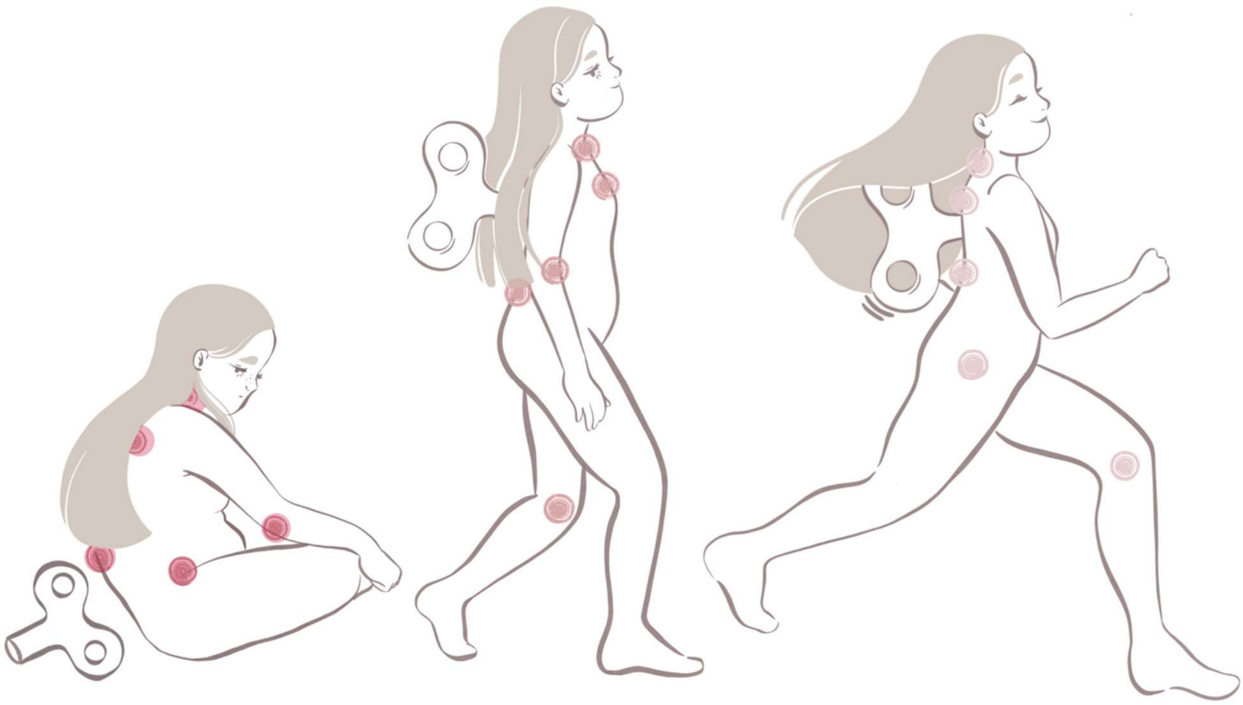
INTERNATIONAL DOCTORAL THESIS

PHYSICAL ACTIVITY, SEDENTARY TIME, AND EXERCISE: INFLUENCE ON PAIN, DISEASE IMPACT, AND HEALTH-RELATED QUALITY OF LIFE IN WOMEN WITH FIBROMYALGIA

Blanca Gavilán Carrera



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Physical activity, sedentary time, and exercise: influence on pain, disease impact, and health-related quality of life in women with fibromyalgia.

Actividad física, tiempo sedentario y ejercicio: influencia sobre el dolor, impacto de la enfermedad y calidad de vida relacionada con la salud en mujeres con fibromialgia.

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A mamá,

más cerca que lejos,

en un allá que siempre es aquí.

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ABBREVIATIONS

ACC: Accelerometer

ACR: American College of Rheumatology

AF: Actividad Física

AFMV: Actividad Física Moderada-Vigorosa

ASCM: American College of Sports Medicine

ANCOVA: Analysis of Covariance

CI: Confidence Interval

CPM: Counts Per Minute

CVRS: Calidad de Vida Relacionada con la Salud

FIQ: Fibromyalgia Impact Questionnaire

FIQR: Revised Fibromyalgia Impact Questionnaire

FSS: Fibromyalgia Severity Score

HRQoL: Health-Related Quality of Life

LPA: Light Physical Activity

MANCOVA: Multivariate Analysis of Covariance

MCS: Mental Component Summary

MVPA: Moderate-to-Vigorous Physical Activity

PA: Physical Activity

PAR-Q: Physical Activity Readiness Questionnaire

PCS: Physical Component Summary

SE: Standard Error

SD: Standard Deviation

SF-36: 36-item Short Form Health Survey

SSS: Symptom Severity Scale

ST: Sedentary Time

TS: Tiempo Sedentario

VAS: Visual Analog Scale

WPI: Widespread Pain Index

ABSTRACT

Fibromyalgia is a chronic condition of unknown etiology, characterized by chronic widespread pain in addition to multiple comorbidities. Fibromyalgia greatly impacts health-related quality of life (HRQoL) and poses a burden for health care system. It is of clinical and public health interest to identify factors associated to a better prognosis of the disease, especially in the form of non-pharmacological therapies.

The overall objective of this Doctoral Thesis has been to analyze the influence of physical activity (PA), sedentary time (ST), and exercise on disease impact, pain, and HRQoL in women with fibromyalgia. To address these aims, six studies were conducted in the context of two projects: the al-Ándalus cohort study and the al-Ándalus trial.

Project I (studies 1-5) included a total of 407 women with fibromyalgia that were re-evaluated after 2 and 5 years. PA intensity levels (light, moderate, and moderate-to-vigorous [MVPA]) and ST variables (duration and patterns of accumulation of prolonged periods) were measured using triaxial accelerometry. Project II (study 6) included a total of 244 women with fibromyalgia that were quasi-randomized to either land-based exercise (*n*=80), water-based exercise (*n*=79) or usual care (*n*=85) groups. The intervention groups performed multicomponent exercise (including aerobic, muscle-strengthening, and flexibility training) for 24 weeks and participants were assessed at baseline (pre-test), at week 24 (post-test), and at 12-week follow-up. The same outcomes were evaluated in both projects, including: disease impact (Revised Fibromyalgia Impact Questionnaire [FIQR]), pain (algometry, visual analog scale [VAS], pain subscale of FIQR, and pain subscale from 36-item Short-Form Health Survey [SF-36]), and HRQoL (SF-36).

The main findings of this Doctoral Thesis suggest that, in women with fibromyalgia: **i)** higher PA and lower ST are linked to better HRQoL, being ST and MVPA independently associated. Participants meeting the PA recommendations have better HRQoL, **ii)** Higher levels of total and prolonged ST accumulated in different bout lengths are individually and jointly associated with worse disease impact and HRQoL. These associations were generally independent of MVPA, **iii)** Replacing 30 minutes of ST with light PA or MVPA in isotemporal substitution models is associated with lower disease impact and better HRQoL, **iv)** Objectively measured variables (pressure pain threshold, PA, and ST) slightly change towards less favorable values at 2- and 5-year follow-up, while self-reported outcomes (disease impact, pain, and HRQoL) show a trend for improvement over years. Baseline ST or light PA levels do not predict future outcomes and contradictory findings for baseline MVPA are found. Changes in ST (negatively), light PA, and MVPA (positively) predict future pain and HRQoL, **v)** 24 weeks of land- or water-based multicomponent exercise do not improve overall disease impact. Modest benefits in pain and physical HRQoL (for land-based exercise) and in mental HRQoL (for water-based exercise) are obtained. These improvements are more consistent and persistent for land-based exercise when a fair level of attendance is reached, whereas benefits of exercise in warm water are independent of exercise adherence.

The results of this Doctoral Thesis provide greater insights on the influence of PA intensity levels, ST duration and patterns, and multicomponent exercise performed in two settings, in relation to disease impact, pain, and HRQoL in women with fibromyalgia. Future research complementing these findings will enhance our understanding about the preventive and therapeutic value of daily activity and exercise as modifiable health behaviors in this population.

RESUMEN

La fibromialgia es una enfermedad crónica de origen desconocido que se caracteriza por dolor crónico generalizado y una elevada comorbilidad. La fibromialgia tiene un gran impacto en la calidad de vida relacionada con la salud (CVRS) y el sistema de salud. Es de interés clínico y de salud pública identificar factores asociados a un mejor pronóstico de la enfermedad, especialmente en el marco de las terapias no farmacológicas.

El objetivo general de esta Tesis Doctoral ha sido analizar la influencia de la actividad física (AF), el tiempo sedentario (TS) y el ejercicio sobre el impacto de la enfermedad, el dolor y la CVRS de las mujeres con fibromialgia. Para ello se llevaron a cabo seis estudios en el contexto de dos proyectos: estudio de cohortes al-Ándalus y estudio de intervención al-Ándalus.

El Proyecto I (estudios 1-5) incluyó un total de 407 mujeres con fibromialgia que fueron reevaluadas en un seguimiento a 2 y 5 años. Los niveles de intensidad de AF (ligera, moderada y moderada-vigorosa [AFMV]) y las variables de TS (duración total y patrones de acumulación de periodos prolongados) se midieron con acelerometría triaxial. El proyecto II (estudio 6) incluyó un total de 244 mujeres con fibromialgia que fueron cuasi-aleatorizadas a grupo de ejercicio en seco (*n*=80), ejercicio en agua (*n*=79) o cuidado habitual (*n*=85). Los grupos de intervención realizaron ejercicio multicomponente (incluyendo entrenamiento aeróbico, fuerza y flexibilidad) durante 24 semanas y se evaluó a los participantes al inicio (pre-test), a la semana 24 (post-test) y después de 12 semanas de seguimiento. Las mismas variables dependientes se evaluaron en ambos proyectos incluyendo impacto de la enfermedad (*Revised Fibromyalgia Impact Questionnaire* [FIQR]), dolor (algómetro, escala visual analógica, subescala de dolor de FIQR y subescala de dolor del cuestionario de salud SF-36) y CVRS (SF-36).

Los resultados de esta Tesis Doctoral sugieren que, en mujeres con fibromialgia: **i)** Mayores niveles de AF y menores niveles de TS se relacionan con una mejor CVRS, relacionándose el TS y la AFMV de forma independiente. Las mujeres que cumplen las recomendaciones de AF tienen una mejor CVRS, **ii)** Mayores niveles de TS total y prolongado acumulado en bloques de diferente duración se asocian de forma individual y conjunta con una peor CVRS y un mayor impacto de la enfermedad. Estas asociaciones fueron generalmente independientes del nivel de AFMV, **iii)** Sustituir 30 minutos de TS con AF ligera o AFMV en los modelos de sustitución *isotemporales* se asocia con una mejor CVRS y un menor impacto de la enfermedad, **iv)** Las variables medidas de forma objetiva (sensibilidad al dolor, AF y TS) cambian ligeramente a valores menos favorables a lo largo de 2 y 5 años, mientras que las variables autorreportadas (impacto de la enfermedad, dolor y CVRS) tienen una ligera tendencia a la mejora a lo largo de los años. Los niveles basales de TS o AF ligera no predicen la salud futura y existen resultados contradictorios con relación al nivel basal de AFMV. Los cambios de TS (de forma negativa), AF ligera y AFMV (de forma positiva) se asocian con el dolor y la CVRS futuros, **v)** 24 semanas de ejercicio multicomponente en seco o en agua no disminuyen el impacto de la enfermedad. Se observan modestas mejoras para el dolor y CVRS física (en el grupo de ejercicio en seco) y para la CVRS mental (en el grupo de ejercicio en agua). Estas mejoras son más consistentes y persistentes en el grupo de ejercicio en seco cuando el nivel de asistencia es óptimo mientras que los beneficios del ejercicio en agua son independientes de la adherencia al ejercicio.

Los resultados de esta Tesis Doctoral proporcionan un mayor conocimiento sobre la influencia de los diferentes niveles de AF, la duración y patrones del TS y el ejercicio multicomponente en diferentes medios en relación con el impacto de la enfermedad, el dolor y la CVRS en mujeres con fibromialgia. Futuros estudios que complementen esta evidencia ayudarán a evaluar el valor preventivo y terapéutico de la actividad física diaria y el ejercicio en esta población.

GENERAL INTRODUCTION

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Fibromyalgia: characteristics of the disease

Definition

Fibromyalgia is a chronic multi-dimensional condition of unknown etiology, characterized by chronic widespread pain as the dominant symptom[1,2*]. Fibromyalgia is considered a central sensitivity syndrome in which sensory input is amplified and there is an enhanced response to sensation[3,4]. This results in the perception of pain from non-painful stimuli (allodynia) and greater pain than would be expected from painful stimuli (hyperalgesia)[5]. A wide array of other symptoms such as fatigue, stiffness, sleep disturbances, or cognitive difficulties, are also common but not universal[6]. The presence of pain, in addition to the variable number of comorbidities, have a substantial impact on daily life of patients[7] and emphasize that it is a complex and heterogeneous condition.

Prevalence

General prevalence of fibromyalgia ranges from 2% to 8% depending on the country and the criteria used for diagnosis[3]. The prevalence of fibromyalgia in Spain is ~2.4% according to the 1990 American College of Rheumatology (ACR) diagnosis criteria[8]. The clinical manifestation of fibromyalgia appears between 40 and 50 years of age and it is markedly more prevalent in women (4.2%) than in men (0.2 %)[8]. The use of new preliminary fibromyalgia criteria for diagnosis could lead to a greater proportion of men diagnosed[9,10]. Due to the considerable low prevalence among men, research has been typically focused on women.

Burden

Fibromyalgia is associated with a burden for the health care system, with significant direct health care costs and indirect costs[11,12]. Direct health care costs are defined as medical care

** The numbering of references will be independent for each part of the Doctoral Thesis* expenditures (medical visits, diagnostic complementary studies, drug and non-drug therapy, etc.) whereas indirect costs are attributable to productivity losses (early sick leave and retirement, or productivity losses among housewives), payment of people needed for help, patient transportation, etc.[13]. In Spain, it has been estimated that people with fibromyalgia result in a total annual extra cost of 5.011 € per patient, derived from direct (614 €) and, mostly, indirect (4.397 €) costs[12]. Annual drug expenditure per patient, on average, is also considerably higher compared to people without fibromyalgia[12], although it seems to be compensated for by less use of other health care resources and fewer days off work[14]. An increased disease severity and delay in the diagnosis of the disease are correlated to higher total costs[15]. Treatment for fibromyalgia not only improves their clinical status but is also accompanied by a significant reduction in the costs of the illness[14]. All these evidence underline the clinical and economical relevance of optimizing early diagnosis and strategies for the management of the disease.

Diagnosis

In 1990, the ACR first approved criteria for fibromyalgia, that depended entirely on the physical examination of 18 tender points[2] shown in figure 1*. This criteria required widespread pain for at least 3 months and the presence of 11 of 18 tender points when 4 kg/cm^2 of force is applied. Pain was considered widespread when is present in the left and right sides of the body, above and below the waist, and in the axial skeletal pain (cervical spine or anterior chest or thoracic spine or low back)[2].

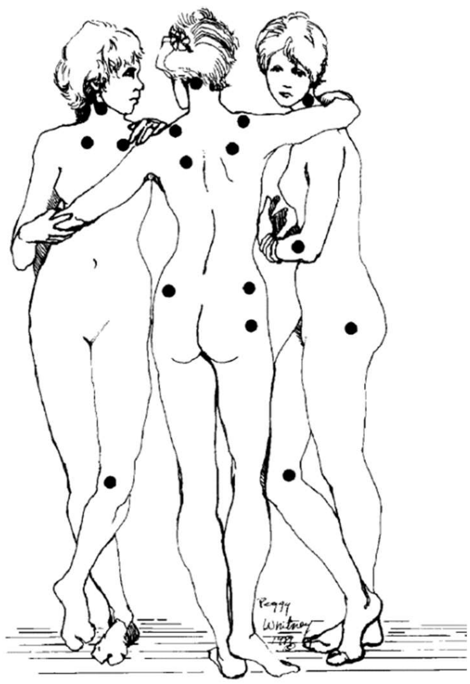

Figure 1. Tender point locations for the first diagnosis criteria raised in 1990 (Wolfe et al. 2011 adaptation from Peggy Whitney's drawing)

** The numbering of figures will be independent for each part of the Doctoral Thesis*

Over time, a number of practical concerns arose about this diagnosis criteria[16]. The tender points' examination was rarely performed in clinical settings and required extensive training[16]. Also, it was very difficult to measure the force exerted, all this leading to unreliable measures[16]. Lastly, by concentrating on tender points, the 1990 criteria ignored other key symptoms of the disorder[16].

In 2010, the ACR proposed the "Preliminary Diagnostic Criteria for Fibromyalgia and Measurement of Symptom Severity" as an alternative method of diagnosis[9]. This method abandoned the tender point count, and used the widespread pain index (WPI) instead, a 0–19 count of the number of body regions reported as painful by the patient. In addition, the presence and severity of fatigue, unrefreshed sleep, cognitive difficulty, and the extent of somatic symptoms was rated by the physician from 0 to 3. These items were combined into a 0–12 symptom severity scale (SSS). This diagnostic criterion established 3 conditions: i) WPI ≥ 7, and SSS ≥5, or WPI 3-6 and SSS ≥ 9, ii) presence of symptoms at least for 3 months, and iii) patients do not have a disorder that would otherwise explain the pain[9]. The 2010 criteria altered the fibromyalgia concept allowing patients with moderate musculoskeletal pain to be diagnosed if they had a high enough symptom score. This, in turn, helped expand understanding about the complexity and heterogeneity[17,18] of this disease. A modification of 2010 ACR criteria were introduced in 2011 allowing self-reporting for their use in epidemiologic and clinical studies, although its validity for diagnosis is questioned[10]. In addition, the 2011 modifications introduced a Fibromyalgia Severity Score (FSS), a sum of WPI and SSS that allowed quantitative measurement of severity of disease-related symptoms[10]. An investigation implemented in our research group[19] demonstrated the validity of the modified 2010 criteria in the Spanish populations and underlined the interest of its use in conjunction with the 1990 criteria for an improved diagnosis.

In 2016, an update of the modified 2010 criteria was proposed, introducing slight changes based on experience in clinical and research settings[20]. These changes include: i) changes in

WPI minimal score, being necessary WPI ≥ 7 and SSS ≥5, or WPI **4**-6 and SSS ≥ 9, ii) the use of a generalized pain criterion (defined as pain in at least 4 of 5 regions excluding jaw, chest, and abdominal areas), to insure that regional pain syndromes are not captured by the criteria, iii) the return to the recommendation that "fibromyalgia remains a valid construct irrespective of other diagnoses and does not exclude the presence of other clinically important illnesses", iv) the recommendation for the use of the FSS, and iv) the combination of the ACR 2010 "physician" based criteria with the 2011 modified "patient" criteria into a single set of criteria that can be used by physicians or patients[20].

Beyond pain in fibromyalgia: health-related quality of life and disease impact

The complex symptomatology in fibromyalgia can be prolonged and debilitating, resulting on considerable impact on health-related quality of life (HRQoL). The term HRQoL is not well defined[21] but could be understood as a subjective concept that represents how individuals' perceive their physical and mental health[22]. People with fibromyalgia have significantly deteriorated HRQoL compared to healthy individuals[7,23]. Depending on the instrument used to measure it, two basic approaches (general or specific) can be taken to understand HRQoL. General instruments (e.g. 36-item Short Form Health Survey[SF-36]) are broadly applicable across different health conditions, whereas specific instruments focus on problems associated with single disease states, patient groups or areas of function[22]. In fibromyalgia, the Fibromyalgia Impact Questionnaire (FIQ) and its revised version (FIQR)[24] are disease-specific instruments to assess the henceforth called "disease impact". Because each approach has potential advantages and drawbacks[22], a combination of general and disease-specific tools would provide a more comprehensive understanding of HRQoL.

HRQoL is an outcome that is self-reported by the patient. Traditional clinical methods of evaluation, which relied on the musculoskeletal system or measures of impairment, are insufficient to describe the multidimensional issues associated with chronic painful rheumatic conditions[25]. Specifically, in fibromyalgia, patient-reported outcomes remain the best approach for assessing the multiple facets of the disease for the purposes of diagnosis, disease monitoring, phenotyping, and clinical trials[26]. In addition, clinical measures might not necessarily correlate with how patients feel and function. Indeed, it is a commonly observed phenomenon that two patients with the same clinical criteria often have dramatically different responses[22]. Consideration of HRQoL has become increasingly important in rheumatic diseases as suggested by different scientific societies[27–29] that also emphasize the need for its inclusion in clinical trials and observational studies[30]. Given its relevance, improving HRQoL is regarded as the main goal in the management of the fibromyalgia[31]. Measuring HRQoL has also the positive effect of giving prominence to the views and experiences of patients, creating a scenario in which the patient contributes to manage his or her own illness[32]. Greater insights on therapeutic interventions that could potentially be related to HRQoL in fibromyalgia are, therefore, warranted.

Approaches to the management of fibromyalgia

Treatment strategies for the management of fibromyalgia include a variety of pharmacological and non-pharmacological therapies[31]. Recent evidence-based guidelines on the management of fibromyalgia[31,33] agree on the inclusion of the following principles: i) a graduated approach, ii) comprehensive assessment of symptoms, iii) initial patient education, iv) tailored therapy to the individual, and v) the first-line of non-pharmacological treatment. According to the most recent guidelines based on meta-analyses and expert opinions[31], first line non-pharmacologic management involves exercise, cognitive behavioral therapies, multicomponent therapies, meditative movement therapies or mindfulness therapy, among others. In this line, diverse studies from our research group have demonstrated the efficacy of some of these non-pharmacological therapies (e.g.

exercise[34,35], biodanza[36–38], tai-chi[39–42] or multidisciplinary therapy[38,43,44]) to improve different health outcomes in fibromyalgia. In case of non-response, supplementary therapies should be adjusted to the specific needs and may include psychological therapies (for mood disorders and unhelpful coping strategies), pharmacotherapy (for severe pain or sleep disturbance) and/or a multimodal rehabilitation (for severe disability)[31].

Although these recommendations were built on high-quality reviews and meta-analyses, the size of effect for most treatments was rated as relatively modest[31]. Among all the treatments evaluated, exercise was found to be the only "strong for" therapy-based recommendation[31], given its effect on relevant fibromyalgia-related outcomes, availability, relatively low cost, and lack of safety concerns. An even more recent umbrella review that summarized the findings of all systematic reviews on the effects of exercise in fibromyalgia, confirmed exercise as an effective way to treat key disease-symptoms, with a low incidence of related adverse events[45]. Despite the generally agreement on the benefits of exercise in this group of patients, there is no consensus on the precise regimes (frequency, duration, intensity, or type of activity) to maximize these improvements.

Physical activity and sedentary time: conceptualization and association with health outcomes in fibromyalgia

There are many methods of categorizing activities performed throughout the day each of them providing information related to different aspects of health[46]. Into a 24-h model, behaviors can be classified according to its energy expenditure into physical activity (PA), sedentary behavior, and sleep[47]. The Sedentary Behavior Research Network have proposed over time different consensus for terminology in the area of PA and sedentary behavior, due to the extensive confusion existing in the literature[47,48]. **Physical activity (PA)** is defined as "any bodily movement produced by skeletal muscles that results in energy expenditure above resting metabolic rate"[46]. According to its intensity, PA is typically classified as light, moderate, or vigorous PA[47]. **Sedentary time (ST)** is defined as the time spent for any duration (e.g., minutes per day) or in any context (e.g., at school or work) in sedentary behaviors[47]. Sedentary behaviors are defined as "any waking behavior characterized by an energy expenditure ≤1.5 metabolic equivalents (METs), while in a sitting, reclining or lying posture"[47].

To better characterize PA and ST, further variables have been defined, allowing to know not only the impact of total duration of these behaviors on health, but also its pattern of accumulation. Patterns of accumulation are typically studied for moderate-to-vigorous PA (MVPA) and specially, ST variables, as they have been extensively connected to health outcomes[49,50]. Patterns of accumulation are described through the timing, duration, and frequency of **bouts** (this is, uninterrupted periods) and **breaks** (interruptions between two bouts) of MVPA and ST. According to sedentary patterns, people could be categorized as *prolongers* (someone who accumulates ST in extended continuous bouts) or *breakers* (someone who accumulates ST with frequent interruptions and in short bouts)[47].

Based on the increasing knowledge in the field, PA guidelines have been developed for different age-groups[50]. A minimum of 150 min of MVPA per week accumulated in bouts of at least 10 min has been recommended for health benefits in adults ages 18-64 years in the general population[49]. However, the most recent PA guidelines concluded that any bout length could provide health benefits, implying that all durations of MVPA should be considered[50]. Based on these recommendations, individuals can be categorized as *active* (achieving PA recommendations) and *inactive* (not achieving PA recommendations)[47]. In addition, current PA recommendations emphasized the importance of reducing total ST[50] but there is no specific cutoff established to reduce health risk.

Physical activity and sedentary time in fibromyalgia

The assessment of PA and ST is challenging, especially for adults with fibromyalgia. Self-reported measures of PA are easy and inexpensive to administer but are potentially subject to response bias and miss-reporting[51]. People with fibromyalgia usually have cognitive difficulties[52,53] that makes PA difficult to recall and the large symptomatology associated with the disease[3] might also alter their perception of their PA levels and the intensity of the PA performed. Several publications from our research group[54–56] in addition to other studies[57] have demonstrated the low reliability of self-reported measures in fibromyalgia[55,56] and the low agreement with different devices to objectively measure PA[54–57]. Therefore, device-measured PA (e.g.: accelerometry) has been recommended since they provide more reliable information regarding PA and ST in fibromyalgia.

Our previous accelerometer-measured study reported that people with fibromyalgia spent, on average, 48% of their waking time (8 hours) engaged in sedentary behaviors[58]. Although they spent 45 minutes/day in MVPA, overall, these activities were not continuous for at least 10 minutes[58]. Only 20.6% of the patients met the weekly PA recommendations in bouts while 75.1 % met the recommendations without bouts required[58]. Levels of MVPA among these patients are thought to be reduced compared to healthy controls based on different observational studies[58–60]. Contradictory findings were found regarding light PA and ST: while some investigations found differences compared to healthy individuals[58] others described similar worrying levels between fibromyalgia individuals and healthy controls[59,60]. These reduced levels of activity are considered to be the result of psychological barriers as fear of movement and avoidance behavior toward PA[61]. Although movement is avoided in an attempt to avoid an aggravation of their symptoms, adopting this behavior might also be connected to greater health risks.

Association between PA, ST and health outcomes in fibromyalgia: current evidence and questions that have yet to be answered

A number of relevant investigations from our research group[62–66] along with previous research[67–71] has suggested the connection of stepping[71], light PA[62,64,70], light-moderate PA[68], MVPA[62–64,66,69], and total PA[62,65,67] with self-reported pain[64,65,70,71], brain processing of pain[63,67,68], disease-impact[63–65,69,71] and other health outcomes[62–66,70] in fibromyalgia.

However, it is unclear to what degree this association also extends to different dimensions of HRQoL. In addition, there is still no consensus on which intensity of PA might be advisable for people with fibromyalgia. While health promotion in the general population is based on levels of MVPA[50], light PA has recently gained attention as a possible health-enhancing behaviour[72,73], particularly in individuals with reduced physical capacity or inactive individuals[49,74]. Therefore, more evidence on which PA intensity level (e.g., light, moderate, or vigorous) is the best indicator of relevant health outcomes in fibromyalgia, such as HRQoL, is needed for the future development of disease-specific PA recommendations.

Although the study on ST has received much less attention compared to PA, ST has been directly associated with higher risk incident of fibromyalgia[75]. Furthermore, recent studies have shown that greater total ST is associated with worse symptomatology[62,64,68]. Emerging evidence in the general population has demonstrated that not only the total amount of ST but also the pattern of accumulation of sedentary behaviors is relevant to health, being prolonged periods particularly harmful[76–78]. Evidence about the association of prolonged ST with symptoms in fibromyalgia is scarce and limited to one study[68]. Ellingson et al. observed a worsening in the regulation of pain in people with fibromyalgia who presented with high patterns of prolonged ST[68]. Although reductions of ST are recommended by health organizations[50], there is no specific information on how total ST or patterns of accumulation should be modified to minimize health risks. The analysis of the impact of different patterns of sustained ST on fibromyalgia is of interest to detect potentially harmful patterns.

Evidence to date linking PA and ST to health in fibromyalgia entirely relied on traditional regression models, which analyze each behavior in isolation. However, because time available during a day is fixed (24 hours), behaviors are codependent and the effects of an activity depend not only in the specific activity that is increased but also in the activity it displaces[79]. For instance, would a reduction of 30 min/day of ST yield the same health benefits if replaced by light PA or MVPA? Novel approaches such as isotemporal substitution models[79] would provide greater insights into the intrinsic codependence of physical behaviors on their association with health in fibromyalgia.

Finally, PA, ST, and health outcomes have been well-characterized in observational research but there is little evidence on how these variables evolve over time. In addition, evidence examining the predictive value of PA on future health in fibromyalgia is based on inaccurate self-reported measures[80,81] with no previous studies analyzing the potential of ST. Based on all these gaps initially detected, the present Doctoral Thesis would contribute to a better understanding of how PA and ST are linked to disease impact, pain, and HRQoL in fibromyalgia.

Exercise: conceptualization and association with health outcomes in fibromyalgia

Current evidence and questions that have yet to be answered

Exercise is considered a subset of PA that is planned, structured, and repetitive[46] with the aim to improve or maintain physical fitness[46]. Physical fitness is a set of attributes a person has or achieves and relates to a person's ability to perform specific types of PA efficiently and effectively[46]. Health-related fitness components (e.g. cardiorespiratory fitness, muscular strength, or flexibility) are considered relevant markers of health in fibromyalgia as extensively demonstrated by our research group[65,82–92]. Benefits of different exercise modalities on symptoms have been widely studied in fibromyalgia[45]. A series of recent systematic reviews have demonstrated that aerobic [93], resistance [94], and flexibility training [95] improves HRQoL [93–95], physical function [93,94], and pain[93,94], among other health outcomes [93,94]. Which type of exercise or whether multicomponent exercise (this is, a combination of two or more types of exercise) provides greater benefits is still a matter of debate[31,96,97]. Multicomponent exercise interventions are thought to improve HRQoL, physical function, fatigue, stiffness[97], and depression[95]. These effects are, however, uncertain because of the very low-quality evidence obtained from very heterogeneous trials[95] and the insufficiently detailed exercise protocols not adhering to recommended exercise guidelines[95].

Exercise therapy in fibromyalgia has been usually carried out in either land or water-based settings. Although water-based exercise was initially considered to provide greater health improvements in this population[98,99], most recent evidence questions this idea[100,101]. A recent meta-analysis concluded that similar results for overall well-being, physical function, pain, and stiffness are obtained in both conditions and only a moderate difference in strength favoring land-based training was detected[101]. Intervention studies published at a later time found similar benefits between both contexts in terms of pain and function[100] or slightly greater benefits in physical and psychological health in water-based exercise[102]. So far, a number of limitations preclude to establish the superiority of a setting over another: the reduced sample size, the limited and varied duration of interventions, the absence of a control group, or the unequalled exercise protocols.

To evaluate the persistence of the effects of exercise on health is a relevant labor poorly investigated in fibromyalgia so far. To date, two meta-analyses have examined the follow-up effects of exercise after land[97] or water-based exercise[101] in this group of patients. After land-based exercise, HRQoL, fatigue, and physical function improvement were found to persist at 6 to 52 or more weeks post intervention but improvements in stiffness and pain did not[97]. Evidence regarding long-term effects of water-based exercise is more limited and inconclusive[101]. Other reviews, however, suggested that water-based exercise-induced improvements in physical function, pain and mood may continue for up to two years[103]. The long-term benefits of exercise are still imprecise due to lack and limited length of follow-up or scarce follow-up phase information in previous research[99]. Accurately reported interventions studies[45,104] with adequate sample sizes, longer duration of exercise intervention and follow-up phase are needed to ascertain the effects of multicomponent exercise, the advantages of each setting, and their long-term benefits.

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AIMS

AIMS

Overall aim

The overall objective of this Doctoral Thesis has been to analyze the influence of PA, ST, and exercise on disease impact, pain, and HRQoL in women with fibromyalgia.

Section 1. PA, ST, disease impact, and HRQoL: cross-sectional studies

Specific aim 1. To examine i) the independent association of PA intensity levels and ST with HRQoL in women with fibromyalgia and, ii) whether women meeting the PA guidelines present better HRQoL.

Specific aim 2. To examine i) the association of the patterns of ST with HRQoL in women with fibromyalgia, ii) the combined association of total ST and prolonged ST with HRQoL, and iii) whether these associations are independent of MVPA.

Specific aim 3. To examine i) the associations of prolonged ST with disease impact in women with fibromyalgia, ii) the combined association of total ST and prolonged ST with disease impact, and iii) whether these associations are independent of MVPA and fitness.

Specific aim 4. To examine the association with HRQoL and disease impact upon substituting ST with light PA or MVPA in women with fibromyalgia.

Section 2. PA, ST, disease impact, pain, and HRQoL: prospective cohort study

Specific aim 5. To analyze i) trends of ST, PA intensity levels, disease impact, pain, and HRQoL at 2- and 5-year follow-up, and ii) how baseline and changes in ST and PA intensity levels are associated with future outcomes (disease impact, pain, and HRQoL) in women with fibromyalgia.

Section 3. Land- and water-based exercise, disease impact, pain, and HRQoL: an intervention study

Specific aim 6. To assess i) the effects of 24 weeks of land- or water-based exercise on disease impact, pain, and HRQoL in women with fibromyalgia, and ii) the persistence of the effects at 12-week follow-up.

OBJETIVOS

Objetivo general

El objetivo general de esta Tesis Doctoral ha sido analizar la influencia de la AF, el TS y el ejercicio sobre el impacto de la enfermedad, el dolor y la CVRS en mujeres con fibromialgia.

Sección 1. AF, TS, impacto de la enfermedad y CVRS: estudios observacionales.

Objetivo específico 1. Analizar i) la asociación de los niveles de intensidad de AF y el TS con la CVRS en mujeres con fibromialgia y ii) si las mujeres que cumplen las recomendaciones de AF presentan mejor CVRS.

Objetivo específico 2. Analizar i) las asociaciones de los patrones de TS con la CVRS en mujeres con fibromialgia, ii) la asociación combinada del TS total y prolongado con la CVRS y iii) si estas asociaciones son independientes de la AFMV.

Objetivo específico 3. Analizar i) las asociaciones de los patrones de TS con el impacto de la enfermedad en mujeres con fibromialgia, ii) la asociación combinada del TS total y prolongado con el impacto de la enfermedad y iii) si estas asociaciones son independientes de la AFMV y la condición física.

Objetivo específico 4. Analizar la asociación con la CVRS y el impacto de la enfermedad de sustituir TS con AF ligera o AFMV en mujeres con fibromialgia.

Sección 2. AF, TS, impacto de la enfermedad, dolor y CVRS: estudio longitudinal.

Objetivo específico 5. Analizar i) tendencias de cambio en niveles de intensidad de AF, TS, impacto de la enfermedad, dolor y CVRS en un seguimiento a 2 y 5 años y ii) cómo los valores basales y los cambios a lo largo del tiempo en AF y TS se asocian con los valores futuros del impacto de la enfermedad, el dolor y la CVRS en mujeres con fibromialgia.

Sección 3. Ejercicio en seco y en agua, impacto de la enfermedad, dolor y CVRS: estudio de intervención.

Objetivo específico 6. Analizar i) el efecto de 24 semanas de ejercicio en seco o en agua sobre el impacto de la enfermedad, el dolor y la CVRS en mujeres con fibromialgia y ii) la persistencia de los cambios después de 12 semanas.

METHODS

METHODS

The al-Ándalus project

Designs

The al-Ándalus project is a multi-centric study that was carried out in Andalusia (southern Spain) between 2011-2017. This project aimed to improve diagnosis and characterization of fibromyalgia, to identify prognostic factors of the disease, and to establish effectiveness of exercise as a therapy. It is divided in two main parts with different methodological designs: **1) The al-Ándalus cohort study:** a longitudinal study including 2- and 5- year follow-ups (Sections 1 and 2 of this thesis), and **2) The al-Ándalus trial:** a quasi-randomized controlled trial (Section 3 of this thesis). Two outlines of these projects and sections are shown in figures 1 and 2. The Medical Ethics Committee of Hospital Virgen de las Nieves (Granada, Spain) approved the studies' designs, study protocols and informed consent procedure.

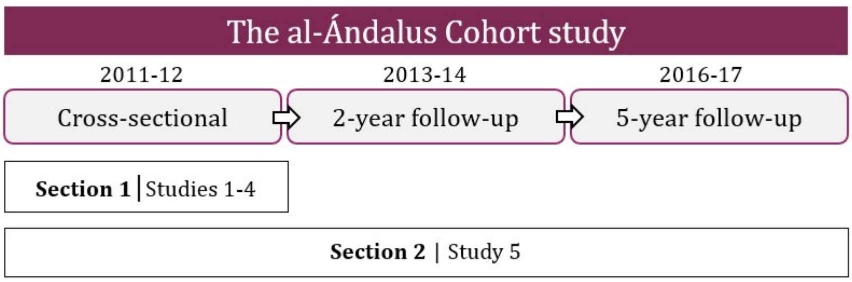

Figure 1. The al-Ándalus cohort study outline including sections and studies of this thesis

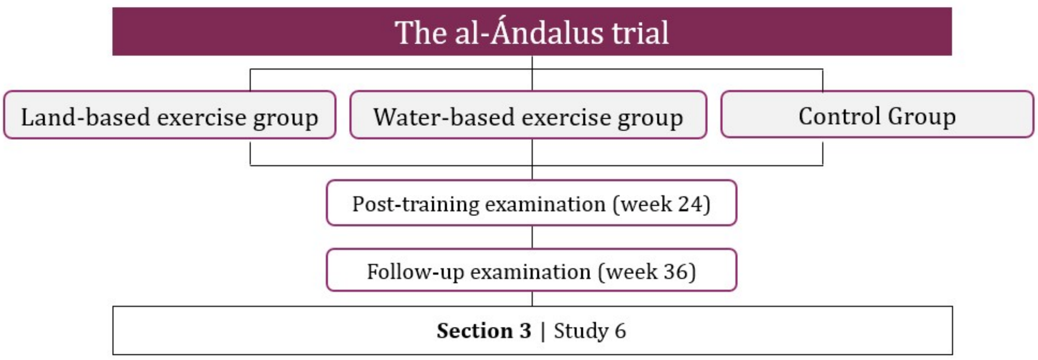

Figure 2. The al-Ándalus trial outline including sections and studies of this thesis

The al-Ándalus cohort study (Sections 1 and 2)

Participants

This project aimed to recruit a fibromyalgia sample representative of the Andalusian population (i.e. 8 provinces from southern Spain). The number of participants to be included was estimated using the level of accuracy obtained in previous studies assessing the 6-minute walk test in a population with fibromyalgia[1]. We used the level of accuracy as a fraction (k) of the standard deviation of the population (accuracy= k × standard deviation). We selected a k of 10-50%, which is common in clinical studies. For a confidence interval level of 95%, a sample consisting of 300 participants were needed to obtain an accuracy of 11%. Given this sample size, we would be able to estimate the maximum distance (in meters) that women with fibromyalgia are able to walk, in average, within 6 minutes with an accuracy of 8 meters. The sample was selected using a two-phase (sex and province), proportional sampling using the database of the Spanish Association of Rheumatology and the Census of the 8 provinces of Andalusia as references. The sample was oversized in order to prevent loss of information and more than 600 participants were initially recruited (more information in flowchart diagrams of studies 1-5).

In 2011/2012 (baseline) patients were contacted through fibromyalgia associations from the 8 provinces of Andalusia, as well as via e-mail, social media, letter or telephone. In 2013/2014 and 2016/2017 the cohort was contacted again for the follow-up evaluations.

Inclusion criteria were: i) to be previously diagnosed by rheumatologist, and ii) to meet the 1990[2] or modified 2010 ACR[3,4] criteria. Exclusion criteria were: i) acute or terminal illness (i.e. cancer, stroke, recent cardiomyopathy, severe coronary disease, schizophrenia, and severe chronic obstructive pulmonary disease), and ii) severe cognitive dysfunction (Mini Mental State Examination < 10[5]).

Procedures

A very similar evaluation process was performed at three time points. The assessments were carried out in two alternate days (e.g. Monday and Wednesday), either at the fibromyalgia associations or at University Facilities, and either in morning or afternoon sessions (according to the participants' convenience). The whole evaluation process was performed by researchers who had previously received specific training to ensure harmonization of data collection.

On day one, the Mini Mental State Examination was interviewed for inclusion purposes. Tender points' examination was performed by a single trained researcher and anthropometry and body composition were also assessed. In addition, participants filled out the modified 2010 ACR preliminary criteria, sociodemographic data and drug consumption questionnaires, and a pain intensity visual analogic scale. Questionnaires related to HRQoL and disease impact were given to patients to be completed at home. On day 2, patients returned to the laboratory where questionnaires were collected and verified by the research team. Thereafter, physical fitness assessment was undertaken. Finally, participants received instructions on how to complete the sleep diary and the accelerometers were provided. The accelerometers and sleep diaries were returned to the research team 9 days later. More details about the measures of other variables and statistical analyses for each study belonging to the al-Ándalus cohort study are included in the *Results and Discussion* part (Sections 1 and 2).

The al-Ándalus trial (Section 3)

Participants

The al-Ándalus trial was registered as a 24-week randomized controlled exercise trial with a 12-week follow-up (ClinicalTrials.gov ID: NCT01490281). Women with fibromyalgia were recruited from the local associations of fibromyalgia patients in Andalucía (Southern Spain) with a similar recruitment process as described for the al-Ándalus cohort study. Before starting the study, a screening of all candidates was performed. Inclusion and exclusion criteria are shown in table 1. After baseline measurements, participants were allocated to the land-based exercise, water-based exercise or usual care (control) groups.

The required sample size was determined for disease impact, which was defined as the primary outcome of the study protocol[6]. According to previous research[7], a 14% reduction in the total score of the Fibromyalgia Impact Questionnaire (FIQ[8]) is considered a clinically relevant change. Assuming a unilateral alternative we can detect differences of at least 15% with a power of 95% and α of 0.05 with two groups (intervention and usual care group) of 45 participants, with a mean in the FIQ of ~70 and a standard deviation of ~20 points. The sample was oversized in order to compensate loss to follow-up and a recruitment of 180 women with fibromyalgia (60 in each group) was initially planned.

