Universidad del País Vasco
Euskal Herriko Unibertsitatea
HEZKUNTZA ETA KIROL FAKULTATEA
FACULTAD DE EDUCACIÓN Y DEPORTE

Master Degree in Sports Science

MASTER'S FINAL PROJECT

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

Maitane Ruiz-Ríos

Vitoria-Gasteiz, May 2021

Title of Master's Final Project

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

*** The guidelines (http://edmgr.ovid.com/meno/accounts/ifauth.htm) of the Menopause Journal have been followed in the writing of this paper.**

Master's final project to obtain the certification of **Sports Science Master Degree.**

Presented by Maitane Ruiz-Ríos

Supervisor Sara Maldonado-Martin Ph.D

In Vitoria-Gasteiz, May 20th, 2021

Signed by: D./ Dª Maitane Ruiz-Ríos

Vº.Bº. of the supervisor:

Signed by: Sara Maldonado-Martin Ph.D

University Master Degree of Sports Science

MASTER'S FINAL PROJECT

ACADEMIC YEAR 2020-21

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

ABSTRACT:

Importance: The apparent cardioprotective effects of endogenous estrogens to prevent cardiovascular disease in premenopausal women are reduced with the loss of hormonal effects. Cardiorespiratory fitness (CRF) and cardiovascular risk factors (CVRF) are closely related to physical activity (PA) levels.

Objective: This study conducted a critical assessment of studies that analyze the effects of PA programs in CRF and CVRF in women comparing pre and postmenopausal status, through a systematic review of randomized controlled trials.

Evidence Review: Publications from January 1999 to July 2020 assessing the effects of PA intervention in CRF or CVRF. Women of all ages were engaged in most of the studies, regarding PA intervention.

Findings: Fourteen scientific articles were included. Great variability was found in PA. 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, which obtained high methodological quality.

Conclusions and Relevance: Only one article considered the differences in the menopausal state to observe the effects of PA intervention highlighting the importance of PA in both states. Most of the articles included in this systematic review had a high risk of bias so that new systematic reviews with a low risk of bias are needed. Studies with differentiation in the menopausal state are needed to apply the results to clinical practice.

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

Key Points
Scientific articles have shown that PA can improve both CRF and CVRF in pre and postmenopausal women. However, there is a lack of studies in women, and those distinguishing the menopausal state when analyzing the effects of PA.
Fourteen scientific articles were included, showing a great variability in PA intervention, with a high risk of bias.
Studies with differentiation in the menopausal state are needed to apply the results to clinical practice.

.

1. Introduction

Cardiovascular disease (CVD) is a major cause of morbidity and the leading cause of death worldwide due to different cardiovascular risk factors (CVRF).[1] Traditionally, CVD has been considered to have a higher prevalence in men, although it is currently prevalent in women.[2] The apparent cardioprotective effects of endogenous estrogens to prevent CVD in premenopausal women are reduced with the loss of hormonal effects.[3] Additionally, differences between sexes can be observed in several CVRF, such as high blood pressure, total cholesterol, and sedentary lifestyle. Most of these are modifiable when identified early and addressed.[2]

Higher cardiorespiratory fitness (CRF) (*i.e.*, the maximum amount of oxygen that can be taking in, transport to, and utilized by the working tissue during exercise) and physical activity (PA) patterns are inversely associated with CVD mortality.[4] This finding highlights the potential survival impact of exercise/PA intervention.[5] Thus, it has been observed how PA intervention can largely reduce CVRF in postmenopausal women, especially triglycerides and cholesterol concentrations.[6] Furthermore, the prevalence of developing hypertension in premenopausal women has increased by 19%, and by 75% in postmenopausal due to an increase in visceral fat and decreased PA.[7]

Taking into account the relevance of decreasing CVRF and improving CRF to prevent the onset of CVD and the role of PA in this aspect,[8-12] along with the lack of studies in women, a manuscript is needed that analyzes the results found in scientific articles on this subject. In addition, it seems necessary to distinguish women regarding menopausal state when analyzing the effects of PA.[6] It is also of interest to evaluate if these manuscripts have been performed correctly in terms of methodology since they could present a risk of bias and influence the results obtained.[13,14]

2. Objectives

The primary aim of this study was to analyze the effects of PA programs on CRF and CVRF in women comparing pre and postmenopausal status, through a systematic review of randomized controlled trials (RCT).

3. Methods

The current systematic review has been completed and reported following the recommendations proposed by the Preferred Reporting Items for Systematic Review and Meta-analyses: The PRISMA Statement including the 27 items in the checklist.[15]

3.1. Identification and Selection of Studies

The scientific articles selected were those that had performed a RCT and that assessed the following PICOT (Participant, Intervention, Comparison, Outcome, Time) question to have as much accuracy as possible. In this way, it is a precise and understandable systematic review in which all the variables mentioned before will be considered. In this approach: P: women up to 18 years old; I: the study included a PA intervention; C: pre *vs.* postmenopausal state; O: at least one proxy of CRF and/or CVRF; and T: RCT.[14] On the one hand, research on pre and postmenopausal women would be useful, through which the investigators will be able to visualize the predominant factors whereas, on the other hand, it will be beneficial to set up the objectives of the study.

