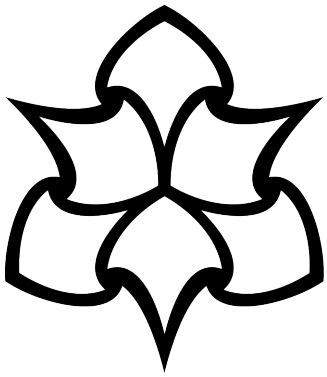


Manchester Metropolitan University

Peçanha, T, Bannell, DJ, Sieczkowska, SM, Goodson, N, Roschel, H, Sprung, VS and Low, DA (2021) Effects of physical activity on vascular function in autoimmune rheumatic diseases: A systematic review and meta-analysis. Rheumatology, 60 (7). pp. 3107-3120. ISSN 1462-0324

Downloaded from: https://e-space.mmu.ac.uk/629957/

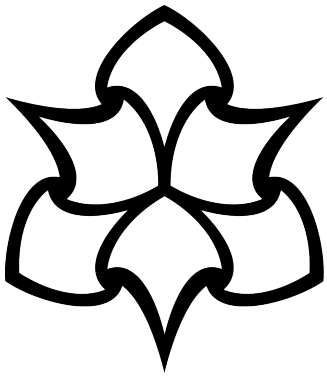
Version: Accepted Version

Publisher: Oxford University Press (OUP)

DOI: https://doi.org/10.1093/rheumatology/keab094

Please cite the published version

https://e-space.mmu.ac.uk



Manchester Metropolitan University

Peçanha, Tiago, Bannell, Daniel J, Sieczkowska, Sofia Mendes, Goodson, Nicola, Roschel, Hamilton, Sprung, Victoria S and Low, David A (2021) Effects of physical activity on vascular function in autoimmune rheumatic diseases: a systematic review and meta-analysis. Rheumatology (Oxford), 60 (7). pp. 3107-3120.

Downloaded from: https://e-space.mmu.ac.uk/629957/

Version: ["content_typename_Accepted version" not defined]

DOI: https://doi.org/10.1093/rheumatology/keab094

Please cite the published version

https://e-space.mmu.ac.uk

OXFORD UNIVERSITY PRESS | Rheumatology

EFFECTS OF PHYSICAL ACTIVITY ON VASCULAR FUNCTION IN AUTOIMMUNE RHEUMATIC DISEASES: A SYSTEMATIC REVIEW AND META-ANALYSIS

Journal:	*Rheumatology*
Manuscript ID	RHE-20-2874.R1
Manuscript Type:	Systematic Review and Meta Analysis
Date Submitted by the Author:	n/a
Complete List of Authors:	Peçanha, Tiago; University of Sao Paulo, Applied Physiology and Nutrition Research Group, School of Physical Education and Sport and Laboratory of Assessment and Conditioning in Rheumatology, Hospital das Clínicas HCFMUSP, Faculdade de Medicina FMUSP. Bannell, Daniel; Liverpool John Moores University, Research Institute for Sport and Exercise Sciences Sieczkowska, Sofia Mendes; University of Sao Paulo, Applied Physiology and Nutrition Research Group, School of Physical Education and Sport and Laboratory of Assessment and Conditioning in Rheumatology, Hospital das Clínicas HCFMUSP, Faculdade de Medicina FMUSP. Goodson, Nicola; University of Liverpool, Academic Rheumatology, Musculoskeletal Biology, Institute of Chronic Disease and Ageing Roschel, Hamilton; University of Sao Paulo, Applied Physiology and Nutrition Research Group, School of Physical Education and Sport and Laboratory of Assessment and Conditioning in Rheumatology, Hospital das Clínicas HCFMUSP, Faculdade de Medicina FMUSP. Sprung, Victoria S. ; Liverpool John Moores University, Research Institute for Sport and Exercise Sciences Low, David; Liverpool John Moores University, Research Institute for Sport and Exercise Sciences
Keywords Please select a minimum FIVE keywords from the list provided. These keywords will be used to select reviewers for this manuscript. The keywords in the main text of your paper do not need to match these words.:	Rheumatoid arthritis < RHEUMATIC DISEASES, Spondylarthropathies (including psoriatic arthritis) < RHEUMATIC DISEASES, Systematic lupus erythematosus and autoimmunity < RHEUMATIC DISEASES, Cardiovascular < TISSUES, Clinical trials and methods < BASIC & CLINICAL SCIENCES, Inflammation < BASIC & CLINICAL SCIENCES, Rehabilitation < THERAPIES

SCHOLARONE™
Manuscripts

EFFECTS OF PHYSICAL ACTIVITY ON VASCULAR FUNCTION IN AUTOIMMUNE RHEUMATIC DISEASES: A SYSTEMATIC REVIEW AND META-ANALYSIS

Tiago Peçanha[1], Daniel Bannell[2], Sofia Mendes Sieczkowska[1], Nicola Goodson[3], Hamilton Roschel[1], Victoria S. Sprung[2], David A. Low[2]

Affiliations:

[1] Applied Physiology and Nutrition Research Group, School of Physical Education and Sport and Laboratory of Assessment and Conditioning in Rheumatology, Hospital das Clínicas HCFMUSP, Faculdade de Medicina FMUSP, Universidade de Sao Paulo, SP, BR.

[2] Research Institute for Sport and Exercise Sciences, Liverpool John Moores University, Liverpool, UK.

[3] Liverpool University Hospitals NHS Foundation Trust, Aintree University Hospital, Liverpool, UK

Corresponding author and address for reprints:

Dr Tiago Peçanha. Tiago Peçanha. Applied Physiology and Nutrition Research Group, School of Physical Education and Sport, Rheumatology Division, Faculty of Medicine FMUSP, University of São Paulo, Av. Dr. Arnaldo, 455-Cerqueira César, São Paulo, Brazil. Zipcode: 01246-903. Phone/Fax: + 55 11 30618789. E-mail address: pecanhatiago@gmail.com

E-mail: tiagopecanha@usp.br

Key words: physical activity, vascular function, autoimmune, rheumatoid arthiritis, meta-analysis

Word count: 4361

For Peer Review

ABSTRACT:

Objectives: To summarise existing evidence and quantify the effects of physical activity on vascular function and structure in autoimmune rheumatic diseases (ARDs). **Methods:** Databases were searched (up to March 2020) for clinical trials evaluating the effects of physical activity interventions on markers of micro- and macrovascular function and macrovascular structure in ARDs. Studies were combined using random-effects meta-analysis, which was conducted using the Hedge's g. Meta-analyses were performed on each of the following outcomes: (1) microvascular function (i.e., skin blood flow or responses to acetylcholine [ACh] or sodium nitropusside [SNP] administration); (2) macrovascular function (i.e., brachial flow-mediated dilation [FMD%] or brachial responses to glyceryl trinitrate [GTN%]; and (3) macrovascular structure (i.e., aortic pulse wave velocity [PWV]). **Results:** Ten studies (11 trials), with a total of 355 participants, were included in this review. Physical activity promoted significant improvements in micro- (skin blood flow responses to ACh [g = 0.92; 0.42 to 1.42]) and macrovascular function (FMD% [g = 0.94; 0.56 to 1.02]; GTN% [g = 0.53; 0.09 to 0.98]). Conversely, there was no evidence for beneficial effects of physical activity on macrovascular structure (PWV [g = -0.41; -1.13 to 0.32]). **Conclusions:** Overall, the available clinical trials demonstrated a beneficial effect of physical activity on markers of micro- and macrovascular function, but not on macrovascular structure, in patients with ARDs. The broad beneficial impact of physical activity across the vasculature identified in this review support its role as an effective non-pharmacological management strategy for patients with ARD.

Keywords: flow-mediated dilation, skin blood flow, rheumatoid arthritis, inflammatory diseases

Key messages:

- Changes in vascular homeostasis are integral to the cardiovascular pathophysiology in autoimmune rheumatic diseases (ARDs);
- This review demonstrates the benefits of physical activity on micro- and macrovascular function in ARDs;
- The available evidence supports the role of physical activity as vascular medicine for ARDs.

For Peer Review

INTRODUCTION

Autoimmune rheumatic diseases (ARDs) are a group of diseases caused by immune dysregulation and characterised by local and chronic inflammation, deterioration of joint tissues, systemic manifestations and increased multimorbidity leading to reduced life expectancy (1). ARDs include conditions such as systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), Sjögren's syndrome (SJ), systemic sclerosis (SSc), spondyloarthritis (SpA; which includes psoriatic arthritis [PsA] and ankylosing spondylitis [AS]), systemic autoimmune myopathies (SAM) and systemic vasculitis (SV). Collectively, these diseases affect over 7% of the World's population (2), and usually appear in mid-life, mostly in women (~ 78 vs. 22%) (3).

Cardiovascular disease (CVD) represents the leading cause of mortality in many ARDs (4, 5). For instance, patients with RA present a 2-fold increased risk of myocardial infarction (6) when compared with healthy individuals (7). Similar estimates have been reported in patients with SLE (5), PsA (8) and SSc (9). The increased cardiovascular burden in ARDs is partly attributed to the presence of traditional cardiovascular risk factors (e.g., hypertension, insulin resistance) (10) but, importantly, also by the direct effects of inflammation upon the vasculature (11-13), leading to changes in vascular properties that precede the development of atherosclerosis (11).

