**Title:** Effectiveness of land- and water-based exercise on fatigue and sleep quality in women with fibromyalgia: the al-Ándalus quasi-experimental study

**Objective:** To assess the effectiveness of 24 weeks of land- and water-based exercise on fatigue and sleep quality in women with fibromyalgia, and the persistence of changes 12 weeks after exercise cessation.

**Design:** quasi-experimental study

**Setting:** University facilities and fibromyalgia associations.

**Participants:** Women with fibromyalgia (N=250; 50.8 ± 7.6 years old)

**Interventions:** Participants were assigned to land-based exercise (n=83), water-based exercise (n=85) or no exercise control (n=82) groups. The intervention groups engaged in a similar multicomponent exercise program for 24 weeks.

**Main outcome measures:** The Multidimensional Fatigue Inventory (MFI) and Pittsburgh Sleep Quality Index (PSQI) were used.

**Results:** Intention-to-treat analyses revealed that, compared to the control group, at week 24: (i) the land-based exercise group improved physical fatigue (mean difference -0.9 units; 95% CI -1.7 to -0.1; Cohen’s d=0.4), and (ii) the water-based exercise group improved general fatigue (-0.8; -1.4 to -0.1, d=0.4), and global sleep quality (-1.6; -2.7 to -0.6, d=0.6). Additionally, compared to the land-based exercise group, the water-based exercise group improved global sleep quality (-1.2; -2.2 to -0.1, d=0.4). Changes were generally not sustained at week 36.

**Conclusion:** Land-based multicomponent exercise improved physical fatigue, whereas water-based exercise improved general fatigue and sleep quality. The magnitude of the changes was small-to-medium and no benefits were maintained after exercise cessation.

ClinicalTrials.gov ID: NCT01490281

**Keywords**: Chronic pain, Management, Physical exercise, Rehabilitation, Training Vitality

**Abbreviations:**

ACR: American College of Rheumatology

ANCOVA: Analysis of Covariance

CI: Confidence Interval

BMI: Body Mass Index

FIQR: Fibromyalgia Impact Questionnaire

ITT: Intention-to-treat

MFI: Multidimensional Fatigue Inventory;

PSQI: Pittsburgh Sleep Quality Index

**INTRODUCTION**

The prevalence of fibromyalgia is approximately 2% in the general population1, leading to a substantial clinical and economic burden 2,3. Fatigue and poor sleep quality are two core symptoms of fibromyalgia 4,5. A remarkably high proportion (>80%) of people with fibromyalgia experience severe fatigue 6 or important sleep difficulties 7 and identify these symptoms as the most important clinical features of fibromyalgia besides pain 7. Although exercise is often recommended as a first-line therapy tomanage fatigue and poor sleep quality in fibromyalgia 8,9, there is no consensus on which type of exercise, land- or water-based exercise, is more advisable 10.

To date, the limited evidence available comparing the effectiveness of land- and water-based exercise on fatigue and sleep quality in fibromyalgia precludes establishing the superiority of any setting over the other. Although a recent meta-analysis 11 suggested that both settings seem to provide similar benefits for fatigue reduction, the number of high-quality studies is scarce and precludes firm conclusions. Another narrative review 12 suggested slight superior benefits for sleep quality after water-based exercise. Given that type of exercise and the setting could differentially benefit various outcomes 9, to better understand the effectiveness of both land- and water-based interventions is important from both research and clinical perspectives.

A recent umbrella review highlighted that, in order to move forward in the use of exercise as a therapy in fibromyalgia, there is a need for: (i) further evidence using accurately reported exercise interventions on other symptoms beyond pain and, (ii) greater insights on the long-term effects of exercise 10. Therefore, the aims of this study in women with fibromyalgia were to assess: (i) the influence of 24 weeks of land- and water-based exercise on fatigue and sleep quality, and (ii) the persistence of the changes in the outcomes 12 weeks after exercise cessation. Based on the available literature, the hypotheses were that: (i) land- and water-based exercise will have similar and moderate effects for lowering fatigue 11, (ii) water-based exercise will have superior (vs. land-based exercise) but small effects for enhancing sleep quality 11,12, and (iii) these improvements will not be sustained after exercise cessation 13. These are secondary analyses from the al-Ándalus trial, which aimed to investigate the effectiveness of land- and water-based exercise to improve the overall impact of fibromyalgia (primary outcome) and other health-related outcomes 14, which main results are reported elsewhere15.

