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Research Protocol

The Impact of Exercise Training Interventions on Flow-Mediated Dilation: An Umbrella Review Protocol

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Abstract

Introduction. (Cardio)vascular diseases are among the top causes of death in Western societies. The impact of exercise training interventions to improve endothelial-dependent, flow-mediated dilation (FMD) responses has been reviewed extensively. These reviews may differ in their inclusion criteria, exercise type, exercise mode, exercise intensity, specific research questions, and conclusions. Comparing and contrasting these reviews will assist with the determination of optimal exercise programs across healthy and clinical populations. **Objectives.** We will conduct an umbrella review (or review of reviews) on systematic reviews and meta-analyses that examined the impact of exercise training interventions on peripheral artery FMD. The impact of exercise training design, population or artery studied, FMD methodology, and quality of reviews will be explored. **Methods.** A database search will be conducted in Scopus, Embase, MEDLINE, CINAHL, and Academic Search Premier for systematic reviews and meta-analyses on exercise training and FMD. All reviews must be conducted in adults (≥18 years). No limitation will be placed on the population (disease status, sex, etc.) or type of exercise training. Study quality will be determined using the JBI critical appraisal checklist for systematic reviews. Two independent screeners will examine titles, abstracts, and full texts of relevant sources and conduct the quality assessments. The results will be presented narratively and in a tabular format to align with the review objectives. **Conclusion.** This umbrella review may provide insight into the optimal training program to improve arterial health and act as an agent of change for modifying existing community exercise programs or clinical rehabilitation programs.

Introduction

Peripheral artery diseases are characterized by a narrowing or blockage of peripheral arteries, which impairs blood flow to tissues and drastically increases the risk of experiencing an adverse cardiovascular event (Howell et al., 1989). Dysfunction of the vascular endothelium is an initial stage in the etiology of peripheral artery diseases (Brevetti et al., 2003). Endothelial-dependent vasodilatory function can be non-invasively determined using high-resolution ultrasound via the flow-mediated dilation (FMD) technique. This peripheral arterial assessment quantifies the increase in lumen diameter following a transient hyperemia, induced by a brief period of distal ischemia (Celermajer et al., 1992). A larger relative FMD response (i.e., greater percent increase from baseline) is indicative of a "healthier" artery.

The brachial FMD response is primarily nitric oxide-mediated (Green et al., 2014), strongly correlated to coronary artery function (Broxterman et al., 2019), and predictive of cardiovascular disease risk (Yeboah et al., 2009). Heterogeneous FMD responses exist between upper- and lower-limb arteries (O'Brien et al., 2019; Thijssen et al., 2008), with lower-limb arteries being the most common site of atherosclerosis development (Debasso et al., 2004; Lowry et al., 2018). Lower-limb arteries are directly involved in supplying active tissues when engaging in traditional lower body modes of aerobic exercise (e.g., running and cycling). As such, investigating the impact of these aerobic exercise interventions on endothelial-dependent vasodilation may provide insight into pragmatic strategies for improving cardiovascular health.

Previous systematic reviews and meta-analyses have focused on comparing the impact of resistance versus aerobic exercise programs (Ashor et al., 2015) and moderate-intensity continuous versus high-intensity interval training (Ramos et al., 2015) on vascular function. Furthermore, the impact of exercise training on peripheral artery endothelial function has attracted the interest of numerous researchers and practitioners hoping to improve cardiovascular health through lifestyle behaviours (O'Brien et al., 2020; Rakobowchuk et al., 2008; Sales et al., 2020; Sawyer et al., 2016). Such studies incorporated varied exercise training programs, populations, arteries of interest, and other methodological characteristics (e.g., cuff position or inflation pressure for FMD, inclusion of a control group, etc.). Accordingly, there have been several systematic reviews examining exercise training and endothelial function, which vary in the studies included and provide inconsistent evidence as to whether exercise training augments FMD (Ashor et al., 2015; Early et al., 2017; Ramos et al., 2015) or not (Campbell et al., 2019). Systematic reviews and meta-analyses provide a high level of evidence but conflicting reviews, or multiple reviews on a single topic, make it challenging to discern the true impact of an intervention on health outcomes.

Umbrella reviews (or a review of reviews) summarize, compare, and contrast existing systematic reviews and meta-analyses (Fusar-Poli & Radua, 2018). Umbrella reviews are among the highest level of evidence synthesis (Aromataris et al., 2015). There is variability in how exercise training interventions are implemented (frequency, intensity, type, time; Marriott et al., 2021), populations of interest, and how/where FMD was conducted (Thijssen et al., 2019). Given this, along with the inconsistent findings among previous reviews (Ashor et al., 2015; Campbell et al., 2019; Early et al., 2017; Ramos et al., 2015), an overview of existing reviews and meta-analyses could provide high-level evidence into the impact of exercise on endothelial function. This may confirm that there is not a "one size fits all" approach for every population, artery, and/or exercise training intervention.