ARD patients present with accelerated atherosclerosis and have a more unstable plaque profile, with increased prevalence of rupture-prone plaques (14, 15). The endothelium plays a major role in the regulation of vascular wall homeostasis (16) and endothelial dysfunction in the micro- and macrocirculations is regarded as an early marker for atherosclerosis in many disease states, including ARDs (11, 12, 17). This pathophysiological condition is associated with increased expression of adhesion molecules, increased vascular permeability to lipoproteins and increased oxidative stress. This process is aggravated by systemic and vascular inflammation, hallmarks of many ARDs, which interacts with intracellular regulatory processes promoting smooth muscle cell proliferation and arterial wall thickening (11). These maladaptive vascular processes are paralleled by impairment in the elastic properties of large arteries, with increase in stiffness in the central arteries (18). Consequently, measures of micro- and macrovascular endothelial function and macrovascular structure have been used as surrogate markers of cardiovascular risk in individuals with ARDs (19).

Changes in vascular function and structure play a central role in the pathophysiology of CVDs in ARDs and underscore the importance of therapeutics that can beneficially affect vascular

For Peer Review

health in ARDs. Physical activity (PA) has been recognised for some time as an important non-pharmacological therapeutic with beneficial effects on vascular function and structure (20). In ARDs, PA has been linked with reduced disease activity (21), inflammation (22) and pain (23), and with improved cardiovascular risk profile (21, 24). Specific to the vasculature, cross-sectional studies have demonstrated improved vascular function in physically active compared with physically inactive ARD patients (25, 26). However, available clinical trials examining the effects of PA on vascular health in ARDs have elicited equivocal findings (27-29), which may be partially explained by small sample sizes and thus reduced statistical power. Additionally, the effects of PA on the vasculature may vary according to the vascular bed, with previous evidence demonstrating that physical activity may differentially impact the micro- and macrovasculature (30, 31), as well as vascular function and structure (32, 33). Finally, the magnitude of the improvement on vascular parameters promoted by PA in ARDs remains unclear. As even slight improvements in markers of endothelial function are associated with substantial reduction in the risk of cardiovascular events (34, 35), a better understanding of the effects of PA on vascular function and structure in ARDs may yield important clinical information to be used in the management of CVD in ARDs.

Resultantly, we conducted this systematic review and meta-analysis to summarise the existing evidence and to quantify the effects of PA on micro- and macrovascular function and macrovascular structure in ARDs. As a secondary outcome, we have also described the characteristics of existing PA programmes for this population and reviewed data on adherence to PA, and potential side effects.

METHODS

Registration

This systematic review with meta-analysis was reported according to the PRISMA statement and is registered in the PROSPERO database (CRD42020196023).

Search strategy and study selection

Searches were performed on 5 databases (PubMed, Web of Science, EMBASE, Cochrane Library and Scopus) by entering key words related to population, intervention and outcome (Supplementary Table S1). Searches were limited to peer-reviewed articles in English, published from the inception of each database up until March 2020.

For Peer Review

For inclusion, studies were required to fulfill the following criteria: (1) randomised controlled trials (RCTs), non-RCTs or uncontrolled trials (UCT; pre vs. post only) with an experimental condition that included a PA intervention; (2) interventions should have lasted ≥2 weeks, and should have been performed ≥1x week; (3) conducted on adults (≥18 years) with a diagnosis of SLE, RA, SpA, SJ, SSc, AS, SAM or SV; (4) included assessments of at least 1 of the following; brachial or lower-limb flow-mediated dilation (FMD%), or brachial responses to glyceryl trinitrate (GTN%), pulse wave velocity (PWV), cutaneous blood flow reactivity to pharmacologic, mechanical or local heat stimuli. Studies were excluded if they were protocol studies, observational studies, acute exercise studies, studies with physiotherapy interventions (e.g., joint manipulation, kinesio taping) or studies involving pediatric rheumatic diseases.

On completion of the searches, 2 members of the study team (TP and DL) independently selected the studies to be included based on the title, abstract and full text of each potential manuscript. Discrepancies were identified and solved through discussion with a third author (TS).

Data extraction

Two members of the study team (TP and SMS) independently extracted study data using a purpose developed data extraction sheet, after which a mutual consensus was reached. Discrepancies were identified and solved through discussion. Missing data were requested by contacting the corresponding authors of specific studies. The following characteristics were extracted from each selected study: (1) author (data); (2) study design; (3) participant information; (4) characteristics of the intervention; (5) outcome data.

Assessment of the risk of bias

Quality was appraised using the Cochrane risk-of-bias tool (RoB-2) (36), by two members of the study team (DB and TP). This tool considers bias arising from 5 domain (randomization process, deviations from the intended interventions, missing outcomes, measurement of the outcome and selection of reported results) and an overall bias analysis. The risk of bias of each domain and the overall risk were judged as “high”, “low” or “some concerns”. All studies were analysed with this tool, even non-RCTs and UCTs, assuming that they would already be at high risk due to their design.

For Peer Review

Data analysis: Systematic Review

A narrative synthesis was performed to describe the data from the studies. Studies were described in the text and tables and were organized by key details, such as study design, summary of the population, intervention, comparison, and outcomes (divided by micro- and macrovascular function, and macrovascular structure). In addition, we reported data on participants' adherence to the interventions (i.e., the degree of compliance to the exercise sessions), and on the safety of the interventions (i.e., the occurrence of any health-related complications as a result of the intervention, such as disease relapses, acute flare-ups, cardiovascular complications, *etc*).

Data analysis: Meta-Analysis

Following data extraction, weighting, and missing data imputation, a meta-analysis was performed on each of the following outcomes: (1) microvascular function (i.e., skin blood flow or vascular conductance responses to acetylcholine [ACh] or sodium nitropusside [SNP] administration); (2) macrovascular function (i.e., FMD% or GTN%); (3) macrovascular structure (i.e., PWV). The UCTs were not included in the meta-analyses, but were qualitatively described along with the manuscript.

The effects of PA interventions on each vascular outcome were calculated as the standardized mean differences (SMD). The SMDs were estimated as the difference between the intervention and control group pre-post changes, divided by the pooled standard deviation for the changes. For microvascular function, we only used the post values due to the lack of available data to calculate pre-to-post changes. Studies were combined using random-effects meta-analysis, which was conducted using the Hedge's g (37). Cohens standard threshold values of 0.2, 0.5, 0.8 were used to describe effect sizes (based on the SMDs) as small, moderate and large, with values between 0 and 0.2 described as trivial (38). In addition, in order to infer the clinical relevance of PA on FMD%, we also calculated the absolute changes in FMD% as the mean difference (MD) between the intervention and control groups pre-post changes. To estimate the between-study variance we used restricted maximum-likelihood estimator (39). Meta-analyses were performed in RStudio version 4.02, with the 'metacont' function of the meta package.

RESULTS

Literature search

For Peer Review

A total of 577 published articles were identified through independent searches in all the five databases. Following removal of duplicates (*n*=237), 340 publications were screened for inclusion. Of these, 322 records were excluded after reviewing the title and/or abstract. The remaining 18 papers were selected for full text reading and 8 were excluded for either not presenting any vascular outcome (*n*=7) or by not including PA as a major component of the intervention (*n*=1). Ultimately, 10 studies (11 trials) were included in the review and are listed in the qualitative analysis. Among these, 8 studies (9 trials) were suitable for inclusion in the meta-analysis, however we were unable to obtain relevant data from 2 studies (40, 41) (i.e., data were presented as median ± interquartile interval, and authors did not respond to emails soliciting original data or did not provide the required data). Therefore, 6 studies (7 trials) were included in the meta-analysis (Figure 1).

A general description of each study is detailed in Table 1. Among the 10 included studies, 3 were RCTs, 5 were non-RCTs and 2 were UCTs. These studies enrolled 355 middle-aged to older participants, with a large majority of women (88% *vs*. 12%). The included studies were conducted in participants with limited cutaneous SSc (lcSSC), axial SpA, SLE, RA and SAM.

Risk of bias

Nine studies presented a 'high risk' of bias and one study presented 'some concerns' considering the overall judgement (Figure 2A). Most of the methodological issues arose from the 'randomisation process' (7 out of 10 were not RCTs) or from 'bias due to deviation from intended interventions' (with most of the studies using 'per-protocol' analyses and/or presenting >5% drop out rates). The remaining domains were judged with 'some concerns' or 'low risk of bias' (Figure 2B).

Characteristics of the physical activity/exercise interventions

Most PA interventions lasted between 12-16 weeks and sessions were performed 2-3 days/week for 30-80 min/session (Table 1). All studies included a structured exercise programme and one study also employed a web- and pedometer-based PA programme (42). Exercise workouts comprised a mix of exercise types including high-intensity interval training (HIIT), moderate-intensity interval training (MIIT), moderate-intensity continuous training (MICT), resistance training (RT) and Tai-Chi. Aerobic exercise modalities included arm cranking, cycling, rowing,

For Peer Review

swimming, and walking/running on a treadmill or in a public park. Aerobic exercise intensities ranged from low- (e.g., 35-60% of heart rate reserve) to high-intensity (e.g., 100% of maximal power output). RT sessions were composed of 4-10 whole-body exercises at 50-80% of 1 repetition maximum (Table 1). Interventions were either fully (6 out of 10) or partially (4 out of 10) supervised, and were conducted in different settings such as a hospital gyms (27, 40, 43-45), fitness/exercise centres (28, 29, 41), at home (40, 45), or in public gyms (42) or parks (46).

