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ORIGINAL STUDY

A 16-week multicomponent exercise training program improves menopause-related symptoms in middle-aged women. The FLAMENCO project randomized control trial

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Abstract

Objective: To investigate the influence of a supervised multicomponent exercise training program on menopause-related symptoms, particularly vasomotor symptoms (VMS), in middle-aged women.

Methods: A total of 112 middle-aged women (mean age 52 ± 4 y old, age range 45-60 y) from the FLAMENCO project (exercise [$n = 59$] and counseling [$n = 53$] groups) participated in this randomized controlled trial (per-protocol basis). The exercise group followed a multicomponent exercise program composed of 60-minute sessions 3 days per week for 16 weeks. The 15-item Cervantes Menopause and Health Subscale was used to assess the frequency of menopause-related symptoms.

Results: After adjusting for body mass index and Mediterranean diet adherence, the subscales measuring menopause-related symptoms and VMSs decreased 4.6 more in the exercise group compared to the counseling group (between-group differences [B]: 95% CI: -8.8 to -0.2; $P = 0.040$). The exercise group also showed significant improvements in the subscales of couple relationships (between-group differences [B]: -1.87: 95% CI: -3.29 to -0.45; $P = 0.010$), psychological state (between-group differences [B]: -2.3: 95% CI: -5 to -0.2; $P = 0.035$), and VMSs (between-group differences [B]: -4.5: 95% CI: -8.8 to -0.2; $p = 0.040$) in the Cervantes Menopause and Health Subscale compared with the counseling group.

Conclusions: A 16-week multicomponent physical exercise program showed a positive effect on menopause-related symptoms especially in couple relationships, psychological state, and VMS, among 45 to 60 year old women.

Key Words: Climacteric – Exercise – Hot flashes – Menopausal symptoms – Psychological health – Vasomotor symptoms.

Menopause is a natural process that begins with a decrease in the number of follicles and a reduced responsiveness of the ovary to follicle-stimulating hormone (FSH) and luteinizing hormone, and therefore, decreased estrogen and progesterone levels.[1] These changes in hormone concentrations are related to the appearance of highly frequent symptoms during this period, such as hot flashes, night sweats, and palpitations (ie, vasomotor symptoms [VMS]).[2] In addition, women might experience psychological and cognitive changes,[3] atrophic effects,[4] and sexual dysfunction,[5,6] which altogether could negatively affect their health-related quality of life.[7]

Advances in health care promote an aging population.[8] As a result, women live longer within the postmenopausal stage. This fact makes it necessary to explore new strategies to promote a healthier menopausal transition to provide a better

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health status for these years. With this in mind, physical exercise could have great applicability and influence on women's health status during this physiological stage.[9] A sedentary lifestyle is associated with more severe symptoms of menopause[10] and a greater risk of sarcopenia and osteoporosis.[11] In contrast, the benefits of exercise in middle-aged women's health have been widely described.[9,12,13] Additionally, exercise increases physical fitness,[14] which is highly associated with better mental and cardiometabolic health during perimenopause.[15] However, women often show a loss of physical fitness during menopause, especially if they are sedentary,[16] which makes exercise even more relevant at this stage.[17] To date, the available evidence seems to be insufficient to show the efficacy of specific physical exercise programs on the reduction of the symptoms associated with menopause, especially regarding VMS.[7,18,19] In fact, our group previously failed in finding associations of VMS with physical activity and physical fitness[20] by using the Blatt-Kupperman Menopausal Index.[21] Furthermore, the most appropriate type of exercise program recommended to minimize menopause-related symptoms is still unclear.

We hypothesized that a multicomponent exercise training program (ie, which includes the development of all the physical fitness components: muscle strength, cardiorespiratory fitness, flexibility, static and dynamic balance, and agility) might have positive effects on menopause-related symptoms. Therefore, the purpose of this study was to investigate the influence of a multicomponent exercise program on menopause-related symptoms, particularly VMS, in middle-aged women.

METHODS

Study population

One hundred ninety-eight women ages 45 to 60 years who met the inclusion criteria (see Supplementary Table 1, http://links.lww.com/MENO/A901, which shows the inclusion and exclusion criteria in the Fitness League Against MENopause COst [FLAMENCO] project) were initially recruited by medical staff in primary care centers. A complete summary of the cohort recruitment and procedure carried out in the FLAMENCO project (ClinicalTrials.gov Identifier: NCT02358109) has been previously published.[22] This study protocol was reviewed and approved by the Ethics Committee for Research Involving Human Subjects at the University of Granada (*no.* 861). Participants were enrolled in the study at the same time in a single recruitment period.

