Do women with fibromyalgia present higher cardiovascular disease risk profile than healthy women? The al-Ándalus project

P. Acosta-Manzano[1], V. Segura-Jiménez[1,2], F. Estévez-López[1,3], I.C. Álvarez-Gallardo[1], A. Soriano-Maldonado[1,4], M. Borges-Cosic[1], B. Gavilán-Carrera[1], M. Delgado-Fernández[1], V.A. Aparicio[5]

[1]*Department of Physical Education and Sport, Faculty of Sport Sciences, University of Granada, Spain;*
[2]*Department of Physical Education, Faculty of Education Sciences, University of Cádiz, Spain;*
[3]*Department of Psychology, Faculty of Social and Behavioural Sciences, Utrecht University, The Netherlands;*
[4]*SPORT Research Group (CTS-1024), Department of Education, Faculty of Education Sciences, University of Almeria, Spain;*
[5]*Department of Physiology, Faculty of Pharmacy, Faculty of Sport Sciences, and Institute of Nutrition and Food Technology, University of Granada, Spain.*

Pedro Acosta-Manzano, MSc
Víctor Segura-Jiménez, PhD
Fernando Estévez-López, MSc
Inmaculada C. Álvarez-Gallardo, PhD
Alberto Soriano-Maldonado, PhD
Milkana Borges-Cosic, MSc
Blanca Gavilán-Carrera, MSc
Manuel Delgado-Fernández, PhD
Virginia A. Aparicio, PhD

Please address correspondence to:
Dr Pedro Acosta-Manzano,
Department of Physical Education and Sport, Faculty of Sport Sciences, University of Granada,
Carretera de Alfacar, s/n,
18011 Granada, Spain.
E-mail: acostapedro23@ugr.es

Received on December 30, 2016; accepted in revised form on March 13, 2017.

Clin Exp Rheumatol 2017; 35 (Suppl. 105): S61-S67.

Key words: physical activity, accelerometry, risk factors, cardiometabolic, cardiorespiratory fitness, adiposity.

Funding: see page S-66.

Competing interests: none declared.

ABSTRACT

Objective. *To analyse the cardiovascular disease risk profile of women with fibromyalgia and compare it with control women; and to test whether physical activity is associated with the cardiovascular disease risk profile in this population.*

Methods. *This cross-sectional study comprised 436 women with fibromyalgia (51.4±7.5 years old) and 217 controls (48.4±9.6 years old) from Andalusia, Spain. Clinical data, waist circumference, body fat percentage, resting heart rate, blood pressure and cardiorespiratory fitness were assessed. Moderate-to-vigorous physical activity was objectively assessed with accelerometry. A clustering of individual cardiovascular disease risk factors was represented by the number of cigarettes/day, adiposity, mean arterial pressure, resting heart rate and cardiorespiratory fitness.*

Results. *Women with fibromyalgia presented higher waist circumference and body fat percentage, greater number of cigarettes/day consumption and lower levels of cardiorespiratory fitness after controlling for age, marital status, educational level, occupational status, medication for cholesterol and monthly regular menstruation (all, $p<0.05$). Women with fibromyalgia showed higher clustered cardiovascular disease risk than control women after controlling for the potential confounders described above ($p<0.001$). Women with fibromyalgia who did not meet moderate-to-vigorous physical activity recommendations showed increased clustered cardiovascular disease risk after adjusting for the potential confounders described above ($p<0.001$).*

Conclusion. *Women with fibromyalgia may present higher risk of cardiovascular disease than controls. Inadequate levels of moderate-to-vigorous physical activity may play a significant role as an additional predisposing factor for cardiovascular disease risk in this population.*

Introduction

Cardiovascular diseases (CVD) represent the main cause of mortality worldwide (1). Among the most important CVD risk factors, high blood pressure, high central and general adiposity, tobacco consumption, low cardiorespiratory fitness (CRF) or physical inactivity have shown to be important predictors of cardiovascular events (2-7).

In the current century, literature has emphasised the importance of both predisposing risk factors, low CRF and physical inactivity (3, 4). Indeed, CRF is an important predictor of cardiovascular mortality (8) and the attributable risk of all-cause mortality associated with low CRF may be higher to that of hypertension, smoking, or any other established risk factor (3). Similarly, physical inactivity has also been proved to be a widespread and major contributor of CVD (4, 9).

Fibromyalgia is a complex disorder of uncertain aetiology characterised by chronic widespread pain, fatigue, poor sleep quality and cognitive difficulties, among other physical and psychological symptoms (10-12). Fibromyalgia is also associated with low levels of physical fitness (13), low physical activity (PA) (14) and higher prevalence of obesity (15), which are major contributors to the overall risk of CVD (4, 8, 16). Thus, the prevalence of CVD is a worrisome issue that should be also considered in women with fibromyalgia who might be more prone to exhibit greater CVD risk than controls.