Effects of physical activity on vascular function

Microvascular function

Microvascular function was assessed in 4 studies (5 trials) via the evaluation of the responses of forearm skin blood flow or vascular conductance to ACh (endothelium-dependent) or SNP (endothelium-independent) iontophoresis (Table 1). Metsios *et al.* (40) reported increases in the skin blood flow response to ACh and SNP after 24 weeks of combined MIIT and RT in RA patients. In this same population, 12 weeks of MIIT promoted an increase in skin blood flow responses to SNP, but not to ACh (45). In patients with lcSSc, Mitropoulos et al (29) reported increased maximal forearm cutaneous vascular conductance in response to ACh after 12 weeks of upper-limb HIIT, however no benefits were observed after lower limb HIIT. Neither upper- or lower-limb training were able to improve microvascular responses to SNP. A latter study from the same group (28) observed that 12 weeks of combined HIIT and RT increased maximal forearm cutaneous vascular conductance in response to SNP, but not to ACh (Supplementary Table S2).

Overall, the meta-analysis revealed a large significant improvement in microvascular function responses to ACh in the PA group compared with the control group (Figure 3; [g=0.92; IC95%, 0.42 to 1.42]). On the other hand, no significant differences were found between PA and control groups in the microvascular responses to SNP (Figure 3; [g=1.62; IC95%, -0.27 to 3.51]).

Macrovascular function

Macrovascular function was assessed in 5 studies (5 trials) through the evaluation of FMD% (endothelium-dependent) and in 3 studies (3 trials) using the GTN% (endothelium independent) (Table 1). Van Zanten *et al*. (45) and Metsios *et al.* (40) reported increases in both FMD% and GTN% after 12 weeks of MIIT and 24 weeks of combined MIIT and RT, respectively, in RA patients. A study employing 1 day/week of Tai-Chi for 12 weeks also verified an increase

For Peer Review

in FMD% in RA patients (44). Reis-Neto (46) observed increase in FMD% and no changes in GTN% after 16 weeks of moderate-intensity walking in a public park in patients with SLE. On the other hand, Misse *et al*. (43) did not observe increase in FMD% after 12 weeks of combined aerobic and RT in patients with SAM (Supplementary Table S2).

Overall, the meta-analysis revealed a large significant increase in FMD% (Figure 4 [g = 0.94; IC95%, 0.56 to 1.32]) and a moderate increase in GTN% (Figure 4 [g = 0.53; IC95%, 0.09 to 0.98]) favoring the intervention group. On average, FMD% increased 5.07% after the PA interventions (1.26 to 8.88) (Supplementary Figure S1).

Macrovascular structure

Macrovascular structure was assessed in 5 studies (5 trials) via the quantification of arterial stiffness by carotid-femoral PWV (cfPWV), aortic PWV, and augmentation index (AIx). Additionally, one study also included the assessment of carotid intima-media thickness (cIMT) as a measure of macrovascular structure (Table 1). The majority of studies (3 out of 5) did not observe changes in any marker of macrovascular structure following completion of a PA intervention in ARDs (27, 42, 43). On the other hand, Sveaas *et al*. (41) reported a decrease in arterial stiffness (AIx and cfPWV) after 12 weeks of combined HIIT or MICT and RT in patients with axial SpA, and Shin *et al*. (44) reported a reduction in cfPWV after 12 weeks of Tai-Chi in RA patients (Supplementary Table S2).

Overall, the meta-analysis revealed no significant effects of PA on PWV (Figure 5 [g = -0.41; IC95%, -1.13 to 0.32]).

Adherence and safety

Adherence to the PA sessions was >85% in 4 studies (27, 29, 40, 43). Sveeas *et al.* (41) reported that all participants in the intervention group attended the minimum requirement of ≥80% of the sessions, and Reis-Neto (46) did not report exclusion of any participants based on the minimum allowed attendance which was set at 75% of the PA sessions. Four studies did not report data on adherence to the PA interventions (28, 42, 44, 45).

Five studies reported no adverse effects related to the PA interventions (27-29, 41, 43). In one study (40), one participant was discontinued from the intervention due to arrhythmia, but it is

For Peer Review

not clear if this was related to the intervention. Four studies did not report data on the safety of the PA interventions (42, 44-46).

Group mean disease activity measured using disease-specific tools was reported to be unchanged by the PA intervention in 4 studies (42, 44-46) and to be reduced in 2 (40, 41). Individual data on disease activity was reported by two studies only (41, 43). In one of them (41), 2 participants (out of 10) had a slight increase in their disease activity, while the others either decreased or did not change their disease activity. Four studies did not report data on the effects of the interventions on disease activity (27-29).

DISCUSSION

Our systematic review and meta-analysis summarised the evidence on the effectiveness of PA on vascular function and structure in ARDs. Although limited by the reduced number and low quality of the studies, data reviewed herein demonstrated a beneficial effect of PA on micro- and macrovascular function in ARDs. However, results from available studies observed no effect of PA on macrovascular structure. Furthermore, where this is reported, evidence suggests that PA is safe and well adhered by individuals with ARDs.

The results of the present review support the notion that PA may counter vascular impairment observed in ARDs (17, 47). More specifically, PA interventions were effective in improving micro- and macrovascular function, with clearer and larger effects observed on endothelium-dependent (FMD% and skin blood flow responses to Ach) as opposed to endothelium-independent (GTN% and skin blood flow responses to SNP) function. This information corroborates previous studies demonstrating that vascular adaptations promoted by PA are largely mediated by its direct effects on the endothelium rather than on smooth muscle vasodilator function (48, 49). Beneficial effects of PA on the endothelium are a consequence of repeated hemodynamic stimulation (e.g., shear stress and transmural pressure), which favors the production of nitric oxide and vascular relaxation (20). As for the clinical impact of these findings, PA yielded a ~5% increase in FMD% (Figure S1), which may be seen as clinically relevant, as there is an associated reduction in 12-13% in the risk of cardiovascular events for every 1% increase in FMD% (34, 35). Additionally, previous reviews indicated that patients with ARDs present 1-3% reduced FMD% compared to controls (17, 47); therefore, the present review indicates that PA may reverse the endothelial dysfunction observed in these patients.

For Peer Review

The improvements in both macro- and microvascular endothelial function highlight the broad effects of PA across the vasculature in this population. These data prove relevant, as a recent study identified that changes in macrovascular and microvascular function may occur at different stages in the progression of CVD in ARDs, and reflect different and complementary aspects of vascular pathology (12). For instance, in an experimental model of adjuvant-induced arthritis, endothelial dysfunction in mesenteric arteries (i.e., microvasculature) occurred earlier than dysfunction in the aorta (i.e., macrovasculature) along the course of the disease. Moreover, microvascular dysfunction persisted even in the late stage of the disease, while macrovascular dysfunction returned to pre-disease values when inflammation was resolved (50). Data from cohort studies further support the different prognostic information provided by markers of micro- and macrovascular function, as the former seems to be a more powerful predictor of cardiovascular events in subjects without pre-existing cardiovascular conditions (51, 52), while the latter seems to be more important in subjects with existing CVD (35). Therefore, PA may beneficially affect ARD patients with different vascular phenotypes, in different stages of the cardiovascular continuum and along the course of the diseases.

The results of this review do not support the hypothesis that PA promotes positive changes in vascular structure in ARDs. Notwithstanding the reduced number of studies, the absence of any clear effects of PA on vascular structure may be explained by the small duration of most of the studies' interventions (~12 weeks). Changes in vascular function and structure in response to PA often follow a distinct time-course, with improvements in function preceding structural remodeling (20, 32). Therefore, it is likely that longer interventions (>16 weeks) might have elicited more consistent effects on vascular structure, as reviewed elsewhere (53). It is also possible that persistent inflammation may cause profound changes in vascular structure (*e.g.,* collagen and cholesterol deposition, fibrosis, plaque formation) that may be less prone to be reversed by PA (54). Finally, PA alone may also be a 'weak' intervention to produce consistent changes in vascular structure. In this respect, previous evidence suggests that multicomponent interventions (e.g., PA, low-fat diet, smoking cessation and lipid-lowering drugs) with intensive control of cardiovascular risk factors may be the most effective strategy to produce consistent vascular remodeling in clinical populations (55, 56), which may also hold true for ARDs.