Randomization and blinding

A computer-generated simple randomization sequence was used to assign participants to the exercise or counseling groups after the first assessment. Members of the research team involved in the assessments and the data analysis were blinded to the group allocation. A total of 150 middle-aged women were randomized into the counseling ($n = 75$) and exercise ($n = 75$) groups. Subsequently, participants signed a written informed consent before taking part in the study.

Procedures

Sociodemographic and clinical characteristics, dietary patterns, body weight, and height were assessed in a single day in the first assessment. Menopause-related symptoms were collected through questionnaires both in the first assessment and after finishing the physical exercise program.

Exercise group

Women in the exercise group participated in a 16-week physical exercise program and trained 3 days/week (60 min/session). The exercise program consisted of a 10-minute warm-up period with walks and mobility exercises and a 40-minute main conditioning part, which was modified throughout the week. The sessions finished with a 10-minute cool-down period of stretching and relaxation exercises. The weekly program of exercises consisted of resistance strength exercises on Monday, balance-oriented activities on Wednesday, and a combination of aerobic, resistance strength, and coordination exercises on Friday. Complete details about the structure of each physical training session are shown in Supplementary Table 2, http://links.lww.com/MENO/A902 (which describes the exercise intervention carried out in the FLAMENCO project). The attendance to the training sessions was recorded. In addition, both the counseling group and the exercise group received four lectures about the health benefits of physical exercise and the Mediterranean dietary pattern.

Counseling group

Women in the counseling group did not attend the physical exercise program sessions but they were not urged to limit their daily activities. For ethical reasons and to maintain their adherence to the study, they were invited to the four lectures addressing nutritional education, ergonomic advice, exercise to perform at home (eg, stretching and strength training), strategies to increase their daily physical activity levels, the benefits of exercise for disease prevention and treatment and longevity, and the benefits of the Mediterranean diet.[22]

Measured outcomes

Sociodemographic and clinical data

Sociodemographic and clinical characteristics (ie, age, marital and working status, having regular menstruation, physical or psychological disease diagnosis, taking medication for sleep, and receiving hormone therapy) were self-reported through a questionnaire.

Menopause-related symptoms

To assess menopause-related symptoms and VMS, we employed the 15-item Cervantes Menopause and Health Subscale of the validated Cervantes Scale.[23] This scale is composed of 31 items and covers four domains (menopause and health, sexuality, couple relationships, and physical domain). The 15-item Cervantes Menopause and Health Subscale ranges from 0 to 75, where higher scores indicate more frequent problems.[23,24]

Body composition

Weight (kg) was assessed with a scale (InBody R20, Biospace, Seoul, South Korea). Height (cm) was measured with a stadiometer (Seca 222, Seca, Hamburg, Germany). The body mass index (BMI) was calculated as weight (kg)/height (m^2).

Mediterranean diet adherence

The adherence to the traditional Mediterranean dietary pattern was evaluated with the Mediterranean Diet Score developed by Panagiotakos et al.[25] It is composed of 11 items (nonrefined cereals, potatoes, fruits, vegetables, legumes, fish, olive oil, red meat and subproducts, poultry, full-fat dairy products, and alcohol) ranging from 0 to 5 based on the frequency of consumption. The total score ranges from 0 to 55, where higher scores indicate greater adherence to the Mediterranean dietary pattern and, subsequently, a better diet quality.[25]