**MATERIAL AND METHODS**

*Study design and protocol registration*

This study included two secondary outcomes from the al-Ándalus trial 14. Further details about the study design, procedures and protocol were covered elsewhere 14. This study was registered as a randomized controlled exercise trial (ClinicalTrials.gov ID: NCT01490281). But ultimately, a strict randomized design was not feasible (see the *Allocation and blinding* section). The study design, study methods, and informed consent process were approved prior to the enrollment of participants by the Medical Ethics Committee. All participants gave their written informed consent.

*Participant recruitment and eligibility criteria*

Participants for this multicenter project were recruited from local fibromyalgia patient associations in 7 provinces of Andalusia (southern Spain). We had one center in each of the provinces. Email, letters, phone calls, and online advertisements were used to contact participants. All participants underwent a screening process before the study began. The inclusion criteria were: i) to be 35-65 years old, ii) to be previously diagnosed with fibromyalgia by a rheumatologist and meeting the American College of Rheumatology criteria 16, iii) answer “no” to all questions on the Physical Activity Readiness Questionnaire-PAR-Q 17, iv) not to be engaged in regular physical activity (>20 min on > 3 days/week) in the past 3 months, v) be able to communicate in Spanish and, vi) be able to walk without assistance. Exclusion criteria were: i) being men, ii) to have an acute or terminal illness, iii) unstable medical condition, iv) severe dementia (Mini Mental State Examination <10 18), v) refusal to comply with study conditions or to be randomly assigned to the training or control group, and vi) presence of neuromuscular disease or drugs affecting neuromuscular function.

*Allocation and blinding*

Although this study was initially designed as a randomized controlled trial, randomization was not finally possible given the difficulties in maintaining adequate temperature (~30°C) in pools from some study locations. Consequently, randomization (computed-generated random sequence) was limited to one province (n=79; 32.4% of participants) while participants in the other provinces were allocated to the exercise (i.e., land-based or water-based exercise) or control group depending on the possibility of accessing appropriate facilities. Due to the nature of the intervention (exercise), participant blinding was not possible. Baseline and follow-up measurements were performed at the local fibromyalgia patient associations or at sport facilities. Assessors were not blinded to group allocation during the evaluations.

*Procedures*

The assessments were conducted at baseline, at the end of the exercise intervention (24 weeks) and 12 weeks after the training ceased. Participants were asked not to initiate any other exercise program or therapy during the 24 weeks of the intervention program or during the 12 weeks after exercise cessation. The measurements were performed on two alternate days. On day one, the inclusion criteria were confirmed, including the tender points examination following the American College of Rheumatology (ACR) guidelines16. In addition, anthropometry and body composition were assessed and sociodemographic and clinical data were self-reported by participants. Fatigue and sleep-related questionnaires were given to patients to be completed at home. Two days later, the questionnaires were collected, revised by the research team to minimize missing data, and completed with the participants (if needed). This article followed the CONSORT guidelines19 (Supplementary Table 1).

*Intervention groups*

All the participants continued their usual care (mostly pharmacological treatment) during the study.

*Exercise interventions*

The interventions were performed in 17 waves from 2011 to 2013, between the months of November and May. The exercise intervention groups (land- and water-based) trained following the same exercise protocol, three non-consecutive days/week (45-60 min per session) over a 24-week period (72 sessions in total). The exercise intervention was designed to improve physical fitness components (cardiorespiratory fitness, muscle strength, and range of motion), which are inversely associated with fibromyalgia symptomatology 20–27. The intervention followed the standards of the American College of Sports Medicine (ACSM) for exercise prescription in patients with fibromyalgia28.

