

Physical Activity on Cardiorespiratory Fitness and Cardiovascular Risk in Pre- and Postmenopausal Women: A Systematic Review of Randomized Controlled Trials

Running title: Menopausal state and physical activity

The authors of this manuscript are:

Maitane Ruiz-Rios, MS¹; Sara Maldonado-Martin, PhD^{2,3}

¹ Department of Physical Education and Sport. Faculty of Education and Sport-Physical Activity and Sport Sciences Section. University of the Basque Country (UPV/EHU). Vitoria-Gasteiz. Araba/Álava. Basque Country, Spain.

² Glizartea, Kirola eta Ariketa Fisikoa Ikerkuntza Taldea (GIKAFIT). Society, Sports, and Physical Exercise Research Group. Department of Physical Education and Sport. Faculty of Education and Sport- Physical Activity and Sport Sciences Section. University of the Basque Country (UPV/EHU). Vitoria-Gasteiz. Araba/Álava. Basque Country, Spain

³ Bioaraba Health Research Institute. Physical Activity, Exercise, and Health group. Vitoria-Gasteiz. Araba/Álava. Basque Country, Spain

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Corresponding author: Sara Maldonado-Martin. Department of Physical Education and Sport. Faculty of Education and Sport-Physical Activity and Sport Sciences Section. University of the Basque Country (UPV/EHU). Vitoria-Gasteiz. Araba/Álava. Basque Country, Spain. Portal de Lasarte, 71. 01007 Vitoria-Gasteiz (Araba/Álava). Basque Country, Spain. Phone: +34 945013534

Fax: +34 945013501. E-mail: sara.maldonado@ehu.eus

ABSTRACT:

Importance: The apparent cardioprotective effects of endogenous estrogens to prevent cardiovascular disease in pre-menopausal women are reduced with the loss of hormonal effects. Cardiorespiratory fitness and cardiovascular risk factors are closely related to physical activity levels.

Objective: This study conducted a critical assessment of studies for health prevention that analyze the effects of physical activity programs on cardiorespiratory fitness and cardiovascular risk factors in women, comparing pre-and post-menopausal states, through a systematic review of randomized controlled trials.

Evidence Review: A computerized literature search was performed to include articles up until December 2021 in the following online databases: PubMed, Cochrane, Scopus, SportDiscus, and Web of Science. Regarding physical activity intervention, women of all ages were engaged. The PEDro scale and Oxford's Evidence Levels were used for the assessment of the risk of bias in the included articles.

Findings: Fourteen scientific articles met the inclusion criteria. Great variability was found in physical activity variables. All the studies found an improvement in at least one variable. The risk of bias was high, with all the articles obtaining a low methodological quality, except two with high methodological quality. Only one article considered the differences in the menopausal state observing the effects of physical activity intervention, and highlighting the importance of physical activity in both states

Conclusions and Relevance: To strengthen the evidence for the benefits of physical activity programs in women, and to observe the effects depending on their menopausal state, there is an ongoing need for more rigorous randomized controlled trials of appropriate length and dose, with individualized exercise intensity.

Key Words: Exercise; physical activity; women; cardiorespiratory fitness; cardiovascular risk; menopausal state

Key Points

Question/Objective: Can physical activity have different impacts on cardiorespiratory fitness and cardiovascular risk factors depending on the menopausal state?

Findings: The fourteen scientific articles included showed great variability in physical activity intervention, with a high risk of bias. Exercising for at least three months was beneficial in improving cardiorespiratory fitness and reducing cardiovascular risk factors in pre- and post-menopausal women.

Meaning: Based on the results of the systematic review, physical activity improves cardiorespiratory fitness and cardiovascular risk factors in women. However, studies with differentiation in the menopausal state are needed to apply the results to clinical practice.