Statistical analysis

Descriptive statistics for continuous and categorical variables were performed to show the sociodemographic and clinical characteristics (Table 1). Only women who attended at least 75% of the exercise sessions and completed both the baseline and follow-up assessments were included in the statistical analyses. Subsequently, linear regression analyses were used to explore the differences in menopause-related symptoms between the counseling and exercise groups. Menopause-related symptoms were included in the regressions as dependent variables and the group (counseling or exercise) as the independent variable. After considering relevant confounders suggested by the previous literature, Model I was unadjusted and Model II was adjusted for BMI and the adherence to the Mediterranean dietary pattern.[24,26,27] Since other variables according to the literature showed a weak relationship or no relationship with the studied outcomes (eg, marital status and hormonal therapy), these variables were only tested as additional confounders in secondary sensitive analyses (data not shown). The Benjamini-Hochberg procedure was applied to account for the random effect in multiple comparisons for all the tests included in the analysis with $q = 0.05$.[28] Single imputation was performed for those cases with missing data in specific outcomes to assess more realistically the effectiveness of the physical training program according to the CONSORT guidelines (see Supplementary Table 3, http://links.lww.com/MENO/A903, which illustrates the intention to treat basis analysis performed showing the association of the changes in menopause-related symptoms after a 16-week multicomponent exercise training program for the intervention and control groups). The statistical analyses were conducted using the Statistical Package for Social Sciences (IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp). The statistical significance was set at $P < 0.05$.

RESULTS

Of the 150 middle-aged women who were initially randomized into counseling ($n = 75$) and exercise ($n = 75$) groups, a final sample of 112 women were allocated into the counseling ($n = 53$) and exercise group ($n = 59$), since 28 women ($n = 20$ in the counseling and $n = 8$ in the exercise group) dropped out at the follow-up. In addition, eight women in the exercise group did not attend 75% of the exercise sessions and two women in the counseling group did not have data in all of the studied

TABLE 1. *Baseline, clinical, and sociodemographic characteristics*

	Counselling Group mean (SD) ($n = 53$)	Exercise Group mean (SD) ($n = 59$)
Age, y	51.9 (4.1)	52.3 (4.4)
Menopause-related symptoms		
Cervantes Menopause and Health Subscale score (0-75)[a] ($n = 51$ vs 56)	26.1 (14.3)	30.0 (12.5)
Sexuality (0-20)[a] ($n = 48$ vs 54)	10.9 (5.2)	10.8 (5.1)
Couple relationship domain (0-15)[a] ($n = 48$ vs 49)	3.8 (4.2)	4.6 (7.9)
Psychological domain (0-45)[a] ($n = 52$ vs 57)	9.7 (78.0)	12.1 (8.0)
Vasomotor symptoms domain (0-75)[a] ($n = 51$ vs 56)	26.1 (14.3)	30.0 (12.5)
Body composition		
Weight (kg)	69.7 (12.2)	69.2 (11.6)
Height (cm)	159.2 (5.7)	159.7 (6.2)
Body mass index, kg/m^2	27.5 (4.3)	27.3 (4.1)
Mediterranean diet adherence (0-55)	30.9 (5.2)	31.1 (3.9)
Marital status		
Single/separated/divorced/widow	11 (20.8)	18 (30.5)
With partner/married	42 (79.2)	41 (69.5)
Working status		
Employed	25 (47.2)	33 (55.9)
Unemployed	28 (52.8)	26 (44.1)
Regular menstruation (yes) ($n = 111$)	17 (32.7)	16 (27.1)
Physical/psychological disease diagnosis (yes)	38 (71.7)	41 (69.5)
Medication for sleep (yes)	14 (26.4)	15 (25.4)
Hormone therapy (yes) ($n = 108$)	3 (6.1)	1 (1.7)
Percentage of attendance (per-protocol basis analysis)		90.3 (6.33)
Percentage of attendance (intention-to-treat basis analysis)		81.2 (22)

[a]Higher scores reflect greater menopause-related symptoms. Values shown as mean (standard deviation) unless otherwise is indicated. SD, standard deviation.

variables. Thus, the total number of women included for the per-protocol analyses was 112 divided into counseling ($n = 53$) and exercise ($n = 59$) groups (Fig. 1).

The clinical and sociodemographic characteristics of the study sample are shown in Table 1. Most of the samples (mean age 52 ± 4 y old) had a low/medium Mediterranean diet adherence (74% in the counseling group and 72% in the intervention group) and had irregular menstruation (67% in the counseling group and 73% in the intervention group). The mean percentage of attendance to the training program was 90.3%. No differences between groups were found in menopause-related symptoms, body composition, and clinical and sociodemographic characteristics at the baseline (all, $P > 0.05$) (data not shown). Per-protocol basis analyses of menopause-related symptoms pre- and post-intervention for the counseling and exercise groups are shown in Table 2. After adjusting for BMI and the adherence to the Mediterranean diet, menopause-related symptoms and VMS subscales decreased 4.6 more in the