Each session lasted 45-60 min and was divided into: warm-up (8-10 min), conditioning [muscle-strengthening (15-17 min) and aerobic (15-25 min)], and cool-down (10 min). The warm-up included mobility exercises and global movements. Muscle-strengthening training volume ranged from 1 set of 4 exercises x 12 repetitions (week 1) to 3 sets of 10 exercises x 16 repetitions (week 24) and included circuit exercises for the major muscle groups. The intensity was tailored to the individual by means of perceived exertion (RPE). Borg’s conventional scale (6-20 points)29 was planned ranging from 6-11 (week 1) to 13-17 (week 24). Aerobic exercise duration ranged from 15 min (week 1) to 25 min (week 24) and intensity ranged from 40-50% Heart Rate Reserve (HRR) (week 1) to 65-80%HRmax (week 24); this involved low-impact exercises for the major muscle groups. The cool-down included static stretching and relaxation activities. Exercise progression was achieved by increasing the volume first and, finally, increasing the intensity or load. The same exercise protocols were used in both settings to increase comparability between the programs.

*Land-based exercise adaptations*

Some exercises were initially adapted to be performed seated. Participants were encouraged to gradually perform all exercises in an upright position. A sports rubber band and dumbbells (0.5-2kg) were included to achieve the established RPE.

*Water-based exercise adaptations*

The water-based exercise intervention group trained in a chest-high (~120 cm) warm (~30°C) pool. The same exercise intervention program as that of the land-based program was used, adapted to the singularity imposed by the water. The training intensity and the muscle groups activated were kept as similar as possible in the two intervention modalities. The muscle-strengthening and aerobic exercises were performed using water and aquatic materials as resistance or aids. Stretching was performed in a standing position and relaxation activities while floating.

*Usual care group (Controls)*

Participants assigned to the usual care (control) group, where waiting-list conditions applied, received general information about fibromyalgia and general advice about the positive effects of being physically active. Informative pamphlets were provided describing the benefits of physical activity and general guidelines about how to increase daily physical activity levels. After the follow-up assessment, these participants were offered to participate in the exercise program, not for research purposes.

*Participant retention and adherence*

Attendance rates and reasons for missed sessions and drop outs were recorded. Several strategies were conducted to increase adhere, including: music during sessions, individualized attention and telephone calls following missed sessions.

*Fatigue*

The Spanish version of the Multidimensional Fatigue Inventory (MFI) 30 was used. This questionnaire has demonstrated adequate psychometric properties in people with fibromyalgia 30. The MFI is composed of 20 items that evaluate fatigue experienced in the time frame “lately” in five dimensions 31: i) general fatigue (which concerns physical sensations of fatigue), ii) physical fatigue (which includes general statements about fatigue and decreased functioning), iii) mental fatigue (which includes cognitive symptoms and mental feelings of fatigue), iv) reduced activity (which refers to the influence of physical and psychological factors on the level of activity), and v) reduced motivation (which refers to lack of motivation to starts any activity). Each subscale consists of four items ranging from 4 to 20, where higher scores indicate more fatigue.

*Sleep quality*

Sleep quality over the last month interval was assessed with the Spanish version of the Pittsburgh Sleep Quality Index 32. This questionnaire is considered a reliable instrument with a good convergent validity for people with fibromyalgia 33. This questionnaire is composed of 19 questions addressing seven components: subjective sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disturbances, sleep medication, and daytime dysfunction. Each component includes items with four-point Likert scales (0-3). The sleep quality global score is the sum of all components, and the score ranges from 0 to 21. Higher scores indicate worse sleep quality.