Some studies have stated that women with fibromyalgia present worsened

CVD risk factors than controls (17, 18). However, this association has not been analysed deeply in relation to controls and these studies lack a representative sample (17, 18) or a suitable clinical diagnosis of fibromyalgia (19). In addition, none of the previous studies have considered the potential role of tobacco consumption, CRF and PA. Since specific chronic conditions, such as CVD, can hinder diseases management and treatment, it is of clinical interest to determine whether fibromyalgia is associated with CVD risk factors. This might lead to a more effective design and implementation of future clinical interventions.

Therefore, the aims of the present study were: i) to analyse the CVD risk profile of women with fibromyalgia and compare it with controls; ii) to test whether PA is associated with the CVD risk profile of this specific population.

Material and methods

Design and participants

In the present cross-sectional study, a representative sample of women with fibromyalgia (required sample size, n=300) from Andalusia (southern Spain) was recruited and assessed between September 2011 and January 2013. Women with fibromyalgia were contacted through different fibromyalgia associations via e-mail, mail or telephone. We also recruited a group of control with similar age, socio-demographic characteristics, and demographic area with Internet advertisements. Additionally, women with fibromyalgia were also asked to search non-fibromyalgia peers with similar age and demographic area (10). All interested participants (n=960) gave their written informed consent after receiving detailed information about the aims and study procedures. The inclusion criteria for fibromyalgia participants were: (i) to be previously diagnosed by a rheumatologist and (ii) to meet the 1990 fibromyalgia criteria. The inclusion criteria for non-fibromyalgia controls were (i) not to have a previous clinical diagnosis of fibromyalgia and (ii) not to meet the 1990 ACR fibromyalgia criteria. Additionally, neither men, nor women >65 years old, nor women with acute or terminal illness or with severe cognitive impairment (*i.e.* Mini Mental State Examination (MMSE) score <10) (20) were included. Therefore, from all interested participants (n=960), the final study sample was composed of 436 women with fibromyalgia (age 51.4±7.5 years old) and 217 control women (age 48.4±9.6 years old). The study was reviewed and approved by the Ethics Committee of the "Hospital Virgen de las Nieves" (15/11/2013-N72), (Granada, Spain).

Procedures

The assessment procedure was performed on 2 non-consecutive days. On the first appointment, the fibromyalgia diagnosis was confirmed through the tender points assessment, body composition, blood pressure and resting heart rate were evaluated, and participants completed the MMSE and a self-reported socio-demographic survey. On the second appointment, CRF was assessed.

• *Socio-demographic and clinical data*

An initial self-report survey was used to record socio-demographic information of the study participants. Additionally, participants were asked: "Have you ever been diagnosed with an acute or terminal illness?" for inclusion purposes. Clinical history of CVD risk factors, cardiometabolic diseases and pharmacology were also collected.

• *Anthropometry and body composition*

Waist circumference (cm) was measured with the participant standing at the middle point between the ribs and the iliac crest (Harpenden anthropometric tape; Holtain Ltd, Crymych, UK) and was considered a measure of central adiposity (5, 16). A portable eight-polar tactile-electrode impedanciometer (InBody R20; Biospace, Seoul, Korea) was used to measure body weight (kg) and total body fat (kg), and to estimate body fat percentage. Body mass index (BMI) was calculated as weight (kg) divided by squared height (m^2).

• *Blood pressure and resting heart rate*

We used a blood pressure monitor (M6 upper arm blood pressure monitor Omron. Omron Healthcare Europe B.V., Hoolddorp, the Netherlands) to assess systolic and diastolic blood pressure and resting heart rate when women were seated in a proper relaxed state at rest. Two measurements were taken with five minutes rest between them. The lowest value of the two measurements of each parameter was used for the analysis. The mean arterial pressure was calculated as: Mean arterial pressure = [Systolic blood pressure + (Diastolic blood pressure*2)]/3.

• *Cardiovascular disease risk factors*

In this study, predisposing and independent CVD risk factors were assessed (*i.e.* those parameters associated with higher global risk of CVD). Self-reported CVD risk factors were obtained with individual questions through the sociodemographic questionnaire, asking the participants whether (yes/no) they had suffered stroke or other heart diseases, varicose veins, type 2 diabetes, hypercholesterolaemia or embolism and whether they still had or not (yes/no) monthly regular menstruation. Women were also asked whether they had consumed specific medication for hypertension, cholesterol and diabetes during the last two weeks. Regarding smoking status, participants were asked whether they were current smokers or not. If they were current smoker, the average of cigarettes/day they smoked, with frequency and amount of cigarettes were collected. Waist circumference, body fat percentage, mean arterial pressure, resting heart rate and CRF were considered objectively measured CVD risk factors. A clustered CVD risk index was created from age-specific (<45, 45–55, >55 years old) z scores [(value-mean)/standard deviation] of the number of cigarettes per day, adiposity (composed of waist circumference and body fat percentage), mean arterial pressure, resting heart rate and CRF in women groups.

