general fatigue (12.9 ± 2.2), mental fatigue (10.1 ± 4.1), physical fatigue (13.7 ± 4.1), reduced activity (12.1 ± 4.1), and reduced motivation (10.4 ± 3.4)). Fatigue associated with McArdle symptom severity ($p < 0.005$), lower levels of physical activity (assessed by IPAQ-SF) ($p < 0.05$), and poor sleep (assessed by ISI) ($p < 0.05$). These findings call for clinical focus and future research into fatigue, sleep and mental health in patients with McArdle disease.

1. Introduction

McArdle disease is an autosomal, recessively inherited metabolic disorder caused by pathogenic variants in the myophosphorylase gene (*PYGM*) [1], leading to a virtual absence of the enzyme myophosphorylase in skeletal muscle [2]. Consequently, patients cannot obtain energy from their muscle glycogen stores. The blocked muscle glycogen breakdown clinically presents itself as physical activity (PA) intolerance, muscle fatigue, and PA/exercise-induced muscle pain, which can lead to the feeling of loss of power, and in severe cases to muscle contractures and even rhabdomyolysis and myoglobinuria [3].

Fatigue is debilitating and a multidimensional construct combining physiological, psychological, sociocultural, and clinical aspects [4,5]. No standard definition of fatigue exists, however, it has classically been described in terms of peripheral (physical) or central fatigue [6]. Muscle fatigue in McArdle disease is well recognized [3]. It is especially present during the first minutes of a PA before blood-borne free fatty acids and hepatic-derived glucose are available to be oxidized in the muscle fibers. In addition to the aforementioned muscle fatigue during PA characteristic of McArdle disease [3], some patients in our clinic report more central fatigue, not necessarily related to PA. Central fatigue in patients with McArdle disease has not been investigated. Therefore, we set out to investigate fatigue, with the Multidimensional Fatigue Inventory (MFI-20) [7], in an international cohort of patients with McArdle disease using a web-based survey. The MFI-20 assesses five fatigue domains: physical fatigue, general fatigue, reduced activity, reduced motivation, and mental fatigue [7], and thus seeks to cover the fatigue spectrum broadly. Previous studies have indicated that the MFI-20 is a valid and reliable instrument [7,8].

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The objective of this study was to investigate multiple dimensions of fatigue with possible contributing and associated factors in people with McArdle disease. Relevant demographic factors, comorbidities, and disease-specific symptoms were included in the survey in order to investigate fatigue-contributing factors broadly. Furthermore, fatigue is known to be correlated with PA [9–12], and we hypothesized that disordered sleep could also contribute to fatigue. Hence, we included the International Physical Activity Questionnaire Short Form (IPAQ-SF) and the Insomnia Severity Index (ISI) in the survey.

2. Materials and methods

We performed an international cross-sectional web-based survey in six parts. Results from parts 1 and 3–5 are presented in this study. The results from part 2, which focused on the ketogenic diet, are published elsewhere [13].

2.1. Standard protocol approvals, registrations, and patient consents

The survey was approved by the Knowledge Center for Data reviews, Capital Region, Denmark (P-2019–517) and listed on clinical trials.gov (NCT04694547). Written informed consent with a detailed information on the research study was requested as the first step of the survey to proceed. According to the regulations of the different countries, involved in recruitment for this survey, surveys such as the present one do not require ethical approval.

2.2. Survey part 1

Demographic information and symptoms specific to McArdle disease were the first part's focus. A stop-question allowed only respondents replying "yes" to a confirmed McArdle disease diagnosis to continue in the survey. Other questions included: age, sex, height, weight, country of residence, job and family status, and comorbidities, along with questions concerning symptoms' intensity and frequency related to McArdle disease. For descriptive and statistical purposes, we created a McArdle symptom rating scale. Patients rated five core symptoms (muscle pain at rest and during activity, muscle cramps, exercise intolerance, muscle fatigue) on a 5-point scale (1=no symptom, 2=very mild symptoms, 3=mild symptoms, 4=moderate symptoms, and 5=severe symptoms), with a total score between 5 and 25 points. For the full survey part 1 outline see Supplementary File 1.

2.3. Survey part 3: international physical activity questionnaire short form

The IPAQ-SF consists of 7 items assessing PA over the last week. The range of PA is arranged into categories: vigorous activity (e.g., heavy lifting), moderate activity (e.g., bicycling at a regular pace), walking, and sedentary time. Following each question, the participant is asked about the duration and frequency of the activity [14]. The metabolic equivalent of task (MET)-minutes/week was calculated and subsequently divided into three levels of PA, "low", "moderate" or "high", as described in the IPAQ Reliability Study [14].

2.4. Survey part 4: multidimensional fatigue inventory twenty

The MFI-20 is a self-report questionnaire consisting of 20 items measuring fatigue [7]. The items are arranged in five different domains: general fatigue (GF) (e.g., "*I feel tired*"), physical fatigue (PF) (e.g., "*Physically I feel I am in a bad condition*"), reduced activity (RA) (e.g., "*I think I do a lot in a day*"), reduced motivation (RM) (e.g., "*I dread having to do things*"), and mental fatigue (MF) (e.g., "*I can concentrate well*"). The fatigue severity is scored on a five-level scale of truthness from "*Yes, that is true*" to "*No, that is not true*"; the score for each domain ranges from 4 to 20, whereby higher scores indicate more fatigue [7,15].