Studies included in the present review employed different protocols of PA. Five studies (28, 40-43) used a combination of aerobic training with RT, which is in compliance with public

For Peer Review

health recommendations for PA in ARDs (57). Exercise intensity ranged from moderate to very intense, which reveals the feasibility of more intense exercise interventions for this population, diverging from the previous notion that intense PA could be detrimental to ARDs (58). In fact, 3 studies (28, 29, 41) employed HIIT, which has only in the last two decades been recognised as a form of therapeutic exercise for clinical populations (59). Two studies (28, 41) also employed high-intensity dynamic RT, which has been recently advocated as a means to counteract functional decline in elderly and in population with chronic diseases, including ARDs (60). More importantly, the studies included in the review reported no serious adverse effects related to all these interventions, suggesting that PA is safe across a broad range of exercise types, modalities and intensities in ARDs. This information supports previous findings from studies addressing the safety of PA to ARDs (61, 62).

Data on adherence is also encouraging as it was reported to be above 75% across all studies that reported this variable, which is in agreement with previous studies specifically designed to assess adherence to PA interventions in ARDs (63, 64). However, it must be highlighted that most interventions included in this review were fully supervised and conducted in specialised exercise facilities (e.g., hospital gym and fitness centres). While intense monitoring by health professionals may be the most effective way to encourage adherence, it does not represent the real-world exercise setting for most of these patients. Interestingly, 2 studies (40, 45) employed a mixed monitoring approach with two supervised centre-based PA sessions and one unsupervised home-based session, also reporting good adherence (88% (24)) and benefits on vascular function. Future studies should examine the feasibility and effectiveness of even less controlled interventions (e.g., full time home-based PA, web-based or mHealth PA programmes), with the intent to subside public health initiatives that may be directly applied to this population.

Risk of bias

The generalisability of the present review findings are limited by the quality of the studies composing the review. In this regard, it should be noted that only 3 studies were RCTs, and one of them (29) did not provide specific information about the randomisation process. Another aspect that affected the overall risk of bias is the inherent difficulty to blind the participants and those delivering the intervention to group allocation, which may have caused results to be impacted by the expectations about the intervention, both by the participant and the intervention team. In this

For Peer Review

scenario, additional effort must be given to blind the remaining personnel involved in the conduct of the study, such as testing staff and outcome assessors. In fact, some of the vascular outcomes in the present review present a degree of operator dependence for data analysis (65). Therefore, absence of blinding of testing staff and, especially, data analysts may be considered an important limitation of these studies. In the present review, only 4 studies reported that data assessors were blinded for group assignment (27, 40, 41, 44). Overall, the high-risk of bias presented in all, but one, of the studies included in this review highlight the incipience of this study area and points to the urgent need of well-designed RCTs.

Limitations

This review is not without limitations. Firstly, due to the limited number of studies and diseases included in the review, the results reported herein should not be generalized to all ARDs, therefore they should be interpreted with caution. For the same reason, it was not possible to perform sensitivity and meta-regression analyses to test the robustness of the observed outcomes and the potential effects of moderators on the study results. For instance, the vascular responses to PA may vary across different ARDs and protocols of PA, however the reduced number of studies precludes subgroup analyses. Secondly, the included studies presented relatively small sample sizes and follow-up periods. As the ultimate goal of PA is to reduce the number of clinically overt cardiovascular events in ARDs, future studies should investigate the effects of long-term interventions on the occurrence of cardiovascular events using adequately powered sample sizes. Thirdly, we included SpA (including PsA and AS) as ARDs. In fact, these diseases are better classified as autoinflammatory rather than autoimmune diseases, as they are not associated with the production of autoantibodies (66). However, these are chronic inflammatory musculoskeletal conditions and previous studies have included them among the ARDs (2, 67). Therefore, in order to preserve the original search strategy, we decided to maintain SpA in the study review. Fourth, as considered in this review, arterial stiffness is largely determined by aspects of the vascular structure, such as collagen/elastin ratio and smooth muscle cell hypertrophy (68); however, factors related to vascular function (e.g., smooth muscle tone, sympathetic activity) may also effect arterial stiffness (69), therefore arterial stiffness is sometimes seen as a marker of both vascular function and structure. Finally, we only searched and selected papers written in English, which may have caused some selection bias.

For Peer Review

CONCLUSION

The present review provides evidence supporting the role of physical activity as effective vascular medicine/management for patients with ARDs. Overall, the available clinical trials with ARDs demonstrated broad effects of PA across the vasculature, with larger and clearer effects on micro- and macrovascular endothelial function, and less consistent effects on endothelium-independent function and macrovascular structure. Furthermore, this review revealed that PA interventions including a broad range of types, intensities and volumes achieved a high rate of adherence and resulted in no adverse events. This augments the argument that PA is a feasible and effective non-pharmacological strategy in this population. This is the first review to address the effects of PA on vascular function in ARDs, a population characterised by a high cardiovascular morbidity and mortality. Data presented herein provides relevant information to health professionals working with ARDs, supporting evidence-based approaches regarding the management of cardiovascular risk in this population. Information provided by this review may also inform future study designs in this field.

Funding

This work was supported by Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP; 2016/23319-0; 2019/07150-4; 2019/15231-4) and Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq; 406196/2018-4; 428242/2018-9).

Acknowledgements

Not applicable.

Conflict of interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

For Peer Review

REFERENCES

1. Goldblatt F, O'Neill SG. Clinical aspects of autoimmune rheumatic diseases. Lancet (London, England). 2013;382(9894):797-808.
2. Cooper GS, Bynum ML, Somers EC. Recent insights in the epidemiology of autoimmune diseases: improved prevalence estimates and understanding of clustering of diseases. Journal of autoimmunity. 2009;33(3-4):197-207.
3. Oliver JE, Silman AJ. Why are women predisposed to autoimmune rheumatic diseases? Arthritis research & therapy. 2009;11(5):252.
4. Avina-Zubieta JA, Thomas J, Sadatsafavi M, Lehman AJ, Lacaille D. Risk of incident cardiovascular events in patients with rheumatoid arthritis: a meta-analysis of observational studies. Ann Rheum Dis. 2012;71(9):1524-9.
5. Bruce IN. 'Not only...but also': factors that contribute to accelerated atherosclerosis and premature coronary heart disease in systemic lupus erythematosus. Rheumatology (Oxford, England). 2005;44(12):1492-502.
6. Solomon DH, Karlson EW, Rimm EB, Cannuscio CC, Mandl LA, Manson JE, et al. Cardiovascular morbidity and mortality in women diagnosed with rheumatoid arthritis. Circulation. 2003;107(9):1303-7.
7. Meune C, Touze E, Trinquart L, Allanore Y. High risk of clinical cardiovascular events in rheumatoid arthritis: Levels of associations of myocardial infarction and stroke through a systematic review and meta-analysis. Arch Cardiovasc Dis. 2010;103(4):253-61.
8. Ahlehoff O, Gislason GH, Charlot M, Jørgensen CH, Lindhardsen J, Olesen JB, et al. Psoriasis is associated with clinically significant cardiovascular risk: a Danish nationwide cohort study. Journal of internal medicine. 2011;270(2):147-57.
9. Dave AJ, Fiorentino D, Lingala B, Krishnan E, Chung L. Atherosclerotic cardiovascular disease in hospitalized patients with systemic sclerosis: higher mortality than patients with lupus and rheumatoid arthritis. Arthritis care & research. 2014;66(2):323-7.
10. Baghdadi LR, Woodman RJ, Shanahan EM, Mangoni AA. The impact of traditional cardiovascular risk factors on cardiovascular outcomes in patients with rheumatoid arthritis: a systematic review and meta-analysis. PLoS ONE. 2015;10(2):e0117952.
11. Skeoch S, Bruce IN. Atherosclerosis in rheumatoid arthritis: is it all about inflammation? Nat Rev Rheumatol. 2015;11(7):390-400.
12. Bordy R, Totoson P, Prati C, Marie C, Wendling D, Demougeot C. Microvascular endothelial dysfunction in rheumatoid arthritis. Nat Rev Rheumatol. 2018;14(7):404-20.
13. Liu Y, Kaplan MJ. Cardiovascular disease in systemic lupus erythematosus: an update. Current opinion in rheumatology. 2018;30(5):441-8.
14. Karpouzas GA, Malpeso J, Choi TY, Li D, Munoz S, Budoff MJ. Prevalence, extent and composition of coronary plaque in patients with rheumatoid arthritis without symptoms or prior diagnosis of coronary artery disease. Ann Rheum Dis. 2014;73(10):1797-804.
15. Aubry MC, Maradit-Kremers H, Reinalda MS, Crowson CS, Edwards WD, Gabriel SE. Differences in atherosclerotic coronary heart disease between subjects with and without rheumatoid arthritis. J Rheumatol. 2007;34(5):937-42.
16. Lüscher TF, Barton M. Biology of the endothelium. Clinical cardiology. 1997;20(11 Suppl 2):II.
17. Di Minno MN, Ambrosino P, Lupoli R, Di Minno A, Tasso M, Peluso R, et al. Clinical assessment of endothelial function in patients with rheumatoid arthritis: A meta-analysis of literature studies. EUR J INTERN MED. 2015;26(10):835-42.
18. Palombo C, Kozakova M. Arterial stiffness, atherosclerosis and cardiovascular risk: Pathophysiologic mechanisms and emerging clinical indications. Vascular pharmacology. 2016;77:1-7.