*Other variables*

Disease severity was measured with the Spanish version of the revised Fibromyalgia Impact Questionnaire (FIQR)34,35. All the participants filled out a socio-demographic and clinical data questionnaire to gather information related to age, marital status, educational level, occupational status, time since diagnosis, menstruation, analgesic and antidepressant consumption, and participation in psychotherapist or physical therapy. Weight (kg) was measured with a bioimpedance device (InBody R20, Seoul, Korea), height (m) was measured using a stadiometer (Seca 22, Hamburg, Germany), and the body mass index (BMI) was calculated (kg/m2).

*Statistical analyses*

These are secondary analysis of the al-Ándalus trial 14. The sample size was originally calculated to detect a clinically relevant change in the primary trial outcome (i.e. disease impact), estimating that a total of 135 participants (45 in each group) were needed 14. Due to relatively large sample size, the normal distribution of the main study variables was assumed. Descriptive continuous data were presented as the mean and standard deviation and categorical data as frequency and percentage. To compare baseline characteristics between groups, the Student t-test (for continuous variables) and the Chi square test (for categorical variables) were used. To examine differences between groups, linear mixed models were conducted including the fixed, categorical group of intervention, time, and time x group interaction. Bonferroni post-hoc adjustments for multiple comparisons were used. The *Cohen’s d* was used to calculate the standardized effect size and was interpreted as small (~0.2), medium (~0.5) or large (~0.8 or greater).

The primary analyses were performed using the intention-to-treat (ITT) principle and imputed data. Simple imputations were performed to complete missing values at baseline (<1%). Multiple imputation by chained equations (MICE) methodology was used for imputing missing values at weeks 24 and 36. This was implemented with the “R v3.6” statistical software using the "mice v3.7"36 and "VIM v4.8"37 libraries. All analyses were replicated using complete data-case analyses (i.e. without imputed data) to assess the robustness of the results. Additionally, to assess the efficacy of the exercise interventions, per-protocol analyses were performed including only those participants attending at least 70% of the sessions. The Statistical Package for the Social Sciences (International Business Machines (IBM) SPSS Statistics for Windows, Version 22.0. Armonk, NY, USA: IBM Corp) was used. The statistical significance was set at *P*<0.05.

**RESULTS**

A total of 318 patients were initially contacted. The flowchart of the study participants throughout the trial is presented in Figure 1. A total of 250 patients who volunteered met the inclusion criteria, gave their written informed consent, and were assigned to either the land-based exercise group (n=83), the water-based exercise group (n=85), or the control group (n=82). The mean attendance was 82.9% and 79.1% of the sessions in the land- and water-based exercise groups, respectively. A total of 54 participants (65.1%) in the land-based group and a total of 46 participants (54.1%) in the water-based group attended ≥70% of the sessions.

The water-based exercise group presented better sleep latency compared to the land-based exercise group (Mean Difference (MD) -0.36 units; *P*=0.031). The land-based exercise group presented lower scores for sleep medication compared to the control group (MD -0.5 units; *P*=0.023). In the water-based exercise group, the number of university-educated participants was 11% and 15.7 % lower than in the control and land-based exercise groups (*P*=0.007). No significant differences between groups at baseline were observed in the other variables (*P*>0.05*)*. Table 1 shows the baseline characteristics of the study participants.

Figure 2 shows how the means in the outcomes (fatigue-related variables and sleep global score) evolved for each intervention group at each time point: baseline, post-exercise program (week 24) and 12 weeks after exercise cessation in intention to treat analyses.

Table 2 shows the ITT analyses assessing the differences between groups regarding post-intervention changes (week 24) in the outcomes. The land-based exercise group improved physical fatigue and sleep medication compared to the control group (MDs ranging from 0.4 to 0.9, *Cohen’s d* =0.4). The water-based exercise group improved general fatigue, subjective sleep quality, sleep medication, daytime dysfunction and global sleep quality compared to the control group (MDs ranging from 0.2 to 1.6, *Cohen’s d* ranging from 0.4 to 0.7). The water-based exercise group also improved subjective sleep quality, sleep latency and global sleep quality compared to the land-based exercise group (MDs ranging from 1.2 to 2.2, *Cohen’s d* ranging from 0.4 to 0.7).