3.2. Eligibility Criteria

Randomized clinical trials were included in this systematic review. Studies were assessed by two reviewers (S.M.-M. and M.R.-R.) concerning the following inclusion criteria: (1) women; (2) menopausal state; (3) CRF; (4) CVRF; (5) exercise or PA; (6) RCT, clinical trials or experimental trials, and non-experimental trials; (7) studies published in English; (8) scientific articles but not books, magazines, online websites, guidelines or recommendations, reports, dissertations or thesis. Texts were excluded if they did not fit the eligibility PICOT questions and contained the following exclusion criteria:[16] (1) women with significant medical condition 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; (2) included men or mixed sample in the study; (3) included only women in primary prevention; (4) included animals or rats; (5) there was not a comparison between pre and postmenopausal women; (6) there was no PA intervention.

3.3. Data Sources and Search Strategy

A comprehensive search of the following online databases was systematically performed up to March 26, 2021: Medical Literature Analysis and Retrieval System online via

PubMed, Cochrane Central Register of Controlled Trials (CENTRAL), Scopus (Elsevier), SPORTDiscus, and Web of Science (WOS) electronic databases (limited by date). The search strategy comprised the following Medical Subject Headings or keywords, associated with a sensitive list of search terms for RCT, developed by:[17] (1) exercise or physical activity, (2) women, (3) cardiorespiratory fitness, (4) cardiovascular risk, and (5) menopausal state. For the combination of the keywords, it was used the Boolean term known as AND, except cardiorespiratory fitness, cardiovascular risk, exercise, physical activity, RCT, clinical trials, experimental trials, animal, and rat, which were used with OR, it was also used the term NOT to exclude animals or rats from the search. Duplicates were removed after all databases were searched. The descriptors used in English were: 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).

3.4. Data Screening and Extraction

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 by 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 mean results.[18]

3.5. Outcome Parameters

The main outcome parameters for this analysis were measures of CRF and those related to CVRF.

3.6. Quality Appraisal

To quantify the methodological quality of the included studies, it was used the Physiotherapy Evidence Database (PEDro) scale[14] and Oxford's Evidence levels.[13] PEDro rates RCT on a scale from 0 (low quality) to 11 (high quality) related to scientific rigor.[14] This scale consists of 11 criteria: rates the interval validity and the presence of statistically replicable information; the first is not included in the total score. Each

criterion is rated 'yes' or 'no'. 'Yes' only applicable when a criterion is satisfied as well as the maximum score that can be given is 10 if all criteria are satisfied. The cut-off score for rate a study as high quality is >6/10 and underscores considered as low methodological quality.[13] Item 1 is rated as Yes/No, while Items 2-11 are rated using 0 (absent) or 1 (present). Given that the assessors are rarely blinded, and that is impossible to blind the participants and investigators in supervised PA interventions the items related to blinding (5–7) were removed from the scale.[19] 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 that used in previous exercise-related systematic reviews[19] as follows: 6–7="excellent"; 5="good"; 4="moderate"; and, 0–3="poor". The Oxford's Evidence levels range from 1a to 5, with 1a being systematic reviews of high-quality RCT and 5 being expert opinions. 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.

3.7. Statistical Analysis

As this is a systematic review, when RCT were methodologically heterogeneous, there is no available method to directly assess the relative effect of one intervention compared to another one.

4. Results

Figure 1 shows the outline of our systematic review in which the search of all databases yielded a total of articles: 476 from PubMed, 2627 in CENTRAL, 0 in Scopus, 91 in SPORTDiscus, and 441 in WOS. After removing duplicates and screening the titles and abstracts, they were removed 3374 articles so that 121 articles were assessed for eligibility. Reference's list of selected manuscripts was also examined for any other potentially eligible manuscripts. Following this examination, three potential manuscripts were added. A total of 11 articles were included in this systematic review, having removed 3624 articles and having included three additional articles checked in the reference list of the included articles (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.[6,8-12,20-27]

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 was seen in the populations because of the reduced sample size.[6,8-12,20-27] With regard to the type of PA assessed, it was generally observed that nearly all the scientific articles included traditional training in their interventions. For example, aerobic training,[27] resistance exercises,[12] High-Intensity Interval Training (HIIT),[21] treadmill walking, [11,25] Zumba fitness, [20,23] or Tai Chi,[22] and these are detailed in Table 1. However, other scientific articles focused on concurrent training.[24,26]

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 length of each session had not a fairly wide range, lasting from 40 to 60 minutes, depending on the type of PA. Additionally, 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, CRF[8,9,20-27] and CVRF[6,8-12,20-27] improved significantly in most of the studies, with positives changes also found in behavioral and psychosocial variables leading to emotional well-being.[20,22,23,25] It is important to note that all the analyzed articles,[6,8-12,20-27] except one,[6] took into account different aged women, 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 before and after menopause to assess whether differences were depending on the state of menopause. The only article who analyze pre and postmenopausal women showed significant decreases in total and low-density lipoprotein cholesterol concentrations in both groups, while only the postmenopausal women decreased significantly in triglycerides after PA intervention.[6]

The pooled effects of PA in CRF and CVRF in pre and postmenopausal women are summarized in Table 1.

Fig. 1. Flowchart of the systematic review following the PRISMA statement.

