# Cardiorespiratory Fitness, Physical Activity, and Quality of Life in Patients with McArdle Disease

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**ABSTRACT**

MUNGUÍA-IZQUIERDO, D., A. SANTALLA, and A. LUCIA. Cardiorespiratory Fitness, Physical Activity, and Quality of Life in Patients with McArdle Disease. *Med. Sci. Sports Exerc.*, Vol. 47, No. 4, pp. 799–808, 2015. **Background**: This study sought to determine whether health-related quality of life (HRQoL) could be related to cardiorespiratory fitness (CRF) and/or physical activity (PA) in patients with McArdle disease and to compare the CRF and HRQoL data obtained with normative data for age- and sex-matched healthy subjects. **Methods**: Eighty-one adult patients with McArdle disease underwent aerobic capacity testing to determine peak oxygen uptake ($\dot{V}O_{2peak}$), among other variables. HRQoL (Short Form 36-Item Health Survey questionnaire version 2 (SF-36 version 2)) and PA (International Physical Activity Questionnaire) questionnaires were completed by 45 of the patients. HRQoL and $\dot{V}O_{2peak}$ data were compared with published normative data. **Results**: Positive correlations were observed between $\dot{V}O_{2peak}$ and leisure time PA versus the physical component summary score and scores for several domains of the SF-36 questionnaire after adjusting for age, body mass index, and disease severity ($R$ values, 0.42–0.68; all $P < 0.01$). In a regression analysis, the physical component summary score was directly linked to $\dot{V}O_{2peak}$ ($B = 1.28$; 95% confidence interval, 0.78–1.78; $P < 0.001$; $R^2 = 0.422$). The mean $\dot{V}O_{2peak}$ recorded for patients with McArdle disease was 57% lower than the normative value (17.1 ± 5.3 vs 40.0 ± 9.5 $mL \cdot kg^{-1} \cdot min^{-1}$, respectively; $P < 0.001$). All patients showed a CRF below their age-/sex-matched normality value and scored clinically lower in the physical component summary and in most SF-36 domains compared with the Spanish general population. **Conclusions**: Patients showed a consistent link between higher physical HRQoL scores and higher CRF. Patients fulfilling leisure time PA recommendations showed higher CRF and physical HRQoL scores than those not meeting guideline recommendations. According to normative data for healthy subjects, CRF and physical HRQoL are severely impaired in adult patients with McArdle disease. **Key Words:** MCARDLE DISEASE, CARDIORESPIRATORY FITNESS, QUALITY OF LIFE, PHYSICAL ACTIVITY

McArdle disease (or glycogen storage disease type V) is an inherited muscle glycogen metabolism disorder caused by a deficiency in the muscle enzyme *myophosphorylase*, which catalyzes the first step of glycogen breakdown (23). The disorder is arguably the paradigm of exercise intolerance (16) and mainly manifests as acute "crises" of fatigue, myalgia, and muscle contractures (especially during the first minutes of exercise), often accompanied by myoglobinuria as a result of skeletal muscle breakdown, or rhabdomyolysis. In some cases, myoglobinuria may lead to renal damage. Owing to the risk of exertion-induced rhabdomyolysis, physical activity (PA) has long been contraindicated in these patients. However, it has been reported that a sedentary lifestyle further exacerbates the exercise intolerance of patients with McArdle disease (22).

A sedentary lifestyle has been described as a major public health problem of the 21st century (7). Several longitudinal studies have shown the negative health consequences of a sedentary lifestyle (25,33). Physical inactivity leads to poor cardiorespiratory fitness (CRF), and a CRF below the 20th percentile has been linked to increased risk of all-cause mortality (8,9). The variable peak oxygen uptake ($\dot{V}O_{2peak}$) recorded during volitional incremental exercise is considered an essential biological indicator of human health, cardiovascular fitness, and exercise capacity.

It has been established that a sedentary lifestyle and reduced CRF worsen health-related quality of life (HRQoL) both in the general adult population (6,19) and in populations with a chronic disease (21,30,31). However, the effects of McArdle disease on HRQoL have not yet been addressed and there is a lack of data on interrelations among CRF, PA levels, and HRQoL in patients with this disease.

Published data for patients with McArdle disease have been limited in terms of sample size. Several studies have identified lower peak exercise capacity during cardiopulmonary exercise testing in patients with McArdle disease compared with healthy matched controls (23,28,29). However, no comparisons have

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been made with normative data for healthy individuals and only in one study observed a positive association between PA (although not assessed using a validated questionnaire) and $\dot{V}O_{2peak}$ in patients with McArdle disease (23). The present study was therefore designed to 1) determine whether HRQoL is related to CRF and PA (assessed through a validated questionnaire) in a relatively large sample of adult patients with McArdle disease and 2) to examine CRF and HRQoL in these patients and compare these variables with normative data for healthy subjects stratified by age and sex.

Our working hypothesis was that in patients with McArdle disease, higher fitness levels would be associated with better HRQoL and that patients fulfilling PA guideline recommendations would report higher HRQoL than those not fulfilling such recommendations. We also hypothesized that CRF, as measured by $\dot{V}O_{2peak}$, and HRQoL would be low in patients with McArdle disease when compared with normative values for healthy individuals.

## METHODS

**Participants.** The study protocol was approved by the ethics committees of the Universidad Europea de Madrid and Universidad Pablo de Olavide (Spain) and adhered to the tenets of the Declaration of Helsinki 1961 (revision Edinburgh 2000). This observational study was conducted in the exercise physiology laboratory of the Universidad Europea de Madrid from July 2012 to December 2013. Inclusion criteria were age ≥18 yr and the absence of pregnancy, cancer, obstructive lung disease, or cardiovascular disease contraindicating maximal exercise testing. Participants were also subjected to a brief interview about their medical condition and underwent ECG before $\dot{V}O_{2peak}$ testing. Patients were recruited through the Spanish national McArdle disease registry ($n$ = 239 diagnosed patients, according to the most recent registry update) (23). After contacting 228 adult patients or their relatives, a written informed consent was obtained from 45 patients after receiving detailed information about the study's aims and procedures. An informed consent was given at least 1 wk after this information was given. In an effort to increase the statistical power of comparisons between patients' $\dot{V}O_{2peak}$ values and normative values, once informed consent was obtained, we retrieved $\dot{V}O_{2peak}$ data from the Spanish registry for the patients ($n$ = 36) not wishing to participate in this study. These data were derived from the same test performed at our laboratory over the period 2006–2010 (23) using the same protocol and equipment described in the following section for the 45 participants of this study. Thus, the final study sample size for statistical analysis consisted of 81 adult patients with McArdle disease (representing 36% of the total adult patient population) who performed the aerobic capacity test and the subset of 45 patients (20%) who also completed the HRQoL and PA questionnaires. The recruitment procedure is illustrated in the flow diagram in Figure 1.