• *Cardiorespiratory fitness*

The 6-minute walk test (21) was used to assess CRF. Participants were asked to walk the maximum possible distance in 6 minutes along a 45.7 metres rectangular course. The final number of metres completed was used for the

analysis. The 6-minute walk test has been proved to be feasible and reliable, and a moderately valid estimate of CRF in this population (22).

• *Physical activity*

The procedures of PA assessment has been published previously elsewhere (14). PA was objectively assessed with accelerometry (ActiGraph GT3X+, Pensacola, Florida, US). During 9 whole consecutive days (24 h), women wore the accelerometers on their lower back attached by an elastic belt during waking and sleeping hours, excepting water-based activities. A total of 7 days of recording (minimum registration of ≥10hours/day) was necessary to be included in the study. Accelerometer wearing time was calculated by subtracting the non-wear time and the sleeping time from the total registered time for the entire day (typically 1.440 min). Bouts of 90 continuous minutes of 0 activity intensity counts were excluded from the analyses. Values with recording of more than 20,000 counts per minute were also excluded (potential malfunction). The time involved in Moderate-Vigorous Physical Activity (MVPA) was calculated based on recommended PA vector magnitude cut point ≥2,690 counts per minute (23) and was expressed in min/day. The minutes of MVPA bouts per week was also calculated. Bouted MVPA was defined as a period of ≥10 consecutive minutes spent in that behaviour (up to 2 minutes below the cut point allowance).

PA categories in women with fibromyalgia were established according to the PA recommendations for adults: not meeting PA recommendations <150 minutes/week of bouted MVPA *vs*. meeting PA recommendations ≥150 minutes/week of bouted MVPA.

Data download, reduction, cleaning, and analyses were performed using ActiGraph software (ActiLife v. 6.11.9).

Statistical analysis

Differences in socio-demographic and clinical characteristics between women with fibromyalgia and controls were tested using Student's *t*-test for continuous variables, whereas Chi-square test was employed for categorical variables. The comparisons of CVD risk factors (average of cigarettes/day, body composition, blood pressure parameters, resting heart rate, CRF and PA) between women with fibromyalgia and controls were performed with one-way analysis of covariance (ANCOVA) after adjusting for potential confounders. In model 1, we adjusted for age; in model 2, we adjusted for age, marital status, educational level, occupational status, medication for cholesterol during the last 2 weeks and monthly regular menstruation. The Cohen's d was used to calculate the standardised effect size and was interpreted as small (~0.2), medium (~0.5) or large (~0.8 or greater) (24). A clustered CVD risk was created from the mean of the age-specific z scores for cigarettes per day, adiposity, mean arterial pressure, resting heart rate and CRF in women groups. The "adiposity z score" was calculated with the means of the z scores of waist circumference and body fat percentage. The comparison of clustered CVD risk between women with fibromyalgia and controls was analysed with one-way ANCOVA using the same models described above. Subsequently, a new clustered CVD risk was created from age-specific z scores for cigarettes per day, adiposity, mean arterial pressure, resting heart rate and CRF in the fibromyalgia group. Then, one-way ANCOVA was employed to examine the differences of clustered CVD risk between PA categories in women with

Table I. Demographic and clinical characteristics of the study sample by groups.

	Women with fibromyalgia (n=436)	Control women (n=217)	*p*-value[a]
Tender points - mean (SD)			
Total tender points (0-18)	16.8 (1.9)	3.1 (2.9)	<0.001
Algometer score (18-144)	42.8 (13.3)	106.5 (21.0)	<0.001
Age (years) mean (SD)	51.4 (7.5)	48.4 (9.6)	<0.001
Height (cm) mean (SD)	158.1 (6.0)	159.9 (6.3)	<0.001
BMI (kg/m²) mean (SD)	28.4 (5.3)	26.5 (4.8)	<0.001
Marital status, n (%)			
Married	333 (76.4)	151 (69.6)	0.039
Single	34 (7.8)	31 (14.3)	
Separated	15 (3.4)	13 (6.0)	
Divorced	35 (8.0)	13 (6.0)	
Widow	19 (4.4)	9 (4.1)	
Educational level, n (%)			
No studies	40 (9.2)	12 (5.5)	0.002
Primary school	210 (48.2)	78 (35.9)	
Professional training	68 (15.6)	37 (17.1)	
Secondary school	54 (12.4)	37 (17.1)	
University medium degree	40 (9.2)	28 (12.9)	
University higher degree	24 (5.5)	25 (11.5)	
Occupational status, n (%)			
Working	113 (25.9)	90 (41.4)	<0.001
Housewife	137 (31.4)	72 (33.2)	
Retired/pensioner	68 (15.6)	11 (5.1)	
Sick leave	32 (7.3)	2 (0.9)	
Student/Unemployed	86 (19.7)	42 (19.3)	
Time since fibromyalgia diagnosis, n (%)			
Less than 5 years	176 (41.6)		
More than 5 years	247 (58.4)		
Hypertension diagnosis, n (%)	101 (24.3)	33 (23.1)	>0.05
Diabetes diagnosis, n (%)	22 (2.3)	4 (2.8)	>0.05
High total cholesterol diagnosis, n (%)	147 (35.4)	28 (19.6)	<0.001
Obesity diagnosis, n (%)	152 (34.9)	43 (19.8)	<0.001