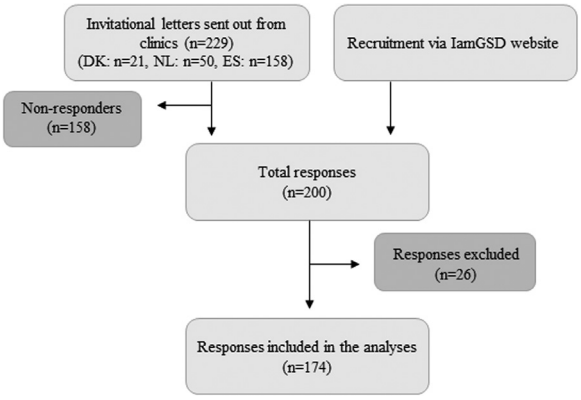

Fig. 1. Flowchart of included and excluded responses.

2.5. Survey part 5: insomnia severity index

The ISI is a self-report questionnaire consisting of seven items, including different domains related to sleep [16]. The seven items are scored on a scale from 0 to 4, where 0 is no issue, and 4 is very severe insomnia, yielding a total score from 0 to 28 [17], which can be further subdivided into four groups: scores from 0 to 7 suggest no clinical sign of insomnia, scores 8–14 mild-moderate severity of insomnia, scores 15–21 moderate severity of insomnia, and finally scores 22–28 suggest severe insomnia [17].

2.6. Survey distribution and data collection

The study group translated part one of the survey into Danish (NL), English (NL), Spanish, and Dutch (WK, NV). From the official IPAQ website, translated versions of the IPAQ-SF in all four languages were downloaded [17,18]. Using the program REDCap (©2018 Vanderbilt University, TN), the survey parts were assembled and set up as four web-based surveys (English, Danish, Spanish, and Dutch). Recruitment happened through three neuromuscular clinics and the patient organization, IamGSD (Fig. 1). Patients with McArdle disease in Denmark and the Faroe Islands (n = 21), the Netherlands (n = 50), and Spain (n = 158) received an invitation letter with a link to the online survey via secure email from their respective neuromuscular clinic. IamGSD used a direct invitation technique and released the invitation letter in both English and Spanish on their website, hence recruiting people more internationally. The invitation letter included an explanation of the various survey parts and their objectives. Each survey response was saved in the secure REDCap database.

2.7. Statistical analyses

Categorical parameters were presented by numbers and percentages. Normally distributed continuous variables were presented by means and standard deviation (SD). Histograms and quantile-quantile-plots were used to assess normality visually. Data, which did not distribute normally, were presented by medians and interquartile ranges (IQR).

We performed five general linear regression analyses to investigate the associations between the five fatigue domains and, a priori chosen, covariates, with the five MFI-20 total scores as the outcomes. Subsequently, we performed a similar linear regression

analysis with the ISI score as the outcome. The MFI-20 scores were included as continuous variables. The covariates that were included in the statistical analyses were both continuous (age, BMI, total ISI score, McArdle severity, total sedative time per week, and total MET-minutes per week) and categorical (sex, comorbidity (yes/no), living situation, IPAQ score, education, children, country, and job status). The model assumptions were checked and were not violated. A p-value of ≤ 0.05 was considered significant. Statistical analyses were conducted using R version 4.1.0 (R Foundation for Statistical Computing, Vienna, Austria).

2.8. Data availability statement

Most data supporting this study are presented in this manuscript. Due to ethical concerns and GBDR regulations, supporting data cannot be made openly available. Data can be shared under some conditions upon request.

3. Results

3.1. Study cohort

Two hundred responded to the survey. Of these 200 respondents, 26 were excluded due to incomplete or double responses (Fig. 1). One hundred sixty-eight respondents completed all parts, and six completed the survey almost entirely, resulting in a total of 174 respondents included in the data analyses. All included respondents gave written consent to participate in the study. The demographic characteristics and the computed McArdle symptom severity scores are presented in Table 1 & Table 2. All respondents confirmed having a McArdle disease diagnosis. One hundred fifty-eight replied that their diagnosis was confirmed with a DNA test and/or muscle biopsy or screening after a positive diagnosis of a family member. Six of the remaining 15 respondents were included via a neuromuscular clinic, thus the diagnosis was confirmed. The last nine reported that their diagnosis was based on either elevated creatine kinase or after a handgrip/cycle exercise test. Selected predetermined comorbidities are presented in Table 2. Of "other comorbidities" the respondents reported: 1 stress, 1 post-traumatic stress syndrome, 5 hypothyroidism, 2 migraines, 4 chronic fatigue, 3 Gilberts syndrome, 5 irritable bowel syndrome, 1 bipolar disorder, and 1 attention deficit hyperactivity disorder, in addition to other diseases/deficiencies.