**Procedure.** For each participant, a visit was scheduled at the university in which the sociodemographic data, anthropometric data, medical records, resting ECG, blood chemistry work, CRF, and perceived effort of the patients were examined. In addition, the Spanish versions of the International Physical Activity Questionnaire (IPAQ) and Short Form 36-Item Health Survey questionnaire version 2 (SF-36) were completed by each patient.

**Blood variables and CRF measures.** All participants arrived at our laboratory after an overnight fast. After an examination (including ECG—see following text for instrumentation) to rule out contraindications for exercise testing, a peripheral venous blood sample (antecubital vein) was collected from each patient before and 1 h after exercise to determine serum levels of the cardiac isoform of troponin I, which is highly specific for the early detection of cardiac injury (1). The sensitivity of the test (Access AccuTnI assay; Beckman™) is 0.01 $ng \cdot mL^{-1}$ with a cutoff value of 0.1 $ng \cdot mL^{-1}$. Preexercise blood samples were also used to determine levels of glucose, total, HDL-, and LDL-cholesterol, and triglycerides (Hitachi 911; Boehringer Mannheim, Mannheim, Germany). The upper normality limits for our laboratory are as follows: glucose, 105 $mg \cdot dL^{-1}$; total-cholesterol, 240 $mg \cdot dL^{-1}$; LDL-cholesterol, 29 $mg \cdot dL^{-1}$; and triglycerides, 200 $mg \cdot dL^{-1}$. $\dot{V}O_{2peak}$ was determined in the patients with McArdle disease during cycle ergometry testing (Ergoselect 200 K; Ergoline GmbH, Bitz, Germany). The test to exhaustion was designed to elicit a maximal exercise response. Thirty minutes before the tests, the patients ingested a CHO drink (75 g sucrose) to protect the muscle from the risk of exercise rhabdomyolysis. Starting at 10 W, the workload was increased by 10 $W \cdot min^{-1}$ (using a ramp-like protocol with 1-W increases every 6 s). The pedaling rate of above 60 rpm was maintained throughout the test. The test ended at volitional exhaustion, including a decrease in the pedaling rate to below 60 rpm. At the end of the incremental test, each patient gave their RPE (10) using the Borg 6- to 20-point scale; patients were asked to point to the number that best reflected their exertion for 1) central work or "heart/lungs" and 2) peripheral work or "legs." Patients could not respond verbally because $\dot{V}O_2$ was measured at the same time. During familiarization and before each test, each participant received detailed instructions on the use of the Borg scale and was given examples of how they might rate central and peripheral exertion. All $\dot{V}O_{2peak}$ assessments were performed using the same breath-by-breath metabolic cart (Vmax 29C; Sensormedics Corp., Yorba Linda, CA), under the supervision of the same researchers (A. L. and A. S.). HR was monitored beat-to-beat through a standard ECG lead on the cart. $\dot{V}O_{2peak}$, percentage age-predicted $HR_{max}$ (220 − age (yr)), and peak power output were recorded as widely accepted valid indices of CRF routinely used both in healthy subjects and in those with some form of illness.