SD: standard deviation; BMI: body mass index.
[a]*p*-values calculated using Student's *t*-test (for continuous variables) and Chi-square test (for categorical variables).

Table II. Cardiovascular risk factors of the study sample by groups.

	Fibromyalgia (n=436) mean (SE)[b]	Control (n=217) mean (SE)[b]	*p*-value[a]	*p*-value[b]	Size effect[c]
Smoking (cigarettes/day)	3.2 (0.3)	2.1 (0.4)	0.054	0.032	0.18 (0.03, 0.34)
Body composition					
Weight (kg)	70.7 (0.6)	68.5 (0.9)	0.021	0.057	0.16 (0.01, 0.32)
Waist circumference (cm)	89.3 (0.6)	86.4 (0.8)	0.001	0.005	0.24 (0.08, 0.39)
Fat percentage (%)	39.7 (0.3)	37.4 (0.5)	<0.001	<0.001	0.31 (0.15, 0.46)
Blood pressure (mmHg)					
Systolic blood pressure	128.4 (0.8)	131.7 (1.2)	0.093	0.028	-0.19 (-0.34, -0.03)
Diastolic blood pressure	77.0 (0.5)	76.8 (0.7)	0.532	0.845	0.02 (-0.14, 0.17)
Mean arterial pressure	94.1 (0.6)	95.1 (0.8)	0.630	0.320	-0.08 (-0.24, 0.07)
Resting heart rate (bpm)	71.9 (0.5)	70.9 (0.8)	0.158	0.277	0.09 (-0.06, 0.25)
Cardiorespiratory fitness					
6-min walk test (m)	491.7 (3.5)	564.9 (5.0)	<0.001	<0.001	-1.00 (-1.17, -0.84)
Physical activity					
MVPA (minutes/day)	44.8 (1.6)	64.7 (2.3)	<0.001	<0.001	-0.62 (-0.79, -0.46)
Bouted MVPA (minutes/week)	86.2 (6.2)	165.5 (9.0)	<0.001	<0.001	-0.64 (-0.80, -0.47)

Values expressed as mean (standard error) from model 2; MVPA: moderate-vigorous physical activity; [a]*p*-values calculated with one-way analysis of covariance after adjusting for age (model 1); [b]*p*-values calculated with one-way analysis of covariance after adjusting for age, marital status, educational level, occupational status, medication for cholesterol and monthly regular menstruation (model 2); [c]Size effect statistics was performed between women with fibromyalgia and controls and are expressed as Cohen's d (95% confidence interval). The sample for women with fibromyalgia and controls is the same for all variables, except for physical activity where the sample is 400 and 195, respectively.

fibromyalgia. In model 1, we adjusted for age; in model 2, we adjusted for age, marital status, educational level, occupational status, medication for cholesterol during the last 2 weeks, monthly regular menstruation and time since diagnosis fibromyalgia. All analyses were performed using the Statistical Package for Social Sciences (IBM SPSS Statistics for Windows, v. 22.0, Armonk, NY) and the level of significance was set at $p \leq 0.05$.

Results

The demographic and clinical characteristics of the study groups are shown in Table I. Women with fibromyalgia showed lower educational level ($p=0.002$), lower rates of employment ($p<0.001$) and higher rates of marriage than controls ($p=0.039$).