For Peer Review

19. Ikdahl E, Rollefstad S, Wibetoe G, Olsen IC, Berg IJ, Hisdal J, et al. Predictive Value of Arterial Stiffness and Subclinical Carotid Atherosclerosis for Cardiovascular Disease in Patients with Rheumatoid Arthritis. J Rheumatol. 2016;43(9):1622-30.
20. Green DJ, Hopman MT, Padilla J, Laughlin MH, Thijssen DH. Vascular Adaptation to Exercise in Humans: Role of Hemodynamic Stimuli. Physiological reviews. 2017;97(2):495-528.
21. Khoja SS, Almeida GJ, Chester Wasko M, Terhorst L, Piva SR. Association of Light-Intensity Physical Activity With Lower Cardiovascular Disease Risk Burden in Rheumatoid Arthritis. Arthritis care & research. 2016;68(4):424-31.
22. Perandini LA, Sales-de-Oliveira D, Mello SB, Camara NO, Benatti FB, Lima FR, et al. Exercise training can attenuate the inflammatory milieu in women with systemic lupus erythematosus. Journal of applied physiology (Bethesda, Md : 1985). 2014;117(6):639-47.
23. Mahieu MA, Ahn GE, Chmiel JS, Dunlop DD, Helenowski IB, Semanik P, et al. Fatigue, patient reported outcomes, and objective measurement of physical activity in systemic lupus erythematosus. Lupus. 2016;25(11):1190-9.
24. Stavropoulos-Kalinoglou A, Metsios GS, Veldhuijzen van Zanten JJ, Nightingale P, Kitas GD, Koutedakis Y. Individualised aerobic and resistance exercise training improves cardiorespiratory fitness and reduces cardiovascular risk in patients with rheumatoid arthritis. Ann Rheum Dis. 2013;72(11):1819.
25. Barnes JN, Nualnim N, Dhindsa M, Renzi CP, Tanaka H. Macro- and microvascular function in habitually exercising systemic lupus erythematosus patients. Scandinavian journal of rheumatology. 2014;43(3):209-16.
26. Crilly MA, Wallace A. Physical inactivity and arterial dysfunction in patients with rheumatoid arthritis. Scandinavian journal of rheumatology. 2013;42(1):27-33.
27. Soriano-Maldonado A, Morillas-de-Laguno P. Effects of 12-week Aerobic Exercise on Arterial Stiffness, Inflammation, and Cardiorespiratory Fitness in Women with Systemic LUPUS Erythematosus: Non-Randomized Controlled Trial. 2018;7(12).
28. Mitropoulos A, Gumber A, Akil M, Klonizakis M. Exploring the microcirculatory effects of an exercise programme including aerobic and resistance training in people with limited cutaneous systemic sclerosis. Microvascular research. 2019;125:103887.
29. Mitropoulos A, Gumber A, Crank H, Akil M, Klonizakis M. The effects of upper and lower limb exercise on the microvascular reactivity in limited cutaneous systemic sclerosis patients. 2018;20(1):112.
30. Vinet A, Obert P, Courteix D, Chapier R, Lesourd B, Verney J, et al. Different modalities of exercise improve macrovascular function but not microvascular function in metabolic syndrome: The RESOLVE randomized trial. International journal of cardiology. 2018;267:165-70.
31. Hamdy O, Ledbury S, Mullooly C, Jarema C, Porter S, Ovalle K, et al. Lifestyle Modification Improves Endothelial Function in Obese Subjects With the Insulin Resistance Syndrome. Diabetes Care. 2003;26(7):2119-25.
32. Tinken TM, Thijssen DH, Black MA, Cable NT, Green DJ. Time course of change in vasodilator function and capacity in response to exercise training in humans. The Journal of physiology. 2008;586(20):5003-12.
33. Gomez-Marcos MA, Recio-Rodríguez JI, Patino-Alonso MC, Agudo-Conde C, Lasaosa-Medina L, Rodriguez-Sanchez E, et al. Relationship between objectively measured physical activity and vascular structure and function in adults. Atherosclerosis. 2014;234(2):366-72.
34. Inaba Y, Chen JA, Bergmann SR. Prediction of future cardiovascular outcomes by flow-mediated vasodilatation of brachial artery: a meta-analysis. The International Journal of Cardiovascular Imaging. 2010;26(6):631-40.
35. Matsuzawa Y, Kwon TG, Lennon RJ, Lerman LO, Lerman A. Prognostic Value of Flow-Mediated Vasodilation in Brachial Artery and Fingertip Artery for Cardiovascular Events: A Systematic Review and Meta-Analysis. Journal of the American Heart Association. 2015;4(11).

For Peer Review

36. Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ (Clinical research ed). 2019;366:l4898.
37. Hedges LV, Pigott TD. The power of statistical tests in meta-analysis. Psychological methods. 2001;6(3):203-17.
38. Cohen J. Statistical power analysis for the behavioral sciences: Academic press; 2013.
39. Viechtbauer W. Bias and Efficiency of Meta-Analytic Variance Estimators in the Random-Effects Model. Journal of Educational and Behavioral Statistics. 2005;30(3):261-93.
40. Metsios GS, Stavropoulos-Kalinoglou A, Veldhuijzen van Zanten JJ, Nightingale P, Sandoo A, Dimitroulas T, et al. Individualised exercise improves endothelial function in patients with rheumatoid arthritis. Ann Rheum Dis. 2014;73(4):748-51.
41. Sveaas SH, Berg IJ, Provan SA, Semb AG, Hagen KB, Vøllestad N, et al. Efficacy of high intensity exercise on disease activity and cardiovascular risk in active axial spondyloarthritis: a randomized controlled pilot study. PLoS ONE. 2014;9(9):e108688.
42. Sarajlic P, Fridén C, Lund LH, Manouras A, Venkateshvaran A, Larsson SC. Enhanced ventricular-arterial coupling during a 2-year physical activity programme in patients with rheumatoid arthritis: a prospective substudy of the physical activity in rheumatoid arthritis 2010 trial. 2018;284(6):664-73.
43. Misse R, Borges I, Santos A, Sales de Oliveira D, Souza J, Gualano B, et al. Effects of Exercise Training on Endothelial Function, Arterial Structure, and Physical Conditioning in Patients with Systemic Autoimmune Myopathies: A Case Series Study. Open Journal of Rheumatology and Autoimmune Diseases. 2019:57-68.
44. Shin JH, Lee Y, Kim SG, Choi BY, Lee HS, Bang SY. The beneficial effects of Tai Chi exercise on endothelial function and arterial stiffness in elderly women with rheumatoid arthritis. Arthritis research & therapy. 2015;17:380.
45. Veldhuijzen van Zanten J, Sandoo A. Comparison of the effects of exercise and anti-TNF treatment on cardiovascular health in rheumatoid arthritis: results from two controlled trials. 2019;39(2):219-25.
46. dos Reis-Neto ET, da Silva AE, Monteiro CM, de Camargo LM, Sato EI. Supervised physical exercise improves endothelial function in patients with systemic lupus erythematosus. Rheumatology (Oxford, England). 2013;52(12):2187-95.
47. Mak A, Kow NY, Schwarz H, Gong L, Tay SH, Ling LH. Endothelial dysfunction in systemic lupus erythematosus - a case-control study and an updated meta-analysis and meta-regression. Scientific reports. 2017;7(1):7320.
48. Tinken TM, Thijssen DH, Hopkins N, Dawson EA, Cable NT, Green DJ. Shear stress mediates endothelial adaptations to exercise training in humans. Hypertension (Dallas, Tex : 1979). 2010;55(2):312-8.
49. Hambrecht R, Wolf A, Gielen S, Linke A, Hofer J, Erbs S, et al. Effect of exercise on coronary endothelial function in patients with coronary artery disease. The New England journal of medicine. 2000;342(7):454-60.
50. Totoson P, Maguin-Gaté K, Nappey M, Prati C, Wendling D, Demougeot C. Microvascular abnormalities in adjuvant-induced arthritis: relationship to macrovascular endothelial function and markers of endothelial activation. Arthritis & rheumatology (Hoboken, NJ). 2015;67(5):1203-13.
51. Anderson TJ, Charbonneau F, Title LM, Buithieu J, Rose MS, Conradson H, et al. Microvascular function predicts cardiovascular events in primary prevention: long-term results from the Firefighters and Their Endothelium (FATE) study. Circulation. 2011;123(2):163-9.
52. Lind L, Berglund L, Larsson A, Sundström J. Endothelial Function in Resistance and Conduit Arteries and 5-Year Risk of Cardiovascular Disease. Circulation. 2011;123(14):1545-51.