INTRODUCTION

Cardiovascular disease (CVD) is a major cause of morbidity and mortality for women (35% of total deaths), and it is associated with menopause among other well-established risk factors (*e.g.*, hypertension, dyslipidemia, diabetes, obesity, poor diet, sedentary lifestyle, inactivity, and smoking).¹ It has been hypothesized that the apparent cardioprotective effects of endogenous estrogens to prevent CVD in pre-menopausal women are reduced with the loss of hormonal effects after menopause.^{2,3} However, menopausal hormone replacement therapy is not indicated for primary or secondary prevention of CVD.¹

The fact that higher cardiorespiratory fitness (CRF) and physical activity (PA) patterns are inversely associated with CVD mortality is well documented.⁴ Thus, CRF is promoted as a clinical vital sign, and therefore the need for its assessment.⁴ This assertion highlights the potential impact on the survival of PA intervention,⁵ meeting the international guidelines on PA (*i.e.*, 150-300 min/week of moderate-intensity, or 75-150 min/week of vigorous-intensity, or an equivalent combination of both intensities, plus muscle-strengthening activities).⁶ It has recently been stated that regular exercise, especially at high intensity, leads to higher CRF, which is associated with a better lipoprotein particle profile in perimenopausal and late postmenopausal women.⁷ However, the effect of menopause is still understudied, under-recognized, underdiagnosed, and undertreated globally.¹ Therefore, knowing the relevance of lowering cardiovascular risk factors (CVRF) and increasing CRF to prevent the onset of CVD and the role of PA in this sense,⁸⁻¹² a manuscript is needed that analyzes the results found in studies on this issue specifically in women. In addition, it seems necessary to distinguish the menopausal state when analyzing the effects of PA due to hormonal differences.¹³ Therefore, this systematic review aimed to analyze the effects of PA programs on CRF and CVRF in women by comparing pre-and post-menopausal states.

METHODS

Literature search and data sources

The current study followed the recommendations proposed by the Preferred Reporting Items for Systematic Review and Meta-analyses (PRISMA) guidelines.¹⁴ The

review was registered in PROSPERO, the international prospective register of systematic reviews (CRD42021282525). A comprehensive search of the following online databases was systematically performed up to December 28, 2021: PubMed MEDLINE, Cochrane, Scopus (Elsevier), SPORTDiscus, and Web of Science. The search strategy comprised the following Medical Subject Headings or keywords: “women” AND “menopausal state” AND “cardiorespiratory fitness” OR “cardiovascular risk” AND (exercise OR physical activity) AND (“randomized controlled trials” OR “clinical trials” OR “experimental trials”) NOT (animal OR rat).

Inclusion and exclusion criteria

Randomized controlled trials published in English and those with the following PICOS (Participant, Intervention, Comparison, Outcome, Study design) question were considered. In this approach: P: women up to 18 years old; I: PA intervention; C: pre- vs. post-menopausal state and/or control group comparator; O: at least one proxy of CRF and/or CVRF; and S: randomized controlled trials. The exclusion criteria were as follows: women with significant medical conditions including but not limited to, chronic or recurrent neurological or psychiatric conditions, immunodeficiency diseases, bleeding disorders, chronic thrombotic disorder, malignancies in the past 5 years; men or mixed sample in the study; women in primary prevention; animals; there was no PA intervention.

Review selection

Data extraction was performed by two independent reviewers (S.M.–M., and M.R.–R.) according to titles and abstracts, identified by the search strategy. The reviewers evaluated the complete articles and selected studies according to the eligibility criteria. In the event of discrepancies, a meeting was held to reach a consensus between the reviewers. The following data were extracted from the selected studies using Rayyan Intelligent Systematic Review Software: identification of the publication details of author, sample size and principal characteristics of the participants (N), exercise or PA intervention protocol, and meaningful results.

Quality Appraisal

To quantify the methodological quality of the included studies, the Physiotherapy Evidence Database (PEDro) scale and Oxford's Evidence levels were used.¹⁵ The PEDro scale rates RCT on a scale from 0 (low quality) to 11 (high quality) related to scientific rigor. Given that the assessors are rarely blinded, and that it is impossible to blind the participants and investigators in supervised PA interventions the items related to blinding (5–7) were removed from the scale. For this reason, the maximum result on the modified PEDro 8-point scale was 7 (highest score), as the first item is not included in the total score. The qualitative ratings were adjusted to those used in previous exercise-related systematic reviews as follows: 6–7 = “excellent”; 5 = “good”; 4 = “moderate”; and, 0–3 = “poor”. Oxford's Evidence levels range from 1 to 5, with 1a being systematic reviews of high-quality RCT, 1b individual RCT with a narrow confidence interval, 2a systematic review of cohort studies, 2b individual cohort study, 3a systematic review of a case-control study, 3b individual case-control study, 4 case-series, and 5 being expert opinions.¹⁵ Two researchers (S.M.-M. and M.R.-R.) rated the methodological quality of each study independently. When there was a discrepancy, this was resolved by discussion until consensus was reached. The rates were not blinded to the study authors' place of publications and results.