Table 1*. Inclusion and exclusion criteria for the al-Ándalus trial[6]

Inclusion criteria	Exclusion criteria
- Age: 35-65 years - To be diagnosed with fibromyalgia by a rheumatologist and meeting the 1990 ACR criteria - Not to have other severe somatic or psychiatric disorders, or other diseases that prevent physical loading (answer "no" to all questions on the PAR-Q). - Not to be engaged in regular physical activity > 20 min on > 3 days/week in the past 3 months. - Planning to stay in the same Association during the study. - Able to ambulate without assistance. - Able to communicate. - Informed consent: Must be capable and willing to provide consent.	- Acute or terminal illness - Myocardial infarction in the past 3 months. - Unstable cardiovascular disease or other medical condition. - Upper or lower extremity fracture in the past 3 months. - Unwillingness to either complete the study requirements or to be randomized into control or training group. - Severe dementia (Mini Mental State Examination < 10). - Presence of neuromuscular disease or drugs affecting neuromuscular function. - To be engaged in other physical or psychological treatment.

ACR: American College of Rheumatology, PAR-Q: Physical Activity Readiness Questionnaire

** The numbering of tables will be independent for each part of the Doctoral Thesis*

Procedures

Assessments were conducted at baseline, at the end of the exercise intervention (week 24) and at 12-week follow-up (week 36). Same protocol for evaluation as described for the al-Ándalus cohort study was also carried out in this trial at each time-point.

More details about the measures of variables and statistical analyses for the al-Ándalus trial are included in the *Results and Discussion* part (Section 3).

Methodological overview of studies

The present Doctoral Thesis contains 3 sections including a total of 6 studies. Table 2 shows an overview of the design, participants, and variables included in every study.

Table 2. Overview of the design, participants and variables included in every study contained in this Doc

	Study	Design	Participants	Predictor variables (instruments)
SECTION 1	**Study 1**	Cross-sectional	407 women with fibromyalgia aged 51.4 ± 7.6 years	*Total PA, ST and PA guidelines* Total ST, light PA, and MVPA: min/day Achievement [yes/no] of PA guidelines (Triaxial accelerometer)
	Study 2	Cross-sectional	407 women with fibromyalgia aged 51.4 ± 7.6 years	*Patterns of ST* Total ST and MVPA: min/day Percentage of ST accumulated in bouts and the frequency of sedentary bouts of different lengths: ≥10 min, ≥20 min, ≥30 min, and ≥60 min Combined groups according to total and prolonged ST (Triaxial accelerometer)
	Study 3	Cross-sectional	451 women with fibromyalgia aged 51.3 ± 7.6 years	*Patterns of ST* Percentage of ST in ≥30 min bout and ≥60 min bout Prolongers [yes/no] classification according to ST in ≥60 min bout (Triaxial accelerometer)
	Study 4	Cross-sectional	407 women with fibromyalgia aged 51.4 ± 7.6 years	*Total PA and ST* Total ST, light PA, and MVPA: min/day (Triaxial accelerometer)

FIQR: Revised Fibromyalgia Impact Questionnaire; HRQoL: Health-related quality of life, MVPA: moderate-to-vigorous physi
item Short-form health survey; ST: Sedentary Time.

Table 2 continuation. Overview of the design, participants and variables included in every study contai

	Study	Design	Participants	Independent variables (instruments)
SECTION 2	**Study 5**	Longitudinal: 2-and 5-year follow up	Baseline: 427 women with fibromyalgia aged 51.4 ± 7.6 years 2-year follow-up: 172 women with fibromyalgia aged 54.1 ± 7.3 years 5-year-follow-up: 185 women with fibromyalgia aged 56.1 ± 7.0 years	*Total PA and ST* Total ST, light PA, and MVPA at baseline: min/day Change in total ST, light, and MVPA from baseline to 2-year and 5-year follow-up: min/day (Triaxial accelerometer)
SECTION 3	**Study 6**	Quasi-randomized controlled trial	Land-based exercise group: 79 women with fibromyalgia aged 49.5 ± 7.3 years Water-based exercise group: 80 women with fibromyalgia aged 52.5 ± 8.2 years Control group: 85 women with fibromyalgia aged 50.4 ± 7.3 years	*Exercise* Land-based exercise group: multicomponent exercise (including aerobic, resistance, and flexibility exercise) during for 24 weeks (3 days/week; 45-60-min/day) Water-based: multicomponent exercise (including aerobic, resistance, and flexibility exercise) during for 24 weeks (3 days/week; 45-60-min/day) in a chest-high warm (~30°C) pool Control group: usual care

FIQR: Revised Fibromyalgia Impact Questionnaire; HRQoL: Health-related quality of life, MVPA: moderate-to-vigorous phys
36-item Short-form health survey; ST: Sedentary Time.

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RESULTS AND DISCUSSION

Physical activity, sedentary time, disease impact, and health-related quality of life: cross-sectional studies

Studies 1-4

SECTION 1

SECTION 1

Study 1

Association of objectively measured physical activity and sedentary time with health-related quality of life in women with fibromyalgia: The al-Ándalus project

Journal of Sport and Health Sciences (2019)

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ABSTRACT

Objective: To examine the association of physical activity (PA) intensity levels and sedentary time (ST) with health-related quality of life (HRQoL) in women with fibromyalgia and whether patients meeting the current PA guidelines present better HRQoL.

Methods: This cross-sectional study comprised 407 women with fibromyalgia aged 51.4 ± 7.6 years. The time spent (min/day) in different PA intensity levels (light, moderate, and moderate-to-vigorous (MVPA)) and ST were measured with triaxial accelerometry. The proportion of women meeting the PA recommendations (≥150 min/week of MVPA in bouts ≥10 min) was also calculated. HRQoL domains (physical function, physical role, bodily pain, general health, vitality, social functioning, emotional role, mental health) as well as physical and mental components were assessed using the 36-item Short-Form Health Survey.

Results: All PA intensity levels were positively correlated with different HRQoL dimensions ($r_{partial}$ between 0.10 and 0.23; all P<0.05). MVPA and ST were independently associated with social functioning (P<0.05). Sedentary time was associated in regression models with physical function, physical role, bodily pain, vitality, social functioning, and both the physical and mental components summary score (all P<0.05). Patients meeting the PA recommendations presented better scores for bodily pain [mean, (95%-CI) = 24.2, (21.3–27.2) *vs.* 20.4, (18.9–21.9); P=0.023) and better scores for social functioning (mean, (95%-CI) = 48.7, (43.9–44.8) *vs.* 42.3, (39.8–44.8); P=0.024).

Conclusions: PA (positively) and ST (negatively) are associated with HRQoL in women with fibromyalgia. Meeting the current PA recommendations is significantly associated with better scores for bodily pain and social functioning. These results highlight the importance

INTRODUCTION

Fibromyalgia is a chronic condition with persistent and widespread pain along with other symptoms such as fatigue, non-restorative sleep, and cognitive difficulties [1]. These factors have a considerable negative impact on the patients' health-related quality of life (HRQoL)[2] which represents the individuals' perception of physical, mental, and social health status. Because fibromyalgia has no cure, treatment is usually focused on improving HRQoL along with symptomatology management.

Physical exercise has been shown to be an alternative to pharmacological treatments in fibromyalgia[3], yet adherence to exercise programs is challenging[4]. Modifying daily physical activity (PA) might potentially be a more sustainable behavior over time. Previous studies have observed a positive association between PA and HRQoL both in the general population[5,6] and among those with fibromyalgia[7,8]. Nonetheless, fear of pain and worsening of symptoms lead patients to avoid PAs[9], and only 20% of them seem to meet the American PA recommendations[10,11]. The fulfilment of these PA recommendations for general population has been related to a lower cardiovascular risk in fibromyalgia[12], but is unclear whether this may also extend to other health outcomes such HRQoL. In similar conditions such arthritis, those patients meeting the PA recommendations for arthritis[13] or general population[14] presented a better HRQoL. The intensity and dose of PA to elicit disease specific benefits in fibromyalgia is yet to be defined. Previous research studying the influence of PA on health of these patients is mainly focused in symptoms[15–18] or physical domains of HRQoL outcomes[8,19,20]. Therefore, the extent to which different PA intensity levels (e.g., light, moderate, or vigorous) are associated with all domains of HRQoL and which of them is the best indicator of current HRQoL are currently unknown.

Sedentary behaviors, which includes activities that involve sitting or reclining and demand only low levels of energy expenditure[21], have negative consequences on health independent of those behaviors related to insufficient PA[22]. For instance, sedentary time is linked to lower HRQoL in general population [6,23]. Fibromyalgia patients spend more time of their waking time in sedentary behaviors (on average, 48%) than do healthy individuals[11]. Hence, it is of major clinical interest to assess the extent to which sedentary time is associated with HRQoL in patients with fibromyalgia because preventing prolonged sedentary behaviors might be advisable.

A detailed characterization of how different PA intensity levels and sedentary time are related to diverse domains of HRQoL would provide valuable information for the design of prospective studies and specific PA recommendations for this group of patients. Therefore, the aims of the current study were to test: 1) the association of objectively measured PA intensity levels (i.e., light, moderate, and moderate-to-vigorous (MVPA)) and sedentary time with HRQoL in women with fibromyalgia, 2) whether different PA intensity levels and sedentary time are independently associated with HRQoL among these patients, and 3) and whether patients meeting the current American PA guidelines present better HRQoL compared to those not meeting the PA guidelines. We hypothesized that: 1) all PA intensity levels (positively) and sedentary time (negatively) are associated with HRQoL in women with fibromyalgia, 2) PA and sedentary time are independently associated with HRQoL among these patients, and that, 3) patients who meet the current American PA guidelines present better HRQoL compared to those not meeting the PA guidelines.

METHODS

Participants

A province-proportional recruitment of fibromyalgia patients from Southern Spain (Andalusia) was planned, as described elsewhere[24]. Briefly, patients were contacted through fibromyalgia associations, email, and social media. After providing detailed information about the aims and study procedures, we obtained written informed consent from all study participants. A total of 646 fibromyalgia patients agreed to participate in the study. Inclusion criteria for the current study were: (i) to have neither acute nor terminal illness nor severe cognitive impairment (Mini Mental State Examination (MMSE)[25] score < 10), (ii) to be ≤65 years old, and (iii) to be previously diagnosed by a rheumatologist and meet the official 1990 American College of Rheumatology (ACR) fibromyalgia criteria (widespread pain for more than 3 months and pain with ≤4 kg/cm2 of pressure reported for 11 or more out of 18 tender points)[26]. The study was approved by the Ethics Committee of the "Hospital Virgen de las Nieves, Granada (Spain).

Procedures

On Day 1 of the study, the MMSE was administered, and participants filled out the modified 2010 ACR preliminary criteria, self-reported sociodemographic data, and drug consumption questionnaires. Tender points, anthropometry, and body composition were also assessed. The 36-item Short-Form Health Survey (SF-36)[27] was given to patients to be completed at home. Two days later, patients returned to the laboratory, where questionnaires were collected and checked by the researchers. After that, participants received instructions on how to complete the sleep diary, and the accelerometers were provided. The accelerometers and sleep diaries were returned to the research team 9 days later.

Measurements

Sociodemographic data and drug consumption

We collected sociodemographic data by using a self-reported questionnaire including date of birth, marital status (married/not married), educational level (university/non-university), and occupational status (working/not working). Additionally, to assess an exclusion criterion, participants were asked: "Have you ever been diagnosed with an acute or terminal illness?" Furthermore, patients reported the consumption of antidepressants and analgesics (yes/no) during the previous 2 weeks.

PA levels and sedentary time

Patients were asked to wear a triaxial accelerometer GT3X+ (Actigraph, Pensacola, FL, USA) for 9 days during the whole day (24 h) except for water-based activities. The device was worn around the hip, secured with an elastic belt, and worn underneath clothing. Data were collected at a rate of 30 Hz and at an epoch length of 60 seconds [28,29]. PA from the 9 consecutive days was recorded, although data from the first day (to avoid reactivity) and the last day (device return) were excluded from the analysis. Bouts of 90 continuous minutes (allowance of 2-min interval of nonzero counts with the up/downstream 30-min consecutive zero counts window for detection of artifactual movements) of 0 counts were considered as non-wear periods[30] and were excluded as well. In agreement with prior literature [31], a total of 7 continuous days in total with a minimum of 10 valid hours was required to be included in the analysis. Data download, reduction, cleaning, and analyses were conducted using the manufacturer software ActiLifeTM Version.6.11.7, (Actigraph). Accelerometer wearing time was calculated by subtracting the sleeping time (obtained from the sleep diary, where patients indicated the time they went to bed and time they woke up) from each day. Sedentary time was estimated as the time accumulated below 200 counts per minute (CPM) during periods of wear time [28]. PA intensity levels (light, moderate, vigorous and MVPA) were calculated based upon recommended PA vector magnitude cut points[29]: 200–2689, 2690–6166, ≥6167 and ≥2690 CPM, respectively. All values were expressed in min/day. We calculated the proportion of women meeting the American PA recommendations for adults aged 18–64 years (≥150 min/week of MVPA in at least 10 min at a time)[10].

HRQoL

HRQoL was evaluated using the SF-36. This questionnaire has been validated for Spanish populations[27]. The SF-36 is composed of 36 items that assess 8 dimensions of health (i.e., physical functioning, physical role, bodily pain, general health, social functioning, emotional role, mental health, and vitality) and 2 component summary scores (i.e., physical and mental health). The score in each dimension is standardized and ranges from 0 (worst health status) to 100 (best health status).

Tenderness and diagnostic criteria

Following the 1990 ACR criteria for classification of fibromyalgia[26], we assessed 18 tender points using a standard pressure algometer (FPK 20; Wagner Instruments, Greenwich, CT, USA). We obtained the mean pressure of 2 measurements at each tender point. A tender point was considered as positive when the patient felt pain at pressure ≤ 4 kg/cm2. The total number of positive tender points was recorded for each patient. Because different diagnoses for fibromyalgia currently coexist, we also complementarily used the modified 2010 ACR preliminary diagnosis criteria[32–34] to understand potential discrepancies due to the patients' classifications.

Anthropometry and body composition

Weight (kg) and total body fat percentage was assessed using a portable eight-polar tactile-electrode bioelectrical impedance device (InBody R20; Biospace, Seoul, Korea). The validity and reliability of this instrument has been reported elsewhere[35,36]. As the manufacturer recommends, we requested participants not to have a shower, not to practice intense PA, and not to ingest large amounts of fluid and/or food in the 2 h before the measurement. Patients were also asked not to wear either clothing (except underwear) or metal objects during the measurement. A stadiometer (Seca 22; Hamburg, Germany) was used to measure height (cm), and body mass index (BMI) was calculated as weight (kg) divided by height (m) squared.

Statistical Analysis

Descriptive statistics were used to examine the sociodemographic and clinical characteristics of the sample. Participants presented extremely low values of vigorous PA (0.4 min/day); therefore, vigorous PA was excluded from all the analyses. In preliminary analyses, bivariate correlations were used to explore the role of different variables related to physical, social and psychological factors that have shown to determine HRQoL in patients with fibromyalgia[37]. As a result, age, marital status, education level, current occupational status, total body fat percentage, and drug consumption (both analgesics and antidepressants) were identified as potential confounders and were introduced in all analyses along with total accelerometer wear-time. Partial correlation was used to study the individual association of the different PA levels (light PA, moderate PA and MVPA) and sedentary time with HRQoL (Objective 1) while controlling for all the aforementioned covariates. Then, to explore the independent association of PA intensity levels and sedentary time with HRQoL (Objective 2), linear regression analyses were conducted. All the dimensions of HRQoL (physical functioning, physical role, bodily pain, general health, social functioning, emotional role, mental health, and vitality) and the physical and mental component summary scores (assessing physical and mental health) were entered as dependent variables in separate models. All the PA intensity levels (except vigorous PA), sedentary time, and all the covariates (sociodemographic variables, drug consumption, and total body fat percentage) were entered simultaneously using a forward stepwise procedure based on the exploratory nature of these analyses. Moreover, stepwise procedure was used as the aim was to observe the best indicator of HRQoL among the PA variables (this is, the PA variables that presented the strongest associations). This procedure introduces the variables step by step into the model (if $p < 0.05$) according to the strength of the association with the outcome. The model is reassessed with the addition of every new variable, and variables are left out of the model if $p > 0.10$. Accelerometer wear-time was introduced with the "enter" procedure to control all the analyses for its effect. Normal probability plots of the standardized residual and scatterplots of residuals were generated to test normality, linearity, and homoscedasticity. The non-autocorrelation assumption was also met (Durbin-Watson-test; $1.5< d < 2.5$ for all regression models). No multicollinearity problems among the predictor variables of the model were found (all variance inflation factor statistics < 10).

Differences in HRQoL of patients meeting vs. those not meeting the current PA guidelines (≥150 min/week of MVPA in bouts ≥10 min; Objective 3) were calculated with Multivariate Analysis of Covariance (MANCOVA). The 8 dimensions and the 2 component summary scores of HRQoL were entered as dependent variables; and sociodemographic variables, total body fat percentage, drugs consumption, and accelerometer wear-time were entered as covariates.

Normality was assumed due to the large sample size, and the homoscedasticity assumption of HRQoL (assessed with Levene's test) was reasonably met between patients' meeting vs. not meeting recommendations of PA. All analyses were performed using the Statistical Package for Social Sciences, Version 23.0 (SPSS Statistics for Windows; IBM, Armonk, NY, USA). The level of significance was set at $p < 0.05$.

RESULTS

A total of 39 women with fibromyalgia were not previously diagnosed, 99 did not meet the 1990 ACR criteria, 1 had severe cognitive impairment, and 14 did not meet the age criteria. Men with fibromyalgia were not included in the present study due to the small sample (n=21).

Table 1. Characteristics of the study participants (n=407)

Variables	Mean ± SD
Age(year)	51.4 ± 7.6
Total tender points (11–18)	16.7 ± 2.0
Algometer score (18–144)	43.2 ±13.4
BMI (kg/m^2)	28.4 ± 5.4
Total body fat (%)	40.1 ±7.6
HRQoL, SF–36 (0–100)	
Physical function	39.2 ± 18.9
Physical role	33.2 ± 21.2
Bodily pain	21.2 ± 14.7
General health	28.5 ± 15.3
Vitality	22.3 ± 17.7
Social functioning	43.7 ± 24.7
Emotional role	56.9 ± 27.9
Mental health	46.2 ± 19.7
Physical component	29.5 ± 6.9
Mental component	36.0 ± 11.6
PA and sedentary behavior (min/day)	
Acc. wear-time	923.0 ± 78.9
Sedentary time	460.1 ± 104.1
Light PA	418.6 ± 91.8
Moderate PA	43.9 ± 29.5
Vigorous PA	0.4 ± 2.0
MVPA	44.3 ± 30.1
	n(%)
Marital status	
Married	311 (76.4)
Not married	96 (23.6)
Education level	
Non-university	349 (85.7)
University	58 (14.3)
Occupational Status	
Working	107 (26.3)
Not working	300 (73.7)
Drug consumption	
Analgesics	367 (90.2)
Antidepressants	232 (57.0)
PA recommendations	
Meeting (active)	86 (21.1)
Not meeting (inactive)	321 (78.9)

Acc.=accelerometer; BMI= Body mass index; HRQoL= health-related quality of life; MVPA= Moderate-to-vigorous physical activity; PA= physical activity; SF-36= 36-item Short-Form Health Survey; SD= standard deviation.

A total of 17 participants did not agree to wear the accelerometer and data from 3 participants were lost due to accelerometer malfunction. A total of 17 participants did not meet the accelerometer criteria (insufficient wearing time or incomplete sleep diaries), and 28 did not return completed questionnaires. The final sample size included in the analysis was 407 women with fibromyalgia. Patients' sociodemographic and clinical characteristics are shown in Table 1.

Partial correlations of PA intensity levels and sedentary time with HRQoL are presented in Table 2. Light PA was significantly associated with physical function, bodily pain, vitality, and social functioning (r partial between 0.11 and 0.20, all $p < 0.05$). Moderate PA and MVPA were both significantly associated with physical function, physical role, vitality, social functioning, and physical component (r partial between 0.10 and 0.22, all $p < 0.05$). Sedentary time was inversely associated with all the dimensions of HRQoL (r partial between –0.24 and –0.11, all $p < 0.05$), except for general health, emotional role, and mental health.

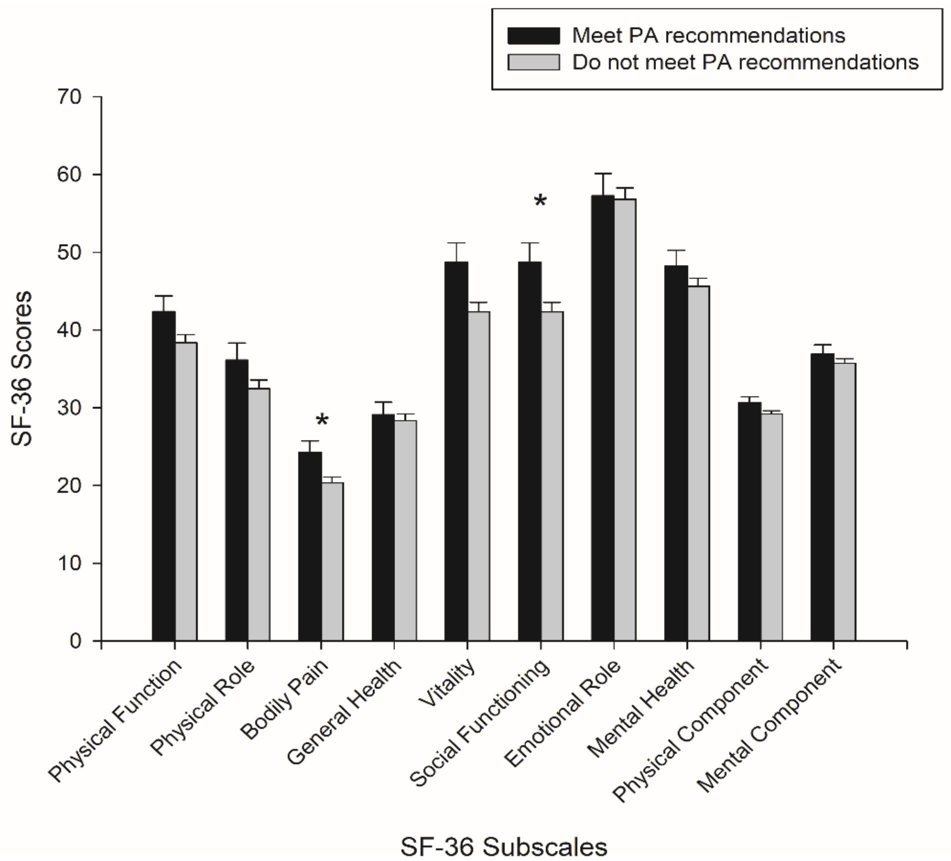
The regression model between PA intensity levels and sedentary time, and SF-36 dimensions as well as the 2 components summary score (physical and mental health) are shown in Table 3. MVPA was the only PA intensity level independently associated with HRQoL, specifically with social functioning (b=0.10, p<0.05). Sedentary time was independently associated with physical function (b= -0.03), physical role (b=-0.03), bodily pain (b=-0.02), vitality (b=-0.03), social functioning (b=-0.05), and both the physical (b = - 0.01) and mental (b=-0.01) components summary score (all $p < 0.05$).

Table 2. Partial correlations of PA intensity levels and sedentary behaviour with HRQoL (*n* = 407)

	Light PA	Moderate PA	MVPA	Sedentary Time
Physical function	0.11 *	0.11 *	0.12 *	-0.13 **
Physical role	0.08	0.12 *	0.12 *	-0.11 *
Bodily pain	0.11 *	0.08	0.09	-0.13 **
General health	0.03	0.02	0.03	-0.04
Vitality	0.13 **	0.13 **	0.13 **	-0.15 **
Social functioning	0.20 ***	0.22 ***	0.22 ***	-0.24 ***
Emotional role	0.07	0.04	0.04	-0.07
Mental health	0.03	0.06	0.06	-0.04
Physical component	0.09	0.10 *	0.10 *	-0.11 *
Mental component	0.09	0.09	0.09	-0.11 *

Notes: Analyses are controlled for age, total body fat percentage, current occupational status, education level, marital status, accelerometer-wear time, consumption of analgesics and antidepressants.* $p \leq 0.05$, ** $p \leq 0.01$, *** $p \leq 0.001$

Abbreviations: HRQoL= Health-related quality of life. MVPA= moderate-to-vigorous physical activity. PA= physical activity.



(Hottelling- T^2: $F_{8,391}$=0.027; p=0.239) * ***p*< 0.05**

Figure 1. Means (95% confidence interval) of scores on the 36-item Short-Form Health Survey (SF-36) for each dimension in patients meeting (*n* = 86) and not meeting (*n* = 321) the current physical activity (PA) recommendations. Differences between groups were studied using multivariable analysis of covariance (MANCOVA) with sociodemographic variables (marital status, occupational status, and education level), total body fat percentage, drug consumption, and accelerometer wear-time entered as

Table 3. Models of regression coefficients assessing the association of PA intensity levels and sedentary time with HRQoL *(n=407)*

	β	b	(95 %CI)	*p*	Adjusted R^2
Physical function					
Accelerometer wear-time	0.16	0.04	(0.01, 0.06)	0.002	0.063
Medication for depression	-0.14	-5.29	(-9.00, -1.57)	0.005	
Sedentary time	**-0.18**	**-0.03**	**(-0.05, -0.01)**	**0.001**	
Physical role					
Accelerometer wear-time	0.14	0.04	(0.01, 0.06)	0.009	
Not working	-0.2	-9.75	(-14.24, -5.25)	<0.001	0.134
Medication for depression	-0.2	-8.46	(-12.47, -4.46)	<0.001	
Sedentary time	**-0.14**	**-0.03**	**(-0.05, -0.01)**	**0.006**	
Bodily pain					
Accelerometer wear-time	0.07	0.01	(-0.01, 0.03)	0.177	
Total body fat percentage	-0.1	-0.2	(-0.38, -0.02)	0.031	0.143
Medication for depression	-0.31	-9.09	(-11.86, -6.32)	<0.001	
Sedentary time	**-0.16**	**-0.02**	**(-0.04, -0.01)**	**0.003**	
General health					
Accelerometer wear-time	0.04	0.01	(-0.01, 0.03)	0.461	
Not working	-0.11	-3.64	(-6.95, -0.32)	0.032	0.086
Medication for depression	-0.24	-7.39	(-10.33, -4.45)	<0.001	
Medication for pain	-0.1	-4.87	(-9.73, -0.02)	0.042	
Vitality					
Accelerometer wear-time	0.11	0.02	(0.00, 0.05)	0.041	
Medication for depression	-0.2	-7.15	(-10.60, -3.70)	<0.001	0.092
Medication for pain	-0.09	-5.58	(-11.14, -0.01)	0.049	
Sedentary time	**-0.18**	**-0.03**	**(-0.05, -0.01)**	**0.001**	
Social functioning					
Accelerometer wear-time	0.14	0.05	(0.01, 0.08)	0.005	
Age	0.1	0.34	(0.05, 0.63)	0.021	
Medication for depression	-0.28	-14.03	(-18.50, -9.55)	<0.001	0.215
Medication for pain	-0.1	-8.26	(-15.50, -1.01)	0.026	
MVPA	**0.12**	**0.1**	**(0.01, 0.18)**	**0.037**	
Sedentary time	**-0.21**	**-0.05**	**(-0.08, -0.02)**	**<0.001**	
Emotional role					
Accelerometer wear-time	0.11	0.04	(0.01, 0.07)	0.014	0.161
Not working	−0.13	−8.04	(−13.82, −2−27)	0.006	
Medication for depression	−0.34	−19.32	(−24.40, −14.24)	<0.001	
Mental health					
Accelerometer wear-time	0.09	0.02	(0.00, 0.05)	0.048	0.143
Medication for depression	−0.36	−14.391	(−18.00, −10.78)	<0.001	
Physical component summary					
Accelerometer wear-time	0.08	0.01	(−0.00, 0.02)	0.149	0.048
Not working	−0.14	−2.24	(−3.77, −0.71)	0.004	
Sedentary time	**-0.17**	**- 0.01**	**(−0.02, 0.00)**	**0.001**	
Mental component summary					
Accelerometer wear-time	0.15	0.02	(0.01, 0.04)	0.002	
Medication for depression	−0.37	−8.59	(−10.73, −6.45)	<0.001	0.193
Medication for pain	−0.09	−3.65	(−7.11, −0.20)	0.038	
Sedentary time	**−0.12**	**−0.01**	**(−0.02, 0.00)**	**0.018**	

Forward stepwise regression using age, marital status, education level, current occupational status, consumption of analgesics and antidepressants, total body fat percentage, light PA, MVPA, and sedentary time. Accelerometer wear-time was used as a covariate (enter method) in all models. PA levels and sedentary time are highlighted in bold. β= standardized regression coefficient. b= non-standardized regression coefficient. CI= confidence interval. HRQoL= health-related quality of life. MVPA= moderate-to-vigorous physical activity. PA= physical activity.

Figure 1 shows the differences in the dimensions of HRQoL in women with fibromyalgia meeting (n = 86) *vs.* not meeting (n = 321) the current American PA recommendations. MANCOVA analysis showed no significant differences between the 2 groups for global HRQoL (Hottelling- T^2: $F_{8,391}$ = 0.027; p = 0.239). In further analysis for each dimension, patients who met the current PA recommendations presented better scores in bodily pain (95%-CI:21.3–27.2 *vs.* 18.9–21.9; p = 0.023) and social functioning (95%-CI:43.9–44.8 *vs.* 39.8–44.8, p = 0.024) dimensions than those who did not meet the current PA recommendations.

Supplementary material includes a replication of all analyses using the modified 2010 ACR preliminary criteria for diagnosis. Overall, both analyses showed similar results except for a lack of association between sedentary time and physical role, bodily pain, and mental health component when using the modified 2010 ACR criteria.

DISCUSSION

The current study showed that light PA and MVPA (positively) and sedentary time (negatively) are associated with different dimensions of HRQoL in women with fibromyalgia. MVPA intensity level and sedentary time were independently associated with HRQoL dimensions (except for general health, emotional role, and mental health). Participants meeting the current PA recommendations showed better scores in bodily pain and social functioning dimensions of HRQoL compared to those not meeting the current PA recommendations. Our findings suggest that fibromyalgia patients should be encouraged to reduce sedentary time and increase their PA levels.

Diverse intervention studies have suggested that PA is effective for improving symptomatology and HRQoL in patients with fibromyalgia[18–20]. However, as far as we know, only 2 previous studies have tested the link between the total PA and patients' perception of health status[7,8]. Sañudo et al.[7] found that patients who reported a moderate level of total PA presented a better physical function and general health. Culos-Reed and Brawley [8] also found evidence that the physical component of HRQoL was independently related with higher frequency of total PA. Overall, our results concur with previous research, but this is the first study supporting the relation of PA with HRQoL using objective measurements of PA in a large and geographically representative sample of women with fibromyalgia. The specific relationship between PA intensity levels and HRQoL in the general populations remains controversial. While some studies have shown that the regular participation in high-intensity levels of PA are related to better HRQoL in women[38], others studies have suggested that participation in high-intensity PA for extended periods might result in poorer HRQoL[39]. In the present study, when PA intensity levels were studied individually, we observed that light, moderate, and MVPA were correlated with different domains of HRQoL. However, MVPA was the only PA intensity level that showed significant associations with HRQoL independently of light PA and sedentary time. This finding agrees with recommendations to increase MVPA levels to promote health improvements[10]. Complementing prior literature that demonstrated that increasing time in MVPA was effective to reduce fibromyalgia impact[18], our results also demonstrated that greater time in MVPA is related to less interference with social activities due to health status.

In line with prior studies in patients with arthritis[13,14], we observed that patients who met the PA recommendations had overall better HRQoL, although MANCOVA analyses only showed significant differences in bodily pain and social function domains. Accumulating MVPA for a reduced reported pain partially contrast with previous studies showing the beneficial role of PA of low and moderate intensity for pain modulation[16], interference[20], and intensity[19] in patients with fibromyalgia. However, it is also noteworthy that light PA was the only PA intensity level associated with better scores in bodily pain domain in the correlation analyses. Therefore, while the link between PA and pain appears to exist[40], the differences in accelerometry devices, cut-points, and tools to assess pain might partly explain the discrepancies when establishing an adequate intensity of PA to promote pain benefits.

The relationship found in the present study between PA and HRQoL is complex and might be explained through intermediate factors. Self-efficacy can be considered to be a consequence of PA but might also be a potential mediator between PA and HRQoL[41]. Positive changes in others' constructs related to mental health (depression, fatigue, social support, mood[42], affect, or self-esteem[43]) have been suggested to mediate in the pathway between PA and HRQoL in previous population-based studies as well. More closely related to physical component, participation in PA tends to be associated with benefits such as reduction of cardiovascular risk factors[12], improved sleep quality, improved fitness level, and reduced functional limitations[10]. Although this indirect relationship has been theoretically grounded in previous research, the intermediate role of the aforementioned factors among fibromyalgia patients is yet to be elucidated.

This study also fills a gap in the literature by evidencing an inverse relationship of objectively measured sedentary time with HRQoL independent of PA in women with fibromyalgia. The strongest association of sedentary time was observed with the social function dimension. The passive nature of different sedentary activities (e.g., watching television or sitting at the computer) is thought to be accompanied by decreased communication and poor social networking[44]. Because social isolation concerns are frequently reported by these patients, preventing prolonged sedentary activities and moving towards a less sedentary lifestyle may positively influence this construct of health. Mechanisms that explain the deleterious relationship of sedentary behavior and HRQoL have been less studied compared to those identified with PA. Nevertheless, some adaptations negatively related to the mental component of HRQoL, such as stress, anxiety, depression, and mental disorders, have been connected to sustained sedentary time[23]. Impaired pain regulation related to sedentary behavior[16] could additionally explain detriments in patients' reported health status. Furthermore, prolonged sedentary time compromises cardiometabolic health, leading to increased cardiovascular risk, hypertension, and diabetes[22]. The fact that sedentary behavior is higher in fibromyalgia patients[9], added to the association found between sedentary time and HRQoL independent of PA, displays the importance of this behavior as a target for health promotion efforts in these patients. Therefore, motivating women with fibromyalgia to become less sedentary seems a valuable strategy, since this behavior would likely result in increases in light PA behaviors, which also presented positive correlations with

HRQoL in the current study, as well as overall symptoms in previous studies[15,19,45].

The absence of a gold standard to identify fibromyalgia makes the evaluation of the disease difficult and controversial. Since the first diagnosis was released in 1990[26], this criterion has been widely used in prior literature and is still the current official criteria for the diagnosis of fibromyalgia. A new understanding of the concept of fibromyalgia arose with the modified ACR 2010 criteria[32], giving greater emphasis to symptoms and dropping the tender point assessment from 1990. The 2011 criteria also has some limitations, however, such as the misclassification of patients that do not have generalized pain but have regional pain syndromes[45]. It is therefore possible that using different diagnosis criteria changes the fibromyalgia case definitions and, consequently, might imply slight modifications in study results. To understand the robustness of our results across different classification criteria, the modified 2010 criteria (see supplementary material) were also used. In our analyses, changes in results related to physical role and bodily pain dimensions as well as mental health component were observed, resulting in a lack of association (but having borderline significance) when using the modified 2010 criteria. These discrepancies were expected since the 2010 symptom severity scale is closely related to those dimensions of health by assessing difficulty in thinking or remembering, pain or cramps in the lower abdomen, depression, and headache.

The present study has some limitations that must be acknowledged. Since our results are derived from a cross-sectional study, the associations found cannot be explained via a causal pathway: while PA might improve HRQoL, it is possible that individuals with impaired HRQoL are less likely to participate in PA behaviour. Additionally, due to the large number of factors related to HRQoL, it is difficult to ascertain the true association between PA intensity levels and sedentary time with HRQoL. Given that only women took part in this study, future studies should investigate whether these associations also occur in men. In spite of these limitations, this study has several strengths, including the use of accelerometers, which allowed us to objectively quantify intensities of PA and time spent in sedentary activities. Furthermore, we assessed a relatively large sample size of women with fibromyalgia who were representative of southern Spain (Andalusia)[24]. We also attempted to enhance the robustness of our analyses by adjusting for a reasonable number of potential confounders.

CONCLUSIONS

This study showed that all PA intensity levels (positively) and sedentary time (negatively) were individually correlated to better scores in different domains of HRQoL. However, among the different PA intensity levels, only MVPA showed an independent association with HRQoL, and specifically with social functioning domain. Moreover, patients who met the American PA recommendations present significantly better scores in bodily pain and social functioning domains. Interestingly, sedentary time was also independently and inversely associated with physical function, physical role, bodily pain, vitality, social functioning, physical component, and mental component dimensions of HRQoL. The effects on HRQoL of strategies aimed at reducing sedentary time, which will result in greater light PA and eventually lead to engagement in MVPA among this population, needs to be further evaluated.

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Supplementary material including replication of all analyses using the modified 2010 ACR preliminary criteria for diagnosis

Supplementary Table 1. Characteristics of the study participants (*n*=428)

Variables	mean±SD
Age(years)	51.4±7.7
Total tender points (11-18)	15.0±4.8
Algometer Score (18-144)	50.1±22.5
Widespread Pain Index (0-19)	14.3±3.4
Symptom Severity Score (0-12)	8.4±1.9
Polysymptomatic Distress Scale (0-31)	22.6±4.2
BMI (Kg/m^2)	28.5±5.5
Total Body fat (%)	40.1±7.7
HRQoL, SF-36 (0-100)	
Physical function	38.2±18.6
Physical role	31.6±21.1
Bodily pain	20.8±14.3
General health	27.6±15.0
Vitality	21.2±16.8
Social functioning	41.2±23.1
Emotional role	54.2±27.3
Mental health	44.6±19.2
Physical component	29.3±7.0
Mental component	34.8±11.1
PA and sedentary behavior (min/day)	
Accelerometer wear-time	922.2±77.8
Sedentary time	465.0±105.6
Light PA	413.8±95.3
Moderate PA	43.1±29.4
Vigorous PA	0.3±1.2
MVPA	43.4±29.8
	N (%)
Marital status	
Married	321 (75)
Not married	107 (25)
Education level	
Non university	366 (85.5)
University	62 (14.5)
Current occupational Status	
Working	112 (26.2)
Not working	316 (73.8)
Drug consumption	
Analgesics	388 (90.7)
Antidepressants	262 (61.2)
PA recommendations	
Meet PA recommendations	86 (20.1)
Not meet PA recommendations	342 (79.9)

BMI= Body mass index; HRQoL= health-related quality of life; MVPA= Moderate-to-vigorous physical activity; PA= physical activity; SF-36= 36-item Short-Form Health Survey; SD= standard deviation.

Supplementary table 2. Partial correlations of PA intensity levels and sedentary behaviour with HRQoL (*n*=428)

	Light PA	Moderate PA	MVPA	Sedentary Time
Physical function	0.10 *	0.08	0.08	-0.11 *
Physical role	0.05	0.11 *	0.10 *	-0.08
Bodily pain	0.03	0.04	0.04	-0.04
General health	- 0.04	0.02	0.03	-0.04
Vitality	0.08	0.13 *	0.13 *	-0.11 *
Social functioning	0.18 ***	0.22 ***	0.22 ***	-0.22 ***
Emotional role	0.03	0.01	0.01	-0.03
Mental health	0.00	0.02	0.02	-0.00
Physical Component	0.06	0.08	0.08	-0.07
Mental Component	0.05	0.07	0.07	-0.07

Notes: Analyses are controlled for age, total body fat percentage, current occupational status, education level, marital status, accelerometer-wear time, consumption of analgesics and antidepressants.

* $p \leq 0.05$, ** $p \leq 0.01$, *** $p \leq 0.001$

HRQoL= Health-related quality of life. MVPA= moderate-to-vigorous physical activity. PA= physical activity.

Supplementary table 3. Models of regression coefficients assessing the association of PA intensity levels and sedentary time with HRQoL *(n*=428*)*

	β	b	(95 % CI)		*p*	Adjusted R^2
Physical Function						
Accelerometer-wear time	0.13	0.03	(0.01,	0.05)	0.013	0.069
Sedentary time	-0.14	-0.02	(-0.04,	-0.01)	0.007	
Medication for depression	-0.12	-4.71	(-8.36,	-1.06)	0.011	
Occupational status: Working	0.1	4.29	(0.29,	8.30)	0.036	
Physical Role						
Accelerometer-wear time	0.09	0.02	(0.00,	0.05)	0.064	0.14
Medication for depression	-0.23	-9.8	(-13.70,	-5.91)	<0.001	
Working	0.2	9.4	(4.89,	13.90)	<0.001	
Total body fat percentage	-0.13	-0.34	(-0.59,	-0.10)	0.006	
University	-0.1	-5.9	(-11.42,	-0.38)	0.036	
Bodily pain						
Accelerometer-wear time	0.01	0	(-0.01,	0.02)	0.807	0.121
Medication for depression	-0.31	-9.02	(-11.67,	-6.38)	<0.001	
Total body fat percentage	-0.15	-0.28	(-0.44,	-0.11)	0.001	
General health						
Accelerometer-wear time	0.01	0	(-0.02,	0.02)	0.753	0.077
Medication for depression	-0.2	-6.12	(-9.01,	-3.23)	<0.001	
Occupational status: Not working	-0.12	-3.53	(-6.36,	-0.70)	0.015	
Medication for pain	-0.11	-5.52	(-10.29,	-0.75)	0.023	
Vitality						
Accelerometer-wear time	0.09	0.02	(0.00,	0.04)	0.095	0.052
Medication for depression	-0.11	-3.81	(-7.16,	-0.47)	0.026	
Sedentary time	-0.14	-0.02	(-0.04,	-0.01)	0.009	
Medication for pain	-0.11	-6.55	(-11.97,	-1.13)	0.018	
Social functioning						
Age	0.13	0.38	(0.11,	0.65)	0.005	0.185
Accelerometer-wear time	0.11	0.03	(0.00,	0.06)	0.033	
Medication for depression	-0.26	-12.25	(-16.48,	-8.02)	<0.001	
Marital status	-0.09	-4.89	(-9.53,	-0.26)	0.039	
Sedentary time	-0.15	-0.03	(-0.06,	-0.01)	0.008	
MVPA	0.14	0.11	(0.02,	0.19)	0.012	
Emotional Role						
Accelerometer-wear time	0.14	0.05	(0.02,	0.08)	0.002	0.154
Medication for depression	-0.34	-18.86	(-23.81,	-13.90)	<0.001	
Occupational status: Housekeeper	-0.11	-6.49	(-11.73,	-1.26)	0.015	
Mental Health						
Accelerometer-wear time	0.12	0.03	(0.01,	0.05)	0.007	0.127
Medication for depression	-0.32	-12.62	(-16.16,	-9.08)	<0.001	
Physical component summary						
Accelerometer-wear time	0.04	0	(-0.01,	0.01)	0.445	0.054
Occupational status: Working	0.13	2.06	(0.54,	3.57)	0.008	
Total body fat percentage	-0.12	-0.1	(-0.19,	-0.02)	0.019	
Sedentary time	-0.1	-0.01	(-0.01,	0.00)	0.045	
Mental component summary						
Accelerometer-wear time	0.12	0.02	(0.00,	0.03)	0.008	0.15
Medication for depression	-0.35	-8.02	(-10.03,	-6.01)	<0.001	

Notes: Forward stepwise regression using age, marital status, education level, current occupational status, consumption of analgesicsand antidepressants, total body fat percentage, light PA, MVPA, and sedentary time. Accelerometer wear-time was used as a covariate (*enter method*) in all models. PA levels and sedentary time are highlighted in bold. β= standardized regression coefficient. b= non-standardized regression coefficient. CI= confidence interval. HRQoL= health-related quality of life. MVPA= moderate-to-vigorous physical activity. PA= physical activity

SECTION 1

Study 2

Patterns of sedentary time and health-related quality of life in women with fibromyalgia: cross-sectional study from the al-Ándalus project

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ABSTRACT

Objective: To examine the association of the patterns of ST with health-related quality of life (HRQoL) in women with fibromyalgia, the combined association of total ST and prolonged ST with HRQoL, and to test whether these associations are independent of moderate-to-vigorous physical activity (MVPA).