Table 3 shows the ITT analyses assessing the differences between groups for changes after exercise cessation (week 36). The land-based and water-based exercise groups worsened sleep duration and medication compared to the control group (MDs ranging 0.3 to 0.4, *Cohen’s d* 0.4).

When considering only participants with complete data (i.e. without imputed data) in sensitivity analyses (Supplementary Tables 2-3), improvements after exercise in sleep-related variables but not in fatigue were confirmed. When considering a minimum of 70% of attendance in per-protocol analyses (Supplementary Tables 4-5), the effects of land-based and water-based exercise on fatigue and sleep quality in the main analyses were generally confirmed.

**DISCUSSION**

The main findings of these secondary analyses indicate that 24 weeks of land-based multicomponent exercise improved physical fatigue and water-based exercise improved general fatigue compared to a usual care control group. The land-based exercise modality had generally no effect on sleep quality, whereas the water-based exercise improved subjective sleep quality, sleep medication, daytime dysfunction and global sleep quality. Twelve weeks after exercise cessation, the improvements with exercise were not sustained. These findings support the inclusion of exercise in the management of fatigue and sleep quality in fibromyalgia and evidence the distinct benefits of exercising in each setting and the reversibility of these benefits when stopped.

The findings from this study showed an improvement of fatigue up to 5.5% with effect sizes ranging from small to moderate. A recent meta-analysis by Bidonde et al. 13 determined that multicomponent exercise interventions carried out in fibromyalgia improved fatigue ~13% compared to a control group 13. This high variability of the effects of exercise on fatigue in fibromyalgia and their overall moderate effect size have been recently evidenced in a meta-analysis 11. There are no previous studies in fibromyalgia to ascertain the clinical relevance of the exercise-induced changes found in fatigue. Of noting, the majority of previous multicomponent exercise interventions in fibromyalgia 13 used unidimensional scales to assess fatigue, which limits a complete description of the fatigue experience 31. The multidimensional questionnaire used in the present study better captures the multifaceted nature of fatigue 31 and the most improved domains according to the setting where exercise was performed.

Physical and general fatigue were the most improved domains of fatigue in the land-based and the water-based exercise groups, respectively. Exercise could positively influence fatigue through different peripheral and central mechanisms 38. Specifically, as higher deconditioning has been related to higher fatigue 38, the additional benefits in land-based exercise for physical fatigue (closely related to functioning) could be due to additional benefits of this setting for muscle strength gains 39. Exercise could also counteract the anomalies in the central nervous system that lead to fatigue in fibromyalgia (by, for instance, regulating the levels of metabolites and promoting angiogenesis, neurogenesis, and connectivity of the hippocampus40,41).

Our results also demonstrated small-to-moderate improvements of sleep quality mostly after water-based exercise. This concurs with a prior meta-analysis 11 and a narrative review 12 which suggested that: i) the effect of exercise on sleep quality in fibromyalgia was small 11, and ii) there are slighter superior benefits of water-based exercise for sleep quality compared to land-based exercise 12. The number of randomized-controlled trials assessing how multicomponent exercise (similar to the present study) influence sleep quality in fibromyalgia is scarce 11 and often include small sample sizes, this hindering comparisons. It is noteworthy that, according to the cutoff of 5 points suggested for the global PSQI 42, all intervention groups could be considered as "poor sleepers” before and after exercise, emphasizing the highly deteriorated sleep quality of these patients.

The evidence showing positive effects of exercise on sleep in fibromyalgia is still of moderate quality 11, but there are plausible mechanisms to explain these benefits. Performing exercise could induce a decrease in sympathetic nervous system activity (which induces to high stress levels and is typically altered in fibromyalgia43) and an increase parasympathetic activity (leading to greater muscular and nervous relaxation and, therefore, greater sleep quality)44. Previous evidence45 also suggests that the relaxation effects of warm water (due to weight-bearing, tactile, and thermal stimulation as well as the inertial effect on movement46,47) could explain improvements of sleep in this setting.

