Effects of aerobic, resistance, and combined training on endothelial function and arterial stiffness in older adults: study protocol for a systematic review and meta-analysis

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Abstract

Introduction: Aging is an independent risk factor for cardiovascular events. It promotes vascular dysfunction which is associated with risk factors for cardiovascular diseases (CVDs). Exercise can modulate vascular function parameters, but little is known about the effects of different modalities of training (aerobic, resistance, and combined) on endothelial function and arterial stiffness in older adults.

Methods: This systematic review study will include randomized controlled trials (RCTs) selected from the electronic databases MEDLINE (PubMed), Cochrane, LILACS, EMBASE, and Web of Science. We will follow the PRISMA guidelines and PICOS framework. Studies involving both male and female older adults (≥60 years old) with or without comorbidities undergoing aerobic, resistance, and/or combined training compared to a control group (no exercise) will be eligible. We will use the Cochrane Risk of Bias 2 (RoB 2) tool to evaluate the quality of individual studies and GRADE to assess the strength of evidence. Statistical analyses will be conducted with RStudio for Windows (v1.3.959) using R package meta.

Discussion: A systematic review and meta-analysis involving data from studies of older adults would deepen our understanding of vascular adaptations to exercise training in this population. It could provide new insights into how health providers can improve patient management and prevention of cardiovascular events in older adults.

Keywords: Exercise, Endothelium, Reactive hyperemia, Vascular stiffness, Pulse wave analysis, Aging
Endothelial function and arterial stiffness are considered important biomarkers of vascular function and predictors of cardiovascular events that are more accurate than well-established traditional risk factor scores [6, 10, 30–35]. Furthermore, epidemiological studies have demonstrated that endothelial dysfunction and increased arterial stiffness are highly prevalent among older adults [4, 36–38]. Therefore, the aging is an independent risk factor associated with vascular dysfunction, which increases the risk for the development of CVDs [2, 4, 32, 38–41].

Flow-mediated dilation (FMD) and pulse wave velocity (PWV) have been widely used in clinical practice and research studies to assess endothelial function and arterial stiffness, respectively [35, 42–46]. Several meta-analyses have shown that every 1% increase in FMD is associated with an 8–16% lower risk of fatal and non-fatal CV events and/or deaths from all causes with even greater effects in individuals with established CVDs [47–50]. Similarly, a 1m/s increase of PWV has been associated with up to 15% increase in the risk of CVD death [51, 52].

Different exercise training modalities (aerobic, resistance, and combined) have been recommended to reduce morbidity and mortality from CVDs and modify CVD risk profiles [53–64]. However, exercise training modalities and their variables (exercise volume, frequency, intensity, order, etc.) are not all similarly effective and may elicit different beneficial effects on vascular function parameters [65–70]. A few studies of resistance training have reported null [71–75] or even negative findings [76, 77] for the effect on arterial stiffness and endothelial function [74, 75], but they relate to healthy young and middle-aged adults [71, 73–76] and adults with comorbidities [70–72, 77]. In a recent meta-analysis conducted by our group [78] evaluating the effect of aerobic training in individuals with hypertension (362; aged 52 to 67 years), we found a 1.45% increase (p=0.001) in FMD, though we considered this hypothesis null (95% CI –0.11 to 3.00). On the other hand, randomized controlled trials (RCTs) and meta-analyses conducted by our group [78, 79] and other authors [80, 81] have found positive effects of different training modalities on endothelial function assessed by FMD. Yet, similar effects on arterial stiffness have not been demonstrated with resistance and combined training [67, 69, 82, 83]. Sample heterogeneity (healthy individuals or individuals with comorbidities) and predominant representation of specific age groups (often young and/or middle-aged adults) are some issues found in several meta-analyses, which shows that this subject has been little explored in older adults. Therefore, a systematic review and meta-analysis of RCTs is necessary to determine whether exercise training (aerobic, resistance, or combined) exert an effect on endothelial function and arterial stiffness in older adults.

Methods
Our systematic review will follow the guidelines of the Preferred Report Items for Systematic Reviews and Meta-Analysis (PRISMA) [84] and the specific PRISMA-P guidelines [85]. This protocol for a systematic review and meta-analysis was registered in the International Prospective Register of Systematic Reviews (PROSPERO) (www.crd.york.ac.uk/PROSPERO/, ID 42021275451, registered on 29 September 2021). For the sake of research transparency, the database used in the systematic review and meta-analysis will be made available on Mendeley Data repository as open access (https://data.mendeley.com/). Figure 1 summarizes the flowchart of the study design.