**HRQoL measures.** The HRQoL questionnaire was designed to provide a subject's perception of overall satisfaction

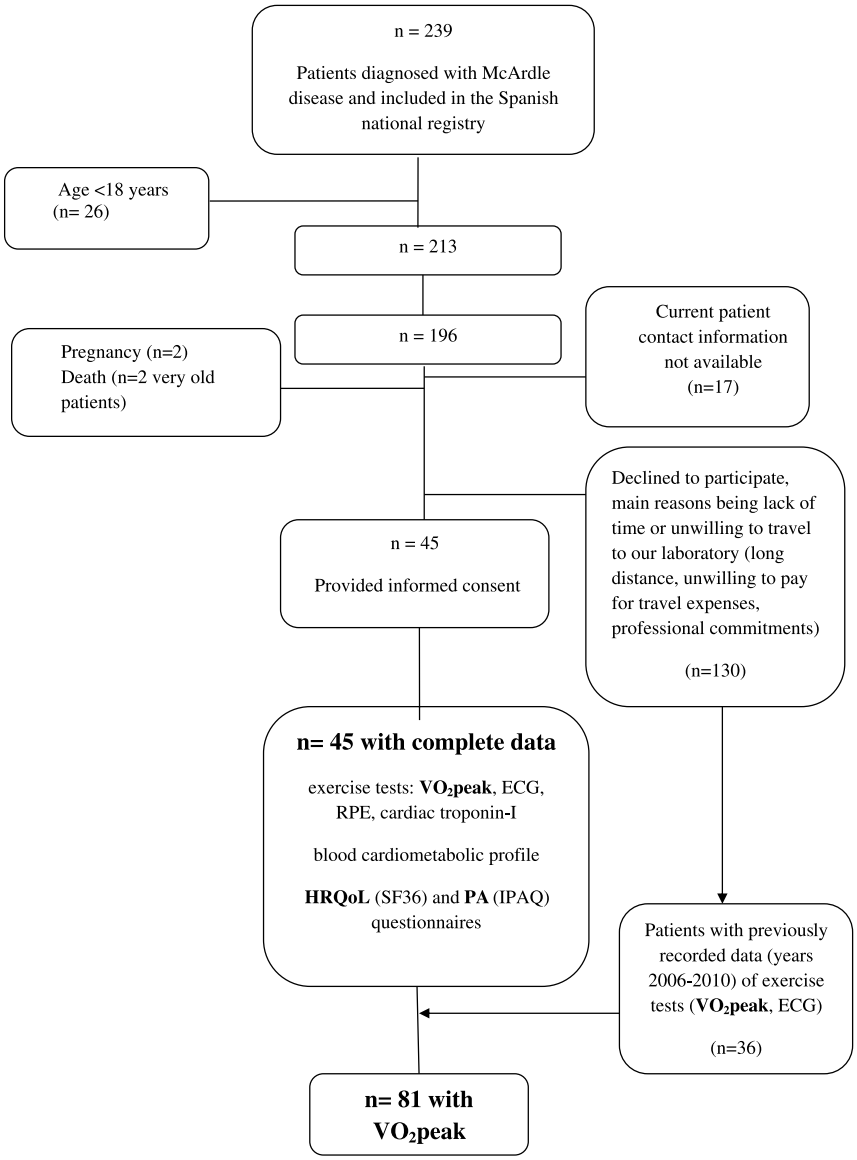


**FIGURE 1—Flow diagram of the study recruitment process. Primary outcomes are indicated in bold).**

with life and involves assessment of functional status in physical, cognitive, emotional, and social health domains. The HRQoL offers a basic understanding of the health status of a given population. We selected the SF-36 version 2 (39). The SF-36 has been shown to have high internal consistency, reliability, and validity across both general populations and specific patient groups (38). The Spanish version has good psychometric properties and uses reference population values (3,36). The SF-36 contains eight domains, four of which assess the physical aspects of HRQoL (physical functioning, physical role, body pain, and general health) and four of which assess the mental aspects of HRQoL (vitality, social functioning, emotional role, and mental health). There is also a physical component summary (PCS) based on the first four domains and a mental component summary (MCS) based on the last four domains. Scores are transformed to a 0-to-100 scale, where a score of 100 represents the best HRQoL. These two summary scales explain 80%–85% of the variance in the eight original dimensions and have shown greater reliability than the eight dimensions (36). The mean score for the general population is 50, with an SD of 10. PCS and MCS are standardized to a mean of 50, with scores above and below 50 representing better or worse than average function, respectively. A difference of half an SD (27) or a five-point difference (domain scores) and two- to three-point difference (summary scores) are considered clinically relevant (37).

**PA measures.** The Spanish long-form version of the IPAQ questionnaire was used to measure the frequency, intensity, and duration of occupational, transport, home, and leisure/sport activity performed in the previous 7 d. The IPAQ is a relatively new instrument that is used to assess health-related PA and physical inactivity in adult population surveys. It has been validated against accelerometry (15) and

shown to have satisfactory psychometric properties (15,35). Before the IPAQ was designed, no standardized self-reported instrument was available for international comparisons. In contrast with most other questionnaires, the IPAQ has been designed to include all the domains of PA (20).

One metabolic equivalent is the amount of oxygen consumed while sitting at rest and is equal to 3.5 mL $O_2 \cdot kg^{-1} \cdot min^{-1}$ and 1.0 $kcal \cdot kg^{-1} \cdot h^{-1}$ as the caloric equivalent for adults (2). PA intensities were set according to IPAQ guidelines, as follows: moderate intensity as 4.0 METs, vigorous intensity as 8.0 METs, and walking as 3.3 METs. Total weekly PA ($MET \cdot min \cdot wk^{-1}$) was computed by multiplying METs by minutes of participation in the specific category of PA. The methods used to score the long IPAQ can be found at the IPAQ Web site (www.ipaq.ki.se). The IPAQ was used to categorize participants into two groups according to their leisure time PA levels. Participants were categorized as "active" if they completed $\geq 600$ $MET \cdot min \cdot wk^{-1}$ or "inactive" if their activity was below this threshold (11).

**Anthropometric measures.** Weight and height were measured to the nearest 100 g and 0.1 cm, respectively, following standard procedures using an electronic balance with an incorporated stadiometer (Seca 780; Seca, Hamburg, Germany) with subjects in their underwear. Body mass index (BMI) was calculated as body mass (kg) divided by height (m) squared.

**Clinical measures.** Patients were allocated to one of the following clinical severity classes according to the most commonly used phenotype severity scale for McArdle disease (24): 0 = asymptomatic or virtually asymptomatic (mild exercise intolerance but no functional limitation in any daily life activity); 1 = exercise intolerance, contractures, myalgia, and limitation during acute strenuous exercise, and occasionally in daily life activities, no record of myoglobinuria, no muscle wasting or weakness; 2 = same as 1 plus recurrent exertional myoglobinuria, moderate restriction in exercise, and limitation in daily life activities; 3 = same as 2 plus fixed muscle weakness with or without wasting and severe limitations on exercise and most daily life activities (24).

**Statistical analyses.** All statistical tests were performed using the Social Sciences package (SPSS 2010, IBM SPSS Statistics 19 Core System User's Guide; SPSS, Inc., Chicago, IL). Significance was set at $\alpha = 0.05$.

To quantify relations between HRQoL and CRF or PA levels, Pearson or Spearman correlation coefficients were used, depending on whether the data showed normal distribution. Correlations were corrected for age, BMI, and disease severity. Correlation values were interpreted as follows: <0.25, weak or null; 0.25–0.50, fair; 0.50–0.75, moderate to good; and >0.75, good to excellent. The relative contributions of several valid indices of maximal CRF and self-reported PA (independent variables) to the summary scales of HRQoL (dependent variables) were determined through multiple regression analyses adjusted for age, BMI, and disease severity.

We calculated estimated means for CRF indices and HRQoL scores by sex, age group, BMI category, number of years since clinical diagnosis, disease severity, and leisure time PA categories. Differences between groups were analyzed by one-way ANOVA. Tukey adjustment was used for multiple comparisons.

The $\dot{V}O_{2peak}$ data obtained for the patients were compared against three published normative data sets, each of which is based on observations from thousands of healthy individuals. Two population normative data sets (5,17) were used to classify each subject as having a $\dot{V}O_{2peak}$ above or below their sex- and age-matched norm. An individual value lower or higher than 2 SD below or over the sex- and age-matched norm mean was considered significantly different. Similarly, each subject's $\dot{V}O_{2peak}$ percentile was identified using age- and sex-matched normative values published by the American College of Sports Medicine (4). An individual value under the 25th or over the 75th percentile of its sex- and age-matched norm value was defined as significantly different. In addition, the number of subjects in each quartile of fitness (i.e., low-to-high fitness) was identified using European normative data (5), in which CRF was associated with cardiovascular risk factors. Bivariate correlations were used to quantify the relations between $\dot{V}O_{2peak}$ and cardiac troponin I, glucose, triglycerides, or total, HDL-, and LDL-cholesterol levels. ANOVA with Tukey adjustment was used to assess differences in these blood measures across $\dot{V}O_{2peak}$ quartile groups.

The SF-36 scores obtained for the study participants were compared against the results of two studies providing SF-36 normative values for the general adult Spanish population (3,36). More specifically, the scores recorded for the SF-36 domains and summary scales in our study population were examined if they fell within the threshold for determining minimally significant differences compared with the Spanish population. In addition, the percentiles of each patient were identified using the age- and sex-matched normative values (3,36).