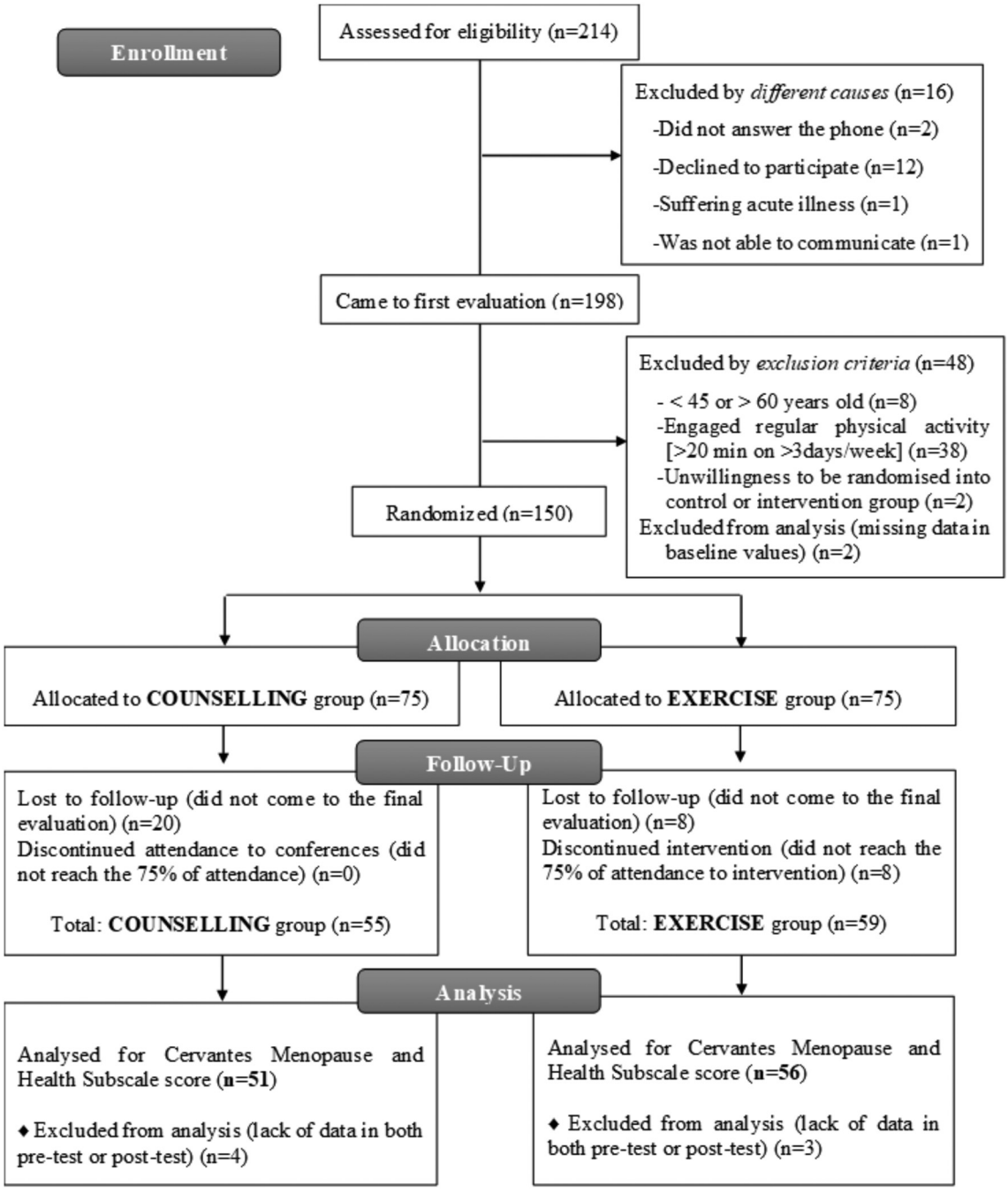

FIG. 1. Flow diagram of the study participants.