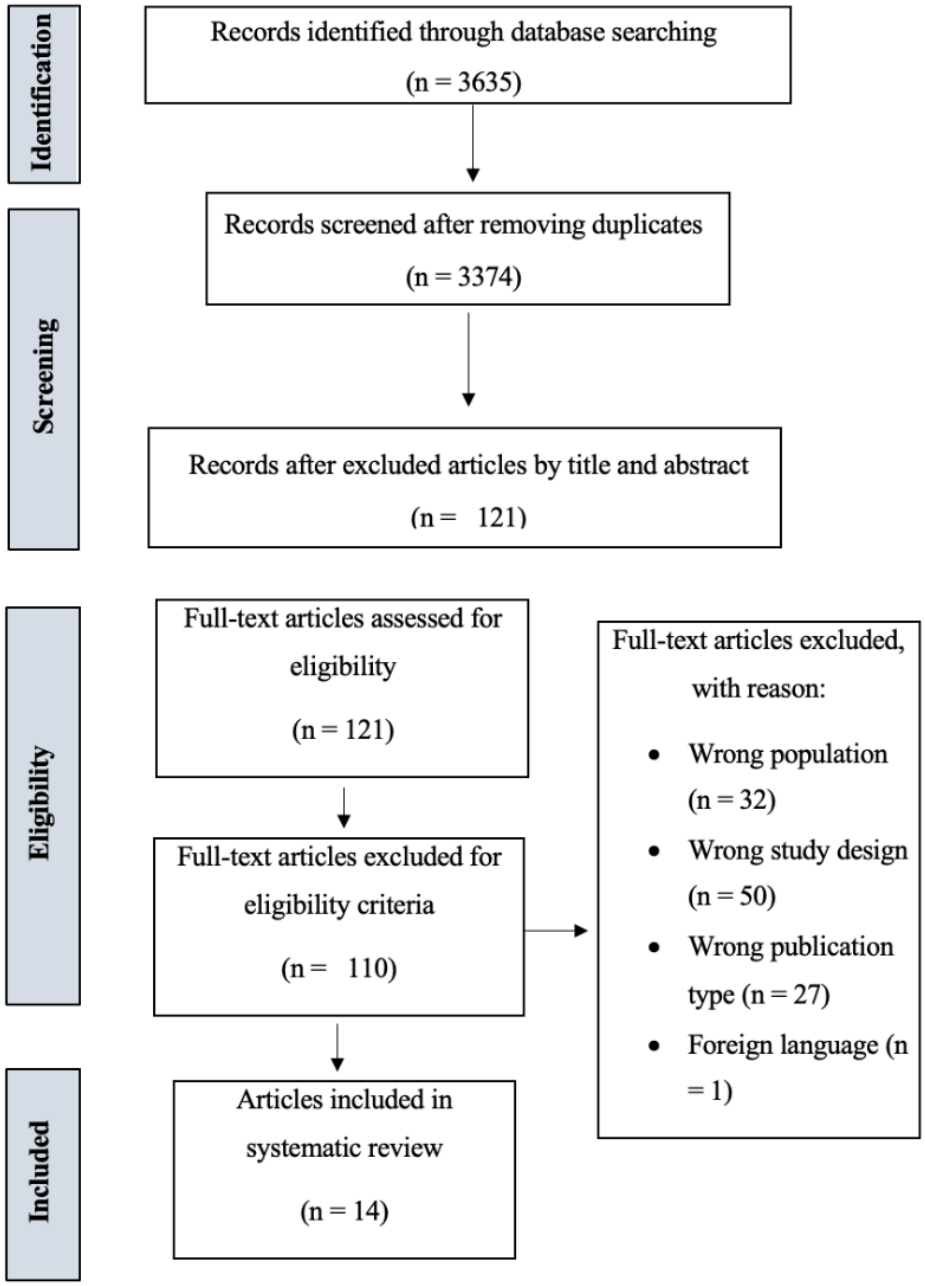

Table 1. Main characteristics of the included scientific articles that analyzed CRF and CVRF after PA intervention.

ELECTRONIC DATABASE	REFERENCE	PRINCIPAL CHARACTERISTICS	INTERVENTION	MAIN RESULTS
CENTRAL				
	Andersen et al. 1999[27]	- Obesity, 21-60 yr (n=33).	- 16-week study + 1-year follow-up. - 1 session → 60 min - Diet + Structured aerobic exercise → 3 step aerobics sessions. - Diet + Moderate lifestyle activity → Increased moderate-intensity PA to 30 min/d in short bouts most days of the week.	- Both groups → TC↓, TG↓, LDL-C↓, HDL-C↓ → After 16-weeks. - TC, HDL-C ratio → = at 16-week, but ↓ in lifestyle group at 68-weeks. - Resting SBP↓ during 16-weeks, remained lower than baseline in lifestyle group at week 68. - $VO_{2max\uparrow}$ during the intervention. - Vigorous aerobic exercise better sparing of lean tissue than did lifestyle activity.
	Ibáñez et al. 2010[12]	- Sedentary, obesity, non-smoking 40-60 yr (n=34).	- 16-week RT intervention. - Dynamic resistance exercises → 2 d/week; 45-60 min/session. - First 8 weeks → Loads of 50-70% 1RM. - Last 8 weeks → Loads of 70-80% 1RM.	- WL → Insulin sensitivity↑, baseline insulin levels↓, with no changes in lipid profile, thigh muscle mass↓ - WL+RT → Insulin sensitivity↑, baseline insulin levels↓, TC↓, LDL-C↓, serum adiponectin levels↓, = thigh muscle mass. - Both groups → Body mass↓, abdominal SAT↓, thigh subcutaneous fat↓, visceral fat mass↓ → After 16-weeks.
	Lee et al. 2006[11]	- Overweight/obesity, sedentary, hypertriglyceridemia, 35-50 yr (n=19).	- 12-week treadmill walking program. - Initially → 20 min walking at 40-50% HR reserve (3 d/week). - Progressively → 50 min walking at 60-70% HR reserve (6 d/week).	- BW, BW+D → TG↓, Apo B↓ - Exercise effects on serum TG are dependent on baseline TG levels, and ↑ when participants' initial TG concentrations are ↑
	Pribulick et al. 2013[10]	- Non-smoking rural, 35-65 yr (n=93).	- 14-month study of dietary fruit and vegetable intake and PA.	- PA + Diet → CRP↓, CVRF↓ - ↑BMI → CRP↑ - Moderately active group → The lowest CRP levels.
	Pullyblank et al. 2020[9]	-Rural women, ≥40 yr, sedentary, BMI ≥ 25 kg/m^2 (n=194).	- 24-week intervention (1 h, 2 d/week). - Aerobic exercise → 20-30 min. - Progressive strength training → 10-15 min. - Goal → 150 min of moderate-vigorous aerobic activity, 3 d/week strength training. - Mediterranean diet + DASH diet.	- Improvements in arm curls → Intervention, control groups. - Strength training → Greater benefits in body composition than weight change. - More intensive program → Major increase in endurance and strength. - Aerobic endurance → Associated with weight loss.
	Ratajczak et al. 2019[26]	- Obesity, 18-65 yr (n=39).	- 3-month physical training program (3 d/week). - ET → Cycle ergometers: 5 min low-intensity warm up + 45 min training 60-80% HR_{max} + 5 min non-weight-bearing cycling + 5 min low-intensity cool down.	- Both groups → Body mass↓, BMI↓, WC↓, resting HR↓, resting DBP↓, SBP↓, VEGF↑, TG↓, TAC↓, ↑VO_2peak post-intervention. - ET + CT → Total-body skeletal muscle mass index↑, TC↓ - CT → VAI↓, LDL-C↓, CRP↓, AIP↓

