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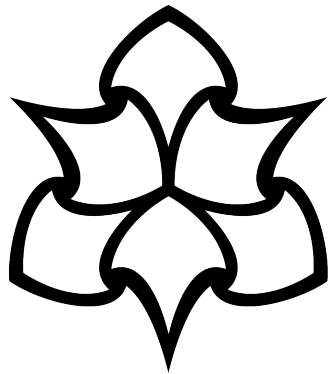
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**EFFECTS OF PHYSICAL ACTIVITY ON VASCULAR FUNCTION
 IN AUTOIMMUNE RHEUMATIC DISEASES: A SYSTEMATIC
 REVIEW AND META-ANALYSIS**

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3 1 ***EFFECTS OF PHYSICAL ACTIVITY ON VASCULAR FUNCTION IN AUTOIMMUNE***
4 ***RHEUMATIC DISEASES: A SYSTEMATIC REVIEW AND META-ANALYSIS***
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3 26 **ABSTRACT:**
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6 28 **Objectives:** To summarise existing evidence and quantify the effects of physical activity on
7 29 vascular function and structure in autoimmune rheumatic diseases (ARDs). **Methods:** Databases
8 30 were searched (up to March 2020) for clinical trials evaluating the effects of physical activity
9 31 interventions on markers of micro- and macrovascular function and macrovascular structure in
10 32 ARDs. Studies were combined using random-effects meta-analysis, which was conducted using
11 33 the Hedge's g. Meta-analyses were performed on each of the following outcomes: (1)
12 34 microvascular function (i.e., skin blood flow or responses to acetylcholine [ACh] or sodium
13 35 nitropusside [SNP] administration); (2) macrovascular function (i.e., brachial flow-mediated
14 36 dilation [FMD%] or brachial responses to glyceryl trinitrate [GTN%]; and (3) macrovascular
15 37 structure (i.e., aortic pulse wave velocity [PWV]). **Results:** Ten studies (11 trials), with a total of
16 38 355 participants, were included in this review. Physical activity promoted significant
17 39 improvements in micro- (skin blood flow responses to ACh [g = 0.92; 0.42 to 1.42]) and
18 40 macrovascular function (FMD% [g = 0.94; 0.56 to 1.02]; GTN% [g = 0.53; 0.09 to 0.98]).
19 41 Conversely, there was no evidence for beneficial effects of physical activity on macrovascular
20 42 structure (PWV [g = -0.41; -1.13 to 0.32]). **Conclusions:** Overall, the available clinical trials
21 43 demonstrated a beneficial effect of physical activity on markers of micro- and macrovascular
22 44 function, but not on macrovascular structure, in patients with ARDs. The broad beneficial impact
23 45 of physical activity across the vasculature identified in this review support its role as an effective
24 46 non-pharmacological management strategy for patients with ARD.
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32 48 **Keywords:** flow-mediated dilation, skin blood flow, rheumatoid arthritis, inflammatory diseases
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35 50 **Key messages:**

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- 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.

57 INTRODUCTION

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

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

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

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

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3 88 health in ARDs. Physical activity (PA) has been recognised for some time as an important non-
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5 89 pharmacological therapeutic with beneficial effects on vascular function and structure (20). In
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7 90 ARDs, PA has been linked with reduced disease activity (21), inflammation (22) and pain (23),
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9 91 and with improved cardiovascular risk profile (21, 24). Specific to the vasculature, cross-sectional
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11 92 studies have demonstrated improved vascular function in physically active compared with
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13 93 physically inactive ARD patients (25, 26). However, available clinical trials examining the effects
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15 94 of PA on vascular health in ARDs have elicited equivocal findings (27-29), which may be partially
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17 95 explained by small sample sizes and thus reduced statistical power. Additionally, the effects of PA
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19 96 on the vasculature may vary according to the vascular bed, with previous evidence demonstrating
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21 97 that physical activity may differentially impact the micro- and macrovasculature (30, 31), as well
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23 98 as vascular function and structure (32, 33). Finally, the magnitude of the improvement on vascular
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25 99 parameters promoted by PA in ARDs remains unclear. As even slight improvements in markers
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27 100 of endothelial function are associated with substantial reduction in the risk of cardiovascular events
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29 101 (34, 35), a better understanding of the effects of PA on vascular function and structure in ARDs
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31 102 may yield important clinical information to be used in the management of CVD in ARDs.

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33 103 Resultantly, we conducted this systematic review and meta-analysis to summarise the
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35 104 existing evidence and to quantify the effects of PA on micro- and macrovascular function and
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37 105 macrovascular structure in ARDs. As a secondary outcome, we have also described the
38
39 106 characteristics of existing PA programmes for this population and reviewed data on adherence to
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41 107 PA, and potential side effects.

42 108

43 109 **METHODS**

44 110 *Registration*

45 111 This systematic review with meta-analysis was reported according to the PRISMA
46
47 112 statement and is registered in the PROSPERO database (CRD42020196023).

48 113

49 114 *Search strategy and study selection*

50 115 Searches were performed on 5 databases (PubMed, Web of Science, EMBASE, Cochrane
51
52 116 Library and Scopus) by entering key words related to population, intervention and outcome
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54 117 (Supplementary Table S1). Searches were limited to peer-reviewed articles in English, published
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56 118 from the inception of each database up until March 2020.