Methods: A total of 407 women (mean 51.4 years of age [SD 7.6]) with fibromyalgia participated. ST and MVPA were measured with triaxial accelerometry. The percentage of ST accumulated in bouts and the frequency of sedentary bouts of different lengths (≥10 min, ≥20 min, ≥30 min, and ≥60 min) were obtained. Four groups combining total ST and sedentary bout duration (≥30 min) were created. We assessed HRQoL using the 36-item Short-Form Health Survey (SF-36).

Results: Greater percentage of ST spent in all bout lengths was associated with worsened physical function, bodily pain, vitality, social function, and physical component summary (PCS) (all $P<0.05$). In addition, higher percentage of ST in bouts of 60 minutes or more was related to worsened physical role ($P=0.04$). Higher frequency of bouts was negatively associated with physical function, social function, the PCS (≥30 min and ≥60 min), physical role (≥60 min), bodily pain (≥60 min), and vitality (≥20 min, ≥30 min, and ≥60 min) (all, $P<0.05$). Overall, for different domains of HRQoL, these associations were independent of MVPA for higher bout lengths. Participants with high total ST and high sedentary bout duration had significantly worsened physical function (mean difference 8.73 units, 95% CI 2.31-15.15; independent of MVPA), social function (mean difference 10.51 units, 95% CI 2.59-18.44; not independent of MVPA), and PCS (mean difference 2.71 units, 95% CI 0.36-5.06; not independent of MVPA) than those with low ST and low sedentary bout duration.

Conclusions: Greater ST in prolonged periods of any length and a higher frequency of ST bouts, especially in longer bout durations, are associated with worsened HRQoL in women with fibromyalgia. These associations were generally independent of MVPA.

INTRODUCTION

Fibromyalgia is a chronic and heterogeneous condition characterized by pain as the dominant symptom, which is frequently accompanied by fatigue, sleep disorders, or cognitive impairment[1]. Fibromyalgia patients, who tend to be highly sedentary, usually reduce their physical activity (PA) levels in order to avoid an aggravation of their symptomatology[2,3]. However, adopting this behavior might trigger a worsening of their condition[4–8]. Importantly, the risks of a sedentary lifestyle are present irrespective of the PA performed[9,10]. Considering that few patients with fibromyalgia fulfil the recommended level of moderate-to-vigorous PA (MVPA)[11], these patients are at an increased health risk not only for being highly sedentary but also for being inactive[12,13]. In the management of fibromyalgia, a graduated approach first focused on nonpharmacological modalities, and the improvement of health-related quality of life (HRQoL) is currently recommended[14]. Therefore, greater insights on how modifiable factors, such as daily sedentary time (ST) and PA, are related to HRQoL among these patients are warranted.

Emerging evidence in the general population has demonstrated that not only the total amount of ST but also the pattern of accumulation of sedentary behaviors is relevant to health[15–17]. Prolonged, unbroken periods (ie, bouts) of ST might be particularly harmful[15,16] due to its relationship with detrimental effects on the metabolism[15–17]. In fibromyalgia, Ellingson et al demonstrated that both total ST, but especially sustained ST, can negatively influence pain modulation processes[5]. In addition, the frequency of sedentary bouts seems to be linked to health outcomes, with frequent interruptions in prolonged ST (ie, breaks) being beneficially related to markers of metabolic risk[18]. Although current PA recommendations emphasize the importance of reducing total ST[19], there is no information on how sedentary behavior patterns (ie, bout duration and frequency) should be modified to maximize health benefits. Sedentary patterns have been typically collected by accelerometers in the research field[17]. In contrast, mobile health (ie, mHealth) tools are more user-friendly devices that are widely used by consumers to track daily activity. These wearable devices, however, do not usually offer sedentary behavior information to users, although the inclusion of accelerometer sensors in wearable devices[20] would make it possible. Therefore, the analysis of the impact of different patterns of sustained ST on HRQoL in fibromyalgia could help in (1) the development of recommendations to reduce overall ST and in the interruption of potentially harmful bout lengths and (2) the implementation of future mHealth tools that deliver actual sedentary pattern information and potentially encourage this population to break prolonged ST.

Therefore, we aimed to examine (1) the association of the patterns of ST (ie, ST accumulated in bouts and frequency of sedentary bouts) in different bout lengths (≥10 min, ≥20 min, ≥30 min, and ≥60 min) with the HRQoL in women with fibromyalgia, (2) the combined association of total ST and sedentary bout duration with HRQoL, and (3) whether these associations are independent of MVPA.

METHODS

A representative sample of fibromyalgia patients from the south of Spain—Andalusia—was recruited for the al-Ándalus project via fibromyalgia associations, Internet advertisement, flyers, and email.

Written informed consent from all participants (N=646) was obtained. Inclusion criteria for this study require that participants[1] be previously diagnosed by a rheumatologist and meet the 1990 American College of Rheumatology fibromyalgia criteria[1], (2) do not have either acute or terminal illness or severe cognitive impairment, and (3) are 65 years of age or younger. The flowchart of participants included in this study is shown in Figure 1. The Ethics Committee of the Hospital Virgen de las Nieves, Granada, Spain, reviewed and approved the study.

Measurements

Sedentary Time and Physical Activity

Patients wore the GT3X+ triaxial accelerometer (ActiGraph) on the hip for 9 days, 24 hours per day, except during water-based activities. Activity counts were measured at a rate of 30 Hz and stored at an epoch length of 1 minute[21]. Accelerometer-wearing time was obtained by subtracting the sleeping time and nonwear periods from each day. Sleeping time was obtained from a sleep diary, in which patients reported the time they went to bed and the time they woke up. Nonwear periods were obtained by applying Choi's algorithm[22]. Bouts of 90 continuous minutes of 0 counts were considered nonwear periods. To eliminate reactivity from the awareness of being monitored, we excluded PA data from the first day. The last day, when the device was returned, was excluded from the analysis as well. A total of 7 continuous days of recording, with a minimum of 10 valid hours per day, was the minimum criteria for being included in the study analysis.

ST and MVPA were calculated based upon recommended PA vector magnitude cut points[21,23]: 0-199 and ≥2690 counts per minute (cpm), respectively. A sedentary bout was defined as the number of consecutive minutes during which the accelerometer registered less than 200 cpm. Four sedentary bout-length categories were used in this study: ≥10 min, ≥20 min, ≥30 min, and ≥60 min. For each sedentary bout length, we obtained the following variables related to patterns of ST: (1) percentage of total ST accumulated in bouts (total time accumulated in bouts/total ST × 100) and (2) frequency of bouts (number of bouts/sedentary hours).

Data download, reduction, cleaning, and analyses were performed using ActiGraph's desktop software: ActiLife, version 6.11.7.

Health-Related Quality of Life

The HRQoL was assessed using the 36-item Short-Form Health Survey (SF-36)[24]. The SF-36 is composed of 36 items that assess eight dimensions of health (ie, physical functioning, physical role, bodily pain, general health, social functioning, emotional role, mental health, and vitality) and two component summary scores (ie, physical component summary [PCS] and mental component summary [MCS]). The score in each of the eight dimensions is standardized and ranges from 0 (worst health status) to 100 (best health status).

Sociodemographic and Clinical Data

We collected sociodemographic and clinical data using a self-reported questionnaire that included age, marital status (married/not married), education level (university/nonuniversity), and occupational status (working/not working). Patients also reported the consumption of antidepressants and analgesics (yes/no) during the previous 2 weeks.

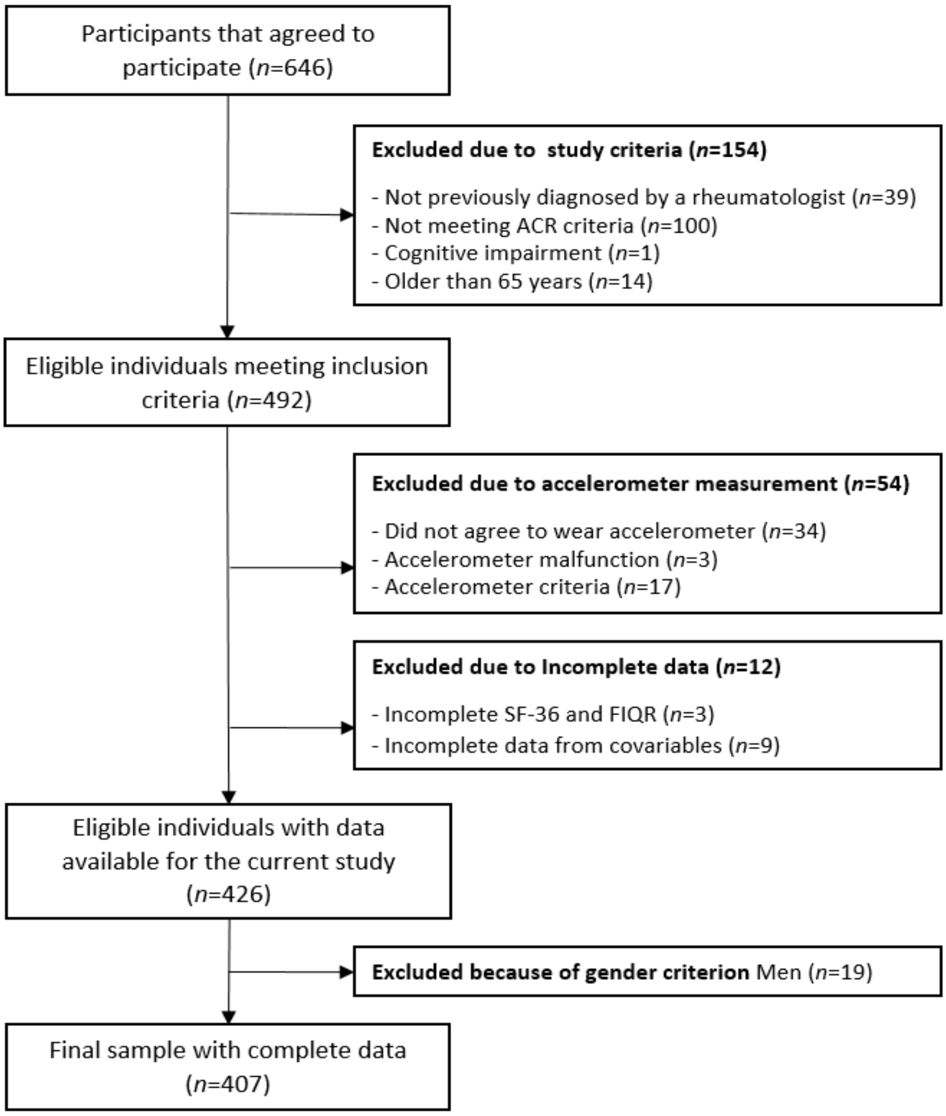

Figure 1. Flow diagram of inclusion of women with fibromyalgia from the al-Ándalus project included in this study (N=407).

Anthropometry and Body Composition

Weight (kg) and total body fat (%) were measured using bioelectrical impedance with the InBody R20 (Biospace) body composition analyzer. Patients were asked neither to have a shower, practice intense PA, nor ingest large amounts of fluid and/or food in the 2 hours before the measurement. Patients released from clothing and metal objects during the assessment.

Impact of the Disease

The Revised Fibromyalgia Impact Questionnaire (FIQR)[25] assesses overall fibromyalgia severity through a wide range of symptoms, comorbidities, and complaints related to this chronic condition. It is a self-administered questionnaire with 21 individual questions, with a rating scale of 0-10. The FIQR total score ranges from 0 to 100, with a higher score indicating greater impact of the syndrome on a person's life.

Statistical Analysis

Descriptive continuous data are shown as mean (SD), whereas categorical data are presented as n (%). To test the association between patterns of ST and HRQoL, we used linear regression analysis. The eight dimensions and the two summary components of the SF-36 were introduced as dependent variables in separate regression models. Patterns of ST (ie, percentage of ST accumulated in bouts and frequency of bouts in all bout lengths) were introduced individually as predictor variables in separate regression models. Two types of models were built: (1) model 1 was controlled for age, total body fat percentage, occupational status, medication for pain and depression, and accelerometer wear time and (2) model 2 included model 1 plus MVPA.

The combined association of total ST and prolonged sedentary bout duration with HRQoL was studied through analyses of covariance. The subject pool was divided into four groups according to the median value of total ST (3216 min/week) and the median value of sedentary bout durations of 30 continuous minutes or more (47.7 min). A minimum duration of 30 continuous minutes was used to define prolonged ST following the criteria of previous studies[26]. The four groups created were (1) low total ST (≤ the median value) + low sedentary bout duration (≤ the median value) (2) low total ST + high sedentary bout duration (> the median value), (3) high total ST (> the median value) + low sedentary bout duration, and (4) high total ST + high sedentary bout duration. The analyses were adjusted for age, total body fat percentage, occupational status, medication for pain and depression, and accelerometer-wear time. Additional analyses including MVPA as covariate were performed.

For analyses, we used IBM SPSS Statistics for Windows, version 20.0 (IBM Corp). The statistical significance was set at P<.05.

Data Exclusion

The final sample size included in the analyses comprised 407 women with fibromyalgia. The flow diagram of women with fibromyalgia included in this study is shown in Figure 1.

RESULTS

Table 1 provides an overview of the patient's' sociodemographic and clinical characteristics. Table 2 includes the information related to PA and ST pattern characteristics (% of total ST and frequency of bouts) in different bout lengths.

Table 1. Sociodemographic and clinical characteristics of the study participants (N=407)

Variables	Mean (SD)
Age (years), mean (SD)	51.4 (7.6)
Algometer score (18-144), mean (SD)	43.2 (13.4)
Body mass index (kg/m^2), mean (SD)	28.4 (5.4)
Total body fat (%), mean (SD)	40.1 (7.6)
FIQR[a] score (0-100), mean (SD)	64.4 (16.7)
Health-related quality of life, SF-36[b] score (0-100), mean (SD)	
Physical function	39.2 (18.9)
Physical role	33.2 (21.2)
Bodily pain	21.2 (14.7)
General health	28.5 (15.3)
Vitality	22.3 (17.7)
Social functioning	43.7 (24.7)
Emotional role	56.9 (27.9)
Mental health	46.2 (19.7)
Physical component	29.5 (6.9)
Mental component	36.0 (11.6)
Marital status, n (%)	n (%)
Married	311 (76.4)
Not married	96 (23.6)
Education level, n (%)	
Nonuniversity	349 (85.7)
University	58 (14.3)
Current occupational status, n (%)	
Working	107 (26.3)
Not working	300 (73.7)
Drug consumption, n (%)	
Analgesics	367 (90.2)
Antidepressants	232 (57.0)

[a] FIQR: Revised Fibromyalgia Impact Questionnaire. [b]SF-36: 36-item Short-Form Health Survey.

Table 2. Sedentary patterns and physical activity variables of the study participants (N=407)

Sedentary behavior and PA	Mean (SD)
Accelerometer-wear time	923.0 (78.9)
Sedentary time (ST)	
Minutes per day	460.1 (104.1)
Percentage of wear time	49.9 (10.6)
Light PA	
Minutes per day	418.6 (91.8)
Percentage of wear time	45.3 (9.1)
Moderate PA	
Minutes per day	43.9 (29.5)
Percentage of wear time	4.8 (3.2)
Vigorous PA	
Minutes per day	0.4 (2)
Percentage of wear time	0.1 (0.2)
Moderate-to-vigorous PA	
Minutes per day	44.3 (30.1)
Percentage of wear time	4.8 (3.2)
Patterns of ST of different bout lengths	
≥10-minute bout	
Percentage of total ST accumulated (%)	59.2 (11.2)
Frequency of bouts (number of bouts/week)	83.7 (25.6)
≥20-minute bout	
Percentage of total ST accumulated (%)	38.5 (12.8)
Frequency of bouts (number of bouts/week)	34.3 (14.6)
≥30-minute bout	
Percentage of total ST accumulated (%)	26.7 (12.3)
Frequency of bouts (number of bouts/week)	17.9 (9.6)
≥60-minute bout	
Percentage of total ST accumulated (%)	10.3 (8.9)
Frequency of bouts (number of bouts/week)	4.3 (3.7)

MVPA: Moderate-to-vigorous physical activity; PA: physical activity; ST: sedentary time

The association of the percentage of ST accumulated in bouts of different lengths with the SF-36 domains are shown in Table 3.

Greater percentages of ST spent in all bout lengths were associated with worse physical function, bodily pain, vitality, and social function domains and the PCS (beta from -.20 to -.10, all P<.05). In addition, a higher percentage of ST spent in bouts of 60 minutes or more was related to a worsened physical role (beta=-.10, P=.04). Overall, these associations were independent of MVPA (all P<.05), except for the bodily pain (for bouts ≥10, ≥20, or ≥30 min) and physical role domains.

Table 4 shows the association of the frequency of bouts of ST of different lengths with the SF-36 domains. A higher frequency of sedentary bouts 20 minutes or longer was associated with worsened vitality and social function (beta=-.12 and -.13, respectively, all P<.05). A higher frequency

of sedentary bouts 30 minutes or longer was associated with worsened physical function, vitality, social function, and PCS scores (beta from -.15 to -.12, all P<.05). A higher frequency of sedentary bouts 60 minutes or longer was associated with worsened physical function, physical role, bodily pain, vitality, social function, and PCS scores (beta from -.19 to -.10, all P<.05). These associations were independent of MVPA, except for the association with physical role, vitality, and social function in bouts 20 minutes or longer.

Figure 2 shows the combined association of total ST and sedentary bout duration with the SF-36 domains, the PCS, and the MCS. Participants with low total ST and low sedentary bout duration presented better physical function (mean difference 8.73 units, 95% CI 2.31-15.15), social function (mean difference 10.51 units, 95% CI 2.59-18.44), and PCS (mean difference 2.71 units, 95% CI 0.36-5.06) compared to participants with high total ST and high sedentary bout duration (all P<.02). Additional analyses showed that the differences in the physical function (P=.045) were independent of MVPA.

Table 3. Association of the percentage of sedentary time accumulated in bouts of different lengths with SF-36 dimensions (n=407)

		Percentage of sedentary time accumulated in bouts of different lengths (%)															
		≥ 10 min bout				≥ 20 min bout				≥ 30 min bout				≥ 60 min bout			
		B	SE	β	*P*	B	SE	β	*P*	B	SE	β	*P*	B	SE	β	*P*
Physical Function	model 1	**-0.267**	**0.086**	**-0.159**	**0.002**	**-0.253**	**0.074**	**-0.171**	**0.001**	**-0.271**	**0.077**	**-0.176**	**<.001**	**-0.428**	**0.104**	**-0.201**	**<.001**
	model 2	**-0.226**	**0.089**	**-0.134**	**0.01**	**-0.221**	**0.077**	**-0.149**	**0.004**	**-0.239**	**0.079**	**-0.156**	**0.002**	**-0.396**	**0.105**	**-0.186**	**<.001**
Physical Role	model 1	-0.126	0.094	-0.067	0.18	-0.137	0.081	-0.082	0.09	-0.159	0.084	-0.092	0.06	**-0.239**	**0.114**	**-0.1**	**0.04**
	model 2	-0.063	0.097	-0.033	0.52	-0.089	0.083	-0.054	0.29	-0.115	0.086	-0.067	0.18	-0.195	0.115	-0.082	0.09
Bodily pain	model 1	**-0.13**	**0.065**	**-0.099**	**0.045**	-0.108	0.056	-0.094	0.05	**-0.114**	**0.058**	**-0.096**	**0.048**	**-0.19**	**0.078**	**-0.115**	**0.02**
	model 2	-0.106	0.067	-0.081	0.12	-0.089	0.058	-0.077	0.13	-0.096	0.059	-0.08	0.11	**-0.171**	**0.079**	**-0.104**	**0.03**
General Health	model 1	-0.034	0.069	-0.025	0.62	-0.048	0.06	-0.04	0.42	-0.058	0.062	-0.047	0.35	-0.076	0.084	-0.044	0.37
	model 2	-0.029	0.072	-0.021	0.69	-0.046	0.062	-0.038	0.46	-0.056	0.064	-0.045	0.38	-0.073	0.085	-0.042	0.39
Vitality	model 1	**-0.252**	**0.08**	**-0.16**	**0.002**	**-0.204**	**0.069**	**-0.148**	**0.003**	**-0.204**	**0.072**	**-0.142**	**0.004**	**-0.278**	**0.097**	**-0.14**	**0.004**
	model 2	**-0.209**	**0.083**	**-0.133**	**0.01**	**-0.168**	**0.071**	**-0.122**	**0.02**	**-0.169**	**0.073**	**-0.117**	**0.02**	**-0.242**	**0.098**	**-0.122**	**0.01**
Social functioning	model 1	**-0.399**	**0.106**	**-0.181**	**<.001**	**-0.351**	**0.091**	**-0.182**	**<.001**	**-0.361**	**0.095**	**-0.18**	**<.001**	**-0.5**	**0.129**	**-0.181**	**<.001**
	model 2	**-0.285**	**0.108**	**-0.13**	**0.01**	**-0.261**	**0.093**	**-0.135**	**0.01**	**-0.275**	**0.095**	**-0.137**	**0.004**	**-0.412**	**0.128**	**-0.149**	**0.001**
Emotional role	model 1	0.04	0.121	0.016	0.74	0.012	0.105	0.005	0.91	-0.016	0.109	-0.007	0.88	-0.034	0.148	-0.011	0.82
	model 2	0.077	0.126	0.031	0.54	0.039	0.109	0.018	0.72	0.008	0.112	0.004	0.94	-0.01	0.15	-0.003	0.95
Mental health	model 1	0.028	0.086	0.016	0.74	-0.015	0.075	-0.01	0.84	-0.029	0.077	-0.018	0.71	-0.104	0.105	-0.047	0.32
	model 2	0.059	0.09	0.034	0.51	0.006	0.077	0.004	0.94	-0.01	0.079	-0.006	0.9	-0.087	0.106	-0.039	0.41
Physical component	model 1	**-0.096**	**0.032**	**-0.156**	**0.003**	**-0.085**	**0.027**	**-0.158**	**0.002**	**-0.089**	**0.028**	**-0.159**	**0.002**	**-0.13**	**0.038**	**-0.168**	**0.001**
	model 2	**-0.083**	**0.033**	**-0.135**	**0.01**	**-0.075**	**0.028**	**-0.139**	**0.01**	**-0.079**	**0.029**	**-0.141**	**0.01**	**-0.119**	**0.039**	**-0.154**	**0.002**
Mental component	model 1	-0.023	0.05	-0.022	0.64	-0.031	0.043	-0.034	0.47	-0.039	0.045	-0.041	0.39	-0.065	0.061	-0.05	0.283
	model 2	0.003	0.052	0.003	0.95	-0.011	0.044	-0.012	0.8	-0.02	0.046	-0.021	0.66	-0.047	0.061	-0.036	0.44

B, non-standardized regression coefficient; β: standardized regression coefficient; SE: Standard Error

Linear regression models built using *Enter* method, with SF-36 domains as dependent variables and % of sedentary time in different bout lengths as independent variables.

Model 1: adjusted for age, fat percentage, occupational status, medication for pain, medication for depression and accelerometer wear time

Model 2: analysis controlled for model 1 + moderate-to-vigorous physical activity

Significant associations are highlighted in bold

Table 4. Association of the frequency of bouts of sedentary time of different lengths with SF-36 dimensions (n=407)

		Frequency of bouts (nº/sedentary hour) of different bout lengths															
		≥ 10 min bout				≥ 20 min bout				≥ 30 min bout				≥ 60 min bout			
		B	SE	β	*P*	B	SE	β	*P*	B	SE	β	*P*	B	SE	β	*P*
Physical Function	model 1	2.386	4.237	0.028	0.57	-10.754	5.882	-0.092	0.07	**-18.793**	**7.663**	**-0.123**	**0.02**	**-61.611**	**16.061**	**-0.188**	**<.001**
	model 2	3.728	4.240	0.044	0.38	-7.970	6.002	-0.068	0.19	**-15.416**	**7.820**	**-0.101**	**0.049**	**-56.713**	**16.208**	**-0.173**	**0.001**
Physical Role	model 1	3.602	4.575	0.038	0.43	-4.921	6.375	-0.038	0.44	-12.379	8.315	-0.072	0.14	**-35.905**	**17.572**	**-0.098**	**0.04**
	model 2	5.161	4.572	0.055	0.26	-1.341	6.490	-0.01	0.84	-8.033	8.469	-0.047	0.34	-29.379	17.693	-0.08	0.1
Bodily pain	model 1	-1.811	3.163	-0.028	0.57	-6.140	4.399	-0.068	0.16	-9.957	5.741	-0.084	0.08	**-31.088**	**12.109**	**-0.122**	**0.01**
	model 2	-1.128	3.179	-0.017	0.72	-4.636	4.500	-0.051	0.3	-8.101	5.873	-0.068	0.17	**-28.355**	**12.245**	**-0.111**	**0.02**
General Health	model 1	1.978	3.370	0.029	0.56	-2.700	4.696	-0.029	0.57	-6.395	6.132	-0.052	0.3	-14.374	12.987	-0.054	0.27
	model 2	2.167	3.399	0.032	0.52	-2.433	4.818	-0.026	0.61	-6.189	6.289	-0.05	0.33	-13.956	13.166	-0.053	0.29
Vitality	model 1	-4.226	3.928	-0.053	0.28	**-13.300**	**5.441**	**-0.122**	**0.02**	**-19.025**	**7.101**	**-0.133**	**0.01**	**-44.261**	**15.015**	**-0.145**	**0.003**
	model 2	-2.976	3.931	-0.038	0.45	-10.617	5.549	-0.097	0.06	**-15.624**	**7.240**	**-0.109**	**0.03**	**-38.871**	**15.125**	**-0.127**	**0.01**
Social functioning	model 1	-2.477	5.242	-0.022	0.64	**-19.997**	**7.237**	**-0.132**	**0.01**	**-30.153**	**9.429**	**-0.151**	**0.001**	**-73.977**	**19.887**	**-0.173**	**<.001**
	model 2	0.493	5.150	0.004	0.92	-13.339	7.267	-0.088	0.07	**-21.717**	**9.472**	**-0.109**	**0.02**	**-60.962**	**19.730**	**-0.143**	**0.002**
Emotional role	model 1	4.353	5.913	0.035	0.46	1.973	8.246	0.011	0.81	-2.809	10.777	-0.012	0.79	-4.716	22.830	-0.01	0.84
	model 2	5.130	5.958	0.041	0.39	3.877	8.449	0.023	0.65	-0.61	11.041	-0.003	0.96	-1.328	23.120	-0.003	0.95
Mental health	model 1	5.702	4.196	0.065	0.18	0.485	5.861	0.004	0.93	-2.013	7.659	-0.013	0.79	-19.328	16.197	-0.057	0.23
	model 2	6.372	4.225	0.072	0.13	1.989	6.003	0.016	0.74	-0.195	7.844	-0.001	0.98	-16.941	16.404	-0.05	0.3
Physical component	model 1	-0.238	1.557	-0.008	0.88	-4.104	2.160	-0.097	0.06	**-6.827**	**2.816**	**-0.122**	**0.02**	**-19.387**	**5.930**	**-0.162**	**0.001**
	model 2	0.186	1.562	0.006	0.91	-3.222	2.208	-0.076	0.15	**-5.754**	**2.877**	**-0.103**	**0.046**	**-17.763**	**5.989**	**-0.149**	**0.003**
Mental component	model 1	1.309	2.431	0.025	0.59	-1.825	3.387	-0.025	0.59	-4.017	4.424	-0.043	0.36	-11.036	9.365	-0.055	0.24
	model 2	1.910	2.440	0.037	0.43	-0.438	3.461	-0.006	0.9	-2.300	4.520	-0.024	0.61	-8.442	9.459	-0.042	0.37

B, non-standardized regression coefficient; β: standardized regression coefficient; SE: Standard Error
Linear regression models built using Enter method, with SF-36 domains as dependent variables and % of sedentary time in different bout lengths as independent variables.
Model 1: adjusted for age, fat percentage, occupational status, medication for pain, medication for depression, accelerometer wear time and sedentary time
Model 2: analysis controlled for model model 1 + moderate-to-vigorous physical activity

Significant associations are highlighted in bold

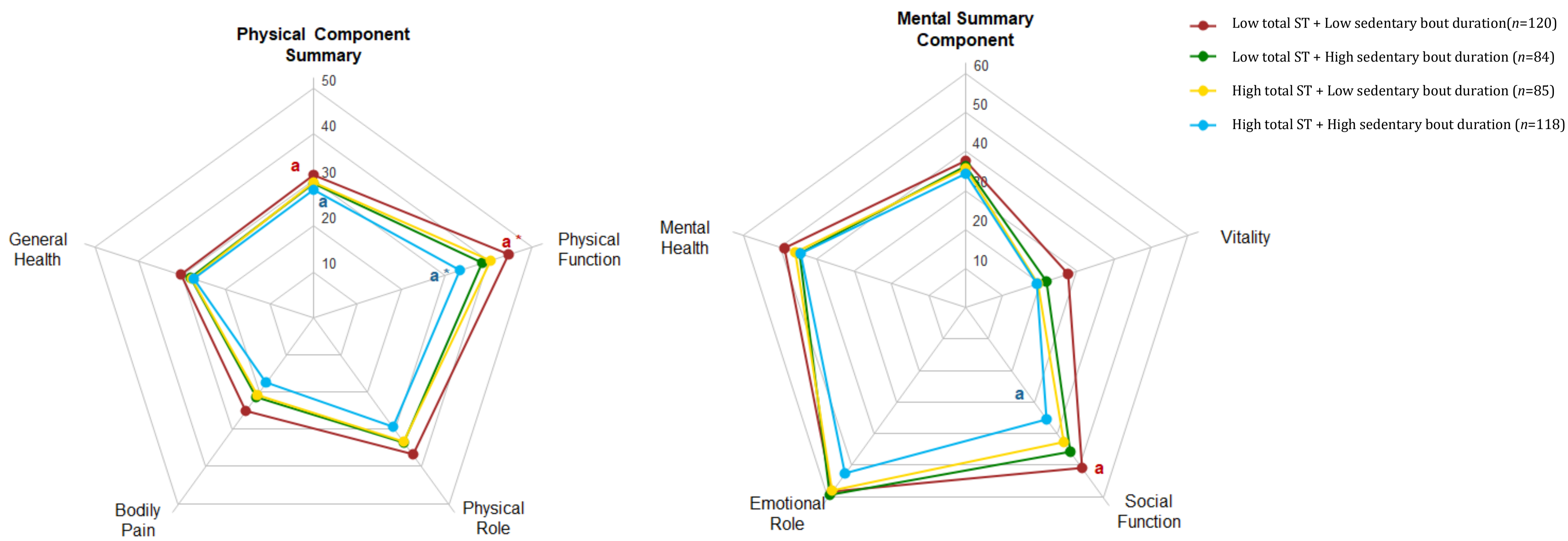

Figure 2. Combined association of total sedentary time (ST) and prolonged sedentary bouts of at least 30 min with health-related quality of life. Estimated mean represent values after adjustment for age, total body fat percentage, occupational status, medication for pain, medication for depression, and accelerometer wear time. Common superscripts indicate significant (P <.05) differences between groups with the same letter when adjusting for age, body fat percentage, occupational status, medication for pain, medication for depression, and accelerometer wear time. Asterisks represent significant differences for additional adjustment for MVPA (*P* =.045)

DISCUSSION

Principal Findings

The main findings of this study suggest that higher percentages of ST spent in different bout lengths were associated with worsened HRQoL, including physical function, bodily pain, vitality, and social function domains as well as the PCS. Also, higher frequencies of sedentary bouts were associated with worsened HRQoL, including physical function, bodily pain, vitality, and social function domains, as well as the PCS, especially in longer bout durations. Patients characterized by high total ST and high sedentary bout duration presented worsened physical function, social function, and PCS scores. These associations were generally independent of the MVPA performed for long bout lengths. These findings entail a first step toward the understanding of free-living sedentary behavior and its association with HRQoL in fibromyalgia. This supports the implementation of mHealth devices, which allow self-monitoring and immediate feedback of daily living behaviors to patients. Future studies might determine whether this approach is successful by reducing prolonged ST in this population.

Limitations

This study has several limitations that should be underlined. Because our results were derived from a cross-sectional design, the associations cannot be explained via a causal pathway. In addition, due to the large quantity of factors related to HRQoL, it is difficult to ascertain the true nature of the association found between variables. Because only women took part in this study, future studies should investigate whether these associations might extend to men as well. Among its strengths, this study includes a relatively large sample size of women with fibromyalgia representative from the south of Spain (ie, Andalucia). According to a recent study, measurement of the actual dose of exercise and daily mobility are essential to establish relationships of these behaviors with health[20]. In this sense, ST and PA were objectively assessed in this study through a wearable tool that enabled researchers to monitor the type, quantity, and quality of everyday activities of patients, via accelerometry, which is considered a more reliable technique than questionnaires in the study of fibromyalgia[27]. Future intervention studies with mHealth devices that incorporate in situ information are warranted in this population to ascertain whether fibromyalgia patients change their sedentary behaviors.

Comparison With Prior Work

To date, most of the previous research on ST and health in fibromyalgia has been limited to the study of total ST[7,28]. In addition, few studies have objectively characterized ST through accelerometry in these patients[5,29] and only one of them[5] reported the values of sustained ST (>1 hour). Ellingson et al demonstrated that sustained ST (>60 min) was associated with worse pain modulation in fibromyalgia—assessed through magnetic resonance imaging—to a greater extent compared to total ST[5]. Congruently, this study showed negative associations between time spent in sedentary bouts (≥10, ≥20, ≥30, and ≥60 min) and the SF-36 body pain dimension. Therefore, we extend the connection between sustained ST and pain to patient-reported instruments. Also, the interruptions of these sedentary bouts might be relevant for pain in this population, given that frequency of sedentary bouts (≥60 min) was negatively associated with bodily pain scores. Following the findings by Ellingson et al, increased pain in sustained ST could be due to the impaired activity in the prefrontal cortices and sensory regions (ie, pre- and postcentral gyri) of these patients[5]. Because the bodily pain domain of the SF-36 not only encompasses objective levels of pain but also the perceived limitations due to it, the contribution of other factors influencing patients' perceptions, such as self-efficacy or pain coping strategies[30], could also take part in this relationship.

Although the influence of patterns of ST has not been explored in fibromyalgia, a direct relationship between increased total ST and fatigue has been described[28]. In agreement with our findings, one previous study in healthy women showed that prolonged ST accumulated in bouts of at least 1 hour were negatively associated with vitality scores of the SF-36 and other fatigue-related variables[31]. Despite the cross-sectional design of these findings that precludes the causal explanation, other experimental studies observed increases in fatigue levels during uninterrupted sitting in adults with overweight and obese status[32] and type 2 diabetes[33], or decreases in fatigue as a result of reducing prolonged sitting[32]. The relationship between ST and fatigue might be explained through physiological, psychological, and social factors that contribute to this multifaceted phenomenon. For instance, prolonged ST could alter the sympathetic nervous system (ie, through a lower heart rate, decreased plasma level of dihydroxyphenylalanine, and increased plasma level of dihydroxyphenylglycol)[32], promote muscle fatigue through sustained activation of low-threshold motor units in sedentary positions[34], or negatively influence sleep quality[7].

In fibromyalgia, there is also a gap in the literature regarding the influence of ST and its patterns on social limitations due to health. For other social-related aspects, Soursa et al stated that patients with fibromyalgia with the lowest PA levels and, presumably, higher levels of ST, had fewer social interactions compared to those doing more PA[35]. No evidence is available on how patterns of ST could influence social function in other populations either, yet interpersonal factors (eg, family, friends, and social networks) are well-known determinants of sedentary behaviors[36]. The passive nature of different sedentary activities (eg, watching television or sitting at the computer) that are accompanied with decreased communication[37] could also lead to poor social networking and participation[38]. Therefore, future research might ascertain whether breaking prolonged ST could positively influence this construct of health (eg, through an increased opportunity to interact with others) or whether strategies aimed at increasing social support may lead to more favorable patterns of accumulation of ST.

To our knowledge, no previous studies have linked patterns of ST to physical function in fibromyalgia. The physical function domain assesses activities of daily living (eg, bathing, dressing, walking several blocks, and lifting or carrying groceries) that typically require a combination of flexibility, strength, and cardiorespiratory fitness, which are related to HRQoL[39]. Previous evidence in adults or older adults showed a decreased physical function, assessed through physical fitness tests, in relation to more deleterious patterns of device-measured ST, such as reduced breaks in ST[40,41], increased sedentary bout duration[40], or increased total prolonged ST[41]. Sedentary periods are linked to skeletal muscle inactivity[42] and are thought to accelerate sarcopenia and loss of aerobic capacity[43], which could negatively affect physical function. Therefore, increases in physical function could be optimized by avoiding the accumulation of ST in prolonged periods and reducing the duration of these ST periods, which needs to be confirmed in future intervention studies.

We observed that, overall, the strength of the associations between the patterns of ST and HRQoL was reduced but still significant when considering MVPA. This finding is congruent with a recent meta-analysis concluding that the deleterious health effects associated with ST generally decrease in magnitude among people with higher levels of PA[13]. Our results also showed that, for certain patterns of ST in shorter bout lengths (<60 min), the associations with HRQoL were not significant anymore when considering MVPA. Therefore, performing MVPA could have a protective effect only when ST is accrued in low-duration bouts and could be especially relevant for certain domains of HRQoL, such as bodily pain, physical role, vitality, or social function. Interestingly, meeting the current guidelines of MVPA in bouts of at least 10 minutes was found to neutralize the negative association of prolonged ST with fatigue in healthy women[31]. Hence, it is possible that the patterns of accumulation of MVPA could also influence the capacity of this behavior of counteracting the negative effects of prolonged ST.

CONCLUSION

In conclusion, our findings indicate that higher ST spent in diverse bout lengths and a higher frequency of sedentary bouts, especially in longer bout durations, is associated with worsened HRQoL, more specifically with physical function, bodily pain, vitality, and social function domains as well as the PCS. Patients that are highly sedentary and present longer sedentary bout durations have worsened physical function, social function, and PCS scores. Although these associations were generally independent of MVPA in long sedentary bout lengths, this intensity of PA could play a positive role when ST is accumulated in shorter bouts. Future intervention studies using mHealth devices that incorporate immediate feedback for users are warranted in this population to ascertain whether fibromyalgia patients change their sedentary behaviors.

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SECTION 1

Study 3

Sedentary time accumulated in bouts is positively associated with disease impact in fibromyalgia: the al-Ándalus project

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ABSTRACT

Objective: To examine the associations of prolonged sedentary time (ST) with disease impact in women with fibromyalgia, the combined association of total ST and prolonged ST with the disease impact in this population, and whether these associations are independent of moderate-to-vigorous physical activity (MVPA) and fitness.

Methods: Women (n=451; 51.3 ± 7.6 years old) with fibromyalgia participated. Sedentary time and MVPA were measured using triaxial accelerometry and ST was processed into 30- and 60-min bouts. Dimensions of fibromyalgia (function, overall, symptoms) and the overall disease impact were assessed with the Revised Fibromyalgia Impact Questionnaire (FIQR). Body fat percentage was assessed using a bio-impedance analyzer, and physical fitness was assessed with the Senior Fitness Tests Battery.

Results: Greater percentage of ST in 30-min bouts and 60-min bouts were associated with worse function, overall, symptoms and the overall impact of the disease (all, $P<0.05$). Overall, these associations were statistically significant when additionally controlling for MVPA and overall physical fitness. Participants with low levels of total ST and prolonged ST (>60-min bouts) presented lower overall impact compared to participants with high levels of total ST and prolonged ST (mean difference = 6.56; 95% confidence interval (CI) = 1.83 to 11.29, P = 0.002).

Conclusions: Greater percentage of ST accumulated in 30- and 60-min bouts and a combination of high levels of total and prolonged ST are related to worse disease impact. Although unable to conclude on causality, results suggest it might be advisable to motivate women with fibromyalgia to break prolonged ST and reduce their total daily ST.

INTRODUCTION

Sedentary behaviour is defined as activities during waking hours in a sitting or reclining posture with energy expenditure ≤ 1.5 metabolic equivalents (METs)[1]. Sedentary behaviour is increasingly recognised as raising the risk of cardiovascular disease events, diabetes and mortality[2] and might be associated with disease risk regardless of moderate-to-vigorous physical activity (MVPA)[3,4]. In fact, current physical activity (PA) recommendations promote the reduction of total sedentary time (ST)[5]. Furthermore, recent findings have shown that not only the total amount of ST, but also the pattern of accumulation, might influence health status[6]. Accordingly, sustained unbroken periods of ST (i.e., bouts) present an inverse association with diverse health[7–9]. This evidence confirms the need for greater awareness of the risks associated with sedentary behaviour[4].