## RESULTS

None of the patients examined previously ($n = 36$, 2006–2010) or patients in the present cohort ($n = 45$) showed ECG or symptomatic evidence of exertional ischemia. Cardiac troponin I levels were below the cutoff value of 0.1 $ng \cdot mL^{-1}$ in all patients, indicating that intense exercise did not produce cardiac damage. However, the cohort did not show an overall favorable "cardiometabolic" profile. BMI values indicated that 34% of the patients were overweight to obese (>25 $kg \cdot m^{-2}$) and 11% were obese (>30 $kg \cdot m^{-2}$). Patients also showed blood variables (mean ± SD) indicative of "cardiometabolic" risk, as follows: glucose, 94.5 ± 30.8 $mg \cdot dL^{-1}$ (22% of patients above reference limits); total cholesterol, 203.6 ± 42.3 $mg \cdot dL^{-1}$ (7% above reference limits); LDL-cholesterol, 123.0 ± 37.5 $mg \cdot dL^{-1}$ (45% above reference

limits); and triglycerides, 151.5 ± 80.9 mg·dL$^{-1}$ (19% above reference limits).

The simple correlation model for the adult patients with McArdle disease revealed significant positive associations for $\dot{V}O_{2peak}$ versus the PCS and all SF-36 domains, except for emotional role and mental health ($R$ values ranging from 0.32 to 0.65; all $P < 0.05$) (Table 1). These associations between CRF and SF-36 scales remained significant after adjustment for age, BMI, and disease severity, except for social function ($P = 0.09$; data not shown). Other significant positive correlations for leisure time PA versus the PCS and all SF-36 domains, except physical role, emotional role, and mental health, were also found ($R$ values, 0.33–0.67; all $P < 0.05$) (Table 1). These links between leisure time PA and SF-36 scales remained significant after adjustment for age, BMI, and disease severity except for the pain, vitality, and social function domains ($P = 0.27$, 0.21, and 0.20, respectively; data not shown). A few significant fairly positive associations were detected between several SF-36 domains and vigorous intensity, walking intensity, active transport, and total PA ($R$ values, 0.30–0.45; $P < 0.05$) (Table 1), but none remained significant after correcting for age, BMI, and disease severity. In the regression analysis, the PCS score was directly associated with $VO_{2peak}$ ($B = 1.28$; 95% confidence interval, 0.78–1.78; $P < 0.001$; $R^2 = 0.422$). The MCS score was not associated with any of the variables analyzed.

The sample for CRF determination consisted of 81 adults (48% women) whose mean ± SD values for age and BMI were 41.2 ± 14.1 yr (range, 18–80 yr) and 25.4 ± 4.5 kg·m$^{-2}$ (range, 17–43 kg·m$^{-2}$), respectively. Table 2 provides the CRF levels of all the adult patients with McArdle disease classified by sex, age group, BMI category, years since clinical diagnosis, disease severity, and leisure time PA category. Inactive patients and female patients showed lower $\dot{V}O_{2peak}$, percentage age-predicted $HR_{max}$, and peak power than active patients and male patients, respectively ($P < 0.03$). Ten (12%) patients (all men) reached the estimated $HR_{max}$ for their age. Central exertion RPE scores were lower than peripheral exertion RPE scores (12.5 ± 3.2 and 15.5 ± 2.7 points, respectively; $P < 0.001$ for paired (one sample) Student's $t$-test). $\dot{V}O_{2peak}$ and peak power decreased with age ($P < 0.01$). $\dot{V}O_{2peak}$ also decreased with BMI category ($P = 0.027$) (Table 2). LDL-cholesterol levels were significantly different across $\dot{V}O_{2peak}$ quartile groups (122 ± 35, 127 ± 37, 143 ± 34, and 86 ± 35 mg·dL$^{-1}$, respectively, from lowest to highest $\dot{V}O_{2peak}$; $P = 0.030$). The remaining multiple comparisons of blood measures across $\dot{V}O_{2peak}$ quartiles and bivariate correlations between $\dot{V}O_{2peak}$ and blood measures were not significant.

The mean $\dot{V}O_{2peak}$ for the patients with McArdle disease was 57% lower than the European normative value (17.1 ± 5.3 vs 40.0 ± 9.5 mL·kg$^{-1}$·min$^{-1}$, respectively; $P < 0.001$, unpaired Student's $t$-test). Most of the patients with McArdle disease ($n = 74$, 91%) tested below the first percentile and all patients were below the $\dot{V}O_{2peak}$ 10th percentile compared with the general population, adjusted for age and sex (4). Using American Heart Association normative data (17) and recent epidemiological data (5) as reference, the CRF level of all the patients was below age- and sex-matched normative values, i.e., in the lowest quartile.

HRQoL was assessed in 45 adult patients (42% women) whose mean ± SD values for age and BMI were 40.6 ± 15.2 yr (range, 18–80 yr) and 25.3 ± 3.4 kg·m$^{-2}$ (range, 19–34 kg·m$^{-2}$), respectively. Table 3 provides the HRQoL scores for all 45 patients classified by sex, age group, BMI category, years since clinical diagnosis, disease severity, and leisure time PA category. Average scores for the subscales ranged from 42.5 points in the vitality domain to 85.2 in the emotional role domain. The PCS score was significantly lower than the MCS score and ranged from 35.8 to 50.2. Women scored significantly lower in MCS and in the three SF-36 domains than men did ($P < 0.05$). More than half ($n = 24$, 53%) of the patients reported that they fulfilled the recommended energy expenditure of ≥600 MET·min·wk$^{-1}$ in leisure time PA. Inactive patients scored significantly lower in PCS and across most domains than active patients did ($P < 0.01$). The

TABLE 1. Associations between HRQoL scores and the rest of variables in adult patients with McArdle disease.