TABLE 2. *Association of the changes in menopause-related symptoms after a 16-week multicomponent exercise training program for the intervention and control groups*

			Model I		Model II	
	Mean changes within counselling group Post-Pre ($n = 53$)	Mean changes within exercise group Post-Pre ($n = 59$)	Between-group standardized difference (β) (95% CI)	*p*	Between-group standardized difference (β) (95% CI)	*p*
Cervantes Menopause and Health Subscale score (0-75)[a] ($n = 51$ vs 56)	−1.23 (11.42)	−5.78 (10.84)	−0.202 (−0.392 to −0.012)	**0.037**	−0.200 (−0.390 to −0.009)	**0.040**
Sexuality (0-20)[a] ($n = 48$ vs 54)	−1.23 (4.58)	−2.39 (4.56)	−0.127 (−0.324 to 0.070)	0.204	−0.126 (−0.320 to 0.068)	0.201
Couple relationship (0-15)[a] ($n = 48$ vs 49)	0.31 (3.67)	−1.55 (3.46)	−0.255 (−0.452 to −0.058)	**0.012**	−0.257 (−0.451 to −0.062)	**0.010**
Psychological state (0-45)[a] ($n = 52$ vs 57)	−0.77 (6.25)	−3.35 (6.31)	−0.203 (−0.391 to −0.015)	**0.034**	−0.204 (−0.393 to −0.015)	**0.035**
Vasomotor symptoms (0-75)[a] ($n = 51$ vs 56)	−1.24 (11.4)	−5.79 (10.84)	−0.202 (−0.392 to −0.012)	**0.037**	−0.200 (−0.390 to −0.009)	**0.040**

[a]Higher scores reflect greater menopause-related symptoms. Model I was unadjusted. Model II was adjusted for body mass index and adherence to the Mediterranean diet. Bold values indicate those outcomes which surpassed the multiple comparison test. Mean results show the differences between post-pre intervention results for each variable with negative values as a reduction in the postevaluation compared to pre-evaluation (standard deviation). CI, confidence interval; β, nonstandardized mean difference between groups.

exercise than the counseling group (between-group standardized differences [**β**]: -0.200 95% CI: -0.390 to -0.009; $P = 0.040$). The exercise group showed significant improvements in the subscales of couple relationships (between-group differences [**β**]: -0.257 95% CI: -0.451 to -0.062; $P = 0.010$), psychological state (between-group differences [**β**]: -0.204: 95% CI: -0.393 to -0.015; $P = 0.035$), and VMS (between-group differences [**β**]: -0.200: 95% CI: -0.390 to -0.009; $P = 0.040$) compared with the counseling group by the Cervantes Menopause and Health Subscale. Of note, after correcting for multiplicity, we confirmed that all the results remained significant. Intention-to-treat basis analyses of menopause-related symptoms pre- and post-intervention for the counseling and exercise groups are shown in Supplementary Table 3, http://links.lww.com/MENO/A903. The exercise group continued showing significant improvements in the couple relationships subscale, but the rest of the associations disappeared.

DISCUSSION

The main findings of this randomized control trial suggest that a multicomponent physical exercise intervention might improve menopause-related symptoms. Specifically, when the exercise program ended, women in the exercise group showed better scores related to self-perception of health, VMS, couple relationships, and mental health than women in the counseling (usual care) group.

Up to now, the role of lifestyle modifications in menopause-related symptoms remains inconclusive. Although previous studies reported that physical exercise could improve psychological health in menopausal women,[29,30] the evidence regarding its influence on specific symptoms is scarce or contradictory.[19,31-33]

It is estimated that 80% of perimenopausal women suffer VMS (eg, palpitations or hot flashes) which negatively affect their quality of life.[34] Of note, VMS involve other alterations, such as sleep problems, negative mood, or stress,[35] which can all together compromise the self-perception of health. Therefore, the improvements of both, psychological state and VMS found in women in the intervention group could be related. It should be noted that chronic stress produces higher levels of cortisol, whose relationship with VMS during menopause has been widely described.[36-38] Moreover, changes in female sex hormone levels during perimenopause seem to be closely related to hot flashes. Specifically, VMS was previously associated with decreased estradiol and greater FSH concentrations.[2,39] Elevated FSH levels during perimenopause[40] appear to be associated to vascular endothelial dysfunction.[41,42] In contrast, androgen levels are inversely related to VMS.[43] Since strength training promotes higher testosterone levels,[44] it is possible that this multicomponent training could provide benefits in this sense. Therefore, we hypothesize that this exercise program might have exerted a positive influence by decreasing stress levels and regulating the concentrations of some hormones related to hot flashes.[29,41]

