Tesis Doctoral Internacional / International Doctoral Thesis

PERCEIVED EXERTION, PHYSICAL FITNESS, DEPRESSION AND DISEASE SEVERITY IN WOMEN WITH FIBROMYALGIA

PERCEPCIÓN DEL ESFUERZO, CONDICIÓN FÍSICA, DEPRESIÓN Y SEVERIDAD DE LA ENFERMEDAD EN MUJERES CON FIBROMIALGIA

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A mi familia,
por enseñarme el verdadero valor de las cosas,
por su entrega y por su eterno amor

A Eva,
por compartirlo todo conmigo,
porque ‘Sei tu’

DEPARTAMENTO DE EDUCACIÓN FÍSICA Y DEPORTIVA
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Que la Tesis Doctoral titulada "Percepción del esfuerzo, condición física, depresión y severidad de la enfermedad en mujeres con fibromialgia" que presenta D. **Alberto Soriano Maldonado** al superior juicio del Tribunal que designe la Universidad de Granada, ha sido realizada bajo mi dirección durante los años 2012-2015, siendo expresión de la capacidad técnica e interpretativa de su autor en condiciones tan aventajadas que le hacen merecedor del Título de Doctor por la Universidad de Granada, siempre y cuando así lo considere el citado Tribunal.

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El doctorando D. ALBERTO SORIANO MALDONADO y los directores de la tesis D. MANUEL DELGADO FERNÁNDEZ, D. JONATAN RUIZ RUIZ y D. FRANCISCO B. ORTEGA PORCEL:

Garantizamos, al firmar esta tesis doctoral, que el trabajo ha sido realizado por el doctorando bajo la dirección de los directores de la tesis y hasta donde nuestro conocimiento alcanza, en la realización del trabajo, se han respetado los derechos de otros autores a ser citados, cuando se han utilizado sus resultados o publicaciones.

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Doctorando

Fdo. Alberto Soriano Maldonado

El doctorando D. **Alberto Soriano Maldonado** ha realizado la presente Tesis Doctoral Internacional como beneficiario de una beca-contrato con cargo al programa de Formación de Profesorado Universitario (FPU) del Ministerio de Educación, Cultura y Deporte (código: FPU12/00963), por Resolución de 28 de febrero de 2013 de la Secretaría de Estado de Educación, Formación Profesional y Universidades (BOE-A-2013-2942, publicado el 18 de Marzo de 2013).

CONTENTS

Research Projects and Funding

The present Doctoral Thesis was performed as a result of the following research projects:

- **Project 1:** Effects of physical activity levels measured as energy expenditure on symptomatology variables in patients with fibromialgia syndrome (Efectos de los niveles de actividad física medidos en gasto energético sobre diferentes variables sintomatológicas de pacientes con síndrome de fibromialgia). Centro Andaluz de Medicina del Deporte, Consejería de Turismo, Comercio y Deporte, Junta de Andalucía. BOJA nº 89 de 4 de Enero de 2008. Duration: from 17-12-2007 to 16-12-2008. Funding: 15.403,21€. Principal investigator: Diego Munguía Izquierdo. [This Project led to Studies I and II of the present Doctoral Thesis]
- **The al-Ándalus Project:** Physical activity in women with fibromialgia: effects on pain, health and quality of life (Actividad física en mujeres con fibromyalgia: efectos sobre el grado de dolor, salud y calidad de vida). DEP2010-15639. Principal investigator: Manuel Delgado Fernández. Date: 01/07/2010 to 30/09/2014. [This Project led to Studies III to VII of the present Doctoral Thesis]

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Abbreviations

ACR, American College of Rheumatology

ANCOVA, analysis of covariance

ANOVA, analysis of variance

BDI-II, Beck depression inventory second edition

BMI, body mass index

CI, confidence interval

CR-10, 11 points category-ratio

CPSS, chronic pain self-efficacy scale

FIQ, fibromyalgia impact questionnaire

FIQR, revised fibromyalgia impact questionnaire

HR, heart rate

HRQoL, health-related quality of life

MFI, multidimensional fatigue inventory

MMSE, mini mental state examination.

OR, odds ratio

PASAT, paced auditory serial addition task

PCS, pain catastrophizing scale

PPT, pressure pain threshold

PSQI, Pittsburgh sleep quality index

Q, quintile

rANOVA, repeated measures analysis of variance

RAVLT, Rey auditory verbal learning test

RER, respiratory exchange ratio (or respiratory quotient)

RPE, rating of perceived exertion

SD, standard deviation

SE, standard error

SF-36, 36-item short form health survey

TPC, tender point count

VAS, visual analogue scale

V_E, minute ventilation

VO_2, oxygen uptake

Resumen

La fibromialgia es una enfermedad debilitante que representa una gran carga para el sistema de salud. Identificar factores asociados con una mejor sintomatología y menor severidad de la enfermedad es de interés clínico y de salud pública. El objetivo principal de esta Tesis Doctoral fue examinar de forma pormenorizada la asociación de la condición física y la depresión con síntomas clave de la fibromialgia, tales como el dolor, y con la severidad global de la enfermedad en mujeres con fibromialgia. Además, se evaluó la utilidad de usar la percepción subjetiva del esfuerzo para monitorizar la intensidad del ejercicio en esta población. Para responder a estos objetivos, se desarrollaron siete estudios en el contexto de dos proyectos.

Proyecto I (Estudios I y II). Treinta y tres mujeres con fibromialgia realizaron un protocolo incremental en tapiz rodante, en el que se registraron respuestas fisiológicas (consumo de oxígeno [VO_2] y frecuencia cardíaca, entre otras), y perceptuales (percepción subjetiva del esfuerzo [escala CR-10 de Borg] y dolor inducido por el ejercicio). Se registró la capacidad aeróbica (VO_2 pico) y se midió la sensibilidad al dolor a la presión (algometría) y la intensidad de dolor clínico (escala visual analógica [EVA]).

Proyecto II (Estudios III a VII). La condición física se evaluó con la batería Senior Fitness Test y dinamometría manual (n=468). El dolor se evaluó con diferentes herramientas (algometría, EVA, y subescalas del cuestionario revisado de impacto de la fibromialgia [FIQR, que evaluó la severidad de la enfermedad] y el SF-36 [que evaluó calidad de vida relacionada con la salud]). La función cognitiva se evaluó con el Paced Auditory Serial Addition Task y el Rey Auditory Verbal Learning Test, y la depresión mediante el Beck Depression Inventory (BDI-II).

Los principales hallazgos y conclusiones fueron: I) La escala CR-10 de Borg es una herramienta moderadamente válida y fiable para monitorizar la intensidad del esfuerzo en mujeres con fibromialgia. Además, las mujeres con fibromialgia son capaces de discriminar entre esfuerzo y dolor inducido por el ejercicio, especialmente cuando la intensidad del ejercicio aumenta; II) Un mayor VO_2 pico se asocia con una menor sensibilidad al dolor a la presión pero no con un menor dolor clínico; III) Una mayor condición física se asocia consistentemente con menores niveles de dolor (medido con diferentes indicadores), menor catastrofización ante el dolor, y mayor autoeficacia ante el dolor crónico en mujeres con fibromialgia. La fuerza muscular y la flexibilidad se asocian de forma independiente con el dolor, mientras que la capacidad aeróbica y la flexibilidad se asocian independientemente con la catastrofización y autoeficacia. Existe un efecto combinado entre diferentes componentes de la condición física sobre el dolor, catastrofización y autoeficacia; IV) Mayores niveles de condición física se asocian de forma consistente a una menor severidad de la fibromialgia en mujeres. La diferencia en la severidad de la fibromialgia entre los grupos con mayor y menor nivel de condición física sobrepasa el umbral de relevancia clínica. El 6-minute walk test (capacidad aeróbica) y el back scratch test (flexibilidad de miembro superior) se asocian de forma inversa e independiente a la severidad de la fibromialgia; V) Una mayor condición física se asocia positivamente con el procesamiento de la información, memoria de trabajo, memoria diferida, aprendizaje verbal y reconocimiento diferido. Por el contrario, la adiposidad no parece asociarse con las tareas cognitivas estudiadas. La capacidad aeróbica parece ser el componente más importante de la condición física en relación con los procesos cognitivos evaluados, aunque la agilidad motora podría también jugar un papel importante; VI) Una mayor condición física está generalmente asociada con menores niveles de depresión en mujeres con fibromialgia. Sin embargo, las asociaciones observadas fueron débiles e inconsistentes, a diferencia de las observabas previamente en personas sanas; VII) Una mayor severidad de los síntomas de depresión se asocia con una peor sintomatología autoinformada y con el componente mental de la calidad de vida relacionada con la salud, pero no con la sensibilidad al dolor ni con la función física en mujeres con fibromialgia.

Los resultados de esta Tesis Doctoral incrementan nuestro conocimiento acerca de la condición física y la depresión en relación con síntomas principales de la fibromialgia, tales como el dolor, y con la severidad global de la enfermedad en mujeres con fibromialgia, así como de la utilidad de la percepción subjetiva del esfuerzo en esta población. Estos resultados darán lugar a futuros estudios para evaluar el valor preventivo y terapéutico de la condición física en esta población.

Abstract

Fibromyalgia is a chronic debilitating disease which represents a heavy burden for the health care system. Identifying factors associated with better symptomatology and lower disease severity is of clinical and public health interest. The major aim of the present Doctoral Thesis was to comprehensively examine the association of physical fitness and depression with core fibromyalgia symptoms, such as pain, and disease severity in women with fibromyalgia. In addition, the utility of rating perceived exertion as a tool for monitoring exercise intensity was also studied. To address these aims, seven studies were conducted in the context of two projects.

Project I (Studies I and II). During an incremental treadmill test, thirty-three women with fibromyalgia were recorded physiological (oxygen uptake [VO_2] and heart rate, among other) and perceptual (rating of perceived exertion [RPE; Borg CR-10 scale] and exercise-induced pain) responses at each workload. Cardiorespiratory fitness [peak VO_2], pressure pain sensitivity (algometry) and clinical pain intensity (visual analogue scale; VAS) were measured.

Project II (Studies III to VII). Physical fitness was assessed with the Senior Fitness Test battery and handgrip dynamometry (n=468). Pain was assessed with different tools (including algometry, VAS, and subscales from the revised fibromyalgia impact questionnaire [that assessed fibromyalgia severity] and the SF-36 [that assessed health related quality of life; HRQoL]). Cognitive function was assessed using the Paced Auditory Serial Addition Task and the Rey Auditory Verbal Learning Test, and depression with the Beck Depression Inventory (BDI-II).

The main findings of this Doctoral Thesis were: I) The Borg CR-10 scale is a moderately valid and reliable tool for monitoring exercise intensity in women with fibromyalgia. In addition, women with fibromyalgia are able to discriminate between exertion and exercise-induced pain while exercising, especially as exercise intensity increases; II) Higher VO_2 peak is associated with lower pressure pain sensitivity but not with clinical pain; III) Higher physical fitness is consistently associated with lower levels of pain (measured through different indicators), lower pain-related catastrophizing and higher chronic pain self-efficacy in women with fibromyalgia. Muscle strength and flexibility are independently associated with pain, while aerobic fitness and flexibility are independently associated with pain-related catastrophizing and chronic pain self-efficacy. There was a combined effect of different fitness components on pain, catastrophizing and self-efficacy; IV) Higher physical fitness is consistently associated with lower fibromyalgia severity in women. The difference in fibromyalgia severity between patients with the lowest and the highest fitness levels surpasses the minimal clinically meaningful difference. The 6-minute walk (aerobic fitness) and back scratch (upper body flexibility) tests are independently associated with fibromyalgia severity; V) Higher physical fitness is positively and consistently associated with information processing, working memory, delayed recall, verbal learning and delayed recognition in women with fibromyalgia. By contrast, body fatness does not seem to be associated with the studied cognitive tasks. Aerobic fitness seems to be the most important fitness indicator of the cognitive processes evaluated, yet motor agility could also play a relevant role; VI) Higher physical fitness is generally associated with lower symptoms of depression in women with fibromyalgia. However, the observed associations were weak and inconsistent, differing from those previously observed in healthy adults; VII) Higher severity of depressive symptoms is associated with poorer self-reported symptomatology and mental HRQoL, but not with pain sensitivity or physical function in women with fibromyalgia.

The results of this Doctoral Thesis enhance our understanding about physical fitness and depression in relation to core fibromyalgia symptomatology and disease severity in women, as well as about the utility of perceived exertion in women with fibromyalgia. These results will lead to future research to understand the preventive and therapeutic value of physical fitness in this population.

INTRODUCTION

INTRODUCTION

1. Fibromyalgia: definition, epidemiology and burden for the health care system

Fibromyalgia is a chronic multi-dimensional condition of unknown etiology, characterized by chronic widespread pain as its main symptom and other important physical and psychological symptoms and comorbidities[1–3] that restrict activities of daily living and have a massive impact on the patient's illness perceptions[4] and quality of life[5,6]. The prevalence of fibromyalgia in the general population ranges from 2 to 8%[7] depending on the criteria used for the diagnosis. Considering the currently official 1990 criteria for the diagnosis of fibromyalgia from the American College of Rheumatology (ACR)[2], the prevalence of fibromyalgia in Spain is 2.4%, being markedly more prevalent in women (4.2%) than in men (0.2%)[8]. This prevalence is similar to that observed in other countries in Europe[3,9] and the United States[10].

Fibromyalgia is currently a burden for the health care system[11], representing the highest unemployment rate (6%)[12], claims for disability benefit (up to 30%)[13], and greatest number of days of absence from work in Europe[12–14]. In Spain, the greater use of health care resources and absenteeism/employment disability in patients with fibromyalgia is accompanied by significantly higher costs, in both the direct (except for hospitalization costs) and the indirect (sick leave and early retirement) costs. After controlling for age and sex, Sicras-Mainar et al.[13] revealed that fibromyalgia patients incurred €614 more in average annual health care (direct) costs and €4,397 more in indirect costs in comparison with the reference group, totaling an extra annual average cost per patient of €5,011. Therefore, it is important to find modifiable factors that may be associated with a more favourable profile in relation to core fibromyalgia symptoms and disease severity in this population.

2. Approaches to the management of fibromyalgia

A recent meta-analysis revealed significant benefits of pharmacological interventions (serotonin–norepinephrine reuptake inhibitors and pregabalin) over placebo on pain and quality of life of patients with fibromyalgia[15]. However, the observed effects were of questionable clinical relevance (~0.6 in a 0-10 VAS)[15]. Among non-pharmacological treatments, multicomponent therapy, cognitive behavioral therapy[16,17] and exercise[18,19] appear to be the most promising alternatives for reducing pain and improving quality of life[15].

There is growing evidence suggesting that aerobic and muscle strengthening exercise[15,20–22] play a key role in the management of fibromyalgia[1,18,23], since it might increase physcal fitness[21], and improve acute[24,25] and long-term pain[18,21,25] and quality of life[26]. Exercise intensity is an essential component of exercise-based intervention programs, which must be individualized according to the severity of the fibromyalgia-related symptoms and the patient's physical fitness.

3. Perceived exertion in fibromyalgia

Exercise intensity for aerobic conditioning is generally established as a percentage of the maximum oxygen uptake (VO_{2max}) or heart rate (HR_{max}). However, clinicians and patients with fibromyalgia rarely have access to devices to monitor these physiological parameters. As an alternative, the ratings of perceived exertion (RPE) represent an inexpensive tool for monitoring exercise intensity[27]. In the model described by Borg[28], it is observed that as exercise performance increases along an intensity-dependent continuum, a positive relationship appears between the reported RPE and several physiological responses such as HR, VO_2, minute ventilation (V_E), or respiratory quotient (RER).

The Borg Category Ratio (CR-10) scale is commonly used in patients with fibromyalgia to rate perceived exertion[29,30] as it is intuitive, feasible, and simple to understand. However, whether it represents a valid and reliable tool for monitoring exercise intensity in women with fibromyalgia is unclear. In addition, it has been suggested that patients with fibromyalgia might not be able to discriminate between perceived exertion and exercise-induced pain[31] while exercising[29]. Therefore, research is needed to determine the validity and reliability of the Borg CR-10 scale in this population and to understand whether women with fibromyalgia are able to discriminate between perceived exertion and exercise-induced pain. This information is of clinical interest since this scale might be used in clinical settings to control exercise intensity as part of therapeutic programs in this population. (Study I)

4. Physical fitness: association with fibromyalgia symptomatology and disease severity

Physical fitness has been defined as a set of attributes related to a person's ability to perform physical activities that require aerobic fitness, endurance, strength or flexibility and is determined by a combination of regular activity and genetically inherited factors[32]. The fitness components studied in the present Doctoral Thesis are aerobic fitness, muscle strength, flexibility and motor agility. From a conceptual point of view, aerobic fitness (or cardiorespiratory fitness) is a health-related component of physical fitness that reflects the overall capacity of the cardiovascular and respiratory systems and the ability of an individual to perform prolonged exercise[33]; Muscle strength is a health-related component of fitness that relates to the amount of external force that a muscle can exert[33]; Flexibility is a health-related component of fitness that relates to the range of motion available at a joint[33]; Agility is a component of fitness that relates to the ability of an individual to rapidly change the position of the entire body in space with speed and accuracy[33].

Physical fitness is a widely known powerful marker of health and morbi-mortality[34–38], that is inversely associated in different populations with the risk for cardiovascular diseases[39,40], back pain[41], low bone mineral density[42], metabolic syndrome[43], or psychiatric conditions[44,45] (among other). It is therefore plausible that physical fitness plays and important role with regards to fibromyalgia symptomatology and disease severity. Indeed, recent studies suggest that fitness testing could be used as a complementary tool in the diagnosis[46] and monitoring[47] of fibromyalgia. As physical fitness is a modifiable factor that might be enhanced through exercise intervention programs, a comprehensive characterization of the association of physical fitness with core fibromyalgia symptoms and disease severity is of clinical and public health interest and will lead to future exercise intervention studies aiming at improving exercise prescription in this population.

4.1. Physical fitness and pain in fibromyalgia

Pain is the principal symptom of fibromyalgia. In fact, the 1990 ACR diagnostic criteria for fibromyalgia are based exclusively on this symptom, requiring the presence of chronic widespread pain for at least three months and 11 out of 18 positive tender points to palpation for its diagnosis[2]. Although these criteria are criticized since they do not account for the wide spectrum of fibromyalgia-related symptoms, and recent (still preliminary) alternative diagnostic criteria are gaining popularity[48,49], pain continues to be the hallmark of fibromyalgia. Chronic widespread pain in this population is characterized by increased sensitivity to painful stimuli (hyperalgesia) and lowered pain threshold (allodynia)[50]. Possible explanations for this deregulation are dysfunctions of the pain inhibitory pathways (disinhibition)[51] and the activation of facilitator pain-related mechanisms (central sensitization)[50,52].

Intervention studies have shown concomitant increases in fitness with reduced levels of pain[20,21] and improved quality of life in fibromyalgia patients. Likewise, low physical fitness has been related to exacerbated pain, fatigue, and stiffnes[46], and to higher risk of falls in this population[53]. Several studies examined the association of different components of physical fitness with pain in fibromyalgia patients with mixed findings[54–57]. Carbonell-Baeza et al.[55] observed that aerobic fitness (distance walked in the 6-minute walk test) was inversely related to pain (as measured by tender points count (TPC) and pressure pain threshold (PPT)) in women with fibromyalgia. By contrast, Hooten et al.[57] reported that peak VO_2 was not associated with the PPT in fibromyalgia patients. Lower body muscle strength seems to be associated with the PPT[54,57] and inversely related to the TPC[55] in fibromyalgia patients. However, Henriksen et al.[56] observed that the association between knee muscle strength and TPC in these patients was weak. The association of flexibility and motor agility with pain has received little attention[54,58], and exercise programs for the management of fibromyalgia rarely focus on improving these fitness components[20,21].

The above-mentioned studies focused on the association of single components of physical fitness and pain separately. However, a comprehensive characterization of the independent and combined association of different components of physical fitness (aerobic fitness, muscle strength, flexibility and motor agility) with pain, as well as with mental factors associated with the experience of pain (e.g. pain-related catastrophizing and chronic pain self-efficacy), is needed to optimize future exercise intervention studies in this population. (Studies II and III)

4.2. Physical fitness and fibromyalgia severity

Fibromyalgia severity is defined as the impact that this chronic condition has on the patient's life, and is commonly assessed through the Revised Fibromyalgia Impact Questionnaire (FIQR)[59] which provides a comprehensive picture of the disease-related profile by evaluating self-reported function, overall impact, and symptoms severity.

To study whether higher levels of physical fitness are associated with lower symptom severity, higher self-reported daily function, and lower overall disease burden in women with fibromyalgia is relevant since it would provide an overall picture of the potential of this modifiable factor to benefit fibromyalgia features. Carbonell-Baeza et al.[60] observed that aerobic fitness was weakly (although significantly) associated with overall fibromyalgia severity in women. Similarly, Henriksen et al[56] observed that isokinetic knee muscle strength was weakly associated with fibromyalgia severity. However, all these studies used the original version of the Fibromyalgia Impact Questionnaire (FIQ)[61] and addressed only individual components of physical fitness. A comprehensive characterization of the association between different components of fitness with fibromyalgia severity in a large sample of women with fibromyalgia is lacking in the literature. In addition, it is important to study whether the association of different components of physical fitness is independent of each other (e.g. when several components are simultaneously considered) and the strength of the associations to provide a clear overview of the relation between performance-based fitness and self-reported measures of health outcomes in fibromyalgia. (Study IV)

4.3. Physical fitness, fatness, and cognitive function in fibromyalgia

Cognitive dysfunction represents one of the most commonly self-reported complaints in fibromyalgia patients[62] and plays an important role interfering in the patient's everyday life. Cognitive dysfunction in patients with fibromyalgia includes working memory, executive control and attention deficits[63–65]. The prevalence of cognitive dysfunction reported among patients with fibromyalgia is high (50-80%)[66] especially considering that memory and concentration problems can be very disruptive for patients[63].

As previously mentioned, enhancing physical fitness (mainly through exercise)[67] or decreasing body fatness[68] are becoming increasingly popular for improving fibromyalgia-related symptomatology [including cognitive functioning[69]] and quality of life. However, little is known about the association between fitness and fatness (and their possible interaction) with cognitive function in women with fibromyalgia.

To our knowledge, only two studies investigated the association between physical fitness and cognitive function in women with fibromyalgia[70,71]. They reported a direct association of fitness (muscle strength, balance and aerobic fitness) with cognitive performance (e.g. attention, processing speed and episodic memory). However, these studies had a relatively small sample size, and pain (which might underlie cognitive dysfunction[64]) was not accounted for as a potential confounder in the analyses. In addition, the authors examined the relationship of single components of fitness with cognitive functioning only. In order to completely characterize the above-mentioned association, it is also important to study which fitness components (aerobic fitness; muscle strength; flexibility; motor agility) present an independent association with cognitive performance (e.g. when all components are simultaneously considered). (Study V)

Obesity has been consistently linked to higher symptoms severity and lower quality of life in women with fibromyalgia[7273,74]. In addition, several studies observed an inverse relationship between fatness and cognitive function in healthy people[75,76]. Therefore, it is possible that excess adiposity might be inversely associated with cognitive performance in women with fibromyalgia, which is currently unknown and need to be study to improve our understanding of the potential negative effects of adiposity in this population. (Study V)

4.4. Physical fitness and depression in fibromyalgia

Depression is a common comorbidity in chronic pain and fibromyalgia patients[62]. A survey of 2,596 people with fibromyalgia (96.8% of respondents were women) conducted by Bennett et al.[62] revealed that 83% of fibromyalgia patients reported emotional distress, which was perceived as the factor that worsened fibromyalgia symptomatology the most[62]. The prevalence of depression among patients with fibromyalgia ranges from 28.6 to 70% across studies[77,78].

A low aerobic fitness is closely related to the incidence of depressive symptoms in the general population[44,45] and it could also be associated with high levels of depressive symptoms in women with fibromyalgia. However, although exercise programs in fibromyalgia patients have shown short and long term (up to 30 months) improvements in depressive symptoms[79,80], these improvements have not been related to improvements in fitness levels[79]. It is therefore plausible that exercise programs produce beneficial effects on depressive symptoms without the need to enhance physical fitness levels. In addition, it is unknown whether other components of physical fitness (e.g. muscle strength or flexibility) are associated with depressive symptoms in this population. A comprehensive characterization of the association of physical fitness with depressive symptoms is warranted to determine the potential relevance of different fitness components in relation to depressive symptoms in women with fibromyalgia. (Study VI)

In addition, it has been reported that fibromyalgia patients with comorbid depression seem to suffer from higher pain-related interference[81], as well as from higher self-reported affective distress and lower social support[82] than healthy controls. However, a comprehensive characterization of the association of different levels of depressive symptoms severity with core fibromyalgia symptoms (e.g. pain, fatigue, sleep, etc.), physical function, disease severity and physical and mental health-related quality of life (HRQoL) in a large sample of women with fibromyalgia is lacking in the literature and would provide wider insights into the potential deleterious effects of depression in this population. (Study VII)

OBJETIVOS / AIMS

OBJETIVOS

El objetivo principal de esta Tesis Doctoral fue examinar de forma pormenorizada la asociación de la condición física y la depresión con síntomas clave de la fibromialgia, tales como el dolor, y con la severidad global de la enfermedad en mujeres con fibromialgia. Además, se evaluó la utilidad de usar la percepción subjetiva del esfuerzo para monitorizar la intensidad del ejercicio en esta población. Los resultados de esta Tesis Doctoral están organizados en forma de siete estudios, basados en los siguientes objetivos:

1. Estudio I. Evaluar la validez y fiabilidad de la escala CR-10 de Borg para monitorizar la intensidad del ejercicio en mujeres con fibromialgia y examinar si estas mujeres son capaces de discriminar entre la percepción de esfuerzo y la de dolor durante el ejercicio.

2. Estudio II. Evaluar la asociación entre la capacidad aeróbica y la sensibilidad al dolor a la presión y el dolor clínico en mujeres con fibromialgia.

3. Estudio III. El objetivo principal fue examinar la asociación de la condición física con el dolor, la catastrofización ante el dolor, y la autoeficacia ante el dolor crónico en mujeres con fibromialgia. Objetivos secundarios de carácter exploratorio fueron 1) examinar si diferentes componentes de la condición física se relacionan de forma independiente con las variables arriba mencionadas; y 2) evaluar si existe un efecto combinado de diferentes componentes de la condición física en las variables estudiadas.

4. Estudio IV. Estudiar la asociación de la condición física con la severidad de la enfermedad en mujeres con fibromialgia (objetivo 1). También se estudió si diferentes componentes de la condición física presentan una asociación independiente con la severidad de la enfermedad en esta población (objetivo 2).

5. Estudio V. Evaluar la asociación del nivel de condición física y adiposidad con la función cognitiva en mujeres con fibromialgia (objetivo 1). Dado que la condición física y la adiposidad representan constructos multifactoriales, también se examinó si varios de sus componentes presentan una asociación independiente con la función cognitiva en esta población (objetivo 2).

6. Estudio VI. Evaluar la asociación entre condición física y síntomas de depresión en mujeres con fibromialgia (objetivo 1) y examinar si diferentes componentes de la condición física se asocian con la depresión de forma independiente (objetivo 2).

7. Estudio VII. Estudiar la asociación entre diferentes niveles de depresión con el dolor, fatiga, calidad del sueño, función física, severidad global de la enfermedad y calidad de vida relacionada con la salud en mujeres con fibromialgia.

AIMS

The major aim of the present Doctoral Thesis was to provide a comprehensive examination of the association of physical fitness and depression with core fibromyalgia symptoms, such as pain, and overall disease severity in women with fibromyalgia. In addition, the utility of rating perceived exertion as a tool for monitoring exercise intensity was also studied. The outcome of this Doctoral Thesis is organized in seven studies, based on the following specific aims:

1. Study I. To assess the validity and reliability of the Borg CR-10 scale for monitoring exercise intensity in women with fibromyalgia and to examine whether women with fibromyalgia are able to discriminate between perceived exertion and exercise-induced pain during exercise.

2. Study II. To assess the association of cardiorespiratory fitness with pressure pain sensitivity and clinical pain in women with fibromyalgia.

3. Study III. The primary aim was to assess the association of physical fitness with pain, pain-related catastrophizing and chronic pain self-efficacy in women with fibromyalgia. Secondary exploratory aims: 1) to assess whether different fitness components are independently associated with the studied pain-related outcomes; 2) to examine whether there is a combined effect of different fitness components on the above-mentioned outcomes.

4. Study IV. To assess the association between physical fitness and fibromyalgia severity in women with fibromyalgia (objective 1). Whether different fitness components present an independent association with fibromyalgia severity was also examined (objective 2).

5. Study V. To assess the association of physical fitness and body fatness with cognitive function in women with fibromyalgia (objective 1). As fitness and fatness represent multidimensional constructs, this study also aimed to examine the independent influence of their single components on cognitive function (objective 2).

6. Study VI. To assess the association between physical fitness and depressive symptoms in women with fibromyalgia (objective 1) and to examine whether different fitness components present an independent relationship with depressive symptoms (objective 1).

7. Study VII. To assess the associations of different levels of depressive symptoms with pain, fatigue, sleep quality, physical function, overall fibromyalgia severity, and HRQoL in women with fibromyalgia.

MATERIALS AND METHODS

MATERIALS AND METHODS

Project I (Studies I and II).

Design and Participants

A formal invitation to participate in this cross-sectional study was sent to all women aged 18–60 years (n=250) from a local association of fibromyalgia (Seville, Spain). Thirty-seven potentially eligible patients responded and gave written informed consent to participate after receiving detailed information about the aims and study protocol. The inclusion criteria were (i) to be previously diagnosed of fibromyalgia by a rheumatologist; (ii) to meet the 1990 ACR criteria for the diagnosis of fibromyalgia[2]; (iii) not to have either acute or terminal illness, nor severe dementia; (iv) not being morbid obese (body mass index [BMI] ≥ 40) and (v) not being at risk for adverse events while exercising. Four patients were excluded, two were morbid obese and two did not attend both test and retest evaluations[83]. Thirty-three participants were finally included. The experimental procedure was reviewed and approved by the Committee on Biomedical Ethics of the University Pablo de Olavide (Seville, Spain).

Protocol

During the first appointment, the medical records and anthropometric characteristics of the study participants were examined by a physician at the university facilities, clinical pain intensity was assessed and the diagnosis of fibromyalgia was confirmed by means of the tender points examination[2]. The participants then performed an incremental treadmill test (Studies I and II) and, in a second appointment (7 days later), the same treadmill exercise was performed (for Study I only). All participants were instructed to avoid the consumption of analgesics for 48 h before the evaluation.

Anthropometric characteristics

Weight was measured with participants in underwear, to the nearest 100 g, and height to the nearest 0.1 cm with an electronic balance with an incorporated stadiometer (Seca 780; SECA Hammer Steindamm, Hamburg, Germany). The participant's body mass index (BMI) was calculated as weight (kg) divided by squared height (m^2).

Pressure pain sensitivity assessment

An electronic pressure dolorimeter (J Tech Medical Industries, Salt Lake City, USA), previously used in fibromyalgia[84], was used to assess the PPTs according to the ACR criteria for the diagnosis of fibromyalgia[2]. The dolorimeter was held perpendicular to the body, and the force was increased gradually at a constant rate of 1 $kg \cdot cm^{-2}$ per second until the patient said "stop". The patients were instructed to say "stop" when the sensation of pressure became painful and the PPT was automatically recorded. All the measurements were taken by the same experienced examiner, and the same order of tender points examination was followed for all patients. The PPT at each tender site was computed as the average of two alternative measurements, and the average PPT from the 18 fibromyalgia tender points was calculated[57]. The TPC was also recorded for each patient as the sum of positive tender points (pressure pain ≥4 $kg \cdot cm^{-2}$).

Clinical pain

We used the pain subscale from the Fibromyalgia Impact Questionnaire (FIQ-pain)[61], which consists in a 10-cm VAS (0= no pain; 10= maximum pain) in which participants rated their current pain intensity.

Incremental treadmill test

The testing protocol has been previously used in women with fibromyalgia[85]. The test consisted of walking and jogging at incremental workloads on a treadmill (Pulsar 4.0; Cosmos, Am Sportplatz 8, DE 83365 Nussdorf-Traunstein, Germany). A 3-min warm-up period at a speed of 2.5 $km \cdot h^{-1}$ was performed before starting the incremental test. The test comprised 6 incremental workloads starting at 2.5 $km \cdot h^{-1}$ and increasing by 2.5 $km \cdot h^{-1}$ every 3 min up to 7.5 $km \cdot h^{-1}$. Thereafter, only the inclination increased by 2.5% every 3 min up to 7.5%, which was maintained until the test termination. The duration of each workload was 3 min so as that the physiological responses achieved a steady state before starting the following workload. All participants were verbally encouraged by the research staff throughout the test. Participants voluntarily terminated the test when they felt they were not able to further sustain the effort (none of the participant tolerated the effort further than completing stage 6). During the test, HR (in $beats \cdot min^{-1}$) and gas exchange data were continuously collected with an automated breath-by-breath system (CPX; Medical Graphics Corporation 350 Oak Grove Parkway St. Paul, MN 55127). Cardiorespiratory fitness (as per Study II) was defined as the peak VO_2 obtained during the last 30 s of the test[85].

Specific methodology for Study I (Validity and reliability of rating perceived exertion: exertion-pain discrimination).

Before the test, a detailed description on the use of the Borg CR-10 scale[86] and the VAS (which assessed the immediate experience of pain)[87], and a careful explanation of the differences between the two constructs (perceived exertion vs. exercise-induced pain), was provided to the participants so as to guarantee that they clearly understood the nature of the two differential constructs. The incremental treadmill test was then performed. The physiological criterion measures were HR, relative VO_2, V_E and RER.

The participant's RPE was obtained at each workload with the Borg CR-10 scale[88,89], which is a 11-point scale ranging from 0 ("nothing at all") to 10 ("very, very strong")[88]. At the end of each workload, the research staff presented the CR-10 scale on a white sheet of paper and the participants pointed at the number representing the overall exertion perceived during the actual workload.

The exercise-induced pain was registered on a 10-cm VAS (without sequential numbering)[87] annotated with the words "no pain" and "maximum pain" at the appropriate ends and presented on a white sheet of paper. The distance between the beginning of the line representing "no pain" and the fingerprint mark of the patients at each workload was measured and used in further analyses.

The physiological and perceptual responses obtained during the final 30 s of each workload level were used in the subsequent analyses. As exertion and pain represent differential constructs, and in order to avoid "cross-scale demand bias", the participants were consistently asked to report perceived exertion first (by the right side of the treadmill) and then the perception of exercise-induced pain (by the left side of the treadmill).

The al-Ándalus project (Studies III to VII).