| | $n$ | Physical Function (0–100) | Physical Role (0–100) | Pain (0–100) | General Health (0–100) | Vitality (0–100) | Social Function (0–100) | Emotional Role (0–100) | Mental Health (0–100) | PCS (0–100) | MCS (0–100) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Age (yr) | 45 | −0.27 | −0.14 | −0.04 | −0.15 | −0.34* | −0.04 | 0.05 | 0.05 | −0.22 | 0.05 |
| BMI (kg·m$^{-2}$) | 43 | 0.13 | −0.04 | 0.01 | −0.11 | −0.06 | −0.14 | −0.03 | 0.15 | −0.04 | 0.05 |
| Disease severity (0–3) | 43 | −0.43** | −0.20 | −0.37* | −0.21 | −0.16 | −0.21 | −0.26 | −0.12 | −0.34* | −0.10 |
| $\dot{V}O_{2peak}$ (mL·kg$^{-1}$·min$^{-1}$) | 39 | 0.55*** | 0.52** | 0.52** | 0.51** | 0.54** | 0.32* | 0.08 | 0.02 | 0.65*** | −0.06 |
| Total PA levels (MET·min·wk$^{-1}$) | 45 | 0.22 | −0.10 | −0.04 | 0.41** | 0.25 | 0.16 | −0.14 | 0.04 | 0.12 | 0.02 |
| Walking intensity (MET·min·wk$^{-1}$) | 45 | 0.27 | −0.04 | 0.06 | 0.45** | 0.25 | 0.28 | 0.05 | 0.18 | 0.15 | 0.25 |
| Moderate intensity (MET·min·wk$^{-1}$) | 45 | 0.03 | −0.06 | −0.08 | 0.18 | 0.16 | −0.04 | −0.27 | −0.16 | 0.04 | −0.20 |
| Vigorous intensity (MET·min·wk$^{-1}$) | 45 | 0.34* | 0.04 | 0.04 | 0.32* | 0.14 | 0.07 | 0.04 | 0.02 | 0.19 | −0.05 |
| Working (MET·min·wk$^{-1}$) | 45 | 0.10 | −0.10 | −0.01 | −0.04 | −0.05 | −0.23 | −0.07 | −0.12 | −0.01 | −0.14 |
| Active transport (MET·min·wk$^{-1}$) | 45 | 0.30* | 0.07 | 0.10 | 0.23 | 0.05 | 0.15 | 0.18 | 0.23 | 0.17 | 0.17 |
| Domestic (MET·min·wk$^{-1}$) | 45 | −0.19 | −0.06 | −0.10 | 0.03 | 0.12 | −0.01 | −0.17 | −0.08 | −0.09 | −0.10 |
| Leisure (MET·min·wk$^{-1}$) | 45 | 0.47** | 0.17 | 0.33* | 0.67*** | 0.38* | 0.50*** | 0.12 | 0.09 | 0.44** | 0.17 |

Correlation values are either Pearson or Spearman correlation.
*$P < 0.05$.
**$P < 0.01$.
***$P < 0.001$.

TABLE 2. CRF levels in all adult patients with McArdle disease and classified by sex, age group, BMI category, disease severity category, and years since clinical diagnosis.

| | *n* | $\dot{V}O_{2peak}$ (mL·kg$^{-1}$·min$^{-1}$) | | Percent $HR_{max}$ | | Peak Power Output (W) | |
|---|---|---|---|---|---|---|---|
| All | 81 | 17.1 | (15.9–18.3) | 84.4 | (81.6–87.2) | 74.7 | (68.3–81.1) |
| European normative data[a] | 4631 | 40.0 (9.5) | | | | | |
| Age groups (yr) | | | | | | | |
| 18–29 | 17 | 21.0 | (18.7–23.2) | 89.8 | (83.5–96.8) | 89.7 | (77.4–102.0) |
| 30–39 | 32 | 16.9 | (15.0–18.8) | 82.8 | (78.5–87.1) | 71.5 | (62.0–81.1) |
| 40–49 | 15 | 16.6 | (14.1–19.1) | 84.1 | (77.1–91.1) | 75.0 | (56.6–93.4) |
| 50–59 | 11 | 15.9 | (12.9–18.9) | 85.5 | (74.1–96.9) | 78.0 | (60.8–95.2) |
| 60–80 | 6 | 10.7 | (7.8–13.5) | 76.6 | (68.8–84.4) | 37.4 | (17.0–57.9) |
| *P* value | | 0.000 | | 0.193 | | 0.005 | |
| BMI category (kg·m$^{-2}$) | | | | | | | |
| <25 | 36 | 18.4 | (16.8–20.1) | 83.9 | (79.9–87.9) | 74.9 | (66.5–83.4) |
| 25–30 | 34 | 16.6 | (14.7–18.5) | 85.5 | (80.7–90.3) | 75.5 | (64.0–86.9) |
| >30 | 9 | 13.4 | (10.4–16.4) | 82.2 | (72.5–91.9) | 69.6 | (42.7–96.5) |
| *P* value | | 0.028 | | 0.751 | | 0.883 | |
| Sex | | | | | | | |
| Men | 42 | 19.2 | (17.8–20.6) | 89.2 | (85.6–92.9) | 86.1 | (78.9–93.3) |
| Women | 39 | 14.9 | (13.2–16.5) | 79.1 | (75.3–82.9) | 61.8 | (52.2–71.4) |
| *P* value | | 0.000 | | 0.000 | | 0.000 | |
| Disease severity | | | | | | | |
| Class 0 | 3 | 23.3 | (12.7–34.0) | 98.3 | (86.6–110.1) | 105.0 | (20.7–189.4) |
| Class 1 | 32 | 16.8 | (15.0–18.7) | 85.7 | (81.6–89.8) | 75.9 | (65.1–86.7) |
| Class 2 | 26 | 16.9 | (14.8–18.9) | 82.2 | (77.5–86.8) | 72.6 | (63.7–81.5) |
| Class 3 | 14 | 15.2 | (12.0–18.4) | 79.7 | (70.5–89.0) | 65.9 | (44.7–87.2) |
| *P* value | | 0.117 | | 0.080 | | 0.192 | |
| Years since diagnosis | | | | | | | |
| ≤5 yr | 33 | 17.1 | (15.4–18.8) | 85.2 | (81.0–89.4) | 73.1 | (65.4–80.9) |
| >5 yr | 47 | 17.1 | (15.5–18.8) | 84.5 | (80.8–88.2) | 75.8 | (66.2–85.4) |
| *P* value | | 0.978 | | 0.791 | | 0.689 | |
| LTPA levels | | | | | | | |
| Inactive | 19 | 15.1 | (13.2–17.0) | 82.0 | (77.4–86.6) | 69.6 | (60.7–78.5) |
| Active | 21 | 20.0 | (17.4–22.7) | 90.5 | (84.7–96.3) | 92.7 | (76.7–108.6) |
| *P* value | | 0.003 | | 0.023 | | 0.015 | |

[a]European normative data are expressed as mean (SD) (5).
% $HR_{max}$, percentage of the estimated $HR_{max}$ (220 − age); LTPA, leisure-time PA.

physical function domain tended to decrease with clinical severity class ($P = 0.056$). The vitality domain increased with years since clinical diagnosis ($P = 0.037$).

Patients with McArdle disease scored lower in all SF-36 domains when compared with the Spanish general population (3). Differences were clinically significant for PCS and all SF-36 domains, except for emotional role and mental health. More than half of the patients with McArdle disease scored below the 20th percentile in PCS and in all domains except emotional role and mental health compared with the Spanish general population, adjusted for sex and age group (3,36).