3.2. IPAQ-SF and ISI

One hundred seventy-two responded to the survey on physical activity (IPAQ-SF) and sleep (ISI). Of the 172 IPAQ-SF responses, four responses were excluded from the analyses due to unrealistically high responses (18,944 – 36,950 MET-min/week), resulting in the inclusion of 168 responses. The total IPAQ-SF score in MET-minutes/week, total sedentary hours per week, and the IPAQ-SF sub-categories frequency are presented in Table 2, along with the total ISI scores and the frequency of ISI sub-categories.

3.3. Multidimensional fatigue inventory twenty

One hundred and seventy-two patients responded to the MFI-20. The MFI-20 scores from the five domains are presented in Fig. 2 and Table 2. All five MFI-20 domains (GF, PF, MF, RA, RM) scored in the higher range of the scale, with the highest scores for PF, GF, and RA.

3.4. Fatigue associations

We found no association between fatigue, age, and sex (Table 3). A high BMI was associated with higher levels of PF but did not associate with the other domains. We found a significant association between fatigue and MET-min/week, indicating that low levels of PA were associated with higher levels of fatigue, except for the RM domain. The McArdle severity score significantly influenced GF, PF, RA, and MF, suggesting that the increased severity of McArdle disease symptoms is associated with higher levels of fatigue. We found that a high ISI score was associated with higher GF, PF, RA, and RM scores but not MF (Table 3, Fig. 2). Job-status did not influence fatigue, apart from being a full-time student that associated with higher levels of RA ($p = 0.02$). Living situation did not influence fatigue. We chose to include

Table 1
Characteristics ($n = 174$).

Age, years	48.6 ± 16.7 (17 – 82)
Sex	
Female	101 (58.6 %)
Male	72 (41.3 %)
Other	1 (0.6 %)
BMI, kg/m^2	27.1 ± 6.24 (15.6–51.5)
Country of residence	
1: GB, IE	27 (15.5 %)
2: AU, NZ	12 (6.9 %)
3: US, CA	42 (24.1 %)
4: DK, SE	16 (9.2 %)
5: ES, IT, FR	33 (18.9 %)
6: NL, BE	31 (17.8 %)
7: DE, MT, pH, KW	13 (6.9 %)
Living situation	
Lives alone	38 (21.8 %)
Lives alone with my child/children	6 (3.4 %)
Lives with my partner without children	32 (18.4 %)
Lives with my partner and child/children	17 (9.8 %)
Lives with my spouse without children	37 (21.3 %)
Live with my spouse and child/children	32 (18.4 %)
"I do not want to answer this question"	12 (6.9 %)
Children	
None	65 (37.4 %)
One child	26 (14.9 %)
Two children	59 (33.9 %)
Three children	17 (9.8 %)
Four children	4 (2.3 %)
More than four children	3 (1.7 %)
Education	
Primary & secondary education	26 (14.9 %)
College or similar	45 (25.9 %)
University undergraduate or similar	58 (33.3 %)
University postgraduate	38 (21.8 %)
Other	7 (4.0 %)
Current job	
Fulltime	74 (42.5 %)
Part-time	18 (10.3 %)
Under education/student	8 (4.6 %)
Temporary sick leave	4 (2.3 %)
Retired	34 (19.5 %)
Early retirement	17 (9.8 %)
Unemployed	12 (6.9 %)
Other	7 (4.0 %)
Job type *	
Stationary job	53 (57.6 %)
Light physical work	32 (34.8 %)
Hard physical work	7 (7.6 %)

Categorical data are presented as frequency (percentage): sex, country of residence. Normally distributed data are presented as mean ± standard deviation (range): age, BMI (body mass index). Some variables do not add up to the full sample size due to incomplete responses (*$n = 92$, n=number of respondents). Abbreviations: GB (Great Britain), IE (Ireland), AU (Australia), NZ (New Zealand), US (United States), CA (Canada), DK (Denmark), SE (Sweden), ES (Spain), IT (Italy), FR (France), NL (The Netherlands), BE (Belgium), DE (Germany), MT (Malta), pH (Philippines), KW (Kuwait).