ST has been directly associated with higher risk incident of fibromyalgia[10], a complex multi-symptomatic and heterogeneous disease[11–14]. Furthermore, recent studies have shown that greater total ST is associated with worse symptoms and cardiovascular profile, and lower health-related quality of life in women with fibromyalgia[15–20]. However, little is known about the association of prolonged ST with symptoms in fibromyalgia. To our knowledge, the study of Ellingson et al.[21] is the only one having observed a worsening in the regulation of pain by the central nervous system in patients with fibromyalgia who presented with high patterns of prolonged ST compared to those who spent less time in prolonged ST. These results suggest that ST in fibromyalgia may have pathophysiological consequences, but was limited by a small sample, which precluded more in-depth analysis of the relationships between prolonged ST and the multiple symptoms that characterise the disease.

Exercise-based therapy has been strongly recommended in fibromyalgia, given its effect on several symptoms and its relatively low cost[22,23]. However, targeting reductions in sedentary behaviour may represent another strategy to improve symptoms in this population, which present very high levels of ST, and tend to be physically inactive[24]. Knowledge about the potentially deleterious impact of sustained ST on disease impact in fibromyalgia might lead to the development of future recommendations for this population. Therefore, we aimed to examine: (i) the association of accelerometer-measured bouts of ST (in bouts ≥ 30 min and ≥ 60 min) with overall disease impact in fibromyalgia women; and (ii) the combined association of total ST and bouted ST.

METHODS

Participants

The sample size needed to obtain a representative sample of women with fibromyalgia from the Andalusian population was calculated in southern Spain previously (n = 300)[25]. Women were recruited via fibromyalgia associations, internet advertisement, flyers and e-mail. Participants were required to be previously diagnosed by a rheumatologist and meet the 1990 American College of Rheumatology (ACR) fibromyalgia criteria[26] or the modified 2011 ACR criteria[11], have neither acute or terminal illness nor severe cognitive impairment (Mini Mental State Examination (MMSE) score < 10) and be ≤65 years old. The Ethics Committee of the Hospital Virgen de las Nieves (Granada, Spain) approved the study (Registration number: 15/11/2013-N72).

Procedures

Participants attended to three appointments: (i) the MMSE was administered via interview, tender points were assessed according to the 1990 ACR criteria, and anthropometry and body composition were measured; (ii) two days later, participants received the accelerometer and sleep diary, and several questionnaires to be completed at home. Furthermore, physical fitness was assessed; (iii) nine days later, participants returned the accelerometer and the sleep diary to the research team.

Measurements

Sociodemographic and Clinical Data

Data was collected using a self-reported questionnaire including age, marital status (married/ not married), education level (university/non-university) and occupational status (working/housekeeper/not working). Patients also reported the consumption of antidepressants and analgesics (yes/no) during the previous two weeks.

Cognitive Impairment

The Spanish version of the Mini Mental State Examination[27] was used to assess 5 areas of cognitive functioning, and was used for exclusion criteria purpose only.

Anthropometry and Body Composition

Weight (kg) and total body fat percentage were measured using a portable eight-polar tactile-electrode impedance analyser (InBody R20, Seoul, Korea). We asked participants not to shower, not to practice intense PA and not to ingest large amounts of fluid and/or food in the two hours before the measurement. Patients were required to remove all clothing (except underwear) and metal objects during the assessment. The validity and reliability of this instrument has been reported elsewhere[28,29].

1990 ACR Fibromyalgia Diagnostic Criteria

A trained researcher used a standard pressure algometer (FPK 20; Wagner Instruments, Greenwich, CT, USA) to assess tender points[26]. The mean pressure of two measurements at each tender point was used. One tender point was considered as positive if the patient reported pain at pressure ≤ 4 kg/cm2, and the total count of positive tender points was recorded for each participant. The sum of the minimum pain-pressure values obtained from each tender point (pressure pain threshold) was also calculated.

Modified 2011 ACR Fibromyalgia Preliminary Diagnostic Criteria

These criteria are based on a self-reported questionnaire[11,13]. The Widespread Pain Index asks participants to grade whether they had experienced pain or tenderness in the previous week on 19 body areas. The Symptom Impact scale is obtained through questions asking participants to indicate the impact of fatigue, trouble thinking or remembering, and waking up tired (unrefreshed) over the previous week, and whether they had pain or cramps in the lower abdomen, depression or headache during the previous six months. Patients are diagnosed if they present Widespread Pain Index ≥ 7 and Symptom Impact ≥ 5, or Widespread Pain Index 3–6 and Symptom Impact scale score ≥ 9. The Spanish version of the modified 2011 ACR fibromyalgia preliminary diagnostic criteria has shown high sensitivity and specificity as a diagnostic tool for fibromyalgia[13].

The Impact of Fibromyalgia

The Revised Fibromyalgia Impact Questionnaire (FIQR) is a valid self-administered questionnaire, comprising 21 individual questions with a rating scale of 0 to 10[30]. These questions compose 3 different domains: function (representing the difficulty to perform daily activities), overall impact (reflecting the overall impact of fibromyalgia on functional ability and the overall impact of fibromyalgia on the perception of reduced function) and symptoms score (including pain, stiffness, lack of restorative sleep, poor energy, anxiety, depression, tenderness, memory, balance and environmental sensitivity), (ranging 0–30, 0–20, and 0–50, respectively). The disease impact (FIQR total score) ranges from 0 to 100, with a higher score indicating greater effect of the condition on the person's life. The Spanish validated version of the tool was used[31].

Sedentary Time and Moderate-to-Vigorous Physical Activity

Activity counts were measured at a rate of 30 Hz, and stored at an epoch length of 60 seconds[32,33] using the Actigraph triaxial GT3X+ accelerometer (Actigraph, Pensacola, FL, USA). Participants wore the device on the hip near to the centre of gravity, underneath clothing and secured with an elastic belt. Accelerometer wear-time was calculated by subtracting sleep time (through a diary where patients reported the time they went to bed and the time they woke up) from each day. Bouts of 90 continuous min (30 min small window length and 2 min skip tolerance) of 0 counts were considered as non-wear periods and excluded from the analysis[34].

Participants wore the accelerometer up to nine days, and the days that they received and returned the devices (non-complete days) were excluded from the analyses. A total of seven continuous days with a minimum of 10 hours/day with valid data were required to be included in the study analyses (accelerometer criteria).

Total ST and MVPA (activities producing large increases in breathing or heart rate, such as jogging, aerobic dance, etc.) (min/day) were calculated based upon recommended vector magnitude cut point[32,33]: 0–199 and ≥2690 cpm, respectively. The time accumulated in bouts (that is sustained unbroken periods) of ≥30 or ≥60 continuous min of ST was obtained as measures of prolonged ST. These cut-points were selected based on previous literature[3,35]. Additionally, the percentage of total ST accumulated in 30-min bouts (total time accumulated in bouts ≥ 30 / total ST) and percentage of total ST accumulated in 60-min bouts (total time accumulated in bouts ≥ 60 / total ST) were calculated. Given that we have previously shown that bouted MVPA presented greater association with disease impact than non-bouted MVPA, in the current study[36], bouted MVPA was defined as MVPA accumulated in periods ≥ 10 continuous (up to 2 min below the cut point allowance), and was used as a measure of MVPA for the present study.

We used the manufacturer software (ActilifeTM v.6.11.7 desktop) for data download, reduction, cleaning and analyses.

Physical Fitness

We used the chair sit and reach (lower-body flexibility), the back scratch (upper-body flexibility), the 30-sec chair stand (lower-body strength), the arm curl (upper-body strength), the 8-foot up-and-go (motor agility) and the 6-min walk (cardiorespiratory fitness) tests to measure physical fitness components[37,38].

Previous literature has shown that diverse physical fitness components are associated with fibromyalgia impact[39–41]. Hence, we used a composite of these physical fitness tests as a measure of overall physical fitness. To create this variable, we calculated a normalised index (z-score) of each physical fitness test. The z-score is calculated as (value – mean) / standard deviation. The motor agility z-score was inverted, given that greater values represent lower performance. Finally, we calculated the weighted average of all these z-scores together, using this formula: overall physical fitness = ((z-lower-body flexibility + z-upper-body flexibility)/2) × 0.25) + ((z-lower-body strength + z-upper-body strength) /2) × 0.25) + (z-motor agility × (-1) × 0.25) + (z-cardiorespiratory fitness × 0.25)).

Statistical Analysis

Descriptive continuous data are shown as mean ± standard deviation, whereas categorical data are presented as n (%).

To test the association between bouts of ST and FIQR dimensions (function, overall, symptoms) and the impact of fibromyalgia, we used multivariate linear regression analysis. FIQR dimensions (function, overall, symptoms) and the impact of fibromyalgia were introduced individually as dependent variables in all models. Percentage of ST in ≥30-min bout and percentage of ST in ≥60-min bout were introduced individually as independent variables in separate models. Given that socio-demographic characteristics and fatness did not substantially modify the model parameters; they were not included as covariates. The following models were tested: Model 1 controlled for age and accelerometer-wear time. Model 2 controlled for Model 1 + bouted MVPA. Model 3 controlled for Model 2 + overall physical fitness. The presence of multicollinearity was tested.

Mean differences in disease impact between groups of participants presenting sedentary bouts ≥60 min and those who did not, were tested using one-way analysis of covariance (ANCOVA). Age, accelerometer wear time, bouted MVPA, and overall physical fitness were included as covariates. Post-hoc analysis with Bonferroni's correction assessed the differences across groups.

The interaction effect between total ST and prolonged ST (total ST × prolonged ST) with the study outcome were also tested in separate regression models. The combined association of total ST and prolonged ST (>60-min bouts) was studied through ANCOVA. We compared the differences in the impact of the disease between the 4 groups created according to the median value of total ST (453 min/day) and the median value of bouts ≥60 min (36 min/day). The four groups created were 1: low total ST (≤ the median value) + low prolonged ST (≤median value); 2: low total ST + high prolonged ST; 3: high total ST + low prolonged ST; and 4: high total ST (> the median value) + high prolonged ST (>the median value). The analyses were controlled for age, accelerometer wear time, bouted MVPA and overall physical fitness. The Cohen's d was used to calculate the standardised effect size and was interpreted as small (~0.2), medium (~0.5) or large (~0.8 or greater).

We used the Statistical Package for the Social Sciences (International Business Machines (IBM) SPSS Statistics for Windows, Version 22.0. Armonk, NY, USA: IBM Corp). The statistical significance was set at $P<0.05$.

RESULTS

Written informed consent was collected from all participants (n = 617). A total of 568 participants agreed to wear an accelerometer. Thirty-six women were not previously diagnosed with fibromyalgia, 16 did not meet the 1990 ACR criteria or the modified 2011 ACR criteria, one had severe cognitive impairment and 13 were older than 65 years old. After the assessment, 32 participants had incomplete data, accelerometer data from three patients were lost due to malfunction when downloading data, and 16 patients did not meet the accelerometer criteria. The final sample included in the analyses comprised 451 women with fibromyalgia. Clinical and socio-demographic characteristics of these patients are in table 1. Furthermore, descriptive data regarding patterns of ST and MVPA are presented in table 2.

Table 1. Clinical and socio-demographic characteristics of fibromyalgia women, n = 451.

Clinical Variable	Mean	SD
Age (year)	51.3	7.6
Body mass index (kg/m^2)	28.5	5.4
Fat percentage (%)	40	7.6
Tender points (11–18)	15.1	4.6
Pressure pain threshold (18–144 kg/cm^2)	50	21.9
Widespread Pain Index (0–19)	13.7	3.8
Symptom Impact Score (0–9)	8	2.2
Polysymptomatic Distress (0–28)	21.7	5
FIQR Function (0–30)	17	6.5
FIQR Overall (0–20)	12.2	5.3
FIQR Symptoms (0–50)	34.7	7.7
FIQR Total Score (0–100)	63.9	16.8
Clinical and sociodemographic variable	*n*	%
Marital Status		
Married	340	75.4
Not Married	111	24.6
Educational Level		
Non-university	390	86.5
University	61	13.5
Current Occupational Status		
Working	126	27.9
Housekeeper	144	31.9
Not Working	181	40.1

FIQR, Revised Fibromyalgia Impact Questionnaire; SD, standard deviation

Table 2. Patterns of sedentary time and moderate-to-vigorous physical activity (MVPA) of women with fibromyalgia, n = 451.

Variable	Mean	SD
Accelerometer wear time (min/day)	923.3	75.1
Sedentary time (min/day)	458.3	104.2
Percentage of sedentary time	49.7	10.9
Time in ≥30-min sedentary bout (min/day)	129.4	81.2
Percentage of time in ≥30-min sedentary bout	14	8.7
Time in ≥60-min sedentary bout (min/day)	50.7	49.8
Percentage of time in ≥60-min sedentary bout	5.5	5.4
Percentage of MVPA	4.9	3.3
Percentage of bouted MVPA	0.6	0.7

SD, standard deviation.

The associations of patterns of ST with FIQR function, overall, symptoms and the overall impact of fibromyalgia are shown in Table 3. Greater percentage of ST in 30-min bouts were associated with worse function (B = 9.08, 95% confidence interval [CI] = 4.18, 13.98) overall (B = 9.12, 95% CI = 5.12, 13.11), symptoms (B = 13.26, 95% CI = 7.49, 19.03) and the overall impact of the disease (B = 31.46, 95% CI = 19.20, 43.90) (all, $P < 0.05$). The results were unchanged after additionally controlling for MVPA and overall physical fitness (all, $P < 0.05$). Greater percentage of ST in 60-min bouted ST were associated with greater function (B = 11.13, 95% CI = 4.36, 17.89), overall (B = 11.18, 95% CI = 5.64, 16.71), symptoms (B = 18.29, 95% CI = 10.34, 26.23) and the overall impact of the disease (B = 40.59, 95% CI = 23.39, 57.78) (all, $P < 0.05$). The results were unchanged after additionally controlling for MVPA and overall physical fitness (all, $P < 0.05$), except for the non-significant association with function ($P = 0.072$). There was no evidence of multi-collinearity in any of the models mentioned above. No interaction effect between total ST and prolonged ST (total ST × prolonged ST) with the study outcome was observed.

Table 3. Association of percentage of bouted sedentary time with disease impact, n = 451

Variables		FIQR Function				FIQR Overall				FIQR Symptoms				FIQR Total			
		β	B	(95% CI)	Adj. R^2	β	B	(95% CI)	Adj. R^2	β	B	(95% CI)	Adj. R^2	β	B	(95% CI)	Adj. R^2
Percentage of ST in ≥30-min bout	Model 1	**0.17**	**9.08**	**(4.18; 13.98)**	**0.04**	**0.21**	**9.12**	**(5.12; 13.11)**	**0.05**	**0.21**	**13.26**	**(7.49; 19.03)**	**0.06**	**0.23**	**31.46**	**(19.02; 43.90)**	**0.07**
	Model 2	**0.15**	**8.02**	**(3.12; 12.93)**	**0.06**	**0.19**	**8.38**	**(4.37; 12.40)**	**0.06**	**0.19**	**12.24**	**(6.44; 18.04)**	**0.07**	**0.21**	**28.64**	**(16.20; 41.09)**	**0.09**
	Model 3	**0.1**	**5.08**	**(0.29; 9.86)**	**0.14**	**0.13**	**5.75**	**(1.79; 9.71)**	**0.11**	**0.14**	**8.59**	**(2.96; 14.22)**	**0.16**	**0.14**	**19.94**	**(8.01; 31.88)**	**0.19**
Percentage of ST in ≥60-min bout	Model 1	**0.15**	**11.13**	**(4.36; 17.89)**	**0.04**	**0.18**	**11.18**	**(5.64; 16.71)**	**0.04**	**0.21**	**18.29**	**(10.34; 26.23)**	**0.06**	**0.21**	**40.59**	**(23.39; 57.78)**	**0.07**
	Model 2	**0.13**	**9.88**	**(3.14; 16.63)**	**0.06**	**0.17**	**10.3**	**(4.77; 15.83)**	**0.06**	**0.19**	**17.1**	**(9.14; 25.05)**	**0.08**	**0.19**	**37.28**	**(20.16; 54.40)**	**0.09**
	Model 3	0.08	6.03	(-0.53; 12.60)	**0.14**	**0.12**	**7.52**	**(2.08; 12.96)**	**0.12**	**0.14**	**12.37**	**(4.66; 20.07)**	**0.16**	**0.15**	**46.01**	**(19.46; 72.57)**	**0.2**

β, standardised coefficient; B, unstandardised coefficient; FIQR, Revised Fibromyalgia Impact Questionnaire; Adj. R2, adjusted coefficient of determination; SE, standard error. Model 1: controlled for age and accelerometer wear time; Model 2: controlled for model 1 bouted moderate-to-vigorous physical activity; Model 3: controlled for model 2 and overall physical fitness. Statistically significant associations (P < 0.05) are highlighted in bold.

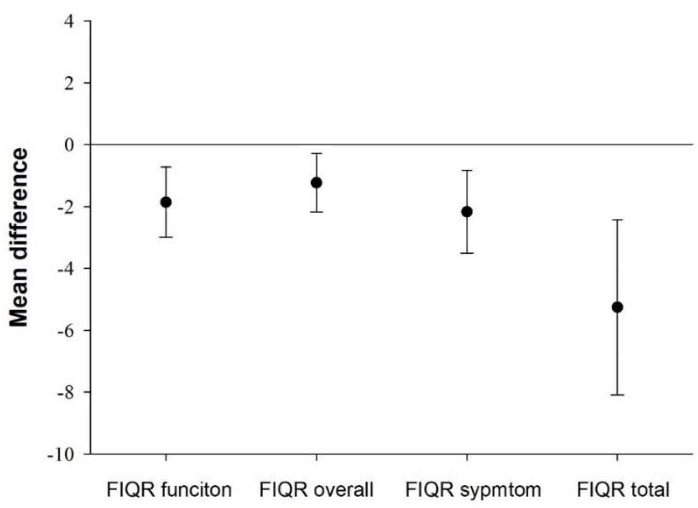

Figure 1. Mean differences with 95% confidence intervals in disease impact between participants not presenting (n = 233) and those presenting sedentary bouts ≥60 min (n = 218). All $P \leq 0.007$. Analysis controlled for age, bouted moderate-to-vigorous physical activity, overall physical fitness and accelerometer wear time. FIQR, Revised Fibromyalgia Impact Questionnaire.

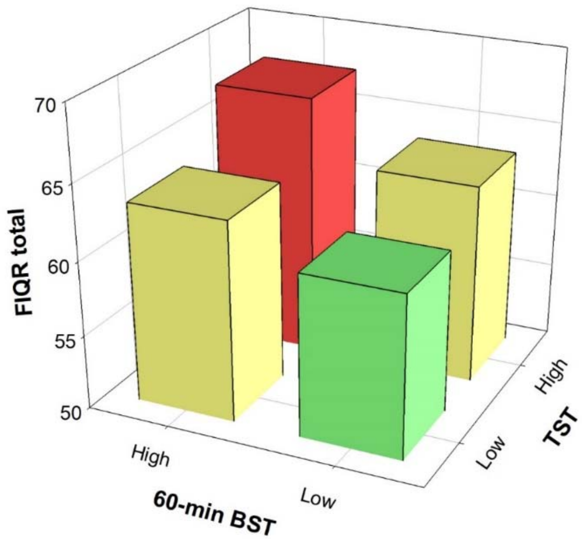

Figure 2. Combined effect of total sedentary time (TST) and 60-min bouted sedentary time (BST) on overall impact of the disease. Bonferroni's post-hoc differences between the Low TST + Low BST and High TST + High BST groups (P = 0.002). Analysis controlled for age, bouted moderate-to-vigorous physical activity, overall physical fitness and accelerometer wear time. FIQR, Revised Fibromyalgia Impact Questionnaire.

Mean differences in disease impact between participants presenting sedentary bouts ≥60 min and those who did not are presented in Figure 1. Participants who did not engage in 60-min sedentary bout presented lower (better) values in function (mean difference = −1,93, 95% CI = −3.05, −0.80, Cohen's d = 0.32), overall (mean difference = −1,30, 95% CI = −2.25, -0.36, Cohen's d = 0.23), symptom (mean difference = −2,27, 95% CI = −3.60, −0.93, Cohen's d = 0.32) and the overall disease (mean difference = −5.50, 95% CI = −8.32, −2.67, Cohen's d = 0.36) (all, P ≤ 0.07) than participants who engaged in 60-min sedentary bouts.

Figure 2 shows the combined effect of total ST and 60-min bouted ST on disease impact. Participants with low total ST and low prolonged ST (60-min bout) presented lower disease impact compared to participants with high total ST and high sedentary bout duration (mean difference = 6.56; 95% CI = 1.83 to 11.29, P = 0.002, Cohen's d = 0.42).

DISCUSSION

These data indicate that greater ST accumulated in bouts ≥30 min and ≥60 min are associated with greater disease impact in women with fibromyalgia. These associations were generally independent of age, MVPA and overall physical fitness. Furthermore, those patients who presented sedentary bouts ≥60 min had worse disease impact than those who did not, which suggests that accumulating ST in longer bouts is associated with worse disease impact. Additionally, women with fibromyalgia characterised by low levels of total ST and prolonged ST presented lower disease impact compared to participants with high total ST and high prolonged ST.

Previous population-based studies have reported that ~31% and ~48% of total ST were accrued in bouts >30 minutes among middle-aged and older women[42] and middle-aged and older adults[43], respectively. Given that women with fibromyalgia are usually highly sedentary[24], we expected women from our study to present similar values to those from previous studies in the elderly population. In fact, participants in the present research accumulated ~27% of total ST in bouts ≥30 minutes. Other previous study in adults confirmed that approximately 40% of total ST was accrued in bouts >30 minutes, with 70% of participants accruing at least 1 sedentary bout per day >60[3]. In the current study, 94% of participants accumulated at least one sedentary bout per day ≥30, whereas only 22% accumulated at least one sedentary bout per day ≥60. Making comparisons between studies is troublesome because of considerable discrepancies related to the use of different accelerometer brands and models, distinct cut-off points for ST, particular definitions of sedentary bout (e.g., with or without allowance of 1-min above the cut point allowance), and disparate populations, among many other reasons. Nonetheless, the high levels of bouted ST observed in women from our study support that regularly breaking up ST might be as important as promoting PA in this population.

Evidence suggests that frequently interrupting prolonged bouts of ST is a way to improve cardio-metabolic outcomes[44,45], obesity[46] or glucose levels[3] in diverse populations. In older adults, uninterrupted ST lasting ≥30 min was associated with increased frailty independent of total ST and bouted MVPA[47]. In cancer survivors, longer sedentary bout duration was significantly associated with lower global quality of life and higher disability and fatigue[48], even after adjustment for PA. In adults, beneficial associations with indicators of obesity were observed by theoretically replacing ST with standing or higher intensity PA[46]. The study of the potential deleterious effect of prolonged ST in fibromyalgia is scarce. As far as the authors know, there is only one study[21] that observed a dysregulation of pain modulation in fibromyalgia patients who presented high prolonged ST compared to those who spent less time in sedentary behaviour[21]. The authors defined prolonged ST as being sedentary (≤100 cpm sustained) for at least 60 consecutive minutes. This is in concordance with the results of the current study, which showed an association between accelerometer-measured ST bouts and the overall impact of the disease. Together, these results suggest that prolonged ST in fibromyalgia may negatively impact pathophysiological features of disease.

Current guidelines on physical activity for the general population recommend all populations minimise the amount of time spent in sedentary behaviour for extended periods[5]. These guidelines; however, do not offer specific recommendations about how often to take sedentary breaks. Therefore, there is no agreed upon definition of prolonged ST; however, the 30-min cut-off was chosen based on previous studies, which are shown to be associated with the development of metabolic syndrome and mortality[3,47]. Furthermore, we also included a 60-min cut-off to check whether longer sustained periods of ST are potentially more deleterious than shorter sustained periods (30-min cut-off). In this context, a previous research in older adults assessed sedentary bouts of 10-20 min, 20-30 min and 30-60 min and found that they were associated with abdominal obesity[49]. Interestingly, the longer the bout, the greater the odds for abdominal obesity[49]. Furthermore, those who performed long periods of continuous ST were more likely to be abdominally obese, independently of total ST itself, MVPA and movement counts within the continuous sedentary bouts[49]. Similarly, another study in adults showed that reallocating time in long sedentary bouts to short sedentary bouts was associated with lower obesity[46]. These results concur with those presented in the current study regarding disease impact. In fact, participants who did not engage in 60-min bouted ST presented lower disease impact than those who did. Furthermore, the results of the association of long sedentary bout (i.e., 60 min) with impact of fibromyalgia were stronger than those of short sedentary bout (i.e., 30 min). A difference of ~10% (or 6.6 points) in disease impact between the low total and bouted ST, and high total and bouted ST groups was observed. Given that 14% (or 8.1 units) change in this tool has been considered clinically relevant[50], we cannot consider these results as clinically relevant. However, we must bear in mind that these analyses were rigorously controlled for age, MVPA and overall physical fitness. Furthermore, a recent intervention study showed that the mean change from baseline to 12, 24 and 52 weeks in FIQR for aerobic exercise in this population was 6.2, 9.2 and 11.7 units[51]. This suggests that just reducing ST might be as effective as a 12-week aerobic exercise intervention. Taking into consideration that some patients with fibromyalgia have difficulties performing and adhering to exercise programs, a potential 10% change based on a single variable (ST) that could be easily targeted and account for a relevant part of the day of these patients, could be still be of interest. In addition, comparison groups were created according to the median value of ST of highly sedentary individuals[24] and might be insufficient to detect relevant differences. Future studies might elucidate whether moving to even lower levels of ST could lead to clinically relevant changes in disease impact.

The evidence shows that regular practice of aerobic or strengthening exercise is advisable in fibromyalgia[22]. Overall, the findings in this study may assist in developing novel lifestyle approaches that consider not only exercising, but also the role of sedentary behavior to potentially reduce the impact of fibromyalgia disease. Although not tested yet in patients with fibromyalgia, prior interventions targeting the reduction in ST have shown to be successful in adult population[52]. Feasible strategies to reduced prolonged sitting might be focused on environmental restructuring and self-regulatory techniques such as self-monitoring[53], problem solving, or providing information on health consequences[54]. In addition, interventions focused on increasing low-energy expenditure activities (such as standing)[55] or including calisthenics as a break during prolonged sitting[56] might lead to more favourable patterns of ST. Indeed, activities of light intensity might be more feasible in these patients who often encounter difficulties in performing recommended amounts of MVPA[21,24]. Disease-specific health recommendations should focus on messaging the benefits of a more physically active lifestyle[17,36] in conjunction with reducing periods of prolonged ST. Therefore, the "Stand Up, Sit Less, Move More, More Often" message in conjunction to the promotion of eventual levels of recommended PA[5] and exercise participation[22] would be advisable in these patients.

Limitations and Strengths

The cross-sectional design of the current study does not allow establishing causal relationships. Therefore, to enable the development of tailored interventions in this population, prospective data are needed to elucidate the temporal direction of associations of different sedentary patterns with disease impact. The GT3X+ accelerometer cannot recognize between different postures such as sitting and standing, thus ST might be overestimated as some standing with imperceptible movement may also be included. Otherwise, ST should not be studied in isolation but rather in addition to the effects of PA[57]. This is important for the overall field, as fibromyalgia women have both limited daily PA and high volumes of ST[24]. In this sense, a strength of the current study was the robust control of the analysis since age, MVPA and overall physical fitness were included as covariates in the analyses, showing that the findings of the current study are independent of these variables. The use of accelerometer measures of PA, which allowed us to objectively quantify ST and MVPA was another strength. Furthermore, the accelerometer criteria were stricter than other previous studies[58,59]. Finally, we assessed a relatively large sample size of fibromyalgia women representative from southern Spain (Andalusia)[25].

CONCLUSIONS

Accumulated ST in prolonged bouts is associated with greater overall impact of the disease in women with fibromyalgia, independently of MVPA and overall physical fitness. Results suggest that accumulating ST in longer bouts is associated with worse disease impact. Additionally, a combined association of total ST and prolonged ST with disease impact was found. The findings of the present study highlight the potential importance of the total volume of ST and its accumulation in prolonged, uninterrupted bouts as important disease impact risk behaviors in fibromyalgia. Interventions targeting reductions in overall and prolonged ST are warranted. If intervention and longitudinal studies confirm these cross-sectional findings, future health recommendations in this population should focus on messaging the benefits of reducing periods of prolonged ST.

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SECTION 1

Study 4

Substituting sedentary time with physical activity in fibromyalgia: association with health-related quality of life and impact of the disease. The al-Ándalus project

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ABSTRACT

Objective. The aim of this study was to examine how a substitution of sedentary time (ST) with light physical activity (LPA) or moderate-to- vigorous PA (MVPA) is associated with health-related quality of life (HRQoL) and disease impact.

Methods. This study comprised 407 women with fibromyalgia, mean ± SD age 51.4 ± 7.6 years. The time spent in ST and PA was measured with triaxial accelerometry. HRQoL and disease impact were assessed using the Short Form 36 (SF-36) health survey and the Revised Fibromyalgia Impact Questionnaire (FIQR), respectively. The substitution of ST with an equivalent time of LPA or MVPA and the associated outcomes were examined using isotemporal substitution analyses.

Results. Substituting 30 minutes of ST with LPA in the isotemporal model was associated with better scores in bodily pain (B = 0.55), vitality (B = 0.74), and social functioning (B = 1.45) according to the SF-36, and better scores at all of the domains (function, overall impact, symptoms, and total impact) of the FIQR (B ranging from −0.95 to −0.27; all $P < 0.05$). When ST was replaced with MVPA, better physical role (B = 2.30) and social functioning (B = 4.11) of the SF-36 and function of the FIQR (B = −0.73) were observed (all $P < 0.05$).

Conclusion. In regression models, allocation of time of sedentary behavior to either LPA or MVPA was associated with better quality of life and lower disease impact in women with fibromyalgia.

INTRODUCTION

Fibromyalgia is a chronic condition with persistent and widespread pain as key symptom[1]. Other symptoms are frequent, including but not limited to fatigue, non-restorative sleep or cognitive difficulties[1]. The disease impact of fibromyalgia includes physical disability, psychological distress, symptoms, and reduced work status[2]. Moreover, patients with fibromyalgia usually have a reduced general quality of life[3], which is the individual perception of health in different spheres of life (physical, mental and social). Because fibromyalgia has no cure, treatments focus on disease management and improvement of quality of life. Thus, it is relevant to identify modifiable factors that might be related to these fibromyalgia-specific (which pertains to the disease impact) and general (which pertains to the quality of life) health outcomes.

Compelling evidence supports the efficacy of physical exercise interventions in the management of fibromyalgia[4]. However, although the benefits of physical exercise interventions in fibromyalgia is endorsed[4], guideline for physical activity (PA) generally do not answer the question whether low-, moderate- or high intensity physical exercise should be recommended. Moreover, patient acceptability, treatment adherence, premature termination, and, most importantly, high dropout rates are serious concerns for exercise-based interventions in fibromyalgia[5]. Moderate or even low-intensity physical exercise programs may be more appropriate to achieve long-term results in this group versus high-intensity programs, because individuals with fibromyalgia are so easily sensitized to pain and other symptoms[6]. Greater insight into the relationship between PA levels and patient-reported outcome measures may indicate the potential usefulness of stimulating low-and moderate-to-vigorous intensity PA levels.

Whereas most effect studies in rheumatic diseases pertain to systematic physical exercise interventions in specific groups, the most frequent intervention is probably education and advice about daily PA given during a consultation or accessed through a brochure or via the internet[7]. A positive relationship between total self-reported PA and quality of life in fibromyalgia has been described[8,9]. Lifestyle interventions[10,11] and observational studies[12–14] have described the positive influence of light PA (LPA) in the physical function domain of quality of life[10,11] and on fibromyalgia symptoms[10,12–14]. Furthermore, an increase of moderate-to-vigorous PA (MVPA) has been shown to promote better physical function and well-being[15], and greater levels of vigorous PA have been associated with less pain, fatigue, and overall impact of the disease[14]. Despite these benefits, a high percentage of patients do not achieve the recommended 150 min of MVPA per week[16,17], and tend to be highly sedentary[16]. While the relationship between PA and symptoms or physical domains of quality of life has been largely addressed on prior research[10–15], evidence is scarce in regard to the potential influence of a reduction of sedentary time (ST), which might be a more attainable goal for some patients. In order to gain insight into the benefits of pursuing this goal, it is necessary to examine how a decrease in ST, through an increase of time in different intensity levels of PA, is specifically related to quality of life and disease impact in fibromyalgia.

ST has shown to exert a deleterious effect on health in the general population[18]. In fibromyalgia ST has been associated with worse pain regulation[12], overall pain, fatigue and disease impact[14]. Although the inverse relationship between ST and quality of life has been described in other conditions[19,20], the precise association between these 2 factors in fibromyalgia is unknown. Therefore, it would be relevant to know the benefits of substituting ST with PA. Given that total daily time is finite (24 hours), decreasing time in one specific behavior requires increasing time in another. The isotemporal substitution model[21] allows to study the effect of time substitution while controlling for the confounding effect of other activities. Therefore, given that ST, light PA, and MVPA have shown to be associated with fibromyalgia symptoms[12–15], it is possible to determine how replacing time spent in one specific behavior (e.g. ST) with an equal amount of time in other behavior (e.g. light PA) might be related to different health outcomes in individuals with fibromyalgia. Prior applications of isotemporal substitution models on replacement of ST with an equal amount of PA of different intensities have demonstrated positive effects on quality of life and health outcomes in adults[22–25] and elderly[19,26,27]. These findings, however, do not necessarily generalize to patients with fibromyalgia. Therefore, the aim of this study was to analyze how substitution of ST with LPA or MVPA was associated with quality of life and disease impact in women with fibromyalgia.

METHODS

Patients from southern Spain (Andalusia) were recruited through fibromyalgia associations via email, letter and social media. After providing detailed information about the aims and study procedures, participants signed an informed consent (n=646). Inclusion criteria for the current study comprised a previous diagnosis by a rheumatologist and meeting the 1990 American College of Rheumatology (ACR) fibromyalgia criteria[28]. Participants were excluded if they had either acute or terminal illness, severe cognitive impairment or were age >65 years (to avoid the influence of other prevalent conditions, such as osteoarthritis). The study was approved by the Ethics Committee of the "*Hospital Virgen de las* Nieves", Granada (Spain).

The assessment protocol was carried out on 2 alternate days. On day one, fibromyalgia diagnosis according to ACR criteria[28] (widespread pain for more than 3 months, and pain with 4 kg/cm^2 of pressure reported for 11 or more of 18 tender points) was confirmed. Body composition was also evaluated and participants filled out self-reported sociodemographic data and clinical data questionnaires. The 36-item *Short-Form Health Survey* (SF-36) and the *Revised Fibromyalgia Impact Questionnaire* (FIQR) (along with other questionnaires) were given to patients to be completed at home. On the second day, questionnaires were collected and checked by the researcher team. Subsequently, participants received instructions on how to complete the sleep diary and the accelerometers were provided.

Quality of life

The quality of life was assessed using the SF-36. This questionnaire has been validated for Spanish populations[29] and has demonstrated a good reliability among chronic pain patients[30]. The SF-36 is composed of 36 items that assess eight dimensions of health (i.e., physical functioning, physical role, bodily pain, general health, social functioning, emotional role, mental health, and vitality) and two component summary scores (i.e., physical and mental health). The score in each dimension is standardized and it ranges from 0 (worst health status) to 100 (best health status).

Impact of the disease

The FIQR[31] represents a disease-specific tool to assess overall fibromyalgia severity through a wide range of symptoms, comorbidities, and complaints related to this chronic condition. It is a self-administered questionnaire with 21 individual questions (rating scale of 0 to 10), divided into three linked sets of domains: function, overall impact, and symptoms severity. The FIQR total score ranges from 0 to 100, with a higher score indicating greater impact of the syndrome on an individual's life.

Physical activity intensity levels and sedentary time

Patients wore a triaxial accelerometer GT3X+ (Actigraph, Pensacola, Florida, USA) around the hip, secured with an elastic belt for nine whole days (24 h) except for water-based activities. Using the default mode filter option, data were collected at a rate of 30 Hz and at an epoch length of 60 seconds[32]. Given that patients received the accelerometer at different times throughout the first day and because time is needed to extinguish reactivity to the awareness of being monitored, we excluded this familiarization day from the analysis. The last day (day of device return) was excluded from the analysis as well. A total of 7 continuous days with a minimum of 10 valid hours/day were required to be included in the analysis. Data download, reduction, cleaning, and analyses were conducted using the manufacturer software (Actilife™ v.6.11.7 desktop).

Accelerometer wear time was calculated by subtracting sleeping time and non-wear periods. Sleeping time was obtained from the sleep diary, where patients indicated the time they went to bed and time they woke up. According to Choi algorithm[33], nonwear periods considered bouts of 90 continuous minutes (30 minutes' small window length and 2 minutes' skip tolerance) of 0 counts. PA intensity levels (light, moderate, and vigorous) were calculated based upon recommended PA vector magnitude cut points [32,34]: 200-2689, 2690-6166 and ≥6167 counts per minute (cpm), respectively. ST was estimated as the time accumulated below 200 cpm during periods of wear time[33]. Participants presented extremely low values of vigorous PA (0.4 min/day); therefore, vigorous PA was excluded from all the analyses and MVPA was used instead. A 10-minute activity bout was defined as 10 or more consecutive min ≥2690 cpm (up to 2 min below the cut point allowance). The proportion of women meeting the current PA recommendations for adults aged 18-64 years (at least 150 minutes/week of MVPA accumulated in bouts ≥10 minutes)[17] was also calculated. All values were initially expressed in min/day but were converted to units of 30 minutes (1 represents 30 minutes) for a better interpretation of the results. To complete this conversion, min/day spent in ST, LPA, MVPA and total wear-time were divided by 30.

Other variables

Tenderness

Following the 1990 ACR criteria for classification of fibromyalgia[28], we assessed eighteen tender points using a standard pressure algometer (FPK 20; Wagner Instruments, Greenwich, CT, USA). We obtained the mean pressure of two measurements at each tender point. A tender point was considered as positive when the patient felt pain at pressure ≤ 4 kg/cm^2. The total number of positive tender points was recorded for each patient.

Sociodemographic and clinical data

We collected socio-demographic and clinical data by using a self-reported questionnaire including date of birth, marital status (married/ not married), education level (university/non-university), and occupational status (working/not working). Furthermore, patients reported the use of antidepressants and analgesics (yes/no) during the previous two weeks. Additionally, to assess an exclusion criterion, participants were asked: 'Are you currently diagnosed with an acute or terminal illness?'.

Anthropometry and body composition

Weight (kg) and total body fat percentage were assessed using a portable eight-polar tactile-electrode bioelectrical impedance device (InBody R20, Biospace, Seoul, Korea). The validity and reliability of this instrument has been reported elsewhere[35,36]. As recommended by the manufacturer, participants were requested not to have a shower, not to practice intense PA, and not to ingest large amounts of fluid and/or food within the 2 hours before the measurement. Patients were also asked not to wear either clothing (except for underwear) or metal objects during the measurement.

Statistical analyses

Descriptive statistics were used to examine the sociodemographic and clinical characteristics of the sample.

Multiple linear regression models were used for isotemporal substitution models in order to examine the associations of substituting ST with LPA and MVPA with quality of life and impact of the disease in women with fibromyalgia. The description and rationale behind these analyses have been described in detail before[21]. Briefly, in this model, the finite nature of time is considered so that performing one activity results in displacing the time spent in another behaviour. These regression models included the total time (sum of ST, LPA and MVPA, which is the total accelerometer wear time variable) and all of the individual activities (e.g., LPA and MVPA) except for the activity of interest (e.g., ST) as independent variables. The coefficient from the regression analysis for each of the included variables is an estimation of the mean effect on the outcome of substituting a fixed amount of time (e.g.: 30 min) of the omitted activity with the same amount of each of the included activities (while holding time spent in other activities constant). For instance, an isotemporal substitution model can be expressed as follows: SF-36 scores = (β_1) LPA + (β_2) MVPA + (β_3) total time + (β_4) covariates

Because ST is omitted from the model, β_1 expresses the change in Quality of Life (SF-36 scores of each dimension) which resulted from reallocating 30 minutes of ST to LPA. The β_2 coefficient would provide the same information in relation to MVPA. Pearson's correlations were used to check for the association of potential confounders (age, marital status, education level, working status, fat percentage, antidepressant use) with quality of life and impact of the disease. As a result of significant associations (p<0.05) with most of the outcomes, the following confounders were entered in all models: age, current occupational status, fat percentage, and use of antidepressants.

Normal probability plots of the standardized residual and scatterplots of residuals were generated to test for normality, linearity, and homoscedasticity. Non-autocorrelation assumption was also met using the Durbin-

Watson-test (1.5<*d*<2.5 for all regression models). No multicollinearity problems among the predictor variables of the model were found (all variance inflation factor statistics <10.0).

All analyses were performed using the Statistical Package for Social Sciences, version 20.0 (SPSS Statistics for Windows, IBM, Armonk, NY, USA), and the level of significance was set at $p<0.05$.

RESULTS

The flow chart of the participants included in this study is shown in **Figure 1**. Thirty-nine participants were not previously diagnosed with fibromyalgia, 100 did not meet the 1990 ACR criteria, 1 had severe cognitive impairment, and 14 did not meet the age criterion. Thirty-four participants did not agree to wear the accelerometer and data from 3 participants were lost due to accelerometer malfunction. Seventeen participants did not meet the accelerometer criterion and 12 did not return completed questionnaires. Due to the small sample size (n=19), men were excluded from the analyses. The final sample size included in the analyses comprised 407 women with fibromyalgia.

Table 1 provides an overview of the patients' sociodemographic and clinical characteristics according to the achievement of the PA recommendations (at least 150/week per week of MVPA in bouts of at least 10 minutes). Overall, women with fibromyalgia meeting the PA recommendations had lower pain, impact of the disease, and fat percentage, consumed less antidepressants, and presented a better quality of life. In the isotemporal substitution models for the SF-36 scores (**Table 2**), replacing 30 minutes of sedentary behaviour with 30 minutes of LPA was associated with better bodily pain (*B*=0.55; 95% Confidence Interval (CI) 0.03 to 1.07), vitality (*B*=0.74; 95% CI, 0.09 to 1.39), and social functioning (*B*=1,45; 95% CI, 0.61 to 2.30), all $p<0.05$. Replacement of 30 minutes of sedentary behaviour with 30 minutes of MVPA was associated with better physical role (*B*=2.30; 95% CI, 0.2 to 4.38) and social functioning (*B*=4.11; 95% CI, 1.78 to 6.44), all $p<0.05$.