## DISCUSSION

This study examines the effects of McArdle disease on CRF, self-reported PA, and HRQoL. Its main finding was that in adult patients, HRQoL, CRF, and leisure time PA were significantly interrelated. According to the correlates observed, lower CRF and leisure time PA were significantly associated with lower physical HRQoL scores. $\dot{V}O_{2peak}$ emerged as the only predictor of physical HRQoL and was able to explain 42% of the variance in the PCS component of quality of life. In addition, our adult patients with McArdle disease showed disproportionally lower CRF and physical domains of HRQoL than age- and sex-matched healthy individuals. Although not unexpected, such findings have not been previously demonstrated.

Our results indicate that in patients with McArdle disease, $\dot{V}O_{2peak}$ and leisure time PA were positively related to the physical components of HRQoL. Correction for the confounders age, BMI, and disease severity did not affect the statistical power of the correlations observed between CRF and physical SF-36 components, although the significance of correlations between leisure time PA and several SF-36 domains was lost. Our findings are broadly consistent with those of other studies conducted in other populations (31,32), and, overall, they suggest that improved fitness confers adult patients with McArdle disease some HRQoL benefits. In our study participants, such benefits were independent of age, BMI, or disease severity.

In patients with McArdle disease, $\dot{V}O_{2peak}$ data are clinically relevant because this variable is an integral biological index that represents the amount of oxygen transported and used in cell metabolism, deficient cardiopulmonary fitness being among the main cardiovascular mortality risk factors in the general population (7). Our patients' mean $\dot{V}O_{2peak}$ was low; 26% of patients (three men and 18 women) did not reach the threshold (13 mL·kg$^{-1}$·min$^{-1}$) for independent living. Women were more severely affected than men, in line with the results of other studies (26). The age-predicted $HR_{max}$ was not reached in female patients. Only three patients (approximately 7%) attained ≥85% of the estimated $HR_{max}$ for their age and ≥17 points in the central work RPE scale. Central RPE scores were significantly lower than peripheral RPE scores, which apparently suggests that peripheral

TABLE 3. HRQoL levels in all adult patients with McArdle disease and classified by sex, age group, BMI category, disease severity category, and years since clinical diagnosis.