			- CT → 5 min low-intensity warm-up + 20 min strength exercises + 25 min endurance exercise at 60-80% HR_{max} + 5 min non-weight-bearing cycling + 5 min low-intensity cool down. - Sets → 16 sets in barbell curls, 30 sets in barbell squats (10-15 s rest between sets).	- CT → More effective visceral fat↓, = or ↑muscle mass than ET alone. - ET → HDL-C↑, eNOS↑, TBARS↓
	Wu et al. 2007[25]	- Taiwan women with at least 1 CVRF, 35-64 yr (n=36).	- 8-week intervention. - Exercise group → 5 min warm-up + 30 min treadmill training + 5 min cooldown (3 d/week). - Control group → Maintain their previous lifestyle.	- Exercise group → BMI↓, waist-to-hip ratio↓, resting SBP↓, DBP↓, mood↑; ↑vigour-activity, fatigue-inertia, and total mood scores after 8 weeks. - TG = → Exercise, control groups. - Participants with SBP↑140 mmHg → Greater reduction than those with SBP↓139 mmHg.
SPORTDiscus				
	Álvarez et al. 2019[24]	- Physically inactive, hyperglycemia, overweight/obesity, 41±6 yr (n=40).	- 20-week of CT intervention: 3 d/week; 5 min warm-up + cool down; 50 min RT + 30 min ET. - RT → 8 exercises with dumbbells at no more than 10%-20% 1RM. - ET → Walking or running at no more than 70% HR_{MAX}.	- Body mass↓, waist-to-hip ratio↓, fat mass↓, lean mass↓, mean SBP↓, fasting glucose↓, 6MWT↑
	Domene et al. 2016[23]	- Physically inactive, overweight/obesity, 18-64 yr (n=20).	- 8-week Zumba fitness intervention. - 12 classes (1 d/week increased progressively). - 1 h length + 48 h between classes.	- Body fat↓, VO_{2MAX}↑, white blood cells↓ - HRQoL → Physical functioning↑, emotional well-being↑, energy/fatigue↑
	Lynne et al. 2016[22]	- Nondiabetic, 35-50 yr (n=63).	- 8-week TCH intervention. - 60 min sessions → Breathing, posture, balance, movement, consciousness for relaxation. - Home practice → 15 min most days of the week.	- Granulocyte colony-stimulating factor↓ post-intervention and = after 2 months. - Fatigue↓ post-intervention. - IL-4↓, IL-8↓, TNF↓, interferon-gamma↓, IL-6↓ → 2 months post-intervention. - Depressive symptoms↓, mindfulness↑, self-compassion↑, spirituality↑, stress↓ 2 months after the intervention.
	Parra-Medina et al. 2011[8]	- Financially disadvantaged African American, ≥35 yr, primarily HTN, diabetes (n=266).	- Telephone counseling intervention (12 months). - Primary health care → Dietary fat↓, moderate-vigorous PA↑ - Standard group (one phone call), comprehensive group (lasted 1 year).	- Comprehensive participants' probability to reduce total PA at 6 months was ↓ than standard participants, but ↑ in leisure PA. - Comprehensive participants → DRA total score↑, CVRF↓