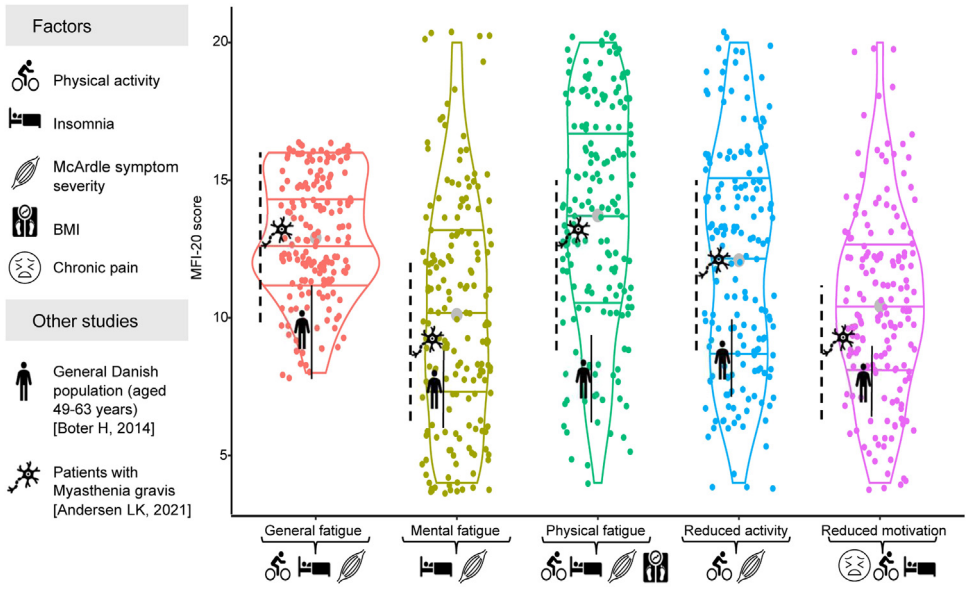

Fig. 2. Violine plot illustrating the 172 individual responses to each of the five fatigue domains included in the multidimensional fatigue inventory (MFI-20). Lines indicate lower quartile, median, and higher quartile of the cohort. The colored dots represent each patient's response. The gray dots are means. The width of the violine illustrates the number of responses. Different factors were found to be associated with different fatigue domains, highlighted here with different icons (Table 3). BMI: body mass index; bed: Insomnia Severity Index result; cycle: International Physical Activity Questionnaure short form scores. The persons illustrate median MFI-20 scores from General Danish Population in the age group 49–63 (Boher H, 2014, PMID: 24,819,423). The neurons illustrate MFI-20 medians from Myasthenia Gravis patients (Andersen LK, 2021, PMID: 34,303,571). The lines illustrate lower and higher quartile of the respective studies.

the comorbidities: chronic pain and anxiety/depression, as the only comorbidities in the regression analyses, as these were the most frequent in the cohort. None of the two were associated with either of the fatigue domains. The remaining comorbidities occurred too infrequently for statistical analyses.

Whether or not the respondents were recruited through a neuromuscular clinic or IamGSD, was used as a covariate in the multivariate linear regression regarding all fatigue domains and had no significance.

3.5. Sleep associations

We found that chronic pain was associated with insomnia, that women were more prone to insomnia than men, and that higher McArdle severity scores were associated with more severe insomnia (Table 4).

4. Discussion

In this survey, 172 patients with McArdle disease reported demographic information, as well as information on disease-related symptoms, fatigue, insomnia, and PA. We found a high level of fatigue in all five domains of the MFI-20, which was associated with McArdle symptom severity, lower levels of PA, and disturbed sleep.

The MFI-20 was chosen due to its broad coverage of different fatigue domains and as it has been utilized and validated in neurological research since 1995 [8,19–21]. Muscle fatigue is a well-described symptom in patients with McArdle disease [3]; it was thus expected that the PF domain scores would be high. It was, however, interesting that all five fatigue domains were affected. GF had the smallest range (8–16) compared to the other domains (4–20), suggesting that most of the cohort experience a moderate degree of GF. In 4964 Danish people from the general population in the age group 49–63 years, the mean GF score was 9.6 ± 3.9 and PF 9.0 ± 3.8, MF 7.7 ± 3.3, RM 7.2 ± 2.5, and RA 7.9 ± 3.3 [22] (Fig. 2, Table 5). The MFI-20 has also been used to investigate fatigue in several other disorders (Table 5). Some of these studies incorporated a control group that had fatigue scores similar to those presented from the Danish population (Table 5) [20,22–24]. Thus, the results from our study indicate that individuals with McArdle disease have higher fatigue scores than the general population. It is important to note, however, that direct comparison is not possible, as the study design conditions were different and the groups were not matched, thus the result should be interpreted with caution. In this survey, we did not include a control group with matched demographic features, nor did we have access to raw data from a study of fatigue in the general population. A matched control group is warranted in future trials.

With the above arguments in mind, we found that fatigue levels in our McArdle disease cohort were comparable to patients with sarcoidosis [23] or stroke [20] but slightly higher than chronically, critically ill patients following intensive care [26] (Table 5). The PF and RM scores in our cohort were higher than those previously reported in patients with multiple sclerosis [21], and GF scores were slightly higher than those found in patients with cancer [23]. Myasthenia Gravis (MG) has classically been described as a peripheral disorder with muscle fatigue as the most prominent symptom. Recent research has, however, established that patients also experience general and mental fatigue [25]. The reported fatigue levels in patients with MG were interestingly comparable to the findings in our cohort of patients with McArdle disease. The mean ISI score in our cohort was slightly higher than that reported in MG patients (mean: 8, range: 4–13), suggesting that patients with McArdle disease experience similar fatigue with more severe insomnia [25]. Conclusively, our findings recognize that individuals with McArdle disease not only suffer from muscle fatigue, which highlights the importance of future research in fatigue in this cohort. Our findings support that fatigue is a complex construct where physical, psychological and sociocultural factors intertwine, which calls for a multidimensional approach to assessing fatigue in McArdle disease.