| | *n* | Physical Function (0–100) | Physical Role (0–100) | Pain (0–100) | General Health (0–100) | Vitality (0–100) | Social Function (0–100) | Emotional Role (0–100) | Mental Health (0–100) | PCS (0–100) | MCS (0–100) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| All | 45 | 53.6 (46.9–60.2) | 55.8 (47.3–64.4) | 49.0 (40.8–57.2) | 45.8 (38.6–53.1) | 42.5 (35.8–49.2) | 74.7 (67.2–82.3) | 85.2 (79.3–91.0) | 68.9 (62.8–75.0) | 35.8 (32.4–39.2) | 50.2 (46.9–53.4) |
| Spanish normative data[a] | | 84.7 (24.0) | 83.2 (35.2) | 79.0 (27.9) | 68.3 (22.3) | 66.9 (22.1) | 90.1 (20.0) | 88.6 (30.1) | 73.3 (20.1) | 50 (10) | 50 (10) |
| Age groups (yr) | | | | | | | | | | | |
| 18–29 | 11 | 60.9 (46.1–75.7) | 58.0 (39.1–76.8) | 49.6 (28.0–71.1) | 52.8 (33.4–72.3) | 50.0 (37.8–62.2) | 73.9 (59.6–88.1) | 87.1 (75.3–99.0) | 66.4 (55.5–77.2) | 38.6 (29.6–47.6) | 49.8 (44.3–55.2) |
| 30–39 | 17 | 51.5 (41.8–61.2) | 61.0 (49.8–72.3) | 49.8 (40.0–59.5) | 45.8 (34.0–57.6) | 45.2 (34.2–56.2) | 81.6 (70.0–93.2) | 85.3 (75.2–95.4) | 72.1 (61.9–82.3) | 35.9 (31.6–40.2) | 52.1 (46.5–57.7) |
| 40–49 | 4 | 66.3 (18.3–114.2) | 64.1 (2.0–126.1) | 56.3 (−1.8 to 114.3) | 36.0 (–22.1 to 94.1) | 40.6 (9.7–71.6) | 71.9 (37.9–105.8) | 81.3 (43.2–119.3) | 63.8 (29.8–97.9) | 40.0 (12.2–67.7) | 45.6 (29.2–62.0) |
| 50–59 | 9 | 53.3 (35.4–71.3) | 45.8 (20.4–71.3) | 48.6 (26.6–70.5) | 48.8 (35.8–61.8) | 36.8 (15.0–58.6) | 77.8 (55.4–100.2) | 87.0 (70.7–103.4) | 76.7 (57.9–95.4) | 33.5 (24.6–42.3) | 52.9 (42.0–63.8) |
| 60–80 | 4 | 30.0 (12.8–47.2) | 42.2 (–19.3 to 103.7) | 38.3 (–30.5 to 107.0) | 30.0 (6.6–53.4) | 25.0 (–11.3 to 61.3) | 43.8 (2.4–85.2) | 79.2 (40.9–117.5) | 50.0 (26.6–73.4) | 29.1 (13.0–45.3) | 41.6 (30.5–52.7) |
| *P* value | | 0.118 | 0.579 | 0.929 | 0.505 | 0.346 | 0.101 | 0.952 | 0.227 | 0.575 | 0.368 |
| BMI category ($kg \cdot m^{-2}$) | | | | | | | | | | | |
| <25 | 20 | 52.3 (41.9–62.6) | 54.7 (40.6–68.8) | 45.9 (32.1–59.6) | 48.6 (36.3–60.9) | 43.4 (33.6–53.3) | 81.3 (70.3–92.2) | 87.5 (78.2—96.8) | 70.5 (60.9–80.1) | 34.9 (29.3–40.5) | 52.3 (47.8–56.7) |
| 25–30 | 20 | 55.5 (44.5–66.5) | 60.6 (46.9–74.3) | 56.2 (44.0–68.4) | 46.6 (35.7–57.4) | 44.7 (33.3–56.1) | 71.3 (58.5–84.0) | 83.3 (74.5–92.2) | 67.3 (57.8–76.7) | 38.3 (33.4–43.2) | 48.5 (43.0–53.9) |
| >30 | 3 | 56.7 (96.0–103.7) | 45.8 (13.5–78.2) | 27.7 (–12.0 to 67.3) | 29.0 (–1.2 to 59.2) | 29.2 (–18.3 to 76.6) | 62.5 (8.7–116.3) | 83.3 (11.6–155.0) | 75.0 (–0.6 to 150.6) | 29.4 (1.6–57.2) | 49.7 (5.5–93.9) |
| *P* value | | 0.883 | 0.649 | 0.189 | 0.435 | 0.542 | 0.312 | 0.793 | 0.788 | 0.366 | 0.564 |
| Sex | | | | | | | | | | | |
| Men | 26 | 57.5 (48.4–66.6) | 64.2 (52.2–76.2) | 55.7 (43.6–67.7) | 46.4 (35.6–57.1) | 47.8 (37.7–58.0) | 77.0 (66.6–87.3) | 91.4 (85.4–97.3) | 75.2 (68.5–81.9) | 37.4 (32.2–42.5) | 53.0 (49.3–56.7) |
| Women | 19 | 48.2 (38.2–58.1) | 44.4 (33.4–55.5) | 40.0 (29.8–50.1) | 45.1 (35.0–55.2) | 35.2 (27.6–42.8) | 71.7 (59.9–83.6) | 76.8 (66.1–87.4) | 60.3 (49.7–70.9) | 33.7 (29.4–38.0) | 46.4 (40.6–52.1) |
| *P* value | | 0.164 | 0.020 | 0.056 | 0.867 | 0.060 | 0.497 | 0.011 | 0.013 | 0.289 | 0.041 |
| Disease severity | | | | | | | | | | | |
| Class 0 | 3 | 75.0 (62.6–87.4) | 83.3 (11.6–155.0) | 74.7 (14.8–134.6) | 70.3 (26.7–114.0) | 58.3 (22.5–94.2) | 87.5 (33.7–141.3) | 88.9 (41.1–136.7) | 66.7 (–4.0 to 137.3) | 49.9 (37.0–62.8) | 49.0 (14.8–83.3) |
| Class 1 | 17 | 59.4 (47.9–70.9) | 55.5 (40.5–70.5) | 52.4 (39.7–65.2) | 49.1 (36.1–62.2) | 44.1 (30.3–57.9) | 76.5 (62.7–90.3) | 89.2 (80.3–98.2) | 70.0 (59.1–80.9) | 37.2 (32.1–42.3) | 51.0 (45.7–56.3) |
| Class 2 | 16 | 48.1 (37.7–58.5) | 57.0 (42.5–71.6) | 48.2 (33.8–62.6) | 36.6 (23.8–49.3) | 39.8 (28.0–51.7) | 78.9 (68.4–89.4) | 91.2 (84.4–97.9) | 76.9 (68.1–85.7) | 32.2 (26.2–38.3) | 54.3 (49.6–59.1) |
| Class 3 | 7 | 40.0 (16.7–63.3) | 43.8 (15.0–72.5) | 31.1 (0.8–61.5) | 49.1 (30.6–67.7) | 39.3 (25.6–52.9) | 60.7 (32.1–89.4) | 65.5 (40.5–90.4) | 54.3 (38.2–70.4) | 33.3 (20.9–45.8) | 42.8 (31.9–53.7) |
| *P* value | | 0.056 | 0.278 | 0.127 | 0.125 | 0.609 | 0.334 | 0.018 | 0.100 | 0.078 | 0.117 |
| Years since diagnosis | | | | | | | | | | | |
| ≤5 yr | 16 | 51.6 (38.6–64.5) | 53.9 (36.8–71.0) | 46.4 (31.2–61.7) | 41.4 (29.1–53.7) | 34.0 (21.8–46.2) | 66.4 (51.1–81.7) | 83.3 (73.2–93.5) | 65.6 (53.8–77.5) | 34.8 (29.0–40.6) | 47.4 (41.2–53.5) |
| >5 yr | 27 | 55.2 (46.9–63.5) | 57.4 (46.7–68.1) | 51.2 (40.5–62.4) | 49.6 (39.7–59.4) | 48.6 (40.5–56.8) | 81.0 (72.4–89.6) | 85.2 (77.1–93.2) | 71.9 (64.3–79.4) | 36.8 (32.3–41.3) | 52.1 (47.9–56.2) |
| *P* value | | 0.608 | 0.703 | 0.571 | 0.291 | 0.037 | 0.066 | 0.769 | 0.338 | 0.577 | 0.176 |
| LTPA levels | | | | | | | | | | | |
| Inactive | 21 | 42.6 (33.5–51.7) | 47.3 (36.0–58.6) | 36.5 (25.9–47.2) | 29.2 (21.3–37.1) | 29.5 (22.6–36.4) | 61.3 (49.7–73.0) | 82.5 (72.7–92.4) | 65.0 (55.6–74.4) | 29.6 (25.2–34.0) | 47.6 (42.3–52.9) |
| Active | 24 | 63.1 (54.9–71.5) | 63.3 (50.6–75.9) | 60.0 (48.9–71.0) | 60.4 (52.1–68.7) | 53.9 (44.8–63.0) | 86.5 (78.9–94.1) | 87.5 (80.2–94.8) | 72.3 (64.0–80.6) | 41.2 (37.1–45.4) | 52.5 (48.4–56.5) |
| *P* value | | 0.001 | 0.060 | 0.003 | 0.000 | 0.000 | 0.000 | 0.400 | 0.232 | 0.000 | 0.133 |

[a]Spanish normative data are expressed as mean (SD) for domain scores (3) and summary scores (36).
Values are expressed as mean (95% confidence interval).
LTPA, leisure time PA.

muscle factors, i.e., early occurrence of severe leg muscle pain/fatigue, would preclude attainment of actual maximal cardiac output during the cycle ergometer tests and thus of a true $\dot{V}O_{2peak}$ value in these patients. The uniqueness of this rare disease, particularly with regard to muscle sensations, must be kept in mind because it makes comparisons of RPE responses or $\dot{V}O_{2peak}$ values between patients with McArdle disease and healthy individuals difficult. Particularly, continuous ramplike cycle ergometer protocols like the one used here do not allow patients with McArdle disease to take one or more short rest periods during the tests, which would likely attenuate muscle pain. In fact, Buckley et al. (12) recently suggested the use of a 12-min self-paced walk test as an alternative to traditional $\dot{V}O_{2peak}$ protocols for assessing exercise capacity in these patients.