Additional articles				
	Alvarez et al. 2018[21]	- Sedentary, overweight/obesity, 18-59 yr (n=49).	- 16-week HIIT program. - Groups: T2DM, DYS, DYSHG, CON. - HIIT (jogging/running) + Low-intensity active recovery (walking). - Pace at 90-100%, 70% below their HR reserve. - Exercise intensity, volume progression.	- DYS, DYSHG → TC↓ - DYSHG → LDL-C↓ - All groups → TG↓, weight↓, BMI↓, WC↓, skinfold thickness↓, endurance performance↑ → After HIIT. - All groups → Fasting glucose↓ → Except CON. - All groups → SBP↓ → Not DBP. - Daily dosage of diabetes medication↓ + No anti-hypertensive medication during HIIT.
	Behall et al. 2013[6]	- Pre and postmenopausal women, 18-77 yr (n=23).	- 12-week training intervention, 3 d/week. - Aerobic training → 20-40 min progressively; 60-65% HR reserve. - Resistance training → 14 exercises; 2 sets of 8-15 reps; 1 min rest interval; 2 min rest sets.	- Both groups → Percent body fat↓ → After aerobic exercise. - Especially postmenopausal → TG↓, cholesterol↓ → After aerobic exercise. - Both groups → TC↓, LDL-C↓, HDL/LDL-C ratio improved, insulin AUC↓, C-peptide AUC↓ → After intervention. - Average glucose concentrations ↓ with aerobic, ↑ with resistance exercise.
	Krishnan et al. 2015[20]	- Sedentary, overweight/obesity, 18-65 yr (n=41).	- 16-week Zumba dance intervention, 3 d/week. - First 3 weeks → Interrupting the pace. - After 3 weeks → No interruption in the pace.	- Body weight↓, BMI↓, WC↓, hip circumference↓ -Aerobic capacity↑, flexibility↑, muscular endurance↑, HR↑ and % HR_{MAX}↑ -Intrinsic motivation↑, commitment↑, enjoyment↑

Abbreviations: AIP, atherogenic index of plasma; Apo B, apolipoprotein B; AUC, areas under the curve; BMI, body mass index; BW, brisk walking group; BW+D, brisk walking plus diet group; CON, healthy control; CRF, cardiorespiratory fitness; CRP, C-reactive protein; CT, concurrent training; CVRF, cardiovascular risk factors; d, days; DASH, Dietary Approaches to Stop Hypertension; DBP, diastolic blood pressure, DRA, Dietary Risk Assessment; DYS, dyslipidemia; DYSHG, dyslipidemia associated with hypertriglyceridemia; eNOS, endothelial nitric oxide synthase; ET, endurance training; HDL-C, high-density lipoprotein cholesterol; HR, heart rate; HRQoL, Health-related quality of life; IL-4, interleukin-4; IL-6, interleukin-6; IL-8, interleukin-8; LDL-C, low-density lipoprotein cholesterol; 6MWT, Six Minute Walk Test; min, minute; PA, physical activity; reps, repetitions; RM, repetition maximum; RT, resistance training; SAT, subcutaneous adipose tissue; SBP, systolic blood pressure; TAC, blood total antioxidant capacity; TBARS, thiobarbituric acid reactive substances; TC, total cholesterol; TCH, Tai Chi; T2DM, type 2 diabetes mellitus; TG, triglycerides; TNF, cytokines tumour necrosis factor; VAI, visceral adiposity index; VEGF, vascular endothelial growth factor; $VO2_{max,}$ maximal oxygen consumption; VO_{2peak}, peak rate of oxygen consumption; WC, waist circumference; WL, diet group; WL-RT, diet plus resistance training group; yr, year.

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 also important to note that all the included articles positively defined the PICOT question correctly, and all the publications, except two,[12,20] maintained the groups at baseline. By contrast, included articles assessed by PEDro scale showed bias regarding no concealed allocation, and at least one measure did not obtain more than 85%. For the menopausal state, only one[6] out of 14 publications made a comparison between pre and postmenopausal 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.

Table 2 Assessment of the PEDro scale and Oxford's Evidence levels of the included scientific articles that analyzed CRF and CVRF after PA intervention.

PEDro ratings References										Oxford's Evidence levels
	1	2	3	4	5	6	7	8	Total	
Andersen et al.[27]	Y	Y	N	Y	N	N	Y	Y	4	2b
Ibañez et al.[12]	Y	Y	N	N	Y	Y	Y	Y	5	2b
Lee et al.[35]	Y	N	N	Y	Y	Y	Y	Y	5	2b
Pribulick et al.[10]	Y	Y	N	Y	Y	Y	Y	Y	6	2b
Pullyblank et al.[9]	Y	Y	N	Y	N	Y	Y	Y	5	1b
Ratajczak et al.[26]	Y	Y	N	Y	N	Y	N	Y	4	2b
Wu et al.[25]	Y	N	N	Y	Y	Y	Y	Y	5	1c
Álvarez et al.[24]	Y	Y	N	Y	N	Y	Y	Y	5	1b
Domene et al.[23]	Y	Y	N	Y	Y	Y	Y	Y	6	1b
Robins et al.[22]	Y	Y	N	Y	N	Y	Y	Y	5	2b
Parra-Medina et al.[8]	Y	Y	N	Y	N	Y	Y	Y	5	1b
Alvarez et al.[21]	Y	N	N	Y	N	Y	Y	Y	4	2b
Behall et al.[6]	Y	N	N	Y	N	Y	Y	Y	4	2b
Krishnan et al.[20]	Y	N	N	N	N	Y	Y	Y	3	2b

Abbreviations: CRF, cardiorespiratory fitness; CVRF, cardiovascular risk factors; N, no; PA, physical activity; Y, yes.
1: eligibility criteria were specified.
2: subjects were randomly allocated to groups.
3: allocation was concealed.
4: the groups were similar at baseline regarding the most important prognostic indicators.
5: measures of at least one key outcome were obtained from more than 85% of subjects initially allocated to groups.
6: all subjects for whom outcome measures were available received the treatment or control condition as allocated or, where this was not the case, data for at least one key outcome was analyzed by "intention to treat".
7: the results of between-group statistical comparisons are reported for at least one key outcome.
8: the study provides both point measures and measures of variability for at least one key outcome.