Design and Participants

The project aimed to recruit a representative sample of women with fibromyalgia from Andalusia (i.e. 8 provinces from southern Spain) for this population-based cross-sectional study. We estimated the number of participants to be included using the level of accuracy obtained in previous studies assessing the 6-minute walk test in a population with fibromyalgia[60]. We used the level of accuracy as a fraction (k) of the standard deviation of the population (accuracy= k × standard deviation). We selected a standard deviation fraction of 10-50%, which is habitual in clinical studies. For a confidence interval level of 95%, a total of 300 participants were needed to obtain an accuracy of 11%. With 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 as a reference the database of the Spanish Association of Rheumatology, as well as the Census of the 8 provinces of Andalucía (southern Spain). The sample was however oversized in order to prevent loss of information. A total of 616 potentially eligible women were recruited through local fibromyalgia associations from the 8 provinces of Andalusia, as well as via e-mail, letter or telephone. All participants were informed of the study aims and procedures and signed written informed consent to participate. Inclusion criteria included a diagnosis of fibromyalgia by a rheumatologist and to meet the 1990 ACR criteria[2]. Exclusion criteria included acute or terminal illness (i.e. cancer, stroke, recent cardiomyopathy, severe coronary disease, schizophrenia, and severe chronic obstructive pulmonary disease), and severe cognitive dysfunction (Mini Mental State Examination [MMSE] < 10)[90].

Thirty-eight potentially eligible participants were not previously diagnosed, and 91 did not meet the 1990 ACR criteria. One fibromyalgia patient had severe cognitive dysfunction. Eighteen participants did not attend the second evaluation day and were excluded from the analyses of the present Doctoral Thesis. A total of 468 women with fibromyalgia were finally included. The study was reviewed and approved by the Ethics Committee of the "Hospital Virgen de las Nieves", Granada, Spain.

General protocol

The evaluation process was performed on two alternate days (e.g. Monday and Wednesday) either at the University facilities or at fibromyalgia associations. The assessments were carried out either in morning or afternoon sessions; according to the participants' convenience. The whole evaluation process was carried out by the same team of researchers who had previously received specific training.

On day 1, the diagnosis of fibromyalgia was confirmed by means of the tender point's examination[2], which was performed by a single trained researcher. In addition, the MMSE was applied in a private room for inclusion purposes, anthropometric measurements and body composition were assessed, and the Beck Depression Inventory second edition (BDI-II) and a complete self-reported socio-demographic questionnaire (assessing age, marital status, educational and occupational status, etc.) was filled by participants. Participants were then given several questionnaires (see **table 1**) to fill at home and bring on the next assessment day. On day 2, the research team verified that the questionnaires were properly and completely filled. Thereafter, cognitive function was assessed through the neuropsychological tests, current pain intensity was reported on a VAS, and the physical fitness assessment was undertaken. **Table 1** presents an overview of the global assessment procedure undertaken in the al-Ándalus project.

Table 1. General overview of the assessments carried out in the al-Ándalus project.

Assessment Day	Assessments
Day 1	MMSE, tender points examination, body composition, anthropometric and sociodemographic characteristics, medication usage, and BDI-II
Home (middle day)	FIQR, PCS, CPSS, PSQI, MFI, SF-36.
Day 2	Check questionnaires, PASAT, RAVLT, VAS, and Physical fitness

MMSE, mini mental state evaluation; BDI-II, Beck Depression Inventory second edition; FIQR, Revised Fibromyalgia Impact Questionnaire; PCS, pain catastrophizing scale; CPSS, chronic pain self-efficacy scale; PSQI, Pittsburgh Sleep Quality Index; MFI, Multidimensional Fatigue Inventory; SF-36, 36-item Short Form health survey; PASAT, Paced Auditory Serial Addition Task; RAVLT; Rey Auditory Verbal Learning Test; VAS, visual analogue scale.

MMSE

The Spanish version[91] of the MMSE[90] was used to assess severe cognitive impairment. It consists of 30 items grouped into seven categories: orientation to place, orientation to time, registration, attention and concentration, recall, language, and visual construction. The MMSE ranges from 0 to 30.

Tender points' examination

A standard pressure algometer (FPK 20; Wagner Instruments, Greenwich, CT, USA) was used to assess the 18 fibromyalgia-related tender points[2]. Participants were asked to refrain from their pain medications for 24h before the evaluation. Two alternative measurements at each tender site were performed and the mean score was recorded. The PPT was defined as the average pressure threshold across the 18 fibromyalgia tender sites. A pressure threshold of ≤4 $kg \cdot cm^{-2}$ defined a positive tender point according to the ACR[2]. The TPC was computed as the sum of positive tender points.

Anthropometric measurements and body composition

A portable eight-polar tactile-electrode bioelectrical impedance device (InBody R20, Biospace, Seoul, Korea) was used to measure weight (kg) and body fat. Height (cm) was measured with a stadiometer (Seca 22, Hamburg, Germany). Waist circumference (cm) was measured at the middle point between the ribs and ileac crest (Harpenden anthropometric tape Holtain Ltd). Body mass index (BMI; [weight/squared height ($kg \cdot m^{-2}$)]), and fat mass index (body fat/squared height; $kg \cdot m^{-2}$) were computed.

Medication usage

The usage of analgesics, antidepressants, anticonvulsants, and stimulants was registered as binary variables (yes/no) to be used as control variables in subsequent analyses as they might influence several fibromyalgia symptoms.

Beck Depression Inventory (BDI-II)

The Spanish version[92] of the BDI-II[93] is a 21-item self-report measure designed to assess depressive symptomatology. Participants rated each item on a 0-3 scale (0 [not present] to 3 [severe]), in the context of the past two weeks. The BDI-II provides one overall score (range 0-63) where higher values represent a more severe degree of depression. A score of ≤13, 14–19, 20–28, and ≥29 represents minimal, mild, moderate, and severe depressive symptoms, respectively[93]. The internal consistency (Cronbach's alpha) of the BDI-II in chronic pain patients has been reported to be of α=0.92[94].

Revised Fibromyalgia Impact Questionnaire (FIQR)

Fibromyalgia severity was assessed with the Spanish version[95] of the FIQR[59]. The FIQR represents the most fibromyalgia-specific instrument to assess overall fibromyalgia severity through the wide range of symptoms, comorbidities, and complaints related to this chronic condition. It was developed by Bennett et al.[59] in an attempt to overcome some limitations of the original fibromyalgia impact questionnaire (FIQ)[61], while maintaining its three domains structure (function, overall impact, and symptoms severity) and properties. It is a self-administered questionnaire comprising 21 individual questions assessed on a numerical rating scale (0-10). These items are organized into 3 subscales (function [0-30], overall impact [0-20], and symptoms severity [0-50]). Among the symptoms subscale, pain intensity was assessed on a numerical rating scale (ranging from 0 to 10). The FIQR total score (0-100; higher is worse) represents an overall measure of fibromyalgia severity (e.g. the burden that fibromyalgia causes on the patient's life) in the context of the past 7 days. The internal consistency (α) of this questionnaire ranges from 0.91 to 0.95.

Pain Catastrophizing Scale (PCS)

The Spanish version of the PCS[96] was used to measure pain-related catastrophizing. It is a 13-item questionnaire in which patients are asked to reflect on past painful experiences and indicate their thoughts or feelings about pain, on a 5-point scale. For this study, the total score (range 0-52) was used, where higher scores represent a more negative appraisal of pain.

Chronic Pain Self-efficacy Scale (CPSS)

The Spanish version[97] of the CPSS[98] was used to measure chronic pain self-efficacy. It contains 19 items grouped into 3 subscales that assess efficacy expectations for coping with pain.. The total score is the sum of the 3 subscales (range 0-300), where higher values represent better self-efficacy.

Pittsburgh Sleep Quality Index (PSQI)

The Spanish version[99] of the PSQI[100] was used as measure of sleep quality (range 0-21; higher score indicating lower sleep quality). The PSQI has an internal consistency (α) of 0.83.

Multidimensional Fatigue Inventory (MFI)

The Spanish version of the MFI[101] was used to assess fatigue. The sum of the 5 MFI subscales comprises an overall measure of fatigue (range 20-100, where higher score indicates greater fatigue). The MFI has an internal consistency (α) of 0.93.

36-items Short Form health survey (SF-36)

The Spanish version[102] of the SF-36[103] was used to measure HRQoL. It is a generic instrument that assesses 8 health domains: 1) limitations in physical activities because of health problems; 2) limitations in social activities because of physical or emotional problems; 3) limitations in usual role activities because of physical health problems; 4) bodily pain [pain intensity and interference]; 5) general mental health; 6) limitations in usual role activities because of emotional problems; 7) vitality; and 8) general health perceptions. The score within each domain ranges from 0 to 100. The standardized physical component summary and mental component summary were computed. Each of these standardized scores range 0-100, where higher score indicate better physical/mental HRQoL. The SF-36 has an internal consistency of α=0.90 and has been widely used in patients with fibromyalgia.

Paced Auditory Serial Addition Task (PASAT)

The PASAT[104,105] measures speed of information processing and working memory. This test has been previously used in fibromyalgia patients[106,107]. Participants were presented a series of single digit numbers (presentation rate: 2.4 seconds) where the two most recent digits were to be summed. For example, if the digits '2', '4' and '1' were presented, the correct sums the participant should respond would be '6' and then '5'. Prior to the beginning of the test, a series of practice trials were performed. The percentage of correct responses, omissions, and errors over 60 trials was recorded[105].

Rey Auditory Verbal Learning Test (RAVLT)

The RAVLT[108,109] measures verbal learning and memory functioning and has been previously employed in fibromyalgia patients[106,110]. It consisted of 5 verbal presentations of a 15-word list (list A; trials A1 through A5), each followed by an immediate recall trial. The number of words recalled on A1 served as a measure of immediate free recall. The sum of words recalled across trials A1 through A5 was used as a measure of verbal learning. Next, a distractor 15-word list (list B) was presented with a recall trial, followed by a post-distraction trial in which participants were asked to recall the initial list (list A). After a resting period of 20-min in a quiet room, participants were asked to recall list A again as a measure of delayed free recall. Finally, participants were read a list of 50 words, and the task (which was used to measure delayed recognition) consisted of recognizing whether each word belonged either to list A or B, or to neither of them.

Pain Visual Analogue Scale (VAS)

A 10-cm VAS[87] was used to assess current pain intensity, with higher scores representing greater pain intensity.

Physical fitness

Physical fitness was assessed with the Senior Fitness Test battery[111] and handgrip dynamometry. These performance-based functional fitness tests have been previously used in women with fibromyalgia[46,47,70,71,112,113], and have shown to be feasible and reliable in this population[112]. We additionally included the handgrip strength test[114].

Aerobic fitness was assessed with the "6-minute walk test", which represents a moderately valid and reliable measure of aerobic fitness in women with fibromyalgia[115] and measures the maximum distance (in meters) that a participant is able to walk along a 45.7 m rectangular course within 6 minutes.

Muscle strength was assessed with several tests. The "30-s chair stand test"[111] measures lower-body muscle strength, as the number of times an individual is able to rise, starting from a seated position, to a full stand within 30 s with the back straight and feet flat on the floor, without pushing off with the arms. The "Arm curl test" measures upper-body muscle strength[111] as the number of times a hand weight (2.3 kg for women) was curled through a full range of motion within 30 s. The average number of repetitions from both arms was used. Handgrip strength was completed with a digital dynamometer (TKK 5101 Grip-D; Takey, Tokyo, Japan) as described elsewhere[114] Participants performed the test twice (alternately with both hands), with 1 minute rest between trials. The best score from both hands were averaged.

Flexibility was measured with two tests. The "chair sit and reach test" measured lower-body flexibility[111]. Starting from a sitting position with one leg extended, participants slowly bended forward sliding the hands along the extended leg in an attempt to touch (or pass) the toes. The distance (in cm) short of reaching the toe (negative score) or reaching beyond it (positive score) was recorded twice for each leg. The average of the best score from each leg was used. The "back scratch test" measured upper-body flexibility[111]. The distance between (or overlap of) the middle fingers behind the back was recorded twice for each arm, and the average of the best value from both of them was used.

Motor agility was measured with the "8 feet up and go" test[111]. This test consists of standing up from a chair, walking 8 feet (2.44 m) to and around a cone, and returning to the chair in the shortest period of time, requiring movement speed, balance and motor coordination. The best (lower) time from two trials was used.

The variables included in each of the seven studies comprising the present Doctoral Thesis are presented in **table 2**.

The questionnaires used in the present Doctoral Thesis are presented as **Annexes** (page 133 et seq).

Table 2. Summary table of the methods used in this Doctoral Thesis.

Project	Study	Design	Participants	Main variables	Methods
Project I	I. Validity and reliability of rating perceived exertion in women with fibromyalgia: exertion-pain discrimination	Cross-sectional	N= 33	RPE, VAS (pain), HR, relative VO_2, RER, V_E	Incremental treadmill test with continuous HR and gas exchange recordings, Borg CR-10 scale and VAS
Project I	II. Association of cardiorespiratory fitness with pressure pain sensitivity and clinical pain in women with fibromyalgia	Cross-sectional	N= 31	Peak VO_2, PPT, TPC and VAS	Incremental treadmill test with continuous HR and gas exchange recordings, tender points examination and pain intensity
The al-Ándalus Project	III. Association of physical fitness with pain in women with fibromyalgia	Cross-sectional	N= 468	Chair sit and reach, back scratch, handgrip (dynamometry), chair stand, arm curl, 8 feet up and go, 6-minute walk, PPT, TPC, pain intensity, pain catastrophizing, and chronic pain self-efficacy	Senior Fitness Test battery and handgrip strength, tender points examination, FIQR (pain), SF-36 (bodily pain), VAS, PCS, CPSS
The al-Ándalus Project	IV. Association of physical fitness with fibromyalgia severity in women	Cross-sectional	N= 444	Chair sit and reach, back scratch, handgrip (dynamometry), chair stand, arm curl, 8 feet up and go, 6-minute walk and fibromyalgia severity	Physical fitness (Senior Fitness Test battery and handgrip strength), and FIQR (total and subscale scores)
The al-Ándalus Project	V. The association of physical fitness and fatness with cognitive function in women with fibromyalgia	Cross-sectional	N= 468	Chair sit and reach, back scratch, handgrip (dynamometry), chair stand, arm curl, 8 feet up and go, 6-minute walk, working memory, information processing, immediate free recall, delayed free recall, verbal learning, and delayed recognition	Physical fitness (Senior Fitness Test battery and handgrip strength), PASAT, and RAVLT
The al-Ándalus Project	VI. The association of physical fitness with depression in women with fibromyalgia	Cross-sectional	N= 444	Chair sit and reach, back scratch, handgrip (dynamometry), chair stand, arm curl, 8 feet up and go, 6-minute walk, and depressive symptoms (both as continuous and categorized variable)	Physical fitness (Senior Fitness Test battery and handgrip strength), and BDI-II
The al-Ándalus Project	VII. Association of different levels of depressive symptoms with symptomatology, overall disease severity and quality of life in women with fibromyalgia	Cross-sectional	N= 451	BDI-II in 4 categories (minimal, mild, moderate, severe), PPT, TPC, pain intensity, sleep quality, fatigue, functional exercise capacity, fibromyalgia severity and HRQoL	Depressive symptoms (BDI-II), tender points examination, FIQR (pain), PSQI, MFI, 6-minute walk, FIQR (total score), SF-36 (physical and mental standardized components)

RPE, rating of perceived exertion; VAS, visual analogue scale; HR, heart rate; VO_2, oxygen uptake; RER, respiratory quotient; V_E, minute ventilation; Borg CR-10 scale, Borg 0-10 Category Ratio scale; PPT, pressure pain threshold, TPC, tender point count; FIQR, Revised Fibromyalgia Impact Questionnaire; SF-36, 36-item Short Form health survey; PCS, pain catastrophizing scale; CPSS, chronic pain self-efficacy scale; PASAT, Paced Auditory Serial Addition Task; RAVLT; Rey Auditory Verbal Learning Test; BDI-II, Beck Depression Inventory second edition; PSQI, Pittsburgh Sleep Quality Index; MFI, Multidimensional Fatigue Inventory; HRQoL, health-related quality of life;.

Statistical analysis

Summary statistics are presented as means (standard deviation; SD), unless otherwise indicated. The normality, linearity and homoschedasticity assumptions of the linear regression models used in the different studies were checked and reasonably met. Studies I, II and III were analyzed with SPSS v. 20 (IBM SPSS Statistics for Windows, Armonk, NY, IBM Corp), while studies IV to VII were analyzed with Stata v.13.1, (StataCorp LP., Texas, USA). Statistical significance was set at the conventional level of α=0.05.

The statistical approach undertaken to accomplish the aims of this Doctoral Thesis is presented below and is summarized in **table 3** (page 56).

Analyses conducted for Study I

The validity of the Borg CR-10 scale for monitoring exercise intensity was assessed with several tests: the Spearman's rank correlation coefficient evaluated the association of RPE with HR, relative VO_2, V_E and RER. In addition, a linear regression model was fitted to predict each physiological variable as a function of RPE and other covariates and to estimate the per cent variability (R^2) of each physiological variable explained by the models. A stepwise method was used to fit the models with the best set of explanatory variables. The covariates included in the models were age and weight. In addition, the exercise-induced pain and the interaction between RPE and exercise-induced pain were also included in the models in order to estimate their potential to improve the per cent variability explained by the models. In order to test whether the physiological and perceptual responses were sensitive to exercise intensity changes and whether they followed an incremental linear tendency, a repeated measures analysis of variance (rANOVA) with polynomial contrasts assessed the linear, quadratic and cubic component of RPE; exercise-induced pain; HR; relative VO_2; V_E and RER, across the first 4 increasing workloads (n= 20). Although assuming an important loss of statistical power, a similar analysis was performed including only those participants who completed all 6 workloads (n= 8) in order to examine whether there was a similar trend on the perceptual and physiological responses at the highest exercise intensities. Data from the retest were used to analyze the validity, since it has been shown that a familiarization period improves the association of the RPE with different physiological responses[27,116].

The test–retest reliability of the Borg CR-10 scale during incremental treadmill exercise was assessed with per cent agreement and Cohen's weighted Kappa (*k*) coefficient, since this scale represents ordered categorical data[117]. For per cent agreement, the methodology employed by Ortega et al.[118] was followed. The difference between the reported RPE at the initial test (RPE1) and the reported RPE at the retest (RPE2) was computed for each participant and workload level. A difference (RPE2 – RPE1) equal to 0 was called "perfect" agreement (same test–retest answer), a difference of 0±1 was called "perfect acceptable" agreement[118] and a difference of 0±2 was called "moderate" agreement. The weighted *k* coefficient not only accounts for strict agreement (as the "unweighted" *k*) but also provides weighting to adjacent categories[117]. For example, exact agreements might be given full weight, one-category difference given weight ½ and so on[118]. Linear (instead of quadratic) weights were chosen because it is recommended when the difference across categories is equally important.

To assess whether women with fibromyalgia are able to discriminate between perceived exertion and exercise-induced pain, the difference between reported RPE and exercise-induced pain was computed for each participant and workload. A one-sample t-test was performed to examine whether the differences between RPE and pain at each workload were statistically significant. In addition, in order to determine if exercise intensity might influence the participants' ability to discriminate between RPE and pain, one-way analysis of covariance (ANCOVA; adjusted for age and weight) with the Bonferroni's correction for multiple comparison assessed the differences between RPE and pain across workloads.

Analyses conducted for Study II

Pearson's correlation between the average PPT and the PPT at each individual site was used to assess if the average PPT was a valid measure of single pain sites. The association of CRF with the average PPT and VAS was analyzed with Pearson's correlation and multiple linear regression. There was a ceiling effect regarding the TPC as ~60% of participants had 18 tender points. Therefore, the TPC was categorized as binary variable (0 if TPC = 18; 1 if TPC<18) and binary logistic regression was used to assess the odds of having TPC<18 as a function of CRF. The pain-related outcomes were introduced as dependent variables, and CRF was included as independent variable. All the analyses were adjusted for age and BMI. The relationship of CRF with PPT and TPC was further adjusted for VAS in order to control for clinical pain[57].

Generation of variables to be included in Studies III to VI

The scores of each fitness test were standardized (z-score: [value−mean]/SD) to allow computing a composite score for each fitness component (aerobic fitness, muscle strength, flexibility and motor agility). Aerobic fitness was computed as the z-score from the 6-minute walk test. Muscle strength (composite score) was computed as the average of the z-scores from the hand-grip, chair stand and arm curl tests. Flexibility (composite score) was computed as the average of the z-scores from the chair sit and reach and back scratch tests. Motor agility was computed as the z-score from the 8 feet up and go test multiplied by -1 (since higher time implies lower performance). To obtain a clustered measure of physical fitness, a 'global fitness profile' was calculated as the average of the aerobic fitness, muscle strength, flexibility and motor agility composite z-scores.

Age-specific quintiles from the above-mentioned fitness (aerobic fitness, muscle strength, flexibility, motor agility and 'global fitness profile') composite scores were derived. First, age was categorized (<45, 45 to 52, 52 to 60 and >60). Within each age category, every fitness variable was divided into 5 approximately equal groups. Quintile 1 (Q1) represented the group with the lowest fitness level. With this procedure, we avoided older people with good fitness for their age being categorized in the lowest fitness quintiles. The differences (and 95% confidence interval [CI]) on fibromyalgia outcomes between extreme fitness quintiles (Q5 vs. Q1) were used to assess the potential clinical relevance of the associations under study. The magnitude of the differences between extreme quintiles was generally assessed using standardized mean differences (Cohen's *d*).

Analyses conducted for Study III

The association of physical fitness with pain, pain-related catastrophizing and chronic pain self-efficacy (primary aim) was analyzed with two complementary approaches. First, multivariate linear regression assessed the (individual) relationship of each physical fitness test with each of the pain-related outcomes, after adjusting for age, BMI and drugs consumption. We considered these covariates as they are known potential confounders of the association under study[73,119,120]. As there is evidence suggesting that improving physical fitness might reduce pain[20,21], each pain-related outcome was treated as dependent variable, and physical fitness as independent variables in all the analyses.

In addition, we conducted one-way analysis of covariance (ANCOVA; with age, BMI and drugs consumption as covariates) to assess the differences on each pain-related outcome across quintiles of each fitness component and the 'global fitness profile'. This procedure was undertaken to provide a comprehensive picture of the tendency (that could potentially be linear or non-linear) of pain levels across different levels of physical fitness and to assess the potential clinical relevance the relation under study.

As there was a consistent pattern of association between fitness and pain as measured by different methods, we computed a clustered 'global pain profile' as a robust measure of the experience of pain. The 'global pain profile' was computed as the average of the z-scores (z-score: [value−mean]/SD) from TPC, PPT, FIQR pain, VAS and SF-36 bodily pain. This procedure for computing clustered scores has been previously shown with cardiovascular and other disease risk factors[121].

We also aimed to assess whether different fitness components are independently associated with pain (we used the 'global pain profile' as a robust measure of pain), pain-related catastrophizing and chronic pain self-efficacy when all the fitness components are simultaneously considered (secondary aim 1). A forward stepwise regression was conducted with each pain-related outcome as dependent variable in separate models. Age, BMI and drugs consumption (model 1) were introduced in the first stage using the '*enter*' method so that they could not be excluded from the models. In the second stage, aerobic fitness, muscle strength, flexibility and motor agility were simultaneously introduced using a '*forward stepwise*' procedure. This procedure introduces the fitness components step-by-step into the model (if $P<0.05$) according to the strength of their association with the outcome. The model will be reassessed with the addition of every new variable and variables will be left out of the model if $P>0.10$.

Finally, we tested whether there was a combined effect of different fitness components on pain ('global pain profile'), catastrophizing and self-efficacy (secondary aim 2). The fitness components independently associated to each outcome (see secondary aim 1) were categorized as 'high'=1 (if z-score≥0) or 'low'=0 (if z-score<0), and a new categorical variable was computed for each of the 3 outcomes. For example, if muscle strength and flexibility were independently associated with the 'global pain profile', the new variable would have 4 categories (1= low strength + low flexibility; 2= low strength + high flexibility; 3= high strength + low flexibility; 4= high strength + high flexibility). One-way ANCOVA (with age, BMI and drugs consumption as covariates) including post-hoc comparisons with the Bonferroni's correction assessed the differences across fitness categories.

Analyses conducted for Study IV

The association of physical fitness with fibromyalgia severity (objective 1) was analyzed using linear regression. The FIQR total score as well as the FIQR subscales were entered as dependent variables in separate models, and each of the fitness tests were entered as independent variables. The models were adjusted for potential confounders (age, % body fat, time since diagnosis, occupational status, and consumption of analgesics, antidepressants, and anticonvulsants).

To further characterize the above-mentioned relation, linear regression (adjusted for potential confounders) was used to assess the association of the 'global fitness profile' with each item of the FIQR subscales (function, overall impact, and symptoms severity). Furthermore, to assess the potential clinical relevance of physical fitness in relation to fibromyalgia severity and to provide an overall picture of the studied relation, 1-way analysis of covariance with the Bonferroni's correction for multiple comparisons was used to assess the differences in the FIQR total score (dependent variable) across 'global fitness profile' quintiles (independent variable). The abovementioned confounders were included as covariates. The difference in the FIQR total score between groups with the lowest (Q1) and highest (Q5) fitness levels was used to assess the potential clinical relevance of physical fitness in relation to fibromyalgia severity in this specific population.

We also aimed to study whether the association of different fitness components with fibromyalgia severity is independent of each other (e.g. when all fitness tests are simultaneously accounted for; objective 2) and the strength of the associations. The FIQR total score was entered as a dependent variable, and the 7 fitness tests were simultaneously entered as independent variables along with all potential confounders. To account for the variability explained by these fitness tests (R^2 change), a previous model including only potential confounders was performed and the difference (in R^2) was computed.

Analyses conducted for Study V

The association of physical fitness and fatness with cognitive function (objective 1) was analyzed with multivariate linear regression. The variables related to cognitive function (PASAT and RAVLT) were entered as dependent variables in separate models, and each of the fitness components (aerobic fitness [6-minute walk], muscle strength [z-score], flexibility [z-score] and motor agility [8 feet up and go]) and fatness indicators (BMI, % body fat, fat mass index and waist circumference) were entered individually as independent variables. Two models were conducted to control potential confounding. The basic model (model 1) was adjusted for age, educational and occupational statuses. A second model (model 2) was additionally adjusted for depression, pain intensity (both current pain and pain in the past 7 days) and stimulants consumption.

To assess the potential clinical relevance of the relationships under study, we conducted ANCOVA (including covariates in model 2) to compare the scores obtained in the cognitive tasks between extreme quintiles (Q5 vs. Q1) of fitness and/or fatness.

We also examined whether any component of physical fitness or fatness presented an independent association with cognitive function once the rest of components were accounted for (objective 2). Potential confounders were entered and kept fixed into the model. Then, fitness and fatness components were entered with a forward stepwise procedure (same procedure as per Study III).

Analyses conducted for Study VI

The association of physical fitness with depressive symptoms (objective 1) was analyzed with linear regression. The BDI-II total score and the 3 subscales were entered as dependent variable in separate models, and each fitness component as independent variable. Two consecutive models were built to account for potential confounding. Model 1 was adjusted for age, BMI, educational level, marital status, and time since diagnosis. Model 2 was additionally adjusted for pain intensity, sleep quality, and drugs consumption (analgesics, antidepressants and anticonvulsants), which are closely related to depressive symptoms.

To further characterize the above-mentioned relationship, binary logistic regression (adjusted for potential confounders; model 2) examined the odds ratio (OR) for severe depression (BDI-II ≥29; versus no severe depression) as a function of the different components of physical fitness in separate models. Furthermore, one way ANCOVA with the Bonferroni's correction for multiple comparisons was used to assess the differences on the BDI-II total score (dependent variable) across 'global fitness profile' quintiles (independent variable). The above-mentioned confounders (model 2) were included as covariates. The difference on the BDI-II total score between participants in the lowest (Q1) and highest (Q5) fitness quintile was use to assess the potential clinical relevance of physical fitness in relation to depressive symptoms in women with fibromyalgia.

We also aimed to assess whether the different fitness components were independently associated with depressive symptoms (as in previous the previous studies; objective 2). We conducted a forward stepwise regression method with the BDI-II total score as dependent variable. In this case, the 7 fitness tests were included in the model together with age, BMI, educational status, marital status, pain intensity, drugs consumption, and sleep quality with a forward stepwise procedure as previously described. In this case, all the variables were susceptible for being included/excluded from the model.

Analyses conducted for Study VII

To examine the association of different levels of depressive symptoms with fibromyalgia symptomatology and disease severity, the participants were divided into 4 levels of depressive symptoms (minimal, mild, moderate and severe) based on the BDI-II scores. We conducted ANCOVA with the fibromyalgia symptomatology factors as dependent variables in separate models and the BDI-II groups as independent variable. Pain intensity and medication usage (analgesics, antidepressants, and anticonvulsants) were included as covariates because they are known to be associated with depressive symptoms in chronic pain patients and the groups were unbalanced in these variables. Moreover, the estimates changed >10% when pain and medication usage were not accounted for in the models. Since the groups did not differ either in age, BMI or educational level, these variables were not considered as confounders and thus not included as covariates. Pairwise group comparisons with the Tukey-Kramer correction for multiple comparisons (given the observed unequal groups size) were applied to the fibromyalgia symptomatology factors that showed a statistically significant association in the previous analysis.

Table 3. Summary table of the statistical approach used in each study included in the present Doctoral Thesis.

Study	Statistical analysis
I. Validity and reliability of rating perceived exertion in women with fibromyalgia: exertion-pain discrimination	Validity: Spearman's correlation, LR (age and weight as covariates) between RPE and physiological variables and rANCOVA of main variables across workloads; Reliability: % agreement and weighted kappa coefficient; Exertion-pain discrimination: t-test and ANCOVA
II. Association of cardiorespiratory fitness with pressure pain sensitivity and clinical pain in women with fibromyalgia	Pearson's correlation and LR between CRF and PPT and VAS. Logistic regression of TPC<18 as a function of CRF. All models were adjusted for age and BMI.
III. Association of physical fitness with pain in women with fibromyalgia	Primary aim: Multivariate LR with pain-related outcomes as DV, and fitness as IV; and ANCOVA of pain-related outcomes (DV) across fitness quintiles; Secondary aim 1: Stepwise regression (confounders locked and the 4 fitness components simultaneously included); Secondary aim 2: ANCOVA. Confounders/covariates: age, BMI and drug consumption.
IV. Association of physical fitness with fibromyalgia severity in women	Objective 1: LR with FIQR variables as DV and fitness as IV; and ANCOVA of FIQR across quintiles of the 'global fitness profile'; Objective 2: Stepwise regression with the 7 fitness tests and all the confounders simultaneously included in the model. Confounders/covariates: age, %BF, time since diagnosis, occupational status, and medication.
V. Association of physical fitness and fatness with cognitive function in women with fibromyalgia	Objective 1: LR with PASAT and RAVLT as DV and fitness and fatness as IV; and ANCOVA of cognitive function across fitness quintiles; Objective 2: Stepwise regression with confounders locked into the model and the 4 fitness components simultaneously included. Confounders/covariates: age, educational and occupational status, depression, pain and stimulants.
VI. Association of physical fitness with depression in women with fibromyalgia	Objective 1: LR with BDI-II as DV and fitness as IV; and ANCOVA of BDI-II (DV) across quintiles of the 'global fitness profile'; and Logistic regression of BDI-II≥29 as a function of fitness; Objective 2: Stepwise regression with confounders and the 4 fitness components simultaneously included. Confounders/covariates: age, BMI, educational and marital status, time since diagnosis, pain and medication.
VII. Association of different levels of depressive symptoms with symptomatology, overall disease severity and quality of life in women with fibromyalgia	BDI-II scores divided into 4 severity categories: ANCOVA with fibromyalgia outcomes as DV and categories of BDI-II as IV. Pairwise group comparisons with Tukey-Kramer correction whenever there was a statistically significant association. Confounders/covariates: pain and medication as covariates

LR, linear regression; RPE, rating of perceived exertion; rANCOVA, repeated measures analysis of covariance; ANCOVA, analysis of covariance; CRF, cardiorespiratory fitness; PPT, pressure pain threshold; VAS, visual analogue scale; TPC, tender point count; BMI, body mass index; DV, dependent variable; IV, independent variable; FIQR, Revised Fibromyalgia Impact Questionnaire; %BF, percentage of body fat; PASAT, Paced Auditory Serial Addition Task; RAVLT, Rey Auditory Verbal Learning Test; BDI-II, Beck Depression Inventory second edition.

RESULTS

RESULTS

The results of each individual study comprising the present Doctoral Thesis are presented below.

Study I. Validity and reliability of rating perceived exertion in women with fibromyalgia: exertion-pain discrimination

The participant's flow diagram is presented in **figure 1**. Thirty-three participants (mean age 48.1, SD = 7.9 years; mean BMI: 27.0, s_x = 5.8 kg · m^{-2}) completed stages 1 and 2; 28 (84.8%) completed stage 3; 20 (60.6%) completed stage 4; 11 (33.3%) completed Stage 5 and 8 (24.2%) completed stage 6.

Validity

The linear association of RPE with the physiological responses is presented in **figure 2**. The correlations ranged from 0.69 to 0.79 (all P<0.001). The regression models explained ~50% of the total variance from the studied physiological responses (**figure 2**). Exercise-induced pain (P>0.05) and the RPE × pain interaction (P>0.05) were not included in the final models since the predictive capacity of the models was unchanged after their inclusion (**figure 2**). The average values and the linear trend of the perceptual and physiological responses during the first 4 (n=20) and 6 (n=8) workloads are displayed in **table 4** and **table 5**, respectively.

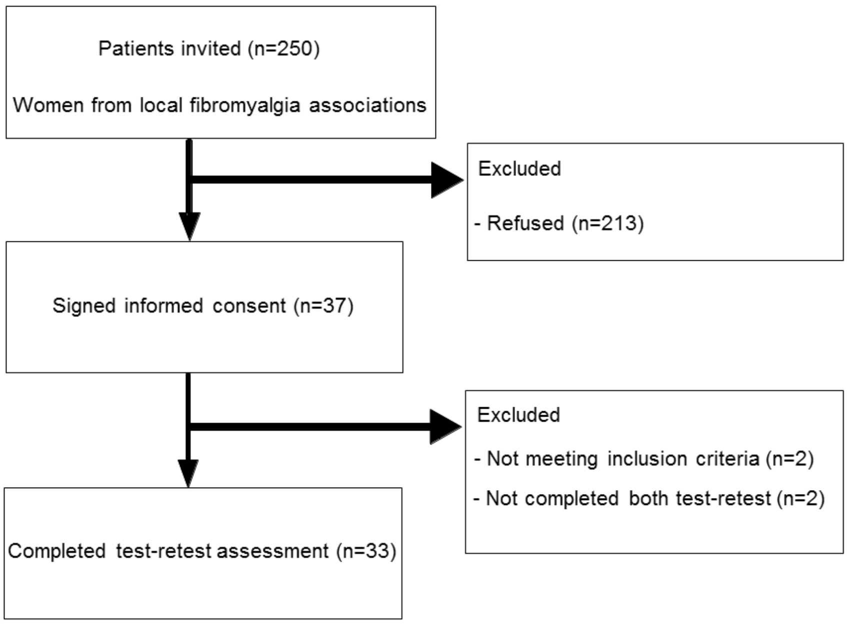

Figure 1. Flow diagram of the study participants in Study I.