RESULTS

Figure 1 shows the outline of our systematic review in which the search of all databases yielded a total of 3875 articles: 522 from PubMed, 2780 in Cochrane, 0 in Scopus, 97 in SPORTDiscus, and 476 in Web of Science. After removing duplicates and screening the titles and abstracts, 3847 articles were removed so that 28 articles were assessed for eligibility. Of these, 17 were eliminated because of wrong population, study design, or publication type. Three additional articles were identified through references to previously identified articles. Consequently, 14 articles were finally selected in the systematic review (Table 1). The 14 included articles were published between 1999 and 2021 (mean 2010) and all of them showed benefits in at least CRF or CVRF after PA intervention.^{8-13,16-23}

Table 1 shows the main features of the scientific articles of RCT included in this systematic review. First, we would like to highlight that no great variability (generally all participants were inactive or sedentary adult women with overweight/obesity, and not

on hormone therapy) was seen in the populations because of the reduced sample size.^{8-13,16-23} Concerning the type of PA assessed, it was generally observed that nearly all the scientific articles included traditional training in their interventions such as aerobic training,¹⁶ resistance exercises,⁸ High-Intensity Interval Training (HIIT),²² treadmill walking,^{9,18} Zumba fitness,²³ Tai Chi,²¹ or concurrent training (Table 1).^{17,19}

Regarding the frequency and time spent doing PA, there was great variability in the scientific articles included (Table 1). First, the frequency varied from two to three days per week to most days of the week, with ranges always provided, since the RCT included in these scientific articles did not always use the same duration. Secondly, the period used to assess a change in CRF or CVRF ranged from 8 to 76 weeks, that is, one year and two months. Finally, after PA intervention, CRF^{11,12,21-23} and CVRF^{8-13,16-23} (*i.e.* all of those related to lipid and glycemic metabolism, body composition, blood pressure, inflammatory index, and autonomic responses) improved significantly in most of the studies, with positive changes also found in behavioral and psychosocial variables leading to emotional well-being.^{18,20,21,23} It is important to note that in all the analyzed articles,^{8-13,16-23} except one,¹³ women of different ages were considered, from the youngest (≈ 18 years old) to the oldest age (≈ 77 years old), but they did not carry out an analysis of the effects of PA according to the menopausal status of the women, to assess whether there were differences between the two periods (pre- vs post-menopause). The only article that analyzes pre-and post-menopausal women showed significant decreases in total and low-density lipoprotein cholesterol concentrations in both groups, while only the post-menopausal women decreased significantly in triglycerides after PA intervention (Table 1).¹³

Table 2 summarizes the PEDro scale and Oxford's Evidence levels for scientific articles included in this systematic review. The overall quality of included articles was critically low. It is noteworthy that all the included articles positively defined the PICOS question correctly, and all the publications, except two,^{8,23} maintained the groups at baseline. By contrast, included articles assessed by the PEDro scale showed bias regarding no concealed allocation, and at least one measurement did not obtain more than 85%. For the menopausal state, only one¹³ out of 14 publications made a comparison between pre-and post-menopausal women. However, none of the 13

manuscripts reported adequate information about the effect of PA intervention in CRF or CVR in pre and postmenopausal women.

DISCUSSION

Overview of the results from this systematic review indicates that regardless of the frequency, intensity, time, and type of PA performed, there are improvements in CRF and CVRF in both pre- and post-menopausal women. However, there was low-to-moderate heterogeneity of effects for all outcomes among randomized controlled trials.