The CVD risk factors in women with fibromyalgia and controls are shown in Table II. Women with fibromyalgia presented higher weight [mean difference (standard error)= 2.6kg (1.1)], waist circumference [3.5cm (1.0)] and body fat percentage [2.6% (0.6)], and smoked a greater number of cigarettes/day [1.0 cigarette (0.5)] compared to controls (model 1, all $p \leq 0.05$). Women with fibromyalgia also performed worse in the 6-minute walk test [73.2 metres (6.2)] and spent lower time on MVPA per day [19.9 min/day (2.8)] and week [79.3 min/week (11.1)] than controls (model 1, all $p<0.001$). When we included all covariates (model 2), systolic blood pressure was lower [3.3 mmHg (1.5)] in women with fibromyalgia compared to controls ($p=0.028$). The effect size was overall small (Cohen's d ~ 0.25), except for the 6-minute walk test and the time of MVPA per day/week, where the effect sizes were large (Cohen's d >0.8) and medium (Cohen's d ~ 0.5), respectively. We also conducted an exploratory analysis using time since fibromyalgia diagnosis as independent variable. Women with fibromyalgia with less than 5 years since fibromyalgia diagnosis presented slightly greater waist circumference ([2.5cm (1.3)], $p=0.048$) and fat percentage ([1.5% (0.8)], $p=0.047$) and performed worse in the 6-minute walk test ([23.4 metres (8.0)], $p=0.003$) than those with more than 5 years since fibromyalgia diagnosis (data not shown).

Clustered CVD risk in women with fibromyalgia and controls is shown in Figure 1. After adjusting for age (model 1), women with fibromyalgia showed higher clustered CVD risk than controls ([0.32 (0.04)], $p<0.001$). When the rest of covariates were included (model 2), the results remained unchanged ([0.29 (0.04)], $p<0.001$). The effect size observed in the clustered CVD risk between women with fibromyalgia and controls was medium (Cohen's d ~ 0.5).

Clustered CVD risk by PA categories in women with fibromyalgia is shown in Figure 2. After adjusting for age (model 1), women with fibromyalgia who did not meet MVPA recommendations showed higher clustered CVD risk than those who met the MVPA recommendations ([0.25 (0.06)], $p<0.001$). Subsequently, when we included the rest of covariates (model 2), the results remained statistically significant ([0.24 (0.06)], $p<0.001$). The effect size observed in the clustered CVD risk between women who met and did not meet the PA guidelines was medium (Cohen's d ~ 0.5).

Clustered CVD risk by time since fibromyalgia diagnosis in women with fibromyalgia was performed as an additional exploratory analysis. Women with fibromyalgia with less than 5 years since fibromyalgia diagnosis showed a higher clustered CVD risk than those with more than 5 years since fibromyalgia diagnosis ([0.12 (0.05)], $p=0.031$).

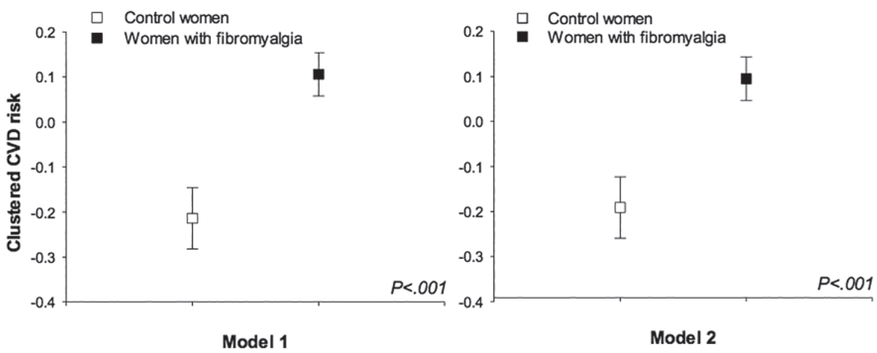

Fig. 1. Clustered cardiovascular disease (CVD) risk with cardiorespiratory fitness included as additional risk factor in women with fibromyalgia and controls. Dots represent estimated mean and 95% confidence intervals. Model 1, adjusted for age; Model 2, adjusted for age, marital status, educational level, occupational status, medication for cholesterol and monthly regular menstruation.

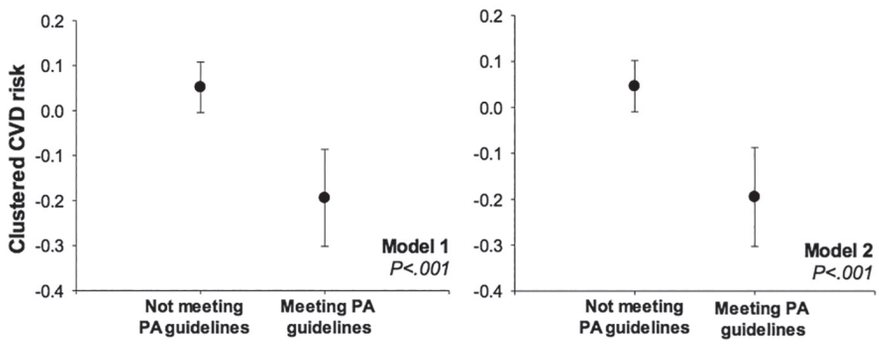

Fig. 2. Clustered cardiovascular disease (CVD) risk profile (cardiorespiratory fitness included) in women with fibromyalgia by physical activity. Dots represent estimated mean and 95% confidence intervals. Model 1, adjusted for age; Model 2, adjusted for age, educational level, occupational status, medication for cholesterol, monthly regular menstruation and time since fibromyalgia diagnosis; PA, physical activity. Meeting PA guidelines, engage in ≥150 min/week of 10-minute bouted moderate-to-vigorous PA.