Eligibility criteria
We used PICOS as a framework to develop the study design, research questions, and searches for our systematic review as follows: Population (individuals aged ≥ 60 years), Intervention (aerobic and/or resistance and/or combined exercise training), Comparison (training group vs. control group [no exercise]), Outcome (endothelial function assessed by FMD and arterial stiffness assessed by PWV), and Study (RCTs).

The inclusion criteria for studies in this systematic review are (1) direct evidence from RCTs comparing one or more interventions (aerobic, resistance, or combined training) to a control group (no exercise training, usual care, education, placebo, and/or waiting list for intervention); (2) 4 weeks or more of intervention; (3) assessment of endothelial function and/or arterial stiffness as the primary or secondary outcome; (4) study population of both male and female adults aged ≥ 60 years; and (5) no language restrictions.

Since our systematic review will involve physical activity and its variables, we will adopt the following conceptual definitions for the searches: (I) physical activity: any bodily movement produced by skeletal muscles that results in energy expenditure, but it does not require or imply any specific aspect or quality of movement, and it may encompass work, leisure, recreational, sports, and fitness activities among others [86, 87]; (II) exercise: a subgroup of physical activity that is planned, structured, repetitive (i.e., exercise training) and designed to improve or maintain one or more components of physical fitness, physical performance, and health [86, 87]; (III) aerobic training: any form of activity that predominantly uses the aerobic energy system involving large muscle groups in a...
rhythmic manner for a sustained period of time to maintain or improve cardiorespiratory fitness [62, 87]; (IV) **resistance training**: any form of activity that involves voluntary, repeated and short muscle contractions, either dynamic, or isometric, carried out against an external resistance (load) that is greater than that usually found in
activities of daily living to maintain or increase muscular strength, power, endurance, and mass [87, 88]; and (V) **combined training**: a combination of aerobic plus resistance exercises (in any order) carried out in the same session or on alternate days of the week designed to improve both aerobic fitness and muscle strength [89, 90].

**Search strategy**

We will conduct searches in five databases: (1) MEDLINE (via PubMed), (2) LILACS, (3) Embase, (4) Cochrane Central Register of Controlled Trials (CENTRAL), and (5) Web of Science. We will evaluate articles of similar subjects included in previous reviews to avoid missing any potential eligible studies. To minimize any publication bias, we will also conduct searches on online gray literature including OpenGrey (www.opengrey.eu) and the Brazilian Coordination for the Improvement of Higher Education Personnel (CAPES) Bank of Theses and Dissertations (www.catalogodeteses.capes.gov.br). For unpublished ongoing studies, our searches will be undertaken in the following clinical trial registries: Brazilian Clinical Trials Registry (ReBEC, www.ensaiosciencias.gov.br), ClinicalTrial.gov (www.clinicaltrials.gov), and WHO International Clinical Trials Registry Platform (ICTRP, www.who.int/ictrp/en/). We will collect data through careful review of the retrieved articles, and the authors will be contacted by email to obtain any additional information if needed.