Research Question

By performing an umbrella review of existing systematic reviews and meta-analyses on the topic, we will answer the following question: What is the impact of exercise training on FMD? We will explore whether differences exist between the training characteristics, population of interest, arteries of interest, individual review inclusion/exclusion criteria, and study quality of the reviews.

Methods

Inclusion and Exclusion Criteria

Population

Only review studies examining adults (all participants' age: ≥18 years) or results presented separately for adults-only will be included. No restriction will be placed on participants' health status.

Intervention

Any exercise training intervention. No restriction in the length, type, or frequency of the exercise training was implemented. As the focus is on exercise training, reviews on the acute response to exercise (single session) will be excluded. No restriction will be placed on study design (e.g., not exclusive to reviews of randomized controlled trials only), the date of publication, or the language of publication (i.e., non-English). If needed, a language interpreter will be utilized to translate the publication to English. Conducting a meta-analysis is not a requirement of inclusion but will be extracted if presented.

Comparator

No comparator is required. Systematic reviews that examine single interventions without or with a comparator group (e.g., non-exercise controls, usual care, other exercise intervention, etc.) will be included.

Outcome

Systematic reviews that do not utilize FMD as an outcome variable will be excluded. We will include reviews regardless of the artery investigated but will explore the potential impact of artery location on FMD outcomes in response to exercise training.

Study Design

To be included, studies must conduct a systematic review and/or meta-analysis on the impact of exercise training on FMD. Studies published as editorials, opinions, non-systematic reviews (e.g., narrative review, scoping reviews, integrative reviews, rapid reviews), or conference abstracts will be excluded.

Search Strategy

The proposed review will be conducted in accordance with the JBI methodology for umbrella reviews (Aromataris et al., 2020). The search strategy was developed in conjunction with authors who have previous experience conducting exercise training interventions and the FMD technique (Bray et al., 2020; O'Brien et al., 2018, 2019, 2020). The specific search terms are presented in Appendix A along with an example search strategy developed for PubMed (MEDLINE). Database searches will be conducted from inception using Scopus (Elsevier), Embase (Elsevier), PubMed (MEDLINE), CINAHL (EBSCO), and Academic Search Premier (EBSCO) databases. PROSPERO, the JBI Systematic Review Register, and the Cochrane Database of Systemic Reviews were searched in February of 2022 to ensure no other researchers were conducting a study of a similar nature.

Study Screening Process

Following the literature search, article citations will be downloaded to an online research management system (Mendeley) and duplicates removed. Remaining references will be exported to systematic review software for screening (Covidence). The titles and abstracts of citations will be separately screened by two reviewers who will identify potential articles for inclusion. The full text of apparently relevant articles will be obtained and screened by the same two reviewers. If a consensus cannot be reached between the two reviewers regarding inclusion, a third reviewer will serve as the arbiter. The reference lists of included articles will be hand-searched for potentially relevant articles.

Study Quality Assessment

The quality of each included review will be assessed via the JBI critical appraisal tool for evaluating systematic reviews (Aromataris et al., 2015). The tool was developed by the JBI umbrella review methodology working group, and scores each question as met, not met, unclear, or not applicable (Aromataris et al., 2015). The specific 10 questions are presented in Appendix B. Identical to the article screening process, quality assessment will be independently completed by two reviewers. For inconsistencies regarding their quality assessment decisions, a senior third reviewer will be consulted to make a final decision. Reviews will not be excluded based on their quality (out of 10).

Data Extraction

For included reviews, the characteristics of the studies/participants included, as well as the exercise training characteristics, FMD protocols/measures, and meta-analysis results will be extracted. A data extraction template that includes each of the specific variables of interest is provided in Appendix C. All data extraction will be separately conducted by two reviewers using the Data Extraction option in Covidence. The data extraction tool will be piloted on three studies by two reviewers and may be modified, depending on whether additional relevant information is gained from this pilot. Any changes or additional variables extracted will be described in the dissemination of results. If required, authors will be contacted for additional information. Data may be extracted from figures using WebPlotDigitizer (V.3, 2020; Available from https://automeris.io/WebPlotDigitizer), which has demonstrated strong validity (Drevon et al., 2017). All meta-analyses outcomes may use unique effect size metrics but will be converted into a Cohen's d effect size and standardized mean differences (Fusar-Poli & Radua, 2018).

Data Analysis and Preparation

A reporting guideline is currently in development for umbrella reviews, but is not yet released (Preferred Reporting Items for Overviews of Reviews [PRIOR]; Pollock et al., 2019). If the PRIOR guideline is released before completion of the present study, it will be followed. If not, we will follow the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement (Page et al., 2021) and the PRISMA literature search extension (PRISMA-S; Rethlefsen et al., 2021). A sensitivity analysis will be conducted on systematic reviews that exhibit higher study quality versus lower study quality (based on median split). Secondary outcomes include exploring results across exercise training principles (frequency, intensity, type, time, volume, progression), participant health status, sex, race, artery examined, unique inclusion/exclusion criteria, quality of studies included in each review, and inclusion of a meta-analysis.