We can only speculate why patients with McArdle disease score high on all five fatigue domains. One reason could be

Table 2
Characteristics (n = 174).

McArdle symptom severity score	17.0 ± 4.13 (7–25)
Comorbidity (multiple choices possible)	
Anxiety/depression	71 (40 %)
Chronic pain	43 (24.7 %)
Rheumatoid arthritis	7 (4.02 %)
Osteoarthritis	11 (6.3 %)
Chronic lung disease	15 (8.6 %)
Heart disease	14 (8.04 %)
Hypertension	26 (14.9 %)
Hypercholesterolemia	26 (14,9 %)
Diabetes	19 (10.9 %)
Liver/gut disease	7 (4.0 %)
Cancer	4 (2.3 %)
Other comorbidities	19 (10.9 %)
"I don't know"	18 (10.3 %)
"No, I don't have any of the listed diseases"	27 (15.5 %)
IPAQ, total MET-min/week *	2599.5 (1188.0 – 4587.0)
IPAQ, total sedentary min/week	457.5 (322.5 – 600.0)
IPAQ, category	
1 Low	38 (22.3 %)
2 Moderate	56 (32.9 %)
3 High	74 (44.7 %)
MFI-20, total **	
General fatigue	12.9 ± 2.2 (8–16)
Physical fatigue	13.7 ± 4.1 (4–20)
Reduced activity	12.1 ± 4.1 (4–20)
Reduced motivation	10.4 ± 3.4 (4–20)
Mental fatigue	10.1 ± 4.1 (4–20)
ISI, total **	9.6 ± 5.9 (0–26)
ISI, category	
1 No clinical insomnia	70 (40.7 %)
2 Mild-moderate clinical insomnia	64 (37.2 %)
3 Moderate clinical insomnia	35 (20.3 %)
4 Severe clinical insomnia	3 (1.7 %)

Categorical data are presented as frequency (percentage): ISI category. Normally distributed data are presented as mean ± standard deviation (range): McArdle-score & ISI total (Insomnia Severity Index). Non-normal distributed continuous data are presented as median (Interquartile range): IPAQ-SF (International Physical Activity Questionnaire Short Form), total MET(Metabolic Equivalent of Task)- min per week, total sedentary time (min) per week. Some variables do not add up to the full sample size due to incomplete responses (*n = 168, **n = 172, n = number of respondents).

Table 4
ISI associations with a priori determined covariates.

	ISI (β, (CI))
Age	−3.7 (−0.061 – 0.041)
Sex[a]	**−1.8 (−4.5 - −0.095)**
BMI, kg/m^2	0.071 (−0.068 – 0.2)
Anxiety/depression[b]	−0.27 (−1.9 – 1.4)
Chronic pain[c]	**3.6 (1.6 – 5.6)** *
McArdle Symptom Severity	**0.32 (0.073 – 0.56)**
IPAQ (MET-minutes/week)	-4.1×10^{-5} (-3.3×10^{-4} – 2.5×10^{-4})
GF	**0.53 (0.082– 0.97)**

The multivariate linear regression analysis were made as complete-case analyses (n = 172). β: Estimate, CI: confidence intervals.
Abbreviations: BMI (Body Mass Index), MET (Metabolic Equivalent of Task), ISI (Insomnia Severity Index), GF (general fatigue), PF (physical fatigue), RA (reduced activity), RM (reduced motivation), MF (mental fatigue).
[a] Female vs. male.
[b] Anxiety/depression yes or no.
[c] Chronic pain yes or no.
* $p < 0.005$, **In bold:** $p < 0.05$.

inactivity, which is known to contribute to fatigue [27]. Many patients are diagnosed late in life not getting the correct guidance regarding how to perform PA to avoid pain. Consequently, many become exercise-avoidant [28]. Patients with McArdle disease are described as being more sedentary than the healthy population in previous studies [29,30] and a high proportion of them do not meet the minimum (i.e., 150 min/week of moderate activities such as waking) international PA guidelines [31]. By contrast, Ollivier et al. found similar daily energy expenditure in individuals with McArdle disease compared to controls using the Bouchard questionnaire [32]. The IPAQ-SF has been shown to have acceptable validity when assessing levels and patterns of PA [14,33,34]. In one international validity study across 12 countries, the median total MET-min/week was 2514 [14], which is lower than the median found in our McArdle cohort (2599.5 MET-min/week). However, these results should be interpreted with caution as IPAQ-SF typically overestimates PA compared with objective measures of PA [35]. Regarding the present study, we speculate that the high levels of moderate and vigorous activity are due to an activity being perceived as more difficult due to the disease. Patients may indeed be more aware of PA in their daily life due to PA-

Table 3
MFI-20 fatigue domains associations with a priori determined covariates.