5. Discussion

Pre and postmenopausal women may respond differently to the effects of exercise/PA due to differences in hormonal status. However, to our knowledge, the evidence comparing CRF and CVRF changes between both menopausal states has not previously 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 VO_{2max} or decreasing inflammatory factors in women. In addition, not only PA led 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), and except for two scientific articles,[10,23] they all presented a low methodological quality. Regarding articles with high methodological quality,[28] one article[23] showed improvements in both CRF and CVRF after PA intervention, with greater emotional well-being too (n=20). The other article[10] only demonstrated improvements in CVRF, but the sample size was higher than the previous one (n=93). In relation to the included articles with low methodological quality,[28] only five[20,22,24,26,27] out of 12 showed improvements in both CRF and CVRF after PA intervention, having a similar sample size (n≈43).

Results from this systematic review extend results from a previous study, which showed improvements in blood pressure, triglycerides, high-density lipoprotein cholesterol, and glucose only in postmenopausal women, whereas total cholesterol and low-density lipoprotein cholesterol were decreased in pre and postmenopausal women after a weight loss intervention.[29] Overall, anthropometric and metabolic risk factors were improved in both groups regardless their menopause state. However, postmenopausal women had a higher reduction in metabolic risk factors than premenopausal women, which may be possibly linked to their baseline state.[29] In this sense, it has been demonstrated how women with initially higher systolic blood pressure or triglycerides levels, achieved greater reductions in their metabolic syndrome than those women with lower levels.[11,25] 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. Our findings have shown how endurance, strength, or even a HIIT program can

reduce waist circumference or waist-to-hip ratio in women.[20,21,24,26] However, PA may only contribute to prevent higher amounts of fat and not to prevent redistribution of fat.[30] It is important to note that regardless of the starting level of PA, women who increased their PA levels were less likely to gain body mass, as well as women with higher levels of PA.[30] Therefore, PA is important especially in postmenopausal women due to their decrease in energy expenditure with age, which may lead to body mass gain,[31,32] particularly in visceral abdominal fat, with increased risk to become obese if lifestyle changes are not made in menopause onset.[33,34] In fact, associations have been found between changes in plasminogen activator antigen, C-reactive protein, leptin, and adiponectin with change in abdominal fat,[35] in accordance with two of the included articles,[10,22] which previously have mentioned how a decrease in body mass index or an increase in PA levels may be beneficial for C-reactive protein and proinflammatory cytokines. Similarly, reductions in estrogen are related to a decrease in muscle and skeletal mass, as well as resting metabolic rate, which contributes to total daily energy expenditure. 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.[33] Overall, it seems important to be aware of the effects of strength training for instance, because it may have an impact on body composition, but not on weight change.[9] It has also been shown how strength exercise can increase average glucose concentrations and aerobic exercise, decrease its concentrations in pre and postmenopausal women.[6] However, a combination of both endurance and strength[24,26] are needed to reduce visceral fat and maintain or increase muscle mass, as well as to improve atherogenic index of plasma, C-reactive protein, and low-density lipoprotein cholesterol concentrations.[26] Some of the present results have shown improvements in aerobic capacity after PA intervention, which can be sometimes associated with weight loss.[9] Women experienced increases in maximal oxygen consumption,[20,23,27] peak rate of oxygen consumption,[26] flexibility,[20] strength,[9,20] and aerobic endurance[21,24] after PA program. Other studies have also shown that it is possible to reduce fatigue, which may be helpful to work in higher intensities.[23,25] In fact, it has been demonstrated how the more intensive the program is, the major increases in endurance and strength are achieved.[9] Thus, vigorous aerobic exercise was better sparing of lean tissue than did lifestyle activity.[27] On the other hand, only practicing 30 minutes of moderate lifestyle activity in short bouts per day most days of the week, has shown to improve both CRF and CVRF in women with obesity so that even small

lifestyle changes may be relevant in terms of decreasing metabolic risk and being able to tolerate better effort in PA.

Consistent with some of the studies included in this systematic review,[20,22,23,25] increases in PA levels may be beneficial for stress and depressive symptoms.[36] High depressive symptoms have been associated with higher 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. In this sense, body mass index may also contribute to depressive symptoms.[37] Furthermore, PA increases mindfulness, self-compassion, spirituality,[22] as well as intrinsic motivation, enjoyment, and commitment.[20] Our results have shown how Zumba fitness classes may improve the emotional well-being of physically inactive women with overweight/obesity.[23] All these psychological changes may help in women's adherence to PA, and as it was mentioned before, it may also be beneficial to help them in long-term weight maintenance.[33] Finally, we would also like to point out that PA, particularly HIIT program, may also have an impact on the daily dosage of diabetes medication by reducing it, as well as being able not to take any anti-hypertensive medication during HIIT.[21] The only study comparing both menopausal states concludes that the type of exercise is more important for postmenopausal than premenopausal women, with the aerobic exercise having greater effect on the CVRF.[6]

5.1. Strengths and Limitations

The main strength of this review is the research question developed, since it is important to know which clinical options based on PA decrease CVRF or improve CRF, to advise participants who have high-normal values. Another strength is the study design since a systematic review based on RCT has a high level of evidence, provided that it has been properly conducted. To achieve this, we applied the PEDro scale and Oxford's Evidence levels.[13,14]

The main limitation of this systematic review is the lack of publications regarding the effects of a PA intervention in pre and postmenopausal 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 our included articles had low methodological quality, which makes the transfer of the results to clinical practice difficult.

