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Protocol of a Systematic Review with Meta-analysis: Sex differences in Blood Pressure Response to Chronic Exercise

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Abstract

Exercise has been shown to reduce blood pressure (BP) in adults; however, the influence of sex on the hypotensive effects of chronic exercise remains unclear. This study aims to evaluate sex differences in BP responses to chronic exercise. A systematic review with meta-analysis will be conducted using digital databases (EMBASE, PUBMED, LILACS, and SPORTDiscus). Eligible studies will include both randomized and non-randomized clinical trials, as well as crossover studies, involving adult participants (aged 18-65 years). These studies will have representation from both men and women, allowing for sex-based comparisons. The interventions will include chronic exercise (≥ 4 weeks) of any modality. The primary outcomes will include BP values measured pre- and post-exercise (systolic, diastolic, and/or mean BP). Two independent reviewers will evaluate studies during the screening, eligibility, inclusion, and data extraction phases. The methodological quality of the included studies will be assessed using the Tool for the Assessment of Study Quality and Reporting in Exercise. The risk of bias will be assessed using the Joanna Briggs Institute's Critical Appraisal Tools. The overall quality of evidence for each outcome will be rated using the GRADE approach. The pooled results will be presented through forest plots. Subgroup analysis will be conducted based on population and exercise characteristics. Publication bias will be assessed using a funnel plot and Egger's test for asymmetry.

Attachments

PDF

Complete protocol_Ch...

617KB

Guidelines

This protocol was written following the recommendations of PRISMA-P (Moher et al., 2015).

Before start

CPG participated in the idealization, planning, original manuscript, and approval of the final version; TMM participated in the planning, review, and approval of the final version; ACAP participated in the planning, review, and approval of the final version; ACRB participated in the planning, review, and approval of the final version; ALA participated in the planning, review, and approval of the final version; JCS participated in the planning, review, and approval of the final version; IMM participated in the idealization, planning, review, supervision, and approval of the final version; GMP participated in the idealization, planning, review, supervision, and approval of the final version.

The authors declare that they have no conflicts of interest. Financial support: CAPES.

Background

1 Hypertension is a major contributor to cardiovascular disease burden, significantly driving morbidity and mortality worldwide (MILLS et al., 2020; ZHOU et al., 2021). The practice of physical exercise is widely recognized as an effective intervention for reducing blood pressure (BP) (EDWARDS et al., 2023). However, evidence suggests that there are sex differences in BP response to exercise, which may influence the effectiveness of physical activity-based interventions (BASSAREO & CRISAFULLI, 2020). Different mechanisms of BP reduction following exercise have been identified in men and women (SENITKO et al., 2002; QUEIROZ et al., 2013). These differences may result in variations in the magnitude and effectiveness of BP reduction after physical exercise between the sexes. Despite the growing interest in exploring these differences, the results of individual studies have been inconsistent, possibly due to variations in study designs, investigated populations, and types of exercise assessed. Therefore, a systematic review and meta-analysis are needed to synthesize the available evidence and provide a clearer understanding of the sex differences in BP response to chronic exercise. Thus, the aim of this systematic review and meta-analysis is to evaluate sex differences in BP response to chronic exercise, examining factors that may moderate these differences, such as population and exercise characteristics.

Methodology

2 This systematic review with meta-analysis will follow the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and will be registered on the PROSPERO platform (Page et al., 2021).

2.1 **Eligibility criteria**

Eligible studies will need to compare exercise interventions between sexes within the same study and report BP outcomes (systolic blood pressure (SBD), diastolic blood pressure (DBP), or mean blood pressure (MBP)) as primary or secondary endpoints. The eligibility criteria will be as follows: 1) **Population**: adult humans (≥ 18 to 65 years old), with both men and women represented, allowing for sex-based comparisons. Studies that do not specify the age range of participants but report a mean age within the range of 18 to 65 years will be included; 2) **Intervention**: chronic any exercise modality (≥ 4 weeks); 3) **Outcome of interest**: values of BP pre and after exercise (SBP, DBP, and/or MBP); 4) **Languages**: English, Portuguese, and Spanish; 5) **Study designs**: randomized and non-randomized clinical trials and crossover studies; 6) **Publication dates**: studies published from 2000 onwards. The exclusion criteria will be: literature reviews, meta-analyses, letters to the editor, theses, dissertations, conference abstracts, study protocols, observational studies, animal studies, studies involving children or the elderly, and studies that evaluated the effect of exercise on BP in adults but did not stratify the results by sex.