When the FIQR was modelled as the outcome variable (**Table 3**), replacing 30 minutes of ST with the same amount of LPA was associated with better functioning (*B*=-0.32; 95% CI, -0.55 to -0.09), overall impact (*B*=-0.27; 95% CI, -0.45 to -0.08), symptoms (*B*=-0.37; 95% CI, -0.63 to -0.11), and total impact of the disease (*B*=-0.95; 95% CI, -1.52 to -0.38), all $p<0.01$. Substituting 30 minutes of ST with 30 minutes of MVPA was only associated with better functioning (*B*=-0.73; 95% CI, -1.37 to -0.09), $p=0.025$.

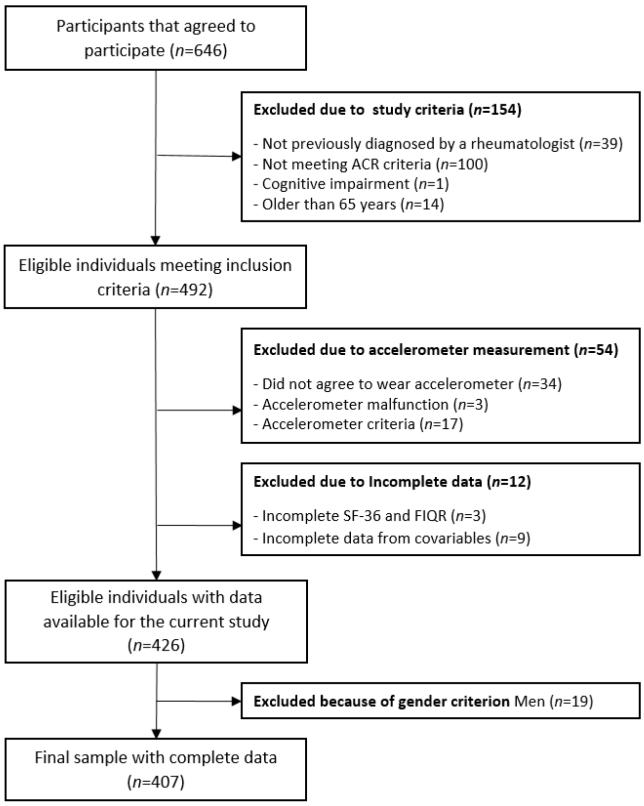

Figure 1. Flow diagram of inclusion of women with fibromyalgia from the al-Ándalus project included in the present study (n=407) ACR: American College of Rheumatology; FIQR: Revised Fibromyalgia Impact Questionnaire SF-36: 36-item Short-Form Health Survey;

Table 1. Clinical and sociodemographic characteristics of women with fibromyalgia by achievement of physical activity recommendations [a] (*n=407)*.

	Total (n=407)		Not meeting PA recommendations (n=321)		Meeting PA recommendations (n=86)	
Variables	*Mean*	*(S.D.)*	*Mean*	*(S.D.)*	*Mean*	*(S.D.)*
Age, years	51.4	(7.6)	51.7	(7.6)	50.3	(7.5)
Married (yes, %)	311	(76.4)	250	(77.9)	61	(70.9)
University (yes, %)	58	(14.3)	46	(14.3)	12	(14.0)
Working (yes, %)	107	(26.3)	78	(24.3)	29	(33.7)
Total tender points (11-18)	16.7	(2.0)	16.8	(1.9)	16.5	(2.2)
Algometer Score (18-144)	43.2	(13.4)	42.8	(13.3)	45.0	(14.0)
Total Body fat (%)	40.1	(7.6)	40.6	(7.7)	38.3	(6.8)
Antidepressants Consumption (yes, %)	232	(57.0)	198	(61.7)	34	(39.5)
Disease impact, FIQR (0-100)						
FIQR Function	17.2	(6.4)	17.9	(6.2)	14.6	(6.7)
FIQR Overall	12.5	(5.4)	12.9	(5.2)	11.1	(6.0)
FIQR Symptoms	34.7	(7.6)	35.5	(7.5)	31.8	(7.5)
FIQR Total score	64.4	(16.7)	66.3	(16.0)	57.5	(17.7)
Health Related Quality of Life, SF-36 (0-100)						
Physical function	39.2	(18.9)	37.9	(18.7)	44.2	(18.8)
Physical role	33.2	(21.2)	31.8	(21.2)	38.7	(20.2)
Bodily pain	21.2	(14.7)	19.8	(14.2)	26.3	(15.5)
General health	28.5	(15.3)	27.9	(14.9)	30.9	(16.6)
Vitality	22.3	(17.7)	21.3	(17.1)	26.2	(19.3)
Social functioning	43.7	(24.7)	41.5	(24.2)	51.7	(24.6)
Emotional role	56.9	(27.9)	55.8	(28.8)	61.1	(24.2)
Mental health	46.2	(19.7)	45.0	(19.6)	50.8	(19.5)
Physical Component	29.5	(6.9)	29.1	(6.9)	31.2	(6.7)
Mental Component	36.0	(11.6)	35.3	(11.7)	38.5	(11.3)
PA and sedentary time (min/day)						
Accelerometer-wear time	923.0	(78.9)	921.2	(83.0)	930.0	(61.3)
Sedentary Time	460.1	(104.1)	473.3	(104.7)	410.8	(86.1)
Light PA	418.6	(91.8)	414.2	(96.9)	435.2	(67.2)
Moderate PA	43.9	(29.5)	33.5	(19.9)	82.6	(27.6)
MVPA	44.3	(30.1)	33.7	(20.0)	84.0	(28.1)

[a] Physical activity recommendation: accumulating at least 150 minutes of MVPA in bouts of at least 10 minutes.

FIQR: Revised Fibromyalgia Impact Questionnaire; MVPA: Moderate-to-vigorous physical activity; PA: physical activity; SD: standard deviation; SF-36: 36-item Short-Form Health Survey.

Table 2. Coefficients for the isotemporal subsituttion analyses examining the association of reallocating 30 minutes of sedentary time to light physical activity (LPA) or moderate-to-vigorous physical activity (MVPA) with quality of life *(n*=407)

SF-36 Dimension	Sedentary time			LPA				MVPA			
	B	95 % (CI)	*p*	*B*	95 % (CI)		*p*	*B*	95 % (CI)		*p*
Physical Function	Dropped			0.64	-0.06	1.34	0.074	1.77	-0.16	3.70	0.072
Physical Role	Dropped			0.47	-0.29	1.22	0.227	**2.30**	**0.21**	**4.38**	**0.031**
Bodily pain	Dropped			**0.55**	**0.03**	**1.07**	**0.040**	0.85	-0.59	2.29	0.247
General health	Dropped			0.08	-0.48	0.65	0.768	0.15	-1.41	1.70	0.853
Vitality	Dropped			**0.74**	**0.09**	**1.39**	**0.026**	1.69	-0.10	3.48	0.064
Social Functioning	Dropped			**1.45**	**0.61**	**2.30**	**0.001**	**4.11**	**1.78**	**6.44**	**0.001**
Emotional Role	Dropped			0.70	-0.28	1.69	0.160	0.65	-2.07	3.36	0.640
Mental Health	Dropped			0.08	-0.63	0.78	0.829	0.88	-1.06	2.82	0.374
Physical component	Dropped			0.19	-0.06	0.45	0.138	0.61	-0.10	1.32	0.093
Mental component	Dropped			0.31	-0.09	0.72	0.129	0.73	-0.38	1.85	0.197

B, non-standardized regression coefficient; *CI*, confidence interval; LPA, light physical activity; MVPA: moderate-to-vigorous physical activity; SF-36: 36-item Short-Form Health Survey.

Isotemporal substitution model included all activity variables (light physical activity, moderate-to-vigorous physical activity), total wear time and covariates (age, current occupational status, fat percentage and antidepressant use) Coefficients of 1 represents reallocating 30 minutes.
Greater scores in SF-36 dimensions indicate better quality of life

Table 3. Coefficients for the isotemporal subsituttion analyses examinig the association of reallocating 30 minutes of sedentary time to light physical activity (LPA) and moderate–to-vigorous physical activity (MVPA) with impact of the disease *(n*=407*).*

FIQR domain	Sedentary time			LPA				MVPA			
	B	*95 % (CI)*	*p*	*B*	*95 % (CI)*		*p*	*B*	*95 % (CI)*		*p*
FIQR function	Dropped			**-0.32**	**-0.55**	**-0.09**	**0.008**	**-0.73**	**-1.37**	**-0.09**	**0.025**
FIQR Overall impact	Dropped			**-0.27**	**-0.45**	**-0.08**	**0.006**	-0.26	-0.77	0.26	0.331
FIQR Symptoms	Dropped			**-0.37**	**-0.63**	**-0.11**	**0.006**	-0.18	-0.90	0.54	0.619
FIQR Total impact	Dropped			**-0.95**	**-1.52**	**-0.38**	**0.001**	-1.17	-2.74	0.40	0.143

B, non-standardized regression coefficient; *CI,* confidence interval; FIQR: Revised Fibromyalgia Impact Questionnaire; LPA, light physical activity; MVPA: moderate-to-vigorous physical activity.

Isotemporal substitution model included all activity variables (light physical activity, moderate-to-vigorous physical activity), total wear time and covariates (age, current occupational status, fat percentage and antidepressant use). Coefficients of 1 represents reallocating 30 minutes.
Greater scores in FIQR domains indicate worse impact of the disease.

DISCUSSION

Our results showed that the substitution of 30 minutes of ST with LPA resulted in better scores in bodily pain, vitality, and the social functioning domains of SF-36 and all domains of FIQR (function, symptoms, overall impact, and total impact). When this amount of ST was conferred instead to MVPA, patients presented better physical role and social functioning in SF-36 and FIQR function. Our results complement previous research[8,9] by estimating how varying the distribution of ST, LPA and MVPA throughout the waking hours is related to patients' quality of life and impact of the disease.

Overall, the results of the isotemporal substitution models allocating ST to LPA displayed smaller estimated effects but in more dimensions (B rating from 0.55 to 1.4 in seven dimensions) of quality of life and impact of the disease in comparison to those allocating ST to MVPA (B rating from 0.73 to 4.1 in three dimensions). Although MVPA is recommended for health benefits[17], the intensity of PA that best correlates with quality of life in fibromyalgia is still unknown and presents mixed results in other populations. Replacement of ST with MVPA showed greater benefits for quality of life in adults[22], whereas increasing LPA might be more effective in elderly[19,26], except for physical domains that were associated with higher intensities. The results in our participants are more similar to those in the elderly population, probably due to similarities when showing a reduced fitness level[37]. Indeed, LPA is of special relevance among individuals with reduced physical capacity[17] or inactive individuals[38], given that low intensity levels of PA are shown to be stimuli that elicit improvements in health[17,38]. In fibromyalgia, small increases in LPA were associated with improvement of key symptoms[10]. Because women with fibromyalgia are highly sedentary[16], it is plausible that one of the adequate intensities of PA to achieve benefits falls below the recommendations of moderate-to-vigorous intensity for the general population[17]. Increasing daily MVPA might, however, be also of interest for patients with fibromyalgia due to its association with a lower physical impact of the disease as shown in the current and a previous research[15]. Therefore, a graded sustainable and thus feasible strategy to achieve health benefits in this condition might be to first replace inactivity with LPA behaviors and to eventually increase PA to moderate-intensity levels.

Increasing time in MVPA was positively related to the physical role in SF-36 and the FIQR function. In fact, this affinity is consistent with the closeness between these domains of both questionnaires[2]. Congruent with our findings, a previous study showed improvements in the function domain of the FIQR after an intervention aimed at increasing MVPA among patients with fibromyalgia[15]. Physical role of SF-36 includes limitations in the kind and amount of work due to physical problems. Physical barriers to continue working such as physical capacity and symptoms[39] have been associated with MVPA[15,17], which is in agreement with the results of the current study. Patients who increase their level of PA might also be more confident and present greater self-efficacy to engage in movement-related tasks of daily living that require physical effort[40] and perceive less limitations in functional status[8]. Hence, promoting behaviors of moderate-to-vigorous intensity as an ultimate goal seems a safe[15] strategy of special interest for benefits in physical domains of quality of life in women with fibromyalgia.

In the present study, when ST was substituted with LPA, better reported symptomatology (bodily pain, vitality, and lower impact of the symptoms) was observed. Our results are consistent with previous interventions where increasing steps per day resulted in better reported pain interference[11] and intensity[10]. Moreover, low levels of PA have been previously linked to better brain responses in pain modulation regions of patients with fibromyalgia[13]. The chronic widespread pain in fibromyalgia may be due to or modulated by an altered processing of nociceptive signals in central nervous system, known as central sensitization[41]. The pain relief promotion mechanisms of PA are thought to act on central pain facilitation (reduced NMDA receptor phosphorylation[41,42]) and endogenous inhibitory systems (reduced serotonin transporter expression, increased serotonin levels, and increased opioids in pathways including different brain areas[12,13], the periaqueductal grey and rostral ventromedial medulla[42,43]). Although the dose of PA to elicit pain modulatory mechanisms is not clear, to maintain even a low level of physical activity and/or avoid periods of sustained sedentary time has been related to modulation of central nervous system in fibromyalgia[12].

Fatigue, which is strongly linked to pain and its mechanisms[44], has also a great impact on quality of life[44]. In agreement with our results in the vitality domain, the level of fatigue has been related to LPA in fibromyalgia[14] and other pain conditions such as arthritis[45]. However, a lifestyle intervention increasing self-selected light PA, unlike the suggestion of our findings, did not produce changes in the fatigue severity of patient with fibromyalgia[12]. The heterogeneity in tools to assess the multiple facets of fatigue[44] and the use of different accelerometers and thresholds to categorize PA, may be representative of the impediments to making direct comparisons to prior studies. Previous research in healthy women has also stressed the importance of meeting the recommended level of MVPA and reducing prolonged sedentary behavior for a better energy and fatigue profile[46]. We also observed a borderline association between increasing MVPA and vitality, but our analyses only showed a significant estimated association derived from reallocating ST to LPA. Accordingly, it has been observed that greater improvements in fatigue of moderate-intensity exercise in healthy population may not extend to sedentary people with persistent fatigue[47], who can benefit from low intensity activities[47]. The central nervous system appears to be involved in the relationship between PA and fatigue[48]. More specifically, PA might perhaps have a positive influence on fatigue in fibromyalgia through changes in IGF-1 and resistin levels[48], yet further research is needed on this topic.

The estimated benefits of LPA in all domains of the FIQR are also in line with previous PA interventions where a change from sedentary to low active habits reduced the total impact of the disease of patients with fibromyalgia[10]. The magnitude of the effect, however, notably differed from our estimations: 10.2 [10] vs 0.95 points reduction in the total score, respectively. Several methodological issues might underlie these differences: 1) The FIQ present different weighting among domains with more importance given to symptoms instead of function as opposed to FIQR[2], 2) the lifestyle intervention not only aimed to increase PA but also coping and adherence strategies, 3) differences in study design. In light of these findings, strategies for health promotion among these patients might also target the replacement of sedentary behaviors with activities of light intensity, which are also the most likely activities that patients would be expected to engage[13].

The greatest estimated benefits were detected in the social functioning domain as a result of substituting ST either with LPA or MVPA. Congruent with our results, Suorsa et al. [49] observed a lower social contact in the most sedentary fibromyalgia patients. This group of patients usually present social isolation concerns[50] and a high prevalence of loneliness[51] that might be negatively influenced by the decreased communication that sedentary behaviors entail[52]. Conversely, it is likely that the practice of PA provides opportunities for social interactions, especially during accessible activities that are shared experiences such as walking, which may support our findings. Nonetheless, further intervention designs are needed to ascertain the nature of this relationship.

Strengths of our study included a relatively large sample size of women with fibromyalgia representative from southern Spain (Andalusia) and the use of accelerometers to objectively assess PA instead of self-reported measures[53]. In addition, we assessed quality of life through general (SF-36) and disease-specific (FIQR) instruments, providing a more comprehensive view of the actual reported health status of these patients[54]. Furthermore, the robustness of our analyses was also enhanced by considering a reasonable number of potential confounders.

Limitations included the cross-sectional study design; thus, the associations found in a between-subjects analysis cannot be explained via a causal pathway as a within-subject mechanism. Indeed, previous research has shown how quality of life can discriminate different levels of PA[8]. Therefore, some of the relationships found work in both directions. Additionally, due to the large quantity of factors related to quality of life and the impact of the disease, it is difficult to ascertain the true association between the variables. Given that only women took part in this study, future studies should investigate whether these associations also occur in men.

In conclusion, this study provided preliminary evidence that replacing 30 minutes of ST with PA of either light or moderate-to-vigorous intensity was positively associated with domains of quality of life and impact of the disease in fibromyalgia. When ST was substituted with LPA, a better bodily pain, social function, vitality, and impact of the disease in all its domains were observed. When ST was substituted with MVPA, we detected better scores in physical role, social functioning, and function. This may be a simple message to communicate in clinical practice. However, longitudinal and intervention studies on actual behavioral reallocation effects are needed to further confirm our results.

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Physical activity, sedentary time, disease impact, pain, and health-related quality of life: prospective cohort study

Study 5

SECTION 2

SECTION 2

Study 5

Longitudinal associations of physical activity and sedentary time with disease impact, pain, and health-related quality of life in women with fibromyalgia: 2- and 5-year follow up study.

Draft

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ABSTRACT

Objective: To analyze trends of sedentary time (ST), physical activity (PA) intensity levels, disease impact, pain, and health-related quality of life (HRQoL) at 2- and 5-year follow-up, and how baseline and changes in ST and PA intensity levels are associated with future outcomes (disease impact, pain, and HRQoL).

Methods. Women diagnosed with fibromyalgia (aged 51.4 ± 7.6 years) with complete data were included at baseline (n=427), at 2-year follow-up (n=172), and at 5-year follow-up (n=185). PA (light and moderate-to-vigorous [MVPA]) and ST were estimated using triaxial accelerometers. Disease impact was assessed with the revised version of the Fibromyalgia Impact Questionnaire (FIQR), pain through pressure pain threshold, the pain subscale of the FIQR, the bodily pain subscale of the 36-item Short-form health survey (SF-36) and a Visual Analog Scale, and HRQoL was assessed with the physical and mental components of the SF-36.

Results: Pressure pain threshold, PA, and ST variables changed towards less favorable values over a 2- and 5-year follow-up (*linear trend* P<0.05). Disease impact, reported pain, and HRQoL exhibited a trend for improvement over a 2- and 5-year follow-up (*linear trend* P<0.05). Baseline ST or light PA levels were not associated with future outcome values (P>0.05). Baseline MVPA was positively associated with VAS (at 2-year follow-up) and SF-36 bodily pain (at 5-year follow-up) all, P>0.05. Changes in ST and light PA were not associated with outcomes at 2-year follow-up (P>0.05) but they were associated with bodily pain and physical component of SF-36 at 5-year follow-up (all, P>0.05). Changes in MVPA were negatively associated with VAS and global pain at 2-year follow-up (all, P>0.05) and positively associated with pressure pain threshold and SF-36 physical component at 2- and 5-year follow-up (all, P>0.05).

Conclusions: Objectively measured variables slightly changed towards less favorable values, while for self-reported outcomes there was a trend for improvement over years. Baseline ST or light PA levels did not predict future outcomes and contradictory findings for baseline MVPA were found. Changes in ST (negatively), light PA, and MVPA (positively) predicted improved future pain and HRQoL.

INTRODUCTION

Fibromyalgia is considered a central sensitivity syndrome principally characterized by chronic widespread pain[1]. A wide-ranging variety of symptoms including fatigue, non-refreshed sleep, mood disturbance, and cognitive impairment are also common[1]. As a result, health-related quality of life (HRQoL) is highly deteriorated at general[2] and disease-specific level (disease impact)[3]. Although fibromyalgia symptoms seem to be persistent and fluctuate over time[4–7], several studies have also reported a slight trend towards improvement[4,8,9]. Management of this heterogeneous disease[10] remains being a challenge, but there is a general agreement on the relevance of patient's education and non-pharmacological therapies on the initial stage of treatment[11].

Daily physical activity (PA), defined as all body movement resulting in increased energy expenditure, is a fundamental modifiable health behavior. Greater PA duration has been positively related to different fibromyalgia-related symptoms including disease impact[12,13], pain[12,14,15], and general HRQoL[13,16], among others [12,17,18]. However, psychological barriers as fear of movement and avoidance behavior toward PA are highly prevalent in this population[19]. Indeed, patients have significantly reduced levels of light[20] and moderate-to-vigorous PA (MVPA)[20–22], spending most of their day in sedentary time (ST)[20].

ST is considered the lowest end of the PA spectrum and includes low energy expenditure activities in sitting or reclining posture during waking hours[23]. According to previous evidence in fibromyalgia, high amounts of ST have been also detrimentally connected to disease impact[12], pain[12,15], as HRQoL[16]. Despite the growing evidence linking ST, PA, and fibromyalgia outcomes, limited knowledge exists on how these variables and its relationship evolve over time.

A short-term follow-up (12 weeks) study showed that fibromyalgia patients that increased and sustained higher volumes of moderate PA appear to experience less pain compared to those not increasing moderate PA[24]. Maintenance of adequate PA levels has been shown to be predictive of pain, fatigue and physical fitness in fibromyalgia patients at 4.5-year follow-up[25]. Other study, however, suggested that exercising regularly did not influence health parameters at 26-year follow-up in this population[26]. The evidence available so far relied on self-reported measures (which typically have poor validity[27]), mainly analyzed the predictive value of baseline PA, and completely omitted the potential role of ST. In other populations, literature shows that higher levels of PA might have a protective role in relation to HRQoL[28–31], low-back pain[32], and functional disability[33] in menopause women [28], adults[31], and older adults[29,30,33]. Although studies focused on ST are scarce, evidence has also shown that ST is detrimentally linked to future musculoskeletal pain[34], and HRQoL [30,35] in adults[34], and older adults[30,35]. A better understanding on how changes in ST are related to relevant outcomes in fibromyalgia or which intensity of PA present the strongest association with future health will help to develop disease-specific recommendations.

This study aimed to examine: i) trends of ST, PA intensity levels, disease impact, pain, and HRQoL at 2- and 5-year follow-up, and ii) how baseline and changes in ST and PA intensity levels are associated with future outcomes (disease impact, pain, and HRQoL).

METHODS

Participants

These data are derived from the al-Ándalus project in which a province proportional recruitment of fibromyalgia patients from Southern Spain was planned[36]. In 2012 (baseline) patients were contacted through fibromyalgia associations, email and social media. In 2014 and 2017 the cohort was contacted for the follow-up evaluations. Inclusion criteria for the current study were: (i) to be previously diagnosed by a rheumatologist and meet the modified 2011 American College of Rheumatology (ACR) fibromyalgia criteria (Widespread Pain Index [WPI] ≥7 and the Symptom Severity [SS] ≥5, or the WPI is 3–6 and the SS ≥9)[37] (ii) to have neither acute nor terminal illness nor severe cognitive impairment (Mini Mental State Examination [MMSE] score < 10[38]) and (iii) to be ≤65 years old.

Procedures

A similar assessment process was carried out at three time points. On day one, the MMSE was interviewed and participants filled out self-reported sociodemographic data and drug consumption questionnaires. Tender points, anthropometry and body composition were also assessed. Questionnaires related to disease impact, pain, and HRQoL were given to patients to be completed at home. Two days later, patients returned to the laboratory, where questionnaires were collected and checked by the researchers. After that, participants received instructions on how to complete the sleep diary and the accelerometers were provided. The accelerometers and sleep diaries were returned to the research team 9 days later.

Written informed consent from all study participants was obtained. The study was approved by the Ethics Committee of the Hospital Virgen de las Nieves", Granada (Spain).

Measures

Sedentary time and physical activity

Participants wore a triaxial accelerometer GT3X+ (Actigraph) on the hip during 9 consecutive days, 24 hours/day except for water-based activities. Data were collected using the default mode filter option, at a rate of 30 Hz and stored at an epoch length of 60 s[39,40]. Data from day 1 (to avoid reactivity) and day 9 (day of deice return) were excluded from the analyses. A total of 7 continuous days with at least 10 valid hours/day were required for inclusion. Data download, reduction, cleaning, and analyses were conducted using the manufacturer software (ActiLife desktop, version 6.11.7).

Accelerometer wear time was calculated by subtracting sleeping time (reported in sleep diaries by patients) and non-wear periods. Non-wear periods were considered to be any bouts of 90 continuous minutes (30-minute small-window length and 2-minute skip tolerance) of 0 counts[41]. Physical activity intensity levels were calculated based upon recommended PA vector magnitude cut points: light (200-2689 counts per minute{cpm}), moderate (2690-6166 cpm) and vigorous (>6167 cpm). ST was estimated as the time accumulated below 200 cpm during periods of wear time[39,40]. Participants presented extremely low values of vigorous PA (0.4 minutes/day); therefore, vigorous PA was excluded from all of the analyses and MVPA (>2690 cpm) was used instead.

Disease impact

The revised version of the Fibromyalgia Impact Questionnaire (FIQR) was used, in which overall disease impact is assessed through a wide range of symptoms and comorbidities[3]. This is a valid self-administered questionnaire consisting of 21 items (rated 0 to 10). FIQR total score ranges from 0 to 100 with higher scores indicating greater impact of fibromyalgia.

Pain-related measures

Pressure pain threshold

The 18 tender points proposed in the 1990 ACR criteria for classification of fibromyalgia[42] were evaluated using a standard pressure algometer (FPK 20; Wagner Instruments). Two alternative measurements at each tender site were performed, and the mean score was recorded. The total number of positive tender points was recorded, considering a positive tender point when the patient felt pain at pressure ≤4 kg/cm^2. The pressure pain threshold was defined as the average pressure threshold across the 18 tender points.

Pain intensity

Pain intensity was assessed with a visual analog scale (VAS). This tool consists of a 10 cm horizontal line on which participants mark pain intensity at the present moment between the extremes: 0 (representing no pain) and 10 (representing the worst pain ever experienced). Clinical pain intensity was also assessed with the an item from the FIQR (FIQR-pain)[3]. Participants were asked to rate their level of pain in the past 7 days on a numeric rating scale (range 0–10), where higher values represent higher pain intensity.

Pain magnitude and interference on quality of life

Pain magnitude and interference over the past 4 weeks were assessed with the Bodily Pain section from Short Form 36 health survey (SF-36)[43]. The scores range 0 to 100, where a higher score represents lower pain.

Health-related quality of life

The Spanish version of the SF-36[43] was used to assess HRQoL. The SF-36 is a generic instrument that has been demonstrated to have good reliability and validity in chronic pain patients[44]. It contains 36 items grouped into 8 dimensions and 2 summary components: the physical and the mental component. Only the 2 summary components were used to describe HRQoL for the present study, scoring from 0 (worst possible health status) to 100 (the best possible health status).

Other variables

Anthropometry and body composition

A portable eight-polar tactile-electrode impedance analyser (InBody R20, Seoul, Korea) was used to estimate weight (kg) and fat percentage. Participants were asked not to shower, not to practice intense PA and not to ingest large amounts of fluid and/or food in the two hours before the measurement. Patients were required to remove all clothing (except underwear) and metal objects during the assessment.

Socio-demographic and clinical data

All participants filled out a socio-demographic and clinical data questionnaire to gather information related to age, marital status, educational level, occupational status, and analgesics and antidepressant consumption.

2.4. Statistical Analyses

A global measure of pain was calculated as the mean of the following normalized z-scores [(value-mean)/SD]: i) VAS, ii) pressure pain threshold (using inverted score), iii) FIQR-pain, and iv) SF-36 Bodily pain (using inverted score). Greater scores in the global measure of pain indicated higher pain experienced.

Descriptive statistics were used to examine the sociodemographic and clinical characteristics of the sample. Generalized linear model were performed to check for linear trends in all variables of interest. To assess potential differences between participants attending to the different evaluations, baseline characteristics were compared with the Student t-test (continuous variables) and the Chi-square test (categorical variables).

To evaluate the longitudinal association between PA variables and the outcomes, separate linear regression models were built introducing the outcome of interest at each time point as the dependent variable. Baseline values of the outcome, age, fat percentage, antidepressant and analgesics consumption (yes/no) along with the predictor of interest were introduced as dependent variables using the *enter* method. To analyze the contribution of baseline and change of PA variables, two types of models were created: model 1= baseline PA variable of interest (ST, light PA or MVPA) + covariates, and model 2) model 1 + changes over time in the PA variable of interest. No multicollinearity problems were found in the data (Variance Inflation Factor <1.5 in all models) and other assumptions of linear regression were met (linear relationship, normality, no autocorrelation, and homocedasticity).

Statistical analyses were performed using the Statistical Package for Social Sciences (IBM SPSS, version 22; Armonk, NY, USA). A two-tailed level of significance was set at $p < 0.05$ for all analyses.

RESULTS

The flow diagram of participants is shown in figure 1. Among the initially eligible participants with valid data at baseline (n=427), a total of 172 and 185 participants attended to 2- and 5-year follow-up, respectively. Table 1 provides an overview of participants' characteristics at each time point. Figure 2 shows mean values of outcomes and predictors in the study at each time point. A linear trend for deterioration in fat percentage, number of total tender points, and pressure-pain threshold (all $P<0.001$), and a linear trend for improvement for VAS, FIQR-pain, FIQR total, SF-36 Bodily pain, SF-36 PCS and SF-36 MCS (all, $P<0.01$) was found. ST was significantly increased whereas there was a linear trend for reductions in light PA and MVPA (all, $P<0.001$).

Differences at baseline between participants attending to baseline only, baseline + 2-year follow-up, baseline + 5-year follow-up or all the assessments are included in supplementary table 1. Participants attending all the assessment had significantly better SF-36 mental health compared to those attending baseline assessment only ($P<0.05$). Also, participants attending all assessments had significantly less ST and more light PA at baseline compare to those attending 5-year follow-up only (all, $P<0.05$). Lastly, participants attending 2-year follow up only had significantly more light PA at baseline than those attending 5-year follow-up ($P<0.05$).

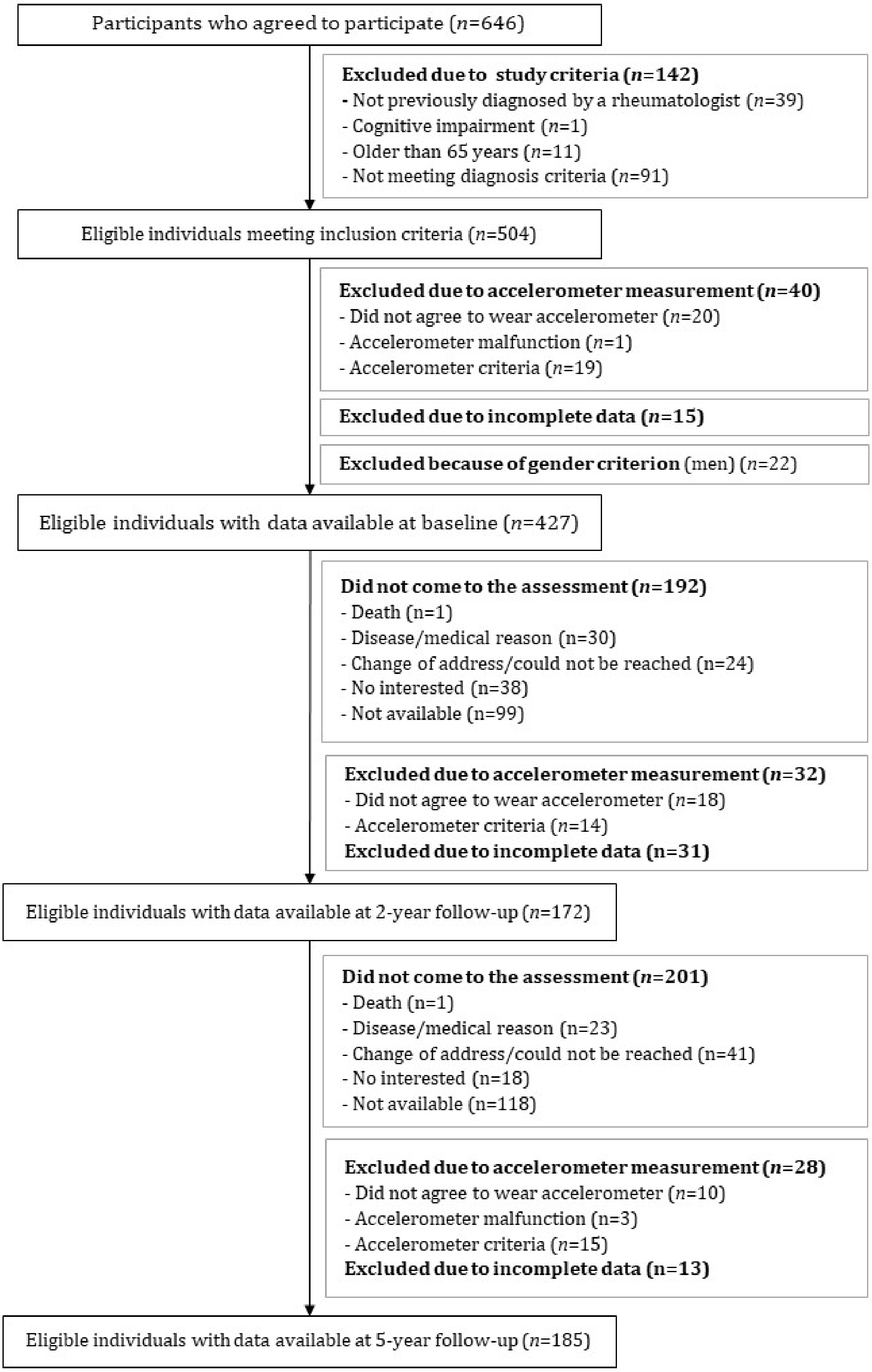

Figure 1. Flowchart diagram of participants

Table 1. Descriptive characteristics of the participants at baseline, 2- and 5-year follow-up.

	Baseline n=427		2-year Follow-up n=172		5-year Follow-up n=185	
	Mean	SD	Mean	SD	Mean	SD
Age (years)	51.4	7.7	54.1	7.3	56.1	7.0
Body fat (%)	40.1	7.7	41.1	7.0	42.5	6.8
Total number tender points (0-18) +	15.0	4.8	17.4	2.1	16.7	3.3
Disease impact, FIQR total (0-100) +	66.1	16.1	61.9	18.5	60.3	19.6
Pain-related variables						
Visual Analogue Scale (0-10) +	6.3	2.3	5.9	2.4	5.9	2.5
Pressure-pain threshold, kg/cm^2 (18-144) *	50.1	22.5	34.6	14.6	44.1	16.1
FIQR-pain (0-10) +	7.6	1.9	7.3	2.2	7.0	2.2
SF-36 Bodily Pain (0-100) *	20.2	14.3	25.4	18.1	24.3	17.4
Health-related quality of life						
SF-36 Physical Component (0-100) *	29.3	7.0	30.9	7.2	30.8	7.4
SF-36 Mental Component (0-100) *	34.8	11.0	36.0	11.9	37.9	12.6
Accelerometry variables						
Sedentary time (min/day)	465.0	105.7	455.0	104.5	481.5	101.1
Light PA (min/day)	414.0	95.4	422.4	100.5	399.6	100.5
MVPA (min/day)	43.3	29.8	42.5	28.5	38.3	26.9
	n	%	n	%	n	%
Marital status						
Married	321	75.2	133	77.3	143	77.3
Not married	106	24.8	39	22.7	42	22.7
Educational status						
Non-universitary	365	85.5	147	85.5	157	84.9
Universitary	62	14.5	25	14.5	28	15.1
Occupational Status						
Working	112	26.2	48	27.9	49	26.5
Not working	315	73.8	123	71.5	135	73.0
Medication por pain						
No	40	9.4	14	8.1	24	13.0
Yes	387	90.6	158	91.9	161	87.0
Medication for depression						
No	166	38.9	78	45.3	94	50.8
Yes	261	61.1	94	54.7	91	49.2
Time since diagnosis						
Less than 1 year	29	6.8	10	5.8	10	5.4
Between 1 and 5 years	141	33.0	59	34.3	58	31.4
More than 5 years	249	58.3	100	58.1	112	60.5

FIQR: Fibromyalgia Impact Questionnaire Revised; MVPA: moderate-to-vigorous PA. PA: Physical Activity. SF-36: 36-item Short-Form Health Survey. + Greater scores indicate worse health status and higher pain; * Greater scores indicate better health status or lower pain. SD: Standard Deviation

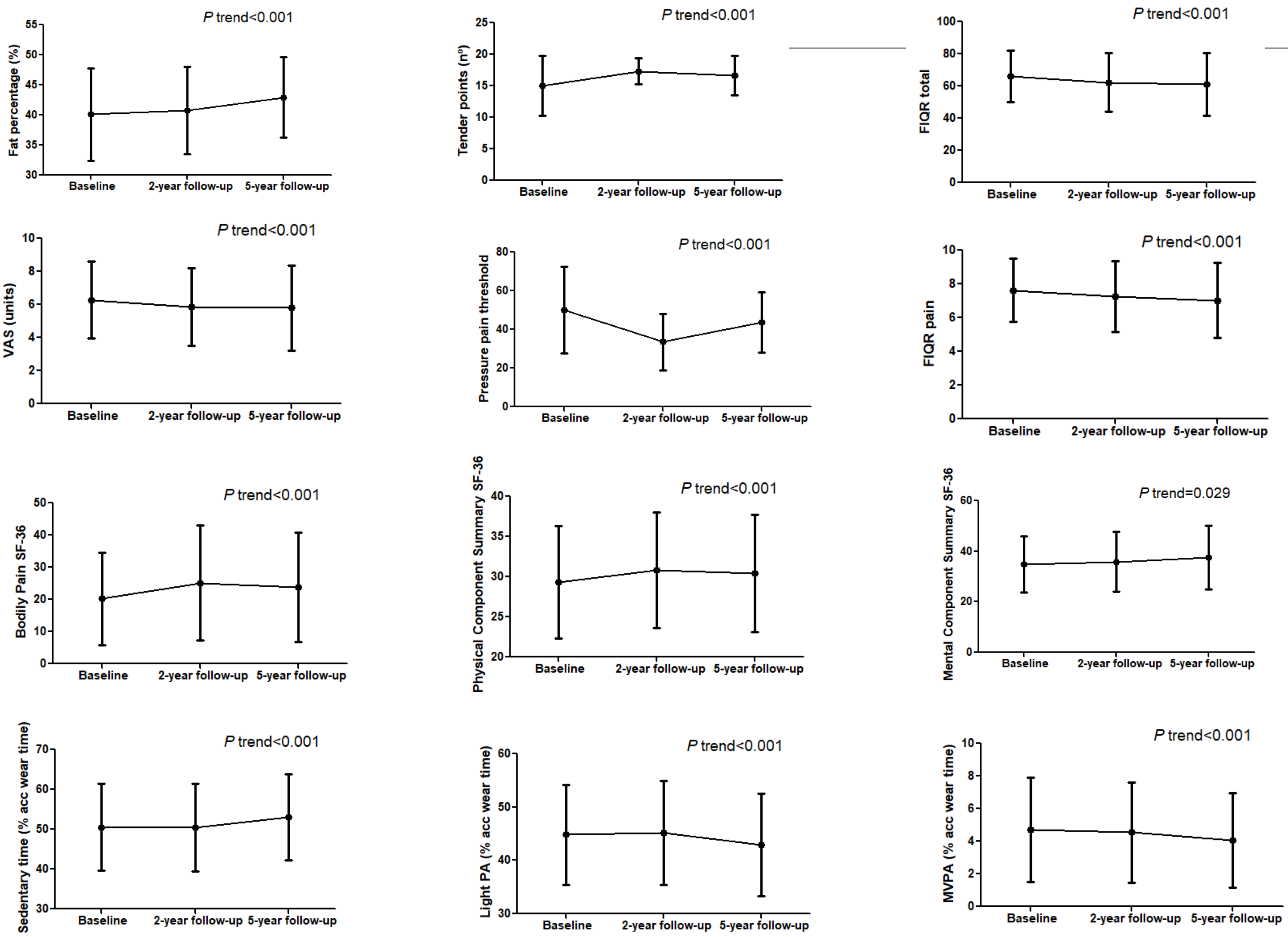

Figure 2. Mean and standard deviation of the variables included in the study at baseline, 2-year, and 5-year follow up and trend analyses. acc: accelerometer; FIQR: Fibromyalgia Impact Questionnaire; MVPA: moderate-to-vigorous physical activity; PA: Physical activity; SF-36: 36-item Short-Form Health Survey; VAS: Visual Analog Scale.

Table 2. Longitudinal association between sedentary time and physical activity with pain-related measures in women with fibromyalgia.