Pre- and post-menopausal women may respond differently to the effects of PA due to differences in endogenous hormonal state. However, to our knowledge, the evidence comparing CRF and CVRF changes between both menopausal states has not previously been systematically reviewed.

Findings from the 14 publications included in our systematic review provide evidence that PA intervention improved at least CRF or CVRF by increasing maximum oxygen uptake (*i.e.*, the gold standard variable to analyze the CRF) or decreasing inflammatory factors in women. In addition, not only did PA ~~lead~~ to large increases in aerobic capacity, but it also improved mood.

There was great variability in their characteristics (different types of PA, intensities, or frequencies), with a low methodological quality except for two studies.^{10,20} Thus, one article showed improvements in both CRF and CVRF after PA intervention, with also greater emotional well-being (n=20),²⁰ and the other study only demonstrated improvements in CVRF, but the sample size was higher than the previous one (n=93).¹⁰ Concerning the included articles with low methodological quality, only five out of 12 showed improvements in both CRF and CVRF after PA intervention, having a similar sample size (n≈43).^{16,17,19,21,23} Further, it is important to note that the small sample size in the chosen RCT articles increased the risk of bias and the ability to assess confounding factors, such as the menopausal state.

~~Results from this systematic review~~ Although the randomized controlled trials included in the present systematic review showed a low-to-medium quality, they still demonstrated a positive effect. Thus, the current ~~extend~~ results are comparable ~~from~~ with a previous study, which showed improvements in blood pressure, triglycerides,

high-density lipoprotein cholesterol, and glucose only in post-menopausal women, whereas total cholesterol and low-density lipoprotein cholesterol were decreased in pre-and post-menopausal women after a weight loss intervention.²⁴ Overall, anthropometric and metabolic risk factors were improved in both groups regardless of their menopause state. However, post-menopausal women had a higher reduction in metabolic risk factors than pre-menopausal women, which may ~~possibly~~ be linked to their baseline state.²⁴ In this sense, in highly fit women, the menopausal status may not have a detrimental effect on the lipoprotein profile, suggesting that a high CRF may attenuate the increase in lipoprotein-related CVD~~E~~ risk associated with menopause.⁷ Further, it has been demonstrated that those women with higher baseline levels of systolic blood pressure or triglycerides levels, achieved greater reductions in their metabolic syndrome-related parameters compared to those with lower baseline levels.^{9,18} Women tend to gain body mass and increase their waist circumference over time, gaining approximately 0.7 kg more per year, regardless of their initial age, race/ethnicity, or body size.²⁵ The results of the present systematic review have shown that endurance, strength, or even a HIIT program can reduce waist circumference or waist-to-hip ratio in women.^{17,19,22,23} However, PA may only contribute to the prevention of increased amounts of fat and not to fat redistribution.²⁵ In this respect, it is important to note that women who increased their PA levels were less likely to gain fat mass, regardless of their initial level of PA.²⁵ Therefore, PA is especially important in post-menopausal women due to the decrease in energy expenditure with age, which leads to visceral fat mass gain,^{26,27} with the added risk of obesity if lifestyle changes are not made at the onset of menopause.^{28,29} In fact, associations have been found between changes in plasminogen activator antigen, C-reactive protein, leptin, and adiponectin with changes in abdominal fat.³⁰ Thus, two of the included articles showed that a decrease in body mass index or an increase in PA levels may be beneficial for C-reactive protein and proinflammatory cytokines.^{10,21} Similarly, reductions in estrogen are related to a decrease in muscle and skeletal mass, as well as resting metabolic rate, which contributes to lower total daily energy expenditure.²⁸ It has been shown that 10,000 steps per day are needed to prevent type 2 diabetes mellitus and other diseases, as well as long-term weight maintenance.²⁹ Overall, it seems important to be aware of the effects of strength/resistance training for instance, because it may have an impact on