Discussion

The main findings of the present study increase our understanding about the CVD risk profile in women with fibromyalgia compared to control women, and the role that PA plays on such profile. Women with fibromyalgia showed higher central and general adiposity, greater cigarettes/day consumption and lower CRF than control women. These findings suggest that women with fibromyalgia might present greater CVD risk profile than controls. Although further prospective research is needed to verify these findings, it is noteworthy that women with fibromyalgia who did not meet MVPA recommendations were characterised by an increased CVD risk profile.

The results of the present study have shown that women with fibromyalgia presented greater waist circumference and fat percentage than controls, which are markers of the relative amount of central and general adiposity. Previous studies demonstrated these findings (13, 15, 18), although Lowe *et al*. (25) did not concur with these results. Waist circumference, which is a marker of abdominal adiposity (5) and is strongly correlated with visceral adipose tissue (26), has been related to metabolic abnormalities, and higher CVD risk (5, 6, 16). Furthermore, there is substantial evidence supporting the relation between abdominal adiposity with insulin resistance, ectopic fat deposition and linked atherogenic abnormalities such as dyslipidaemia, inflammation and prothrombotic state (5, 6). In this line, body fat and obesity have also shown to play a key role on inflammation, insulin resistance and dyslipidaemias, all of them associated with an increased CVD risk (2, 5, 6). Therefore, waist circumference and body fat might be independent contributors to an increased CVD risk profile in women with fibromyalgia.

Among the many hypotheses that could partially explain this adverse cardiometabolic profile found in fibromyalgia patients are: lower resting metabolic rate due to the lower muscle mass (25), inadequate lifestyles such as smoking (7), sedentary lifestyle (27) and reduced levels of PA (4) and physical fitness (8). Moreover, some hormonal disruptions could also partially explain the higher waist circumference and body fat (18, 25).

In the present study, women with fibromyalgia smoked more cigarettes than controls. Previous studies suggested that heavy smoking could be associated with higher risk of obesity and increased risk of metabolic syndrome and type 2 diabetes (28, 29). Smoking has also been associated with CVD mortality (7, 28, 29), with enough evidence to infer a causal relationship (7). In fact, Lee *et al*. (30) emphasised that the combination of non-smoker, having a normal waist circumference and moderate-high CRF are connected with lower risk of CVD.

In agreement with our results, Aparicio *et al*. (13) demonstrated that CRF is drastically reduced in women with fibromyalgia compared to controls. Despite that physical fitness is commonly undervalued by physicians, numerous studies have highlighted the protective role of CRF against CVD mortality and that is at least as important as classical risk factors (3, 8, 31). Moreover, it has been observed that CRF is a powerful predictor of mortality independently (8, 31) or combined with other CVD risk factors (30, 31). Hence, CRF could be an important contributor to an increased CVD risk profile in this population.

Although a recent meta-analysis showed a non-significant relationship between chronic widespread pain with CVD mortality (32), our findings suggest that women with fibromyalgia may present a higher CVD risk profile than controls, as confirmed by the increased waist circumference and body fat percentage, greater cigarettes consumption and lower CRF. To the best of our knowledge, only few studies have analysed the prevalence of CVD risk factors among women with fibromyalgia and have compared them with

controls (17-19). They have observed that women with fibromyalgia present higher waist circumference, total cholesterol and low density lipoprotein-cholesterol concentrations (17, 18). Loevinger *et al*. (18) also stated that women with fibromyalgia present 6 times higher odds ratio of metabolic syndrome than healthy controls. In addition, Su *et al*. (19) showed that women with fibromyalgia presented an increased risk of coronary heart diseases compared with controls. Our results are in the same line with the above mentioned studies despite that we have not assessed biochemical parameters. To note is that we have included detailed tobacco consumption and CRF, which are major predictors of cardiovascular health (7, 8).

This study also sought to determine whether reduced levels of MVPA contribute to this CVD risk profile. As previously reported (14), women with fibromyalgia spent less time in MVPA than controls. The report of the Physical Activity Guidelines Advisory Committee (9) verified a strong inverse relation between the amount and intensity of PA with the risk of metabolic syndrome, type 2 diabetes and CVD mortality. Moreover, several studies have shown that meeting PA recommendations is associated with lower levels of CVD (4). In this line, our findings suggest that women with fibromyalgia who did not meet MVPA recommendations presented higher CVD risk than those who met MVPA recommendations.