Only 3% of patients (two men) had a $\dot{V}O_{2peak}$ ≥8 METs, which is the minimum threshold for optimal health. Age, BMI, and low leisure time PA levels also had a negative effect on $\dot{V}O_{2peak}$. Female, inactive, or obese patients showed a mean $\dot{V}O_{2peak}$ only slightly above levels considered necessary for independent living. This low aerobic capacity is in line with the results of other studies that have examined patients with McArdle disease (23,28,29). When comparing $\dot{V}O_{2peak}$ values in our patients with McArdle disease with normative data for healthy adults (4,5,17), all patients scored below the 10th percentile, indicating severely reduced aerobic capacity. The reasons for this low aerobic fitness of patients with McArdle disease are not fully clear. It may be partly attributable to impaired muscle oxidation because of patients' severely compromised capacity to produce pyruvate, which is thought to play an anaplerotic role in the Krebs cycle (29). However, the exercise restrictions traditionally placed on patients with McArdle disease because of concerns about exercise-induced myalgia and recurrent rhabdomyolysis are likely to be a contributing factor to reduced PA. In turn, lower physical fitness will have a negative effect on maximal aerobic capacity, giving rise to a vicious circle in which inactivity leads to even more deconditioning and further inactivity. A further explanation is that these patients are usually unaccustomed to exercise training or testing, and further research is needed to establish whether $\dot{V}O_{2peak}$ values in patients with McArdle disease tend to be underestimated. It is tempting to speculate that such values could be improved simply by making sure that patients are more trained in exercise testing and more accustomed to the unpleasant feeling associated with maximal or near-maximal exertion.

Regardless of the cause, a lower physical fitness compared with age- and sex-matched normative values will place adult patients with McArdle disease at increased risk of cardiovascular compromise. This is an important aspect, considering the poor cardiometabolic profile showed by the present patients. Hence, even if we apply a +25% correction factor to the $\dot{V}O_{2peak}$ values obtained to offset potential biases (e.g., testing inexperience and occurrence of premature muscle fatigue/pain before attainment of actual maximal cardiac output, preventing the patient reaching his/her "true" $\dot{V}O_{2peak}$), CRF would still be classified as low in approximately 95% of all the male patients, using as reference the data for male patients with hypertension reported by Church et al. (13). This low level of CRF has been linked to approximately four- or threefold greater risk of mortality because of cardiovascular disease compared with men with a similar BMI but a high or intermediate CRF level, respectively (23). In fact, every reduction of 5 $mL \cdot kg^{-1} \cdot min^{-1}$ in $\dot{V}O_{2peak}$ corresponds to approximately 56% higher prevalence of a cardiovascular risk factor (5) and a maximal aerobic capacity below the 20th percentile has been associated with increased risk of all-cause mortality (8). We nevertheless believe that any improvement in $\dot{V}O_{2peak}$ achieved by consistent exercise training in patients with McArdle disease will be of great rehabilitation value and will help restore a capacity for daily living activities. It is important that future studies investigate existing PA barriers in these patients and methods to improve physical fitness, which in turn will enhance mortality, morbidity, and HRQoL in adult patients with McArdle disease.

The HRQoL scores obtained in the patients with McArdle disease are essential to understand the health status of this population. To our knowledge, no previous study has examined the characteristics of HRQoL in patients with McArdle disease. Overall, the mean SF-36 score recorded in the patients was lower for the physical than that for the mental domains. Women were more severely affected than men were in the MCS and several physical and mental domains. Failure to achieve the minimum recommendations of energy expenditure in leisure time PA had a negative effect on PCS and most SF-36 domains. Considering a 5- to 10-point change as clinically significant in patients with a variety of illnesses (37), the differences observed between leisure time PA categories in this study are all the more meaningful. In addition, a graded dose–response relation was established for leisure time PA and HRQoL, strengthening current PA recommendations (18). Scores obtained in the vitality domain were higher in patients clinically diagnosed more years ago. This highlights the importance of an early clinical diagnosis and suggests that patient vitality can improve with time as they become physically active as soon as possible during childhood and adapt to living with the disease.

When comparing HRQoL values in patients with McArdle disease with normative data for age- and sex-matched healthy adults (3,36), most patients scored below the 20th percentile in PCS and most SF-36 domains. In addition, the differences in PCS and most SF-36 domains exceeded the threshold for determining minimally important differences (27), indicating substantial impairment of the physical components of HRQoL. These low scores in patients with McArdle disease could be attributable to their low CRF and PA levels.

The present study is not without limitations. The cross-sectional design of our study precludes the identification of any causal relations. The known limitations of all nonprobability samples, including their less representativeness and

unknown levels of sampling error, are further limitations. The relatively small size of our age and BMI groups also limits the statistical power and validity of the data. By design, the present study does not include a control group with which to compare CRF and HRQoL data. Furthermore, normative CRF data are not available for healthy Spanish adults. To eliminate selection bias, we opted to use normative data representative of large population sets. Thus, the references used are more representative of the non-McArdle population than if we had assessed 81 non-McArdle individuals. Given the self-reported nature of the PA data, PA levels are likely to be overestimated (34). As with all research based on self-reported measures of PA, there are also inherent limitations such as recall bias and social desirability. Future research initiatives should quantify PA levels in patients with McArdle disease using objective methods (e.g., accelerometry).

Our study, nevertheless, has several strengths. CRF and BMI were measured objectively. Self-reported methods of BMI can be biased because of underreporting of weight and overreporting of height (14). Direct measurements of $\dot{V}O_{2peak}$ have been previously conducted in smaller or selected populations of patients with McArdle disease (28,29). In contrast, the present population is larger and consists of a less selected sample of participants given that all adult patients diagnosed in Spain were invited to participate in our study. In addition, the consecutive recruitment process revealed no difference in the sex ratio. We used a well-established, valid, and reliable measure of HRQoL that uses a norm-based scoring methodology. Norm-based scoring allows for comparisons with other studies that have assessed PCS and MCS regardless of the SF version used and avoids the ceiling effect sometimes seen in the eight SF-36 version 2 domains (6).

## CONCLUSIONS

In conclusion, there seems to be a consistent relation between higher physical HRQoL scores and higher CRF levels among adult patients with McArdle disease. In addition, patients with McArdle disease meeting leisure time PA guideline recommendations showed higher CRF and reported higher physical HRQoL than those not fulfilling these recommendations. The CRF and physical HRQoL of the present adult patients with McArdle disease were severely impaired compared with normative data for age- and sex-matched healthy adults. In view of the lack of curative treatment available for McArdle disease (with no effective enzyme replacement/gene therapy in the foreseeable future), randomized controlled trials of PA (e.g., moderate aerobic training) are required to determine whether reduced CRF and HRQoL can be improved.

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