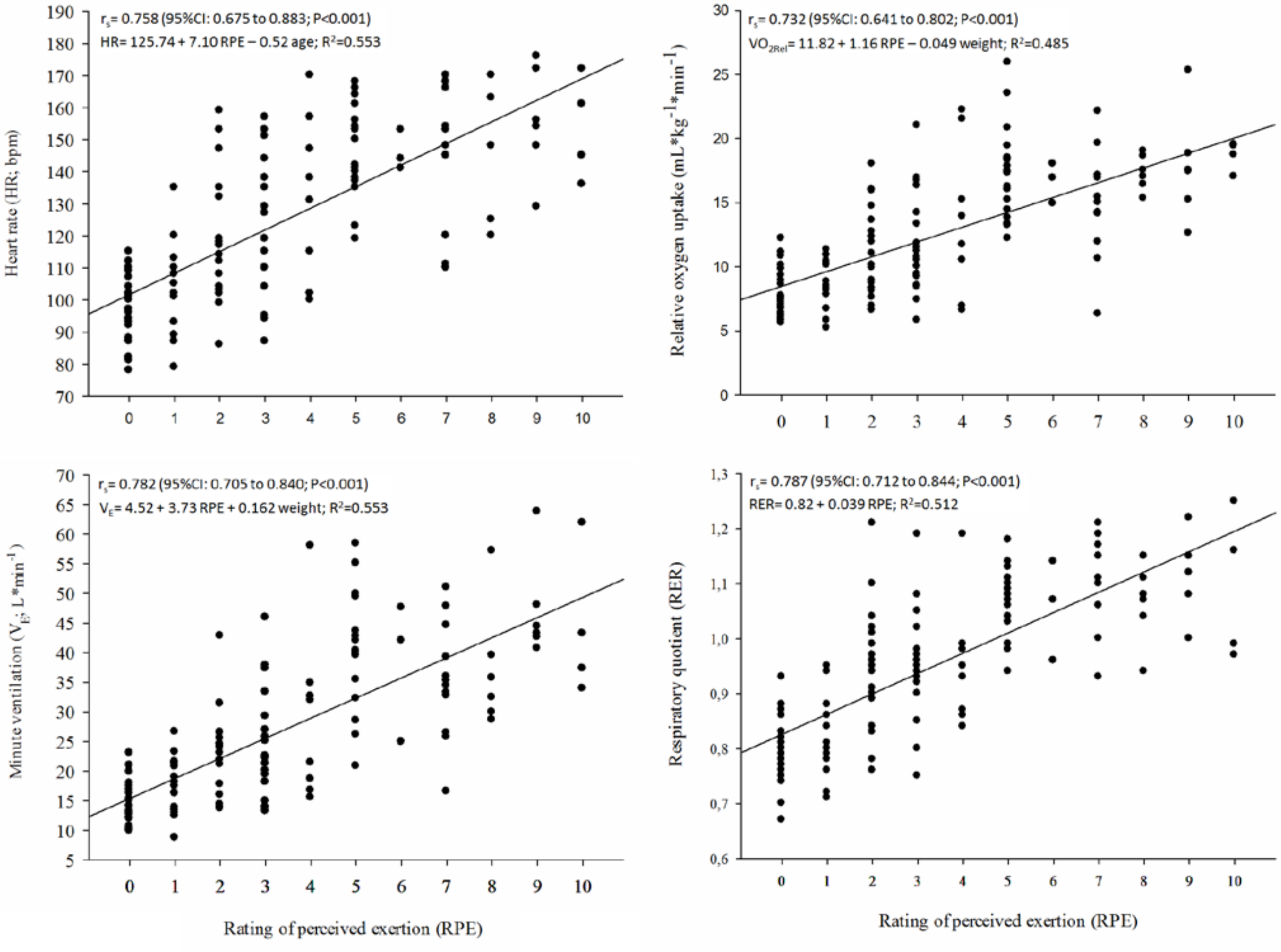

Figure 2. Association between the Rating of Perceived Exertion (RPE) and physiological responses during an incremental treadmill test in women with fibromyalgia.

r_s, Spearman correlation coefficient; CI, confidence interval; R^2, coefficient of determination indicating the proportion of variability explained by the model.

Table 4. Repeated measures ANOVA examining the linear trend of the average perceptual and physiological responses across the first 4 workloads of the incremental treadmill test in women with fibromyalgia.

	Workload 1 (n=20)		Workload 2 (n=20)		Workload 3 (n=20)		Workload 4 (n=20)		P (ANOVA) * Linear trend	Partial eta^2 Linear trend
	Mean	SE	Mean	SE	Mean	SE	Mean	SE		
RPE (CR-10 scale)	0.65	0.221	1.20	0.268	3.90	0.416	5.95	0.515	**<0.001**	0.876
Exercise-induced pain (VAS)	0.59	0.126	0.94	0.158	2.56	0.361	3.87	0.582	**<0.001**	0.676
Heart rate (bpm)	96.3	3.220	106.0	3.530	135.0	4.290	147.7	3.780	**<0.001**	0.950
Relative VO_2 ($mL \cdot kg^{-1} \cdot min^{-1}$)	7.75	0.460	9.59	0.491	14.49	0.734	16.37	0.799	**<0.001**	0.888
RER	0.798	0.015	0.867	0.018	1.045	0.024	1.068	0.022	**<0.001**	0.923
V_E ($L \cdot min^{-1}$)	13.7	0.836	17.4	0.923	31.1	1.931	36.9	2.362	**<0.001**	0.875

RPE, rating of perceived exertion; CR-10, 10-points category ratio scale; VAS, visual analogue scale (range 0-10); % HR max, percentage of the maximal heart rate; % HRR, percentage of the heart rate reserve; VO_2, oxygen uptake; RER, respiratory quotient; V_E, minute ventilation.
* The ANOVA was performed only with the data from the participants who completed workload 4 (n=20).

Table 5. Repeated measures ANOVA examining the linear trend of the average perceptual and physiological responses across the 6 workloads of the incremental treadmill test in women with fibromyalgia.

	Workload 1 (n=8)		Workload 2 (n=8)		Workload 3 (n=8)		Workload 4 (n=8)		Workload 5 (n=8)		Workload 6 (n=8)		P (ANOVA) * Linear trend	Partial eta^2 Linear trend
	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE		
RPE (CR-10 scale)	0.88	0.350	1.25	0.453	3.63	0.706	4.88	0.743	6.13	0.833	7.18	0.730	**<0.001**	0.943
Exercise-induced pain (VAS)	0.44	0.157	0.63	0.216	1.14	0.364	2.03	0.671	2.24	0.695	3.17	0.858	**<0.001**	0.687
Heart rate (bpm)	97.1	5.488	106.6	6.091	131.6	6.231	142.9	4.635	151.6	4.226	161.1	3.948	**<0.001**	0.949
Relative VO_2 ($mL \cdot kg^{-1} \cdot min^{-1}$)	7.70	0.672	9.15	0.681	12.85	0.622	14.54	0.465	17.05	0.702	18.96	1.007	**<0.001**	0.927
RER	0.786	0.030	0.849	0.034	0.979	0.027	1.003	0.034	1.019	0.027	1.046	0.030	**<0.001**	0.956
V_E ($L \cdot min^{-1}$)	13.8	1.459	16.8	1.530	25.9	1.654	30.6	1.811	36.6	1.846	42.3	2.520	**<0.001**	0.957

RPE, rating of perceived exertion; CR-10, 10-points category ratio scale; VAS, visual analogue scale (range 0-10); % HR max, percentage of the maximal heart rate; % HRR, percentage of the heart rate reserve; VO_2, oxygen uptake; RER, respiratory quotient; V_E, minute ventilation.
* The ANOVA was performed only with the data from the participants who completed workload 6 (n=8).

The rANOVA revealed a statistically significant linear increase of perceptual (RPE and exercise-induced pain) and physiological (HR, relative VO_2, V_E and RER) responses during the first 4 incremental workloads (**table 4**). Similar results were obtained when the 6 workloads were included in the analysis (n = 8; **table 5**).

Reliability

"Perfect" agreement was observed in 41.9% (95% confidence interval [CI]: 25.7–58.9%) of the observations, "perfect-acceptable" agreement in 69.0% (95% CI: 52.2–83.6%) and "moderate" agreement in 83.7% (95% CI: 69.7–95.3%) for the test–retest reported RPE. The weighted *k*-coefficient of the test–retest reported RPE was 0.66 (95% CI: 0.59–0.72; P < 0.001).

Exertion-pain discrimination

The difference between RPE and exercise-induced pain across workloads is represented in **figure 3**. There were no differences between the reported RPE and pain during the first 2 workloads (in which exercise intensity was rather low). However, the difference between the two constructs was statistically significant from workload 3 (in which the treadmill speed was 7.5 $km \cdot h^{-1}$) onwards. The ANCOVA revealed that the difference between RPE and exercise-induced pain followed a linear trend with workload increases (**figure 3**).

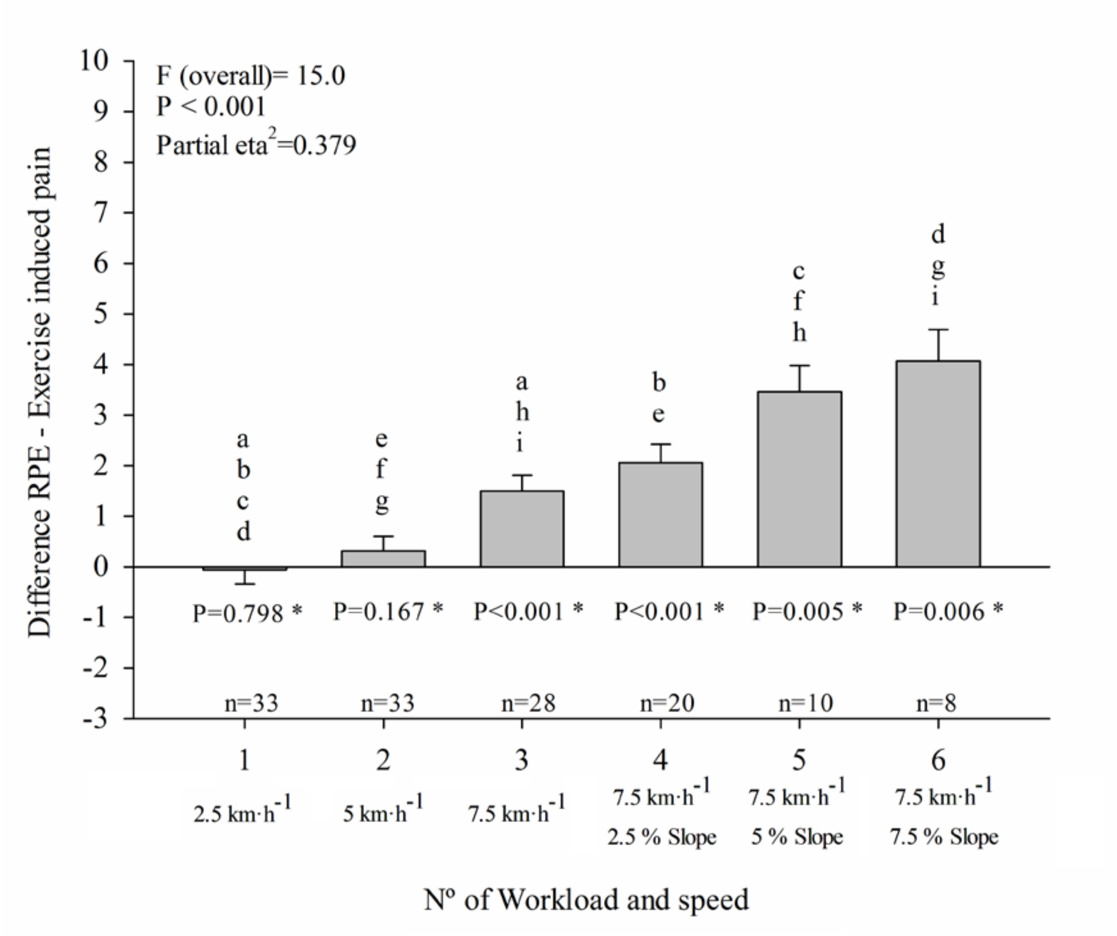

Figure 3. Differences between Rating of Perceived Exertion (RPE) and exercise-induced pain perception across workloads during an incremental treadmill test in women with fibromyalgia.

Common superscripts indicate significant (p < 0.05) differences between the workloads with the same letter (ANCOVA adjusted for age and weight).

* Comparison (one sample t-test vs. 0) between RPE and exercise-induced pain at each workload.

Study II. Association of cardiorespiratory fitness with pressure pain sensitivity and clinical pain in women with fibromyalgia

Thirty-three participants (100%) completed stages 1 and 2 of the treadmill test; 28 (84.8%) completed stage 3; 20 (60.6%) completed stage 4; 11 (33.3%) completed stage 5; and 8 (24.2 %) completed stage 6. Two participants were registered peak VO_2 values of <6 $mL·kg^{−1}·min^{−1}$ and were excluded as they were influencing the consistency of the models, and these values are extremely low to be valid. The characteristics of the study participants are presented in **table 6**. The average peak VO_2 of the study sample was 19.5 $mL·kg^{−1}·min^{−1}$. The average percentage of maximum HR[122] during the test was 93.8% (SD 6.7), and the average maximum (RER) was 1.12 (SD 0.12).

Table 6. Characteristics of the study participants in Study II.

	Women with fibromyalgia (n=31)	
	Mean	**(SD)**
Age (years)	48.3	7.8
Weight (kg)	68.0	13.1
Height (cm)	158.5	5.4
BMI ($kg·m^{-2}$)	27.1	5.2
Average PPT ($kg·cm^{-2}$)	2.3	0.7
TPC (nº positive tender points)	16.7	2.0
Duration of symptoms (years)	17.7	10.8
Peak VO_2 ($mL·kg^{-1}·min^{-1}$)	19.5	3.4
	n (%)	
Marital status (%)		
Married	28 (90.3)	
Single	2 (6.5)	
Widow	1 (3.2)	
Educational status (%)		
Primary school	18 (58.1)	
Secondary school	6 (19.4)	
University medium degree	2 (6.4)	
University higher degree	5 (16.1)	
Current occupational status (%)		
Unemployed	14 (45.2)	
Working full time	6 (19.4)	
Working part time	5 (16.1)	
Sick leave	1 (3.2)	
Inability	1 (3.2)	
Retired/pensioner	4 (12.9)	

Values are mean and standard deviation (SD) unless otherwise indicated. BMI, body mass index; PPT, pressure pain threshold; TPC, tender points count; VO_2, oxygen uptake.

The correlation of the average PPT with the PPT at each of the 18 individual tender points ranged between 0.705 and 0.923 (all, $P<0.001$). The correlations of CRF with the average PPT and VAS were 0.355, ($P<0.001$) and 0.058 ($P>0.05$), respectively. Linear regression revealed that CRF was associated with the PPT (B= 0.093; 95% CI 0.064–0.122; $P<0.001$; R^2= 0.306; **table 7**), but not with VAS (B= 0.068; 95% CI −0.061-0.197; $P>0.05$). Logistic regression revealed that the odds of having <18 tender points was 1.51 (95% CI 1.30–1.75; $P<0.001$) times higher for each additional $mL \cdot kg^{-1} \cdot min^{-1}$ of peak VO_2 (**table 7**). A graphical representation of the relationship of CRF with the average PPT, TCP and VAS is presented in **figure 4**.

Table 7. Multivariable linear and binary logistic regression models assessing the relationship of cardiorespiratory fitness (CRF) with the average pressure pain threshold (PPT) and tender points count (TPC), respectively, in women with fibromyalgia.

	PPT (linear regression)				**TPC (logistic regression)**		
	β	B	95% CI	P	OR	95% CI	P
CRF ($mL \cdot kg^{-1} \cdot min^{-1}$)	0.449	0.093	0.064 , 0.122	**<0.001**	1.506	1.299 , 1.746	**<0.001**
Age (y)	0.012	0.001	-0.011 , 0.014	0.861	1.052	0.995 , 1.113	0.076
BMI ($kg \cdot m^{-2}$)	0.134	0.018	-0.003 , 0.039	0.097	0.995	0.916 , 1.081	0.906
VAS (FIQ-pain, cm)	-0.430	-0.116	-0.149 , -0.083	**<0.001**	0.776	0.670 , 0.900	**0.001**

VO_2, oxygen uptake; BMI, body mass index; VAS, visual analogue scale; FIQ, fibromyalgia impact questionnaire; β, standardized regression coefficient; B, unstandardized regression coefficient; CI, confidence interval; OR, odds ratio.

CRF, Age, BMI and VAS all-together entered into the model as independent variables, while PPT and TPC were entered in separate models as dependent variables. The OR represents the odds of having lower than 18 tender points (divided the odds of having 18 points) as a function of CRF and the other variables in the model. The model was adjusted for Age, BMI and clinical pain (VAS).

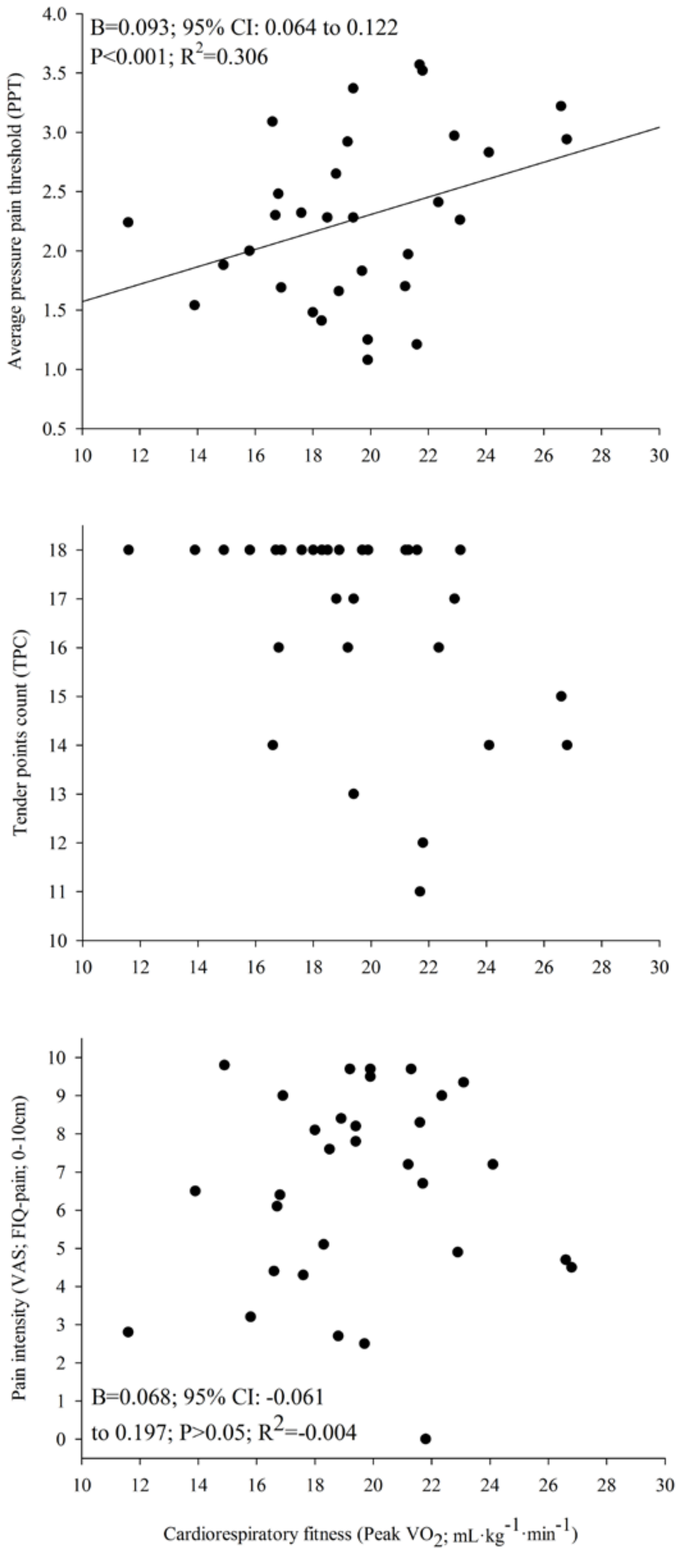

Figure 4. Graphical representation of the association of cardiorespiratory fitness (peak oxygen uptake; VO_2) with experimental (pressure pain threshold and tender points count) and clinical (visual analogue scale) pain in women with fibromyalgia.

B, unstandardized regression coefficient; CI, confidence interval; R^2, proportion of variability explained by the model.

Study III. Association of physical fitness with pain in women with fibromyalgia

The final sample in this study comprised 468 women with fibromyalgia, some of which did not perform some fitness tests due to physical injury (<2.5%). The descriptive characteristics of the study participants are presented in **table 8**. The association of physical fitness with pain, pain-related catastrophizing and chronic pain self-efficacy (primary aim) is presented in **table 9.** Overall, higher performance on physical fitness tests was associated with lower levels of pain (regardless of the assessment tool), lower pain-related catastrophizing and higher chronic pain self-efficacy.

Table 8. Characteristics of the study participants in Study III.

	n	Mean	SD	Min	Max
Age (years)	468	52.1	8.0	28.5	73.5
Weight (kg)	467	71.2	13.8	43.4	130.8
Height (m)	467	157.8	6.0	141.5	177.0
BMI ($kg \cdot m^{-2}$)	467	28.6	5.4	17.4	52.1
Waist circumference (cm)	467	90.5	12.9	60.0	146.0
PPT ($kg \cdot cm^{-2}$)	468	2.4	0.75	1.0	4.2
TPC (number of points)	468	16.8	2.0	11.0	18.0
FIQR-pain (numerical rating scale, 0-10)	468	7.6	1.8	1.0	10.0
VAS (pain; 0-10)	467	6.0	2.2	0.0	10.0
Bodily pain (SF-36 subscale)	466	20.9	14.7	0.0	74.0
PCS (total score)	467	25.0	12.7	0.0	52.0
CPSS (total score)	468	135.4	55.2	6.3	300.0
Chair sit and reach test (cm)	468	-11.3	12.1	-45.0	21.0
Back scratch test (cm)	468	-14.4	12.6	-57.5	17.5
Hand grip strength (kg)	468	19.0	6.5	2.5	40.8
Chair stand test (repetitions)	461	10.3	3.3	2.0	24.0
8 feet up & go test (s)	464	6.9	1.9	4.1	16.9
Arm curl test (repetitions)	458	14.3	5.0	0.0	33.0
6-minute walk test (m)	457	485.4	78.8	246.8	731.2

SD, standard deviation; BMI, body mass index; PPT, pressure pain threshold; TPC, tender point count; FIQR, revised fibromyalgia impact questionnaire; VAS, visual analogue scale; PCS, Pain Catastrophizing Scale; Chronic Pain Self-efficacy Scale; SF-36, short form 36-item health survey.

Table 9. Linear regression models examining the association of physical fitness with pain levels, pain-related catastrophizing and chronic pain self-efficacy in women with fibromyalgia.

	β	B	95% CI	P
PPT				
Sit & reach (cm)	0.206	0.013	0.007 , 0.018	**<0.001**
Back scratch (cm)	0.076	0.004	-0.001 , 0.010	0.135
Hand grip strength (kg)	0.125	0.014	0.004 , 0.025	**0.008**
Chair Stand test (repetitions)	0.231	0.052	0.031 , 0.073	**<0.001**
8 feet up & go (s)	-0.234	-0.075	-0.105 -0.045	**<0.001**
Arm curl (repetitions)	0.239	0.036	0.022 , 0.049	**<0.001**
6-minute walk (m)	0.170	0.001	0.001 , 0.002	**0.001**
TPC				
Sit & reach (cm)	-0.146	-0.024	-0.039 , -0.009	**0.001**
Back scratch (cm)	-0.041	-0.006	-0.022 , 0.009	0.421
Hand grip strength (kg)	-0.079	-0.023	-0.052 , 0.005	0.102
Chair Stand test (repetitions)	-0.111	-0.065	-0.121 , -0.010	**0.020**
8 feet up & go (s)	0.122	0.102	0.022 , 0.182	**0.013**
Arm curl (repetitions)	-0.138	-0.054	-0.091 , -0.017	**0.004**
6-minute walk (m)	-0.124	-0.001	-0.005 , -0.001	**0.015**
FIQR (pain)				
Sit & reach (cm)	-0.193	-0.029	-0.043 , -0.016	**<0.001**
Back scratch (cm)	-0.237	-0.035	-0.049 , -0.020	**<0.001**
Hand grip strength (kg)	-0.199	-0.056	-0.082 , -0.030	**<0.001**
Chair Stand test (repetitions)	-0.194	-0.107	-0.157 , -0.056	**<0.001**
8 feet up & go (s)	0.198	0.156	0.082 , 0.231	**<0.001**
Arm curl (repetitions)	-0.193	-0.071	-0.104 , -0.037	**<0.001**
6-minute walk (m)	-0.266	-0.006	-0.008 , -0.004	**<0.001**
VAS				
Sit & reach (cm)	-0.182	-0.033	-0.049 , -0.016	**<0.001**
Back scratch (cm)	-0.128	-0.022	-0.039 , -0.005	**0.013**
Hand grip strength (kg)	-0.255	-0.084	-0.114 , -0.054	**<0.001**
Chair Stand test (repetitions)	-0.260	-0.169	-0.228 , -0.110	**<0.001**
8 feet up & go (s)	0.178	0.165	0.077 , 0.253	**<0.001**
Arm curl (repetitions)	-0.228	-0.098	-0.137 , -0.059	**<0.001**
6-minute walk (m)	-0.240	-0.006	-0.009 , -0.004	**<0.001**
SF-36 (bodily pain)				
Sit & reach (cm)	0.242	0.294	0.186 , 0.403	**<0.001**
Back scratch (cm)	0.250	0.292	0.177 , 0.406	**<0.001**
Hand grip strength (kg)	0.181	0.405	0.199 , 0.612	**<0.001**
Chair Stand test (repetitions)	0.214	0.949	0.544 , 1.353	**<0.001**
8 feet up & go (s)	-0.215	-1.349	-1.938 , -0.760	**<0.001**
Arm curl (repetitions)	0.233	0.676	0.413 , 0.940	**<0.001**
6-minute walk (m)	0.294	0.050	0.034 , 0.066	**<0.001**

Table 9 (cont.).

	β	B	95% CI			P
PCS (total score)						
Sit & reach (cm)	-0.224	-0.235	-0.327	,	-0.143	**<0.001**
Back scratch (cm)	-0.293	-0.293	-0.389	,	-0.198	**<0.001**
Hand grip strength (kg)	-0.191	-0.368	-0.542	,	-0.194	**<0.001**
Chair Stand test (repetitions)	-0.199	-0.761	-1.106	,	-0.416	**<0.001**
8 feet up & go (s)	0.168	0.906	0.402	,	1.411	**<0.001**
Arm curl (repetitions)	-0.227	-0.571	-0.796	,	-0.346	**<0.001**
6-minute walk (m)	-0.268	-0.039	-0.053	,	-0.025	**<0.001**
CPSS (total score)						
Sit & reach (cm)	0.319	1.445	1.055	,	1.835	**<0.001**
Back scratch (cm)	0.317	1.379	0.965	,	1.793	**<0.001**
Hand grip strength (kg)	0.263	2.205	1.457	,	2.954	**<0.001**
Chair Stand test (repetitions)	0.333	5.508	4.063	,	6.953	**<0.001**
8 feet up & go (s)	-0.342	-8.015	-10.118	,	-5.912	**<0.001**
Arm curl (repetitions)	0.328	3.571	2.620	,	4.522	**<0.001**
6-minute walk (m)	0.437	0.277	0.219	,	0.334	**<0.001**

FIQR, Revised Fibromyalgia Impact Questionnaire; SF-36, 36-Item Short Form health survey; PCS, Pain Catastrophizing Scale; CPSS, Chronic Pain Self-efficacy Scale; VAS, Visual Analogue Scale; β, standardized regression coefficient; B, unstandardized regression coefficient expressing the expected unit change in the dependent variable for each unit change in the independent variable (when the rest of the variables in the model remain unchanged); CI, confidence interval. All the analyses are adjusted for age, body mass index and drugs consumption.

A higher score (s) in the 8 feet up & go test represents lower performance.

A graphical representation of the association of aerobic fitness, muscle strength, flexibility and motor agility (composite scores) with pain, catastrophizing and self-efficacy is presented in **figure 5**. In general, there was a linear (dose-response) relationship so that higher levels of fitness were associated with lower levels of pain and catastrophizing and higher self-efficacy.

The difference on pain-related outcomes between fitness quintiles (Q5 vs. Q1) can be observed in **table 10**. Effect sizes (Cohen's *d*) were generally large ($d \geq |0.80|$) except for PPT that was moderate-to-large ($d=|0.70|$) and TPC that was moderate ($d=|0.47|$).

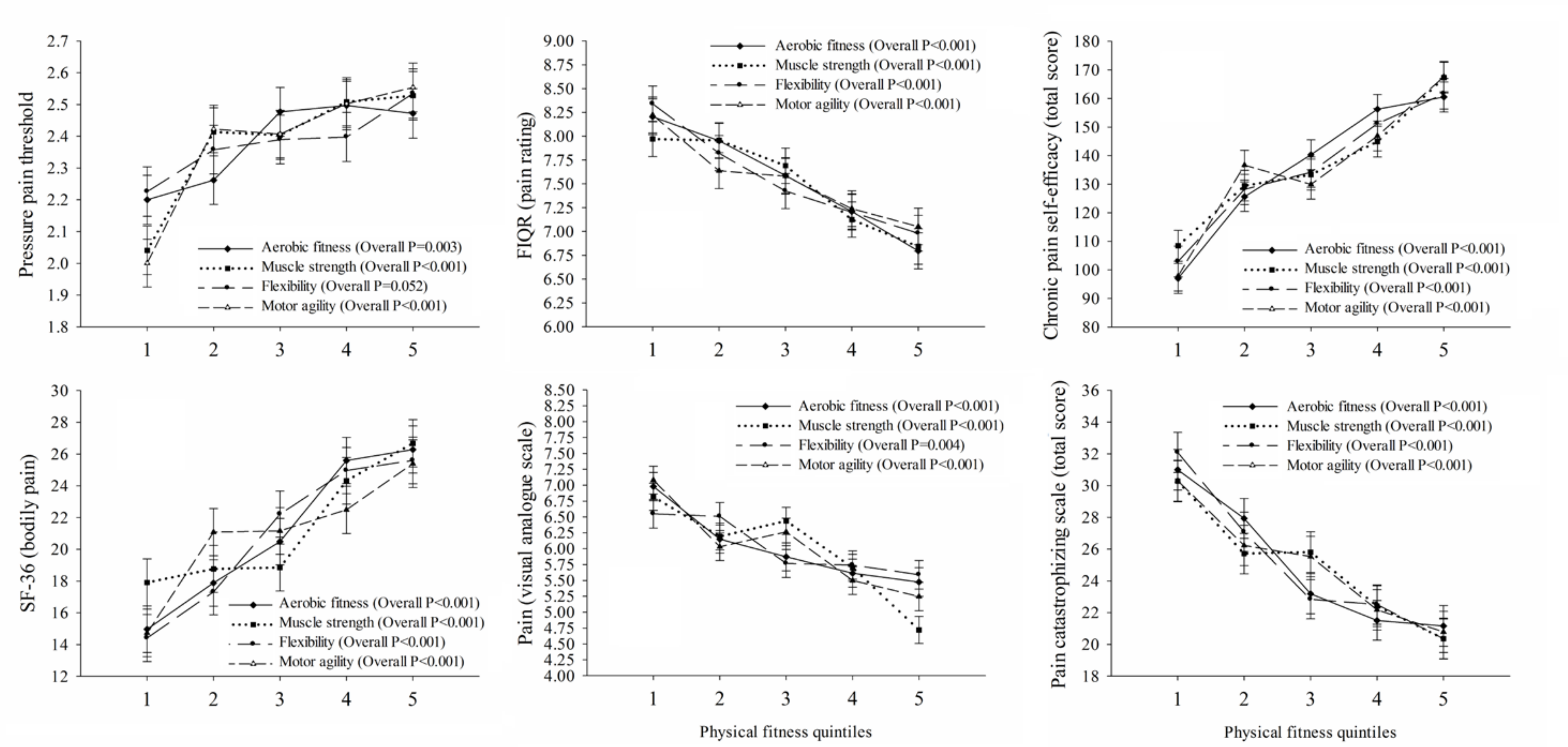

Figure 5. Graphical representation of the association between quintiles of aerobic fitness, muscle strength, flexibility and motor agility with different measures of pain, pain-related catastrophizing and chronic pain self-efficacy in women with fibromyalgia.

Quintile 1 represents the group with the lowest fitness level. Aerobic fitness was computed as the z-score from the 6-minute walk test. Muscle strength was computed as the average of the z-scores from the handgrip, chair stand and arm curl tests. Flexibility was computed as the average of the z-scores from the chair sit and reach and back scratch tests. Motor agility was computed as the z-score from the 8 feet up and go test multiplied by -1 (higher time implies lower performance).

It must be noted that higher pressure pain threshold and bodily pain scores represent lower levels of pain.

Table 10. Differences between participants in quintile 5 (Q5) and quintile 1 (Q1) of the 'global fitness profile' on pain outcomes, pain-related catastrophizing and chronic pain self-efficacy in women with fibromyalgia.

	Q1	Q5	Difference Q5 - Q1	95% CI	P	Cohen's *d*	95% CI of Cohen's *d*
VAS (units)	6.9	5.1	-1.8	-0.3 , -0.9	**<0.001**	-0.85	-1.16 , -0.54
PPT ($kg·cm^{-2}$)	2.06	2.57	0.51	0.20 , 0.82	**<0.001**	0.70	0.40 , 1.00
TPC (number of points)	17.3	16.4	-0.9	-0.2 , -0.1	**0.020**	-0.47	-0.77 , -0.17
Pain rating (FIQR, units)	8.3	6.9	-1.4	-2.1 , -0.6	**<0.001**	-0.80	-1.07 , -0.46
Bodily pain (SF-36)	15.2	27.6	12.4	6.5 , 18.3	**<0.001**	0.88	0.58 , 1.20
PCS (total score)	31.9	19.4	-12.6	-17.7 , -7.5	**<0.001**	-1.02	-1.37 , -0.74
CPSS (total score)	100.5	178.3	77.8	57.2 , 98.3	**<0.001**	1.61	1.27 , 1.94

VAS, visual analogue scale; PPT, pressure pain threshold; TPC, tender point count; FIQR, revised fibromyalgia impact questionnaire; SF-36, 36-Item Short Form health survey; PCS, Pain Catastrophizing Scale; CPSS, Chronic Pain Self-efficacy Scale; Q5 represents the group with the highest 'global fitness profile'; Q1 represents the group with the lowest 'global fitness profile'.