For Peer Review

53. Huang C, Wang J, Deng S, She Q, Wu L. The effects of aerobic endurance exercise on pulse wave velocity and intima media thickness in adults: A systematic review and meta-analysis. Scandinavian journal of medicine & science in sports. 2016;26(5):478-87.
54. Byrkjeland R, Stensæth KH, Anderssen S, Njerve IU, Arnesen H, Seljeflot I, et al. Effects of exercise training on carotid intima-media thickness in patients with type 2 diabetes and coronary artery disease. Influence of carotid plaques. Cardiovascular diabetology. 2016;15:13.
55. Ornish D, Brown SE, Scherwitz LW, Billings JH, Armstrong WT, Ports TA, et al. Can lifestyle changes reverse coronary heart disease? The Lifestyle Heart Trial. Lancet (London, England). 1990;336(8708):129-33.
56. Kim SH, Lee SJ, Kang ES, Kang S, Hur KY, Lee HJ, et al. Effects of lifestyle modification on metabolic parameters and carotid intima-media thickness in patients with type 2 diabetes mellitus. Metabolism. 2006;55(8):1053-9.
57. Rausch Osthoff AK, Niedermann K, Braun J, Adams J, Brodin N, Dagfinrud H, et al. 2018 EULAR recommendations for physical activity in people with inflammatory arthritis and osteoarthritis. Ann Rheum Dis. 2018;77(9):1251-60.
58. Semble EL, Loeser RF, Wise CM. Therapeutic exercise for rheumatoid arthritis and osteoarthritis. Seminars in Arthritis and Rheumatism. 1990;20(1):32-40.
59. Wisløff U, Støylen A, Loennechen JP, Bruvold M, Rognmo Ø, Haram PM, et al. Superior cardiovascular effect of aerobic interval training versus moderate continuous training in heart failure patients: a randomized study. Circulation. 2007;115(24):3086-94.
60. Sveaas SH, Bilberg A, Berg IJ, Provan SA, Rollefstad S, Semb AG, et al. High intensity exercise for 3 months reduces disease activity in axial spondyloarthritis (axSpA): a multicentre randomised trial of 100 patients. British Journal of Sports Medicine. 2020;54(5):292.
61. de Jong Z, Munneke M, Zwinderman AH, Kroon HM, Jansen A, Ronday KH, et al. Is a long-term high-intensity exercise program effective and safe in patients with rheumatoid arthritis? Results of a randomized controlled trial. Arthritis and rheumatism. 2003;48(9):2415-24.
62. Hsieh LF, Chen SC, Chuang CC, Chai HM, Chen WS, He YC. Supervised aerobic exercise is more effective than home aerobic exercise in female chinese patients with rheumatoid arthritis. Journal of rehabilitation medicine. 2009;41(5):332-7.
63. Munneke M, de Jong Z, Zwinderman AH, Jansen A, Ronday HK, Peter WF, et al. Adherence and satisfaction of rheumatoid arthritis patients with a long-term intensive dynamic exercise program (RAPIT program). Arthritis and rheumatism. 2003;49(5):665-72.
64. Baxter SV, Hale LA, Stebbings S, Gray AR, Smith CM, Treharne GJ. Walking is a Feasible Physical Activity for People with Rheumatoid Arthritis: A Feasibility Randomized Controlled Trial. Musculoskeletal care. 2016;14(1):47-56.
65. Thijssen DHJ, Bruno RM, van Mil A, Holder SM, Faita F, Greyling A, et al. Expert consensus and evidence-based recommendations for the assessment of flow-mediated dilation in humans. European heart journal. 2019;40(30):2534-47.
66. Generali E, Bose T, Selmi C, Voncken JW, Damoiseaux JGMC. Nature versus nurture in the spectrum of rheumatic diseases: Classification of spondyloarthritis as autoimmune or autoinflammatory. Autoimmunity Reviews. 2018;17(9):935-41.
67. Liu E, Perl A. Pathogenesis and treatment of autoimmune rheumatic diseases. Current opinion in rheumatology. 2019;31(3):307-15.
68. Chen Y, Shen F, Liu J, Yang GY. Arterial stiffness and stroke: de-stiffening strategy, a therapeutic target for stroke. Stroke and vascular neurology. 2017;2(2):65-72.
69. Holwerda Seth W, Luehrs Rachel E, DuBose L, Collins Michael T, Wooldridge Nealy A, Stroud Amy K, et al. Elevated Muscle Sympathetic Nerve Activity Contributes to Central Artery Stiffness in Young and Middle-Age/Older Adults. Hypertension (Dallas, Tex : 1979). 2019;73(5):1025-35.

For Peer Review

TABLES

Table **1.** Methodological characteristics of studies.

Author (data)	Study design	Population			Intervention					Comparison	Outcomes
		Disease	*n* (Gender)	Age (mean ± SD)	Duration (weeks)	Frequency (days/week)	Type	Workout	Time (min)		
Mitropoulos et al. (2018)	Three-arm RCT	lcSSc	34 (31F, 3M)	65 ± 11*	12	2	I1: HIIT arm crank I2: HIIT cycling	Arm crank or cycling 30s 100% PO + 30s rest	40	Non-exercise control	Microvascular function: ACh CVC_{max}, SNP CVC_{max}
Mitropoulos et al. (2019)	RCT	lcSSc	32 (29F, 3M)	67 ± 12*	12	2	HIIT + RT	HIIT: arm crank/cycling 30s 100% PO + 30s rest RT: 5 upper-body exercises, 3 sets, 10RM	~70	Non-exercise control	Microvascular function: ACh CVC_{max}, SNP CVC_{max}
Sveaas et al. (2014)	RCT	axial SpA	24 (12F, 12M)	49 ± 12	12	3	HIIT + MICT + RT	HIIT: walking/running 4x4min 90-95%HR_{max} + 3min rest RT: 6 whole-body exercises, 2-3 sets, 8-10RM MICT: walking/running 40min 70%HR_{max}	40-60	Non-exercise control	Macrovascular structure: AIx, cfPWV
Soriano-Maldonado (2018)	Non-RCT	SLE	58 (58F)	44 ± 14	12	2	MICT + MIIT	Walking/running on a treadmill MICT: ~40-75 min 35-62.5% HRR MIIT: 2-8 x 5-20 min 50-75% HRR	~75	Usual care	Macrovascular structure: aPWV
Reis-Neto et al. (2013)	Non-RCT	SLE	38 (38F)	33 ± 8	16	3	MICT	Continuous walking at a public park HR(VT_1)	60	Non-exercise control	Macrovascular function: FMD, GTN%
Metsios et al. (2014)	Non-RCT	RA	36 (28F, 12M)	54 ± 10	24	3	MIIT + RT	MIIT: 3 circuit laps (walking, running, cycling, rowing) 3 x 3-4 min 70%VO_{2max} + 1 min rest RT: 4 whole-body exercises,	60-70	Lifestyle change advices	Microvascular function: ACh%, SNP% Macrovascular function: FMD%, GTN%

For Peer Review

								3 sets, 12-15 rep, 70%1RM			
Sarajlic et al. (2018)	UCT	RA	29 (NR)	64 ± 11‡	52	5-7	MVPA + Circuit training (RT + MIIT)	MVPA (30 min): Web page- and pedometer to increase MVPA Circuit training: 3 circuit laps (45 min) RT: 10 whole-body exercises 10 rep, 50-80% 1RM MIIT: aerobic exercises 10 x 30 s, 60-85% HR_{max}	30-45	None	Macrovascular structure: AIx, cfPWV
van Zanten et al. (2019)	Non-RCT	RA	43 (29F, 14M)	52 ± 13*	12	3	MIIT	3 circuit laps (walking, running, cycling, rowing) 3 x 3-4 min 70%VO_{2max} + 1 min rest	60	Anti-TNFa treatment	Microvascular function: ACh%, SNP% Macrovascular function: FMD%, GTN%
Shin et al. (2015)	Non-RCT	RA	56 (56F)	64 ± 6	12	1	Tai-Chi	Twelve Movement tai Chi for arthritis (small and large degree of motion whole body movements)	60	Lifestyle change advices	Macrovascular structure: aPWV, cIMT Macrovascular function: FMD%
Misse et al. (2019)	UCT	SAM (DM and PM)	5 (5F)	44 ± 6	12	2	MICT + RT	MICT: walking/running between HR(VT_1-VT_2) RT: 6 whole-body exercises, 1 set, 8-12 RM	~60-80	None	Macrovascular structure: cfPWV Macrovascular function: FMD%

* weighted mean and standard deviation; † standard deviation was estimated from standard error; ‡ standard deviation was estimated from confidence intervals; ACh% = percentage increases in skin blood flow in response to acetylcholine administration; ACh CVC_{max} = maximal cutaneous vascular conductance in response to acetylcholine administration; AIx = augmentation index; aPWV = aortic pulse wave velocity; cfPWV = carotid-femoral pulse wave velocity; cIMT = carotid intima-media thickness; DM = dermatomyositis; F = female; FMD% = brachial artery flow-mediated dilation; GTN%= brachial artery responses to glyceryl trinitrate; HIIT = high-intensity interval training; HR = heart rate; HRR = heart rate reserve; I1 – intervention 1; I2 – intervention 2; lcSSc – limited cutaneous systemic sclerosis; M = male; MICT = moderate intensity continuous training; MIIT = moderate intensity interval training; MVPA = moderate-to-vigorous physical activity; Non-RCT = non-randomized controlled trial; NR = non reported; PA = physical activity; PO = maximal power output; PM = polymyositis; RA = rheumatoid arthritis; RCT = randomized controlled trial; RT = resistance training; SAM = systemic autoimmune myopathies; SLE = systemic lupus erythematosus; SNP% = percentage increases in skin blood flow in response to sodium nitropusside administration; SNP CVC_{max} = maximal cutaneous vascular conductance in response to sodium nitropusside administration; SpA – spondyloarthritis; UCT = uncontrolled clinical trial; VO_{2max} = maximal oxygen consumption; VT1 = first ventilatory threshold; VT2 = second ventilatory threshold.