Protocol of this systematic review has not yet been prepared in the international prospective register of systematic reviews (PROSPERO).

5.2. Clinical Practice Guidelines

With regard to clinical practice and considering the results together with the quality of the publications, we see 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.[6,8-12,20-27] These PA can be practiced by participants of all ages and improves at least one variable over a period between 8 weeks to 1 year. All activities can be performed outdoors or indoors, and in a group, thereby increasing adherence. Finally, the reviews should be strengthened, improving the peer-review process, which is a key point for the scientific validity of a work.[38] Additionally, the process should be critical of manuscripts that have already been published, applying tools like PEDro scale or Oxford's Evidence levels.[13,14]

6. Conclusions

This systematic review analyzed MEDLINE, CENTRAL, Scopus, SPORTDiscus, and WOS electronic databases, assessing scientific articles that determined the relationship between joining PA intervention and a modification in CRF and CVRF in pre and postmenopausal women. A total of 14 manuscripts were studied. These scientific articles showed great variability in the duration of PA, types, and intensity. Similarly, only one article took into account the differences in the menopausal state when considering the effects of PA highlighting the importance of PA in both states. Most manuscripts' methodological quality was low, except for two scientific articles, which had high methodological quality.

7. References

1. Bull FC, Al-Ansari SS, Biddle S, et al. World health organization 2020 guidelines on physical activity and sedentary behaviour. *Br J Sports Med*. 1451;54(24).

2. Mosca L, Barrett-Connor E, Wenger NK. Sex/Gender Differences in Cardiovascular Disease Prevention: What a Difference a Decade Makes. *Circulation*. 2011;124(19):2145-2154.

3. Mascarenhas-Melo F, Sereno J, Teixeira-Lemos E, et al. Markers of increased cardiovascular risk in postmenopausal women: Focus on oxidized-LDL and HDL subpopulations. *Dis Markers.* 2013;35(2):85-96.

4. Kaminsky LA, Arena R, Ellingsen Ø, et al. Cardiorespiratory fitness and cardiovascular disease - the past, present, and future. *Prog Cardiovasc Dis*. 2019;62(2):86-93.

5. Harber MP, Kaminsky LA, Arena R, et al. Impact of Cardiorespiratory Fitness on All-Cause and Disease-Specific Mortality: Advances Since 2009. *Prog Cardiovasc Dis*. 2017;60(1):11-20.

6. Behall KM, Howe JC, Martel G, Scott WH, Dooly CR. Comparison of resistive to aerobic exercise training on cardiovascular risk factors of sedentary, overweight premenopausal and postmenopausal women. *Nutrition Research*. 2003;23(5):607-619.

7. Brahmbhatt Y, Gupta M, Hamrahian S. Hypertension in premenopausal and postmenopausal women. *Curr Hypertens Rep*. 2019;21(10):74.

8. Parra-Medina D, Wilcox S, Salinas J, et al. Results of the Heart Healthy and Ethnically Relevant Lifestyle Trial: A Cardiovascular Risk Reduction Intervention for African American Women Attending Community Health Centers. *Am J Public Health (1971)*. 2011;101(10):1914-1921.

9. Pullyblank K, Strogatz D, Folta SC, et al. Effects of the Strong Hearts, Healthy Communities Intervention on Functional Fitness of Rural Women. *J Rural Health*. 2020;36(1):104-110.

10. Pribulick M, Fahs P, Spencer G, Grabro T, Wiitala S. C-reactive protein (hsCRP), Diet, and Physical Activity in Rural Women. *Online J Rural Nurs Health Care*. 2013;13(1):92-126.

11. Lee, M.-R. & Wan-Soo, K. The effects of brisk walking versus brisk walking plus diet on triglycerides and apolipoprotein B levels in middle-aged overweight/obese women with high triglyceride levels. *J Korean Acad Nurs*. 2006;36(8):1352-1358.

12. Ibáñez J, Izquierdo M, Martínez-Labari C, et al. Resistance Training Improves Cardiovascular Risk Factors in Obese Women Despite a Significative Decrease in Serum Adiponectin Levels. *Obesity (Silver Spring, Md.)*. 2010;18(3):535-541.

13. OCEBM levels of evidence — centre for evidence-based medicine (CEBM), university of oxford. https://www.cebm.ox.ac.uk/resources/levels-of-evidence/ocebm-levels-of-evidence. Accessed Apr 24, 2021.

14. de Morton NA. The PEDro scale is a valid measure of the methodological quality of clinical trials: A demographic study. *Aust J Physiother*. 2009;55(2):129-133.

15. Urrútia G, Bonfill X. PRISMA declaration: A proposal to improve the publication of systematic reviews and meta-analyses. *Med Clin (Barc)*. 2010;135(11):507-511.

16. Oviedo CP, Viteri JS. Pregunta de investigación y estrategia PICOT. *Medicina*. 2015;19(1):66-69.

17. Robinson KA, Dickersin K. Development of a highly sensitive search strategy for the retrieval of reports of controlled trials using PubMed. *Int J Epidemiol*. 2002;31(1):150-153.

18. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan-a web and mobile app for systematic reviews. *Syst Rev*. 2016;5(1):210. Accessed Apr 24, 2021. doi: 10.1186/s13643-016-0384-4.

19. Schoenfeld BJ, Grgic J, Ogborn D, Krieger JW. Strength and Hypertrophy Adaptations Between Low- vs. High-Load Resistance Training: A Systematic Review and Meta-Analysis. *J Strength Cond Res*. 2017;31(12):3508-3523.