The independent association of different fitness components with the pain-related outcomes (secondary aim 1) is presented in **table 11**. Muscle strength and flexibility were independently associated with the 'global pain profile' (both, P<0.01), while aerobic fitness and flexibility were independently associated with pain-related catastrophizing (both P<0.001) and chronic pain self-efficacy (both P<0.001).

A combined effect (secondary aim 2) was observed so that participants with high muscle strength + high flexibility had significantly lower pain levels than any other group (**figure 6A**). Similar trends were observed for pain-related catastrophizing (**figure 6B**) and chronic pain self-efficacy (**figure 6C**) so that the participants with high aerobic fitness + high flexibility had the best profiles.

Table 11. Stepwise regression models assessing the independent association of the different components of physical fitness with the 'global pain profile', pain-related catastrophizing and chronic pain self-efficacy in women with fibromyalgia.

Global pain profile							
	β	B	95% CI	P (coefficients)	R^2	R^2 change	P (model)
Step 1					0.032	-	**0.001**
Age	0.015	0.001	-0.006 , 0.009	0.754			
BMI	0.054	0.007	-0.005 , 0.018	0.265			
Drugs consumption	0.171	0.128	0.059 , 0.197	<0.001			
Step 2					0.133	0.101	**<0.001**
Age	0.013	0.001	-0.006 , 0.008	0.773			
BMI	0.046	0.006	-0.005 , 0.017	0.321			
Drugs consumption	0.133	0.099	0.033 , 0.165	0.003			
Muscle strength	-0.314	-0.246	-0.315 , -0.177	<0.001			
Step 3					0.148	0.015	**<0.001**
Age	0.014	0.001	-0.006 , 0.008	0.750			
BMI	0.013	0.002	-0.010 , 0.013	0.775			
Drugs consumption	0.121	0.091	0.025 , 0.157	0.007			
Muscle strength	-0.235	-0.184	-0.264 , -0.104	<0.001			
Flexibility	-0.158	-0.128	-0.212 , -0.044	0.003			
Pain-related catastrophizing							
	β	B	95% CI	P (coefficients)	R^2	R^2 change	P (model)
Step 1					0.064	-	**<0.001**
Age	-0.049	-0.006	-0.018 , 0.005	0.301			
BMI	0.139	0.026	0.009 , 0.043	0.003			
Drugs consumption	0.219	0.251	0.148 , 0.355	<0.001			
Step 2					0.138	0.074	**<0.001**
Age	-0.048	-0.006	-0.017 , 0.005	0.290			
BMI	0.078	0.015	-0.002 , 0.032	0.094			
Drugs consumption	0.183	0.209	0.109 , 0.309	<0.001			
Flexibility	-0.285	-0.351	-0.461 , -0.241	<0.001			
Step 3					0.160	0.022	**<0.001**
Age	-0.047	-0.006	-0.017 , 0.005	0.296			
BMI	0.051	0.010	-0.007 , 0.027	0.272			
Drugs consumption	0.167	0.191	0.092 , 0.291	<0.001			
Flexibility	-0.208	-0.257	-0.378 , -0.136	<0.001			
Aerobic fitness	-0.178	-0.185	-0.288 , -0.082	<0.001			

Table 11 (cont.).

Chronic pain self-efficacy							
	β	B	95% CI	P (coefficients)	R^2	R^2 change	P (model)
Step 1					0.048	-	**<0.001**
Age	-0.029	-0.004	-0.015 , 0.008	0.539			
BMI	-0.146	-0.027	-0.044 , -0.010	0.002			
Drugs consumption	-0.166	-0.187	-0.290 , -0.085	<0.001			
Step 2					0.194	0.146	**<0.001**
Age	-0.032	-0.004	-0.014 , 0.007	0.462			
BMI	-0.051	-0.009	-0.026 , 0.007	0.259			
Drugs consumption	-0.106	-0.120	-0.215 , -0.024	0.014			
Aerobic fitness	0.400	0.410	0.320 , 0.499	<0.001			
Step 3					0.236	0.042	**<0.001**
Age	-0.032	-0.004	-0.014 , 0.006	0.452			
BMI	-0.025	-0.005	-0.021 , 0.011	0.565			
Drugs consumption	-0.090	-0.101	-0.195 , -0.008	0.033			
Aerobic fitness	0.295	0.302	0.205 , 0.399	<0.001			
Flexibility	0.239	0.290	0.176 , 0.403	<0.001			

BMI, body mass index; β, standardized regression coefficient; B, unstandardized regression coefficient; CI, confidence interval; R^2, adjusted coefficient of determination, expressing the percent variability of the dependent variable explained by each model; R^2 change, additional percent variability explained by the model due to the inclusion of the new term.

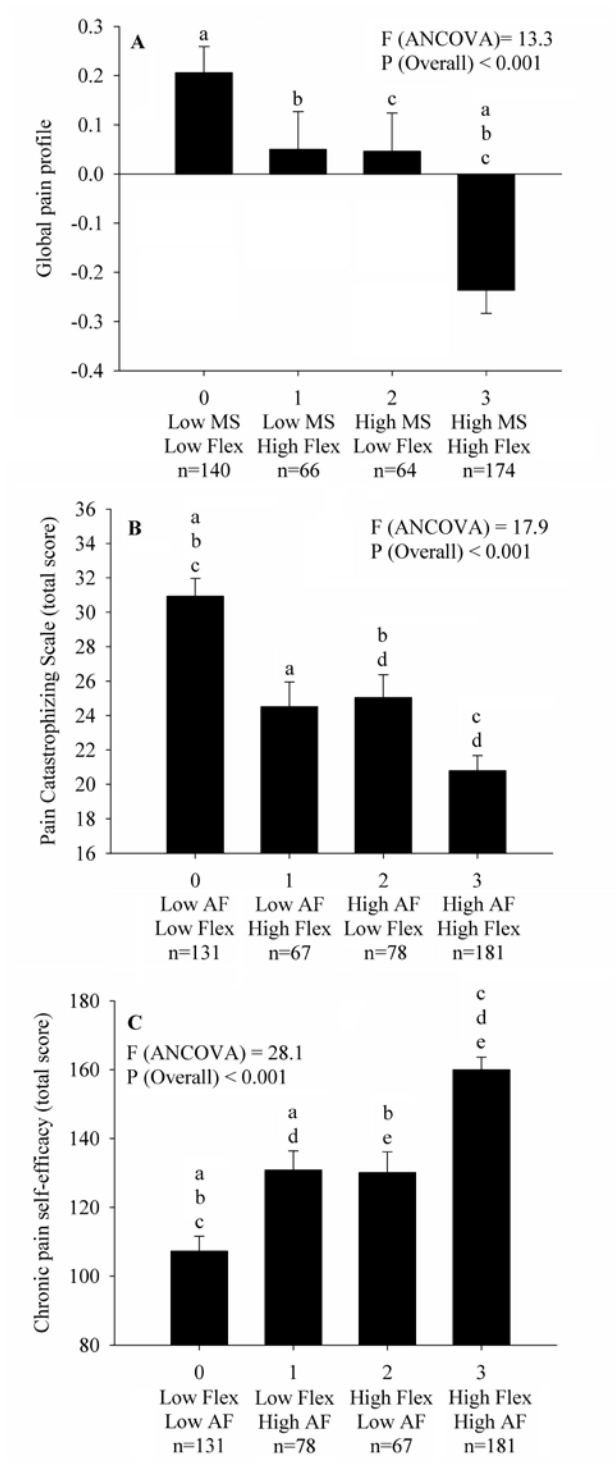

Figure 6. Combined effect of different components of physical fitness on the 'global pain profile', pain-related catastrophizing and chronic pain self-efficacy in women with fibromyalgia.

The reported P-values correspond to the analysis of covariance (ANCOVA; with age, body mass index and drugs consumption as covariates). For each component, high fitness was considered when z-score≥0 and low fitness when z-score<0. MS, muscle strength; AF, aerobic fitness; Flex, flexibility.

Common superscripts indicate significant (P<0.05) differences between the groups with the same letter.

Study IV. Association of physical fitness with fibromyalgia severity in women

The final study sample included in this study consisted of participants with complete data in all study variables (n=444). The descriptive characteristics of the study participants are presented in **table 12**.

The association of physical fitness with the FIQR total score as well as with the different subscales (objective 1) is presented in **table 13**. Higher physical fitness was significantly and consistently associated with lower FIQR total and subscales scores, regardless of the fitness test used. The specific relation of the 'global fitness profile' with each item of the function, overall impact, and symptom severity subscales of the FIQR is presented in **table 14**. With few exceptions, there was a significant association between fitness and self-reported items of the FIQR (P<0.001).

Table 12. Descriptive characteristics of the study participants in Study IV (n=444).

	Mean	**SD**
Age (years)	52.1	7.9
BMI (kg·m^{-2})	28.5	5.2
% body fat	40.1	7.6
FIQR total score (0-100)	64.9	16.7
FIQR function subscale (0-30)	17.3	6.4
FIQR overall impact subscale (0-20)	12.6	5.4
FIQR symptoms subscale (0-50)	34.9	7.7
Chair sit and reach (cm)	-11.3	12.1
Back scratch (cm)	-14.2	12.4
Hand grip (kg)	19.1	6.4
Chair stand (repetitions)	10.4	3.3
Arm curl (repetitions)	14.3	5.0
8 feet up & go (s)	6.9	1.9
6-minute walk (m)	486.0	79.0
	n	**%**
Time since diagnosis		
Less that 1 year	32	7.2
Between 1 and 5 years	154	34.7
More than 5 years	258	58.1
Current occupationa status		
Working	109	24.6
Not working	335	75.5
Drugs consumption		
Analgesics (yes)	400	90.1
Antidepressants (yes)	257	57.9
Anticonvulsants (yes)	75	16.9

SD, standard deviation; BMI, body mass index; FIQR, revised fibromyalgia impact questionnaire.

Table 13. Standardized and non-standardized regression coefficients assessing the association of physical fitness with the FIQR total score and the function, overall impact, and symptoms severity subscales (n=444).

	β	B	SE	95% CI	P
Overall FM severity (FIQR total; 0-100)					
Flexibility (Chair sit and reach, cm)	-0.182	-0.252	0.061	-0.373 , -0.132	**<0.001**
Flexibility (Back scratch, cm)	-0.229	-0.309	0.062	-0.432 , -0.186	**<0.001**
Muscle strength (Hand-grip, kg)	-0.180	-0.473	0.116	-0.701 , -0.245	**<0.001**
Muscle strength (Chair Stand, repetitions)	-0.275	-1.393	0.219	-1.824 , -0.962	**<0.001**
Muscle strength (Arm curl, repetitions)	-0.243	-0.816	0.145	-1.101 , -0.530	**<0.001**
Motor agility (8 feet up and go, s)	0.274	2.471	0.402	1.680 , 3.262	**<0.001**
Aerobic fitness (6-minute walk, m)	-0.307	-0.065	0.010	-0.085 , -0.046	**<0.001**
Function (0-30)					
Flexibility (Chair sit and reach, cm)	-0.162	-0.086	0.025	-0.136 , -0.037	**0.001**
Flexibility (Back scratch, cm)	-0.189	-0.098	0.026	-0.149 , -0.047	**<0.001**
Muscle strength (Hand-grip, kg)	-0.180	-0.182	0.048	-0.275 , -0.088	**<0.001**
Muscle strength (Chair Stand, repetitions)	-0.296	-0.580	0.090	-0.756 , -0.404	**<0.001**
Muscle strength (Arm curl, repetitions)	-0.267	-0.347	0.059	-0.464 , -0.230	**<0.001**
Motor agility (8 feet up and go, s)	0.258	0.901	0.166	0.574 , 1.228	**<0.001**
Aerobic fitness (6-minute walk, m)	-0.299	-0.025	0.004	-0.033 , -0.016	**<0.001**
Overall impact (0-20)					
Flexibility (Chair sit and reach, cm)	-0.142	-0.063	0.020	-0.102 , -0.023	**0.002**
Flexibility (Back scratch, cm)	-0.153	-0.066	0.021	-0.107 , -0.026	**0.001**
Muscle strength (Hand-grip, kg)	-0.090	-0.076	0.038	-0.151 , 0.000	**0.049**
Muscle strength (Chair Stand, repetitions)	-0.210	-0.340	0.073	-0.483 , -0.197	**<0.001**
Muscle strength (Arm curl, repetitions)	-0.172	-0.185	0.048	-0.280 , -0.090	**<0.001**
Motor agility (8 feet up and go, s)	0.185	0.535	0.134	0.272 , 0.799	**<0.001**
Aerobic fitness (6-minute walk, m)	-0.236	-0.016	0.003	-0.023 , -0.010	**<0.001**
Symptoms severity (0-50)					
Flexibility (Chair sit and reach, cm)	-0.163	-0.103	0.028	-0.159 , -0.047	**<0.001**
Flexibility (Back scratch, cm)	-0.235	-0.145	0.029	-0.201 , -0.088	**<0.001**
Muscle strength (Hand-grip, kg)	-0.180	-0.216	0.054	-0.321 , -0.111	**<0.001**
Muscle strength (Chair Stand, repetitions)	-0.205	-0.473	0.102	-0.674 , -0.272	**<0.001**
Muscle strength (Arm curl, repetitions)	-0.184	-0.284	0.068	-0.417 , -0.150	**<0.001**
Motor agility (8 feet up and go, s)	0.251	1.034	0.187	0.667 , 1.402	**<0.001**
Aerobic fitness (6-minute walk, m)	-0.256	-0.025	0.005	-0.034 , -0.016	**<0.001**

β, standardized regression coefficient; B, non-standardized regression coefficient indicating the expected unit change in the dependent variable as one unit increase in the independent variable (once adjusted for potential confounders); CI, confidence interval; FM, fibromyalgia; FIQR, Revised Fibromyalgia Impact Questionnaire.

Each regression model was adjusted for age, % body fat, time since diagnosis, occupational status, and consumption of analgesics, antidepressants and anticonvulsants.

A higher score (s) in the 8 feet up & go test represents lower performance.

Table 14. Regression coefficients assessing the association of the 'global fitness profile' with individual items from the function, overall impact, and symptoms severity subscales from the FIQR (n=444).

	Global fitness profile				
	β	B	SE	95% CI	P
Function subscale					
Comb hair [0-10]	-0.194	-0.862	0.239	-1.331 , -0.393	**<0.001**
Walk for 20 min [0-10]	-0.323	-1.571	0.247	-2.058 , -1.085	**<0.001**
Prepare a meal [0-10]	-0.268	-1.152	0.223	-1.590 , -0.714	**<0.001**
Clean floors [0-10]	-0.247	-0.947	0.203	-1.346 , -0.548	**<0.001**
Carry a bag of groceries [0-10]	-0.185	-0.664	0.193	-1.044 , -0.284	**<0.001**
Climb a flight of stairs [0-10]	-0.219	-0.975	0.232	-1.431 , -0.519	**<0.001**
Change bed sheets [0-10]	-0.308	-1.355	0.226	-1.800 , -0.911	**<0.001**
Sit for 45 minutes [0-10]	-0.168	-0.690	0.223	-1.130 , -0.251	**<0.001**
Go shopping for groceries [0-10]	-0.195	-0.877	0.240	-1.348 , -0.406	**<0.001**
Overall impact subscale					
Can't achieve goals [0-10]	-0.240	-0.928	0.197	-1.314 , -0.541	**<0.001**
Feel overwhelmed [0-10]	-0.189	-0.890	0.241	-1.364 , -0.416	**<0.001**
Symptoms severity subscale					
Pain rating [0-10]	-0.239	-0.603	0.131	-0.859 , -0.346	**<0.001**
Energy rating [0-10]	-0.232	-0.754	0.166	-1.081 , -0.427	**<0.001**
Stiffness rating [0-10]	-0.181	-0.588	0.171	-0.924 , -0.252	**0.001**
Sleep quality [0-10]	-0.147	-0.390	0.141	-0.668 , -0.113	**0.006**
Depression level [0-10]	-0.242	-1.203	0.237	-1.669 , -0.737	**<0.001**
Memory problems [0-10]	-0.176	-0.661	0.201	-1.056 , -0.266	**0.001**
Anxiety level [0-10]	-0.172	-0.746	0.225	-1.188 , -0.305	**0.001**
Tenderness level [0-10]	-0.059	-0.214	0.201	-0.609 , 0.180	0.286
Balance problems [0-10]	-0.251	-0.987	0.206	-1.391 , -0.582	**<0.001**
Environmental sensitivity [0-10]	-0.057	-0.164	0.157	-0.473 , 0.145	0.298

β, standardized regression coefficient; B, non-standardized regression coefficient indicating the expected unit change in the dependent variable as one unit increase in the independent variable (once adjusted for potential confounders); CI, confidence interval; FIQR, Revised Fibromyalgia Impact Questionnaire.

The association of the 'global fitness profile' with the FIQR total score is shown in **figure 7**. There was a linear trend such that higher physical fitness was associated with a lower FIQR total score. The group with the highest fitness level (Q5) had 16% lower fibromyalgia severity (95% confidence interval, 9.0%-22.2%; P<0.001) than did the group with the lowest fitness level (Q1).

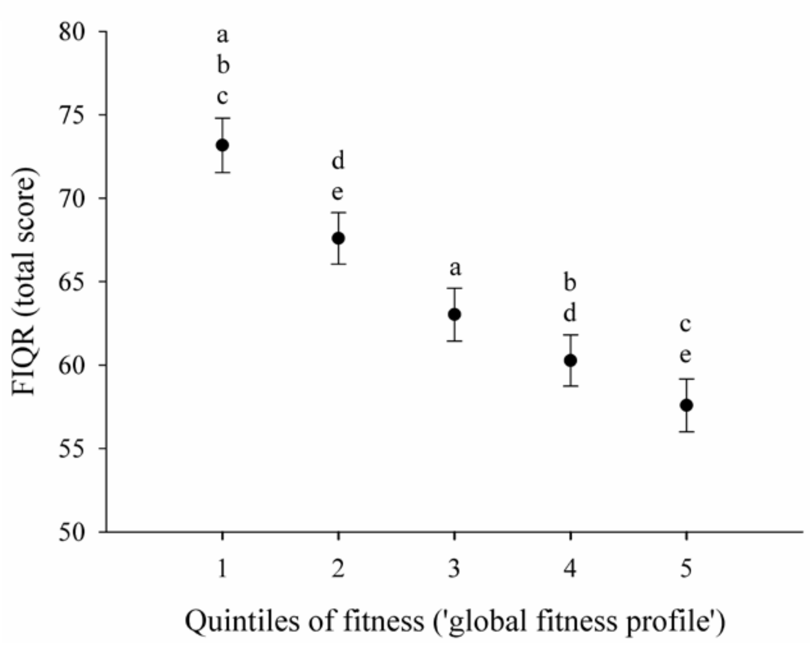

Figure 7. Graphical representation of the association between physical fitness ('global fitness profile') and fibromyalgia severity (as assessed with the Revised Fibromyalgia Impact Questionnaire [FIQR] total score) in women with fibromyalgia.

Comparisons were made using analysis of covariance, with age, % body fat, time since diagnosis, occupational status, and drug consumption as covariates. Bonferroni's correction was applied for multiple comparisons.

Common superscripts indicate significant differences (P<0.05) between the groups with the same letters.

The difference between Q1 (FIQR total score, 73.1) and Q5 (FIQR total score, 57.5) obtained with analysis of covariance was 15.6 (~16%).

The 6-minute walk and the back scratch tests were independently associated with fibromyalgia severity (FIQR total score; objective 2) regardless of potential confounders and the remaining fitness tests that were simultaneously considered (**table 15**).

Table 15. Regression model assessing the independent association of different physical fitness tests with fibromyalgia severity (FIQR total score; n=444).

FIQR total score				
	β	B	SE	P
Age	-0.176	-0.370	0.101	**<0.001**
% body fat	0.015	0.032	0.100	0.747
Occupational status	-0.108	-4.119	1.680	**0.015**
Time since diagnosis	0.086	1.314	0.668	0.050
Analgesics	-0.001	-0.045	2.354	0.985
Antidepressants	0.263	8.826	1.491	**<0.001**
Anticonvulsants	0.115	5.135	1.858	**0.007**
Chair sit and reach	-0.065	-0.092	0.071	0.200
Back scratch	-0.119	-0.166	0.069	**0.016**
Hand-grip	-0.008	-0.020	0.136	0.881
Chair Stand	-0.092	-0.486	0.362	0.180
Arm curl	-0.058	-0.200	0.222	0.367
8 feet up and go	-0.002	-0.022	0.732	0.976
6-minute walk	-0.141	-0.031	0.015	**0.038**

FIQR, Revised Fibromyalgia Impact Questionnaire; β, standardized regression coefficient; B, non-standardized regression coefficient; SE, standard error.

R^2 of the model without fitness variables: 0.186 (18.6%); R^2 change by including the fitness variables: 0.088 (8.8%); Adjusted R^2 of the complete model: 0.274 (27.4%).

Study V. Association of physical fitness and fatness with cognitive function in women with fibromyalgia

The descriptive characteristics of the study participants are presented in **table 16**. Participants were, on average, 52-year old and presented mean BMI and body fat values of 28.6 kg/m^2 and 40%, respectively. Almost 60% of participants reported an educational level of no studies or Primary School and 42% were not working.

Table 16. Descriptive characteristics of the study participants in Study V.

	n	Mean	SD
Age (years)	468	52.2	8.0
Weight (kg)	467	71.2	13.8
Height (cm)	467	157.8	6.0
BMI (kg·m^{-2})	467	28.6	5.4
Body fat (%)	458	40.1	7.6
Fat mass index (kg·m^{-2})	458	11.8	4.2
Waist circumference (cm)	467	90.5	12.9
Waist to height ratio (cm)	466	0.57	0.09
Depression (BDI-II total score, [0-63])	466	26.5	11.6
Pain intensity (FIQR [0-10])	468	7.6	1.8
Chair Sit and reach (cm)	468	-11.3	12.1
Back scratch (cm)	468	-14.4	12.6
Hand grip strength (kg)	467	19.1	6.4
Chair Stand test (repetitions)	461	10.3	3.3
8 feet up and go (s)	461	6.90	1.86
Arm curl (repetitions)	458	14.3	5.0
6-minute walk (m)	457	485.4	78.8
PASAT (correct responses [%])	456	52.0	19.5
PASAT (ommitted responses [%])	456	35.3	18.2
PASAT (incorrect responses [%])	456	12.7	9.3
RAVLT (immediate free recall [0-15])	468	5.4	1.7
RAVLT (delayed free recall [0-15])	466	9.3	3.1
RAVLT (verbal learning [0-75])	468	46.5	9.3
RAVLT (delayed recongnition [0-50])	466	34.7	5.9
		n (%)	
Educationa Status (%)			
No studies		51 (10.9)	
Primary school		227 (48.5)	
Secondary school/Professional training		126 (26.92)	
University medium/higher degree		64 (13.68)	
Current occupationa status (%)			
Not working		198 (42.31)	
Housewife		149 (31.84)	
Working part time/studying		51 (10.9)	
Working full time		70 (14.96)	

SD, standard deviation; BMI, body mass index; BDI, Beck Depression Inventory II; FIQR, revised fibromyalgia impact questionnaire; PASAT, Paced Auditory Serial Addition Task; RAVLT, Rey Auditory Verbal Learning Test.

The association of physical fitness and body fatness with the PASAT and RAVLT scores (objective 1) is displayed in **table 17** and **table 18**, respectively. Overall, model 1 revealed that the four components of physical fitness were associated ($P<0.05$) with fewer omitted responses and a higher number of correct responses (PASAT; $P<0.005$), as well as with better delayed recall, verbal learning and delayed recognition (RAVLT; $P<0.005$). Body fatness (regardless of total or central) was not associated with cognitive performance (all, $P>0.05$), either in model 1 or 2. Model 2 showed that when additional confounders were included, the magnitude of the fitness coefficients decreased, although they remained significant with some exceptions especially in the PASAT, in which only aerobic fitness (correct and omitted responses) and flexibility (correct responses) persisted significant ($P<0.05$; **table 17**). There was no fitness×fatness interaction regarding any of the outcomes (all, $P>0.10$). In order to account for the potential confounding effect of body fat in the fitness-cognition relationship, the analyses regarding physical fitness were repeated including % body fat as covariate and the regression coefficients were unchanged.

Table 17. Linear regression assessing the association of physical fitness and fatness with the Paced Auditory Serial Addition Task (PASAT).

	PASAT							
	Model 1				Model 2			
Correct responses (%)	β	B	95% CI	P	β	B	95% CI	P
Aerobic fitness (6-minute walk, m)	0.186	0.047	0.025 , 0.069	**<0.001**	0.137	0.034	0.011 , 0.058	**0.004**
Muscle strength (z-score)	0.087	2.037	0.040 , 4.034	**0.046**	0.028	0.661	-1.409 , 2.731	0.530
Flexibility (z-score)	0.145	3.417	1.428 , 5.407	**0.001**	0.094	2.209	0.106 , 4.313	**0.040**
Motor agility (8 feet up and go, s)	-0.094	-1.099	-2.107 , -0.091	**0.033**	-0.045	-0.524	-1.561 , 0.513	0.321
Body mass index (kg·m^{-2})	-0.065	-0.235	-0.543 , 0.073	0.134	-0.044	-0.161	-0.468 , 0.146	0.303
Body fat (%)	-0.040	-0.102	-0.324 , 0.120	0.368	-0.021	-0.054	-0.275 , 0.167	0.632
Fat mass index (kg·m^{-2})	-0.050	-0.231	-0.631 , 0.168	0.255	-0.028	-0.130	-0.529 , 0.269	0.523
Waist circumference (cm)	-0.053	-0.081	-0.212 , 0.051	0.227	-0.033	-0.049	-0.180 , 0.081	0.456
Ommitted responses (%)								
Aerobic fitness (6-minute walk, m)	-0.186	-0.044	-0.064 , -0.023	**<0.001**	-0.129	-0.030	-0.052 , -0.009	**0.006**
Muscle strength (z-score)	-0.068	-1.484	-3.376 , 0.408	0.124	-0.004	-0.089	-2.050 , 1.872	0.929
Flexibility (z-score)	-0.133	-2.929	-4.788 , -1.069	**0.002**	-0.078	-1.718	-3.676 , 0.240	0.085
Motor agility (8 feet up and go, s)	0.095	1.046	0.102 , 1.989	**0.030**	0.042	0.460	-0.508 , 1.428	0.351
Body mass index (kg·m^{-2})	0.058	0.197	-0.091 , 0.485	0.179	0.038	0.128	-0.158 , 0.413	0.380
Body fat (%)	0.040	0.095	-0.110 , 0.301	0.364	0.020	0.048	-0.156 , 0.251	0.647
Fat mass index (kg·m^{-2})	0.046	0.201	-0.169 , 0.570	0.286	0.023	0.101	-0.266 , 0.469	0.588
Waist circumference (cm)	0.057	0.080	-0.042 , 0.202	0.199	0.035	0.049	-0.072 , 0.170	0.425
Incorrect responses (%)								
Aerobic fitness (6-minute walk, m)	-0.027	-0.003	-0.015 , 0.009	0.602	-0.035	-0.004	-0.017 , 0.009	0.521
Muscle strength (z-score)	-0.052	-0.553	-1.590 , 0.484	0.295	-0.054	-0.572	-1.667 , 0.522	0.305
Flexibility (z-score)	-0.044	-0.489	-1.568 , 0.591	0.374	-0.044	-0.491	-1.646 , 0.663	0.403
Motor agility (8 feet up and go, s)	0.010	0.053	-0.488 , 0.594	0.847	0.012	0.064	-0.502 , 0.630	0.824
Body mass index (kg·m^{-2})	0.022	0.038	-0.127 , 0.204	0.650	0.019	0.034	-0.135 , 0.202	0.696
Body fat (%)	0.006	0.007	-0.111 , 0.125	0.910	0.005	0.006	-0.113 , 0.126	0.916
Fat mass index (kg·m^{-2})	0.014	0.031	-0.181 , 0.243	0.775	0.013	0.029	-0.187 , 0.244	0.795
Waist circumference (cm)	0.001	0.001	-0.070 , 0.071	0.985	0.001	0.000	-0.071 , 0.072	0.994

β, standardized regression coefficient; B, unstandardized regression coefficient expressing the expected unit change in the dependent variable for each unit change in the independent variable (when the rest of the variables in the model remain unchanged); CI, confidence interval.

The muscle strength z-score was calculated as the weighted average of the standardized scores ([value-mean]/standard deviation) from the chair stand test (lower body strength), hand grip and arm curl tests (upper body strength). The flexibility z-score was calculated as the average of the standardized scores from the chair sit and reach and back scratch tests. A higher score (s) in the 8 feet up & go test represents lower performance.

Model 1: basic model adjusted for age, educational status and occupational status.

Model 2: model 1 + depression (Beck Depression Inventory; BDI-II, total score), pain (FIQR-pain) and stimulants consumption.

Table 18. Linear regression assessing the association of physical fitness and fatness with the Rey Auditory Verbal Learning Test (RAVLT).

	RAVLT									
	Model 1					Model 2				
Immediate free recall (0-15)	β	B	95% CI		P	β	B	95% CI		P
Aerobic fitness (6-minute walk, m)	0.074	0.002	0.000	0.004	0.123	0.052	0.001	-0.001	0.003	0.300
Muscle strength (z-score)	0.053	0.105	-0.077	0.287	0.256	0.039	0.079	-0.113	0.271	0.420
Flexibility (z-score)	0.064	0.129	-0.053	0.311	0.164	0.039	0.078	-0.116	0.273	0.429
Motor agility (8 feet up and go, s)	-0.040	-0.036	-0.118	0.046	0.392	-0.020	-0.018	-0.105	0.068	0.676
Body mass index ($kg \cdot m^{-2}$)	-0.042	-0.013	-0.041	0.015	0.349	-0.038	-0.012	-0.040	0.016	0.401
Body fat (%)	-0.007	-0.002	-0.022	0.019	0.878	-0.004	-0.001	-0.021	0.019	0.933
Fat mass index ($kg \cdot m^{-2}$)	-0.034	-0.014	-0.050	0.022	0.456	-0.030	-0.012	-0.048	0.025	0.523
Waist circumference (cm)	-0.008	-0.001	-0.013	0.011	0.865	-0.004	-0.001	-0.012	0.011	0.924
Delayed free recall (0-15)										
Aerobic fitness (6-minute walk, m)	0.195	0.008	0.004	0.011	**<0.001**	0.186	0.007	0.003	0.011	**<0.001**
Muscle strength (z-score)	0.106	0.380	0.040	0.720	**0.029**	0.088	0.317	-0.041	0.675	0.083
Flexibility (z-score)	0.150	0.556	0.211	0.901	**0.002**	0.128	0.474	0.106	0.841	**0.012**
Motor agility (8 feet up and go, s)	-0.149	-0.246	-0.402	-0.091	**0.002**	-0.125	-0.206	-0.370	-0.043	**0.014**
Body mass index ($kg \cdot m^{-2}$)	0.014	0.008	-0.045	0.061	0.767	0.024	0.013	-0.040	0.066	0.619
Body fat (%)	0.013	0.005	-0.033	0.043	0.787	0.022	0.009	-0.029	0.047	0.656
Fat mass index ($kg \cdot m^{-2}$)	0.014	0.010	-0.058	0.078	0.767	0.025	0.019	-0.050	0.087	0.595
Waist circumference (cm)	0.012	0.003	-0.020	0.025	0.802	0.024	0.006	-0.017	0.028	0.618
Verbal learning (0-75)										
Aerobic fitness (6-minute walk, m)	0.221	0.026	0.016	0.036	**<0.001**	0.185	0.022	0.011	0.033	**<0.001**
Muscle strength (z-score)	0.166	1.813	0.862	2.764	**<0.001**	0.129	1.416	0.421	2.410	**0.005**
Flexibility (z-score)	0.169	1.884	0.926	2.843	**<0.001**	0.118	1.312	0.297	2.327	**0.011**
Motor agility (8 feet up and go, s)	-0.181	-0.900	-1.333	-0.467	**<0.001**	-0.136	-0.678	-1.129	-0.227	**0.003**
Body mass index ($kg \cdot m^{-2}$)	-0.048	-0.083	-0.230	0.065	0.274	-0.030	-0.052	-0.199	0.095	0.485
Body fat (%)	-0.028	-0.034	-0.140	0.073	0.536	-0.010	-0.012	-0.118	0.093	0.816
Fat mass index ($kg \cdot m^{-2}$)	-0.044	-0.097	-0.288	0.095	0.322	-0.022	-0.049	-0.239	0.141	0.611
Waist circumference (cm)	-0.031	-0.022	-0.085	0.041	0.488	-0.012	-0.008	-0.071	0.054	0.789
Delayed recognition (0-50)										
Aerobic fitness (6-minute walk, m)	0.141	0.011	0.004	0.018	**0.003**	0.133	0.010	0.003	0.017	**0.009**
Muscle strength (z-score)	0.140	0.968	0.341	1.596	**0.003**	0.129	0.898	0.233	1.562	**0.008**
Flexibility (z-score)	0.161	1.145	0.507	1.783	**<0.001**	0.146	1.045	0.363	1.728	**0.003**
Motor agility (8 feet up and go, s)	-0.186	-0.594	-0.882	-0.306	**<0.001**	-0.173	-0.554	-0.858	-0.250	**<0.001**
Body mass index ($kg \cdot m^{-2}$)	0.023	0.026	-0.072	0.124	0.608	0.034	0.038	-0.061	0.137	0.454
Body fat (%)	0.022	0.017	-0.054	0.087	0.641	0.032	0.025	-0.046	0.096	0.490
Fat mass index ($kg \cdot m^{-2}$)	0.024	0.034	-0.092	0.161	0.596	0.037	0.052	-0.076	0.181	0.421
Waist circumference (cm)	-0.009	-0.004	-0.046	0.038	-0.190	0.002	0.001	-0.041	0.043	0.960

β, standardized regression coefficient; B, unstandardized regression coefficient expressing the expected unit change in the dependent variable for each unit change in the independent variable (provided other variables remain fixed); CI, confidence interval.