For Peer Review

FIGURE LEGENDS

Figure 1. Flow-chart of the systematic review. ARD, autoimmune rheumatic diseases; PA, physical activity.

Figure 2. Risk of bias of the included studies. Panel A depicts the risk-of-bias judgement for each study and bias domain. Panel B depicts the overall percentage of 'low risk', 'some concerns' and 'high risk' of bias in each of the bias domain.

Figure 3. Effects of physical activity on microvascular function. The upper panel presents the responses to Ach (i.e. endothelium-dependent function) and the bottom panel presents the responses to SNP (endothelium-independent function). SMD, standardised mean difference; CI, confidence interval; SD, standard deviation.

Figure 4. Effects of physical activity on macrovascular function. The upper panel presents the brachial flow-mediated dilation (FMD%; endothelium-dependent function) and the bottom panel presents the brachial artery responses to glyceryl trinitrate (GTN%; endothelium-independent function). SMD, standardized mean difference; CI, confidence interval; SD, standard deviation.

Figure 5. Effects of physical activity on macrovascular structure as assessed by pulse wave velocity analysis. SMD, standardized mean difference; CI, confidence interval; SD, standard deviation.

For Peer Review

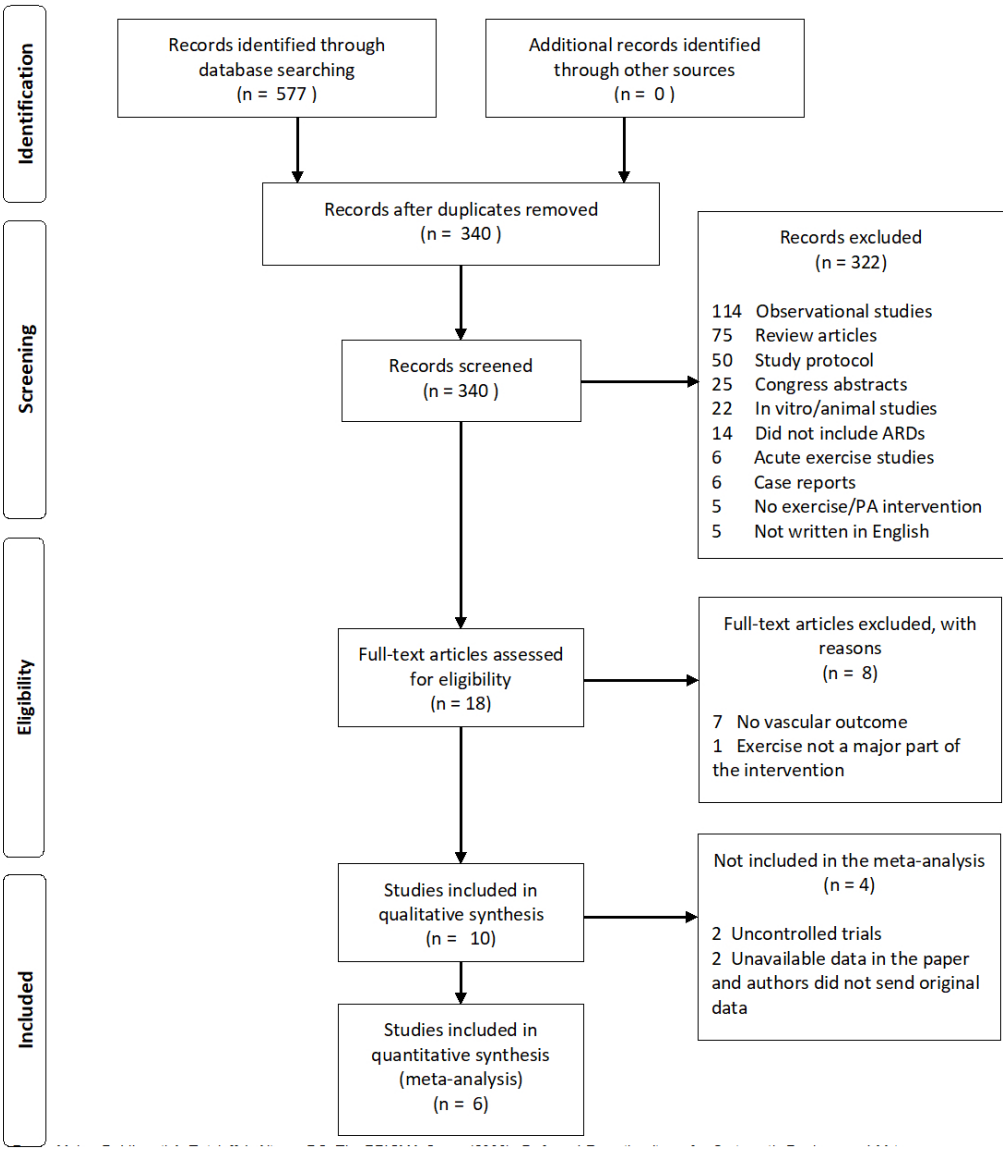


Figure 1. Flow-chart of the systematic review. ARD, autoimmune rheumatic diseases; PA, physical activity.

229x264mm (120 x 120 DPI)

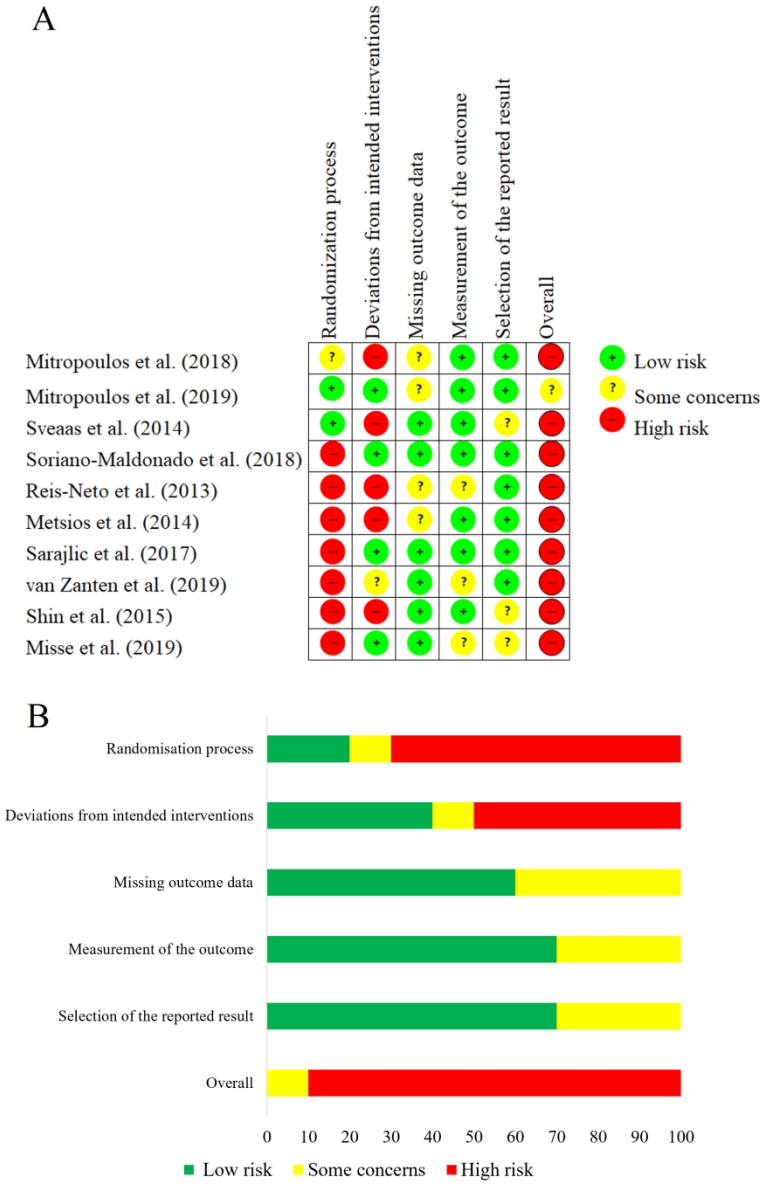


Figure 2. Risk of bias of the included studies. Panel A depicts the risk-of-bias judgement for each study and bias domain. Panel B depicts the overall percentage of 'low risk', 'some concerns' and 'high risk' of bias in each of the bias domain.