20. Krishnan S, Tokar TN, Boylan MM, et al. Zumba® Dance Improves Health in Overweight/Obese or Type 2 Diabetic Women. *Am J Health Behav*. 2015;39(1):109-120.

21. Alvarez C, Ramirez-Campillo R, Martinez-Salazar C, Castillo A, Gallardo F, Ciolac EG. High-Intensity Interval Training as a Tool for Counteracting Dyslipidemia in Women. *Int J Sports Med*. 2018;39(5):397-406.

22. Robins JL, Elswick RK, Sturgill J, McCain NL. The Effects of Tai Chi on Cardiovascular Risk in Women. *Am J Health Promot*. 2016;30(8):613-622.

23. Domene PA, Moir HJ, Pummell E, Knox A, Easton C. The health-enhancing efficacy of zumba® fitness: An 8-week randomised controlled study. *J Sports Sci*. 2016;34(15):1396-1404.

24. Álvarez C, Ramírez-campillo R, Lucia A, Ramírez-vélez R, Izquierdo M. Concurrent exercise training on hyperglycemia and comorbidities associated: Non-responders using clinical cutoff points. *Scand J Med Sci Sports*. 2019;29:952-967.

25. Wu T, Yeh H, Chan P, Chiou Y, Tsai J. The Effects of Simple Eight-Week Regular Exercise on Cardiovascular Disease Risk Factors in Middle-Aged Women at Risk in Taiwan. *Acta Cardiol Sin*. 2007;23(3):169-176.

26. Ratajczak M, Skrypnik D, Bogdański P, et al. Effects of Endurance and Endurance-Strength Training on Endothelial Function in Women with Obesity: A Randomized Trial. *Int J Environ Res Public Health*. 2019;16(21).

27. Andersen RE. Effects of Lifestyle Activity vs Structured Aerobic Exercise in Obese Women A Randomized Trial. *JAMA*. 1999;281(4):335-340.

28. Maher CG, Sherrington C, Herbert RD, Moseley AM, Elkins M. Reliability of the PEDro scale for Rating Quality of Randomized Controlled Trials. *Phys Ther*. 2003;83(8):713-721.

29. Deibert P, König D, Vitolins MZ, et al. Effect of a weight loss intervention on anthropometric measures and metabolic risk factors in pre- versus postmenopausal women. *Nutr J*. 2007;6(1):31.

30. Sternfeld B, Hua Wang, Quesenberry CP, et al. Physical activity and changes in weight and waist circumference in midlife women: Findings from the study of women's health across the nation. *Am J Epidemiol*. 2004;160(9):912-922.

31. Duval K, Prud'homme D, Rabasa-Lhoret R, et al. Effects of the menopausal transition on energy expenditure: A MONET Group Study. *Eur J Clin Nutr*. 2013;67(4):407-411.

32. Macdonald HM, New SA, Campbell MK, Reid DM. Longitudinal changes in weight in perimenopausal and early postmenopausal women: Effects of dietary energy intake, energy expenditure, dietary calcium intake and hormone replacement therapy. *Int J Obes*. 2003;27(6):669-676.

33. Evans EM, Racette SB. Menopause and Risk for Obesity: How Important Is Physical Activity? *J Women's Health (Larchmt)*. 2006;15(2):211-213.

34. Lovejoy JC, Champagne CM, De Jonge L, Xie H, Smith SR. Increased visceral fat and decreased energy expenditure during the menopausal transition. *Int J Obes*. 2008;32(6):949-958.

35. Lee CG, Carr MC, Murdoch SJ, et al. Adipokines, inflammation, and visceral adiposity across the menopausal transition: A prospective study. *J Clin Endocrinol Metab*. 2009;94(4):1104-1110.

36. Owens JF, Matthews KA, Wing RR, Kuller LH. Can physical activity mitigate the effects of aging in middle-aged women? *Circulation*. 1992;85(4):1265-1270.

37. Matthews KA, Schott LL, Bromberger J, Cyranowski J, Everson-Rose SA, Sowers MF. Associations between depressive symptoms and inflammatory/hemostatic markers in women during the menopausal transition. *Psychosom Med*. 2007;69(2):124-130.

38. Moher D. Optimal strategies to consider when peer reviewing a systematic review and meta-analysis. *BMC Med*. 2015;13:274.

8. Appendix

Appendix 1. PRISMA 2020 Checklist.

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	1
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	2
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	2
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	3
Information sources	6	Specify all databases, registers, websites, organizations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	3-4
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	4
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	3-4
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	3-4
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	3-4
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	3-4
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	4-5
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	5
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	4
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data	4-5

Section and Topic	Item #	Checklist item	Location where item is reported
		conversions.	
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	4
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	4
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	4
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	4-5
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	4-5
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	4-5
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	5-7
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	5-6
Study characteristics	17	Cite each included study and present its characteristics.	8-10
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	11
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	-
Results of syntheses	20a	For each synthesis, briefly summarize the characteristics and risk of bias among contributing studies.	8-11
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	-
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	5-6
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	11
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	11
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	11
DISCUSSION			

Section and Topic	Item #	Checklist item	Location where item is reported
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	12
	23b	Discuss any limitations of the evidence included in the review.	14
	23c	Discuss any limitations of the review processes used.	14
	23d	Discuss implications of the results for practice, policy, and future research.	15
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	-
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	15
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	-
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	-
Competing interests	26	Declare any competing interests of review authors.	-
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	-