The muscle strength z-score was calculated as the average of the standardized scores ([value-mean]/standard deviation) from the chair stand test, hand grip and arm curl tests. The flexibility z-score was calculated as the average of the standardized scores from the chair sit and reach and back scratch tests. A higher score (s) in the 8 feet up & go test represents lower performance.

Model 1: basic model adjusted for age, educational status and occupational status.

Model 2: model 1 + depression (Beck Depression Inventory; BDI-II, total score), pain (FIQR-pain) and stimulants consumption.

Since body fatness was not associated with cognitive function, the forward stepwise procedure was only used to assess whether the different fitness components presented an independent association with cognitive function (objective 2; **table 19**). In general, aerobic fitness was the only fitness component associated with most measures of cognitive function regardless of potential confounders and the other fitness components included in the models. However, the only fitness component with independent predictive capacity with regards to delayed recognition [RAVLT] was motor agility (P<0.001).

Table 19. Stepwise forward regression assessing the independent association of different components of physical fitness with cognitive function in women with fibromyalgia.

PASAT: Correct responses (%)					**PASAT: Ommitted responses (%)**				
	β	P	Adj. R^2	R^2 change		β	P	Adj. R^2	R^2 change
1st step			0.256		**1st step**			0.265	
Age	-0.166	<0.001			Age	0.152	0.001		
Educational status	0.278	<0.001			Educational status	-0.296	<0.001		
Housewife	-0.050	0.277			Housewife	0.054	0.238		
Working part-time	-0.045	0.327			Working part-time	0.027	0.549		
Working full-time	0.119	0.010			Working full-time	-0.117	0.011		
Depression (BDI-II)	-0.091	0.042			Depression (BDI-II)	0.106	0.017		
Pain (FIQR)	-0.096	0.032			Pain (FIQR)	0.095	0.033		
Stimulants	0.031	0.459			Stimulants	-0.041	0.322		
2nd step			0.271	0.014	**2nd step**			0.278	0.013
Aerobic fitness	0.137	**0.004**			*Aerobic fitness*	-0.129	**0.006**		
RAVLT: Immediate free recall					**RAVLT: Delayed free recall**				
	β	P	Adj. R^2	R^2 change		β	P	Adj. R^2	R^2 change
1st step			0.132		**1st step**			0.061	
Age	-0.170	<0.001			Age	-0.108	0.032		
Educational status	0.246	<0.001			Educational status	0.111	0.026		
Housewife	-0.054	0.263			Housewife	0.037	0.469		
Working part-time	-0.031	0.515			Working part-time	-0.055	0.277		
Working full-time	-0.058	0.238			Working full-time	-0.017	0.742		
Depression (BDI-II)	-0.004	0.936			Depression (BDI-II)	-0.085	0.086		
Pain (FIQR)	-0.110	0.019			Pain (FIQR)	0.029	0.561		
Stimulants	-0.056	0.209			Stimulants	0.012	0.796		
					2nd step			0.087	0.026
					Aerobic fitness	0.186	**<0.001**		

Table 19 (Cont.).

RAVLT: Verbal Learning					RAVLT: Delayed recognition				
	β	P	Adj. R^2	R^2 change		β	P	Adj. R^2	R^2 change
1st step			0.214		**1st step**			0.130	
Age	-0.197	<0.001			Age	-0.234	<0.001		
Educational status	0.292	<0.001			Educational status	0.118	0.013		
Housewife	-0.009	0.841			Housewife	-0.089	0.069		
Working part-time	-0.034	0.457			Working part-time	-0.055	0.245		
Working full-time	-0.075	0.110			Working full-time	-0.038	0.436		
Depression (BDI-II)	-0.120	0.008			Depression (BDI-II)	-0.057	0.228		
Pain (FIQR)	-0.035	0.440			Pain (FIQR)	0.017	0.722		
Stimulants	0.008	0.849			Stimulants	0.033	0.461		
2nd step			0.241	0.026	**2nd step**			0.154	0.024
Aerobic fitness	0.185	**<0.001**			*Motor agility*	-0.173	**0.001**		

PASAT, Paced Auditory Serial Addition Task; RAVLT, Rey Auditory Verbal Learning Test; BDI, Beck Depression Inventory; FIQR, revised fibromyalgia impact questionnaire; β, standardized regression coefficient; Adj. R^2, adjusted coefficient of determination, expressing the percent variability of the dependent variable explained by each model; R^2 change, additional percent variability explained by the model due to the inclusion of the new term. A higher score in motor agility [8 feet up & go test (s)] represents lower performance.

Variables in step 1 remained fixed in the model, and aerobic fitness (6-minute walk), muscle strength (z-score), flexibility (z-score) and motor agility (s) were entered using a forward stepwise method. Variables would enter into the model when P<0.05, and would be left out when P>0.10.

Occupational status was entered as dummy variable with the lowest category (not working) as reference.

The aerobic fitness z-score was computed as the standardized score ([value-mean]/standard deviation) of the 6-minute walk test. The motor agility z-score was computed as the standardized score ([value-mean]/standard deviation) of the 8 feet up and go test.

One way ANCOVA revealed that participants with the highest fitness levels (aerobic fitness or motor agility; Q5) had significantly higher cognitive function than participants with the lowest fitness levels (Q1; P<0.05; **table 20**), with the exception of immediate recall. Cohen's *d* ranged from |0.38| to |0.51|.

Table 20. Cognitive performance of participants in the highest fitness quintile (Q5) compared to that of participants in the lowest fitness quintile (Q1).

	Q1	Q5	Difference Q5 - Q1	95% CI	P	Cohen's *d*
Correct responses (PASAT, %)	47.8	54.8	6.9	1.6 , 12.3	**0.012**	0.39
Ommitted responses (PASAT, %)	39.1	32.7	-6.4	-11.4 , -1.4	**0.012**	-0.38
Immediate free recall (RAVLT, 0-15)	5.1	5.3	0.1	-0.4 , 0.6	0.590	0.08
Delayed free recall (RAVLT, 0-15)	8.4	9.9	1.5	0.6 , 2.5	**0.001**	0.51
Verbal Learning (RAVLT, 0-75)	43.3	47.7	4.4	1.8 , 6.9	**0.001**	0.51
Delayed recognition (RAVLT, 0-50)	33.0	36.0	3.0	1.2 , 4.6	**0.001**	0.51

PASAT, Paced Auditory Serial Addition Task; RAVLT, Rey Auditory Verbal Learning Test; Q, quintile; CI, confidence interval.

The model was adjusted for age, educational status and occupational statuses, depression and pain.

The values of delayed recognition correspond to Q5 and Q1 of motor agility. The rest of the outcomes correspond to Q5 and Q1 of aerobic fitness (derived from stepwise regression in objective 2).

Study VI. Association of physical fitness with depression in women with fibromyalgia

In this study, only participants with complete data in all study variables were included in the analyses (N=444). The descriptive characteristics of the study participants are presented in **table 21**. There were statistically significant differences in the average items-score across the 3 BDI-II subscales (P<0.001), with the somatic elements subscale presenting the highest average score (**table 22**).

Table 21. Descriptive characteristics of the study participants in Study VI (n=444).

	Mean	**SD**
Age (years)	52.0	8.0
BMI (kg·m^{-2})	28.6	5.4
BDI-II total score (0-63)	26.3	11.6
Chair sit and reach (cm)	-11.1	11.8
Back scratch (cm)	-13.9	12.2
Handgrip (kg)	19.3	6.3
Chair stand (repetitions)	10.5	3.2
Arm curl (repetitions)	14.4	4.9
8 feet up and go (s)	6.8	1.7
6-minute walk (m)	487.5	77.9
Pain intensity (FIQR pain; NRS, 0-10)	7.5	1.8
Sleep quality (PSQI total score, 0-21)	12.7	3.8
	n	**%**
Educational Status		
No studies	49	11.0
Primary school	219	49.3
Secondary school/Professional training	116	26.1
University medium/higher degree	60	13.5
Current occupational status		
Not working	181	40.8
Housewife	145	32.7
Working part time/studying	50	11.3
Working full time	68	15.3
Drugs consumption		
Analgesics (yes)	400	90.1
Antidepressants (yes)	254	57.2
Anticonvulsants (yes)	72	16.2

BMI, body mass index; BDI-II, Beck Depression Inventory second edition; NRS, numerical rating scale; FIQR, Revised Fibromyalgia Impact Questionnaire; PSQI, Pittsburgh Sleep Quality Index; SD, standard deviation.

Table 22. Descriptive profile of the different items comprising the Beck Depression Inventory (BDI-II) in women with fibromyalgia.

	Mean	SD	Mean subscale score	P
Negative attitude [0-30][a]				
Sadness	0.99	0.81		
Pessimism	1.27	0.98		
Past failure	0.90	1.00		
Guilty feelings	0.88	0.87		
Punishment feelings	0.59	1.04	0.98 [a,b]	
Self-dislike	1.12	1.08		
Self-criticalness	1.09	0.99		
Suicidal thoughts	0.46	0.64		
Crying	1.35	1.03		
Worthlessness	1.17	0.97		
Performance difficulty [0-18][b]				**<0.001**
Loss of pleasure	1.28	0.82		
Agitation	1.18	0.85		
Loss of interest	1.19	0.90	1.30 [b,c]	
Indeciciveness	1.46	0.99		
Irritability	1.18	0.88		
Concentration difficulty	1.55	0.77		
Somatic symtoms [0-15][c]				
Loss of energy	1.83	0.72		
Changes in sleep	1.72	0.80		
Changes in appettite	1.19	0.98	1.72 [a,c]	
Tiredness or Fatigue	2.05	0.87		
Loss of interest in sex	1.80	1.03		

SD, standard deviation.

P-values correspond to repeated measures analysis of variance comparing the average score across the three subscales of the Beck Depression Inventory II. Common superscripts indicate significant differences (P<0.05) between the groups with the same letter (after applying the Bonferroni's correction for multiple comparisons).

The association of physical fitness with depressive symptoms (objective 1) is displayed in **table 23**. Initial analyses (model 1) revealed a statistically significant association of all fitness tests with the total BDI-II and subscale scores (all, P<0.001). Adjusting for pain, drugs consumption, and sleep quality (model 2) reduced the magnitude of the coefficients (all >10%). However, all the fitness tests presented a statistically significant inverse association with the total BDI-II score (all, P<0.05), with the exception of the chair sit and reach test (P=0.059). Upper-body flexibility was associated with the total (β=-0.148; P=0.001) and subscales scores of the BDI-II (except the somatic elements subscale [P=0.055]), but lower-body flexibility was not related to neither of the outcomes (all, P>0.05). Upper and lower body muscle strength was associated with the total BDI-II score, although there were inconsistencies across the different subscales. Motor agility was consistently associated to the total (β=0.148; P=0.001) and subscale scores of the BDI-II (all, P<0.01). The distance walked in 6 minutes was associated with the total BDI-II score (β=-0.095; P=0.041), but not with the 3 individual subscales (all, P>0.05).

Table 23. Association between physical fitness and depressive symptoms (Beck Depression Inventory; BDI-II) in women with fibromyalgia.

	BDI-II									
	Model 1					Model 2				
	β	B	95% CI		P	β	B	95% CI		P
Total score [0-63]										
Chair sit and reach, cm	-0.217	-0.209	-0.296 ,	-0.122	**<0.001**	-0.079	-0.076	-0.155 ,	-0.076	0.059
Back scratch, cm	-0.288	-0.265	-0.356 ,	-0.174	**<0.001**	-0.148	-0.136	-0.219 ,	-0.054	**0.001**
Handgrip, kg	-0.215	-0.394	-0.563 ,	-0.226	**<0.001**	-0.092	-0.169	-0.319 ,	-0.019	**0.028**
Chair stand, repetitions	-0.233	-0.826	-1.153 ,	-0.500	**<0.001**	-0.089	-0.317	-0.613 ,	-0.021	**0.036**
Arm curl, repetitions	-0.230	-0.542	-0.758 ,	-0.327	**<0.001**	-0.089	-0.210	-0.404 ,	-0.015	**0.035**
8 feet up and go, s	0.288	1.805	1.217 ,	2.393	**<0.001**	0.148	0.927	0.391 ,	1.463	**0.001**
6-minute walk, m	-0.274	-0.040	-0.055 ,	-0.026	**<0.001**	-0.095	0.014	-0.028 ,	-0.001	**0.041**
Negative Attitude [0-30]										
Chair sit and reach, cm	-0.182	-0.097	-0.145 ,	-0.048	**<0.001**	-0.060	-0.032	-0.077 ,	0.013	0.166
Back scratch, cm	-0.264	-0.135	-0.185 ,	-0.084	**<0.001**	-0.144	-0.073	-0.121 ,	-0.026	**0.003**
Handgrip, kg	-0.183	-0.185	-0.278 ,	-0.092	**<0.001**	-0.077	-0.078	-0.165 ,	0.008	0.076
Chair stand, repetitions	-0.200	-0.392	-0.573 ,	-0.210	**<0.001**	-0.073	-0.144	-0.313 ,	0.026	0.097
Arm curl, repetitions	-0.199	-0.260	-0.380 ,	-0.140	**<0.001**	-0.076	-0.099	-0.211 ,	0.013	0.083
8 feet up and go, s	0.251	0.867	0.540 ,	1.194	**<0.001**	0.127	0.440	0.132 ,	0.747	**0.005**
6-minute walk, m	-0.246	-0.020	-0.028 ,	-0.012	**<0.001**	-0.090	-0.007	-0.015 ,	0.000	0.063
Performance difficulty [0-18]										
Chair sit and reach, cm	-0.203	-0.061	-0.089 ,	-0.034	**<0.001**	-0.077	-0.023	-0.049 ,	0.002	0.074
Back scratch, cm	-0.273	-0.079	-0.108 ,	-0.050	**<0.001**	-0.144	-0.042	-0.069 ,	-0.015	**0.002**
Handgrip, kg	-0.203	-0.117	-0.170 ,	-0.063	**<0.001**	-0.088	-0.050	-0.099 ,	-0.002	**0.043**
Chair stand, repetitions	-0.215	-0.238	-0.341 ,	-0.135	**<0.001**	-0.082	-0.091	-0.188 ,	0.005	0.063
Arm curl, repetitions	-0.233	-0.172	-0.240 ,	-0.105	**<0.001**	-0.105	-0.077	-0.140 ,	-0.014	**0.016**
8 feet up and go, s	0.269	0.527	0.341 ,	0.713	**<0.001**	0.142	0.278	0.104 ,	0.453	**0.002**
6-minute walk, m	-0.242	-0.011	-0.016 ,	-0.007	**<0.001**	-0.079	-0.004	-0.008 ,	0.001	0.103
Somatic elements [0-15]										
Chair sit and reach, cm	-0.211	-0.051	-0.073 ,	-0.029	**<0.001**	-0.085	-0.020	-0.041 ,	0.000	0.051
Back scratch, cm	-0.225	-0.052	-0.075 ,	-0.029	**<0.001**	-0.092	-0.021	-0.043 ,	0.000	0.055
Handgrip, kg	-0.203	-0.093	-0.135 ,	-0.051	**<0.001**	-0.088	-0.040	-0.079 ,	-0.001	**0.045**
Chair stand, repetitions	-0.222	-0.197	-0.279 ,	-0.114	**<0.001**	-0.093	-0.082	-0.159 ,	-0.005	**0.037**
Arm curl, repetitions	-0.187	-0.110	-0.165 ,	-0.056	**<0.001**	-0.057	-0.033	-0.084 ,	0.018	0.199
8 feet up and go, s	0.263	0.411	0.263 ,	0.559	**<0.001**	0.134	0.209	0.069 ,	0.349	**0.004**
6-minute walk, m	-0.249	-0.009	-0.013 ,	-0.006	**<0.001**	-0.084	-0.003	-0.007 ,	0.000	0.086

BDI-II, Beck depression inventory second edition; β, standardized regression coefficient; B, non-standardized regression coefficient; CI, confidence interval.

A higher score (s) in the 8 feet up & go test represents lower performance.

[1] Model 1: adjusted for age, body mass index, educational level, marital status and time since diagnosis.

[2] Model 2: adjusted for 'model 1' + pain intensity, drugs (analgesics, antidepressants and anticonvulsants) consumption and sleep quality.

Table 24 presents the adjusted OR for severe depressive symptoms (versus no depressive symptoms) as a function of the different physical fitness tests. The odds of severe symptoms of depression was: 3.7% (95%CI: 5.7 to 1.7%; P<0.001) lower for each additional cm. of performance in the back scratch test; 4.8% (95%CI: 8.2 to 1.2%; P=0.010) lower for each additional kg in the handgrip test; 5.3% (95%CI: 0.6 to 9.8%; P=0.027) lower for each additional repetition on the arm curl test; and 16.9% (95%CI: 2.7 to 33.1%; P=0.018) higher for each additional second (worse performance) on the 8 feet up and go test.

Figure 8 shows the relationship between quintiles of the 'global fitness profile' and the total BDI-II score. The group of patients with the highest 'global fitness profile' (Q5) had, in average, 5.3 (95% CI: 0.6 to 9.9) units (8.4%) lower BDI-II total score than the group with the lowest fitness levels (Q1; P=0.014).

Table 24. Odds ratio (OR) for severe depressive symptoms (versus no severe depressive symptoms) as a function of different components of physical fitness in women with fibromyalgia.

	Severe depressive symptoms		
	OR	95% CI	P
Flexibility (Chair sit and reach, cm)	0.990	0.971 , 1.009	0.301
Flexibility (Back scratch, cm)	0.963	0.943 , 0.983	**<0.001**
Muscle strength (Handgrip, repetitions)	0.952	0.918 , 0.988	**0.010**
Muscle strength (Chair stand, repetitions)	0.942	0.876 , 1.014	0.111
Muscle strength (Arm curl, rep)	0.947	0.902 , 0.994	**0.027**
Motor Agility (8 feet up and go, s)	1.169	1.027 , 1.331	**0.018**
Aerobic fitness (6-minute walk, m)	0.997	0.994 , 1.000	0.059

CI, confidence interval.

Model was adjusted for age, body mass index, educational level, marital status and time since diagnosis, pain intensity, drugs (analgesics, antidepressants and anticonvulsants) consumption and sleep quality.

A higher score (s) in the 8 feet up & go test represents lower performance.

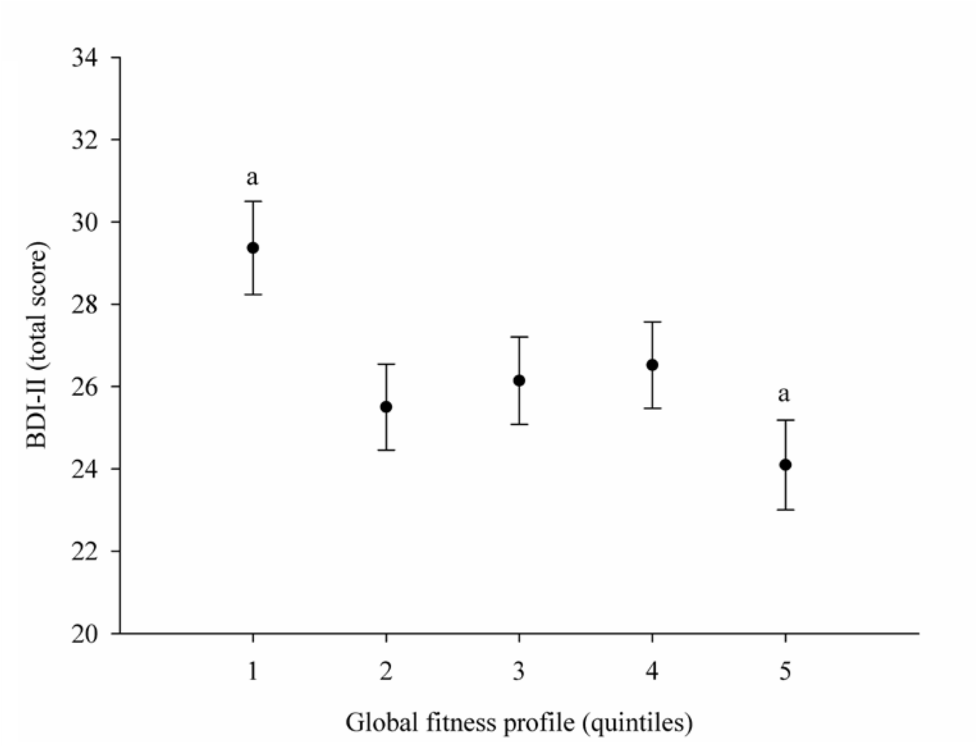

Figure 8. Graphical representation of the association between physical fitness (‘global fitness profile’) and depressive symptoms in women with fibromyalgia.

BDI-II, Beck depression inventory second edition.

Analysis of covariance with the Bonferroni’s correction for multiple comparisons was applied. Covariates: age, body mass index, educational level, marital status and time since diagnosis, pain intensity, drugs (analgesics, antidepressants and anticonvulsants) consumption and sleep quality

Common superscripts indicate significant differences (P<0.05) between the groups with the same letter.

The physical fitness variables that were independently associated to the total BDI-II score (objective 2) are displayed in **table 25**. Among all the fitness tests included in the stepwise procedure, only upper body flexibility (as measured with the back scratch test) was independently related with depressive symptoms. Flexibility entered the model in third position, after sleep quality (R^2=0.186) and antidepressants (R^2=0.064), explaining an additional 2.3% of the BDI-II variance. Age, pain, anticonvulsants and time since diagnosis were included thereafter and explained between 0.9 and 1.3% of the variability.

Table 25. Forward stepwise regression assessing the independent association of different components of physical fitness with depressive symptoms in women with fibromyalgia.

BDI-II Total score				
	β	P	Adj R^2	R^2 change
Step 1			0.186	
Sleep quality	0.300	**<0.001**		
Step 2			0.250	0.064
Antidepressants	0.210	**<0.001**		
Step 3			0.273	0.023
Flexibility (Back scratch)	-0.139	**0.001**		
Step 4			0.284	0.012
Age	-0.089	**0.033**		
Step 5			0.297	0.013
Pain intensity	0.135	**0.001**		
Step 6			0.306	0.009
Anticonvulsants	0.103	**0.010**		
Step 7			0.315	0.009
Time since diagnosis	-0.106	**0.010**		

BDI-II, Beck Depression Inventory second edition; BMI, body mass index; β, standardized regression coefficient; B, non-standardized regression coefficient; Adj. R^2, adjusted determination coefficient expressing the percent variability explained by the model; R^2 change, percent variability change as a result of the inclusion of a new variable in the model.

Study VII. Association of different levels of depressive symptoms with symptomatology, overall disease severity and quality of life in women with fibromyalgia

For all analyses, only participants with complete and valid data for all study variables were included (final sample size: n=451; 92.8%). The descriptive characteristics of the participants are presented in **table 26**. The prevalence of severe and moderate-to-severe symptoms of depression was ~41% and ~71%, respectively. There were no mean differences by level of depressive symptom in PPT, 6-minute walk, and the physical component summary of the SF-36 (all P>0.05), but there were significant group differences in clinical pain intensity, sleep quality, fatigue, overall fibromyalgia severity, and the mental component summary of the SF-36 (all, P<0.001; **table 26**).

Table 26. Descriptive characteristics of the study participants (Study VII) across categories of depressive symptoms severity in women with fibromyalgia (n=451).

			BDI-II depressive symptoms severity categories								
	All (n=451)	**SE**	**Severe** n=183 40.6%	**SE**	**Moderate** n= 133 29.5%	**SE**	**Mild** n=78 17.3%	**SE**	**Minimal** n=57 12.6%	**SE**	**P**
Age (y)	52.0	0.38	51.1	0.588	53.0	0.69	52.6	0.901	51.8	1.1	0.187
BMI (kg·cm^{-2})	28.6	0.25	29.1	0.397	28.5	0.465	27.8	0.608	28.4	0.7	0.337
Educational status (%; [1-2-3-4])‡	11-49-26-14		11-46-25-18		10-52-28-10		18-49-24-9		4-51-26-19		0.122
Drugs Consumption											
Analgesics (yes, %)	90		95		86		86		88		**0.022**
Antidepressants (yes, %)	58		78		50		46		26		**<0.001**
Anticonvulsants (yes, %)	16		25		14		88		77		**<0.001**
Pain											
FIQR-pain (NRS, 0-10)	7.5	0.09	7.9	0.14	7.5	0.15	7.3	0.20	6.8	0.24	**0.001**
PPT [kg·cm^{-2}]	2.4	0.03	2.3	0.06	2.4	0.06	2.5	0.08	2.5	0.10	0.052
TPC [11-18]	16.8	0.09	17.0	0.15	16.8	0.17	16.4	0.22	16.6	0.27	0.152
Sleep Quality											
PSQI [Total score, 0-21]	12.8	0.18	13.8	0.27	12.8	0.30	11.9	0.39	10.6	0.47	**<0.001**
Fatigue											
MFI [global score, 20-100]	75.1	0.56	79.9	0.78	75.1	0.88	70.8	1.17	67.2	1.42	**<0.001**
Functional exercise capacity											
6-minute walk test [m]	486.3	3.71	477.5	5.82	488.2	6.50	497.5	8.53	494.5	10.27	0.235
Fibromyalgia impact											
FIQR total score [0-100]	64.3	0.79	70.2	1.11	64.6	1.25	58.8	1.64	52.6	1.96	**<0.001**
HRQoL											
SF-36 Physical component [0-100]	29.8	0.32	29.7	0.48	30.4	0.53	29.4	0.70	28.9	0.85	0.398
SF-36 Mental component [0-100]	35.7	0.56	30.3	0.72	35.7	0.81	39.9	1.06	47.3	1.28	**<0.001**

Values are mean and standard errors unless otherwise indicated. BDI-II, Beck Depression Inventory second edition; SE, standard error; BMI, body mass index; NRS, numerical rating scale; PPT, pressure pain threshold; TPC, tender points count; PSQI, Pittsburgh Sleep Quality Index; MFI, Multidimensional Fatigue Inventory; FIQR, Revised Fibromyalgia Impact Questionnaire; SF-36, 36-item Short Form health survey.

The P values correspond to analyses of covariance (ANCOVA) for continuous variables and Chi-square for categorical variables.

The comparison of age, BMI, educational status and medication usage across levels of depressive symptoms was performed as a crude (non-adjusted) analysis. The analyses regarding fibromyalgia symptomatology were adjusted for pain intensity (except when pain was the dependent variable) and medication usage (analgesics, antidepressants and anticonvulsants).

‡, 1: No studies; 2: primary school; 3: secondary school/professional training; 4: University degree.

The pairwise comparisons of fibromyalgia-related domains across categories of depressive symptoms are displayed in **table 27**. There was a significant association between severity of depressive symptoms and the fibromyalgia symptomatology factors assessed regardless of pain intensity and medication usage, showing a general trend so that the higher severity of depression, the poorer health-related outcomes. In fact, the group with severe depressive symptoms, compared to the group with minimal signs of depression, presented the largest differences with regards to all fibromyalgia symptomatology factors analyzed (**table 27**).

Table 27. Mean differences (95% confidence intervals [CI]) of symptoms, disease severity and mental health-related quality of life [HRQoL] across different categories of depressive symptoms in women with fibromyalgia (n=451).

	Multiple comparisons across categories of depressive symptoms					
	Severe vs. Minimal	Severe vs. Mild	Severe vs. Moderate	Moderate vs. Minimal	Moderate vs. Mild	Mild vs. Minimal
	Difference (95% CI)	Difference (95% CI)	Difference (95% CI)	Difference (95% CI)	Difference (95% CI)	Difference (95% CI)
Pain						
FIQR-pain (NRS, 0-10)	1.1* (0.3 to 1.8)	0.6 (-0.1 to 1.3)	0.4 (-0.1 to 1.0)	0.6 (-0.1 to 1.4)	0.2 (-0.5 to 0.8)	0.5 (-0.4 to 1.3)
Sleep Quality						
PSQI [Total score, 0-21]	3.2* (1.7 to 4.7)	1.9ǂ (0.6 to 3.2)	1.0 (-0.0 to 2.1)	2.2ǂ (0.7 to 3.6)	0.8 (-0.5 to 2.1)	1.3 (-0.3 to 2.9)
Fatigue						
MFI [Overall score, 20-100]	12.6* (8.2 to 17.1)	9.0* (5.2 to 12.8)	4.8ǂ (1.6 to 7.9)	7.8* (3.5 to 12.2)	4.3ǂ (0.4 to 8.1)	3.6 (-1.2 to 8.4)
Fibromyalgia severity						
FIQR total score [0-100]	17.6* (11.4 to 23.7)	11.4* (6.0 to 16.8)	5.5ǂ (1.0 to 10.0)	12.0* (5.9 to 18.1)	5.9ǂ (0.4 to 11.3)	6.2 (-0.5 to 12.8)
HRQoL						
SF-36 Mental component [0-100]	-17.0* (-21.0 to -12.9)	-9.6* (-13.1 to -6.1)	-5.4* (-8.3 to -2.4)	-11.6* (-15.5 to -7.6)	-4.2ǂ (-7.7 to -0.7)	-7.4* (-11.7 to -3.0)

FIQR, Revised Fibromyalgia Impact Questionnaire; PSQI, Pittsburgh Sleep Quality Index; MFI, Multidimensional Fatigue Inventory; SF-36, 36-item Short Form health survey; CI, confidence interval.
Group comparisons were assessed using analysis of covariance (ANCOVA) adjusted for pain intensity and drugs (analgesics, antidepressants and anticonvulsants) consumption was performed. The Tukey-Kramer's correction for multiple comparisons was applied.
* P<0.001; ǂ P<0.05

DISCUSSION

DISCUSSION

1. Summary of main findings.

The main findings of the present Doctoral Thesis suggest that **I)** The CR-10 scale represents a moderately valid and reliable tool for monitoring exercise intensity in women with fibromyalgia, and women with fibromyalgia seem to be able to discriminate between perceived exertion and exercise-induced pain while exercising; **II)** CRF is severely impaired in women with fibromyalgia, with an average peak VO_2 below the 10^{th} percentile of the American population of the same sex and age[123]. Higher CRF is associated with lower pressure pain sensitivity although not with clinical pain intensity; **III)** Higher performance-based physical fitness is consistently associated with lower levels of pain (regardless of the method used to assess pain), lower pain-related catastrophizing, and higher chronic pain self-efficacy in women with fibromyalgia. Muscle strength and flexibility showed an independent association with pain and a high performance on both components, simultaneously (combined effect), was associated with the lowest levels of pain. Aerobic fitness and flexibility showed independent association with pain-related catastrophizing and chronic pain self-efficacy, and a high performance on both fitness components, simultaneously (combined effect), was associated with the best catastrophizing and self-efficacy profiles; **IV)** Higher physical fitness is consistently associated with lower overall fibromyalgia severity, better function, and lower overall impact and symptom severity in women with fibromyalgia, regardless of potential confounders and the fitness component evaluated. The difference in fibromyalgia severity between the patients with the lowest and the highest fitness levels surpassed the minimal clinically meaningful difference. The 6-minute walk (aerobic fitness) and the back scratch (flexibility) tests, are independently associated with fibromyalgia severity; **V)** Higher physical fitness is positively and consistently associated with information processing, working memory, delayed recall, verbal learning and delayed recognition in women with fibromyalgia. By contrast, body fatness (either total or centrally distributed) does not seem to be associated with the studied cognitive tasks in this population. Aerobic fitness seems to be the most important fitness indicator of the cognitive processes evaluated; **VI)** Higher physical fitness is generally associated with lower depressive symptoms. However, the associations are not consistent across different analyses and BDI-II subscales. **VII)** The prevalence of severe depressive symptoms in women with fibromyalgia from southern Spain is ~41% and the prevalence of moderate-to-severe depression is ~71%. The patients with severe signs of depression have the poorest profile regarding pain intensity, sleep quality, fatigue, overall fibromyalgia severity, and the mental component of HRQoL. However, pressure pain sensitivity, functional exercise capacity, and the physical component of HRQoL are not associated with depressive symptomatology.

2. Discussion of main findings.

2.1. Validity and reliability of rating perceived exertion in women with fibromyalgia: exertion-pain discrimination (Study I)

The correlations of RPE with physiological responses observed in our study (r_s: 0.69–0.79; figure 2) concur with those observed in healthy people[124,125]. Coquart et al.[124] found RPE correlations of 0.75, 0.77 and 0.74 with HR, VO_2 and V_E, respectively. In the same line, Scherr et al.[125] observed an RPE-HR correlation of 0.74. Although the abovementioned studies[124,125] used the Borg 6-20 RPE scale, the association of perceptual and physiological responses seems to be similar to those observed in the present study with the CR-10 scale. Previous research compared the Borg 6-20 RPE scale with the CR-10 scale and concluded that both are similarly valid for monitoring exercise intensity, with the CR-10 scale presenting excellent properties[126]. We observed that the reported RPE explained more than 50% of the variance from most of the studied physiological responses, in agreement with Scherr et al. (2013), who showed that the RPE explained 55% of the HR variance in healthy people. In addition, the perceptual and physiological responses followed an increasing linear trend as exercise intensity increased, suggesting that the studied outcomes (and specifically the RPE obtained with the Borg CR-10 scale) are sensible to exercise intensity changes. Our results therefore indicate that the Borg CR-10 scale represents a valid tool for monitoring exercise intensity in women with fibromyalgia.

The test–retest reliability analysis revealed "perfect-acceptable" agreement in 69% of the observations and the weighted *k* coefficient ranged from 0.59 to 0.72, suggesting that the Borg CR-10 scale is moderately reliable[127] for monitoring exercise intensity in women with fibromyalgia. These results are in line with previous research in healthy people[89]. It is important to note that women with fibromyalgia commonly suffer from cognitive disturbances[64] and depression[128]. As perceived exertion at the same exercise intensity might vary from one day to another as a result of physical and emotional negative factors even in healthy people[129], it is suggested that the percentage of observations with a test–retest difference over 2 units (~17% observations) could be partially explained by the different emotional states commonly observed in women with fibromyalgia.

Whether patients with fibromyalgia are able to discriminate between RPE and exercise-induced pain during exercise, and especially as exercise intensity increases, is unclear. Several studies found that the RPE responses to exercise of patients with fibromyalgia are higher in comparison to those of healthy participants even at low intensities[29,31]. This finding has been explained by the fact that patients with fibromyalgia might not be able to discriminate between perceived exertion and exercise-induced pain during exercise[29]. In this line, as a result of an enhanced exercise-induced pain with workload increments[31], women with fibromyalgia might have been expected to overestimate perceived exertion[29]. In contrast to this hypothesis, our results suggest that women with fibromyalgia are able to discriminate between RPE and exercise-induced pain, since the differences between both constructs were increasingly higher, especially from workloads 3 to 6. These results indicate that there must be other factors explaining the higher perceived exertion observed in patients with fibromyalgia in comparison to healthy people[29,31]. The implicit fatigue generally observed as one of the main symptoms in women with fibromyalgia, which has been recently suggested to be of central instead of muscular origin[130], could partially explain the above-mentioned results.

