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Protocol of a systematic review with network meta-analysis: Chronic effects of physical exercise on blood pressure responsiveness to non-cardiopulmonary stress tests

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Laboratory stress tests can help compose the clinical profile of individuals and predict the development of future cardiovascular events and depression. These tests work by disturbing the individual's homeostasis to assess the body's responses to it. To assess responses to these stressors, several markers are used, of which we will highlight the blood pressure (BP). One of BP's control strategies is to perform physical exercises. It is known that even an exercise training phase, blood pressure levels can be below baseline levels at rest, but its influence on blood pressure levels under stress is still poorly understood. Thus, the objective of the scientific review proposed here is to answer the following question: what are the chronic effects of physical exercise training on BP responsiveness to non-cardiopulmonary stress tests in adults?For this, we will carry out a systematic review with network meta-analysis on digital bases (PUBMED, LILACS, EMBASE and Psycinfo), of studies that are carried out in adult humans and that indicate BP values under stress after a physical exercises training phase.

Complete protocol.pdf

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Blood Pressure, Exercise, Stress, Reactivity, Aerobic, Resistance, Stroop, Cold pressor

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The complete protocol PDF can be downloaded here: **Complete protocol.pdf**

The present protocol is a modification of a protocol for similar research with acute exercises by the same authors:
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Background

1 **Background**

Laboratory stress tests can help compose the clinical profile of individuals and predict, among others, the development of future cardiovascular events and depression [1]. These tests work by disturbing the individual's homeostasis in a controlled way to assess the body's responses to it. This is accomplished through physical stressors (Physiological or environmental), mental stressors (emotional or cognitive) or a mix of both [2]. To assess responses to these stressors, several biochemical (e.g. cortisol, interleukins, norepinephrine), physiological (e.g. heart rate variability, pupil size) and cardiovascular (e.g. blood pressure (BP), heart rate) markers are used [2], of which we will highlight the BP.

High BP is one of the main preventable factors associated with premature death globally [3] and is associated with the risk of cardiovascular events, strokes and kidney disease [4]. One of BP's control strategies is to perform physical exercises. It is known that after an exercise training phase, BP levels can be below baseline levels at rest [5] but its influence on BP levels under stress is still poorly understood. In a previous meta-analysis, Hamer and colleagues [6] evaluated the acute effects of aerobic exercise on BP under stress and found promising results. Besides that, a review [7] without a meta-analysis assessed the chronic effects of exercise and the physical activity level on several cardiovascular markers. However, the meta-analytic effects of recurrent (i.e., chronic) exercise on BP under stress have not yet been described.

Thus, the objective of the review proposed here is to answer the following question: what are the chronic effects of physical exercise training on BP responsiveness to non-cardiopulmonary stress tests in adults?

Methods

2 Methods

Eligibility criteria

Studies with the following characteristics will be eligible: **1)Population**: Human, both sexes, adults; **2) Intervention**: Physical exercise training phase for at least 4 weeks; **3) Control**: as this is a network meta-analysis, studies comparing exercise training methods will also be included whether or not they included a control group without exercise; **4) Outcome of interest**: peak BP (Systolic and/or diastolic) during non-cardiopulmonary stress test or BP variation (values during stress minus basal BP) after exercise training phase; **5) Languages**: English, Portuguese and Spanish; **6) Study designs**: no design limitations as long as it has a comparison with a group/situation without exercise or with another training method; **7) Publication dates:** No time limit.

The exclusion criteria are: Literature reviews, meta-analysis, letters to the editor, observational studies, animal studies, studies in children, studies written in other languages not described above, studies whose exercise intervention is relaxation sessions, breathing exercises, stretching only or cardiovascular rehabilitation after serious cardiovascular events, and studies that do not measure blood pressure during the stress tests.

3 *Search strategy*

The searches will be carried out in digital databases (PUBMED, LILACS, EMBASE and Psycinfo), in the references of the main articles, and through manual search in the CORE and Google Scholar platforms. If necessary, there will be contact with authors of the studies requesting relevant data.