The limitations of the present study should be acknowledged. The cross-sectional design of the study do not allow ascertaining any cause-effect relationship. Moreover, the present study was carried out only in women; future studies should replicate this analysis in men with fibromyalgia. Additionally, the clustered CVD risk profile did not include biochemical parameters as fasting glucose, triglycerides or high density lipoprotein-cholesterol concentrations. On the other hand, the number of subjects included in this study was large and the fibromyalgia sample was geographically representative from the south of Spain (10). Furthermore, this study also included important CVD risk markers such as objectively measured PA.

The results from the current study may have important clinical implications, since our data suggest that women with fibromyalgia also present some CVD risk factors that may even worsen their health status. Therefore, the awareness of this issue might guide clinicians to focus on more effective combined prevention programmes aimed at reducing symptomatology and severity of fibromyalgia, but also on promoting fat mass loss and PA and reducing inadequate lifestyle habits such as smoking. In conclusion, the findings of the present study suggest that women with fibromyalgia may present a higher CVD risk profile than control women. The higher total and central body fat and the low CRF exhibited in fibromyalgia patients could be potentially related to future cardiovascular events. However, further prospective research is needed to confirm these findings. In addition, we observed that reduced levels of MVPA could play an important role as additional predisposing factor on CVD risk in women with fibromyalgia.

Funding

This study was supported by the Spanish Ministry of Science and Innovation (I+D+I DEP2010-15639; I+D+I DEP2013-40908-R; BES-2014-067612). VAA was also supported by the Andalucía Talent Hub Programme launched by the Andalusian Knowledge Agency, co-funded by the European Union's Seventh Framework Programme, Marie Skłodowska-Curie actions (COFUND – Grant Agreement nº 291780) and the Ministry of Economy, Innovation, Science and Employment of the Junta de Andalucía, Spain. The Master's Degree Initiation Research Scholarship from the University of Granada was granted to PAM. This study is included in the thesis of PAM enrolled in the Doctoral Programme in Biomedicine of the University of Granada.

References

1. WHO – WORLD HEALTH ORGANIZATION: A global brief on hypertension: silent killer, global public health crisis. World Health Day 2013. Switzerland, 2013. Geneva. Report, 1-39.
2. ORTEGA FB, LEE DC, KATZMARZYK PT *et al*.: The intriguing metabolically healthy but obese phenotype: cardiovascular prognosis and role of fitness. *Eur Heart J* 2012; 34: 389-97.
3. BLAIR SN: Physical inactivity: the biggest public health problem of the 21st century. *Br J Sports Med* 2009; 43: 1-2.
4. LEITZMANN MF, PARK Y, BLAIR A *et al*.: Physical activity recommendations and decreased risk of mortality. *Arch Intern Med* 2007; 167: 2453-60.
5. DESPRES JP, LEMIEUX I, BERGERON J *et al*.: Abdominal obesity and the metabolic syndrome: Contribution to global cardiometabolic risk. *Arterioscler Thromb Vasc Biol* 2008; 28: 1039-49.
6. VAN GAAL LF, MERTENS IL, DE BLOCK CE: Mechanisms linking obesity with cardiovascular disease. *Nature* 2006; 444: 875-80.
7. HHS: U.S. Department of Health and Human Services. The Health Consequences of Smoking: A Report of the Surgeon General. Atlanta (GA), 2004: US Dept of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health.
8. LEE DC, ARTERO EG, SUI XM, BLAIR SN: Mortality trends in the general population: the importance of cardiorespiratory fitness. *J Psychopharmacol* 2010; 24: 27-35.
9. ODPHP: Physical Activity Guidelines Advisory Committee. 2008. Report of the Physical Activity Guidelines Advisory Committee. DHHS website <http://health.gov/paguidelines>.
10. SEGURA-JIMENEZ V, ALVAREZ-GALLARDO IC, CARBONELL-BAEZA A *et al*.: Fibromyalgia has a larger impact on physical health than on psychological health, yet both are markedly affected: The al-Andalus project. *Semin Arthritis Rheum* 2015; 44: 563-70.
11. BAZZICHI L, GIACOMELLI C, CONSENSI A *et al*.: One year in review: fibromyalgia. *Clin Exp Rheumatol* 2016; 34 (Suppl. 96): S145-S9.
12. PALAGINI L, CARMASSI C, CONVERSANO C *et al*.: Transdiagnostic factors across fibromyalgia and mental disorders: sleep disturbances may play a key role. A clinical review. *Clin Exp Rheumatol* 2016; 34 (Suppl. 96): S140-S4.
13. APARICIO VA, SEGURA-JIMENEZ V, ALVAREZ-GALLARDO IC *et al*.: Fitness testing in the fibromyalgia diagnosis: The al-Andalus project. *Med Sci Sports Exerc* 2015; 47: 451-9.
14. SEGURA-JIMENEZ V, ALVAREZ-GALLARDO IC, ESTEVEZ-LOPEZ F *et al*.: Differences in Sedentary Time and Physical Activity Between Female Patients With Fibromyalgia and Healthy Controls: The al-Andalus Project. *Arthritis Rheumatol* 2015; 67: 3047-57.
15. SEGURA-JIMENEZ V, APARICIO VA, ALVAREZ-GALLARDO IC, CARBONELL-BAEZA A, TORNERO-QUINONES I, DELGADO-FERNANDEZ M: Does body composition differ between fibromyalgia patients and controls? The al-Andalus project. *Clin Exp Rheumatol* 2015; 33 (Suppl. 88): S25-S32.
16. JACOBS EJ, NEWTON CC, WANG Y *et al*.: Waist circumference and all-cause mortality