These findings, overall, suggest that the CR-10 scale might be used to monitor exercise intensity in women with fibromyalgia in research or clinical settings.

2.2. Association of cardiorespiratory fitness with pressure pain sensitivity and clinical pain in women with fibromyalgia (Study II)

Previous literature on the relationship between CRF and pain in women with fibromyalgia is controversial. Carbonell-Baeza et al.[55] observed a direct and inverse relationship between the distance walked in the 6-minute walk test and the PPT and TPC, respectively. By contrast, Hooten et al.[57] reported that peak VO_2 was not related to the PPT in fibromyalgia patients, after controlling for VAS. We observed a positive linear association of CRF with the PPT. However, it is also important to point out that other fitness components, such as muscle strength or flexibility are also related to positive pain-related outcomes in fibromyalgia patients[21,58]. Therefore, the level of muscle strength or flexibility could play a role in the above-mentioned relationship and was not examined in this study. Future studies should address the combined association of CRF and other components of fitness with pain sensitivity and clinical pain in this population.

Some potential pain-related mechanisms could potentially be influenced by increasing CRF through physical activity. McLoughlin et al.[131] observed that self-reported physical activity was directly associated with higher activity in brain regions responsible for pain modulation and inversely related to the activity in areas implicated in the sensory/discriminative aspects of pain processing. Future studies will determine whether higher CRF is related to lower activity of the brain areas involved in the pain-related sensory tasks and higher activity in the modulatory/regulatory areas of the brain.

Peripheral mechanisms, such as aberrations in microcirculatory capillaries[132], or abnormalities at the mitochondrial level[133] might reduce peripheral tissue oxygenation and play an important role in the development of central sensitization. In this context, it could be speculated that an increased tissue oxygenation as a result of increasing CRF through aerobic exercise[134] could reduce peripheral and central sensitization and consequently diminish clinical pain[21]. However, we found no association of CRF with clinical pain, which contrast with previous research reporting pain severity reductions following aerobic exercise training[21]. It is possible that aerobic exercise has a positive effect on clinical pain intensity regardless of CRF changes, which warrants further investigation.

These preliminary results extend current knowledge on the association between CRF and pain in women with fibromyalgia and lead to the possibility that CRF could potentially be involved in some of the mechanisms of pain processing. However, future longitudinal and intervention studies with larger sample size are needed to confirm or contrast the present results. It is also of clinical relevance to highlight that the average peak VO_2 observed in the present study (19.5 mL kg^{-1} min^{-1}) was below the 10th percentile of the American population of the same sex and age [14]. These finding suggest that women with fibromyalgia have a considerably impaired aerobic capacity and, as low CRF is a risk factor for mortality and for many pathologies, exercise programs aiming at improving CRF could be advisable to improve general health in women with fibromyalgia.

2.3. Association of physical fitness with pain in women with fibromyalgia (Study III)

The association between aerobic fitness and pain in women with fibromyalgia is controversial. Previous studies showed that the distance walked in the 6-minute walk test was inversely associated with pain sensitivity[55], self-reported pain intensity[135] or pain interference[135]. Study II of the present Doctoral Thesis revealed that peak VO_2 was associated with pain sensitivity but not with clinical pain intensity. These results from a large sample of women with fibromyalgia from southern Spain indicate that higher aerobic fitness is consistently associated with lower pain levels (regardless of the method used to assess pain).

Muscle strength was the fitness component more strongly associated with the experience of pain. These result support previous findings on the association between muscle strength (as assessed with either isometric[57], isokinetic[56,57], or with functional fitness tests[54,55]) and pain. The association of flexibility with pain in fibromyalgia patients has received limited attention. Our results also support previous studies[54,55] suggesting that flexibility might be a relevant component of physical fitness in this population. Although exercise programs rarely focus on specific flexibility training, the present study provide evidence suggesting that it should be taken into account in future exercise interventions studies, since it is consistently and independently (from other fitness components) associated with lower pain levels, but also with psychological dimensions of pain (i.e. catastrophizing and self-efficacy).

Our exploratory analyses suggest that muscle strength and flexibility could be more strongly associated with pain levels, while aerobic fitness and flexibility could be more strongly associated with the psychological experience (i.e. catastrophizing and self-efficacy) of pain. However, Hooten et al.[21] revealed equal reductions in pain severity following either strengthening or aerobic exercise training. Aerobic fitness has also been reported to be inversely associated with overall fibromyalgia severity[136] and most exercise intervention programs in fibromyalgia patients involve both aerobic and muscle strengthening exercises[22,80,137,138]. Therefore, these exploratory results must be interpreted with caution.

Potentially, several pain-related mechanisms could be positively influenced by enhancing different components of physical fitness through exercise. Previous research has shown that reduced resting-state functional connectivity in sensory-motor systems and augmented unpleasantness to non-painful sensory stimuli are strongly predictive of clinical pain in fibromyalgia patients[139,140]. It might be hypothesized that a low basal muscle tone could contribute to this reduced connectivity in a process leading to peripheral sensitization. In this sense, enhancing basal muscle tone (e.g. through multicomponent exercise programs) could potentially improve resting-state functional connectivity in sensory-motor systems and reduce peripheral sensitization and clinical pain, which warrants further research. Similarly, peripheral mechanisms (e.g. abnormalities in microcirculatory capillaries[132] or irregularities in mitochondrial[133]) might reduce peripheral tissue oxygenation and lead to central sensitization in fibromyalgia patients. Thus, it might be speculated that increasing tissue oxygenation as a results of aerobic exercise could potentially diminish peripheral and central sensitization and reduce clinical pain[21]. The exercise-induced endogenous opioid activity in the central and peripheral nervous system[141] could also partially justify pain reductions observed following exercise programs in fibromyalgia [20,21].

The inverse association observed between physical fitness and pain-related catastrophizing suggests that fitness might have a positive role on the negative attitudes that women with fibromyalgia have towards pain. Previous studies have shown inverse associations between aerobic fitness and depression[44], which might underlie a less negative appraisal of pain and, consequently, lower catastrophizing scores. Similarly, the direct association observed between fitness and chronic pain self-efficacy concurs with previous intervention studies reporting concurrent improvements in fitness and self-efficacy following an exercise intervention[142]. The mere improvement of physical fitness as a result of exercise training could enhance self-efficacy through a feedback of higher ability to deal with activity of daily living, although mood changes following exercise training might also mediate the patient's ability to cope with chronic pain[142]. Further research on the relationship between fitness levels and the psychological experience of pain in women with fibromyalgia and their ability to cope with the disease is warranted.

The average pain intensity in the group with highest 'global fitness profile' (Q5) was 1.8 units lower (as measured by VAS) than was in the group with lowest fitness (Q1). This equals the minimal clinically meaningful difference in chronic pain patients[143]. To our knowledge, the minimal clinically meaningful difference with regards to the rest of the study outcomes in fibromyalgia patients is unclear. Therefore, we used standardized mean difference (Cohen's *d*) as a measure of the potential clinical relevance of our findings. The magnitude of the difference between participants on extreme fitness quintiles (Q5 vs. Q1) ranged from moderate to large, being particularly larger on pain-related catastrophizing and self-efficacy. These results, overall, provide further consistency to our findings and highlight that physical fitness might be an important factor to consider in the management of this population. However, future prospective studies are needed to confirm or contrast our results.

2.4. Association of physical fitness with fibromyalgia severity in women (Study IV)

This study represents the first comprehensive characterization of the association between different components of physical fitness and fibromyalgia severity in women with fibromyalgia. Our results indicate that physical fitness (as assessed with field-based tests) is not only significantly associated with the FIQR total and subscales scores but is also consistently associated with individual items of self-reported daily function (e.g. comb hair, change bedsheets, or go shopping for groceries), overall impact (e.g. achieve goals), or symptom severity (e.g. pain, stiffness, sleep, memory, or depression) in women with fibromyalgia. We showed that the highest fitness group (Q5) had 16% lower fibromyalgia severity than did the lowest fitness group (Q1). It is likely that this surpasses the minimal clinically meaningful difference on the basis of the 14% cut point reported by Bennett et al.[144] with the original version of the FIQ. These results suggest that the association of physical fitness with fibromyalgia severity should be further explored because it might potentially have implications for the rehabilitation of patients with fibromyalgia. Although several studies reported simultaneous increase in physical fitness and improvement in symptoms and quality of life after exercise programs[20,21,80], modest effect sizes, especially in the long run, are generally observed and it is still unclear to what extent an increase in fitness is directly associated with an improvement in self-reported outcomes. Future studies should address these issues to determine the importance of enhancing specific components of fitness as part of multidisciplinary rehabilitation programs in patients with fibromyalgia.

This study also sought to determine which fitness components were independently associated with fibromyalgia severity. The results revealed that aerobic fitness (as assessed with the 6-minute walk test) and flexibility (back scratch test) were independently associated with fibromyalgia severity, suggesting that these components of fitness are the most relevant with regard to the overall burden of fibromyalgia on the patient's life. Our results extend previous evidence that fitness testing could be used as a complementary tool in the diagnosis of fibromyalgia[46] and reveal that different fitness components are consistently associated with lower fibromyalgia severity in this population. Future longitudinal studies should determine the extent to which changes in these performance-based fitness tests (measures at the body level) are associated with changes in observed and self-reported measures of activity and participation in this population.

Although there is a consistent association between fitness and disease severity, it was somewhat surprising that the total variability explained by fitness tests (<10%) was fairly low, especially considering that function accounts for 30% of the FIQR total score. It must be noted that we included potential confounders (age, drug consumption, occupational status, etc.) in our model to obtain adjusted estimates of the associations. Mannerkorpi et al.[135] observed that the 6-minute walk test explained 24% of the function FIQ (original version) subscale. However, the absence of potential confounders in their models might have led to an overestimated explained variance. It has been previously suggested that performance-based measures of physical function at the body (aerobic capacity, muscle strength, etc.)[56,60,145] or activity (assessment of motor and process skills) level[145] present only a weak to moderate association with self-reported outcomes in patients with chronic pain and fibromyalgia[56,60,145]. Bandak et al.[130] observed that patients with fibromyalgia overestimated self-perception of muscle fatigue in comparison with objective (electromyography) muscle signs of fatigue and suggested that central mechanisms are likely to explain the disagreement between objective and self-perceived performance. Similarly, although cognitive dysfunction is a core self-reported symptom among patients with fibromyalgia[62], some studies have failed to find significant differences in neuropsychological measures between patients with fibromyalgia and healthy controls[5]. Therefore, it seems that some kind of disconnection between self-reported and performance-based measures exists in this population. Further research aiming at explaining the factors influencing potential disagreement between performance-based and self-reported outcomes in fibromyalgia would be of major interest for the implementation of multidisciplinary rehabilitation programs tailored at improving specific limitations of certain subgroups of patients with differential characteristics.

2.5. Association of physical fitness and fatness with cognitive function in women with fibromyalgia (Study V)

This study represents the first comprehensive examination of the relationship between fitness and fatness with cognitive function in a large sample of women with fibromyalgia. Our results revealed that aerobic fitness seems to be the fitness component more strongly associated with information processing and working memory in women with fibromyalgia. In fact, the group with the lowest aerobic fitness had the lowest percentage of correct responses and the highest percentage of omitted responses in our population. We also observed that with some exception, aerobic fitness, muscle strength, flexibility and motor agility were all directly associated with verbal learning and memory functioning (delayed recall and delayed recognition), although not with immediate recall. These results partially contrast with Cherry et at.,[71] who found no relationship of physical performance with either immediate or delayed recall. Nonetheless, our results reinforce the role of physical fitness in relation to cognitive performance in fibromyalgia and warrant further longitudinal and intervention studies to determine its potential to predict cognitive functioning at follow-up. It is also of interest to study whether improvements in different fitness components following exercise interventions might be associated with better cognitive performance.

Aerobic fitness was the fitness component most strongly associated with information processing and working memory, as well as with delayed recall and verbal learning. Although it is difficult to determine whether these results are clinically relevant, the effect size of the difference in the above-mentioned cognitive tasks of participants with the highest (Q5) versus lowest (Q1) fitness levels ranged from $d=|0.38|$ to $d=|0.51|$ (except immediate recall that was not statistically significant), indicating a moderate effect size that could be important. These findings are supported by observational and intervention studies in healthy older adults in which higher aerobic fitness is consistently associated with better cognitive function[146,147]. Specifically, higher brain activation in the frontal, temporal and parietal areas of the brain cortex (related to executive control: attention, working memory or task switching) have been observed in participants with higher aerobic fitness during highly demanding cognitive tasks[146,148]. In addition, aerobic training preserves brain gray and white matters[149], which are associated with working memory in fibromyalgia patients[65,150].

Motor agility was the only fitness component independently associated with delayed recognition. As reported by Voelcker et al.[151] this fitness component involves movement speed, balance, and fine coordination, and shows strong associations with cognitive functioning and brain activation in healthy older adults[151,152]. These authors suggested that motor agility seems to be associated with less effort to inhibit distracting information, which could be beneficial for delayed recognition tasks.

To our knowledge, this is the first study addressing the relationship between body fatness and cognitive function in fibromyalgia. In contrast to our hypothesis, our results suggest that there is no association between fatness and cognitive function regardless of the cognitive process or the measure of body fatness evaluated. These results contrast emerging evidence in healthy adults, in which obesity has been linked to decreased brain volume[153], reduced white matter integrity[154] and diminished gray matter volume in the frontal lobe[155], which is suggestive of an inverse relationship between obesity and cognition[156]. It could be speculated that age-related morphological alterations in fibromyalgia[150,157] play a more prominent role in brain damage than obesity itself. However, further research on potential factors associated to a better cognitive performance in this population is needed.

The assessment of cognitive function by the PASAT and RAVLT tests does not represent a complete assessment of cognition, which is a limitation of this study. However, these tests have repeatedly been used in the assessment of cognitive tasks related to executive function which is particularly impaired in fibromyalgia patients[106,110,158]. Therefore, our results represent new findings into the importance of physical fitness in relation to several important aspects of cognitive performance in this population.

2.6. Association of physical fitness with depression in women with fibromyalgia (Study VI)

Most of the current literature on the relationship between physical fitness and depression has focused on either aerobic fitness or muscle strength[44,45,159]. Gerber et al.[160] reported that moderate or high cardiorespiratory fitness had protective effects against depressive symptoms in health care workers. A large epidemiological study in previously healthy women[44] revealed that women with moderate and high aerobic fitness (maximal metabolic equivalents; METs) had between 46 and 54% lower odds of incident depression, respectively, than those with low aerobic fitness. By contrast, we observed only a borderline significant association between the 6-minute walk distance and the total BDI-II score, and this association was inconsistent across BDI-II subscales. Furthermore, aerobic fitness was not associated with the odds of severe depressive symptoms. Although the methods used to assess depressive symptoms and aerobic fitness differ between studies, our results suggest that the relationship between aerobic fitness and depressive symptoms in women with fibromyalgia might not be, in practical terms, clinically relevant. Several studies have observed improvements in depressive symptoms following exercise intervention programs, although it has been suggested that improvements in aerobic fitness in fibromyalgia is not related to improvements in depression[79]. Therefore, it is possible that exercise could have beneficial effects on depressive symptoms (e.g. through an increase of endorphins) without the need of enhancing aerobic capacity[79].

Summary evidence suggests that strength training reduces the level of depression in healthy adults[161] and also in patients with fibromyalgia[80,162]. Sener et al.[163] observed that hand-grip strength modestly correlated (r_P=-0.26 to -0.23) with depressive symptoms (BDI total score) in women with fibromyalgia, although confounding might have played a role in this relationship. Our results support a modest association between muscle strength (especially upper body) and depressive symptoms, since the odds of severe depressive symptoms was 4.8% and 5.3% lower for each additional unit in the hand-grip and arm curl tests, respectively. However, it is unclear whether these associations are clinically meaningful.

To our knowledge, this is the first study reporting on the relationship between motor agility and depressive symptoms in women with fibromyalgia. Motor agility was associated with both the total BDI-II score and the 3 subscales representing different aspects of depression (negative attitude, performance difficulty and somatic elements). The odds of severe depressive symptoms was 16.9% higher for each additional second (worse performance) in the 8 feet up and go test. Although future longitudinal studies are needed, it could be speculated that low levels of motor agility (which relates to the ability to rapidly change the position of the entire body in space[32], requiring movement speed, balance and motor coordination) could provide a feedback of poor ability to undertake challenging tasks[164] and have a deleterious influence on self-esteem and signs of depression.

There was a different pattern in the association between lower and upper body flexibility with depressive symptoms in this population, which is difficult to explain. Lower body flexibility showed no association with depressive symptoms, whereas upper body flexibility was the fitness component presenting the strongest association and the only one independently related with the total BDI-II score when all fitness tests were simultaneously considered. Although the direction of causality cannot be determined due to the study design, it could be speculated that higher upper body flexibility could enhance self-perception of the ability to perform activities of daily living, improving psychosocial factors such as self-esteem[165] or social interaction[166], which are related to mental health and mood. However, it must be underlined that the contribution of flexibility, as well as of other important variables like age, pain intensity, anticonvulsants usage or time since diagnosis to explain the total BDI-II variability was relatively low.

Overall, the present findings point out that the relationship between fitness and depressive symptoms in women with fibromyalgia is rather weak and contrast previous findings in healthy adults[44,45]. Several potential explanations might justify our results. First, it is possible that the true relationship between fitness and depression in fibromyalgia patients is rather weak or clinically irrelevant, and a high statistical power as a result of our relatively large sample size could have yielded non-important but statistically significant associations. Second, although the Senior Fitness Test battery and hand grip are feasible, reliable, and very commonly used measures of physical fitness in fibromyalgia patients[46,71,112,113,167,168], the gold standards (e.g. maximal oxygen uptake for aerobic fitness, isokinetic dynamometry for muscle strength, goniometer-based measures for range of motion, etc.), might have provided more precise estimates of the studied relationship. Third, measures of activity and participation rather than measures at the body level[169] could provide wider insights of important factors associated to depressive symptoms in fibromyalgia.

In addition, it is noteworthy the potentially important role that measurement error of assessing depressive symptoms in patients with chronic pain might have played in our results[170]. Following Pincus et al.[170], the clinical concept of depression comprises somatic symptoms but these are not predominant among patients clinically diagnosed with major depression[171]. By contrast, chronic pain patients may obtain a clinically significant score on most depression measures by endorsing somatic items such as sleep, fatigue, reduced activity, etc. In fact, these 3 items were those with the highest scores in this study. Although a factor structure of the BDI-II in fibromyalgia patients is currently lacking in the literature, Harris et al.[94] revealed that women with chronic pain scored higher on the somatic elements subscale than the other subscales, which was confirmed in this study. Therefore, a lack of criterion validity on the measure of depressive symptoms (BDI-II) in the present study might also have influence the results.

2.7. Association of different levels of depressive symptoms with symptomatology, overall disease severity and quality of life in women with fibromyalgia (Study VII)

The present results support previous studies revealing lack of association between signs of depression and pain sensitivity in fibromyalgia patients[82,172,173]. However, in contrast to prior reports[172], we observed that participants with severe depressive symptoms reported, in average, 1.1 units higher pain intensity (NRS) than those with minimal signs of depression, which parallels the minimal clinically important difference in chronic pain[174]. The link between depression and clinical pain intensity in fibromyalgia should therefore be further explored.

Patients with severe signs of depression also reported poorer scores in other core fibromyalgia-related symptoms, higher overall disease severity, and poorer mental HRQoL than patients with minimal signs of depression. For instance, sleep quality and fatigue were ~15% worse in the group with severe vs. minimal depressive symptoms. This finding was not surprising since depression, sleep and fatigue are highly interrelated and both fatigue and sleep dysfunction represent core symptoms of depression included in the BDI-II. Likewise, patients with severe depressive symptoms had 17.6% higher overall fibromyalgia severity and 17% lower mental HRQoL than patients with minimal signs of depression. As a 14% difference represents a minimal clinically important difference in overall fibromyalgia severity (with the old FIQ version)[144], it is likely that the 17.6% difference observed between groups in this study (with the FIQR) can be considered clinically meaningful. These results underlie the potential relevance of depressive symptoms with regards to fibromyalgia severity and HRQoL in women with fibromyalgia.

It is important to highlight that physical function (either self-reported [physical composite score of the SF-36] or performance-based [6-minute walk]) was similar across groups. These results contrast previous findings indicating that depressive symptoms is associated with physical disability in chronic pain patients[175] and suggest that while depressive mood is consistently associated with psychological and self-reported perception of health, it does not seem to interact with physical function in women with fibromyalgia. In fact, we examined the relationship between depressive symptoms and performance-based physical fitness in women with fibromyalgia in study VI, and the results revealed inconsistent and relatively weak associations between depression and different fitness components.

Interestingly, the proportion of patients reporting not only antidepressants, but also analgesics and anticonvulsants intake was higher in the group with severe signs of depression than in any other group, and a cost-utility analysis of reducing depressive symptoms in fibromyalgia might be warranted. From a clinical perspective, the high prevalence of severe depressive symptoms and its association with self-reported outcomes, suggests that this subgroup of patients could potentially benefit from specific psychological therapies aiming at alleviating depressive symptomatology. Luciano et al. observed that acceptance and commitment therapy significantly improved pain catastrophizing, pain acceptance, subjective pain, quality of life, anxiety, and depression in fibromyalgia patients[16]. Therefore, it seems that the possibility of simultaneously improve both pain and depression in fibromyalgia exists. Further prognosis research should also determine whether patients with different levels of depression display differential responses to treatment. We suggest this as an important research agenda as no properly conducted randomized prospective studies with stratification according to depressive symptoms have been conducted.

Limitations and Strengths

Limitations

The studies comprising this Doctoral Thesis have several limitations that must be underlined. Importantly, the cross-sectional design of the studies precludes any establishment of causality and reverse causation cannot be discarded. In this sense, it is also possible (and it is logical to think) that participants with higher disease severity perform worse in the fitness testing. However, there is consistent evidence that exercise is effective for enhancing physical fitness[20,21,176,177] and for improving fibromyalgia symptoms[21,80,138] and quality of life and, consequently, it is likely that the causal pathway might turn in the sense that enhancing specific components of physical fitness (especially muscle strength, flexibility and aerobic fitness) through exercise interventions can lead to significant (and possibly clinically relevant) improvements in core fibromyalgia features. Future intervention studies focused on enhancing physical fitness should carefully look at the clinical relevance of the effects observed. It is also possible that the low fitness levels observed in some participants might have been partially influenced by fear-avoidance[178]. Additionally, only women were included in the study because fibromyalgia is markedly more prevalent in women and the sample of men in the al-Ándalus project was very low (n=21). The results of this Doctoral Thesis might therefore not apply to men and further research in men with fibromyalgia is warranted. Finally, the fitness tests used in the al-Ándalus project do not represent the gold standard to assess the fitness components evaluated, and more precise measures of cardiorespiratory fitness (maximal VO_2), muscle strength (isokinetic dynamometry), or flexibility (goniometer-based measures) could provide more precise estimates of the associations under study.

Strengths

In project I, cardiorespiratory fitness was assessed by peak VO_2 (the gold standard) during an incremental treadmill test to exhaustion. The efforts made to recruit a representative and relatively large sample of women with fibromyalgia from Andalucía (8 provinces from southern Spain) is a strength of the al-Ándalus project. In addition, the full set of fitness tests used to assess the different components of fitness, the comprehensive protocol employed, the different methods used to assess pain (the hallmark of fibromyalgia) and the consistency of the findings are strengths of this work. It must be noted that although they do not represent gold standards, these tests have been widely used to assess physical fitness in fibromyalgia patients[47,55,60,70,71,113,115,179] and have shown to be feasible and reliable in this population[112].

Future Research Directions

The results of Study I suggest that the Borg CR-10 scale could be used in clinical settings as an inexpensive tool for monitoring exercise intensity of women with fibromyalgia during aerobic exercise intervention programs. However, the cognitive and physiological factors that mediate perceived exertion are commonly investigated by using two distinct paradigms: estimation and production[28]. In the estimation paradigm (used for monitoring exercise intensity), RPE is estimated by the participant based on momentary level of stimulation, as in Study I. In the production paradigm (used for exercise intensity prescription), the participant is asked to actively produce exercise intensity by producing pre-determined target RPE levels that correspond to specific physiological responses (e.g. HR). Future research is needed to determine whether women with fibromyalgia might use the CR-10 scale to produce target RPE levels that correspond to targeted physiological responses.

The findings of Studies II to VI suggest that specific components of physical fitness (especially muscle strength, flexibility and aerobic fitness) could potentially be associated with a better prognosis of core fibromyalgia features and disease severity. Future prospective research is warranted to determine the extent to which baseline levels of physical fitness are related to more favorable outcomes at follow-up, whether changes in fitness are associated to changes in disease severity or whether fitness might mediate treatment responses. In addition, future exercise intervention studies in women with fibromyalgia should not only aim at increasing the amount of physical activity, but also at enhancing specific components of physical fitness and carefully examine the clinical impact on core symptoms and disease severity. In particular, studying the extent to which enhancing fitness might be associated to better short and long term cerebral pain processing is of potential clinical interest.

A particular interesting and unexpected finding of this Thesis is that flexibility was consistently and inversely associated with major symptoms of fibromyalgia, such as pain or depression and disease severity across the different studies. Although this fitness component is not as strongly related to health outcomes as aerobic fitness or muscle strength in the general population and it usually receives little attention during exercise intervention programs, these results suggest that having a certain level of flexibility might be relevant in this population. As fibromyalgia patients suffer from joint stiffness, a proper degree of flexibility might positively influence the natural course of the disease. Therefore, it is suggested that flexibility might be an important component to consider in future intervention studies in this population.

Another interesting finding of this Doctoral Thesis is that, although significant (and even clinically relevant) associations were generally observed, the variability explained by physical fitness was generally low (in all cases <20%). It is important to highlight that fibromyalgia is a rather heterogeneous condition. In fact, recent studies using cluster analysis have begun to identify subsets of patients with distinct characteristics and potentially with different prognosis[180,181]. Therefore, it is possible that physical fitness might be more strongly associated with specific fibromyalgia features in determined subsets of patients, which requires further research.

Future intervention studies with stratification according to depressive symptoms are warranted to determine the extent to which women with fibromyalgia with concomitant severe depressive symptoms might particularly benefit from specific interventions (e.g. acceptance and commitment therapy).

Finally, it must be underlined that the findings of this Doctoral Thesis are not necessarily applicable to men, and future investigation is warranted to determine the potential relation of fitness and depression with core symptomatology and disease severity in men with fibromyalgia.

CONCLUSIONES / CONCLUSIONS

CONCLUSIONES

Los resultados de la presente Tesis Doctoral sugieren que:

I. La escala CR-10 de Borg es una herramienta moderadamente válida y fiable para monitorizar la intensidad del ejercicio en mujeres con fibromialgia. Además, las mujeres con fibromialgia son capaces de discriminar entre la sensación de esfuerzo y de dolor durante el ejercicio, especialmente a medida que la intensidad del ejercicio aumenta.

II. La capacidad aeróbica (medida mediante VO_2 pico) se asocia inversamente con la sensibilidad al dolor a la presión pero no con el dolor clínico (evaluado mediante escala visual analógica) en mujeres con fibromialgia.

III. Una mayor condición física se asocia consistentemente con menores niveles de dolor (medido con diferentes indicadores), menor catastrofización ante el dolor, y mayor autoeficacia ante el dolor crónico en mujeres con fibromialgia. La fuerza muscular y la flexibilidad se asocian de forma independiente con el dolor, mientras que la capacidad aeróbica y la flexibilidad se asocian independientemente con la catastrofización ante el dolor y la autoeficacia. Se observó un efecto combinado de diferentes componentes de la condición física sobre el dolor, catastrofización y autoeficacia en esta población.

IV. Mayores niveles de condición física se asocian de forme consistente a una menor severidad de la fibromialgia en mujeres. La diferencia en la severidad de la enfermedad entre los grupos (quintiles) con mayor y menor condición física sobrepasa el umbral de la relevancia clínica. La capacidad aeróbica (6-minute walk test) y la flexibilidad (back scratch test) son indicadores independientes de la severidad de la fibromialgia.

V. Una mayor condición física se asocia positiva y consistentemente con el procesamiento de la información, memoria de trabajo, memoria diferida, aprendizaje verbal y reconocimiento diferido. Por el contrario, la adiposidad no parece asociarse con las tareas cognitivas estudiadas. La capacidad aeróbica parece ser el componente más importante de la condición física en relación a los procesos cognitivos evaluados, aunque la agilidad motora podría también jugar un papel importante.

VI. Una mayor condición física está generalmente asociada con menores niveles de depresión en mujeres con fibromialgia. Sin embargo, las asociaciones observadas fueron débiles e inconsistentes, a diferencia de las observabas previamente en personas sanas.

VII. Una mayor severidad de los síntomas de depresión se asocia con una peor sintomatología autoinformada y con el componente mental de la calidad de vida relacionada con la salud, pero no con la sensibilidad al dolor ni con la función física en mujeres con fibromialgia.

CONCLUSIONS

The results of the present Doctoral Thesis suggest that:

I. The Borg CR-10 scale is a moderately valid and reliable tool for monitoring exercise intensity in women with fibromyalgia. In addition, women with fibromyalgia are able to discriminate between exertion and exercise-induced pain while exercising, especially as exercise intensity increases.

II. Higher CRF (measured as peak VO_2) is associated with lower pressure pain sensitivity (i.e. higher PPT and lower TPC) but not with clinical pain (as assessed with a VAS) in women with fibromyalgia.

III. Higher physical fitness is consistently associated with lower levels of pain (assessed with different indicators), lower pain-related catastrophizing and higher chronic pain self-efficacy in women with fibromyalgia. Muscle strength and flexibility were independently associated with pain, while aerobic fitness and flexibility were independently associated with pain-related catastrophizing and chronic pain self-efficacy. There was a combined effect of different fitness components on pain, catastrophizing and self-efficacy in this population.

IV. Higher physical fitness is consistently associated with lower fibromyalgia severity in women with fibromyalgia. The difference in fibromyalgia severity between patients in the lowest and the highest fitness quintiles surpassed the minimal clinically meaningful difference. Aerobic fitness (as assessed with the 6-minute walk test) and flexibility (back scratch test) are independent indicators of fibromyalgia severity.

V. Higher physical fitness is positively and consistently associated with information processing, working memory, delayed recall, verbal learning and delayed recognition in women with fibromyalgia. By contrast, body fatness does not seem to be associated with the studied cognitive tasks. Aerobic fitness seems to be the most important fitness indicator of the cognitive processes evaluated, yet motor agility could also play a relevant role.

VI. Higher physical fitness is generally associated with lower symptoms of depression in women with fibromyalgia. However, the observed associations were weak and inconsistent, differing from those previously observed in healthy adults.

VII. Higher severity of depressive symptoms is associated with poorer self-reported symptomatology and mental HRQoL, but not with pain sensitivity or physical function in women with fibromyalgia.

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Short CV

ALBERTO SORIANO MALDONADO

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Department of Physical Education and Sport

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Academic training

- GRADUATE DEGREE IN SPORT SCIENCES. Faculty of Sport Sciences, University of Granada. Date: 2006-2011
- MÁSTER DEGREE IN HUMAN NUTRITION (M28/56/1; 60 ECTS credits). Faculty of Pharmacy. University of Granada.
  Date: 2011-2012
- POSGRADUATE DIPLOMA IN DESIGN AND STATISTICS IN HEALTH SCIENCES (30 ECTS credits). Autonomous University of Barcelona.
  Date: 2012-2014
- STAY ABROAD (1.5 months). Summer Courses (Genetics Laboratory). Loyola University (Chicago, United States). Date: 05/07/2010 to 15/08/2010
- RESEARCH STAY (3 months). Department of Metabolism and Nutrition, Institute of Food Science, Technology and Nutrition (ICTAN), Spanish Research Council (CSIC).
  Date: June and September 2010 – April 2012
- RESEARCH STAY (3 months). The Parker Institute (Department of Rheumatology) – Bispebjerg and Frederiksberg Hospitals, Copenhagen University Hospitals (Denmark).
  Date: 29/08/2014 to 29/11/2014
- RESEARCH STAY (1.5 months). Department of Education, University of Almería.
  Date: 15/06/2014 to 31/07/2014
- RESEARCH STAY (3 months) to be conducted at the Arnold School of Public Health. Department of Exercise Science (Division of Health Aspects of Physical Activity) and Department of Epidemiology and Biostatistics. University of South Carolina (Columbia; United States).
  Date: 29/08/2015 to 29/11/2015
- FORMAL UNIVERSITY TEACHING. Department of Physical Education and Sport, Faculty of Sport Sciences, University of Granada. Academic year 2014-2015:
  - Physical Activity and Health (corresponding to the 3rd academic course from the degree in Sport Sciences): 6 credits.
- INVITED LECTURE at the "European Master in Public Health: EUROPUBHEALTH", Module IV: Health Promotion. Andalusian School of Public Health. Duration: 2 hours.
  Date: 30/04/2013

Scientific Publications directly derived from the present Doctoral Thesis:

1. [Study I] **Soriano-Maldonado A**, Ruiz J, Álvarez-Gallardo I, Segura-Jiménez V, Santalla A, Munguia-Izquierdo D. Validity and reliability of rating perceived exertion in women with fibromyalgia: exertion-pain discrimination. *Journal of Sports Sciences*. Accepted 24/12/2014 [Epub ahead of print] doi: 10.1080/02640414.2014.994661: IF: 2.10 (Q2 Sports Sciences)

2. [Study II] **Soriano-Maldonado A**, Ortega FB, Munguía-Izquierdo D. Association of cardiorespiratory fitness with pressure pain sensitivity and clinical pain in women with fibromialgia. *Rheumatology International*. Accepted 31/12/2014 [Epub ahead of print] doi: 10.1007/s00296-014-3203-z. IF: 1.63 (Q3 Rheumatology)

3. [Study III] **Soriano-Maldonado A**, Ruiz JR, Aparicio V, Estévez-López F, Segura-Jiménez V, Álvarez-Gallardo IC, Carbonell-Baeza A, Delgado-Fernández M, Ortega FB. Association of Physical Fitness with Pain in Women with Fibromyalgia: the al-Ándalus Project. *Arthritis Care & Research*. Accepted 28/04/2015 [Epub ahead of print]. doi: 10.1002/acr.22610. IF: 4.04 (Q2 Rheumatology)

4. [Study IV] **Soriano-Maldonado A**, Henriksen M, Segura-Jiménez V, Aparicio V, Carbonell-Baeza A, Delgado-Fernández M, Amris K, Ruiz JR. The association of physical fitness with fibromyalgia severity in women: The al-Ándalus project. *Archives of Physical Medicine and Rehabilitation*. Accepted 22/03/2015 [Epub ahead of print] doi: 10.1016/j.apmr.2015.03.015. IF: 2.44 (Q1 Sports Sciences)

5. [Study V] **Soriano-Maldonado A**, Artero EG, Segura-Jiménez V, Aparicio V, Estévez-López F, Álvarez-Gallardo IC., Munguía-Izquierdo D, Casimiro AJ, Delgado-Fernández M, Ortega FB. Association of physical fitness and fatness with cognitive function in women with fibromyalgia. Submitted.