	2-year follow-up (*n*=172)						5-year follow-up (*n*=185)					
Pain: Visual Analogue Scale	β	B	(95% CI)		*P*	Adj. R^2	β	B	(95% CI)		*P*	Adj. R^2
Sedentary time (baseline)	-0.04	-0.01	-0.04	0.02	0.639	0.18	0.03	0.01	-0.03	0.04	0.665	0.14
Δ Sedentary time	-0.02	-0.01	-0.06	0.04	0.741	0.18	0.04	0.01	-0.04	0.06	0.626	0.14
Light PA (baseline)	-0.02	0.00	-0.04	0.03	0.845	0.18	-0.04	-0.01	-0.05	0.03	0.584	0.14
Δ Light PA	0.09	0.03	-0.02	0.08	0.219	0.18	-0.02	-0.01	-0.06	0.05	0.781	0.14
MVPA (Baseline)	**0.17**	**0.13**	**0.02**	**0.24**	**0.023**	0.21	0.01	0.01	-0.10	0.12	0.873	0.14
Δ MVPA	**-0.18**	**-0.19**	**-0.34**	**-0.04**	**0.015**	0.23	-0.06	-0.06	-0.23	0.10	0.454	0.14
Pain: Algometer score	β	B	(95% CI)		*P*	Adj. R^2	β	B	(95% CI)		*P*	Adj. R^2
Sedentary time (baseline)	-0.03	-0.04	-0.24	0.16	0.684	0.20	-0.05	-0.07	-0.27	0.12	0.474	0.25
Δ Sedentary time	-0.01	-0.02	-0.31	0.27	0.886	0.20	-0.09	-0.19	-0.49	0.11	0.211	0.26
Light PA (baseline)	0.01	0.02	-0.20	0.24	0.846	0.20	0.05	0.08	-0.15	0.30	0.490	0.25
Δ Light PA	-0.03	-0.06	-0.37	0.25	0.714	0.20	0.05	0.12	-0.21	0.45	0.460	0.26
MVPA (Baseline)	0.06	0.28	-0.41	0.97	0.418	0.20	0.03	0.13	-0.54	0.81	0.699	0.25
Δ MVPA	0.13	0.81	-0.13	1.75	0.090	0.21	**0.15**	**1.02**	**0.01**	**2.03**	**0.047**	0.24
FIQR pain	β	B	(95% CI)		*P*	Adj. R^2	β	B	(95% CI)		*P*	Adj. R^2
Sedentary time (baseline)	-0.02	-0.01	-0.03	0.02	0.744	0.30	-0.04	-0.01	-0.03	0.02	0.541	0.29
Δ Sedentary time	0.00	0.00	-0.04	0.04	0.948	0.29	0.09	0.03	-0.01	0.07	0.179	0.29
Light PA (baseline)	0.00	0.00	-0.03	0.03	0.977	0.30	0.04	0.01	-0.02	0.04	0.538	0.29
Δ Light PA	0.04	0.01	-0.03	0.06	0.548	0.29	-0.06	-0.02	-0.06	0.02	0.363	0.29
MVPA (Baseline)	0.07	0.05	-0.05	0.15	0.293	0.30	0.02	0.01	-0.08	0.10	0.804	0.29
Δ MVPA	-0.14	-0.13	-0.26	0.00	0.054	0.31	-0.13	-0.12	-0.25	0.01	0.075	0.30
SF-36 Bodily Pain	β	B	(95% CI)		*P*	Adj. R^2	β	B	(95% CI)		*P*	Adj. R^2
Sedentary time (baseline)	0.06	0.09	-0.14	0.33	0.439	0.25	-0.10	-0.15	-0.35	0.05	0.149	0.28
Δ Sedentary time	-0.07	-0.17	-0.52	0.18	0.343	0.25	**-0.17**	**-0.38**	**-0.68**	**-0.07**	**0.015**	0.30
Light PA (baseline)	-0.05	-0.09	-0.36	0.17	0.482	0.25	0.06	0.11	-0.12	0.34	0.344	0.28
Δ Light PA	0.03	0.09	-0.28	0.47	0.630	0.24	**0.18**	**0.46**	**0.12**	**0.79**	**0.008**	0.30
MVPA (Baseline)	-0.03	-0.21	-1040.00	0.63	0.624	0.25	**0.14**	**0.76**	**0.06**	**1.45**	**0.034**	0.29
Δ MVPA	0.11	0.88	-0.26	2.02	0.131	0.25	0.02	0.13	-0.92	1.18	0.803	0.29

MVPA: moderate-to-vigorous PA. PA: physical activity; SF-36: 36-item Short-Form Health Survey. β, standardized regression coefficient; Δ: change. Linear regression models were built using the *enter* method with the outcome at follow-up as dependent variable. Baseline values of the outcome, age, fat percentage, antidepressant and analgesics consumption (yes/no) along with the predictor of interest were introduced as dependent variables. Models including Δ of the predictor of interest were additionally adjusted by baseline predictor. Percentage of wear time in each PA variable was used.

Table 3. Longitudinal association between sedentary time and physical activity with pain, disease impact and quality of life in women with fibromyalgia.

	2-year follow-up (*n*=172)						5-year follow-up (*n*=185)					
FIQR	β	B	(95% CI)		*P*	Adj. R^2	β	B	(95% CI)		*P*	Adj. R^2
Sedentary time (baseline)	-0.02	-0.03	-0.23	0.17	0.737	0.49	-0.04	-0.08	-0.28	0.12	0.448	0.46
Δ Sedentary time	0.03	0.08	-0.22	0.37	0.614	0.49	0.09	0.22	-0.08	0.53	0.145	0.46
Light PA (baseline)	0.01	0.01	-0.21	0.23	0.913	0.49	0.05	0.11	-0.12	0.34	0.352	0.46
Δ Light PA	-0.01	-0.03	-0.35	0.29	0.853	0.49	-0.07	-0.19	-0.53	0.14	0.253	0.46
MVPA (Baseline)	0.05	0.29	-0.40	0.99	0.405	0.49	-0.01	-0.07	-0.76	0.62	0.844	0.46
Δ MVPA	-0.06	-0.47	-1.43	0.48	0.331	0.49	-0.10	-0.80	-1.83	0.24	0.129	0.45
Global Pain score	β	B	(95% CI)		*P*	Adj. R^2	β	B	(95% CI)		*P*	Adj. R^2
Sedentary time (baseline)	-0.03	0.00	-0.01	0.00	0.614	0.35	0.02	0.00	0.00	0.01	0.724	0.37
Δ Sedentary time	0.02	0.00	-0.01	0.01	0.770	0.35	0.12	0.01	0.00	0.02	0.067	0.38
Light PA (baseline)	0.01	0.00	-0.01	0.01	0.892	0.35	-0.01	0.00	-0.01	0.01	0.858	0.37
Δ Light PA	0.04	0.00	-0.01	0.01	0.569	0.32	-0.10	-0.01	-0.02	0.00	0.127	0.38
MVPA (Baseline)	0.09	0.01	-0.01	0.04	0.180	0.36	-0.10	-0.01	-0.02	0.00	0.127	0.37
Δ MVPA	**-0.17**	**-0.04**	**-0.07**	**-0.01**	**0.011**	0.38	-0.11	-0.02	-0.05	0.01	0.111	0.38
SF-36 Physical Component	β	B	(95% CI)		*P*	Adj. R^2	β	B	(95% CI)		*P*	Adj. R^2
Sedentary time (baseline)	-0.09	-0.06	-0.15	0.04	0.223	0.23	-0.11	-0.07	-0.16	0.02	0.112	0.27
Δ Sedentary time	-0.08	-0.08	-0.22	0.06	0.259	0.23	**-0.19**	**-0.18**	**-0.31**	**-0.05**	**0.006**	0.30
Light PA (baseline)	0.10	0.07	-0.03	0.18	0.176	0.23	0.11	0.08	-0.02	0.18	0.105	0.28
Δ Light PA	0.03	0.03	-0.13	0.18	0.720	0.22	**0.15**	**0.16**	**0.02**	**0.31**	**0.028**	0.29
MVPA (Baseline)	0.00	0.00	-0.33	0.33	0.997	0.22	0.04	0.09	-0.22	0.39	0.571	0.27
Δ MVPA	**0.19**	**0.61**	**0.16**	**1.06**	**0.008**	0.25	**0.18**	**0.56**	**0.11**	**1.01**	**0.015**	0.29
SF-36 Mental Component	β	B	(95% CI)		*P*	Adj. R^2	β	B	(95% CI)		*P*	Adj. R^2
Sedentary time (baseline)	0.10	0.11	-0.04	0.26	0.142	0.32	0.03	0.04	-0.10	0.18	0.605	0.33
Δ Sedentary time	0.04	0.07	-0.15	0.29	0.528	0.32	-0.07	-0.11	-0.33	0.11	0.318	0.33
Light PA (baseline)	-0.09	-0.11	-0.27	0.06	0.193	0.32	-0.06	-0.07	-0.23	0.09	0.386	0.33
Δ Light PA	-0.03	-0.06	-0.30	0.18	0.627	0.32	0.09	0.17	-0.07	0.41	0.163	0.34
MVPA (Baseline)	-0.07	-0.27	-0.79	0.25	0.305	0.32	0.05	0.21	-0.28	0.70	0.405	0.33
Δ MVPA	-0.05	-0.28	-0.99	0.43	0.432	0.32	-0.05	-0.28	-1.02	0.46	0.452	0.33

MVPA: moderate-to-vigorous PA. PA: physical activity; SF-36: 36-item Short-Form Health Survey. β, standardized regression coefficient; Δ: change. Linear regression models were built using the *enter* method with the outcome at follow-up as dependent variable. Baseline values of the outcome, age, fat percentage, antidepressant and analgesics consumption (yes/no) along with the predictor of interest were introduced as dependent variables. Models including Δ of the predictor of interest were additionally adjusted by baseline predictor. Percentage of wear time in each PA variable was used.

Table 2 and Table 3 show the longitudinal association between ST and PA intensity levels with disease impact, pain-related measures, and HRQoL in women with fibromyalgia. Baseline

MVPA was positively associated with VAS (B=0.13, 95% CI=0.02-0.24, *P*=0.023) at 2-year follow-up and with SF-36 bodily pain scores (B=0.76, 95% CI=0.06-1.45, *P*=0.034) at 5-year follow-up. No associations were found between ST or light PA at baseline with any outcomes at 2- or 5-year follow-up.

Changes in ST were negatively associated with SF-36 bodily pain (B=-0.38, 95% CI=-0.68, -0.07, *P*=0.015) and SF-36 physical component (B=-0.18, 95% CI=-0.31, -0.05, *P*=0.006) at 5-year follow-up. Changes in light PA were associated with changes in SF-36 bodily pain (B=0.46, 95% CI=0.12, 0.8, *P*=0.008) and SF-36 physical component (B=0.16, 95% CI=0.02, 0.31, *P*=0.028) at 5-year follow-up. No associations were found between changes in ST or light PA and any outcome at 2-year follow-up, or other pain-related variables, disease impact or mental component of SF-36 at 5-year follow-up.

Changes in MVPA were negatively associated with global pain (B=-0.04, 95% CI=-0.07, -0.01, *P*=0.011) and positively associated with SF-36 physical component (B=0.61, 95% CI=0.16, 1.06, *P*=0.008) at 2-year follow-up. Also, changes in MVPA was associated with pressure pain threshold (B=1.02, 95% CI=0.01, 2.03, *P*=0.047) and SF-36 physical component (B=0.56, 95% CI=0.11, 1.01, *P*=0.015) at 5-year follow-up. No associations were found between changes in MVPA and disease impact, others pain-related variables, or mental component of SF-36 at 2- or 5-year follow-up.

DISCUSSION

The findings of this study suggest that objectively measured variables (i.e. pressure pain threshold and PA variables) slightly changed towards less favorable values over a 2- and 5-year follow-up in women with fibromyalgia. On the contrary, for self-reported outcomes (i.e. disease impact, reported pain, and HRQoL), there was a trend for improvement. Baseline MVPA was positively associated with VAS (at 2-year follow-up) and SF-36 bodily pain (at 5-year follow-up) whereas baseline ST or light PA was not associated with any future outcome. Changes in ST (negatively) and light PA (positively) were related with bodily pain and physical component SF-36 at 5-year follow-up but not associated with outcomes at 2-year follow-up. Changes in MVPA were negatively associated with VAS and global pain at 2-year follow-up and positively associated with pressure pain threshold and SF-36 physical component at 2- and 5-year follow-up.

Although symptoms of fibromyalgia are commonly persistent, a slight trend towards improvement in different self-reported outcomes has been described in previous longitudinal studies[4,8,9]. Other investigations in this population reported no substantial change on health parameters over time[4–7], and fewer reported a worsening of pain[8]. Our findings demonstrate that symptoms severity stay high over time and magnitude of changes across different evaluations was small. Variables related to perceived health (this is patient-reported outcomes such as FIQR, SF-36) were slightly improved irrespective of the deterioration in objectively measured outcomes. These findings could support the idea that patients slightly adapt and learn how to cope with the disease[8].

Changes over time for ST and PA variables were less consistent and occurred specially in the long-term. Over the years, ST slightly increased and PA decreased. So far, no previous studies have concisely analyzed trends of ST and PA over time in fibromyalgia nor other rheumatic condition. Only one previous follow-up study described that 79% of fibromyalgia patients followed at 6 to 8 years reported being engaged in PA one day or more per week[7]. Importantly, these high rates of PA could be overestimated due to the use of questionnaires[22,45] and the insufficiently detailed questions not including duration or intensity of the activity. Our findings, based on device-measure data, confirm that the high levels of ST[20] and low levels of PA[20–22] described in observational studies[20–22] seem to continue and slightly change towards a less favorable profile over the years.

Previous evidence based on short-term follow-up (12 weeks) showed that fibromyalgia patients that increased and sustained higher volumes of self-reported moderate PA appear to experience less pain compared to those not increasing moderate PA[24]. Another longitudinal study (4.5-year follow-up) in this group of patients suggested that maintaining adequate self-reported PA levels was associated with less future VAS-pain[25]. Finally, in a 26-year follow-up, stating participation in physical activities regularly did not influence health parameters in fibromyalgia[26]. To our knowledge, this study analyzed for the first time the longitudinal association between objectively-measured ST and PA intensity levels and key health outcomes in women with fibromyalgia. Previous research using device measures of PA have been limited to cross sectional[12] and lifestyle interventions[46] suggesting the relationship between light[12,46] and moderate[12] PA with pain-related outcomes in this disease. Our findings suggest contradictory findings for baseline MVPA due its negative relationship with VAS at 2-year follow-up but its positive relationship with bodily pain of SF-36 at 5-year follow-up. Changes in MVPA over time, on the contrary, was consistently related to better prognosis of certain pain-related measures (VAS, global pain, pressure pain threshold, and SF-36 physical component). MVPA was, indeed, the PA intensity level linked to more outcomes in both time points studied. The importance of MVPA over other levels of PA is consistent with current PA guidelines for general population[47]. It is relevant to note that light PA was also found to be associated with future SF-36 bodily pain at 5 year-follow-up. Although spending more time in MVPA could hold potential for future pain reductions, light PA is a more sustainable behavior over time and this could lead eventually to increases in MVPA. Central nervous system mechanism of pain processing has been related to PA in fibromyalgia[14]. People with fibromyalgia who report being more physically active demonstrate greater response in pain regulatory regions of brain (dorsolateral prefrontal cortex, posterior cingulate cortex, and the posterior insula) and decreases in brain regions implicated in the sensory/discriminative aspects of pain (the primary sensory and superior parietal cortices)[14]. In addition, other factors related to lower pain experience (reduced fear of movement and catastrophizing or increased self-efficacy)[48] could be derived from increased PA intensity levels.

Our findings showed that HRQoL (SF-36 physical component) was predicted by change in MVPA at 2-year follow-up and by changes in MVPA and light PA at 5-year follow up. Although research on PA and HRQoL in fibromyalgia is limited, this issue has been extensively addressed in other populations. However, literature available so far is heterogeneous in terms of subjects' characteristics, PA and HRQoL assessment, or length of follow-up. Steps count or MVPA have been related to higher future functional disability among older adults with chronic pain at 2-year follow-up[33]. Also, baseline self-reported leisure time PA was found to be related with future physical and mental HRQoL (6-year follow-up) in older adults[30]. In contrast with these findings, changes over time but not initial level at baseline predicted future HRQoL in our study sample. A similar trend has been described in older adults as changes in self-reported leisure time PA (but not baseline values) were associated with better SF-36 physical components in women at 10-year follow-up[29]. Some studies also support that adult[31] and menopause women[28] who increased self-reported PA over years improved their HRQoL[28,31]. Based on previous longitudinal findings in fibromyalgia[25], it can be hypothesized that MVPA could be predictive of levels of physical fitness. This combination of strength, cardiorespiratory fitness, and flexibility could also be related to reduced obesity, increased muscle mass and, consecutively, better SF-36 physical component[49,50]. Indeed, as longitudinal association between HRQoL and physical fitness has shown to be bidirectional[49], this might also be the case for MVPA.

Changes in ST over time was found to be negatively associated with SF-36 bodily pain and physical component scores at 5-year follow-up. These findings extend prior cross-sectional research linking ST to pain[12,15] and HRQoL[13,16] in fibromyalgia, yet longitudinal studies are lacking. Previous evidence in adults reported that baseline self-reported levels of ST were associated with future pain[34] and HRQoL[30,35]. Reduced ST is probably related to increased PA[13] and, therefore, some of the aforementioned mechanisms connecting PA to pain and HRQoL could be shared among behaviors. ST itself could also additionally contribute to impaired pain regulation[15] explain our findings for SF-36 bodily pain. Also, sedentary periods are characterized by skeletal muscle inactivity[51] and are thought to be related to reduced aerobic capacity and muscle strength[52]. All this accelerates deconditioning that occurs with aging[52] and could negatively impact SF-36 physical scores.

Contrary to the initial hypothesis, no longitudinal relationships between ST, PA, and disease impact or SF-36 mental component were found. Total FIQR and SF-36 mental component are summary variables of other specific dimensions that could be each of them differently related to PA and ST[53]. Also, if patients were to adapt to disease[8], greater changes in the PA and ST could be needed to detect associations at disease-specific level. Patients that attended to all assessment presented better initial SF-36 mental component scores compared to the sample only attending to baseline. Despite the statistical adjustment for baseline levels, residual confounding in the analyzed associations cannot be discarded. In addition, the activity performed during the time spent in different PA categories seem to be relevant to mental health[54]. For instance, sedentary but cognitively stimulating activities will have a different impact on cognitive performance compared to totally passive sedentary activities[54]. Therefore, further research on how particular sedentary and active behaviors are related to specific dimensions of FIQR and HRQoL are warranted.

This study has several limitations that must be acknowledged. Although the design of the study was longitudinal, the direction of the causality remains uncertain. The loss of study participants at follow-up could also affect generalizability of findings. In addition, there is a considerable number of factors that influence disease impact, pain, and HRQoL and that could be mediating the relationship under analysis. The strengths of this study include the use of accelerometer measures of PA, which allowed us to quantify ST and PA more accurately compared to self-reported measures[27]. Also, a relatively large sample size of women with fibromyalgia representative from southern Spain[36] was examined and followed at two different points in time.

CONCLUSIONS

The findings of this study suggest that objectively measured outcomes (pressure pain threshold, ST, and PA) changed towards less favorable values, while self-reported outcomes (disease impact, pain, and HRQoL) slightly tend to improve over a 2- and 5-year follow-up. Neither ST nor light PA at baseline predicted future outcomes and contradictory findings were found for baseline MVPA in relation to pain. Changes in ST (negatively) and light PA (positively) were associated with pain and HRQoL in at 5-year follow-up whereas changes in MVPA (positively) were more consistently related to pain and HRQoL at 2-and 5-year follow-up.

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Supplementary table 1. Differences at baseline between participants attending to each assessment.

	Total sample (n=427)		Attended Baseline assessment only (n=183)		Attended baseline + 2 year follow-up (n=59)		Attended baseline + 5 year follow-up (n=72)		Attended all the assessment (n=113)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Age (years)	51.43	7.65	50.94	8.31	53.14	7.39	50.88	6.69	51.68	7.17
Fat percentage (%)	40.09	7.7	39.71	7.58	40.97	7.75	40.31	8.26	40.11	7.57
Total number tender points (0-18) ┼	15.04	4.75	15.05	4.65	14.81	4.86	14.72	5.14	15.35	4.62
Disease impact, FIQR total (0-100) ┼	20.2	14.3	19.4	13.18	18.19	13.15	19.25	14.89	23.17	15.9
Pain-related variables	6.27	2.32	6.07	2.27	6.88	2.47	6.65	2.11	6.04	2.4
Visual Analogue Scale (0-10) ┼										
Pressure-pain threshold, kg/cm^2 (18-144) *	50.07	22.54	50.11	22.77	50.46	21.79	52.07	24.43	48.53	21.47
FIQR-pain (0-10) ┼	7.63	1.86	7.6	1.95	7.9	1.87	7.6	1.73	7.57	1.79
SF-36 Bodily Pain (0-100) *	66.12	16.09	65.91	15.66	67.11	16.42	67.12	16.53	65.3	16.47
Health-related quality of life										
SF-36 Physical Component (0-100) *	29.31	6.97	29.51	7.09	29.44	5.66	28.79	7.69	29.23	6.97
SF-36 Mental Component (0-100) *	34.84	11.04	**33.04** [a]	**9.75**	34.37	12.65	34.77	11.85	**38.05** [a]	**11.01**
Accelerometry variables										
Sedentary time (min/day)	465.02	105.74	472.86	106.77	448.25	107.65	**484.81** [a]	**95.67**	**448.46** [a]	**106.88**
Light PA (min/day)	413.95	95.35	410.62	89.99	**426.74** [a]	**95.00**	**386.90** [a,b]	**95.18**	**429.90** [b]	**100.85**
MVPA (min/day)	43.34	29.78	43.92	31.96	38.96	22.49	40.49	28.5	46.48	30.2
	n	%	n	%	n	%	n	%	n	%
Marital status										
Married	321	75.2	**130** [a]	**71**	43	72.9	55	76.4	**93** [a]	**82.3**
Not married	106	24.8	53	29	16	27.1	17	23.6	20	17.7
Educational status										
Non-universitary	365	85.5	153	83.6	52	88.1	62	86.1	98	86.7
Universitary	62	14.5	30	16.4	7	11.9	10	13.9	15	13.3
Occupational Status										
Working	112	26.2	48	26.2	10	16.9	19	26.4	35	31
Not working	315	73.8	135	73.8	49	83.1	53	73.6	78	69
Medication por pain										
No	40	9.4	15	8.2	6	10.2	6	8.3	13	11.5
Yes	387	90.6	168	91.8	53	89.8	66	91.7	100	88.5
Medication for depression										
No	166	38.9	65	35.5	20	33.9	28	38.9	53	46.9
Yes	261	61.1	118	64.5	39	66.1	44	61.1	60	53.1
Time since diagnosis										
Less than 1 year	29	6.8	14	7.7	5	8.5	5	6.9	5	4.4
Between 1 and 5 years	141	33	59	32.2	24	40.7	23	31.9	35	31
More than 5 years	249	58.3	107	58.5	30	50.8	42	58.3	70	61.9

FIQR: Fibromyalgia Impact Questionnaire Revised; MVPA: moderate-to-vigorous PA. PA: Physical Activity. SF-36: 36-item Short-Form Health Survey. Common superscripts indicate significant differences at baseline between groups. Differences between groups for sedentary time, light PA and MVPA were analyzed using percentage of wear time spent in each intensity level.

┼ Greater scores indicate worse health status and higher pain; * Greater scores indicate better health status or lower pain

Exercise, disease impact, pain, and health-related quality of life: an intervention study

Study 6

SECTION 3

SECTION 3

Study 6

Effect of land- and water-based exercise on disease impact, pain, and health-related quality of life in women with fibromyalgia: the al-Ándalus quasi-randomized controlled trial.

Draft

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ABSTRACT

Objective: To assess the effects of 24 weeks of land- and water-based exercise on disease impact (primary outcome), pain, and health-related quality of life (HRQoL; secondary outcomes) in women with fibromyalgia and the persistence of changes in the outcomes at 12-week follow-up.

Methods: A total of 244 women with fibromyalgia were quasi-randomized to either land-based (*n*=80), water-based (*n*=79) or control group (*n*=85). The intervention groups performed multicomponent exercise (including aerobic, resistance, and flexibility exercise) for 24 weeks (3 days/week; 45-60-min/day). Participants were assessed at baseline, at week 24, and at week 36 (12 weeks after the end of the intervention). Disease impact was assessed with the revised version of the Fibromyalgia Impact Questionnaire (FIQR), pain through pressure pain threshold, the pain subscale of the FIQR, the bodily pain subscale of the 36-item Short-form health survey (SF-36) and a Visual Analog Scale, and HRQoL was assessed with the physical and mental components of the SF-36. Intention-to-treat (ITT) and per-protocol analyses (≥70 of attendance) were conducted.

Results: No differences in any group comparisons were observed for FIQR either after the intervention or at follow-up based on ITT or per-protocol analyses. At week 24, ITT analyses showed that the land-based exercise group worsened pressure pain threshold to a lesser extent (mean difference (MD) -4.08, 95% CI -7.39 to -0.77) and improved physical component of SF-36 (MD -2.32, 95% CI -4.42 to -0.23) while water-based exercise group improved mental component of SF-36 (MD -5.67, 95 % CI -9.56 to -1.79) compared to the control group (all, $P<0.05$). At week 36, the water-based exercise group improved mental component of SF-36 (MD 4.29, 95 % CI 0.59 to 8.18) compared to the control group and pressure pain threshold (MD -3.28, 95 % CI 0.25 to 6.30) compared to land-based exercise group (all, $P<0.05$). Per-protocol analyses at week 24 showed improvements in the land-based group for bodily pain (MD -6.1, 95 % CI -12.0 to -0.2), physical (MD -2.9, 95 % CI -5.3 to -0.6), and mental component (MD -4.5, 95 % CI -8.6 to -0.3) of SF-36 compared to the control group (all, $P<0.05$) and no effects for water-based exercise. At week 36, land-based group improved VAS (MD 0.8, 95 % CI 0.0 to 1.6) and SF-36 bodily pain (MD -6.0, 95 % CI -11.9 to -0.2) compared to control group and bodily pain (MD -8.8, 95 % CI -15.9 to -1.8) and physical component of SF-36 (MD -4.5, 95 % CI -7.6 to -1.4) compared to water-based exercise group (all, $P<0.05$).

Conclusion: 24 weeks of land-or water-based multicomponent exercise did not improve disease impact in women with fibromyalgia. However, modest benefits in pain and physical HRQoL for land-based exercise were found that were consistent and persistent when a fair level of attendance was reached. Modest improvement for mental HRQoL in water based exercise were found, that persisted independently of adherence. Although unable to conclude the superiority of a setting, these findings support further research assessing the potential of land-based training in fibromyalgia as an easily accessible exercise modality.

INTRODUCTION

Fibromyalgia is a chronic disorder with a global prevalence of 2.7% that predominantly affects women[1]. Fibromyalgia is considered a central sensitivity syndrome in which there is a perception of pain from non-painful stimuli and greater pain than would be expected[2,3]. In addition to pain, wide-ranging symptoms such as fatigue, sleep disturbance, or cognitive difficulties are also common but not universal[2,4]. Patients with fibromyalgia experience significantly reduced health-related quality of life (HRQoL) and higher rates of service utilization[5], stressing the substantial clinical and economic burden of the disease.

Treatment strategies for the management of fibromyalgia include a variety of pharmacological and non-pharmacological therapies[6–8] with the aim of improving HRQoL[4]. Different institutions' guidelines are in agreement on the relevance of the first-line role of non-pharmacological approaches[4] being exercise the only "strong for" recommendation across guidelines[4,9]. A series of recent systematic reviews have demonstrated that aerobic[10], resistance[11], and flexibility training[12] improves HRQoL[10–12], physical function[10,11], and pain[10,11], among other health outcomes[10,11]. Which type of exercise or whether multicomponent exercise (this is, a combination of two or more types of exercise) provides greater benefits is still a matter of debate[4,13,14]. Multicomponent exercise could improve HRQoL, physical function, fatigue, stiffness[14], and depression[12] in fibromyalgia, yet these effects are still uncertain because of the very low-quality evidence obtained from very heterogeneous and insufficiently detailed trials[14].

Exercise therapy in fibromyalgia has been usually carried out in either land- or water-based settings. Although water-based exercise was initially considered to provide greater health improvements in this population[15,16], most recent evidence questions this idea[17,18]. Two meta-analyses comparing the effects of exercise in both settings concluded that similar results for overall well-being, physical function, pain, stiffness[17], and fatigue[19] are obtained in both conditions and only a moderate difference in strength favoring land-based training was detected[17]. Intervention studies published at a later time that also aimed to compare land- and water-based exercise found similar benefits between both contexts in terms of pain and function[18] or greater benefits in water-based settings for physical and psychological health[20], functional capacity, pain and flexibility[21]. So far, a number of limitations such as the small size and limited duration of interventions, the absence of a control group, or unequalled exercise protocols, preclude establishing superiority of a setting.

Evaluating the persistence of exercise effects is relevant but have only recently begun to be investigated in fibromyalgia. To date, two meta-analyses have examined the follow-up effect of exercise after land-[14] or water-based exercise[17] in this group of patients. After land-based exercise, HRQoL, fatigue, and physical function improvement were found to persist at 6 to 52 or more weeks post intervention but improvements in stiffness and pain did not[14]. Evidence regarding long-term effects of water-based exercise is more limited and inclconclusive[17]. Other reviews, however, suggested that water-based exercise-induced improvements in physical function, pain and mood may continue for up to two years[22]. The long-term benefits of exercise are still imprecise due to lack of follow-up, limited length of follow-up, or limited follow-up phase information in previous research[14].

Despite the generally agreement on the benefits of exercise in fibromyalgia, there is no consensus on the precise exercise regimes to optimize these improvements[12,14]. Accurately reported interventions studies[23,24] with adequate sample sizes, longer duration of exercise intervention and follow-up are needed to ascertain the effects of multicomponent exercise, the advantages of land- and water-based settings, and the persistence of exercise effects. The aim of this study was to assess the influence of 24 weeks of land- and water-based exercise on overall disease impact (primary outcome), pain, and HRQoL (secondary outcomes) in women with fibromyalgia. The persistence of changes in the outcomes at 12-week follow-up was also analyzed.

METHODS

Study design and protocol registration

The study design and procedures are described in detail elsewhere[25]. The present study was registered as a 24-week randomized controlled exercise trial with a 12-week follow-up (ClinicalTrials.gov ID: NCT01490281), although a strict randomized design was not finally possible (see section *Allocation and blinding*). The full trial protocol can be consulted elsewhere[25]. The Medical Ethics Committee of Hospital Virgen de las Nieves (Granada, Spain) approved the study design, study protocols and informed consent procedure. All participants provided a written informed consent.

Participants recruitment and eligibility criteria

Participants for this multicenter project were recruited from local associations of fibromyalgia patients in 7 out of the 8 provinces of Andalusia (Southern Spain). The recruitment was coordinated with the Fibromyalgia Andalusian Federation with a total of 10 local associations collaborating in the project. Participants were contacted via e-mail, letter, telephone, and internet advertisement. Before starting the study, a screening was performed of all candidates. The inclusion and exclusion criteria for the study are shown in Supplementary Table 1.

Allocation and blinding

Initially, this study was designed as a randomized control trial. However, randomization was not feasible in some provinces because of difficulties to find adequate pools (chest-high, ~30°C, with capacity for at least 10 participants) at all locations of the study. Finally, randomization was limited to one province (n=79; 32.4% of participants) and participants in other provinces were allocated to exercise or control group depending on the possibility to access appropriate facilities. After baseline measurements, randomization was performed via computer-generated random sequence by V.S.J. into three groups: land-based exercise, water-based exercise, or usual care (control). Participants were assigned to interventions by I.A.G. As these were exercise interventions, participants blinding was not possible. All the baseline and follow-up examinations were performed at local associations of fibromyalgia patients or sport facilities. Only part of the research team was blinded to group allocation during evaluations.

Sample size

The required sample size was determined for the primary outcome variable, i.e. overall score of Fibromyalgia Impact Questionnaire (FIQ)[26]. The sample size procedure has been described elsewhere[25]. Assuming a maximum loss of follow-up of 30%, we planned to recruit a total of 180 women with fibromyalgia (60 per group at baseline).

Procedures

Outcome assessments were conducted at baseline, at the end of the exercise intervention (24 weeks) and after 12 weeks of training cessation (follow up). Participants were requested not to start any structured and supervised exercise program or therapy during the follow-up period. The assessments were carried out in two alternate days. On day one, inclusion criteria were confirmed including tender points examination according to the American College of Rheumatology (ACR)[27]. Anthropometry and body composition were also evaluated, and participants filled out self-reported sociodemographic and clinical data questionnaires. Disease impact, self-reported pain, and HRQoL questionnaires were given to patients to be completed at home. Two days later, questionnaires were collected and checked by the research team. This article follows the CONSORT statement[28] (supplementary table 2).

Intervention groups

Throughout their participation in the study, all participants continued to receive the standard care (mostly, pharmacological treatment) provided by their health care providers.

Exercise interventions

The interventions were performed in 17 waves between the months of November-December and April-May between 2011 and 2013. All training sessions were conducted in fitness centers or patient associations facilities supervised face-to-face by certified Sport Sciences professionals. There were no other home program or non-exercise components. Patients were organized in groups of 7–15 women, each one supervised by the same instructor throughout the exercise intervention. The instructors performed a program-specific training before the intervention. Moreover, to standardize implementation of the intervention, a manual of operations was developed, which provided the program with all the sessions and detailed guidelines. A total of 13 instructors monitored 17 different exercise groups in 9 cities.

The land- and water-based exercise groups trained three non-consecutive days/week (45-60 min per session) for a 24-week period (72 sessions in total) following the same exercise protocol. The intervention aimed at improving cardiorespiratory fitness, muscle strength, and joint range of motion, which are inversely associated with disease impact[29] and fibromyalgia symptomatology[30–36]. The exercise interventions initially planned met the minimum training standards of the American College of Sports Medicine (ACSM) for patients with fibromyalgia[37]. To maximize replicability, the al-Ándalus trial is described following the Consensus on Exercise Reporting Template (CERT)[38] in supplementary table 3.

A detailed summary of the general principles for exercise prescription (type, duration, frequency, intensity, volume and mode of exercise) for each session is included in **table 1**. More information

Table 1. Summary of the exercise progression planned for the al-Ándalus trial

Month 1 Session duration: 45-50 min │F: 3d/week					
Session structure	**Type**	**1st Week** I: 6-11 RPE	**2nd week** I: 6-11 RPE	**3rd week** I: 8-12 RPE	**4th week** I: 8-12 RPE
Warm-up	Mobility	D:10 min	D:10 min	D:10 min	D:10 min
Conditioning	Muscle-strengthening	D: 15 min V: 1set 12rep M: 4 exercises: 2 upper body, 2 lower body I: 10 RPE	D: 15 min V: 1set 15rep M: 4 exercises: 2 upper body, 2 lower body I: 11 RPE	D: 15 min V: 1set 12rep M: 6 exercises: 3 upper body, 3 lower body I: 12 RPE	D: 15 min V: 1set 15rep M:6 exercises: 3 upper body, 3 lower body I: 12 RPE
	Aerobic	D: 15 min I: 40-50% HRR; 50-60% HRmax	D: 15 min I: 40-50% HRR; 50-60% HRmax	D: 15 min I: 45-50% HRR; 55-60% HRmax	D: 15 min I: 45-55% de HRR; 55-60% HRmax
Cool-down	Stretching and relaxation	D:5 min	D:10 min	D:10 min	D:10 min
Month 2 Session duration: 50 min │F: 3d/week					
Session structure	**Type**	**1st Week** I: 9-12 RPE	**2nd week** I: 9-12 RPE	**3rd week** I: 9-13 RPE	**4th week** I: 9-13 RPE
Warm-up	Mobility	D:10 min	D:10 min	D:10 min	D:10 min
Conditioning	Muscle-strengthening	D: 15 min V: 2 sets x 8 reps M: 6 exercises: 3 upper body, 3 lower body I: 12 RPE	D: 15 min V: 2 sets x 10 reps M: 6 exercises: 3 upper body, 3 lower body I: 13 RPE	D: 15 min V: 2 sets x 12 reps M: 6 exercises: 3 upper body, 3 lower body I: 13 RPE	D: 15 min V: 2 sets x 14 reps M: 6 exercises: 3 upper body, 3 lower body I: 13 RPE
	Aerobic	D: 15 min I: 50-60% HRR; 60-70% HRmax	D: 15 min I: 50-60% HRR; 60-70% HRmax	D: 15 min I: 50-60% HRR; 60-70% HRmax	D: 15 min I: 50-60% HRR; 60-70% HRmax
Cool-down	Stretching and relaxation	D: 10 min	D: 10 min	D: 10 min	D: 10 min
Month 3 Session duration: 55 min │F: 3d/week					
Session structure	**Type**	**1st Week** I: 10-13 RPE	**2nd week** I: 10-13 RPE	**3rd week** I: 10-14 RPE	**4th week** I: 10-14 RPE
Warm-up	Mobility	D:10 min	D:10 min	D:10 min	D:10 min
Conditioning	Muscle-strengthening	D: 15 min V: 3 sets x 8 reps M: 6 exercises: 3 upper body, 3 lower body I: 13 RPE	D: 15 min V: 3 sets x 10 reps M: 6 exercises: 3 upper body, 3 lower body I: 13 RPE	D: 15 min V: 3 sets x 12 reps M: 6 exercises: 3 upper body, 3 lower body I: 14 RPE	D: 15 min V: 3 sets x 14 reps M: 6 exercises: 3 upper body, 3 lower body I: 14 RPE
	Aerobic	D: 20 min I: 50-60% HRR; 60-70% HRmax	D: 20 min I: 50-60% HRR; 60-70% HRmax	D: 20 min I: 50-60% HRR; 60-70% HRmax	D: 20 min I: 50-60% HRR; 60-70% HRmax
Cool-down	Stretching and relaxation	D: 10 min	D: 10 min	D: 10 min	D: 10 min

Month 4 Session duration: 55 min │ F: 3d/week					
Session structure	**Type**	**1st Week** I: 11-14 RPE	**2nd week** I: 11-14 RPE	**3rd week** I: 11-15 RPE	**4th week** I: 11-15 RPE
Warm-up	Mobility	D:10 min	D:10 min	D:10 min	D:10 min
Conditioning	Muscle-strengthening	D: 15 min V: 3 sets x 8 reps M: 8 exercises: 4 upper body, 4 lower body I: 14 RPE	D: 15 min V: 3 sets x 10 reps M: 8 exercises: 4 upper body, 4 lower body I: 14 RPE	D: 15 min V: 3 sets x 12 reps M: 8 exercises: 4 upper body, 4 lower body I: 15 RPE	D: 15 min V: 3 sets x 14 reps M: 8 exercises: 4 upper body, 4 lower body I: 15 RPE
	Aerobic	D: 20 min I: 55-65% HRR; 65-75% HRmax	D: 20 min I: 55-65% HRR; 65-75% HRmax	D: 20 min I: 55-65% HRR; 65-75% HRmax	D: 20 min I: 55-65% HRR; 65-75% HRmax
Cool-down	Stretching and relaxation	D: 10 min	D: 10 min	D: 10 min	D: 10 min
Month 5 Session duration: 60 min │ F: 3d/week					
Session structure	**Type**	**1st Week** I: 12-15 RPE	**2nd week** I: 12-15 RPE	**3rd week** I: 12-16 RPE	**4th week** I: 12-16 RPE
Warm-up	Mobility	D:8 min	D:8 min	D:8 min	D:8 min
Conditioning	Muscle-strengthening	D: 17 min V: 3 sets x 8 reps M: 10 exercises: 5 upper body, 5 lower body I: 15 RPE	D: 17 min V: 3 sets x 10 reps M: 10 exercises: 5 upper body, 5 lower body I: 15 RPE	D: 17 min V: 3 sets x 10 reps M: 10 exercises: 5 upper body, 5 lower body I: 16 RPE	D: 17 min V: 3 sets x 12 reps M: 10 exercises: 5 upper body, 5 lower body I: 16 RPE
	Aerobic	D: 25 min I: 55-65% HRR; 65-75% HRmax	D: 20 min I: 55-65% HRR; 65-75% HRmax	D: 20 min I: 55-65% HRR; 65-75% HRmax	D: 20 min I: 55-65% HRR; 65-75% HRmax
Cool-down	Stretching and relaxation	D: 10 min	D: 10 min	D: 10 min	D: 10 min
Month 6 Session duration: 60 min │ F: 3d/week					
Session structure	**Type**	**1st Week** I: 13-16 RPE	**2nd week** I: 13-16 RPE	**3rd week** I: 13-17 RPE	**4th week** I: 13-17 RPE
Warm-up	Mobility	D:8 min	D:8 min	D:8 min	D:8 min
Conditioning	Muscle-strengthening	D: 17 min V: 3 sets x 12 reps M: 10 exercises: 5 upper body, 5 lower body I: 16 RPE	D: 17 min V: 3 sets x 14 reps M: 10 exercises: 5 upper body, 5 lower body I: 16 RPE	D: 17 min V: 3 sets x 14 reps M: 10 exercises: 5 upper body, 5 lower body I: 17 RPE	D: 17 min V: 3 sets x 116 reps M: 10 exercises: 5 upper body, 5 lower body I: 17 RPE
	Aerobic	D: 25 min I: 55-70% HRR; 65-80% HRmax	D: 25 min I: 55-70% HRR; 65-80% HRmax	D: 25 min I: 55-70% HRR; 65-80% HRmax	D: 25 min I: 55-70% HRR; 65-80% HRmax
Cool-down	Stretching and relaxation	D: 10 min	D: 10 min	D: 10 min	D: 10 min

D: Duration; I: Intensity; F: Frequency; HRR: Heart rate reserve; HRmax: maximum heart rate; M: Mode; rep: repetition; RPE: rating of perceived exertion; V: Volume; More details about the general principles of exercise prescription considered in the design of the program is included in supplementary material.

about the rationale behind the design of the exercise program is included in supplementary material. Briefly, each session duration ranged from 45 min (week 1) to 60 min (week 24) and was divided into the following parts: warm up (8-10 min), conditioning [muscle-strengthening (15-17 min) and aerobic (15-25 min)], and cool-down (10 min). Warm-up included mobility exercises and global movements to increase body temperature and blood flow. Muscle-strengthening training ranged from 1 set of 12 repetitions of 4 exercises (week 1) to 3 sets of 16 repetitions of 10 exercises (week 24) including mayor muscle groups exercises in circuit. Aerobic exercise ranged from 40-50% Heart Rate Reserve (HRR); 50-60% maximum heart rate (HRmax; week 1) to 55-70%HRR; 65-80%HRmax (week 24), involving low-impact exercises of large muscle groups. Cool-down included active and static stretching (to the point of gentle tension) and relaxation. Exercise progression was achieved by increasing firstly volume and finally, increasing intensity or load. Exercises were modified or adapted if exacerbation of symptoms was experienced. The program was tailored to the individual depending on the severity of fibromyalgia by means of perceived exertion (RPE). Borg's conventional scale (6-20 point)[39] was used. Each participant indicated global RPE after each session. Heart rate was also controlled using a monitor (Polar RCX-3) that was worn by a subsample in each group of three alternating participants in every three sessions.

Land-based exercise adaptations

Some exercises were initially adapted to be performed seated during the first weeks. Afterwards, participants were encouraged to perform the exercises in an upright position. Sports rubber band and light dumbbells (0.5-2kg) were gradually included to increase the load and achieve the established RPE.

Water-based exercise adaptations

The water-based exercise intervention group trained in chest-high warm (~30°C) pool. The same exercise intervention program than land-based, adapted to the restrictions and peculiarities imposed by water, was used. The training intensity and the muscle groups activated were maintained as similar as possible in the two intervention modalities. The muscle-strengthening and aerobic exercises were performed at a slow pace using water and aquatic materials as resistance or aids. Stretching was adapted to stand position and relaxation was performed in flotation.