The search will be divided into three categories of terms: Exercise, Blood Pressure and Stress Tests. Within each category the terms will be separated by union operators (i.e. “OR”) and the categories will be separated by parentheses and intersection operators (i.e. “AND”). All terms that will be added to the search are shown in table 1.

Table1 - Categorized search terms.

Exercise			Blood Pressure	Stress test
Exercise	Hand grip	Tai chi	Arterial pressure	Reactivity
Exercise Therapy	Hand-grip	Tai-chi	Blood pressure	Cold pressor
Physical activity	Handgrip	Isometric	Diastolic	Stroop
Physical training	Walking	Hiit	Systolic	Stress test
Aerobic	Walk	Hit		Psychosocial
Cycling	Weight training	Siit		Psychosocial test
Bicycle	Weight-training	Sit		Psychosocial stress
Treadmill	Weight exercise	High intensity		Psychosocial task
Cycle ergometer	Weight-exercise	Moderate intensity		Stress task
Cyclergometer	Resistance exercise	Low intensity		math task
Cycle-ergometer	Resistance training	Combined training		Speech task
Swimming	Strength	Combined exercise		Speech
Swim	Pilates	Concurrent training		Math
Running	Yoga	Concurrent exercise		Arithmetic
Run	Ioga			Arithmetic test
				Arithmetic task

4 *Study records*

During the screening, eligibility, inclusion in the meta-analysis and data extraction phases, the studies will be evaluated in duplicate by 2 independent reviewers. After checking the reviewers' responses, the disagreements will be resolved by a third reviewer. These studies will be organized in the Mendeley reference manager (https://www.mendeley.com/) and subsequently registered in a spreadsheet for data extraction and organization. If there are studies in which the data are presented only in graphs or figures without clear numerical representation, the data will be extracted by the web-based software WebPlotDigitalizer.

The data extraction will include: 1) the values referring to the primary outcome of the study (peak BP or BP variation during stress test in mmHg); 2) characteristics of the population (sex, exercise training level, average age, and health status), exercise (modality, intensity, frequency, training duration, and volume), stress test (type of test, method of BP measurement, and moment of application), and study design (Type of design, sample size, and type of control); 3) Other characteristics (conflicts of interest, other cardiovascular results, and idiosyncrasies of the exercise and the study population).

5 *Risk of bias in individual studies*

The analysis of risk of bias will be carried out at the level of studies using the tool “Risk of Bias 2.0” from the Cochrane collaboration [7]. This analysis will be divided into the following domains: randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, selection of the reported result and overall bias. These data will be presented in the results section in textual and/or graphic form and will help to explore the weaknesses of the studies in the discussion section. In addition, we will describe the conflicts of interest reported by the studies.

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6 *Data synthesis and quantitative approaches*

The data will be evaluated using the programming language “R” [9] through the supplements "meta" [10], "metafor" [11] and “netmeta” [12]. They will be analyzed based on weighted or standardized mean differences. Kendall's tau and I^2 consistency measures will be presented. The summary meta-analysis values will be presented through a forest plot, carried out from a random effects approach by Hunter Smith method. The random effects model was defined due to the inherent heterogeneity of the characteristics of the studies, such as exercises of different modalities and varied stress tests. If there are sufficient studies, there will be a subgroup analysis dividing them based on the type of exercise intervention (aerobic exercises, dynamic resistance exercises, isometric exercises, and alternative exercises). Besides that, as comparisons between types of exercise are recurrent in this type of study, we will perform a network meta-analysis with direct and indirect comparisons between the types of exercise identified.

The sensitivity analysis will be done through the search for outliers using the “externally standardized residuals” method, and the search for influential points using the Difference in Fits (DFFITS), Covariance Ratio and Cook’s distance methods. Publication bias analyzes will be carried out through a funnel plot and asymmetry hypothesis tests (fail-safe n, Egger and Beggs).

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