Our results are in line with other previous studies. For example, Villaverde-Gutiérrez et al[29] carried out an exercise program based on aerobic resistance, strength resistance, flexibility, and relaxation exercises in a group of perimenopausal women for 12 months. At the end of the program, the intervention group showed improvements in quality of life and a reduction in symptoms associated with menopause.[29] However, positive effects on hot flashes were not found by Luoto et al,[45] who carried out an exclusively aerobic exercise program for 6 months. This could indicate that the training of a single physical fitness component could be insufficient to significantly improve the symptoms of menopause, or that the strength component is mandatory to reduce VMS.

Of note is the fact that the methodology and scales employed to measure VMS are highly variable in the different clinical trials,[46] which makes difficult comparisons between studies. However, until now, it was assumed that, although exercise could bring improvements in several menopause-related symptoms, it should not be recommended as a unique treatment for the management of VMS.[18,47,48]

Regarding other important domains, in our study, couple relationships improved in the exercise group compared to the counseling group. Sexuality is a state of physical, psychological, social, and emotional well-being that is related to sexual desire, whose affectation negatively influences the quality of life.[49] In addition, being in a relationship could reduce the impact of sexual problems on quality of life,[50] so the results obtained in this domain are highly positive. Although the scale used to assess the symptoms of menopause is separated into domains,[23,24] women's health must be understood as a whole paradigm. Consequently, the improvement of VMS and couple relationships could both positively influence self-perception of health and sexual response.[6] After performing the intention-to-treat basis analysis, only the couple relationship domain shows significantly higher scores in the exercise group compared to the counseling group. It is noteworthy that the mean percentage of adherence to the training program is lower than in the per-protocol basis analysis. This may indicate that not only is the type of exercise program that is carried out with middle-aged women important but also achieving a high adherence to it, in order to obtain improvements in menopause-related symptoms.

As with other physiological female processes, such as menstruation or pregnancy, menopause has been highly medicalized.[51] Although the use of synthetic hormones, known as hormonal therapy, has been shown to be effective in reducing menopause-related symptoms,[52] it carries inherent potential future health problems for women, such as increased cardiovascular disease risk.[53] Moreover, hot flashes usually reappear when hormonal therapy is discontinued.[54] In addition, it is important to highlight that the number of studies related to pharmacological treatment of females is greater than the number of studies related to healthy lifestyle habits that can improve self-management of health and quality of life during this process. The success achieved in relation to greater longevity, together with the progressive aging of the population, makes it necessary to find interventions that promote improvements of women health during the peri- and postmenopausal periods. In this sense, this study reflects that a well-designed and specific multicomponent exercise program in this population is an important tool to consider and to promote, especially in women for whom the use of pharmacology is not clearly justified.[55]

Limitations and strengths

The present study has some limitations that ought to be mentioned. First, given that it is a relatively small sample, we were unable to establish differences by menopausal state. However, the mean age did not differ between the counseling and exercise groups. Second, we did not measure serum hormone levels that might help to a better interpretation of the studied outcomes and a more reliable determination of the menopausal status. Third, all study participants were White women, so ethnicity was not considered. Regarding strengths, this exercise program is an individually tailored intervention designed by an expert multidisciplinary team in this field, and the percentage of attendance was monitored periodically, including only those women who attended at least 75% of the training sessions. Moreover, following recent evidence,[56] we incorporated the development of all the physical fitness components within the same exercise program (ie, muscle strength, cardiorespiratory fitness, flexibility, static and dynamic balance, and agility), which may provide additional benefits. Furthermore, the tool used to assess menopause-related symptoms is valid and reliable.[23]

CONCLUSIONS

This study has shown a positive effect of a 16-week multicomponent physical exercise program on menopause-related symptoms, especially in couple relationships, psychological state, and VMS. Therefore, enrolling in a well-designed physical exercise program could be an effective tool for the management of the most frequent menopause-related symptoms and, thus, promoting a healthier menopausal and postmenopausal status. However, more research focused on the vascular effects of different types of exercise programs in relation to menopause-related symptoms is needed to draw clearer conclusions, as well as the potential physiological mechanisms involved in each type of exercise and physical fitness component.

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