body composition, but not on body mass change.¹¹ ~~Further~~In addition, it has also been shown that resistance exercise may increase average glucose concentrations, while aerobic exercise, on the contrary, may lower them in pre-and post-menopausal women.¹³ However, a combination of both endurance and resistance exercise (*i.e.*, concurrent training) is needed to reduce visceral fat and maintain or increase muscle mass, as well as to improve the atherogenic index of plasma, C-reactive protein, and low-density lipoprotein cholesterol concentrations.^{17,19} Some of the present results have shown improvements in aerobic capacity after PA intervention, which can sometimes be associated with weight loss.¹¹ Women experienced increases in maximum oxygen consumption,^{16,20,23} peak oxygen consumption,^{17,19} flexibility,²³ strength,^{11,23} and aerobic endurance^{11,19,22,23} after PA programs. Other studies have shown that it is possible to reduce fatigue, which may be helpful to work at higher intensities.^{18,21} In fact, it has been demonstrated that the more intensive the program is, the greater the increases in endurance and strength that are achieved.¹¹ Thus, vigorous aerobic exercise resulted in significantly greater lean tissue preservation than normal lifestyle activity did.¹⁶ On the other hand, only practicing 30 minutes of moderate lifestyle activity in short bouts per day most days of the week, has been shown to improve both CRF and CVRF in women with obesity, so even small lifestyle changes may be relevant in terms of decreasing metabolic risk and being able to tolerate effort better in PA.¹⁶

Consistent with some of the included studies,^{18,20,21,23} increases in PA levels may be beneficial for stress and depressive symptoms.³¹ In this way, depressive symptoms have been associated with higher body mass index, fibrinogen, plasminogen activator inhibitor type 1, and tissue plasminogen activity, which may contribute to the development of coronary heart diseases, such as coagulation and fibrinolytic processes. On the other hand, PA increases mindfulness, self-compassion, spirituality,²¹ as well as intrinsic motivation, enjoyment, and commitment.²³ Further, Zumba fitness classes may improve the emotional well-being of physically inactive women with overweight/obesity.²⁰ All these psychological changes may help in women's adherence to PA, and it may also be beneficial to help them in long-term body mass maintenance.²⁹ Finally, it is necessary to point out that PA, particularly HIIT programs, may also have an impact on the daily dosage of diabetes medication by reducing it.²² The only study

comparing both menopausal states concluded that the type of exercise is more important for post-menopausal than pre-menopausal women, with aerobic exercise having a greater effect on the CVRF.¹³ Taking into account the aforementioned results, it seems to be a paucity of studies analyzing the effect of exercise differentiating the menopausal state of women, and compare whether there are differences between the two states (pre- vs. post-menopausal).

Strengths and Limitations

The current review has two main strengths: 1) the developed research question since it is important to know which clinical options, based on PA, decrease CVRF or improve CRF, to advise participants who have high-to-normal values, 2) the study design based on randomized controlled trials with a high level of evidence, providing that it has been properly conducted by applying the PEDro scale and Oxford's Evidence levels.¹⁵

The main limitation of this systematic review is the lack of publications regarding the effects of a PA intervention in pre-and post-menopausal women. It is also possible that other articles met our eligibility criteria but were not in the electronic databases mentioned above. In addition, most of the included articles had low methodological quality, which makes the transfer of the results to clinical practice difficult.

Clinical Practice Guidelines

Concerning clinical practice and considering the results together with the quality of the publications, it was shown that for women with at least one CVRF or with low CRF, there is strong scientific evidence to recommend many types of activities such as Zumba, concurrent training, endurance or resistance training, Tai Chi, or HIIT.^{8-13,16-23} The aforementioned PA programs can be practiced by participants of all ages and improve, consequently, at least one variable over a period between 8 weeks to 1 year. All activities can be performed outdoors or indoors, and in groups, to increase adherence. Finally, the review should be strengthened, improving the peer-review process, which is a key point for the scientific validity of a work. Additionally, the process should be critical of manuscripts that have already been published, applying tools like the PEDro scale or Oxford's Evidence levels.¹⁵

CONCLUSIONS

All the studies analyzed underline the importance and beneficial effects of PA regardless the menopausal state of women. However, there is great variability concerning the FITT principle (frequency, intensity, type, and time-volume) with only two studies showing good quality. To strengthen the evidence for the benefits of PA programs in women, and to observe the effects depending on their menopausal state, there is an ongoing need for more rigorous randomized controlled trials of appropriate length and dose, with individualized exercise intensity.

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