Usual care group (control)

Participants assigned to the usual care wait-list control condition, received general information about fibromyalgia and general advice about the positive effects of being physically active. Informative pamphlets describing the benefits of physical activity and general guidelines about how to increase the daily physical activity levels were delivered. After the follow-up assessment, these participants were invited to participate in the exercise program.

Participant retention and adherence

Attendance and reasons for non-attendance each session were recorded by instructors. To maximize adherence, several strategies were implemented including music in all sessions, individualized attention and telephone calls following missed sessions.

Outcome Measures

Primary outcome: overall disease impact

The Spanish version of the revised version of the Fibromyalgia Impact Questionnaire (FIQR) was used[26,40]. The FIQR is a self-administered questionnaire, composed of 21 individual questions that assess disease impact through a wide range of symptoms and comorbidities related to this condition. The total score ranges from 0 to 100, with a higher score indicating greater impact of the syndrome on an individual's life.

Secondary outcomes measures

Pain-related measures

The pressure pain threshold was defined as the average pressure threshold across the 18 fibromyalgia-related tender points[27]. A standard pressure algometer (FPK 20, Wagner Instruments) was used to assess the 18 tender points according to the ACR[27]. Two alternative measurements at each tender site were performed, and the mean score was recorded. The total count of positive tender points was also recorded.

Clinical pain intensity was assessed with the FIQR pain subscale[26,40]. Participants were asked to rate their level of pain in the past 7 days on a numeric rating scale (range 0–10), where higher values represent higher pain intensity.

Pain intensity at the moment was assessed with the visual analog scale (VAS) for pain. This is an assessment tool consisting of a 10 cm line with 0 on one end (representing no pain) and 10 on the other (representing the worst pain ever experienced). Participants marked to indicate the severity of their pain in the present moment.

Pain magnitude and interference were assessed with a dimension of the Short Form 36 health survey (SF-36)[41] named "SF-36 Bodily pain". Scores range 0 to 100, where a higher score represents lower pain magnitude and interference.

Health-related quality of life

The Spanish version of the 36-item Short-Form Health Survey (SF-36)[41] was used to assess HRQoL. The SF-36 is a generic instrument that has been demonstrated to have good reliability and validity in chronic pain patients[42]. It contains 36 items grouped into 8 dimensions and 2 summary components: the physical and the mental summary components. Only the 2 summary components were used to describe HRQoL for the present study, which scores range from 0 (worst possible health status) to 100 (the best possible health status).

Other variables

All 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, and analgesics and antidepressant consumption. Weight (kg) was measured with a bioimpedance device (InBody R20, Seoul, Korea), height (m) was measured using a stadiometer (Seca 22, Hamburg, Germany), and body mass index (BMI) was calculated (kg/m^2).

Statistical analyses

The normal distribution of the main study variables was assumed due to the relatively large sample size. Descriptive continuous data are presented as mean and standard deviation, whereas categorical data are presented as n and percentage. Simple imputations were performed to complete missing values at baseline (<1%). Between-groups baseline characteristics were compared with the Student t-test for continuous variables and the Chi square test for categorical variables. Student t-tests were also used to assess differences between exercise groups in average RPE and %HRmax for each week and the whole program. To determine the influence of exercise on the outcomes, one-way analysis of covariance (ANCOVA) was conducted. The mean change (post minus baseline values) was inserted as dependent variable, the group as fixed factor, and age, pressure pain threshold, educational level at baseline along with the corresponding baseline value of the outcome were entered as covariates. The same procedure was used to analyze the persistence of the changes at follow-up, including follow-up minus baseline values as the dependent variable. Although other physical or psychological treatment was not allowed during the intervention, the participation in occasional physical therapy (yes/no) was collected by the research team and included as an additional covariate in further analysis.

The primary analyses were performed using the intention-to-treat (ITT) principle. Multiple imputation by chained equations (MICE) methodology was used for imputing missing values at week 24 and 36. This was implemented with the statistical software "R v3.6", using the "mice v3.7"[43] and "VIM v4.8"[44] libraries. To assess the efficacy of the exercise programs, per-protocol analyses were additionally carried out including only those participants attending at least 70% of sessions. To assess the robustness of the results, all analyses were replicated using complete-case analyses (sensitivity analyses). 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 Statistical Package for the Social Sciences (International Business Machines (IBM) SPSS Statistics for Windows, Version 22.0. Armonk, NY, USA: IBM Corp) was used for all the analyses. The statistical significance was set at $P<0.05$.

RESULTS

Among the potential participants that were initially contacted, a total of 270 women with fibromyalgia were invited to participate. The flowchart of the study participants throughout the trial is presented in Figure 1. A total of 244 patients volunteered to participate, met the inclusion criteria, signed informed consent, and were assigned to either the land-based exercise group (n=79), the water-based exercise group (n=80), or the control group (n = 85). The mean attendance was 70.4% and 66.6% of the sessions in the land- and water-based exercise groups, respectively. A total of 50 participants (63.3%) in the land-based group and a total of 42 participants (52.5%) in the water-based group attended ≥70% of the sessions and were included in per-protocol analyses. A total of 12 (15.19%), 16 (20%), and 17 (20%) participants were lost to follow-up at week 24 in the land-based, water-based and control groups, respectively. A total of 17 (21.5%), 18 (22.5%), and 16 (18.8%) participants were lost to follow-up at week 36 in the land-based, water-based and control groups, respectively.

Supplementary figure 1 shows a graphical representation of RPE and HRmax values for each group across each week of the exercise program.

Table 2. Baseline descriptive characteristics of the study participants in the al-Ándalus trial

	All (*n*=244)		Land-based (*n*=79)		Water-based (*n*=80)		Control (*n*=85)		
	mean	(SD)	mean	(SD)	mean	(SD)	mean	(SD)	*P-value*
Age (years)	50.8	7.7	49.5 [a]	7.3	52.5	8.2 [a]	50.4	7.3	**0.038**
BMI (kg/m^{2})	28.6	5.6	27.7	5.3	29.5	5.6	28.4	5.9	0.135
FIQR total (0-100)†	65.5	15.8	66	16.1	63	15.2	67.4	16.1	0.184
FIQR pain (0-10)†	7.7	1.8	7.5	1.9	7.7	1.6	7.8	1.8	0.523
SF-36 Bodily pain (0-100)*	20.1	13.8	19.2	14	22	14.2	19.1	13	0.330
Algometry: tender point count (0-18)†	17.1	1.7	17.1	1.5	17.4 [a]	1.3	16.8 [a]	2	**0.040**
Algometry: pressure-pain threshold, kg/cm^2 (0-144)*	39.6	12.7	39.1	12.5	36.4 [a]	11.2	43.1 [a]	13.3	**0.002**
Visual Analogic Scale – Pain (0-10)†	6.3	2.1	6.5	1.9	5.9	2.1	6.6	2.3	0.121
SF-36 Physical Component Summary (0-100)*	29.6	6.8	29.6	6.5	30.2	5.4	29	8.3	0.173
SF-36 Mental Component Summary (0-100)*	34.1	12.2	33.4	12.3	34.7	11.1	34.2	13.2	0.214
Time since diagnosis									
Less than 1 year	19	7.8	6	7.6	6	7.5	7	8.2	
Between 1 and 5 years	94	38.5	33	41.8	33	41.3	28	32.9	0.764
More than 5 years	131	53.7	40	50.6	41	51.2	50	58.8	
	n	%	n	%	n	%	n	%	*P-value*
Marital status (n, %)									
Married	180	73.8	60	75.9	60	75	60	70.6	0.704
Not married	64	26.2	19	24.1	20	25	25	29.4	
Educational level (n, %)									
Non-universitary	214	87.7	63[b]	79.7	77[a,b]	96.3	74[a]	87.1	**0.006**
Universitary	30	12.3	16	20.3	3	3.8	11	12.9	
Occupational status (n, %)									
Working full/part time	59	24.2	20	25.3	16	20	23	27.1	0.548
Unemployed/Retired/Housekeeper	185	75.8	59	74.7	64	80	62	72.9	
Current menstruation (n, %)									
Yes	78	32	27	34.2	21	26.3	30	35.3	0.404
No	166	68	52	65.8	59	73.8	55	64.7	
Analgesics consumption (n,%)									
Yes	220	90.2	71	89.9	71	88.8	78	91.8	0.805
No	24	9.8	8	10.1	9	11.3	7	8.2	
Antidepressant consumption (n,%)									
Yes	147	60.2	47	59.5	50	62.5	50	58.8	0.878
No	97	39.8	32	40.5	30	37.5	35	41.2	

BMI: Body Mass Index; FIQR: Revised Fibromyalgia Impact Questionnaire; SF-36: 36-item Short Form Health Survey.

Statistically significant differences are highlighted in bold. Common superscripts indicate significant differences between groups with the same letter

† Greater scores indicate worse health status or higher pain

* Greater scores indicate better health status and lower pain

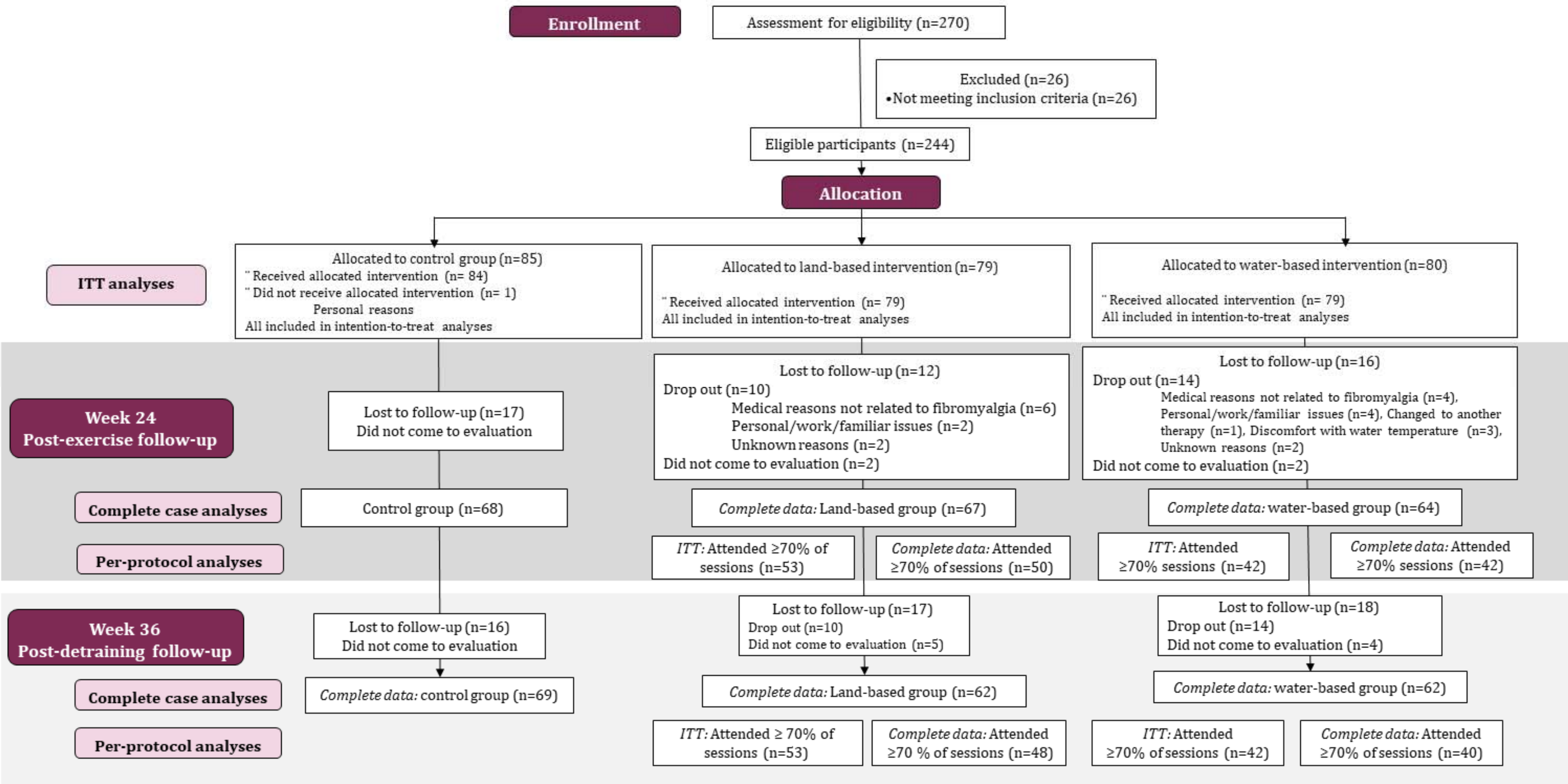

Figure 1. Flow chart of the study participants throughout the al-Ándalus trial

ITT: Intention-to-treat. Per-protocol analyses included participants with an attendance of at least 70% to all sessions.

The mean RPE was 12.1 ± 1.6 and 11.7 ± 1.6 points, the mean HR was 101.3 ± 8.6 and 91.2 ± 9.0 beats per minute, and the mean %HRmax was 58.5 ± 5.2 and 53.3 ± 5.3 in the land- and water-based groups, respectively. Supplementary table 8 and Supplementary table 9 include a comparison of RPE and %HRmax values between land- and water-based groups across all weeks. No differences between groups were found for average RPE and differences in %HRmax between land- and water-based (mean difference=-5.2 units, Standard Error=0.9, *P*<0.001). One adverse event related to an allergic reaction to water was reported. A total of 12 women (8 in land-based and 4 in water-based interventions) took part in occasional physical therapy.

Table 2 shows the baseline descriptive characteristics of the study participants. The water-based exercise group presented differences compared to the land-based group for age (mean difference (MD) 3.0 years, *P*=0.041), and compared to the control group for tender point count (MD 0.65 units; *P*=0.034) and pressure pain threshold (MD -6.74 units; *P*=0.002). The number of participants in the water-based exercise group with non-university studies (96.3%) was higher compared to control (87.1%) or land-based exercise group (79.7%). No significant differences between groups at baseline were observed in other variables (*P*>0.05).

Table 3 shows ITT analyses assessing the differences between groups in post-intervention changes (week 24) in the outcomes. No significant differences between groups in any of the comparisons (either interventions vs. control group or land- vs. water-based groups) were found for disease impact. The land-based exercise group worsened pressure pain threshold to a lesser extent (MD -4.08 units; 95% Confidence Interval (CI) -7.39 to -0.77; *P*=0.010; *Cohen's d*=0.46) and improved physical component of SF-36 (MD -2.32 units; 95%CI -4.42 to -0.23; *P*=0.024; *Cohen's d* =0.42) compared to the control group. The water-based exercise group improved mental component of SF-36 (MD -5.67 units; 95% CI -9.56 to -1.79; *P*=0.002; *Cohen's d*=0.54) compared to the control group. No significant differences between groups were found for other comparisons. Results remained unchanged when additionally adjusting for occasional attendance to physical therapy. When considering participants with complete data (supplementary table 4), no differences were observed in physical component of SF-36 between land-based and control groups (MD -1.90 units; 95% CI -4.29 to -0.49; *P*=0.169).

Table 4 shows ITT analyses assessing the differences between groups for changes at follow-up (week 36). No significant differences between groups in any of the comparisons (either interventions vs. control group or land- vs. water-based groups) were found for disease impact. The water-based exercise group improved mental component SF-36 (MD 4.29 units; 95 % CI 0.59 to 8.18; *P*=0.017; *Cohen's d* =0.44) compared to the control group and pressure pain threshold (MD -3.28 units; 95 % CI 0.25 to 6.30; *P*=0.029; *Cohen's d* =0.42) compared to land-based exercise group. No significant differences between groups were found for other comparisons. Results remained generally unchanged when additionally adjusting for attendance to physical therapy program except for the additional significant differences between water- and land-based exercise groups in mental component of SF-36 (MD -3.94 units; 95% CI -7.85 to -0.02; *P*=0.048; *Cohen's d*=0.39).

When considering participants with complete data only (supplementary table 5) no differences were observed in the mental component of SF-36 between water-based and control groups (MD 3.38 units; 95 % CI -0.77 to 7.53; *P*=0.152*)*.

Table 5 shows per-protocol analyses assessing the differences between groups in post-intervention changes (week 24) in the outcomes for participants attending at least 70% of the sessions. No significant differences between groups in any of the comparisons (either interventions vs. control group or land- vs. water-based groups) were found for disease impact. The land-based exercise group improved bodily pain of SF-36 (MD -6.96 units; 95% CI -11.96 to -0.17; *P*=0.041; *Cohen's d* =0.43), physical component of SF-36 (MD -2.94 units; 95% CI -5.27 to -0.60; *P*=0.008; *Cohen's d* =0.52), and mental component of SF-36 (MD -4.45 units; 95 % CI -8.55 to -0.34; *P*=0.029; *Cohen's d* =0.46) compared to the control group. No significant differences between groups were found for other comparisons. Results remained generally unchanged when additionally adjusting for attendance to physical therapy program except for the non-significant differences between control vs land-based groups in mental component of SF-36 (*P*=0.071). When considering participants with complete data only (supplementary table 6), land-based exercise group improved pressure pain threshold (MD -4.72 units; 95 % CI -8.64 to -0.79; *P*=0.013; *Cohen's d*=0.54) compared to the control group.

Table 6 shows per-protocol analyses assessing the differences between groups for changes at follow-up (week 36) for participants attending at least 70% of the sessions. No significant differences between groups in any of the comparisons (either interventions vs. control group or land- vs. water-based groups) were found for disease impact. The land-based exercise group reduced VAS-pain (MD 0.815 units; 95% CI 0.03 to 1.60; *P*=0.041; *Cohen's d*=0.14) and improved bodily pain of SF-36 (MD 6.00 units; 95% CI 0.16 to 11.85; *P*=0.042; *Cohen's d*=0.43) compared to the control group. In addition, land-based exercise group improved physical component of SF-36 (MD 4.46 units; 95% CI 1.36 to 7.57; *P*=0.002; *Cohen's d*=0.51) and bodily pain of SF-36 (MD 8.81 units; 95% CI 1.77 to 15.85; *P*=0.009; *Cohen's d*=0.59) compared to the water-based group. No significant differences between groups were found for other comparisons. Results remained generally unchanged when additionally adjusting for attendance to physical therapy program except for the significant difference between control and land-based exercise groups in VAS-pain (*P*=0.071). When considering participants with complete data only (supplementary table 7), no differences were observed in VAS-pain between land-based and control groups (MD -0.68 units; 95% CI -1.56 to 0.19;*P*=0.180*)*.

Table 3. Mean change (week 24 minus baseline) and differences between groups in the mean change for disease impact, pain, and quality of life following exercise: intention to treat analyses

	Land (n=79)		Water (n=80)		Control (n=85)		Control vs Land			Control vs Water			Water vs Land		
	Mean	(95% CI)	Mean	(95% CI)	Mean	(95% CI)	Mean	(95% CI)	*P*	Mean	(95% CI)	*P*	Mean	(95% CI)	*P*
FIQR total†	-6.0	(-9.1, -3.0)	-4.7	(-7.8, -1.6)	-4.31	(-7.3, -1.4)	1.7	(-3.5, 6.9)	1.000	0.4	(-5.0, 5.8)	1.000	1.3	(-4.1, 6.7)	1.000
Pressure-pain threshold *	-5.3	(-7.2, -3.3)	-8.0	(-10.0, -6.0)	-9.3	(-11.2, -7.5)	**-4.1**	**(-7.4, -0.8)**	**0.010**	-1.4	(-4.7, 2.0)	1.000	-2.7	(-6.2, 0.7)	0.172
VAS - pain†	-0.4	(-0.8, 0.1)	-0.6	(-1.0, -0.1)	-0.4	(-0.8, 0.1)	0.0	(-0.7, 0.8)	1.000	0.2	(-0.6, 1.0)	1.000	-0.2	(-1.0, 0.6)	1.000
FIQR pain†	-0.5	(-0.9, -0.1)	-0.9	(-1.3, -0.5)	-0.5	(-0.9, -0.2)	0.0	(-0.7, 0.7)	1.000	0.4	(-0.3, 1.1)	0.618	-0.4	(-1.1, 0.3)	0.590
SF-36 Bodily pain*	6.0	(2.9, 9.2)	6.9	(3.7, 10.1)	3.6	(0.5, 6.6)	-2.5	(-7.8, 2.9)	0.799	-3.3	(-8.8, 2.2)	0.447	0.8	(-4.7, 6.4)	1.000
SF-36 PCS*	2.9	(1.7, 4.2)	2.0	(0.8, 3.3)	0.6	(-0.6, 1.8)	**-2.3**	**(-4.4, -0.2)**	**0.024**	-1.4	(-3.6, 0.7)	0.347	-0.9	(-3.1, 1.3)	0.934
SF-36 MCS*	2.6	(0.4, 4.8)	5.9	(3.6, 8.1)	0.2	(-2.0, 2.4)	-2.4	(-6.2, 1.4)	0.393	**-5.7**	**(-9.6, -1.8)**	**0.002**	3.3	(-0.7, 7.2)	0.137

Analyses of covariance after Bonferroni's correction. Outcome at baseline, age, pressure-pain threshold (except for when it was the outcome), and educational level at baseline were included as covariates in all the analyses. Missing values were imputed using multiple imputation by chained equations. When considering participation in occasional physical therapy as an additional covariates results remained unchanged. CI: Confidence Interval; FIQR: Revised Fibromyalgia Impact Questionnaire; MCS: Mental Component Summary; PCS: Physical Component Summary; SF-36: 36-item Short-form Health survey; VAS: Visual Analogic Scale. † Greater scores indicate worse health status or higher pain * Greater scores indicate better health status and lower pain.

Table 4. Mean change (week 36 minus baseline) and differences between groups in the mean change for disease impact, pain, and quality of life at follow-up: intention to treat analyses

	Land (n=79)		Water (n=80)		Control (n=85)		Control vs Land			Control vs Water			Water vs Land		
	Mean	(95% CI)	Mean	(95% CI)	Mean	(95% CI)	Mean	(95% CI)	*P*	Mean	(95% CI)	*P*	Mean	(95% CI)	*P*
FIQR total†	-1.6	(-4.6, 1.3)	-5.1	(-8.1, -2.1)	-3.9	(-6.7, -1.0)	-2.2	(-7.3, 2.8)	0.845	1.2	(-4.0, 6.4)	1.000	-3.4	(-8.7, 1.8)	0.341
Pressure-pain threshold *	-11.5	(-13.2, -9.8)	-8.3	(-10.0, -6.5)	-9.7	(-11.4, -8.1)	1.8	(-1.1, 4.7)	0.411	-1.5	(-4.5, 1.5)	0.705	**3.3**	**(0.3, 6.3)**	**0.029**
VAS - pain†	-0.4	(-0.8, 0.1)	-0.5	(-1.0, 0.0)	0.0	(-0.5, 0.4)	0.4	(-0.4, 1.1)	0.803	0.5	(-0.3, 1.3)	0.478	-0.1	(-0.9, 0.7)	1.000
FIQR pain†	-0.5	(-0.9, -0.1)	-0.9	(-1.3, -0.5)	-0.6	(-1.0, -0.2)	-0.1	(-0.8, 0.6)	1.000	0.3	(-0.5, 1.0)	1.000	-0.4	(-1.1, 0.3)	0.585
SF-36 Bodily pain*	4.6	(1.5, 7.7)	2.5	(-0.7, 5.6)	3.0	(0.1, 6.0)	-1.6	(-6.8, 3.6)	1.000	0.6	(-4.8, 5.9)	1.000	-2.2	(-7.6, 3.3)	1.000
SF-36 PCS*	1.1	(-0.3, 2.5)	-0.6	(-2.0, 0.8)	0.0	(-1.3, 1.4)	-1.1	(-3.4, 1.3)	0.836	0.6	(-1.8, 3.0)	1.000	-1.7	(-4.1, 0.8)	0.294
SF-36 MCS*	2.1	(-0.1, 4.3)	6.0	(3.7, 8.2)	1.6	(-0.6, 3.7)	-0.5	(-4.2, 3.2)	1.000	**-4.4**	**(-8.2, -0.6)**	**0.017**	3.9	(0.0, 7.7)	0.050

Analyses of covariance after Bonferroni's correction. Outcome at baseline, age, pressure-pain threshold (except for when it was the outcome), and educational level at baseline were included as covariates in all the analyses. Missing values were imputed using multiple imputation by chained equations. When considering attendance to occasional physiotherapy as a covariate same results were obtained except for the significant difference between water- and land-based exercise groups in SF36 MCS: *P*=0.048. CI: Confidence Interval; FIQR: Revised Fibromyalgia Impact Questionnaire; MCS: Mental Component Summary; PCS: Physical Component Summary; SF-36: 36-item Short-form Health survey; VAS: Visual Analogic Scale. † Greater scores indicate worse health status or higher pain * Greater scores indicate better health status and lower pain. Missing values were imputed using multiple imputation by chained equations.

Table 5. Mean change (week 24 minus baseline) and differences between groups in the mean change for disease impact, pain, and quality of life following exercise: per-protocol analyses (participants in the exercise groups were included if attendance ≥70%)

	Land (n=53)		Water (n=42)		Control (n=85)		Control vs Land			Control vs Water			Water vs Land		
	Mean	(95% CI)	Mean	(95% CI)	Mean	(95% CI)	Mean	(95% CI)	*p*	Mean	(95% CI)	*p*	Mean	(95% CI)	*p*
FIQR total†	-8.7	(-12.6, -4.8)	-6.4	(-10.8, -1.9)	-4.1	(-7.2, -1.0)	4.6	(-1.6, 10.7)	0.219	2.3	(-4.5, 9.0)	1.000	2.3	(-4.9, 9.6)	1.000
Pressure-pain threshold *	-6.2	(-8.6, -3.8)	-7.4	(-10.2, -4.6)	-9.9	(-11.8, -7.9)	-3.7	(-7.5, 0.1)	0.063	-2.5	(-6.7, 1.7)	0.472	-1.2	(-5.8, 3.4)	1.000
VAS - pain†	-0.6	(-1.1, 0.0)	-0.6	(-1.3, 0.0)	-0.4	(-0.8, 0.1)	0.2	(-0.7, 1.1)	1.000	0.3	(-0.7, 1.2)	1.000	-0.1	(-1.1, 1.0)	1.000
FIQR pain†	-0.7	(-1.2, -0.2)	-0.8	(-1.3, -0.2)	-0.5	(-0.9, -0.1)	0.2	(-0.6, 0.9)	1.000	0.2	(-0.6, 1.1)	1.000	-0.1	(-1.0, 0.8)	1.000
SF-36 Bodily pain*	9.8	(6.1, 13.6)	9.3	(5.0, 13.7)	3.8	(0.8, 6.8)	**-6.1**	**(-12.0, -0.2)**	**0.041**	-5.6	(-12.1, 1.0)	0.126	-0.5	(-7.6, 6.6)	1.000
SF-36 PCS*	3.5	(2.0, 5.0)	1.3	(-0.4, 3.0)	0.5	(-0.7, 1.7)	**-2.9**	**(-5.3, -0.6)**	**0.008**	-0.8	(-3.4, 1.8)	1.000	-2.1	(-5.0, 0.7)	0.200
SF-36 MCS*	4.7	(2.0, 7.3)	3.8	(0.8, 6.8)	0.2	(-1.9, 2.3)	**-4.5**	**(-8.6, -0.3)**	**0.029**	-3.6	(-8.2, 0.9)	0.169	-0.8	(-5.8, 4.1)	1.000

Analyses of covariance after Bonferroni's correction. Outcome at baseline, age, pressure-pain threshold (except for when it was the outcome), and educational level at baseline were included as covariates in all the analyses. Missing values were imputed using multiple imputation by chained equations. When considering participation in occasional physical therapy as an additional covariates results remained unchanged except for the non-significant differences between control vs land-based groups in SF-36 MCS (*P*=0.071) CI: Confidence Interval; FIQR: Revised Fibromyalgia Impact Questionnaire; MCS: Mental Component Summary; PCS: Physical Component Summary; SF-36: 36-item Short-form Health survey; VAS: Visual Analogic Scale. † Greater scores indicate worse health status or higher pain * Greater scores indicate better health status and lower pain.

Table 6. Mean change (week 36 minus baseline) and differences between groups in the mean change for disease impact, pain, and quality of life at follow-up: per-protocol analyses (participants in the exercise groups were included if attendance ≥70%)

	Land (n=53)		Water (n=42)		Control (n=85)		Control vs Land			Control vs Water			Water vs Land		
	Mean	(95% CI)	Mean	(95% CI)	Mean	(95% CI)	Mean	(95% CI)	*p*	Mean	(95% CI)	*p*	Mean	(95% CI)	*p*
FIQR total†	-4.3	(-7.9, -0.7)	-2.7	(-6.8, 1.4)	-3.7	(-6.5, -0.8)	0.6	(-5.1, 6.3)	1.000	-1.0	(-7.3, 5.3)	1.000	1.6	(-5.1, 8.3)	1.000
Pressure-pain threshold *	-11.8	(-13.8, -9.8)	-9.6	(-11.9, -7.2)	-10.2	(-11.8, -8.6)	1.6	(-1.6, 4.7)	0.686	-0.7	(-4.2, 2.8)	1.000	2.3	(-1.5, 6.0)	0.461
VAS - pain†	-0.9	(-1.4, -0.4)	0.0	(-0.6, 0.6)	-0.1	(-0.5, 0.4)	**0.8**	**(0.0, 1.6)**	**0.041**	-0.1	(-1.0, 0.8)	1.000	0.9	(-0.1, 1.9)	0.070
FIQR pain†	-0.5	(-1.0, -0.1)	-0.6	(-1.1, 0.0)	-0.6	(-1.0, -0.2)	0.0	(-0.8, 0.7)	1.000	0.0	(-0.9, 0.8)	1.000	0.0	(-0.9, 0.9)	1.000
SF-36 Bodily pain*	9.3	(5.6, 13.0)	0.5	(-3.8, 4.8)	3.3	(0.3, 6.3)	**-6.0**	**(-11.9, -0.2)**	**0.042**	2.8	(-3.7, 9.3)	0.895	**-8.8**	**(-15.9, -1.8)**	**0.009**
SF-36 PCS*	2.4	(0.7, 4.0)	-2.1	(-4.0, -0.2)	0.1	(-1.3, 1.4)	-2.3	(-4.9, 0.3)	0.097	2.2	(-0.7, 5.0)	0.213	**-4.5**	**(-7.6, -1.4)**	**0.002**
SF-36 MCS*	3.2	(0.5, 5.8)	3.3	(0.2, 6.3)	1.6	(-0.6, 3.7)	-1.6	(-5.8, 2.6)	1.000	-1.7	(-6.3, 2.9)	1.000	0.1	(-4.9, 5.1)	1.000

Analyses of covariance after Bonferroni's correction. Outcome at baseline, age, pressure-pain threshold (except for when it was the outcome), and educational level at baseline were included as covariates in all the analyses. Missing values were imputed using multiple imputation by chained equations. When considering attendance to occasional physiotherapy as a covariate same results were obtained except for the significant difference between control and land-based exercise groups in VAS-pain (*P*=0.071) CI: Confidence Interval; FIQR: Revised Fibromyalgia Impact Questionnaire; MCS: Mental Component Summary; PCS: Physical Component Summary; SF-36: 36-item Short-form Health survey; VAS: Visual Analogic Scale. † Greater scores indicate worse health status or higher pain * Greater scores indicate better health status and lower pain.

DISCUSSION

The main findings of the al-Ándalus trial suggest that, compared to a control group, 24 weeks of land- or water-based exercise did not improve overall disease impact (primary outcome) in women with fibromyalgia. When studying the influence on pain and HRQoL (secondary outcomes), ITT analyses showed that land-based exercise attenuated deterioration of pressure pain threshold observed in all groups and improved physical component of SF-36, while water-based exercise improved mental component of SF-36 compared to the control group. At follow-up, benefits in the water-based group persisted for mental component of SF-36 and additional improvements emerged for pressure pain threshold compared to the land-based group. When a minimum attendance (70%) was considered in per-protocol analyses, land-based exercise improved bodily pain, physical and mental components of SF-36 while water-based group showed no improvement for any outcome after the intervention. At follow-up, improvements in land-based exercise persisted for SF-36 bodily pain and physical component of SF-36 compared to the control and water-based groups and differences emerged for VAS compared to control group.

Previous literature directly comparing land- and water-based exercise in fibromyalgia[18,20,21,45–48] is restricted to comparisons between protocols as no usual care control group was included in the designs. Those studies comparing effects of exercise on overall FIQ[18,21,46] found similar improvements in land- and water-based groups when applying very different exercise protocols (aerobic exercise[18,46], strengthening exercises[21], or pilates[18]). The present study, including similar multicomponent exercise in land and water, showed no effect of exercise on disease impact in either setting compared to the control group and no differences between settings. These findings are in contrast with previous literature. A recent meta-analysis[14] showed that land-based or water-based multicomponent exercise interventions reduced FIQ total score in exercise groups compared to control group. This review included heterogeneous multicomponent exercise programs combining two or more type of exercise that could also greatly differ from our intervention protocol[14]. Interventions that are comparable to our program (supervised interventions, similar multicomponent exercise, and including usual care control group) are more limited, and studied the effects of exercise separately for each setting. Those available mostly observed improvements in FIQ after 12 weeks[49,50], 16 weeks[51], 18 weeks[52], 24 weeks[53–55] of training compared to a control group in land[49,52–55] and water[50,51]. Only one previous intervention did not find any improvement in FIQ scores after 12 weeks of exercise in water[56]. Several hypotheses might partially explain these discrepancies. First, relatively higher attendance rates were reported in previous studies (85-90%[49,53,54] vs ~ 69% in ours) that could have been reached due to the lower duration of the programs (up to 18 weeks[49–52]) or lower frequency of sessions (2/week) for studies of same duration (24 weeks[53–55]). Also, certain differences in the planned exercise intensity for aerobic exercise could be noted (60-70% to 75-85% HRmax[49,54,55] vs 50 to 80% of HRmax in ours). Importantly, our findings showed that patients exercised, on average, between 53.5 and 58.5% of HRmax, which is below the planned intensity. As none of the aforementioned studies reported intensity reached during the sessions, only planned data can be compared. In addition, exercise progression in previous studies was based only on increasing exercise intensity whereas our study increased first volume and later (and unsuccessfully), intensity. Indeed, there is evidence that higher intensity exercise might lead to better results in these patients as long as it remains below the pain and fatigue threshold[46]. Differences in exercise order between interventions (aerobic followed by strength[49,53,54] vs strength followed by aerobic in ours) could also be noted. Furthermore, the use of the FIQ (previous version of FIQR) that apply different weighting among domains of the questionnaire[40] and variations of the total score (up to 80 points in some studies excluding job-related items)[49,53,55] could also be argued to explain differences between studies.

Pain is considered the main symptom in fibromyalgia and different measures of this variable (pressure pain threshold, FIQR pain, VAS, and SF-36 bodily pain dimension) were analyzed. ITT analyses revealed that all groups worsened their pressure pain thresholds after the intervention but land-based exercise group did it to a lesser extent. Although previous studies have reported an improvement in algometry-measured variables after exercise[51,57], one study have also reported a similar worsening trend on pressure pain thresholds to that of the present study[58]. Our results indicate that worsening in pressure pain threshold was consistent across groups but not aligned with the improvement tendency observed in other pain-related variables. It could be hypothesized that patients in the first visit could be used to bear pain while in subsequent assessments, when they are trained in algometry, they are more capable to recognize pressure pain threshold at an earlier point. In addition, a number of limitations have been linked to tender point examination (e.g. extensive training required with difficulties to exert same force always[59]) that could lead to unreliable measures explaining our contradictory findings. In per-protocol analysis further differences in SF-36 bodily pain scores emerged, showing a post-intervention improvement in the land-based exercise vs control group that was sustained after the detraining period. Greater benefits of exercise in per-protocol analyses vs. ITT analyses have been previously described[57]. Previous multicomponent land-based exercise interventions have demonstrated an improvement in SF-36 bodily pain scores[49] or found no effect in this variable[53,55]. Improvement in the present study for SF-36 bodily pain occurred while an absence of effect on pain intensity VAS and FIQR pain scales. This could suggest that the studied exercise protocol had greater influence on perceived limitations due to pain (assessed in the SF-36) rather than pain intensity itself (assessed in VAS and FIQR scales). In addition, measures of pain such as VAS and FIQR pain could not have been sufficiently sensitive to therapeutic changes[56,57]. The effects on pressure pain threshold and SF-36 bodily pain were of a moderate magnitude and could not be considered clinically important[14]. The magnitude of the change in SF-36 bodily pain scores (6.1 points) is, however, in line with the results found in a previous meta-analysis (5.2 points)[14]. Although our findings do not suggest a consistent improvement in all pain-related measures, the potential of land-based exercise to positively influence pain when exercise protocol is constantly followed, must be recognized. Most effective approaches to chronic pain acknowledge this symptom as a biopsychosocial phenomenon in which exercise could influence through a wide range of mechanisms[60], including: biological (e.g. increased physical function, pain tolerance, induced analgesia, structural adaptations in the brain), psychological (e.g. reduced fear of movement, increased self-efficacy, reduced catastrophization) or social factors (e.g., group interaction)[60].

According to ITT analyses, physical component of SF-36 was improved in land-based and mental component of SF-36 in the water-based exercise groups compared to the control group. In per-protocol analyses, physical and mental components of SF-36 were improved in the land-based exercise group whereas water-based group showed no effects. These findings, along with the aforementioned for pain, suggest different health benefits and relationships with exercise adherence for each setting: while land-based exercise improved more consistently physical HRQoL as adherence is increased, water-based exercise was related to mental HRQoL regardless of compliance with exercise. A number of studies using multicomponent exercise have shown benefits in general SF-36 scores followed 12 weeks[49] and 24 weeks[53,54] of combined land-based exercise[49,53,54] whereas other 6-month exercise program found no effect on HRQoL[55]. Although other interventions found an effect of water-based exercise in physical and mental domains of HRQoL[56], we only observed inconsistent effect for mental component of SF-36. In line with our findings, some studies comparing water- and land-based exercise in fibromyalgia found more benefits in emotional aspects for water[45,46]. A recent metanalysis comparing exercise in both settings in this population[14] did not analyze mental health but suggested similar benefits of land- and water-based exercise for key fibromyalgia-symptoms and greater benefits in strength for land-based exercise[17]. This hypothesis could explain our findings related to more consistent improvements in physical HRQoL in the land-based exercise group. It must be bear in mind that immersion in warm water might provoke a slight increase in heart rate[46]. Therefore, if the intervention presented similar intensity in both setting, a slightly higher heart rate would be expected in the water-based program compared to the land-based program. However, water-based exercise group presented lower (-5.2%HRmax) than land-based exercise group while exercising, which indicates that intensity was considerably higher in land-based setting. Perceived effort was, however, similar in both conditions (~12 RPE). As warm-water could affect energy levels, the intensity at which exercise is performed and its perception might be affected[17]. Relaxation effects of warm water (due to weight-bearing, tactile, and thermal stimulation as well as the inertial effect of the movement[46,61]) could explain our results more related to mental health. Other aspects related to activity in the pool (e.g. acceptance of self-image, increased self-efficacy as more activities can be performed in water, increased social interactions in pool facilities) could also positively influence mental health to a greater extent in this setting.

Long-term benefits of exercise interventions in fibromyalgia are not well understood due to lack and limited follow-up in the interventions carried out so far[14]. On the basis of ITT analyses, effects of water-based exercise on mental component of SF-36 were sustained after a 12-week detraining period. However, these results were not consistent in per-protocol analyses. According to per-protocol analyses, among all the post-intervention changes observed in the land-based group, only SF-36 bodily pain improvements were maintained after detraining. Land-based group also showed differences in some outcomes at follow-up vs. water-based group. When trends for changes are checked, non-significant improvements in water-based group in bodily pain or physical component of SF-36 appeared after the intervention. However, these changes were lost at follow-up in contrast with the maintained gains in the land-based group. The heterogeneity in follow-up lengths from none (majority of studies) to 52 weeks in prior research hinders comparisons[14]. It has been concluded that pain reductions are not maintained at any follow-up length after multicomponent exercise interventions[14]. However, a strict detraining period including no exercise was not always considered during follow-up periods. Very limited evidence could suggest long-term effects on other outcomes such as FIQ, fatigue, and physical function[14], including studies with strict detraining[55]. Therefore, further research is needed to better understand the long-term effects of exercise benefits in fibromyalgia patients.

Some limitations need to be highlighted. The random allocation of participants was only partially kept due to difficulties related to facilities and instructors' availability. It is worth noting that trial quality may have a greater impact on treatment effect size than randomization alone, and non-randomized controlled studies of high quality can produce outcomes that approximate to those found in randomized controlled trials[62]. Also, adherence was relatively low compared to other intervention studies. This study has also some strengths: i) the exercise program is described following the CERT guidelines[38] to enhance replicability and follows ACSM guidelines for fibromyalgia[37], ii) the same exercise protocols were used in both settings to assure comparability of the programs, iii) several pain-related measures were measured, iv) the relatively higher sample size compared to previous studies of similar characteristics, and v) the inclusion of: a usual-care control group, effectiveness and efficacy analyses, and a follow-up phase, all traditionally lacking in previous research[14].

CONCLUSIONS

In conclusion, 24 weeks of land-or water-based multicomponent exercise did not improve disease impact in women with fibromyalgia. However, modest benefits in pain and physical HRQoL in land-based exercise and for mental HRQoL in water-based exercise were found. These improvements were more consistent and persistent at follow-up for land-based exercise when a fair level of attendance was reached, whereas benefits of exercise in warm water were independent of exercise adherence. These findings preclude to establish superiority of a setting, but support further research assessing the potential of land-based training in fibromyalgia as an easily accessible exercise modality.

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Supplementary table 1. Inclusion and exclusion criteria in the al-Ándalus trial

Inclusion criteria	Exclusion criteria
Age: 35-65 years.	- Acute or terminal illness.
- To be diagnosed with fibromyalgia by a rheumatologist and meeting the American College of Rheumatology criteria: widespread pain for more than 3 months, and pain with 4 kg/cm of pressure reported for 11 or more of 18 tender points.	- Myocardial infarction in the past 3 months.
- Not to have other severe somatic or psychiatric disorders, or other diseases that prevent physical loading (answer "no" to all questions on the Physical Activity Readiness Questionnaire-PAR-Q).	- Unstable cardiovascular disease or other medical condition.
- Not to be engaged in regular physical activity > 20 min on > 3 days/week in the past 3 months.	- Upper or lower extremity fracture in the past 3 months.
- Planning to stay in the same Association during the study.	- Unwillingness to either complete the study requirements or to be randomized into control or training group.
- Able to ambulate without assistance.	- Severe dementia (Mini Mental State Examination < 10).
- Able to communicate.	- Presence of neuromuscular disease or drugs affecting neuromuscular function.
- Informed consent: Must be capable and willing to provide consent.	- To be engaged in other physical or psychological treatment.