| Table 1  | Search strategy |
|----------|-----------------|
| MEDLINE (PubMed) | (EXERCISE [MeSH Terms] OR Exercises OR Physical Activity OR Activities, Physical OR Activity, Physical OR Physical Activities OR Exercise, Physical OR Exercises, Physical OR Physical Exercise OR Physical Exercising OR Acute Exercise OR Acute Exercises OR Exercise, Acute OR Exercises, Acute OR Isometric OR Isometric Exercises OR Isometric Exercise OR Exercise, Aerobic OR Aerobic Exercise OR Aerobic Exercises OR Exercises, Aerobic OR Exercise Training OR Exercise Trainings OR Training, Exercise OR Trainings, Exercise) OR (Resistance Training [MeSH Terms] OR Training, Resistance OR Strength Training OR Training, Strength OR Weight-Lifting Strengthening Program OR Strengthening Program, Weight-Lifting OR Weight Strengthening Program OR Weight-Lifting Strengthening Programs OR Weight-Lifting Exercise Program OR Exercise Program, Weight-Lifting OR Exercise Programs, Weight-Lifting OR Weight Lifting Exercise Program OR Weight-Lifting Exercise Programs OR Weight-Bearing Strengthening Program OR Weight-Bearing Strengthening Programs OR Weight-Bearing Exercise Program OR Exercise Program, Weight-Bearing OR Weight Bearing Exercise Programs, OR (Endurance Training [MeSH Terms] OR Training, Endurance) AND (Vascular Endothelium [MeSH Terms] OR Endothelium, Vascular OR Endotheliums, Vascular OR Vascular Endothelium OR Capillary) AND (Exercise OR training OR physical activity) AND (endothelium OR vasodilation OR vasorelaxation OR hyperemia) AND (vascular OR arterial OR venous OR congestion OR congestion, venous OR passive hyperemia OR hyperemia, passive OR reactive hyperemia OR hyperemia, reactive OR reactive hyperemia) AND (Vascular Stiffness [MeSH Terms] OR Vascular OR Stiffness OR Stiffnesses OR Arterial Stiffness OR Arterial Stiffnesses OR Stiffness, Arterial OR Aortic Stiffness OR Aortic Stiffnesses OR Stiffness, Aortic OR Pulse Wave Analysis [MeSH Terms] OR Analyses, Pulse Wave OR Analysis, Pulse Wave OR Pulse Wave Analyses OR Wave Analyses, Pulse OR Wave Analysis; Pulse OR Pulse Wave Velocity OR Pulse Wave Velocities OR Velocities, Pulse Wave OR Velocity, Pulse Wave OR Wave Velocities, Pulse OR Pulse Transit Time OR Pulse Transit Times OR Time, Pulse Transit OR Times, Pulse Transit OR Transit Time, Pulse OR Transit Times, Pulse OR Pulse Wave Transit Time) AND (randomized controlled trial OR controlled clinical trial OR controlled clinical trials OR random allocation OR double-blind method OR single-blind method OR clinical trial OR clinical trials) AND (clinical trial OR randomized controlled trial OR randomization OR random controlled trial OR random controlled trials OR randomized controlled trial OR randomized controlled trials) |
of interest assessed by techniques other than FMD or PWV; and ineligible study designs (cohort, observational, case-control and case report studies, reviews and protocols). Any disagreements will be resolved by a third reviewer (MIS or GW).

### Data extraction and management

Our reviewers (RSNS and DSS) will read separately the full text of all eligible studies. If a study is relevant for inclusion in the review, each reviewer will manually extract and compile the main data in a pre-structured database in Excel 365 for Windows. For the extraction of data from RCTs with the outcomes of interest presented in graphs, we will use WebPlotDigitizer to extract the data (https://apps.automeris.io/wpd/). For studies assessing changes in endothelial function or arterial stiffness at different time points after the intervention, we will independently compare baseline measurements with results at each time point. For studies assessing arterial stiffness with different PWV indices, we will prioritize central PWV (carotid-femoral/carotid PWV) [46, 51] over peripheral PWV measurements brachial-ankle/femoral-ankle PWV) [44, 45].

The data extracted will be divided into five main groups: study identification (authors and year of publication), participants (age, gender, and medical conditions), material and methods (randomization, blinding, and sample size), intervention (FITT components), secondary outcomes of interest (anthropometric measures, biochemical data, oxygen consumption, strength level), and techniques (FMD and PWV detailed description: location of the measurement) [45, 93].

### Risk of bias

The risk of bias of eligible studies will be assessed using Cochrane Risk of Bias 2 (RoB) 2 tool [94]. The assessment is based on a set of six domains of bias: (1) randomization process, (2) deviations from intervention (allocation concealment sequence), (3) incomplete outcome data,

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**Table 2** Interpretation of heterogeneity results

| Interpretation of $I^2$ | Remarks |
|-------------------------|---------|
| 0 to 40%: might not be important | $I^2$ confidence interval: uncertainty of the value of $I^2$ is substantial when there is a small number of studies |
| 30 to 60%: moderate heterogeneity | $I^2$ confidence interval: uncertainty of the value of $I^2$ is substantial when there is a small number of studies |
| 50 to 90%: substantial heterogeneity | $I^2$ confidence interval: uncertainty of the value of $I^2$ is substantial when there is a small number of studies |
| 70 to 100%: considerable heterogeneity | $I^2$ confidence interval: uncertainty of the value of $I^2$ is substantial when there is a small number of studies |

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**Table 3** Script used for the meta-analysis of data from systematic review