	GF (β, (CI))	PF (β, (CI))	RA (β, (CI))	RM (β, (CI))	MF (β, (CI))
Age	−0.0071 (−0.025 – 0.011)	0.00073 (−0.032 – 0.033)	0.018 (−0.018 – 0.053)	0.0051 (−0.026 – 0.036)	−0.033 (−0.07 – 0.0035)
Sex[a]	0.29 (−0.30 – 0.90)	1.0 (−0.086 – 2.1)	−0.43 (−1.6 – 0.77)	−0.32 (−1.3 – 7.1)	0.69 (−0.54 – 1.9)
BMI, kg/m^2	0.037 (−0.011 – 0.087)	**0.18 (0.029 – 0.21)**	0.082 (−0.016 – 0.18)	0.077 (−0.0068 – 0.16)	−0.011 (−0.11 – 0.089)
Anxiety/depression[b]	−0.30 (−0.89 – 0.29)	−0.31 (−1.4 – 0.77)	0.039 (−1.1 – 1.2)	−0.66 (−1.7 – 0.36)	−0.047 (−1.3 – 1.2)
Chronic pain[c]	0.18 (−0.54 – 0.91)	0.20 (−1.1 – 1.5)	0.65 (−0.79 – 2.1)	**1.3 (0.055 – 2.5)**	1.0 (−0.47 – 2.5)
McArdle Symptom Severity	**0.22 (0.13–0.29)** *	**0.33 (0.18 – 0.48)** *	**0.23 (0.068 – 0.39)** *	0.13 (−0.0071 – 0.27)	**0.19 (0.031 – 0.36)**
IPAQ (MET-min/week)	**-1.01×10^{-4} (-2.1×10^{-4} – -5.5×10^{-6})**	**-3.5×10^{-4} (-5.3×10^{-4} – -1.6×10^{-4})** *	**-3.7×10^{-4} (-5.7×10^{-4} – -1.7×10^{-4})** *	**-2.0×10^{-4} (-3.8×10^{-4} – -3.1×10^{-5})**	-6.6×10^{-5} (-2.7×10^{-4} – 1.4×10^{-4})
ISI total	**0.066 (0.01 – 0.12)**	**0.13 (0.027 – 0.23)**	0.099 (−0.011 – 0.21)	**0.097 (0.0013 – 0.19)**	**0.20 (0.086 – 0.32)***

The multivariate linear regression analyses were made as complete-case analyses (n = 174). β: Estimate, CI: confidence intervals.
Abbreviations: BMI (Body Mass Index), MET (Metabolic Equivalent of Task), ISI (Insomnia Severity Index), GF (general fatigue), PF (physical fatigue), RA (reduced activity), RM (reduced motivation), MF (mental fatigue).
[a] Female vs. male.
[b] Anxiety/depression yes or no.
[c] Chronic pain yes or no
* $p < 0.005$. **In bold:** $p < 0.05$.

Table 5
MFI-20 scores in chronic diseases and controls.

Disease	Study design	Cohort	Age	GF	PF	RA	RM	MF
Danish general population [22]	Cross-sectional study	$n = 4964$	Range 49–63	Mean ± SD 9.6 ± 3.9	Mean ± SD 9.0 ± 3.8	Mean ± SD 7.9 ± 3.3	Mean ± SD 7.2 ± 2.5	Mean ± SD 7.7 ± 3.3
Sarcoidosis[24]	Cross-sectional study	$n = 1197$	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
Controls		$n = 2037$	54.3 ± 11.6 Range 14 – 92	14.3 ± 3.9 8.7 ± 3.6	13.1 ± 3.2 8.4 ± 4.1	9.8 ± 3.7 8.0 ± 3.3	12.2 ± 4.4 8.4 ± 3.8	11.1 ± 4.2 7.7 ± 3.3
Post stroke [20]	Cross-sectional study	$n = 165$	Median (IQR)	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
Controls		$n = 1069$	64.5 (55.8 - 72.5) 47.6 (34.6 - 62.6)	10 ± 4 10 ± 4	12 ± 3 9 ± 4	7 ± 3 7 ± 3	10 ± 4 8 ± 4	8 ± 4 8 ± 4
Chronically critically ill patients following intensive care[26]	Cross-sectional study	$n = 195$	Median (IQR) 61.6 (55.7 – 65.6)	Mean ± SD 12.2 ± 4.0	Mean ± SD 13.4 ± 3.7	Mean ± SD 12.6 ± 4.6	Mean ± SD 8.9 ± 3.5	Mean ± SD 8.7 ± 4.5
Multiple sclerosis [21]	Cross-sectional study	$n = 154$	Mean ± SD 40.0 ± 9.9	Mean ± SD 13.99 ± 4.44	Mean ± SD 13.42 ± 4.86	Mean ± SD 10.96 ± 4.74	Mean ± SD 8.56 ± 3.65	Mean ± SD 10.38 ± 4.50
Cancer[24]	Cross-sectional study	$n = 1818$	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
Controls		$n = 1993$	58.4 ± 11.2 Range 18 – 93	12.2 ± 4.5 9.3 ± 3.7	12.2 ± 4.6 9.2 ± 4.2	11.9 ± 4.6 9.1 ± 4.0	8.9 ± 3.8 8.6 ± 3.3	9.6 ± 4.5 8.2 ± 3.4
Myasthenia gravis [25]	Cross-sectional study	$n = 779$	Mean ± SD 60.8 ± 15.5	Median (IQR) 13 (10–16)	Median (IQR) 13 (9–15)	Median (IQR) 12 (9–15)	Median (IQR) 9 (6–11)	Median (IQR) 9 (6–12)