Supplementary material. Details about the general principles of exercise prescription considered in the design of the al-Ándalus trial

During the first weeks, the main part of the sessions focused on familiarization with the exercises and learning basic movement patterns. Each session included 10 min of warm-up with slow walks and mobility exercises, followed by resistance strength training involving major muscle groups through circuits to improve performance in functional activities. The strengthening exercises included single-joint and multi-joint such as biceps curls, arm extensions, arm side lifts, shoulder elevations, lateral leg elevations, stands up from seated position, semi-squat, lunge, sideways lunge and step-up/step-down (similar exercises and with slight variations) with an intensity ranging from 10 RPE (week 1) to 17 RPE (week 24). All major muscle groups were exercised using movements that imply minimal work over the head and that were performed near the midline of the body. The speed of concentric contractions was slow and eccentric and isometric contractions were kept to a minimum. Starting level (week 1) included 1 set of 10-12 repetitions with 4 exercises and progressively increased each week until the final level (week 24) including 3 sets of 16 repetitions with 10 exercises. Progression was achieved by increasing firstly volume and then intensity Lower and upper limb exercises were alternate and wide periods of active resting were included between each set. Resistance strength training was followed by 15-25 min of aerobic exercises, developed progressively from 40-50% Heart Rate Reserve/50-60% Maximum Heart Rate (at the beginning of the intervention) and progressed to 55-70% Heart Rate Reserve/65-80% Maximum Heart Rate (the last month of the intervention). Low-impact exercises that involve large muscle groups were performed (e.g. aerobic circuits, dance and games involving displacements and walking at different speeds). Progression was achieved by increasing firstly volume and then intensity. Finally, each session ended with 10 min of cooling down with active and static stretching holding the stretch for 10-30s (to the point of gentle tension) and relaxation exercises. Stretches involved neck, shoulders, chest, arms, lower back, upper back, hands, glutes, hamstrings and calves. Stretches were individualized to teach each patient to avoid overstretching. Progressive relaxation included guided imagery with breathing awareness, diaphragmatic respiration, progressive muscular relaxation and contraction–relaxation techniques.

Supplementary table 2. CONSORT 2010 checklist

Section/Topic	Item No	Checklist item	Page No/table
		Title and abstract	
	1a	Identification as a randomized trial in the title	143
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	145
		Introduction	
Background and objectives	2a	Scientific background and explanation of rationale	145-156
	2b	Specific objectives or hypotheses	164
		Methods	
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	156
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	156
Participants	4a	Eligibility criteria for participants	Suppl table 1
	4b	Settings and locations where the data were collected	147
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	151, table 1 and suppl. material
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	151-152
	6b	Any changes to trial outcomes after the trial commenced, with reasons	N/A
Sample size	7a	How sample size was determined	148
	7b	When applicable, explanation of any interim analyses and stopping guidelines	N/A
Randomization:			
Sequence generation	8a	Method used to generate the random allocation sequence	147
	8b	Type of randomization; details of any restriction (such as blocking and block size)	147
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	147
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	147
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	147
	11b	If relevant, description of the similarity of interventions	148-151 and Table 1
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	152-153
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	152-153
		Results	
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analyzed for the primary outcome	Fig 1
	13b	For each group, losses and exclusions after randomization, together with reasons	Fig 1
Recruitment	14a	Dates defining the periods of recruitment and follow-up	148
	14b	Why the trial ended or was stopped	N/A
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Table 2
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	Tables 3-6
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	Tables 3-6
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	N/A
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	Tables 3-6 Supp tables 4-7
Harms	19	All-important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	156 and Fig 1
		Discussion	
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	163
Generalizability	21	Generalizability (external validity, applicability) of the trial findings	163
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	160-163
		Other information	
Registration	23	Registration number and name of trial registry	147
Protocol	24	Where the full trial protocol can be accessed, if available	147
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	Research Projects and Funding section

Supplementary table 3. Consensus on Exercise Reporting Template (CERT) checklist from the al-Ándalus physical activity trial

Section/topic	Item No	Checklist item	Location (page No and table)
WHAT: materials	1	Detailed description of the type of exercise equipment	Suppl. material
WHO: provider	2	Detailed description of the qualifications, expertise and/or training	148
HOW: delivery	3	Describe whether exercises are performed individually or in a group	148
	4	Describe whether exercises are supervised or unsupervised; how they are delivered	148
	5	Detailed description of how adherence to exercise is measured and reported	164
	6	Detailed description of motivation strategies	164
	7a	Detailed description of the decision rule(s) for determining exercise progression	Suppl. material
	7b	Detailed description of how the exercise program was progressed	152, table 1, and suppl. material
	8	Detailed description of each exercise to enable replication	Suppl. material
	9	Detailed description of any home program component	N/A
	10	Describe whether there are any non-exercise components	151
	11	Describe the type and number of adverse events that occur during exercise	156
WHERE: location	12	Describe the setting in which the exercises are performed	151
WHEN, HOW MUCH: dosage	13	Detailed description of the exercise intervention	148-151, table 1, and suppl. material
	14a	Describe whether the exercises are generic (one size fits all) or tailored	148-151, table 1, and suppl. material
	14b	Detailed description of how exercises are tailored to the individual	148-151, table 1, and suppl. material
	15	Describe the decision rule for determining the starting level	Supplementary material
HOW WELL: planned, actual	16a	Describe how adherence or fidelity is assessed/measured	151
	16b	Describe the extent to which the intervention was delivered as planned	151, supplementary material

Supplementary Table 4. Mean change (week 24 minus baseline) and differences between groups in the mean change for disease impact, pain, and quality of life following exercise: intention to treat analyses (complete data only)

	Land (n=67)		Water (n=64)		Control (n=68)		Control vs Land			Control vs Water			Water vs Land		
	Mean	(95% CI)	Mean	(95% CI)	Mean	(95% CI)	Mean	(95% CI)	*P*	Mean	(95% CI)	*P*	Mean	(95% CI)	*P*
FIQR total†	-6.0	(-9.3, -2.7)	-6.3	(-9.9, -2.8)	-4.5	(-7.9, -1.1)	1.4	(-4.4, 7.3)	1.000	1.8	(-4.4, 8.0)	1.000	-0.4	(-6.3, 5.6)	1.000
Pressure-pain threshold *	-6.0	(-8.1, -3.9)	-7.6	(-9.8, -5.4)	-10.8	(-12.9, -8.7)	**-4.8**	**(-8.4, -1.2)**	**0.004**	-3.2	(-7.0, 0.6)	0.126	-1.6	(-5.3, 2.1)	0.896
VAS - pain†	-0.6	(-1.1, -0.1)	-0.7	(-1.2, -0.2)	-0.2	(-0.7, 0.3)	0.4	(-0.5, 1.2)	0.775	0.5	(-0.5, 1.4)	0.696	-0.1	(-0.9, 0.8)	1.000
FIQR pain†	-0.5	(-1.0, -0.1)	-0.9	(-1.3, -0.5)	-0.4	(-0.8, 0.1)	0.2	(-0.6, 0.9)	1.000	0.5	(-0.2, 1.3)	0.283	-0.4	(-1.1, 0.4)	0.764
SF-36 Bodily pain*	7.4	(4.0, 10.8)	7.6	(4.0, 11.2)	2.5	(-1.0, 6.0)	-4.9	(-10.9, 1.1)	0.148	-5.1	(-11.4, 1.2)	0.159	0.2	(-6.0, 6.4)	1.000
SF-36 PCS*	2.8	(1.4, 4.2)	1.8	(0.3, 3.2)	0.9	(-0.5, 2.3)	-1.9	(-4.3, 0.5)	0.169	-0.9	(-3.4, 1.7)	1.000	-1.0	(-3.5, 1.4)	0.924
SF-36 MCS*	3.2	(0.8, 5.7)	5.0	(2.5, 7.6)	0.2	(-2.3, 2.7)	-3.1	(-7.3, 1.2)	0.253	**-4.8**	**(-9.3, -0.4)**	**0.028**	1.8	(-2.6, 6.2)	0.961

Analyses of covariance after Bonferroni's correction. Outcome at baseline, age, pressure-pain threshold (except for when it was the outcome), and educational level at baseline were included as covariates in all the analyses. When considering participation in physical therapy results remained unchanged except for the non-significant differences between control vs land-based groups in SF-36 MCS (*P*=0.207)

CI: Confidence Interval; FIQR: Revised Fibromyalgia Impact Questionnaire; MCS: Mental Component Summary; PCS: Physical Component Summary; SF-36: 36-item Short-form Health survey; VAS: Visual Analogic Scale. † Greater scores indicate worse health status or higher pain * Greater scores indicate better health status and lower pain

Supplementary Table 5. Mean change (week 36 minus baseline) and differences between groups in the mean change for disease impact, pain, and quality of life at follow-up: intention to treat analyses (complete data only)

	Land (n=62)		Water (n=62)		Control (n=69)		Control vs Land			Control vs Water			Water vs Land		
	Mean	(95% CI)	Mean	(95% CI)	Mean	(95% CI)	Mean	(95% CI)	*P*	Mean	(95% CI)	*P*	Mean	(95% CI)	*P*
FIQR total†	-2.5	(-5.9, 0.9)	-5.4	(-8.9, -1.9)	-4.6	(-7.8, -1.3)	-2.1	(-7.9, 3.7)	1.000	0.8	(-5.1, 6.8)	1.000	-2.9	(-8.9, 3.0)	0.709
Pressure-pain threshold *	-11.6	(-13.5, -9.6)	-8.1	(-10.1, -6.2)	-9.8	(-11.7, -8.0)	1.7	(-1.5, 5.0)	0.611	-1.7	(-5.1, 1.6)	0.639	**3.4**	**(0.1, 6.8)**	**0.045**
VAS - pain†	-0.6	(-1.1, -0.1)	-0.3	(-0.9, 0.2)	-0.2	(-0.7, 0.3)	0.4	(-0.5, 1.2)	1.000	0.1	(-0.8, 1.0)	1.000	0.2	(-0.7, 1.2)	1.000
FIQR pain†	-0.3	(-0.8, 0.1)	-0.9	(-1.4, -0.5)	-0.5	(-0.9, -0.1)	-0.1	(-0.9, 0.6)	1.000	0.5	(-0.3, 1.2)	0.465	-0.6	(-1.4, 0.2)	0.207
SF-36 Bodily pain*	6.1	(2.7, 9.6)	3.0	(-0.5, 6.5)	3.0	(-0.4, 6.3)	-3.2	(-9.0, 2.7)	0.577	-0.1	(-6.1, 6.0)	1.000	-3.1	(-9.2, 3.0)	0.658
SF-36 PCS*	1.1	(-0.5, 2.6)	-1.0	(-2.6, 0.6)	0.5	(-0.9, 2.0)	-0.5	(-3.1, 2.1)	1.000	1.5	(-1.2, 4.2)	0.535	-2.0	(-4.8, 0.7)	0.230
SF-36 MCS*	2.2	(-0.2, 4.6)	5.2	(2.7, 7.6)	1.8	(-0.5, 4.1)	-0.4	(-4.4, 3.7)	1.000	-3.4	(-7.5, 0.8)	0.152	3.0	(-1.2, 7.2)	0.264

Analyses of covariance after Bonferroni's correction. Outcome at baseline, age, pressure-pain threshold (except for when it was the outcome), and educational level at baseline were included as covariates in all the analyses. When considering participation in physical therapy as an additional covariate results remained unchanged.

CI: Confidence Interval; FIQR: Revised Fibromyalgia Impact Questionnaire; MCS: Mental Component Summary; PCS: Physical Component Summary; SF-36: 36-item Short-form Health survey; VAS: Visual Analogic Scale. † Greater scores indicate worse health status or higher pain * Greater scores indicate better health status and lower pain

Supplementary Table 6. Mean change (week 24 minus baseline) and differences between groups in the mean change for disease impact, pain, and quality of life following exercise: per-protocol analyses (participants in the exercise groups were included if attendance >70% - complete data only)

	Land (n=50)		Water (n=42)		Control (n=68)		Control vs Land			Control vs Water			Water vs Land		
	Mean	(95% CI)	Mean	(95% CI)	Mean	(95% CI)	Mean	(95% CI)	*P*	Mean	(95% CI)	*P*	Mean	(95% CI)	*P*
FIQR total†	-8.3	(-12.2, -4.4)	-6.2	(-10.6, -1.8)	-4.5	(-7.9, -1.0)	3.8	(-2.6, 10.2)	0.452	1.7	(-5.3, 8.8)	1.000	2.1	(-5.1, 9.3)	1.000
Pressure-pain threshold *	-6.5	(-8.9, -4.1)	-7.4	(-10.1, -4.6)	-11.2	(-13.3, -9.1)	**-4.7**	**(-8.6, -0.8)**	**0.013**	-3.8	(-8.2, 0.5)	0.107	-0.9	(-5.4, 3.6)	1.000
VAS - pain†	-0.7	(-1.3, -0.2)	-0.7	(-1.4, -0.1)	-0.3	(-0.8, 0.2)	0.4	(-0.5, 1.3)	0.783	0.4	(-0.6, 1.5)	0.953	0.0	(-1.0, 1.0)	1.000
FIQR pain†	-0.7	(-1.2, -0.2)	-0.8	(-1.3, -0.2)	-0.3	(-0.8, 0.1)	0.4	(-0.4, 1.2)	0.734	0.4	(-0.5, 1.3)	0.744	0.0	(-0.9, 0.9)	1.000
SF-36 Bodily pain*	9.7	(5.8, 13.6)	9.2	(4.7, 13.7)	2.6	(-0.9, 6.0)	**-7.1**	**(-13.5, -0.7)**	**0.024**	-6.6	(-13.7, 0.5)	0.075	-0.5	(-7.8, 6.9)	1.000
SF-36 PCS*	3.5	(2.0, 5.1)	1.2	(-0.6, 3.0)	0.9	(-0.5, 2.3)	**-2.7**	**(-5.2, -0.1)**	**0.037**	-0.3	(-3.1, 2.5)	1.000	-2.4	(-5.3, 0.6)	0.156
SF-36 MCS*	4.4	(1.7, 7.2)	3.8	(0.7, 6.9)	0.2	(-2.2, 2.6)	-4.2	(-8.7, 0.2)	0.070	-3.6	(-8.5, 1.3)	0.241	-0.6	(-5.7, 4.5)	1.000

Analyses of covariance after Bonferroni's correction. Outcome at baseline, age, pressure-pain threshold (except for when it was the outcome), and educational level at baseline were included as covariates in all the analyses. When considering participation in occasional physical therapy as an additional covariate results remained unchanged.

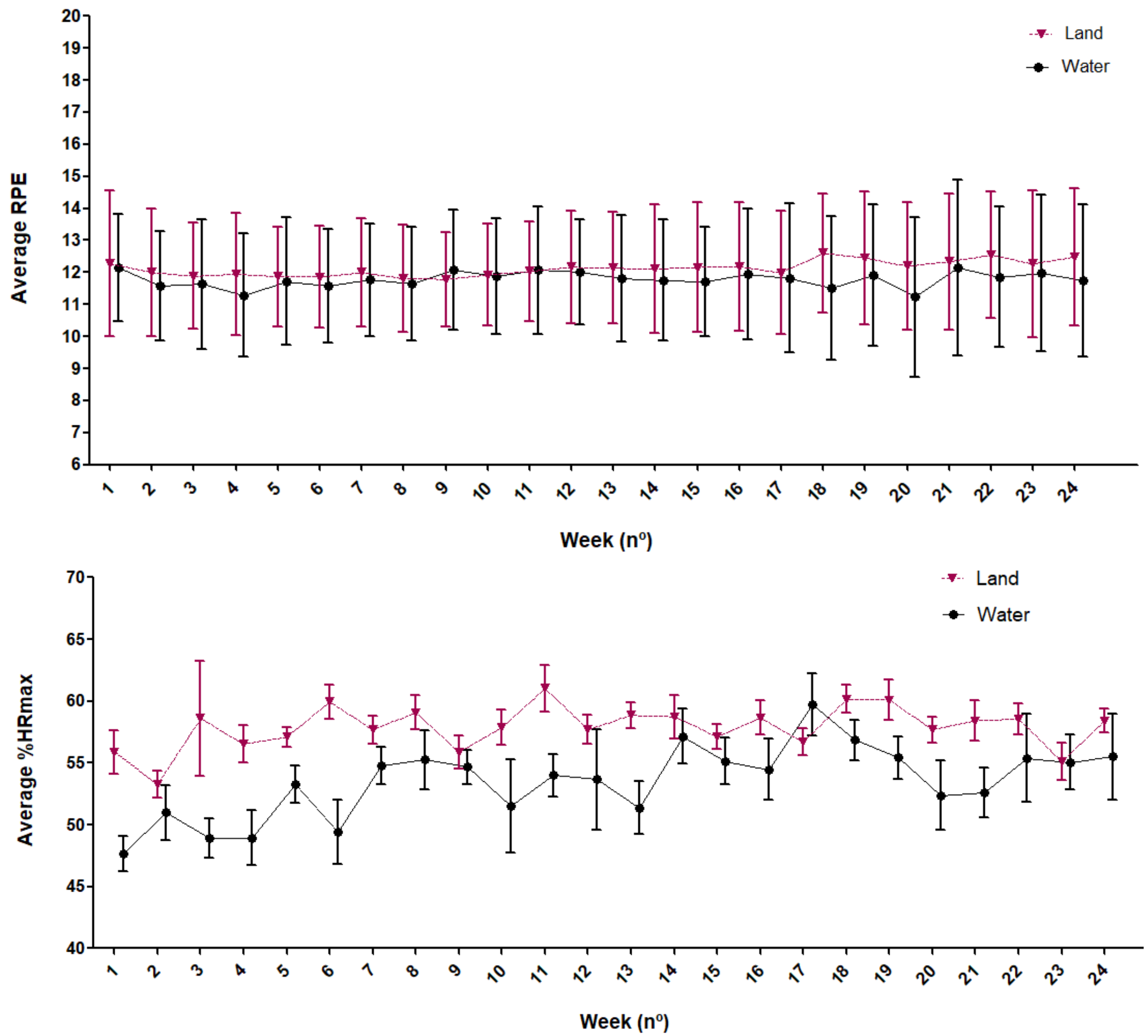
CI: Confidence Interval; FIQR: Revised Fibromyalgia Impact Questionnaire; MCS: Mental Component Summary; PCS: Physical Component Summary; SF-36: 36-item Short-form Health survey; VAS: Visual Analogic Scale. † Greater scores indicate worse health status or higher pain * Greater scores indicate better health status and lower pain

Supplementary Table 7. Mean change (week 36 minus baseline) and differences between groups in the mean change for disease impact, pain, and quality of life at follow-up: per-protocol analyses (participants in the exercise groups were included if attendance >70% - complete data only)

	Land (n=48)		Water (n=40)		Control (n=69)		Control vs Land			Control vs Water			Water vs Land		
	Mean	(95% CI)	Mean	(95% CI)	Mean	(95% CI)	Mean	(95% CI)	p	Mean	(95% CI)	p	Mean	(95% CI)	*p*
FIQR total†	-4.0	(-7.8, -0.2)	-2.6	(-6.8, 1.7)	-4.6	(-7.8, -1.4)	-0.6	(-6.7, 5.6)	1.000	-2.0	(-8.7, 4.7)	1.000	1.4	(-5.7, 8.5)	1.000
Pressure-pain threshold *	-11.9	(-14.0, -9.8)	-9.5	(-11.8, -7.1)	-10.1	(-11.9, -8.4)	1.8	(-1.6, 5.2)	0.624	-0.7	(-4.4, 3.0)	1.000	2.4	(-1.5, 6.4)	0.411
VAS - pain†	-1.0	(-1.5, -0.4)	0.0	(-0.6, 0.6)	-0.3	(-0.7, 0.2)	0.7	(-0.2, 1.6)	0.180	-0.3	(-1.2, 0.7)	1.000	0.9	(-0.1, 2.0)	0.079
FIQR pain†	-0.6	(-1.0, -0.1)	-0.6	(-1.1, -0.1)	-0.5	(-0.9, -0.1)	0.1	(-0.7, 0.8)	1.000	0.1	(-0.7, 0.9)	1.000	-0.1	(-0.9, 0.8)	1.000
SF-36 Bodily pain*	9.7	(5.9, 13.5)	1.0	(-3.3, 5.3)	3.3	(0.13 , 6.5)	**-6.4**	**(-12.5, -0.2)**	**0.039**	2.3	(-4.4, 9.0)	1.000	**-8.7**	**(-15.8, -1.5)**	**0.011**
SF-36 PCS*	2.3	(0.6, 4.0)	-2.3	(-4.2, -0.3)	0.5	(-0.9, 1.9)	-1.8	(-4.5, 0.9)	0.325	2.8	(-0.2, 5.7)	0.083	**-4.6**	**(-7.8, -1.4)**	**0.002**
SF-36 MCS*	2.6	(-0.2, 5.3)	3.1	(0.0, 6.2)	1.9	(-0.4, 4.2)	-0.7	(-5.1, 3.7)	1.000	-1.2	(-6.0, 3.5)	1.000	0.5	(-4.6, 5.6)	1.000

Analyses of covariance after Bonferroni's correction. Outcome at baseline, age, pressure-pain threshold (except for when it was the outcome), and educational level at baseline were included as covariates in all the analyses. When considering participation in occasional physical therapy as an additional covariate results remained unchanged.

CI: Confidence Interval; FIQR: Revised Fibromyalgia Impact Questionnaire; MCS: Mental Component Summary; PCS: Physical Component Summary; SF-36: 36-item Short-form Health survey; VAS: Visual Analogic Scale. † Greater scores indicate worse health status or higher pain * Greater scores indicate better health status and lower pain



Supplementary figure 1. Summary of rating of perceived exertion (RPE) and percentage of Maximum Heart Rate (%HRmax) during each week of the exercise program for land- and water-based exercise groups.

Supplementary tables 8 and 9. Comparisons of rating of perceived exertion (RPE) and percentage of maximum heart rate (%HRmax) for each week between land- and water-based exercise groups.

RPE									
	Land-based			Water-based					
	Mean	SD	n	Mean	SD	n	Mean Difference	SE	*P*
Week 1	12.3	2.3	72	12.2	1.7	72	-0.1	0.3	0.738
Week 2	12.0	2.0	73	11.6	1.7	71	-0.4	0.3	0.180
Week 3	11.9	1.7	73	11.6	2.0	70	-0.3	0.3	0.412
Week 4	11.9	1.9	72	11.3	1.9	68	-0.7	0.3	0.043
Week 5	11.9	1.6	66	11.7	2.0	66	-0.1	0.3	0.644
Week 6	11.9	1.6	68	11.6	1.8	62	-0.3	0.3	0.331
Week 7	12.0	1.7	67	11.8	1.8	63	-0.2	0.3	0.440
Week 8	11.8	1.7	68	11.6	1.8	64	-0.2	0.3	0.581
Week 9	11.8	1.5	68	12.1	1.9	59	0.3	0.3	0.320
Week 10	11.9	1.6	68	11.9	1.8	55	0.0	0.3	0.877
Week 11	12.0	1.6	66	12.1	2.0	60	0.0	0.3	0.922
Week 12	12.2	1.8	64	12.0	1.7	55	-0.2	0.3	0.618
Week 13	12.1	1.7	64	11.8	2.0	54	-0.3	0.3	0.350
Week 14	12.1	2.0	65	11.8	1.9	53	-0.4	0.4	0.324
Week 15	12.2	2.0	64	11.7	1.7	54	-0.5	0.3	0.199
Week 16	12.2	2.0	63	11.9	2.0	54	-0.2	0.4	0.522
Week 17	12.0	1.9	63	11.8	2.3	56	-0.2	0.4	0.672
Week 18	12.6	1.9	62	11.5	2.2	56	-1.1	0.4	0.005
Week 19	12.5	2.1	60	11.9	2.2	53	-0.5	0.4	0.180
Week 20	12.2	2.0	62	11.2	2.5	47	-1.0	0.4	0.026
Week 21	12.3	2.1	59	12.2	2.8	51	-0.2	0.5	0.686
Week 22	12.5	2.0	59	11.9	2.2	53	-0.7	0.4	0.083
Week 23	12.3	2.3	56	12.0	2.4	51	-0.3	0.5	0.517
Week 24	12.5	2.1	57	11.7	2.4	52	-0.7	0.4	0.089
Average	12.2	1.6	78	11.7	1.6	73	-0.4	0.3	0.088

Percentage of Maximum Heart Rate (% HRmax)									
	Land-based			Water-based					
	Mean	SD	n	Mean	SD	n	Mean Difference	SE	*P*
Week 1	55.9	3.5	4	47.6	2.5	3	-8.3	2.4	0.018
Week 2	53.3	3.4	9	51.0	6.0	7	-2.3	2.3	0.345
Week 3	58.6	12.3	7	48.9	3.9	6	-9.7	5.3	0.092
Week 4	56.5	6.5	19	48.9	6.6	9	-7.6	2.6	0.008
Week 5	57.1	4.2	30	53.3	5.2	12	-3.8	1.5	0.017
Week 6	59.9	7.3	29	49.4	9.0	12	-10.5	2.7	<0.001
Week 7	57.7	5.8	25	54.8	5.1	11	-2.9	2.0	0.156
Week 8	59.1	7.1	27	55.2	9.0	14	-3.8	2.6	0.143
Week 9	55.9	7.0	26	54.7	5.0	13	-1.2	2.2	0.580
Week 10	57.9	8.1	32	51.5	11.3	9	-6.4	3.3	0.063
Week 11	61.0	10.0	28	54.0	5.9	12	-7.0	3.1	0.029
Week 12	57.7	6.4	31	53.7	11.6	8	-4.0	3.0	0.189
Week 13	58.9	5.7	28	51.4	6.4	9	-7.5	2.2	0.002
Week 14	58.7	9.7	30	57.1	8.0	13	-1.6	3.1	0.607
Week 15	57.1	4.9	23	55.2	5.9	10	-2.0	2.0	0.324
Week 16	58.6	6.4	21	54.5	8.1	11	-4.2	2.6	0.119
Week 17	56.7	5.5	26	59.7	8.8	12	3.0	2.3	0.203
Week 18	60.1	5.9	27	56.9	5.9	13	-3.3	2.0	0.106
Week 19	60.1	7.8	23	55.4	5.4	10	-4.7	2.7	0.095
Week 20	57.7	5.2	26	52.4	8.9	10	-5.3	2.4	0.032
Week 21	58.4	7.7	23	52.6	6.9	12	-5.8	2.7	0.037
Week 22	58.6	5.5	19	55.4	10.0	8	-3.2	3.0	0.295
Week 23	55.1	5.7	14	55.1	6.4	8	0.0	2.6	0.989
Week 24	58.4	2.9	9	55.5	9.1	7	-2.9	3.2	0.376
Average	58.5	5.2	69	53.3	5.3	60	-5.2	0.9	<0.001

GENERAL DISCUSSION

GENERAL DISCUSSION

The present Doctoral Thesis provided greater insights on the influence of PA, ST and exercise in relation to disease impact, pain, and HRQoL in women with fibromyalgia. A summary of the specific findings of sections 1 to 3 and their contribution to what is already known on the topic is shown in tables 1 to 3, respectively. A detailed discussion including limitations and strengths for each study separately was included in the previous part of this Doctoral Thesis (*Results and Discussion*). Altogether, these findings contribute to the discussion of relevant questions initially identified as gaps in the literature of PA and exercise in fibromyalgia.

Contribution to ongoing debates, practical implications, and future lines of research

Physical activity recommendations for fibromyalgia: reducing ST, modifying sedentary patterns, increasing light PA or increasing MVPA?

According to our longitudinal findings, reduced levels of PA and increased levels of ST seem to persist and change towards an even less favorable profile over years. Also, changes over time in ST and PA, rather than initial levels, seemed to predict future health. These results reinforce the need for strategies aimed at increasing PA and reducing ST levels in this group of patients. Currently, there are no disease-specific recommendations for people with fibromyalgia that establish a certain duration and intensity of daily PA to achieve health benefits. Based on cross-sectional evidence of this thesis, all levels of PA (light, moderate, and vigorous) and ST were related to some extent with HRQoL and disease impact. In particular, ST and MVPA showed the strongest associations with these outcomes according to our cross-sectional, isotemporal and longitudinal findings. Furthermore, MVPA was shown to possibly counteract the associations of prolonged ST and was longitudinally associated with more outcomes in comparison to ST or light PA. If confirmed in future studies, from a “potential to influence health” perspective, increasing MVPA could be of clinical relevance as a final goal for patients. Of noting, prolonged and total ST were detrimentally related to the studied outcomes and theoretical increases in light PA were positively related to a lesser degree but with more outcomes in isotemporal substitution models. As people with fibromyalgia perceived exercise as scary[1] and avoidance behavior toward PA is highly prevalent[2], interrupting prolonged sedentary activities and substituting them with activity of light intensity could be a more feasible intermediate goal to achieve. Most of this evidence relied on cross-sectional designs, thus future interventions studies are needed to confirm the potential of the hypothesized strategies to actually influence HRQoL and other outcomes in fibromyalgia. It is also worth noting that the relationship between PA, ST and HRQoL seem to be bidirectional and operate through intermediate factors[3,4]. In models proposed for older adults, PA increases proximal factors (e.g. self-esteem) that in turn, lead to more distal changes related to global quality of life (e.g. satisfaction with life)[5]. Several psychological variables have demonstrated to mediate the relationship between PA and HRQoL, including self-esteem, self-efficacy[3,4] or positive affect[5]. Higher levels of self-efficacy are predictors and consequences of PA that have also been linked to higher PA in fibromyalgia[6], although it is unknown how these intermediate factors operate in this condition. Further research is needed to establish the duration, intensity, and potential mechanisms that maximize the association between PA, ST, and health outcomes in fibromyalgia. These potential PA guidelines could be incorporated to patients' education in the initial stage of management of fibromyalgia[7]. Indeed, PA recommendations can be easily delivered in clinical settings and doctors' advice might reinforce promotion of activity in these patients[8].

Exercise in fibromyalgia: how should it be prescribed?

Aerobic and strength training have been the most studied exercise modalities for fibromyalgia[7]. It is still unclear which exercise modality provides greater benefits in fibromyalgia[7] or whether multicomponent exercise (mixed of modalities) may act synergistic to obtained further health benefits[9,10]. The multicomponent exercise intervention study included in this Doctoral Thesis did not influence fibromyalgia impact although some other modest effects were found for pain and HRQoL. These findings should not question the validity of multicomponent exercise in this population, as compelling evidence have suggested the benefits of different exercise interventions to treat fibromyalgia key symptoms[10]. In the intervention study included in this Doctoral Thesis, an analysis of the specific limitations of the applied exercise protocol was attempted. For this purpose, our exercise protocol was compared against those previously interventions that successfully reduced disease impact. However, exercise protocols in fibromyalgia are typically insufficiently detailed[11] and hinders comparisons. It was found that low intensity achieved and low adherence rates were two relevant factors possibly influencing lack of effects on disease impact of the present exercise intervention. In order to improve studies comparability and knowledge on exercise prescription for fibromyalgia, more accurately reported exercise interventions combining different regimes of training (in terms of intensity, frequency, duration or modality) are needed. It would be of relevance as well to clarify how factors previously related to exercise adherence in fibromyalgia (e.g. self-efficacy, previous exercise participation, depression, social network[12]) operate in different exercise interventions. In addition, the exercise intervention included in this Doctoral Thesis, along with those previously published, recognized the relevance of adapting and individualizing exercise in fibromyalgia. However, it is needed a consensus on what factors (e.g. initial levels, tolerance or preference of patients) and how should these factors be considered for adaptation. The intervention study included in this Doctoral Thesis supported more effects for land-based exercise in comparison to water-based exercise. Similar benefits between land- and water-based exercise have been suggested according to recent metanalysis[13,14] and certain variables (e.g. strength) could be improved to a greater extent with land-based exercise[13]. Both settings (land and water) appear to be well tolerated and present similar rates of withdrawals[13]. Beyond effectiveness on symptoms, the number of limitations encountered when accessing to warm water facilities in addition to the economic costs of this settings should be also taken into account when considering potential advantages and drawbacks of water-based exercise. Our findings along with previous literature preclude to establish superiority of a setting, but support further research assessing the potential of land-based training in fibromyalgia as an easily accessible exercise modality.

Table 1. Contribution to the field and specific findings of section 1

What is already known in this subject	
Higher PA of different intensity levels and lower total ST have been related to better overall symptomatology (reported pain, pain modulation, disease impact, etc.) in fibromyalgia. Prolonged bouts of ST have been connected to worse pain modulation in fibromyalgia.	
What this Doctoral Thesis adds	
The link between PA, ST, and health in fibromyalgia also extends to HRQoL. Higher levels of PA and lower levels of ST are related to better HRQoL in women with fibromyalgia, being ST and MVPA particularly relevant. Both total ST and its accumulation in prolonged periods are related worse HRQoL and higher disease impact, independently of MVPA and physical fitness of patients. Substituting ST with light PA appears to have a positive association in more dimensions of HRQoL and impact of fibromyalgia, while MVPA is related to stronger theoretical changes in these outcomes.	
Specific findings	
Study 1	• Higher duration of light PA and MVPA and lower duration of ST were associated with better HRQoL (except for general health, emotional role and mental health subscales). • MVPA and ST were independently associated with social functioning dimension of HRQoL. • Participants meeting the PA recommendations (150 min/week of MVPA accumulated in 10-min bouts) had better scores in bodily pain and social functioning dimensions of HRQoL compared to those not meeting PA recommendations.
Study 2	• Higher percentages of ST spent in different bout lengths (≥10 min, ≥20 min, ≥30 min, and ≥60 min) were associated with worsened HRQoL (including physical function, bodily pain, vitality, and social function domains as well as the physical component). • Higher frequencies of sedentary bouts were associated with worsened HRQoL (including physical function, bodily pain, vitality, and social function domains, as well as the physical component) especially in longer bout durations. • Patients characterized by high total ST and high sedentary bout duration presented worsened physical functioning, social functioning, and physical component scores compared to participants with high total ST and high sedentary bout duration. • These associations were generally independent of the MVPA performed for ST accumulated in long bout lengths.
Study 3	• Greater ST accumulated in bouts ≥ 30 min and ≥ 60 min were associated with greater disease impact in women with fibromyalgia. These associations were generally independent of MVPA and overall physical fitness. • Those patients who presented sedentary bouts ≥ 60 min had higher disease impact than those who did not • Women with fibromyalgia characterized by both low levels of total ST and prolonged ST presented lower disease impact compared to participants with both high total ST and high prolonged ST.
Study 4	• Replacing 30 minutes of ST with LPA in isotemporal substitution models was associated with better scores in bodily pain, vitality, social functioning domains of HRQoL and all domains of disease impact. • Substitution of 30 minutes of ST with MVPA instead, was associated with better physical role and social functioning of HRQoL and FIQR function domain.

Table 2. Contribution to the field and specific findings of section 2

What is already known in this subject	
Fibromyalgia symptoms seem to be persistent over years with different trends of fluctuation and slight improvement been described. Evidence examining evolution of PA levels in fibromyalgia is very limited and suggest maintenance of high levels of self-reported PA over years. Self-reported PA levels seem to predict health status (pain, fatigue, and physical fitness) up to 5 years but not followed 26 years.	
What this Doctoral Thesis adds	
Over a 2- and 5-year follow-up, objectively measured variables (pressure pain threshold, PA, and ST) slightly changed towards less favorable values, while self-reported outcomes (disease impact, reported pain, and HRQoL) slightly tended to improve. Neither ST nor light PA at baseline predicted future disease impact, pain, or HRQoL, and contradictory findings were found for baseline MVPA in relation to pain. Changes over time towards lower ST and higher light PA (at 2-year follow-up) or towards higher MVPA (at 2- and 5-year follow-up) are associated with improved pain and HRQoL in the future.	
Specific findings	
Study 5	• Objectively measured variables (i.e. pressure pain threshold, PA, and ST variables) slightly changed towards less favorable values over a 2- and 5-year follow-up. • Self-reported outcomes (i.e. disease impact, reported pain, and HRQoL) exhibited a trend for improvement over a 2- and 5-year follow-up. • Baseline ST or light PA levels were not associated with future pain, disease impact, or HRQoL. • Baseline MVPA was positively associated with VAS (at 2-year follow-up) and SF-36 bodily pain (at 5-year follow-up). • Changes in ST (negatively) and light PA (positively) were not associated with outcomes at 2-year follow-up and, however, they were associated with bodily pain and physical component of SF-36 at 5-year follow-up. • Changes in MVPA were negatively associated with VAS and global pain at 2-year follow-up and positively associated with pressure pain threshold and SF-36 physical component at 2- and 5-year follow-up.

Table 3. Contribution to the field and specific findings of section 3

What is already known in this subject	
Exercise is effective to treat symptoms of fibromyalgia (specially pain and HRQoL), being aerobic and strength training the most investigated exercise modalities. Multicomponent exercise (a combination of two or more exercise modalities) could also improve HRQoL, physical function, fatigue, and stiffness. Land- and water-based exercise seem to produce similar benefits in fibromyalgia and only greater gains in strength in land-based exercise have been reported. It is unclear whether the long-term effects of multicomponent exercise are maintained for all outcomes.	
What this Doctoral Thesis adds	
24 weeks of land- or water-based multicomponent exercise (strength, aerobic, and flexibility training) did not improve disease impact in women with fibromyalgia. Modest benefits in pain and physical HRQoL in land-based exercise and for mental HRQoL in water-based exercise were found. These improvements were more consistent and persistent for land-based exercise when a fair level of attendance is reached, whereas benefits in water-based exercise group were independent of exercise adherence.	
Specific findings	
Study 6	• 24 weeks of land- or water-based exercise did not improve overall disease impact (primary outcome) in women with fibromyalgia compared to a usual care control group. • ITT analyses for secondary outcomes showed that land-based exercise attenuated deterioration of pressure pain threshold and improved physical component of SF-36, while water-based exercise improved mental component of SF-36 compared to the control group. • Based on ITT analyses, at 12-week follow-up, benefits in the water-based group persisted for mental component of SF-36 and additional improvements emerged for pressure pain threshold compared to the land-based group. • When a minimum of attendance (at least 70%) was considered in per-protocol analyses, land-based exercise improved bodily pain, physical and mental components of SF-36 while water-based group showed no improvement for any outcome after the intervention. • Per-protocol analyses at follow-up revealed that the improvements in land-based exercise group persisted for bodily pain and physical component of SF-36 compared to the control and water-based groups, and differences emerged for VAS compared to control group.

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CONCLUSIONS

CONCLUSIONS

The results of the present Doctoral Thesis suggest that, in women with fibromyalgia:

- Higher PA and lower ST are correlated to better HRQoL in different domains, being ST and MVPA independently associated. Participants meeting the PA recommendations have better HRQoL than those not meeting the recommendations.

- Higher levels of total and prolonged ST in different bout lengths are individually and jointly associated with worse HRQoL, and these associations are generally independent of MVPA.

- Higher levels of total and prolonged ST in different bout lengths are individually and jointly associated with worse disease impact, and these associations are generally independent of MVPA and physical fitness.

- Replacing 30 minutes of ST with LPA or MVPA in isotemporal substitution models is associated with better HRQoL and lower disease impact.

- Objectively measured variables (pressure pain threshold, PA, and ST) slightly change towards less favorable values over years, while for self-reported outcomes (disease impact, reported pain, and HRQoL) there is a trend for improvement. Baseline ST or light PA levels do not predict future outcomes and contradictory findings for baseline MVPA are found. Changes in ST (negatively), light PA, and MVPA (positively) predict improved future pain and HRQoL.

- 24 weeks of land- or water-based multicomponent exercise do not improve disease impact. Modest benefits in pain and physical HRQoL (for land-based exercise) and in mental HRQoL (for water-based exercise) are observed. These improvements are more consistent and persistent for land-based exercise when a fair level of attendance is reached, whereas benefits of exercise in warm water are independent of exercise adherence.

CONCLUSIONES

Los resultados de esta Tesis Doctoral sugieren que, en mujeres con fibromialgia:

- Mayores niveles de AF y menores niveles de TS se relacionan con una mejor CVRS, relacionándose el TS y la AFMV de forma independiente. Las mujeres con fibromialgia que cumplen las recomendaciones de AF tienen una mejor CVRS.

- Mayores niveles de TS total y prolongado acumulado en diferentes bloques de duración se asocian de forma independiente y conjunta con una peor CVRS. Estas asociaciones son, en general, independientes de la AFMV.

- Mayores niveles de TS total y prolongado acumulado en diferentes bloques de duración se asocian de forma independiente y conjunta con un mayor impacto de la enfermedad. Estas asociaciones son, en general, independientes de la AFMV y el nivel de condición física.

- Sustituciones de 30 de min de TS por AF ligera o AFMV en los modelos de sustitución *isotemporales* se asocia con una mejor CVRS y un menor impacto de la fibromialgia.

- Las variables medidas de forma objetiva (sensibilidad al dolor, AF y TS) cambian ligeramente a valores menos favorables a lo largo de 2 y 5 años, mientras que las variables autorreportadas (impacto de la enfermedad, dolor y CVRS) tienen una ligera tendencia a la mejora a lo largo de los años. Los niveles basales de TS o AF ligera no predicen la salud futura y existen resultados contradictorios con relación al nivel basal de AFMV. Los cambios de TS (de forma negativa), AF ligera y AFMV (de forma positiva) se asocian con el dolor y la CVRS futuros.

- 24 semanas de ejercicio multicomponente en seco o agua no disminuyen el impacto de la enfermedad. Se observan modestas mejoras para el dolor y la CVRS física (en el grupo de ejercicio en seco) y para la CVRS mental (en el grupo de ejercicio en agua). Estas mejoras son más consistentes y persistentes en el grupo de ejercicio en seco cuando el nivel de asistencia es óptimo mientras que los beneficios del ejercicio en agua son independientes de la adherencia al ejercicio.

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J. Sabina

ACTIVIDAD FÍSICA, TIEMPO SEDENTARIO Y EJERCICIO: INFLUENCIA SOBRE DOLOR, IMPACTO DE LA ENFERMEDAD Y CALIDAD DE VIDA RELACIONADA CON LA SALUD EN MUJERES CON FIBROMIALGIA

PROGRAMA DE DOCTORADO EN BIOMEDICINA

UNIVERSIDAD DE GRANADA

GAVILÁN-CARRERA B