Given that a 1% absolute increase in relative brachial artery FMD is associated with a ~13% relative risk reduction in experiencing an adverse cardiovascular event (Inaba et al., 2010), a 1% standardized mean difference will be considered clinically significant a priori for studies examining the brachial artery. Such thresholds do not exist for relative FMD changes in other arteries (e.g., popliteal, radial, etc.), and therefore will be based on thresholds of Cohen's d, with very small = <0.2, small = 0.2–0.5, medium = 0.5–0.8, and large = >0.8 (Cohen, 1992). Cohen's d will still be determined for brachial FMD.

The screening results will be presented visually via a PRISMA flow diagram with reasons presented for full-text exclusions. Our primary results will be presented in tables and potentially summarized using a graphic figure and/or infographic of main findings.

Potential Implications

The information gained from the umbrella review may provide insight into the optimal exercise training program for endothelial function and, consequently, into the improvement of cardiovascular health. As with all umbrella reviews, our study can only report on what researchers have systematically reviewed and/or meta-analyzed. There may be instances when a potentially impactful factor could influence results (e.g., biological sex), but if few studies have evaluated that factor, the level of evidence the umbrella review can provide on this potentially impactful variable is limited. Amalgamating systematic reviews will provide a current description of what is known regarding the impact of exercise training on endothelial function assessed using FMD, which may provide insight into future areas of investigation to advance our knowledge on therapeutic approaches to improving cardiovascular health. For example, findings may be applied to the design of community exercise programs and/or prompt changes to existing programs (e.g., cardiac rehabilitation) to enhance cardiovascular function in prevention, pre-habilitation, and rehabilitation settings.

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Appendix A

Search Strategy and Example Search Results

Search	Terms	Results
1.	"Aerobic"[All Fields] OR "Resistance"[All Fields] OR "Resistance Intervention"[All Fields] OR "Strength training"[All Fields] OR "Physical exercise"[All Fields] OR "High-intensity exercise"[All Fields] OR "Exercise training"[All Fields] OR "Aerobic training"[All Fields] OR "Physical activity training"[All Fields] OR "Yoga"[All Fields] OR "Tai-Chi"[All Fields] OR "Flexibility Training"[All Fields] OR "Balance Training"[All Fields] OR "Weightlifting"[All Fields] OR "Vigorous Exercise"[All Fields]	1,114,620
2.	("Flow-mediated dilation"[All Fields] OR "Endothelial function"[All Fields] OR "FMD"[All Fields] OR "Endothelial-dependent dilation"[All Fields] OR "Shear-mediated dilation"[All Fields]) NOT "Cerebral"[All Fields]	25,328
3.	"Review"[All Fields] OR "Meta-analysis"[All Fields]	3,779,350
4.	1 AND 2 AND 3	730

Note. The search strategy will be adapted for each database as needed. A test of this search strategy on February 2, 2022, yielded 730 results using PubMed only, indicating a reasonable number of citations to screen using this database.

Appendix B

JBI Critical Appraisal Tool for Evaluating Systematic Reviews

1. Is the review question clearly and explicitly stated?
2. Were the inclusion criteria appropriate for the review question?
3. Was the search strategy appropriate?
4. Were the sources and resources used to search for studies adequate?
5. Were the criteria for appraising studies appropriate?
6. Was critical appraisal conducted by two or more reviewers independently?
7. Were the methods used to combine studies appropriate?
8. Was the likelihood of publication bias assessed?
9. Were recommendations for policy and/or practice supported by the reported data?
10. Were the specific directive for new research appropriate?

Appendix C

Data Extraction Template

Variable
General Characteristics
Author Last Name & Year
Title
Country
Number of Databases Searched
Date Searched and Date Range
Number of Studies Included
Names of Each Study Included in Review
Number of Participants (Males/Females)
Population of Interest
Inclusion/Exclusion Criteria
Pre-registered Review (Yes/No)
Author Funding
Review Study General Exercise Training Characteristics
Frequency
Intensity
Type
Time
Volume
Progression
Ultrasound Measures
Artery of Interest
General Relative FMD Outcomes (if no meta-analyses)
General Absolute FMD Outcomes (if no meta-analyses)
General Normalized FMD Outcomes (if no meta-analyses)
General Baseline Diameter Outcomes (if no meta-analyses)
FMD protocol (if provided)
Study Quality Tool
Average Study Quality
Key Systematic Review Findings
Meta-Analyses
FMD Results (with units of effect size)
Normalized FMD Results (with units of effect size)
Baseline Artery Diameter Results (with units of effect size)
Comparator (e.g., control group, moderate intensity training)
Heterogeneity
Potential Biases (e.g., funnel plot)
Sensitivity Analyses

Note. FMD: flow-mediated dilation.