2.2 **Search strategy**

Searches will be carried out in the following digital databases: EMBASE, PUBMED, LILACS, and SPORTDiscus. The unstructured search will be conducted in the references of the main articles and through a manual search on the Google Scholar platform to identify additional studies that may not have been captured in the systematic search. Secondary sources, such as systematic reviews and related meta-analyses, will also be examined to identify potentially eligible studies. If necessary, the authors of the studies will be contacted to request data. The search will be divided into three categories of terms: (1) Exercise, (2) Blood Pressure, and (3) Population. Within each category, terms will be separated by union operators (i.e., "OR"), and categories will be separated by parentheses and intersection operators (i.e., "AND"). The terms to be searched in the title, abstract, and keywords indexed in the aforementioned databases will be formatted as follows:

(Exercise OR "Physical activity" OR "Physical training" OR Aerobic OR Cycling OR Treadmill OR Swim OR Running OR Run OR "Hand grip" OR "Hand-grip" OR Walk* OR "Weight training" OR "Strength training" OR "Resistance exercise" OR "Resistance training" OR "Endurance training" OR "Endurance exercise" OR Plyometric OR Pilates OR Yoga OR Isometric OR "Combined training" OR "Combined exercise" OR "Concurrent training" OR "Concurrent exercise") AND ("Post-exercise hypotension" OR "Post exercise hypotension" OR "Blood pressure" OR "Blood pressures" OR "Arterial pressure" OR Systolic OR Diastolic) AND (Gender OR Sex OR ((Man OR Men OR Male) AND (Woman OR Women OR Female)))*

2.3 **Screening and data extraction**

During the screening, eligibility, inclusion, and data extraction phases, studies will be evaluated in duplicate by 2 independent reviewers. After verifying the reviewers' responses, disagreements will be resolved by a third reviewer. These studies will be organized in the reference manager Rayyan (https://www.rayyan.ai/) and later recorded in a spreadsheet for data extraction and organization. If there are studies in which the data are represented only in graphs or figures without numerical representation, the data will be extracted by the software WebPlotDigitalizer (https://automeris.io/WebPlotDigitizer/). Data extraction will include: 1) General description (identification code, author, year of publication, language, and study design); 2) Description of participants (sex, sample size, BP status, health status, and age); 3) Description of the exercise (modality, intensity, frequency, duration, and volume); 4) Values of pre- and post-intervention resting and/or ambulatory BP measurements (SBP, DBP, and MBP). For the data analysis, the BP value considered after exercise will be the peak hypotensive response, defined as the lowest BP value recorded post-exercise. If this value is unavailable, the average of the recorded measurements will be used.

2.4 **Risk of bias and quality methodology**

The evaluation of the quality methodology of the included studies will be performed according to the criteria proposed by Tool for the Assessment of Study Quality and Reporting in Exercise (TESTEX). The tool is a 15-point scale (5 points for study quality and 10 points for reporting) and addresses previously unmentioned quality assessment criteria specific to exercise training studies. Quality assessment will be independently performed by 2 blinded reviewers and disagreements will be resolved by consensus or by a 3 rd reviewer (SMART et al., 2015). The risk of bias analysis will be conducted using the Joanna Briggs Institute's Critical Appraisal Tools for Randomized Controlled Trials and Quasi-Experimental Studies (BARKER et al., 2023; LOCKWOOD et al., 2024).

2.5 **Quality of evidence**

The quality of evidence for each outcome will be classified using the GRADEpro GDT software®, developed by the Classification of Recommendations, Assessment, Development, and Evaluation Working Group (GRADE) (SCHUNEMANN et al., 2023). The GRADE approach will assess the quality of a body of evidence, defined as confidence in the estimates of the effects of alternative management strategies. Outcomes will be categorized as ⊕⊕⊕⊕ (high), ⊕⊕⊕○ (moderate), ⊕⊕○○ (low), or ⊕○○○ (very low). The results of these assessments will be presented in the results section in both textual and graphical formats.

2.6 **Data synthesis and quantitative approaches**

Data analysis will be performed with the “R” programming language (VIENNA, 2019) through the “meta” and “metafor” packages (VIECHTBAUER, 2010). They will be analyzed based on mean differences in clinical units. Kendall's tau and I^2 will be used as measures of heterogeneity. The meta-analysis values will be presented through “forest plots”. If the studies are sufficient, a subgroup analysis will be conducted based on population and exercise characteristics. The random effects model will be used due to the inherent heterogeneity of the interventions (exercises of different modalities, volumes, frequencies, intensities, etc). Sensitivity analysis will be done through the search for outliers using the “externally standardized residuals” method (standard deviation values greater than 1.96 in the standardized residuals plot), and the search for influential points using the Difference of Fits methods (identifying values above 1 or below −1). Publication bias analysis will be performed using a funnel plot and asymmetry hypothesis test (Egger’s test).

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