Abbreviations: n (number). SD (Standard Deviation), IQR (interquartile ranges), GF (general fatigue), PF (physical fatigue), RA (reduced activity), RM (reduced motivation), MF (mental fatigue).

induced symptoms. Nonetheless, engaging in more PA associates with less fatigue, thereby suggesting that the more active patients experience less fatigue and/or that the less fatigued patients engage in more PA. More research is needed to determine the direction of the association, which a cross-sectional study as the present one, due to the design, cannot identify. Larger studies that include a healthy control group and objective PA measurements (e.g., accelerometers) are also required to properly explore the pattern of habitual PA in patients with McArdle disease and its relation to fatigue.

McArdle disease is a chronic disease. Multiple chronic diseases' relation to fatigue has been investigated in a large multidisciplinary prospective population-based cohort study by Goërtz et al. [36]. They found that fatigue was more common and severe in people with a chronic disease compared to the general population [36]. They found that many factors contributed to increased fatigue severity such as sex (female sex), living situation (living in a single-parent household), lower education level, high BMI, pain, and physical inactivity [36]. In our cohort of patients with McArdle disease, we also found that physical inactivity was associated with fatigue and that a high BMI associated with the domain PF. In the present cohort, patients were generally classified as overweight with a mean BMI over 25 kg/m^2 [37]. That overweight is associated with more PF is not surprising; however, based on the current study, we cannot determine causality. We could speculate a vicious cycle with overweight causing inactivity, inactivity causing more overweight, with subsequent PF. In contrast, chronic pain, and demographics such as sex, age, living situation, and education did not influence fatigue in our cohort. The study by Goërtz et al. found that anger, self-consciousness, and vulnerability correlated with fatigue [36]. Patients with McArdle disease have reported worrying about their disease [38], which could be a contributing factor to fatigue.

We found that the computed McArdle symptom severity score was associated with MF, GF, PF, and RA, with higher severity scores yielding more fatigue. Interestingly, RM did not correlate with McArdle symptoms' severity, thereby reflecting that feeling motivated is not lessened if symptoms are worsened. RM was associated with chronic pain and, contrary to the other fatigue domains, did not correlate with McArdle severity, suggesting that chronic pain is more hindering concerning motivation than the severity of McArdle disease-related symptoms. Of note, the computed McArdle symptoms' severity score is based on the patients' reports and thus indicates the subjectively perceived severity of their symptoms. Therefore, our findings suggest that if the patients perceive their symptoms as more severe, they will also tend to be more fatigued.

This survey found a high frequency of patients, 40 %, with the comorbidity "anxiety and/or depression". The finding was self-reported by ticking yes to having one or more diseases from a list, where anxiety and/or depression was one option (Table 2). We can, in this study, not distinguish between the two and, thus not say if anxiety or depression is most prevalent. Furthermore, we have not scored the two with standardized anxiety and depression scales, and we cannot tell if the cases have a clinical diagnosis. Considering the clear information bias, the results are still surprising. In the EUROMAC study [29], which is a large registry study published on a European McArdle cohort, mental disorders were described in 16 (6.6 %) of 241 patients, with nine cases of depression and four of anxiety. Mental disorders are not always diagnosed and listed in the patient journal, and for this reason, the retrospective EUROMAC finding might have potentially underestimated the occurrence of depression/anxiety. More in line with the present study, Gandhi et al. found that 50 % of a Scottish McArdle disease cohort of 14 patients had a psychological comorbidity [39]. The rest of the comorbidities in this survey were in line with frequencies reported in the EUROMAC registry study [29]. In our study, there was no association between depression/anxiety and fatigue. In the study by Goërtz et al. [36], they found that an anxiety disorder was associated with fatigue severity in all chronic diseases. Moreover, they found that depression correlated with increased fatigue severity [36]. This is interesting as it contradicts our findings despite McArdle disease being a chronic condition, suggesting it is not anxiety or depression that increases fatigue severity in individuals with McArdle disease. Nonetheless, the results encourage future studies exploring the mental health in individuals with McArdle disease and moreover how treatment of psychological comorbidities would affect levels of fatigue, chronic pain, and insomnia as well as levels of PA and vice versa.

Whether it is psychological factors, sociocultural factors, physical inactivity, comorbidity, high BMI, or having a chronic disease that is most determining for developing fatigue in our cohort, we can only speculate. As fatigue is a complex multidimensional construct, multiple factors account and most likely intertwine [4,5]. Previous studies have highlighted that neuropsychological aspects are highly determinant for the perception of fatigue. Future studies should explore the

impact of different factors on the different domains of fatigue, also with a focus on neuropsychological aspects of fatigue, incorporating neuropsychological testing. In a study by Birnbaum et al., neuromuscular fatigue was investigated with myoelectrical indicators; they found that well-controlled and stable MG patients did not demonstrate greater neuromuscular fatigue compared to healthy controls [40]. In individuals with McArdle disease it would be interesting to compare objective measurements of muscular fatigue with patient-reported fatigue, in addition to comparison with healthy controls.