in a large US Cohort. *Arch Intern Med* 2010; 170: 1293-301.
17. INAL S, INAL EE, OKYAY GU, OZTURK GT, ONEC K, GUZ G: Fibromyalgia and nondipper circadian blood pressure variability. *J Clin Rheumatol* 2014; 20: 422-6.
18. LOEVINGER BL, MULLER D, ALONSO C, COE CL: Metabolic syndrome in women with chronic pain. *Metabolism* 2007; 56: 87-93.
19. SU CH, CHEN JH, LAN JL *et al*.: Increased risk of coronary heart disease in patients with primary fibromyalgia and those with concomitant comorbidity – a Taiwanese population-based cohort study. *PLoS One* 2015; 10: 13.
20. FOLSTEIN MF, FOLSTEIN SE, MCHUGH PR: Mini Mental State. A practical method for grading cognitive state of patients for the clinician. *J Psychiatr Res* 1975; 12: 189-98.
21. RIKLI RE, JONES CJ: Development and validation of a functional fitness test for community-residing older adults. *J Aging Phys Act* 1999; 7: 129-61.
22. KING S, WESSEL J, BHAMBHANI Y, MAIKALA R, SHOLTER D, MAKSYMOWYCH W: Validity and reliability of the 6 minute walk in persons with fibromyalgia. *J Rheumatol* 1999; 26: 2233-7.
23. SASAKI JE, JOHN D, FREEDSON PS: Validation and comparison of ActiGraph activity monitors. *J Sci Med Sport* 2011; 14: 411-6.
24. NAKAGAWA S, CUTHILL IC: Effect size, confidence interval and statistical significance: a practical guide for biologists. *Biol Rev* 2007; 82: 591-605.
25. LOWE JC, YELLIN J, HONEYMAN-LOWE G: Female fibromyalgia patients: Lower resting metabolic rates than matched healthy controls. *Med Sci Monitor* 2006; 12: CR282-CR9.
26. FOX CS, MASSARO JM, HOFFMANN U *et al*.: Abdominal visceral and subcutaneous adipose tissue compartments - Association with metabolic risk factors in the Framingham Heart Study. *Circulation* 2007; 116: 39-48.
27. BISWAS A, OH PI, FAULKNER GE *et al*.: Sedentary time and its association with risk for disease incidence, mortality, and hospitalization in adults a systematic review and meta-analysis. *Ann Intern Med* 2015; 162: 123-32.
28. CHIOLERO A, FAEH D, PACCAUD F, CORNUZ J: Consequences of smoking for body weight, body fat distribution, and insulin resistance. *Am J Clin Nutr* 2008; 87: 801-9.
29. SLAGTER SN, VAN VLIET-OSTAPTCHOUK JV, VONK JM *et al*.: Combined effects of smoking and alcohol on metabolic syndrome: The LifeLines Cohort Study. *PLoS One* 2014; 9: e96406.
30. LEE CD, SUI XM, BLAIR SN: Combined effects of cardiorespiratory fitness, not smoking, and normal waist girth on morbidity and mortality in men. *Arch Intern Med* 2009; 169: 2096-101.
31. BLAIR SN, KAMPERT JB, KOHL HW *et al*.: Influences of cardiorespiratory fitness and other precursors on cardiovascular disease and all-cause mortality in men and women. *JAMA* 1996; 276: 205-10.
32. SMITH D, WILKIE R, UTHMAN O, JORDAN JL, MCBETH J: Chronic pain and mortality: a systematic review. *PLoS One* 2014; 9: 17.