- library (readxl)
- FMD_RV <- read_excel("C:/Metanalysis_Raphael/database_analysis/FMD_RV.xlsx")
- View (FMD_RV)
- Meta_1 <- metacont (t_n, t_mean, t_dp, c_n, c_mean, c_dp, Study, predict = TRUE, data = FMD_RV, sm = "MD")
- Meta_1
- forest (Meta_1, sortvar = Study, xlim = c (-10.0, 10.0), predict = TRUE, col.square = "grey", col.diamond = "black", digits = 2)
- forest (Meta_1, comb.fixed = FALSE, sortvar = Study, xlim = c (-10.0, 10.0), digits.sd = 2, digits.I2 = 2, print.I2 = TRUE, digits.tau2 = 2, digits.pval.Q = 3, squaresize = 0.5, lab.e = "Experimental", lab.c = "Control", col.inside = "black", col.square = "grey", col.diamond = "black", col.predict = "transparent", digits = 2)
- baujat (Meta_1, ylim = c (-1.0, 1.0), xlim = c (-200, 200))
- metaainf (Meta_1, pooled = "random")
- metabias (Meta_1, method.bias = "linreg")
- funnel (meta_Raphael)
(4) outcome assessment, (5) selective reporting, and (6) absolute bias. Based on that, the studies will be classified as low risk of bias (in all domains for this result), some concerns of bias (in at least one domain, but not at high risk of bias in any domain), or high risk of bias (in at least one domain for this result or the study was judged to be at some concerns for several domains in a way that significantly reduces confidence in the outcome). Since it is not possible to blind participants to exercise training interventions, all studies will be classified as high risk of bias in the domain “deviations from intervention.”

Quality of evidence
The strength of the body of evidence will be assessed using the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) tool (www.gradeworkinggroup.org/) [95, 96]. This tool classifies the quality of evidence into four levels (high, moderate, low, and very low) based on the assessment of confidence in specific estimates in five domains: methodological limitations (risk of bias), inconsistency, indirectness of evidence, imprecision, and publication bias.

Statistical analysis
The outcomes of interest are changes in FMD and PWV in response to exercise training compared to the control group. We will calculate the difference (delta) of absolute values between post and pre-training in both the intervention group and the control group. We will use the same procedure to calculate the standard deviations (SDs).

All measures of effect will be presented as mean differences (MDs) between training versus control groups, and their related 95% confidence intervals (95% CIs). If the studies do not have sufficient similarities to warrant a fixed-effects model, the mean differences will be pooled using a random-effects model. Since the 95% CI from random effects refer to uncertainty in the location of the mean of systematically different effects in the studies, we will consider the calculated values for a prediction interval (PI) as they reflect the interval of uncertainty of the effects to be expected in future RCTs [97].

To assess the consistency of training effect among studies, the degree of heterogeneity (relative variability in effect estimates attributed to heterogeneity) will be tested using the Higgins inconsistency test ($I^2$) for every pairwise comparison [98, 99] (Table 2). To explore the heterogeneity ($p<0.05$), we will conduct (observational) subgroup analyses and/or meta-regression (statistics; ≥10 studies) for effect modifiers with normal distribution in a quartile-quartile plot (qq-plot) and confirm it with the Shapiro-Wilk test ($p>0.05$) [100]. In addition, to remove discrepant data from the meta-analysis, forest plots will be constructed to visualize the effect estimate of individual studies and detect outliers based on non-CI overlapping that is due to heterogeneity [100]. If there is significant heterogeneity between studies that cannot be explained, we will not perform a meta-analysis and estimates of intervention effects from the studies selected will be presented individually instead.

Potential effect modifiers, including age, body mass index (BMI), baseline FMD, baseline arterial stiffness indices (intervention and control), and FITT components will be analyzed separately. If applicable (≥ 10 studies), we will perform the Egger’s test using a funnel plot to assess potential publication bias in the meta-analysis.

All statistical tests will be two-tailed and the significance level will be set at $p<0.05$. All measures of dispersion presented as CIs or standard errors will be converted into SDs before the meta-analysis. Alternative analyses to the primary analysis, including a sensitivity analysis, could be performed to determine the robustness of our decisions (i.e., missing value imputation method used, inclusion of studies with high risk of bias, data from conference abstracts and others) [101].

Data modelizations will be performed with RStudio (version 1.3.959) using the R package meta (version 3.6.1) for Windows (https://www.r-project.org/). A RStudio script for conducting the meta-analysis is shown in Table 3.

Discussion and conclusions
Different modalities of exercise training appear to improve or at least do not cause harm to endothelial function in different populations [68, 78, 80, 81]. In contrast, resistance and combined exercise training exert null [69, 83] or even negative effects [70, 76, 77] on different of vascular function parameters especially arterial stiffness. These findings may be associated with strength training variables and heterogeneity of the populations studied [66, 69, 102]. Given that aging is an independent risk factor for CVDs [1, 2, 40], a systematic review may help further understand the changes elicited in vascular structure and function from interventions with different modalities of exercise training in older people.

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Authors’ contributions
R.S.N.S, D.S.S, and G.W were involved in conception and design of the study, data collection, and data analysis plans, as well as drafting the manuscript. G.W and M.I.S were involved in the critical review of the article. M.I.S was involved in writing, drafting, and editing the final document for publication. The authors have read and approved the manuscript.
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