The ISI is a reliable instrument to assess perceived insomnia severity [17,41,42]. In the present cohort, 59.2 % of the respondents reported experiencing insomnia ranging from mild to severe. In total, 22.1 % had moderate-severe insomnia with an ISI score similar to individuals diagnosed with insomnia in previous research [41]. We found that the report of more McArdle symptoms was associated with higher ISI scores. Chronic pain is also associated with more insomnia, a result previously described as a bidirectional relationship [43]. Female sex correlated with more insomnia, which has been previously described in another cohort [44]. Insomnia is, however, also prevalent in the general population. In an international study by Aernout et al. they found that 11.3 % out of 57,298 participants had short-term insomnia disorder. They did not utilize ISI to investigate insomnia so a direct comparison cannot be done. Interestingly, they also found that insomnia seemed to be more profound in people with anxiety disorders [45]. To our knowledge, patients with McArdle disease reporting insomnia to such a degree has not been described before. This finding warrants further investigations into sleep patterns in this cohort, preferably with inclusion of objective sleep outcomes (e.g., polysomnography) and compared to a matched background population. Furthermore, we suggest that clinicians should be aware of the potential problem of insomnia in the care of patients with McArdle disease.

4.1. Strengths and limitations

This study had several strengths. One is the inclusion of a relatively large cohort of patients for this rare disease. Another is that patients were from an international cohort. Patient-reported surveys have many sources of error, and selection, information, and recall bias are at high risk. In the present study, patient inclusion had two arms: recruitment through the neuromuscular clinics and the patient organization. For the recruitment through the clinics, we found varying response rates. For instance, the response rate in the Spanish cohort was relatively low (19.6 %) and thus perhaps not representative of the entire Spanish McArdle disease cohort. We can only speculate if patients with more severe symptoms are more prone to answer or if it is the other way around. Perhaps patients who perceive their symptoms as more severe are more prone to engage in the patient organization community and, therefore, more prone to reply to this survey. Thus, posing the risk of selection bias. Other sources of bias are information and recall bias, in that we cannot control if patients recall and report/inform about their symptoms correctly. It should be noted that fatigue [46], insomnia [45], and chronic pain [47] are all prevalent in the general population, which account as additional biases. Nonetheless, collecting patient-reported experiences is warranted to report the patients' voices, and inspire and generate new hypotheses for future research.

5. Conclusion

In this international web-based survey study, we found that patients with McArdle disease experience not only PF but also fatigue in the other four domains assessed with the MFI-20. Fatigue was associated with lower levels of PA, disordered sleep, and severely perceived McArdle disease-related symptoms. This finding warrants future research into fatigue in McArdle disease incorporating multiple fatigue domains, possible associated factors, and objective measures of fatigue. Moreover, this study reports severe sleep problems, which should also be studied in the future, incorporating objective sleep measurements. Finally, this study suggests incorporating an evaluation of fatigue, sleep, and mental health in the clinical workup of patients with McArdle disease.

Abbreviations

PA	Physical activity
MFI-20	Multidimensional Fatigue Inventory
IPAQ-SF	The International Physical Activity Questionnaire Short Form
ISI	Insomnia Severity Index
GF	General fatigue
PF	Physical fatigue
RA	Reduced activity
RM	Reduced motivation
MF	Mental fatigue
MET-minutes	The metabolic equivalent of task

Ethical approval and patient consent statement

Ethical approval was not required for this anonymized survey study. All included respondents gave written consent to participate in the study.

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This study did not receive any funding.

Declaration of Competing Interest

Nicoline Løkken declares that she has no conflict of interest, Nicol C. Voermans declares that she has no conflict of interest, Linda Kahr Andersen declares that she has no conflict of interest, Walaa Karazi declares that she has no conflict of interest, Anna Slipsager declares that he has no conflict of interest, Alfredo Santalla declares that he has no conflict of interest, Alejandro Lucia declares that he has no conflict of interest and John Vissing declares that he has no conflict of interest.

CRediT authorship contribution statement

Anna Slipsager: Formal analysis, Writing – original draft. **Linda Kahr Andersen:** Conceptualization, Methodology, Data curation, Formal analysis, Writing – review & editing. **Nicol Cornelia Voermans:** Data curation, Formal analysis, Writing – review & editing. **Alejandro Lucia:** Data curation, Writing – review & editing. **Walaa Karazi:** Data curation, Writing – review & editing. **Alfredo Santalla:** Data curation, Writing – review & editing. **John Vissing:** Formal analysis, Supervision. **Nicoline Løkken:** Conceptualization, Methodology, Data curation, Formal analysis, Writing – original draft.

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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.2023.11.003.

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