The improvements in fatigue or sleep quality were not sustained 12 weeks after exercise cessation. In general, the long-term benefits of exercise interventions on fibromyalgia are not well understood due to the limited follow-up in interventions carried out so far 13. The meta-analysis by Bidonde et al.13 concluded that, based only on 3 randomized controlled trials, the positive effects of multicomponent exercise on fatigue were not sustained 13-26 weeks after the end of the intervention, although an effect was seen after 27-52 weeks. One of these interventions also demonstrated that improvements in sleep were not sustained after 24 weeks 48. Although evidence in this regard is very limited 10,13, available data along with the findings of the present study suggest that the small benefits fatigue and sleep quality disappear after exercise cessation.

*Practical implications and future lines of research*

This study provides a multicomponent exercise program for people with fibromyalgia. The positive effects of this exercise program were based at group level but it should be noted that individuals with fibromyalgia are highly heterogeneous 49. As the exercise setting differently impacted fatigue and sleep quality, future studies exploring which individuals could benefit the most from each intervention setting are needed. Given that positive effects of exercise were reversible, it seems relevant to apply strategies to make exercise an habit and to transfer the “use it or lose it” health message among patients. Although this study included elements traditionally lacking in previous trials comparing land vs. water-based exercise (i.e., control group and a follow-up 13) in a relatively large sample size, further intervention studies with long follow-up phases and well-described exercise programs will provide greater insights on the long-term effects of exercise in this population.

**Study limitations**

Some study limitations need to be underlined. The random allocation of participants was only partial. However, the trial quality may have a greater impact on the treatment effect size than the randomization alone, and high quality non-randomized controlled trials may result in similar effects that those found in randomized controlled trials50.

**CONCLUSION**

In summary, land-based exercise improved physical fatigue whereas water-based exercise improved general fatigue and showed superiority for improving sleep quality in women with fibromyalgia. The improvements in each exercise group were of small-to-medium magnitude and not sustained 12 weeks after exercise cessation. These findings support strategies that include exercise in management of fatigue and sleep quality in fibromyalgia and warrant further research examining the relevance of exercising regularly to sustain such benefits.

**Data sharing**

The data that support the findings of this study are available from the corresponding author, MBC, upon reasonable request.

**APPENDICES**

Supplementary table 1. TREND statement checklist

Supplementary Table 2. Differences in fatigue and sleep quality between groups after 24 weeks of water or land-based exercise (complete cases)

Supplementary table 3. Differences in fatigue and sleep quality between groups 12 weeks after water-based or land-based exercise cessation (complete cases)

Supplementary table 4. Differences in fatigue and sleep quality between groups after 24 weeks of water or land-based exercise (per protocol analyses-70% attendance)

Supplementary table 5. Differences in fatigue and sleep quality between groups 12 weeks after water-based or land-based exercise cessation (per protocol analyses-70% attendance)

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**Suppliers**

a. InBody R20; Biospace.

b. FPK 20; Wagner Instruments.

c. IBM SPSS Statistics for Windows, version 22.0; IBM.

**Figure legends:**

**Figure 1.** Flow chart of the study participants throughout the al-Ándalus trial. ITT: Intention-to-treat

**Figure 2.** Means of fatigue and sleep quality variables at baseline, at week 24 (after exercise intervention program) and at week 36 (12 weeks after exercise cessation) for each intervention group in intention-to-treat analyses. Greater scores indicate worse health status

MFI: Multidimensional Fatigue Inventory, PSQI: Pittsburgh Sleep Quality Index

\*Significant differences between mean change of land vs. control group

╪ Significant differences between mean change of water vs. control group

┼ Significant differences between mean change of land vs. water group