387x600mm (120 x 120 DPI)

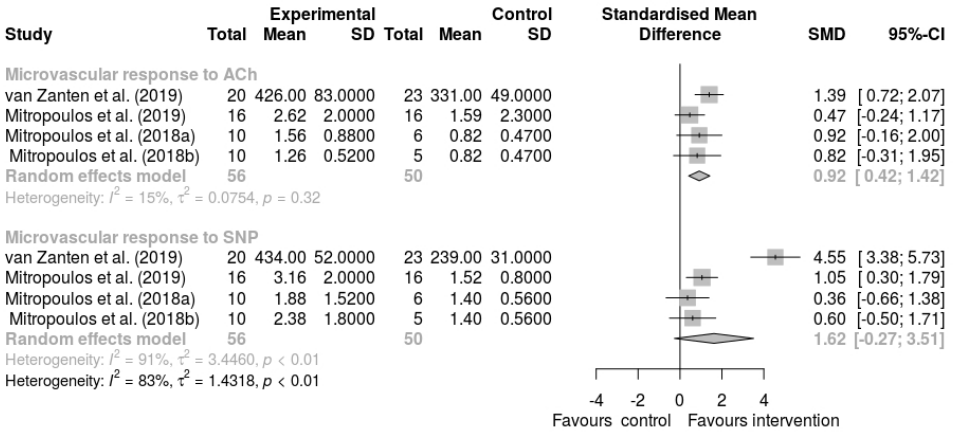


Figure 3. Effects of physical activity on microvascular function. The upper panel presents the responses to Ach (i.e. endothelium-dependent function) and the bottom panel presents the responses to SNP (endothelium-independent function). SMD, standardised mean difference; CI, confidence interval; SD, standard deviation.

200x94mm (120 x 120 DPI)

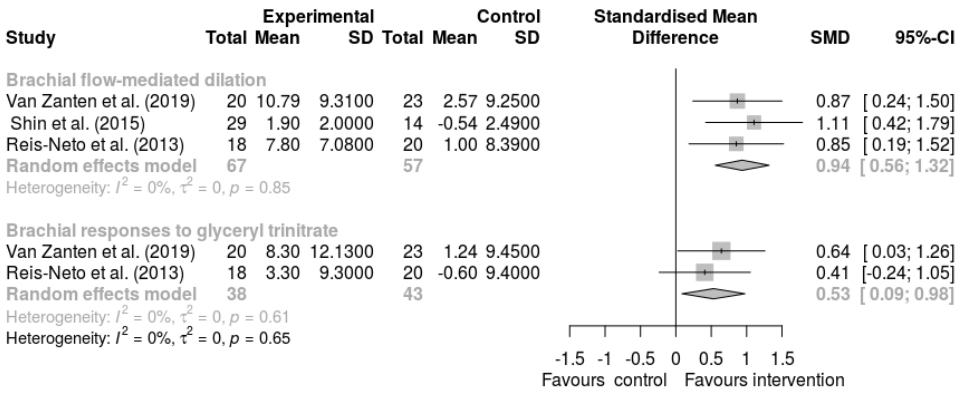


Figure 4. Effects of physical activity on macrovascular function. The upper panel presents the brachial flow-mediated dilation (FMD%; endothelium-dependent function) and the bottom panel presents the brachial artery responses to glyceryl trinitrate (GTN%; endothelium-independent function). SMD, standardized mean difference; CI, confidence interval; SD, standard deviation.

189x86mm (120 x 120 DPI)

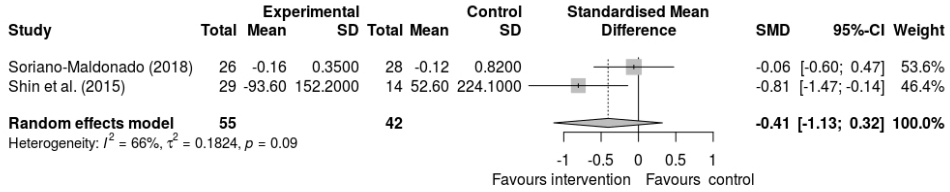


Figure 5. Effects of physical activity on macrovascular structure as assessed by pulse wave velocity analysis. SMD, standardized mean difference; CI, confidence interval; SD, standard deviation.

218x63mm (120 x 120 DPI)

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	#1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	#2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	#3-4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	#4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	#4
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	#5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	#5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	TableS1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	#5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	#5-6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	#5-6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	#6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	#7
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	#7

For Peer Review

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	NA
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	NA
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	#7 Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	#7
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	#8 Figure 2
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	#9-10 Table 1 Figures 3, 4 and 5
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	#9-10 Figures 3, 4 and 5
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	NA
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	NA
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	#11
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	#15
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	#15-16
FUNDING			

For Peer Review

PRISMA 2009 Checklist

Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	#16

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: **www.prisma-statement.org**.

For Peer Review

SUPPLEMENTARY MATERIAL

Table S1. Search strategy.

Search terms	Descriptors
1. Autoimmune rheumatic diseases	(“rheumatic disease*” OR "lupus" OR "rheumatoid arthritis" OR "Sjögren’s" OR "systemic sclerosis" OR "scleroderma" OR "inflammatory myositis" OR “ankylosing spondylitis” OR “spondyloarthritis” OR "systemic vasculitides" OR "vasculitis" OR “connective tissue diseases” OR “arthritis” OR “joint disease*” OR “psoriatic arthritis” OR “psoriatic arhtiris”)
2. Physical activity	(“physical activity” OR “sport*” OR “exercise” OR “physiotherapy” OR “fitness” OR “accelerometer” OR “aerobic” OR “training” OR “resistance training” OR “strength training” OR “swimming” OR “lifestyle” OR “physical conditioning” OR “gymnastics” OR “running” OR “jogging” OR “sitting” OR “sedentary behavior” OR “sedentary behaviour” OR “sedentarism”).
3. Vascular function	(“flow-mediated dilation” OR “vascular function” OR “macrovascular” OR “microvascular” OR “pulse wave velocity” OR “pulse wave analysis” OR “vascular stiffness” OR “arterial stiffness” OR “laser Doppler” OR “subendocardial viability ratio” OR “coronary flow reserve” OR “endothelium” OR “tonometry”).
Combination	#1, #2, #3

For Peer Review

Table S**2.** Summary of the study results

Author (data)	Disease	Intervention	Microvascular function				Macrovascular function		Macrovascular structure			
			ACh CVC_{max}	SNP CVC_{max}	ACh%	SNP%	FMD%	GTN%	aPWV	AIx	cfPWV	cIMT
Mitropoulos et al. (2018)	lcSSc	HIIT cycling	↔	↔								
		HIIT arm crank	↑	↔								
Mitropoulos et al. (2019)	lcSSc	HIIT + RT	↔	↑								
Sveaas et al. (2014)	axial SpA	HIIT + RT + MICT								↓	↓	
Soriano-Maldonado (2018)	SLE	MICT + MIIT							↔			
Reis-Neto et al. (2013)	SLE	MICT					↑	↔				
Metsios et al. (2014)	RA	MIIT + RT			↑	↑	↑	↑				
Sarajlic et al. (2018)	RA	MVPA + Circuit training (RT + MIIT)								↔	↔	
van Zanten et al. (2019)	RA	MIIT			↔	↑	↑	↑				
Shin et al. (2015)	RA	Tai-Chi					↑		↓			↔
Misse et al. (2019)	SAM (DM and PM)	MICT + RT					↔				↔	

ACh% = percentage increases in skin blood flow in response to acetylcholine administration; ACh CVC_{max} = maximal cutaneous vascular conductance in response to acetylcholine administration; Aix = augmentation index; aPWV = aortic pulse wave velocity; cfPWV = carotid-femoral pulse wave velocity; cIMT = carotid intima-media thickness; FMD% = brachial artery flow-mediated dilation; GTN%= brachial artery responses to glyceryl trinitrate; HIIT = high-intensity interval training; MICT = moderate intensity continuous training; MIIT = moderate intensity interval training; MVPA = moderate-to-vigorous physical activity; RT = resistance training; SNP% = percentage increases in skin blood flow in response to sodium nitropusside administration; SNP CVC_{max} = maximal cutaneous vascular conductance in response to sodium nitropusside administration.

For Review

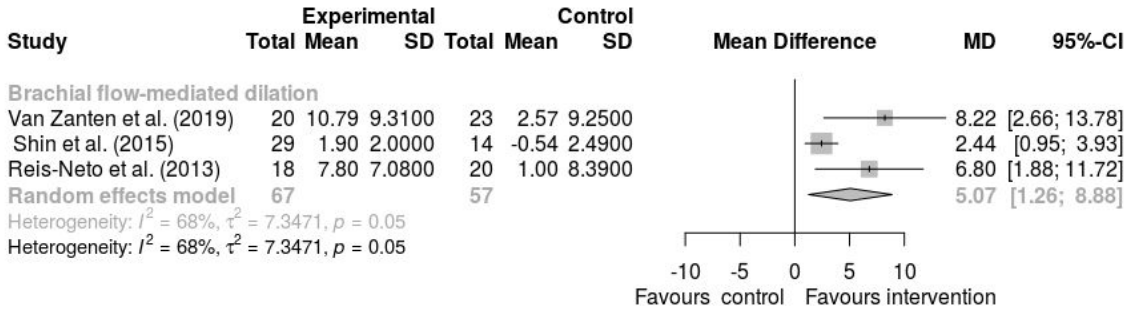


Figure S1. Absolute changes in flow-mediated dilation (FMD%) calculated as mean difference (MD) between intervention and control groups pre-post changes. CI, confidence interval; SD, standard deviation.

For Peer Review