6. [Study VI] **Soriano-Maldonado A**, Estévez-López F, Segura-Jiménez V, Aparicio V, Álvarez-Gallardo IC, Herrador-Colmenero M, Ruiz JR, Henriksen M, Amris K, Delgado-Fernández M. Association of physical fitness with depression in women with fibromyalgia. Submitted.

7. [Study VII] **Soriano-Maldonado A**, Amris K, Ortega FB, Segura-Jiménez V, Estévez-López F, Álvarez-Gallardo IC., Aparicio V, Delgado-Fernández M, Henriksen M, Ruiz JR. Association of different levels of depressive symptoms with symptomatology, overall disease severity and quality of life in women with fibromyalgia. *Quality of Life Research.* Accepted 04/06/2015 [Epub ahead of print] doi: 10.1007/s11136-015-1045-0. IF: 2.86 (Q1 Public, Environmental & Occupational Health)

Other scientific publications:

8. **Soriano-Maldonado A**, Cuenca-García M, Moreno LA, González-Gross M, Leclercq C, Androutsos O, Guerra-Hernández EJ, Castillo MJ, Ruiz JR. Ingesta de huevo y factores de riesgo cardiovascular en adolescentes; papel de la actividad física. Estudio HELENA. *Nutrición Hospitalaria*. 2013;28(3):868-877. doi:10.3305/nh.2013.28.3.6392. IF: 1.12 (Q4 Nutrition and Dietetics).

9. **Soriano-Maldonado A**, Romero L, Femia P, Roero C, Ruiz JR, Gutiérrez A. A learning protocol improves the validity of the Borg 6-20 RPE scale during indoor cycling. *International Journal of Sports Medicine*; 2014 35(5):379-84. doi: 10.1055/s-0033-1353166. IF: 2.27 (Q1 Sports Sciences).

10. **Soriano-Maldonado A**, Hidalgo M, Arteaga P, de Pascual-Teresa S, Nova E. Effects of regular consumption of vitamin C-rich or polyphenol-rich apple juice on cardiometabolic markers in healthy adults: a randomized crossover trial. *European Journal of Nutrition*. 2014; 53: 1645–57. doi: 10.1007/s00394-014-0670-7. IF: 3.84 (Q1 Nutrition and Dietetics).

11. Segura-Jiménez V, Aparicio V, Álvarez-Gallardo I, **Soriano-Maldonado A**, Estévez-López F, Delgado-Fernandez M, Carbonell-Baeza A. Validation of the modified American College of Rheumatology 2010 diagnostic criteria for fibromyalgia in a Spanish population. *Rheumatology*. 2014 53(10):1803-11. doi: 10.1093/rheumatology/keu169. IF: 4.44 (Q1 Rheumatology).

12. Aparicio V, Álvarez-Gallardo I, Segura-Jiménez V, **Soriano-Maldonado A**, Castro-Piñero J, Delgado-Fernandez M, Carbonell-Baeza A. Fitness testing in the fibromyalgia diagnosis: the Al-Ándalus Project. *Medicine and Science in Sport and Exercise*. 2015, 47(3):451-9. doi: 10.1249/MSS.0000000000000445. IF: 4.48 (Q1 Sports Sciences).

13. Estévez-López, F, Gray C, Segura-Jiménez V, **Soriano-Maldonado A**, Álvarez-Gallardo I, Arrayas-Grajera M, Carbonell-Baeza A, Aparicio V, Delgado-Fernandez M, Pulido-Martos M. Independent and combined association of physical fitness and subjective well-being with fibromyalgia severity: the al-Ándalus Project. *Quality of Life Research* 2015 [Epub ahead of print]. doi: 10.1007/s11136-015-0917-7. IF: 2.86 (Q1 Public, environmental and Occupational Health).

14. Segura-Jiménez V, **Soriano-Maldonado A**, Álvarez-Gallardo IC, Estévez-López F, Carbonell-Baeza A, Delgado-Fernández M. Subgroups of fibromyalgia patients using the 1990 and the modified 2010 American College of Rheumatology Criteria: the al-Ándalus project. *Clinical and Experimental Rheumatology 2015* Accepted 04/04/2015 [Epub ahead of print] IF: 2.97 (Q2 Rheumatology).

15. Carbonell-Baeza A, **Soriano-Maldonado A,** Gallo FJ, et al. Cost-effectiveness of an exercise intervention program in perimenopausal women. The Fitness League Against MENopause COst (FLAMENCO) randomized controlled trial. *BMC Public Health*. Accepted 26/05/2015. IF: 2.32 (Q2 Public, Environmental & Occupational Health)

16. Segura-Jiménez V, Álvarez-Gallardo IC, Estévez-López F, **Soriano-Maldonado A**, Delgado-Fernández F, Ortega FB, Aparicio VA, Carbonell-Baeza A, Mota J, Silva P, Ruiz JR. Differences in sedentary time and physical activity between fibromyalgia and healthy control women: the al-Ándalus project. Arthritis and Rheumatology. Accepted 05/06/2015 [Epub ahead of print] IF: 7.9 (Q1 Rheumatology)

17. Segura-Jiménez V, Castro-Piñero J, **Soriano-Maldonado A**, Álvarez-Gallardo IC, Delgado-Fernández M, Carbonell-Baeza A. The association of total and central body fat with pain, fatigue and the impact of fibromyalgia in women; role of physical fitness: the al-Ándalus project. 2nd revision submitted to *European Journal of Pain.*

18. Álvarez-Gallardo IC, **Soriano-Maldonado A**, Carbonell-Baeza A, Segura-Jiménez V, Estévez-López F, McVeigh JG, Delgado-Fernández M, Ortega FB. The International FItness Scale (IFIS): construct validity and reliability in women with fibromyalgia: The al-Ándalus project. 2nd revision submitted to *Archives of Physical Medicine and Rehabilitation*.

19. Segura-Jiménez V, Estévez-López F, **Soriano-Maldonado A**, Álvarez-Gallardo IC, Ruiz JR, Aparicio VA. Sex differences in symptomatology, health-related quality of life, sleep quality, mental health, cognitive performance, pain-cognition and positive health in Spanish fibromyalgia individuals: the al-Ándalus project. Submitted.

20. Segura-Jiménez V, Borges-Cosic M, **Soriano-Maldonado A**, Estévez-López F, Álvarez-Gallardo IC, Herrador-Colmenero M, Delgado-Fernández M, Ruiz JR. Association of sedentary time and physical activity with pain, fatigue and the impact of fibromyalgia: the al-Ándalus project. Submitted.

21. Herrador-Colmenero M, Álvarez-Gallardo IC, Segura-Jiménez V, Estévez-López F, **Soriano-Maldonado A**, Ruiz-Montero PJ, Tercedor P, Girela-Rejón MJ, Delgado-Fernández M, Chillón P. Associations between patterns of active commuting and socioeconomic factors in women with fibromyalgia: the al-Ándalus project. Submitted.

Research Grants

1. Introduction to Research grant, 2010. Department of Metabolism and Nutrition, Institute of Food Science, Technology and Nutrition. Spanish Research Council (CSIC). Duration: 2 months.

2. Collaboration grant from the Spanish Ministry of Education, 2010/2011. Department of Physiology, School of Medicine, University of Granada. Duration: 1 academic year.

3. Scholarship for summer courses at Loyola University, Chicago (United States). Published by the Vice-Chancellor of International Relationships, University of Granada. 2 credit course performed: Genetics Laboratory. Duration: 1.5 months.

4. Mobility grant of the Spanish Ministry of Education for students during Master Degree studies, 2011/2012. Department of Metabolism and Nutrition, Institute of Food Science, Technology and Nutrition, Spanish Research Council (CSIC), Madrid (Spain). Duration: 1 month.

5. Collaboration grant to contribute to the implementation of the ECTS system at the School of Sports Sciences, University of Granada (Granada, Spain), 2011-2012. Duration: 4 months.

6. Research Fellowship: University Teaching Training Program [Formación de Profesorado Universitario (FPU)] from the Spanish Ministry of Education, Culture and Sport [grant number: FPU12/00963). March 2013 to march 2017.

7. International mobility grant for PhD students from University of Granada and CEI BioTic Granada, 2013/2014. Research stay conducted at The Parker Institute, Copenhagen University Hospital (Copenhagen, Denmark). Duration: 3 months.

8. International mobility grant for PhD students from the Spanish Ministry of Education, Culture and Sport, 2014/2015. Research stay granted (to be conducted): Arnold School of Public Health (Department of Exercise Science), University of South Carolina (Columbia, United States). Duration: 3 months.

Research Projects

1. **PROJECT:** Efectos de los niveles de actividad física medidos en gasto energético sobre diferentes variables sintomatológicas de pacientes con síndrome de fibromialgia
   FUNDING SOURCE: Centro Andaluz de Medicina del Deporte, Consejería de Turismo, Comercio y Deporte, Junta de Andalucía
   DATE AND DURATION: 17-12-2007 to 16-12-2008
   PRINCIPAL INVESTIGATOR: Diego Munguía Izquierdo
   PARTICIPATION TASKS: Collaboration in data processing, statistical analyses, interpretation and scientific dissemination of results.
   FUNDING: 15.403,21€

2. **PROJECT:** Physical activity in women with fibromyalgia: effects on pain, health and quality of life (Actividad física en mujeres con fibromialgia: efectos sobre el grado de dolor, salud y calidad de vida). DEP2010-15639 (subprograma DEPO). The al-Ándalus Project.
   FUNDING SOURCE: Plan Nacional I+D+i 2008-2011, Ministerio de Ciencia e Innovación
   DATE AND DURATION: 07/02/2012 al 30/9/2014
   PRINCIPAL INVESTIGATOR: Manuel Delgado Fernández
   PARTICIPATION TASKS: investigador.
   FUNDING: 118.580 €

3. **PROJECT:** Exercise and Steroid in Knee Osteoarthritis
FUNDING SOURCE: Danish Research Council (Code: 101.04)
DATE AND DURATION: From 01/10/2012 to 01/04/2014 (last patient's last visit).
PRINCIPAL INVESTIGATOR: Marius Henriksen, Senior researcher, PhD.
PARTICIPATION TASKS: Collaboration in data processing, statistical analyses, interpretation and scientific dissemination of results.
FUNDING: 3.000.000 DKK - (403.122 €)
Clinicaltrials.gov: NCT01945749

4. **PROJECT:** PROGRESS towards healthy ageing in Europe (VS/2011/0489)
FUNDING SOURCE: the European Union Programme for Employment and Social Solidarity
DATE AND DURATION: From 01/12/2011 to 30/11/2013.
PRINCIPAL INVESTIGATOR: En Europa: Elspeth Gibson. Suffolk County Council. En España: Inmaculada Mateo Rodríguez. Escuela Andaluza de Salud Pública.
PARTICIPATION TASKS: Investigador con funciones de diseño, desarrollo y seguimiento del programa de intervención en actividad física, y evaluación de actividad física, composición corporal y condición física.
FUNDING: Para España: 53.564 €; Para Europa: 469.722,19 €

5. **PROJECT:** Evaluación de los efectos beneficiosos para la salud humana de una alimentación rica en frutas y hortalizas ecológicas" (Ministerio de Ciencia e Innovación. AGL-2009-10415/ALI).
FUNDING SOURCE: Plan nacional I+D+i 2009, Ministerio de Ciencia e Innovación.
DATE AND DURATION: From 31/12/2007 to 31/12/2009
FUNDING: 30.000€
PRINCIPAL INVESTIGATOR: Esther Nova Rebato
PARTICIPATION TASKS: Becario-investigador.

6. **PROJECT:** Adaptación del Modelo Europeo de Excelencia a la Materia de Educación Física: el caso de los centros de enseñanza secundaria obligatoria de la provincia de Granada.
FUNDING SOURCE: Grupo de Investigación HUM 161: Formación y actualización del profesor-entrenador deportivo de la Consejería de Educación de la Junta de Andalucía.
DATE AND DURATION: From 01/02/2010 to 30/04/2010.
FUNDING: 4.000€
PRINCIPAL INVESTIGATOR: Miguel Ángel Delgado Noguera.
PARTICIPATION TASKS: Alumno colaborador.

7. **PROJECT:** Coste efectividad de un programa de ejercicio físico en mujeres peri-menopáusicas (PI-0667/2013)
FUNDING SOURCE: Consejería de Igualdad, Salud y Políticas Sociales de la Junta de Andalucía.
DATE AND DURATION: From 01/01/2014 to 31/12/2015.
PRINCIPAL INVESTIGATOR: Virginia Aparicio García-Molina.
PARTICIPATION TASKS: Investigador colaborador.
FUNDING: 30.000€
Clinicaltrials.gov: NCT02358109

8. **PROJECT:** Seguimiento Longitudinal y Modulación Genética en Fibromialgia. Efectos del Ejercicio Físico y la Hidroterapia en Dolor, Salud y Calidad de Vida (DEP2013-40908-R)
FUNDING SOURCE: Ministerio de Economía y Competitividad. Programa Estatal de Investigación, Desarrollo e Innovación Orientada a los Retos de la Sociedad, modalidad 1, "Retos Investigación": Proyectos de I+D+I.
DATE AND DURATION: From 01/01/2014 to 31/12/2016
PRINCIPAL INVESTIGATOR: Manuel Delgado Fernández.

PARTICIPATION TASKS: Member of the work team.
FUNDING: 121000 €

9. **PROJECT:** Activating Brown Adipose Tissue through Exercise: estudio ACTIBATE. Efectos de un programa de ejercicio sobre la actividad y cantidad de tejido adiposo marrón en adultos jóvenes: Estudio aleatorizado controlado.
   FUNDING SOURCE: Ministerio de Economía y Competitividad, Fondo de Investigación Sanitaria del Instituto de Salud Carlos III (ref: PI13/01393)
   DATE AND DURATION: From 01/01/2014 to 31/12/2016
   PRINCIPAL INVESTIGATOR: Jonatan Ruiz Ruiz
   PARTICIPATION TASKS: Investigador colaborador con funciones de evaluación y control de la actividad física, control de las cargas de entrenamiento y preparación de evaluación de la grasa parda.
   FUNDING: 171215 €
   Clinicaltrials.gov: NCT02365129

Academic awards

1. Books Award to the 150 best Academic Performances from the University of Granada (2007/2008). Date: 03/03/2009.

2. Extraordinary Award for the best Academic Performance (Degree in Sports Sciences, promotion 2006-2011). Faculty of Sport Sciences, University of Granada, Spain. Date: 21/03/2012.

3. University of Granada - Caja Rural Award to Academic Excellence. Best Performance in the area of Social and Educational Sciences (2010-2011). University of Granada, Spain. Date: 27/04/2012.

4. National Award (Accésit) to the best Academic Performance in the area of Social Sciences and Law. Degree in Sports Sciences (2010-2011). Spanish Ministry of Education, Culture and Sport. Date: 06/05/2014 (BOE-A-2014-4844).

5. Excellence Award (Mention) on International Mobility Program (2013-2014). Vice-chancellorship of International Relations, University of Granada. Date: 27/04/2015.

Other merits

a) Reviewer for scientific journals:

   - BMC Public Health
   - Pain Medicine
   - American Journal of Men's Health
   - Journal of Sport and Health Science

b) Practical training at the High Performance Sports Center at Sierra Nevada (Monachil). Consejo Superior de Deportes (CSD; 2010/2011). Duration: 120 h. Date: 10/08/2011.

c) Elementary Degree in Music (Violoncello). Royal Conservatory of Music of Almería. Date: 22/8/2007.

d) Spanish University Championships (Tennis). Mixed doubles champion representing the University of Granada (2007/2008 and 2008/2009).

Agradecimientos [Acknowledgements]

Quizás la atracción que siento por la investigación se justifique por la estrecha relación que guarda esta con el deporte. Enorme sacrificio, lucha incansable por alcanzar objetivos, motivación a prueba de bombas, y un largo etcétera siempre en la línea del esfuerzo y la superación personal. La cerrera investigadora (que realmente merezca llamarse así) no existe sin una vocación total y absoluta hacia lo que uno hace, pues implica un compromiso de trabajo y dedicación tal, que nunca llega a estar pagado, ni recompensado, ni reconocido, máxime cuando uno escoge vivir en España. Sin embargo, por encima de todas las dudas (que las tengo), quizás por mi motivación intrínseca hacia la sensación de estar progresando, quizás sin una justificación racional, reconozco que este mundo ha llenado mi vida durante los últimos 5 años y, aunque he perdido algunas experiencias a su costa, he ganado otras y he disfrutado del proceso. Qué duda cabe que defender mi Tesis Doctoral en el día de hoy me hace pensar que en estos últimos años he hecho las cosas bien.

La investigación es también como la vida, las personas (investigadores) van y vienen y tan solo perviven los grupos y las instituciones. Eso sí, el paso de las personas debe tender a mejorar las cosas con el paso del tiempo y, de no ser así, todo es susceptible de desaparecer (he ahí la importancia de las personas). Este trabajo que hoy presento como si fuera "mío", no es sino el fiel reflejo del incalculable trabajo que muchas personas han venido realizando desde mucho antes de que yo siquiera existiese como investigador. Personas a las que estoy especialmente agradecido. Esta Tesis, además, se ha visto apoyada por muchísimas personas que, de forma directa o indirecta, me han aportado la base de la felicidad que una persona necesita para trabajar, y a quienes también querría dedicar unas palabras de gratitud.

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Granada, sino a España como potencia en investigación (tiempo al tiempo).

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Querría dar las gracias también de forma muy especial y con mucho cariño al grupo de investigación EFFECTS CTS-262 (grupo en el que me inicié como investigador con una beca de colaboración), y muy especialmente a **Ángel Gutiérrez**. Gracias por servir de inspiración y por motivar a muchísimos alumnos que pasan por tus manos. Gracias por enseñar la Fisiología del Ejercicio (con MAYÚSCULA aunque la hayan querido escribir con minúscula) desde un punto de vista práctico y aplicable, y por despertar en tus alumnos la curiosidad por aprender, que es el mayor éxito que puede tener un profesor. Gracias al grupo por ser la base de la pirámide y el referente para muchos que estamos viniendo detrás. Gracias también por el apoyo que siempre he sentido de vosotros. Siempre os estaré agradecido. Fruto de EFFECTS nacemos prácticamente todos, pero yo me quiero acordar de **Magdalena**. Tú me enseñaste a trabajar con rigurosidad y eso no se olvida. Muchas gracias por el tiempo que dedicaste a mi TFM y del que aprendí mucho. Y **Enrique**…sólo tú y yo sabemos que nuestra relación se remonta a muchos años vista…es sorprendente que tras más de 25 años volvamos a encontrarnos con metas comunes, ¿será el destino? No me cabe duda de que nos quedan muchas experiencias profesionales y personales juntos. Muchas gracias por tenderme tu mano.

Y qué no voy a decir de mis compañeros de viaje, de las personas con las que he compartido unos 125 billones de emails en los últimos 3-4 años. Gracias a todos por aceptarme de buen grado en el grupo desde el inicio y por hacer de este proceso una experiencia enriquecedora al máximo. Gracias **Inma** por tu esfuerzo incansable. Sin tu trabajo, este proyecto no habría salido adelante, o al menos una buena parte de él. Gracias por afrontar millones de situaciones sin tener la respuesta y dar siempre lo mejor de tí. Gracias por tirar para adelante con muchas más cosas de las que podías. Gracias, en general, por tu humildad y por tu capacidad inmensa de trabajo. Eres una gran compañera con la que cualquiera querría trabajar. Gracias **Fernan**, por tu siempre positiva predisposición a colaborar y tu gran espíritu de equipo. Gracias por tener siempre un "sí" o un "yo lo hago" en la boca cuando hay cosas pendientes que "hay" que hacer. Gracias por ser un gran compañero y por todo el trabajo, a veces invisible, que llevas a tus espaldas en este proyecto. Gracias **Víctor** por subir el nivel de grupo, por poner el listón alto, por tirar del carro y sacar adelante un trabajo para el que pocos están preparados, la generación de bases de datos. Te has dejado la piel por este proyecto y tu trabajo se está viendo recompensando como te mereces. Creo, además, que has sabido aprender y evolucionar mucho durante este proceso y ahora eres un post-doc que cualquiera querría tener en sus filas. Quizás sea hora de que vayas enseñando a otros todo lo que has hecho durante este tiempo para no tener que ser un becario predoctoral de por vida... **Milkana**, gracias por crear buen ambiente dentro del grupo y por decir siempre las cosas como las piensas. Creo que es la mejor forma de trabajar, aunque siempre la mano izquierda te ayudará. Espero que este proceso que comienza con la concesión de tu beca sea una experiencia única y te sirva para complementar tu formación. Deseo para tí que tengas tu propio sueño y vayas a por él, ya que eso es lo que te va a llenar el día de mañana. Siempre que necesites, tendrás mi apoyo y mi ayuda, no sólo como compañera, sino como amiga. **Manu**, gracias por tu trabajo y por tu evolución e integración dentro del grupo. Creo que entre todos somos un equipo y tú

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Siento la necesidad de hacer alusión a la importantísima colaboración que hemos tenido con las diferentes **Asociaciones de Fibromialgia de Andalucía**. Sin vuestro apoyo, esto no habría sido posible, lo cual denota la importancia de establecer vínculos Universidad-Sociedad para que la investigación llegue a producirse, y el conocimiento pueda tener transferencia real. Mi máximo deseo sería que la pequeña aportación a la Ciencia que supone esta Tesis Doctoral pueda tener en algún momento una influencia positiva (aunque fuese de forma indirecta) en la calidad de vida de las personas que sufren la fibromialgia. De corazón, gracias.

A mis compañeros 'del iMUDS', menudo equipazo de investigadores y personas! Es un auténtico placer trabajar y aprender con vosotros…Gracias **Guille** y **Borja** por esa eficiencia y esa formación y actitud…no tenéis límites, seguid así que vais a romper barreras... Y gracias también a todo el equipo, **Juanma**, **María V.**, **Daniela**, **José Carlos**, **Cristi**, **Pepe**, etc.

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Hay una persona especial que ha sabido transmitir su actitud inconformista y luchadora a las generaciones actuales, y que merece todo mi respeto y admiración. Una persona que ha hecho mucho por las Ciencias del Deporte y porque la nuestra sea hoy una carrera universitaria, y que además ha contribuido de forma importante en mi proceso de formación. Gracias **Miguel Ángel Delgado**. Para mí has sido un profesor importante y siempre te recordaré como un ejemplo a seguir.

I would like to have a special word for the great people I met during my stay in Copenhagen at The Parker Institute. Thank you all for a wonderful life experience, which has signified much to me in all senses. I would like to special thank Dr. **Marius Henriksen** for a really efficient and straightforward communication and work together, and Dr. **Kirstine Amris**, for taking me out of my comfort zone and making me go further with the discussion of my study results. It's been a pleasure to work together with you two and hope to keep collaborating in the near future. Thank you **Bente** and **Ulrik** for your generosity offering your house to me when I was spending all my money in different apartments throughout the city. It's been a pleasure to stay with you and to have so many nice conversations about the differences between Denmark and Spain. Thank you **Claus**, thanks so much for your hospitality, you made me feel like at home from the first day at the institute. And of course I couldn't forget every single moment I spent with all of you guys, especially **Cecilie(s)**, **Marianne**, **Louise**, **Jack**, **Elisabeth**, **Julie**, **Tanja** and **Signe**. Thanks so much!

Conforme llegamos al final nos vamos acercando a las personas que tocan más mi sensibilidad, y jamás podría olvidarme de 3 personas con las que me une mucho más que 5 años de carrera juntos. Mis niñas y hermanitas, **Cristina** (Gracious), **Patri** (Patriux), **Lidi** (Litriux). Hemos compartido todo durante una

bonita carrera, momentos hermosos y momentos duros. Nunca olvidaremos nuestra aventura con el Pinaccle hasta las 5 de la mañana y muchas otras que quizás nos hicieron más fuertes… Nos hemos peleado y hemos cometido errores, pero hemos aprendido tanto y crecido tanto juntos que siento que sois mis hermanas para siempre. La mejor prueba es que se me hayan saltado las lágrimas escribiendo estas líneas… Estoy muy orgulloso de en lo que os estáis convirtiendo y de que estéis cumpliendo e incluso superando vuestros sueños! Os quiero.

Los **amigos** son la salsa de la vida, y yo tengo la suerte de tener suficientes amigos para sentirme bien condimentado! Esta Tesis está dedicada también, con todo mi cariño, a toda persona que si leyese estas palabras se sintiera identificado con la sensación de ser mi amig@. Si eres uno de ellos, gracias!

A mi familia política que no es política pero sí familia de verdad, gracias por hacer de la nuestra una relación especial y cercana en la que todos nos sentimos queridos y parte de un equipazo que no está al completo sino cuando nos reunimos todos. Gracias **Juan**, **Marti**, **Olgui**, **Javi**, **Luci**, **Chris**, y **Elisita**, este trabajo es también vuestro y os quiero mucho. Y a tí **Guille**, porque me acuerdo de tí todos los días. Me acuerdo de todas las salidas en bici, carreras, reuniones, charlas sobre deporte, risas, y un largo etc., que nos quedaban por vivir juntos. Aun me tienes que enseñar a nadar… Gracias por regalarme tanto cariño y por ser tan valiente. Esta Tesis va también por tí!

Tratando de buscar palabras inexistentes, quiero dedicar esta Tesis Doctoral con todo mi amor a la memoria de mis abuelos, trabajadores incansables, y muy especialmente a mis padres y hermano. **Papá**, gracias por inculcarme el valor del esfuerzo y del trabajo. Gracias por regalar cada instante de tu vida a tus hijos y tu familia. Gracias por cada viaje que hiciste para que yo pudiera soñar jugando al Tenis (qué bonito dejar que un niño consiga soñar y luchar por sus sueños! [yo intentaré dejar que mis hijos sueñen]) y tocar el violoncello, por invertir todas tus tardes, sin pensar jamás en tí (o acaso pensar en tí tenía el mismo significado). Gracias por inculcarme que hay que ser buena persona y ayudar a los demás. Creo que representas la generosidad en estado puro. Gracias por representar el concepto de amor de una forma tan intensa que es complejo llegar a entender y que yo en (demasiadas) ocasiones no he sido (ni sigo siendo) capaz de interpretar ni asumir. Soy consciente de que nunca existirá un ser en este mundo capaz de preocuparse tanto por mí como lo haces tú. Tan solo quiero poder disfrutar de tus abrazos tanto tiempo como la vida quiera regalarnos. **Mamá**, tú eres fiel reflejo de la persona en la que yo querría convertirme y mi ejemplo a seguir. Jamás he conocido a alguien con ese saber estar, esa serenidad y esa sensatez. Gracias por educarme tan bien y por tus sabios consejos, que me han guiado siempre. Gracias por aportar calma a mi vida y por regalarme un amor precioso que me llevo conmigo para siempre. Sólo con pensar en tí ya me siento arropado, dentro de tí, como antes de nacer, es bonito, ¿verdad? Gracias a ambos por vuestra generosidad al dejarme ir tan pequeño… **Pablo**, eres mi hermano pequeño aunque en ocasiones has demostrado tener mucha más madurez que yo. Gracias por compartir todo conmigo, por confiar siempre en mí y por hacerme creer que yo era ejemplo para tí, cuando en realidad, desde un tiempo a esta parte, todo ha sido siempre recíproco. Gracias por ser a la vez mi hermano y mi mejor amigo, por guardar mis secretos, y por estar ahí para todo. Estoy seguro de que tu trabajo, tu generosidad y tu corazón te van a llevar a donde tengas que estar para ser feliz! Os quiero con todo. Y **Rocío**, eres excepcional, única, encantadora, irrepetible e inigualable, imposible no quererte tanto. Gracias por querer tanto a Pablo y por darnos tanto cariño a todos.

Evita, este lugar, el más importante, es sólo para tí, para mi bombón! Es imposible que una simples palabras reflejen la complicidad y el amor tal y como lo sentimos juntos. Esta Tesis es para tí, para nosotros, y ojalá suponga el pasaporte para estar juntos…Hace ya cinco años que me enamoré de tu sonrisa, tu seña identificativa, un reflejo de Eva como persona, como mujer, y como amiga… una atracción inevitable para mí y una de las razones por las que hoy estamos aquí…Gracias por estar a mi lado compartiéndolo todo y queriéndome tanto. Sei tu. Te amo.

Annexes

Annexes

1. Mini-mental State Examination
2. Beck Depression Inventory - second edition
3. Revised Fibromyalgia Impact Questionnaire
4. Pain Catastrophizing Scale
5. Chronic Pain Self-efficacy Scale
6. Pittsburgh Sleep Quality Index
7. Multidimensional Fatigue Inventory
8. 36-item Short Form health survey
9. Paced Auditory Serial Addition Task
10. Rey Auditory Verbal Learning Test
11. Visual Analogue Scale

MINI MENTAL STATE EXAMINATION (MMSE)

Universidad de Granada

FECHA

Por favor, marque la opción que se corresponda con su respuesta y siga las instrucciones determinadas en cada caso.

MARQUE CORRECTAMENTE

Bien Mal Mal Mal Mal

CLAVE

Nº pág.

ORIENTACIÓN TEMPORAL (Máx.5)

¿En qué año estamos? 0-1
¿En qué estación? 0-1
¿En qué día (fecha)? 0-1
¿En qué mes? 0-1
¿En qué día de la semana? 0-1

0 1 2 3 4 5

ORIENTACIÓN ESPACIAL (Máx.5)

¿En qué hospital (o lugar) estamos? 0-1
¿En qué piso (o planta, sala, servicio)? 0-1
¿En qué pueblo (ciudad)? 0-1
¿En qué provincia estamos? 0-1
¿En qué país (o nación, autonomía)? 0-1

0 1 2 3 4 5

FIJACIÓN- Recuerdo inmediato (Máx.3)

Nombre tres palabras Peseta-Caballo-Manzana (o Balón-Bandera-Árbol) a razón de 1 por segundo. Luego se pide al paciente que las repita. Esta primera repetición otorga la puntuación. Otorgue 1 punto por cada palabra correcta, pero continúe diciéndolas hasta que el sujeto repita las 3, hasta un máximo de 6 veces.

Peseta 0-1	**Caballo 0-1**	**Manzana 0-1**
(Balón 0-1	**Bandera 0-1**	**Árbol 0-1)**

0 1 2 3

ATENCIÓN - CÁLCULO (Máx.5)

Si tiene 30 pesetas y me va dando de tres en tres, ¿cuántas le van quedando? Detenga la prueba tras 5 sustracciones. Si el sujeto no puede realizar esta prueba, pídale que deletree la palabra MUNDO al revés.

30 0-1	**27 0-1**	**24 0-1**	**21 0-1**	**18 0-1**
(O 0-1	**D 0-1**	**N 0-1**	**U 0-1**	**M 0-1)**

0 1 2 3 4 5

RECUERDO diferido (Máx.3)

Preguntar por las tres palabras mencionadas anteriormente.

Peseta 0-1	**Caballo 0-1**	**Manzana 0-1**
(Balón 0-1	**Bandera 0-1**	**Árbol 0-1)**

0 1 2 3

MINI MENTAL STATE EXAMINATION (MMSE)

CLAVE

Nº pág.

Por favor, marque la opción que se corresponda con su respuesta y siga las instrucciones determinadas en cada caso.

MARQUE CORRECTAMENTE

Bien Mal Mal Mal Mal

LENGUAJE (Máx. 9)

DENOMINACIÓN. Mostrarle un lápiz o un bolígrafo y preguntar ¿qué es esto? Hacer lo mismo con un reloj de pulsera.

Lápiz 0-1
Reloj 0-1

REPETICIÓN. Pedirle que repita la frase:
"ni sí, ni no, ni pero" o ("En un trigal había 5 perros"). **0-1**

ÓRDENES. Pedirle que siga la orden: "coja un papel con la mano derecha, dóblelo por la mitad, y póngalo en el suelo".

Coje con mano derecha 0-1
Dobla por mitad 0-1
Pone en suelo 0-1

LECTURA. Escriba legiblemente en un papel *"Cierre los ojos"*. Pídale que lo lea y haga lo que dice la frase. **0-1**

ESCRITURA. Que escriba una frase (con sujeto y predicado). **0-1**

COPIA. Dibuje 2 pentágonos intersectados y pida al sujeto que los copie tal cual. Para otorgar un punto deben estar presentes los 10 ángulos y la intersección. **0-1**

Puntuación Total (Máx: 30 puntos)

Puntuaciones de referencia.

27 ó más: normal

24 ó menos: sospecha patológica

12-24: deterioro

9-12: demencia

BECK DEPRESSION INVENTORY - second edition

Universidad de Granada

(BDI-II)

Por favor, marque la opción que se corresponda con su respuesta y siga las instrucciones determinadas en cada caso.

MARQUE CORRECTAMENTE

Bien Mal Mal Mal Mal

CLAVE

Nº pág.

FECHA

Este cuestionario consta de 21 grupos de enunciados. Por favor, lea cada uno de ellos cuidadosamente. Luego elija **uno** de cada grupo, el que mejor describa el modo como se ha sentido las **últimas dos semanas, incluyendo el día de hoy**. Marque el número correspondiente al enunciado elegido. Si varios enunciados de un mismo grupo le parecen igualmente apropiados, marque el número más alto. Verifique que no haya elegido más de uno por grupo, incluyendo el ítem 16 (Cambio en los Hábitos de Sueño) y el ítem 18 (Cambios en el Apetito).

0 1 2 3

1. Tristeza.

0= No me siento triste.
1= Me siento triste gran parte del tiempo.
2= Estoy triste todo el tiempo.
3= Estoy tan triste o soy tan infeliz que no puedo soportarlo.

0 1 2 3

2. Pesimismo.

0= No estoy desalentado respecto de mi futuro.
1= Me siento más desalentado respecto de mi futuro que lo que solía estarlo.
2= No espero que las cosas funcionen para mí.
3= Siento que no hay esperanza para mi futuro y que sólo puede empeorar.

0 1 2 3

3. Fracaso.

0= No me siento como un fracasado.
1= He fracasado más de lo que hubiera debido.
2= Cuando miro hacia atrás veo muchos fracasos.
3= Siento que como persona soy un fracaso total.

0 1 2 3

4. Pérdida de placer.

0= Obtengo tanto placer como siempre por las cosas de las que disfruto.
1= No disfruto tanto de las cosas como solía hacerlo.
2= Obtengo muy poco placer de las cosas que solía disfrutar.
3= No puedo obtener ningún placer de las cosas que solía disfrutar.

0 1 2 3

5. Sentimiento de culpa.

0= No me siento particularmente culpable.
1= Me siento culpable respecto de varias cosas que he hecho o que debería haber hecho.
2= Me siento bastante culpable la mayor parte del tiempo.
3= Me siento culpable todo el tiempo.

0 1 2 3

6. Sentimiento de castigo.

0= No siento que estoy siendo castigada.
1= Siento que tal vez pueda ser castigado.
2= Espero ser castigado.
3= Siento que estoy siendo castigado.

0 1 2 3

7. Disconformidad con uno mismo.

0= Siento acerca de mí lo mismo que siempre.
1= He perdido la confianza en mí mismo.
2= Estoy decepcionado conmigo mismo.
3= No me gusto a mí mismo.

BDI-II

Universidad de Granada

Por favor, marque la opción que se corresponda con su respuesta y siga las instrucciones determinadas en cada caso.

MARQUE CORRECTAMENTE

Bien Mal Mal Mal Mal

CLAVE

Nº pág.

	0	1	2	3
8. Autocrítica.				

0= No me critico ni me culpo más de lo habitual.
1= Estoy más crítico conmigo mismo de lo que solía estarlo.
2= Me critico a mí mismo por todos mis errores.
3= Me culpo a mí mismo por todo lo malo que sucede.

	0	1	2	3
9. Pensamiento o deseos suicidas.				

0= No tengo ningún pensamiento de matarme.
1= He tenido pensamientos de matarme, pero no lo haría.
2= Querría matarme.
3= Me mataría si tuviera la oportunidad de hacerlo.

	0	1	2	3
10. Llanto.				

0= No lloro más de lo que solía hacerlo.
1= Lloro más de lo que solía hacerlo.
2= Lloro por cualquier pequeñez.
3= Siento ganas de llorar pero no puedo.

	0	1	2	3
11. Agitación.				

0= No estoy más inquieto o tenso que lo habitual.
1= Me siento más inquieto o tenso que lo habitual.
2= Estoy tan inquieto o agitado que me es difícil quedarme quieto.
3= Estoy tan inquieto o agitado que tengo que estar siempre en movimiento o haciendo algo.

	0	1	2	3
12. Pérdida de Interés.				

0= No he perdido el interés en otras actividades o personas.
1= Estoy menos interesado que antes en otras personas o cosas.
2= He perdido casi todo el interés en otras personas o cosas.
3= Me es difícil interesarme por algo.

	0	1	2	3
13. Indecisión.				

0= Tomo mis decisiones tan bien como siempre.
1= Me resulta más dificil que de costumbre tomar decisiones.
2= Encuentro mucha más dificultad que antes para tomar decisiones.
3= Tengo problemas para tomar cualquier decisión.

	0	1	2	3
14. Desvalorización.				

0= No siento que yo no sea valioso.
1= No me considero a mí mismo tan valioso y útil como solía considerarme.
2= Me siento menos valioso cuando me comparo con otros.
3= Siento que no valgo nada.

Universidad de Granada

BDI-II

Por favor, marque la opción que se corresponda con su respuesta y siga las instrucciones determinadas en cada caso.

MARQUE CORRECTAMENTE

Bien Mal Mal Mal Mal

CLAVE

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15. Perdida de Energía. 0 1 2 3

0= Tengo tanta energía como siempre.
1= Tengo menos enrgía que la que solía tener.
2= No tengo suficiente energía para hacer demasiado.
3= No tengo energía suficiente para hacer nada.

16. Cambios en los Hábitos de Sueño. 0 1a 1b 2a 2b 3a 3b

0 = No he experimentado ningún cambio en mis hábitos de sueño.
1a= Duermo un poco más que lo habitual.
1b= Duermo un poco menos que lo habitual.
2a= Duermo mucho más de lo habitual.
2b= Duermo mucho menos de lo habitual.
3a= Duermo la mayor parte del día.
3b= Me despierto 1-2 horas más temprano y no puedo volver a dormirme.

17. Irritabilidad. 0 1 2 3

0= No estoy más irritable que lo habitual.
1= Estoy más irritable que lo habitual.
2= Estoy mucho más irritable que lo habitual.
3= Estoy irritable todo el tiempo.

18. Cambios en el apetito. 0 1a 1b 2a 2b 3a 3b

0 = No he experimentado ningún cambio en mi apetito.
1a= Mi apetito es un poco menor que lo habitual.
1b= Mi apetito es un poco mayor que lo habitual.
2a= Mi apetito es mucho menor que antes.
2b= Mi apetito es mucho mayor que lo habitual.
3a= No tengo apetito en absoluto.
3b= Quiero comer todo el tiempo.

19. Dificultad de concentración. 0 1 2 3

0= Puedo concentrarme tan bien como siempre.
1= No puedo concentrarme tan bien como habitualmente.
2= Me es difícil mantener la mente en algo mucho tiempo.
3= Encuentro que no puedo concentrarme en nada.

20. Cansancio o Fatiga. 0 1 2 3

0= No estoy más cansado o fatigado que lo habitual.
1= Me fatigo o me canso más facilmente que lo habitual.
2= Estoy demasiado fatigado o cansado para hacer muchas cosas de las que solía hacer.
3= Estoy demasiado fatigado o cansado para hacer la mayoria de las cosas que solía hacer.

21. Pérdida de Interés en el Sexo. 0 1 2 3

0= No he notado ningún cambio reciente en mi interés por el sexo.
1= Estoy menos interesado en el sexo de lo que solía estarlo.
2= Ahora estoy mucho menos interesado en el sexo.
3= He perdido completamente el interés en el sexo.

REVISED FIBROMYALGIA IMPACT QUESTIONNAIRE

Universidad de Granada

(FIQR)

FECHA

Por favor, marque la opción que se corresponda con su respuesta y siga las instrucciones determinadas en cada caso.

MARQUE CORRECTAMENTE

Bien Mal Mal Mal Mal

CLAVE

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1. Para cada pregunta, marque la casilla que mejor indique hasta qué punto la fibromialgia le dificultó llevar a cabo las siguientes actividades **en los últimos 7 días.** Si usted no realizó alguna de las actividades en los últimos 7 días, indique la dificultad de la última vez que realizó dicha actividad. Si usted no puede realizar la actividad, marque la última casilla.

	Sin dificultad … Muy difícil
Cepillar o peinar su cabello.	
Caminar 20 minutos de forma continua.	
Preparar comidad casera.	
Aspirar, barrer o fregar el suelo.	
Levantar y transportar una bolsa de comestibles.	
Subir un tramo de escaleras.	
Cambiar las sábanas de la cama.	
Estar sentado en una silla durante 45 minutos.	
Ir a comprar comestibles.	

2. Para cada pregunta, marque la casilla que mejor describa el impacto global de su fibromialgia **en los últimos 7 días**.

	Nunca … Siempre
La fibromialgia me impidió alcanzar algunas metas que me había propuesto para la semana.	
Me sentí completamente superado por los síntomas de la fibromialgia.	

3. Para cada una de las siguientes preguntas, rellene la casilla que mejor indique la intensidad de sus síntomas de fibromialgia **en los últimos 7 días**.

Por favor, valore su grado de dolor.

Ningún dolor … **Dolor insoportable**

Universidad de Granada

FIQR

Por favor, marque la opción que se corresponda con su respuesta y siga las instrucciones determinadas en cada caso.

MARQUE CORRECTAMENTE

Bien Mal Mal Mal Mal

CLAVE

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Por favor, valore su nivel de energía.

Mucha energía ☐☐☐☐☐☐☐☐☐☐☐ **Ninguna energía**

Por favor, valore su grado de rigidez.

Ninguna rigidez ☐☐☐☐☐☐☐☐☐☐☐ **Rigidez severa**

Por favor, valore la calidad de su sueño.

Desperté muy descansado ☐☐☐☐☐☐☐☐☐☐☐ **Desperté muy cansado**

Por favor, valore su grado de depresión.

Sin depresión ☐☐☐☐☐☐☐☐☐☐☐ **Muy deprimido**

Por favor, valore el grado de sus problemas de memoria.

Buena memoria ☐☐☐☐☐☐☐☐☐☐☐ **Memoria muy pobre**

Por favor, valore su nivel de ansiedad.

Sin ansiedad ☐☐☐☐☐☐☐☐☐☐☐ **Muy ansioso**

Por favor, valore su grado de sensibilidad al tacto.

Ninguna sensibilidad ☐☐☐☐☐☐☐☐☐☐☐ **Muy sensible**

Por favor, valore su nivel de problemas de equilibrio.

Ningún desequilibrio ☐☐☐☐☐☐☐☐☐☐☐ **Desequilibrios severos**

Por favor, valore su nivel de sensibilidad a los ruidos altos, luces brillantes, olores y frío.

Ninguna sensibilidad ☐☐☐☐☐☐☐☐☐☐☐ **Sensibilidad extrema**

Compruebe si ha contestado a todas las frases con una sola respuesta.

PAIN CATASTROPHIZING SCALE

Universidad de Granada

ESCALA DE LA CATASTROFIZACIÓN ANTE EL DOLOR

Por favor, marque la opción que se corresponda con su respuesta y siga las instrucciones determinadas en cada caso.

MARQUE CORRECTAMENTE

Bien Mal Mal Mal Mal

CLAVE

0	0	0	0	0	0
1	1	1	1	1	1
2	2	2	2	2	2
3	3	3	3	3	3
4	4	4	4	4	4
5	5	5	5	5	5
6	6	6	6	6	6
7	7	7	7	7	7
8	8	8	8	8	8
9	9	9	9	9	9

FECHA

Todas las personas experimentamos situaciones de dolor en algún momento de nuestra vida. Tales experiencias pueden incluir dolor de cabeza, dolor de muelas, dolor muscular o de articulaciones. Las personas estamos a menudo expuestas a situaciones que pueden causar dolor como las enfermedades, las heridas, los tratamientos dentales o las intervenciones quirúrgicas.

Estamos interesados en conocer el tipo de pensamientos y sentimientos que usted tiene cuando siente dolor. A continuación se presenta una lista de 13 frases que describen diferentes pensamientos y sentimientos que pueden estar asociados al dolor. Utilizando la siguiente escala, por favor, indique el grado en que usted tiene esos pensamientos y sentimientos cuando siente dolor, marcando la casilla correspondiente.

Cuando siento dolor...	**Nada en absoluto** 0	**Un poco** 1	**Moderadamente** 2	**Mucho** 3	**Todo el tiempo** 4
1. Estoy preocupado todo el tiempo pensando en si el dolor desaparecerá.					
2. Siento que ya no puedo más.					
3. Es terrible y pienso que esto nunca va a mejorar.					
4. Es horrible y suento que esto es más fuerte que yo.					
5. Siento que no puedo soportarlo más.					
6. Temo que el dolor empeore.					
7. No dejo de pensar en otras situaciones en las que experimento dolor.					
8. Deseo desesperadamente que desaparezca el dolor.					
9. No puedo apartar el dolor de mi mente.					
10. No dejo de pensar en lo mucho que me duele.					
11. No dejo de pensar en lo mucho que deseo que desaparezca el dolor.					
12. No hay nada que pueda hacer para aliviar la intensidad del dolor.					
13. Me pregunto si me puede pasar algo grave.					

Compruebe si ha contestado a todas las frases con una sola respuesta.

CHRONIC PAIN SELF-EFFICACY SCALE

Universidad de Granada

AUTOEFICACIA EN DOLOR CRÓNICO

FECHA

CLAVE

Nº pág

Por favor, marque la opción que se corresponda con su respuesta y siga las instrucciones determinadas en cada caso.

MARQUE CORRECTAMENTE

Bien Mal Mal Mal Mal

Con este cuestionario estamos interesados en conocer la **CAPACIDAD QUE USTED TIENE PARA REALIZAR UNA SERIE DE ACTIVIDADES O TAREAS**. Siguiendo la escala de respuesta que le presentamos, responda rellenando la casilla que usted crea que corresponde a su grado de capacidad.

A continuación le ponemos un ejemplo; no es necesario que lo conteste. POR EJEMPLO, si la pregunta es:

	Me creo totalmente incapaz 0	1	2	3	4	Me creo moderadamente capaz 5	6	7	8	9	Me creo totalmente capaz 10
¿Se cree capaz de leer El Quijote?											

Si usted cree que es **totalmente incapaz** de leerlo, tendrá que marcar la casilla **0** de la escala de respuesta. Sin embargo, si usted cree que es **totalmente capaz** de leerlo, tendrá que marcar la casilla **10** de la escala de respuesta.

RECUERDE: NO NOS INTERESA SABER SI LO HACE O NO LO HACE. SÓLO NOS INTERESA SABER SI USTED CREE QUE ES CAPAZ DE HACERLO O NO.

MARQUE LA CASILLA DEL NÚMERO QUE CORRESPONDA A LA CAPACIDAD QUE CREE QUE TIENE PARA REALIZAR EN **ESTE MOMENTO** LAS SIGUIENTES ACTIVIDADES O TAREAS.

	Me creo totalmente incapaz 0	1	2	3	4	Me creo moderadamente capaz 5	6	7	8	9	Me creo totalmente capaz 10
1. ¿Se cree capaz de controlar su fatiga?											
2. ¿Se cree capaz de regular su actividad, para poder estar activo pero sin empeorar sus síntomas físicos? (Por ejemplo, fatiga, dolor).											
3. ¿Se cree capaz de hacer algo para sentirse mejor si está triste o bajo de ánimo?											
4. Comparado con otra gente con problemas crónicos como los suyos ¿Se cree capaz de controlar su dolor durante sus actividades diarias?											
5. Se cree capaz de controlar sus síntomas físicos, de manera que pueda seguir haciendo las cosas que le gusta hacer?											
6. ¿Se cree capaz de hacer frente a la frustración de sus problemas físicos crónicos?											
7. ¿Se cree capaz de afrontar dolores leves o moderados?											
8. ¿Se cree capaz de afrontar dolores intensos?											

Universidad de Granada

AUTOEFICACIA EN DOLOR CRÓNICO

Por favor, marque la opción que se corresponda con su respuesta y siga las instrucciones determinadas en cada caso.

MARCA CORRECTAMENTE

Bien Mal Mal Mal Mal

CLAVE

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Marque la casilla del número que corresponda a la capacidad que cree que tiene para realizar las siguientes actividades **sin ayuda de otra persona**. Considere lo que **normalmente** puede hacer. No aquello que suponga un esfuerzo extraordinario.

	0 Me creo totalmente incapaz	1	2	3	4	5 Me creo moderadamente capaz	6	7	8	9	10 Me creo totalmente capaz
1. ¿Se cree capaz de caminar aproximadamente un kilómetro por terreno llano?											
2. ¿Se cree capaz de levantar una caja de aproximadamente 5 kilos de peso?											
3. ¿Se cree capaz de hacer un programa diario de ejercicios en casa?											
4. ¿Se cree capaz de hacer sus tareas domésticas?											
5. ¿Se cree capaz de participar en actividades sociales?											
6. ¿Se cree capaz de ir de compras para adquirir alimentos o ropa?											

Marque la casilla correspondiente al número de la capacidad que cree que tiene **en este momento** para realizar las siguientes actividades:

	0 Me creo totalmente incapaz	1	2	3	4	5 Me creo moderadamente capaz	6	7	8	9	10 Me creo totalmente capaz
1. ¿Se cree capaz de disminuir bastante su dolor?											
2. ¿Se cree capaz de evitar que el dolor interfiera en su sueño?											
3. ¿Se cree capaz de reducir su dolor, aunque sea un poco, haciendo otra cosa que no sea tomar más medicinas?											
4. ¿Se cree capaz de reducir mucho su dolor haciendo otra cosa que no sea tomar más medicinas?											
5. ¿Se cree capaz de cumplir con las mismas obligaciones de trabajo que tenía antes del inicio del dolor crónico? (Para las personas que trabajen en casa, por favor, consideren sus quehaceres domésticos como sus obligaciones).											

Compruebe si ha contestado a todas las frases con una sola respuesta.

Universidad de Granada

ÍNDICE DE CALIDAD DE SUEÑO DE PITTSBURGH

FECHA

Por favor, marque la opción que se corresponda con su respuesta y siga las instrucciones determinadas en cada caso.

MARQUE CORRECTAMENTE

Bien Mal Mal Mal Mal

CLAVE

0	0	0	0	0	0
1	1	1	1	1	1
2	2	2	2	2	2
3	3	3	3	3	3
4	4	4	4	4	4
5	5	5	5	5	5
6	6	6	6	6	6
7	7	7	7	7	7
8	8	8	8	8	8
9	9	9	9	9	9

Nº pág.

0 1 2 3 4 5 6 7 8 9

Las siguientes cuestiones hacen referencia a sus hábitos de sueño sólo durante el último mes. Sus respuestas deben reflejar fielmente lo ocurrido la mayoría de días y noches del último mes. Por favor conteste a todas las preguntas.

1. Durante el último mes, ¿a qué hora solía acostarse por la noche?

Hora habitual de acostarse.
(Rellenar en formato 24 h.).

0	0	0	0
1	1	1	1
2	2	2	2
3	3	3	3
4	4	4	4
5	5	5	5
6	6	6	6
7	7	7	7
8	8	8	8
9	9	9	9

2. Durante el último mes, ¿cuánto tiempo (en minutos) le ha costado quedarse dormido después de acostarse por las noches?

Número de minutos para conciliar el sueño.

0	0	0
1	1	1
2	2	2
3	3	3
4	4	4
5	5	5
6	6	6
7	7	7
8	8	8
9	9	9

3. Durante el último mes, ¿a qué hora se ha levantado habitualmente por la mañana?

Hora habitual de levantarse.
(Rellenar en formato 24 h.).

0	0	0	0
1	1	1	1
2	2	2	2
3	3	3	3
4	4	4	4
5	5	5	5
6	6	6	6
7	7	7	7
8	8	8	8
9	9	9	9

ÍNDICE DE CALIDAD DE SUEÑO DE PITTSBURGH

Por favor, marque la opción que se corresponda con su respuesta y siga las instrucciones determinadas en cada caso.

MARQUE CORRECTAMENTE

Bien Mal Mal Mal Mal

CLAVE

Nº pág.

4. Durante el último mes, ¿cuántas horas de sueño real ha mantenido por las noches? (Puede ser diferente del número de horas que estuvo acostado).

Horas de sueño por la noche.

Para cada una de las cuestiones siguientes, seleccionar la respuesta más adecuada a su situación. Teniendo en cuenta que:

0 = No me ha ocurrido.
1 = Menos de una vez a la semana.
2 = Una o dos veces a la semana.
3 = Tres o más veces a la semana.

Por favor, conteste a todas las preguntas.

5. Durante el último mes, **¿con qué frecuencia ha tenido un sueño alterado a consecuencia de...?**

	0	1	2	3
· No poder conciliar el sueño después de 30 minutos de intentarlo.				
· Despertares en mitad de la noche o de madrugada.				
· Tener que ir al baño.				
· No poder respirar adecuadamente.				
· Tos o ronquidos.				
· Sensación de frío.				
· Sensación de calor.				
· Pesadillas.				
· Sentir dolor.				
· Otra causa(s), describir: .... ¿Con qué frecuencia ha tenido un sueño alterado a consecuencia de ese problema?				

ÍNDICE DE CALIDAD DE SUEÑO DE PITTSBURGH

Universidad de Granada

Por favor, marque la opción que se corresponda con su respuesta y siga las instrucciones determinadas en cada caso.

MARQUE CORRECTAMENTE

Bien Mal Mal Mal Mal

CLAVE

Nº pág.

0 1 2 3

6. Durante el último mes, **¿cómo calificaría, en general, la calidad de su sueño?**

0 = Muy buena.
1 = Bastante buena.
2 = Bastante mala.
3 = Muy mala.

0 1 2 3

7. Durante el último mes, **¿con qué frecuencia tuvo que tomar medicinas (prescritas o automedicadas) para poder dormir?**

0 = No las he necesitado durante el último mes.
1 = Menos de una vez a la semana.
2 = Una o dos veces a la semana.
3 = Tres o más veces a la semana.

0 1 2 3

8. Durante el último mes, **¿con qué frecuencia tuvo dificultad para mantenerse despierto mientras conducía, comía o desarrollaba alguna actividad social?**

0 = No me ha ocurrido durante el último mes.
1 = Menos de una vez a la semana.
2 = Una o dos veces a la semana.
3 = Tres o más veces a la semana.

0 1 2 3

9. Durante el último mes, **¿cómo de problemático ha resultado para usted el mantener el entusiasmo por hacer las cosas?**

0 = No ha resultado problemático en absoluto.
1 = Sólo ligeramente problemático.
2 = Moderadamente problemático.
3 = Muy problemático.

0 1 2 3

10. **¿Tiene usted pareja o compañero/a de habitación?**

0 = No tengo pareja, ni compañero/a de habitación.
1 = Sí tengo, pero duerme en otra habitación.
2 = Sí tengo, duerme en la misma habitación y distinta cama.
3 = Sí tengo y duerme en la misma cama.

MULTIDIMENSIONAL FATIGUE INVENTORY

Universidad de Granada

MFI-20

Por favor, marque la opción que se corresponda con su respuesta y siga las instrucciones determinadas en cada caso.

MARQUE CORRECTAMENTE

Bien Mal Mal Mal Mal

CLAVE

0	0	0	0	0	0
1	1	1	1	1	1
2	2	2	2	2	2
3	3	3	3	3	3
4	4	4	4	4	4
5	5	5	5	5	5
6	6	6	6	6	6
7	7	7	7	7	7
8	8	8	8	8	8
9	9	9	9	9	9

FECHA

Instrucciones:
Por medio de las siguientes afirmaciones, nos gustaría obtener una idea de cómo se ha sentido **últimamente**. Por ejemplo, ante la afirmación: "ME SIENTO RELAJADO", si piensa que esto es **completamente cierto**, que verdaderamente se ha sentido relajado últimamente, por favor, marque la casilla del extremo izquierdo del recuadro; como en el siguiente ejemplo:

Sí, es cierto. ▬ ▭ ▭ ▭ ▭ **No, eso no es cierto.**

Cuanto más en **desacuerdo** esté con las siguientes afirmaciones, más cerca de la dirección del "no, eso no es cierto" tendrá que marcar la casilla correspondiente. Por favor, no deje pasar ninguna afirmación y marque una casilla en cada una.

	Sí, es cierto				No, no es cierto
1. Me siento en forma.	▭	▭	▭	▭	▭
2. Físicamente me siento capaz de hacer poco.	▭	▭	▭	▭	▭
3. Me siento muy activo/a.	▭	▭	▭	▭	▭
4. Tengo ganas de hacer todo tipo de cosas agradables.	▭	▭	▭	▭	▭
5. Me siento cansado/a.	▭	▭	▭	▭	▭
6. Creo que hago muchas cosas al día.	▭	▭	▭	▭	▭
7. Cuando estoy haciendo algo, me cuesta estar pensando en lo que estoy haciendo.	▭	▭	▭	▭	▭
8. Puedo exigirme físicamente.	▭	▭	▭	▭	▭
9. Me da miedo hacer ciertas cosas.	▭	▭	▭	▭	▭
10. Creo que hago pocas cosas al día.	▭	▭	▭	▭	▭
11. Puedo concentrarme bien.	▭	▭	▭	▭	▭
12. Estoy descansado/a.	▭	▭	▭	▭	▭
13. Me supone mucho esfuerzo concentrarme en ciertas cosas.	▭	▭	▭	▭	▭
14. Físicamente siento que estoy en baja forma.	▭	▭	▭	▭	▭
15. Tengo muchos planes.	▭	▭	▭	▭	▭
16. Me canso fácilmente.	▭	▭	▭	▭	▭
17. Hago pocas cosas.	▭	▭	▭	▭	▭
18. No me siento con ganas de hacer nada.	▭	▭	▭	▭	▭
19. Mis pensamientos vagan fácilmente.	▭	▭	▭	▭	▭
20. Físicamente me encuentro en una excelente condición.	▭	▭	▭	▭	▭

Compruebe si ha contestado a todas las frases con una sola respuesta.

Universidad de Granada

SALUD SF-36

FECHA

CLAVE

Nº pág

Por favor, marque la opción que se corresponda con su respuesta y siga las instrucciones determinadas en cada caso.

MARQUE CORRECTAMENTE

Bien Mal Mal Mal Mal

Por favor conteste las siguientes preguntas. Algunas preguntas pueden parecerse a otras pero cada una es diferente.

Tómese el tiempo necesario para leer cada pregunta, y marque la casilla que mejor describa su respuesta.

	Excelente 1	Muy buena 2	Buena 3	Regular 4	Mala 5
1. En general, usted diría que su salud es:					

	1	2	3	4	5
2. ¿Cómo diría usted que es su salud actual, comparada con la de hace un año?					

1= Mucho mejor ahora que hace un año
2= Algo mejor ahora que hace un año
3= Más o menos igual que hace un año
4= Algo peor ahora que hace un año
5= Mucho peor ahora que hace un año

Para cada una de las cuestiones siguientes, seleccionar la respuesta más adecuada. Teniendo en cuenta que:

1. Sí, me limita mucho.
2. Sí, me limita un poco.
3. No, no me limita nada.

3. Las siguientes preguntas se refieren a actividades o cosas que usted podría hacer un día normal. Su salud actual, ¿le limita para hacer esas actividades o cosas? Si es así, ¿cuánto?

	1	2	3
a) Esfuerzos intensos, tales como correr, levantar objetos pesados, o participar en deportes agotadores.			
b) Esfuerzos moderados, como mover una mesa, pasar la aspiradora, jugar a los bolos o caminar más de 1 hora.			
c) Coger o llevar la bolsa de la compra.			
d) Subir varios pisos por la escalera.			
e) Subir un solo piso por la escalera.			
f) Agacharse o arrodillarse.			
g) Caminar un kilómetro o más.			
h) Caminar varios centenares de metros.			
i) Caminar unos 100 metros.			
j) Bañarse o vestirse por sí mismo.			

Universidad de Granada

SALUD SF-36

Por favor, marque la opción que se corresponda con su respuesta y siga las instrucciones determinadas en cada caso.

MARQUE CORRECTAMENTE

Bien Mal Mal Mal Mal

CLAVE

Nº pág

4. Durante las 4 últimas semanas, ¿con qué frecuencia ha tenido alguno de los siguientes problemas en su trabajo o en sus actividades cotidianas, a causa de su salud física?

1= Siempre
2= Casi siempre
3= Algunas veces
4= Sólo alguna vez
5= Nunca

	1	2	3	4	5
a) ¿Tuvo que reducir el tiempo dedicado al trabajo o a sus actividades cotidianas?					
b) ¿Hizo menos de lo que hubiera querido hacer?					
c) ¿Tuvo que dejar de hacer algunas tareas en su trabajo o en sus actividades cotidianas?					
d) ¿Tuvo dificultad para hacer su trabajo o sus actividades cotidianas (por ejemplo, le costó más de lo normal)?					

5. Durante las 4 últimas semanas, ¿con qué frecuencia ha tenido alguno de los siguientes problemas en su trabajo o en sus actividades cotidianas, a causa de algún problema emocional (como estar triste, deprimido o nervioso)?

1= Siempre
2= Casi siempre
3= Algunas veces
4= Sólo alguna vez
5= Nunca

	1	2	3	4	5
a) ¿Tuvo que reducir el tiempo dedicado al trabajo o a sus actividades cotidianas por algún problema emocional?					
b) ¿Hizo menos de lo que hubiera querido hacer por algún problema emocional?					
c) ¿Hizo su trabajo o sus actividades cotidianas menos cuidadosamente que de costumbre, por algún problema emocional?					

	Nada	Un poco	Regular	Bastante	Mucho
6. Durante las 4 últimas semanas, ¿hasta qué punto se salud fisica o los problemas emocionales han dificultado sus actividades sociales habituales con la familia, amigos, los vecinos u otras personas?					

	No, ninguno	Sí, muy poco	Sí, un poco	Sí, moderado	Sí, mucho	Sí, muchísimo
7. ¿Tuvo dolor en alguna parte del cuerpo **durante las 4 últimas semanas**?						

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	Nada	Un poco	Regular	Bastante	Mucho
8. Durante las 4 últimas semanas, ¿hasta qué punto el dolor le ha dificultado su trabajo habitual (incluido el trabajo fuera de casa y las tareas domésticas)?					

9. Las preguntas que siguen se refieren a cómo se ha sentido y cómo le han ido las cosas **durante las 4 últimas semanas**. En cada pregunta responda lo que se parezca más a cómo se ha sentido usted. Durante las últimas 4 semanas ¿con que frecuencia.....

1= Siempre
2= Casi siempre
3= Algunas veces
4= Sólo alguna vez
5= Nunca

	1	2	3	4	5
a) ¿Se sintió lleno de vitalidad?					
b) ¿Estuvo muy nervioso?					
c) ¿Se sintió tan bajo de moral que nada podía animarle?					
d) ¿Se sintió calmado o tranquilo?					
e) ¿Tuvo mucha energía?					
f) ¿Se sintió desanimado y deprimido?					
g) ¿Se sintió agotado?					
h) ¿Se sintió feliz?					
i) ¿Se sintió cansado?					

	1	2	3	4	5
10. Durante las 4 últimas semanas, ¿con qué frecuencia la salud física o los problemas emocionales le han dificultado sus actividades sociales (como visitar a los amigos o familiares)?					

1= Siempre
2= Casi siempre
3= Algunas veces
4= Sólo alguna vez
5= Nunca

11. Por favor, diga si le parece **CIERTA o FALSA** cada una de las siguientes frases:

1= Totalmente cierta
2= Bastante cierta
3= No lo sé
4= Bastante falsa
5= Totalmente falsa

	1	2	3	4	5
a) Creo que me pongo enfermo más fácilmente que otras personas.					
b) Estoy tan sano como cualquiera.					
c) Creo que mi salud va a empeorar.					
d) Mi salud es excelente.					

PACED AUDITORY SERIAL ADITION TASK (PASAT)

Universidad de Granada

FECHA

FUNCIÓN COGNITIVA PASAT

Por favor, marque la opción que se corresponda con su respuesta y siga las instrucciones determinadas en cada caso.

MARQUE CORRECTAMENTE

Bien Mal Mal Mal Mal

CLAVE

0 1 2 3 4 5 6 7 8 9

NOTA: En el cuadro de abajo, los números colocados en la parte superior de cada cuadro son los que se reproducen para que el examinado los sume. Los números colocados en la parte inferior de cada cuadro y sombreado de fondo naranja, son los resultados correctos de cada respuesta.

FRECUENCIA Nº 1 (2,4 segundos)

1+4	8	1	5	1	3	7	2	6	9
5	12	9	6	6	4	10	9	8	15
4	7	3	5	3	6	8	2	5	1
13	11	10	8	8	9	14	10	7	6
5	4	6	3	8	1	7	4	9	3
6	9	10	9	11	9	8	11	13	12
7	2	6	9	5	2	4	8	3	1
10	9	8	15	14	7	6	12	11	4
8	5	7	1	8	2	4	9	7	9
9	13	12	8	9	10	6	13	16	16
3	1	5	7	4	8	1	3	8	2
12	4	6	12	11	12	9	4	11	10

Nº TOTAL DE RESPUESTAS CORRECTAS =

0 1 2 3 4 5 6 7 8 9

Nº TOTAL DE RESPUESTAS INCORRECTAS =

0 1 2 3 4 5 6 7 8 9

Nº TOTAL DE RESPUESTAS NO CONTESTADAS =

0 1 2 3 4 5 6 7 8 9

REY AUDITORY VERBAL LEARNING TEST

Universidad de Granada

RAVLT

FECHA

Por favor, marque la opción que se corresponda con su respuesta y siga las instrucciones determinadas en cada caso.

MARQUE CORRECTAMENTE

Bien Mal Mal Mal Mal

CLAVE

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LISTA A	ENSAYOS DE MEMORIA					LISTA B	ENSAYOS DE MEMORIA		
	A1	A2	A3	A4	A5		B1	A6	A7
PUPITRE						TAMBOR			
PASTOR						CORTINA			
GORRIÓN						ESCUELA			
ZAPATO						LUNA			
HORNO						JARDIN			
LIMÓN						AVIÓN			
CASA						NARIZ			
ESPONJA						PAVO			
COLOR						RIO			
BARCO						GUARDIA			
OVEJA						CHICO			
FUSIL						BOTELLA			
LÁPIZ						ARBOL			
IGLESIA						PATATA			
PEZ						CUNA			

A1 A2 A3 A4 A5 B1 A6 A7

Universidad de Granada

RAVLT

Por favor, marque la opción que se corresponda con su respuesta y siga las instrucciones determinadas en cada caso.

MARQUE CORRECTAMENTE

Bien Mal Mal Mal Mal

CLAVE

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0	0	0	0	0	0
1	1	1	1	1	1
2	2	2	2	2	2
3	3	3	3	3	3
4	4	4	4	4	4
5	5	5	5	5	5
6	6	6	6	6	6
7	7	7	7	7	7
8	8	8	8	8	8
9	9	9	9	9	9

MATRIZ DE 50 PALABRAS DE RECONOCIMIENTO

GORRION (A)	PLUMA (SA)	LUNA (B)	TAMBOR (B)	ESCUELA (B)
BOTA (SA)	CUNA (B)	PASTOR (A)	MASA (FA)	VENTANA (SB)
COLOR (A)	HORNO (A)	ALUMNO (SA)	BARCO (A)	JARDIN (B)
LANA (SA)	CASTOR (FA)	LÁPIZ (A)	CAÑON (SA)	CATEDRAL (SA)
GUARDIA (B)	TEZ (FA)	PATATA (B)	CASA (A)	PATO (SFB)
LIMÓN (A)	BOTELLA (B)	PAVO (B)	LIMA (SFA)	AVIÓN (B)
PLANTA (SB)	NARIZ (B)	PAJARO (SA)	CHICO (B)	JABÓN (SA)
PUPITRE (A)	IGLESIA (A)	CORTINA (B)	OVEJA (A)	ZAPATO (A)
ARCO (FA)	TORNO (PA)	FUSIL (A)	DUNA (FB)	DOLOR (FA)
ARBOL (B)	PEZ (A)	TIO (FB)	ESPONJA (A)	RIO (B)

Numero de aciertos

0	0
1	1
2	2
3	3
4	4
5	5
6	6
7	7
8	8
9	9

Universidad de Granada

FECHA

VISUAL ANALOGUE SCALE (VAS)

Por favor, marque la opción que se corresponda con su respuesta y siga las instrucciones determinadas en cada caso.

MARQUE CORRECTAMENTE

Bien Mal Mal Mal Mal

CLAVE

Nº pág.

En la siguiente pregunta, ponga una marca como esta en el punto de la línea que mejor indique cómo se siente en general. **Ejemplo:**

¿Qué dolor siente en estos momentos?

No he sentido dolor

He sentido un dolor muy intenso

0 1 2 3 4 5 6 7 8 9

0 1 2 3 4 5 6 7 8 9

0 1 2 3 4 5 6 7 8 9