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3 119 For inclusion, studies were required to fulfill the following criteria: (1) randomised
4 120 controlled trials (RCTs), non-RCTs or uncontrolled trials (UCT; pre vs. post only) with an
5 121 experimental condition that included a PA intervention; (2) interventions should have lasted ≥ 2
6 122 weeks, and should have been performed ≥ 1 x week; (3) conducted on adults (≥ 18 years) with a
7 123 diagnosis of SLE, RA, SpA, SJ, SSc, AS, SAM or SV; (4) included assessments of at least 1 of
8 124 the following; brachial or lower-limb flow-mediated dilation (FMD%), or brachial responses to
9 125 glyceryl trinitrate (GTN%), pulse wave velocity (PWV), cutaneous blood flow reactivity to
10 126 pharmacologic, mechanical or local heat stimuli. Studies were excluded if they were protocol
11 127 studies, observational studies, acute exercise studies, studies with physiotherapy interventions
12 128 (e.g., joint manipulation, kinesio taping) or studies involving pediatric rheumatic diseases.

13 129 On completion of the searches, 2 members of the study team (TP and DL) independently
14 130 selected the studies to be included based on the title, abstract and full text of each potential
15 131 manuscript. Discrepancies were identified and solved through discussion with a third author (TS).

16 132

17 133 *Data extraction*

18 134 Two members of the study team (TP and SMS) independently extracted study data using a
19 135 purpose developed data extraction sheet, after which a mutual consensus was reached.
20 136 Discrepancies were identified and solved through discussion. Missing data were requested by
21 137 contacting the corresponding authors of specific studies. The following characteristics were
22 138 extracted from each selected study: (1) author (data); (2) study design; (3) participant information;
23 139 (4) characteristics of the intervention; (5) outcome data.

24 140

25 141 *Assessment of the risk of bias*

26 142 Quality was appraised using the Cochrane risk-of-bias tool (RoB-2) (36), by two members
27 143 of the study team (DB and TP). This tool considers bias arising from 5 domain (randomization
28 144 process, deviations from the intended interventions, missing outcomes, measurement of the
29 145 outcome and selection of reported results) and an overall bias analysis. The risk of bias of each
30 146 domain and the overall risk were judged as “high”, “low” or “some concerns”. All studies were
31 147 analysed with this tool, even non-RCTs and UCTs, assuming that they would already be at high
32 148 risk due to their design.

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150 *Data analysis: Systematic Review*

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

159 *Data analysis: Meta-Analysis*

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

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

179 **RESULTS**

180 *Literature search*

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3 181 A total of 577 published articles were identified through independent searches in all the
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5 182 five databases. Following removal of duplicates ($n=237$), 340 publications were screened for
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7 183 inclusion. Of these, 322 records were excluded after reviewing the title and/or abstract. The
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9 184 remaining 18 papers were selected for full text reading and 8 were excluded for either not
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11 185 presenting any vascular outcome ($n=7$) or by not including PA as a major component of the
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13 186 intervention ($n=1$). Ultimately, 10 studies (11 trials) were included in the review and are listed in
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15 187 the qualitative analysis. Among these, 8 studies (9 trials) were suitable for inclusion in the meta-
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17 188 analysis, however we were unable to obtain relevant data from 2 studies (40, 41) (i.e., data were
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19 189 presented as median \pm interquartile interval, and authors did not respond to emails soliciting
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21 190 original data or did not provide the required data). Therefore, 6 studies (7 trials) were included in
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23 191 the meta-analysis (Figure 1).

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25 192 A general description of each study is detailed in Table 1. Among the 10 included studies,
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27 193 3 were RCTs, 5 were non-RCTs and 2 were UCTs. These studies enrolled 355 middle-aged to
28
29 194 older participants, with a large majority of women (88% vs. 12%). The included studies were
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31 195 conducted in participants with limited cutaneous SSc (lcSSc), axial SpA, SLE, RA and SAM.

32 196 33 197 *Risk of bias*

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35 198 Nine studies presented a 'high risk' of bias and one study presented 'some concerns'
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37 199 considering the overall judgement (Figure 2A). Most of the methodological issues arose from the
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39 200 'randomisation process' (7 out of 10 were not RCTs) or from 'bias due to deviation from intended
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41 201 interventions' (with most of the studies using 'per-protocol' analyses and/or presenting >5% drop
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43 202 out rates). The remaining domains were judged with 'some concerns' or 'low risk of bias' (Figure
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45 203 2B).

46 204 47 205 *Characteristics of the physical activity/exercise interventions*

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49 206 Most PA interventions lasted between 12-16 weeks and sessions were performed 2-3
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51 207 days/week for 30-80 min/session (Table 1). All studies included a structured exercise programme
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53 208 and one study also employed a web- and pedometer-based PA programme (42). Exercise workouts
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55 209 comprised a mix of exercise types including high-intensity interval training (HIIT), moderate-
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57 210 intensity interval training (MIIT), moderate-intensity continuous training (MICT), resistance
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59 211 training (RT) and Tai-Chi. Aerobic exercise modalities included arm cranking, cycling, rowing,
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3 212 swimming, and walking/running on a treadmill or in a public park. Aerobic exercise intensities
4 213 ranged from low- (e.g., 35-60% of heart rate reserve) to high-intensity (e.g., 100% of maximal
5 214 power output). RT sessions were composed of 4-10 whole-body exercises at 50-80% of 1 repetition
6 215 maximum (Table 1). Interventions were either fully (6 out of 10) or partially (4 out of 10)
7 216 supervised, and were conducted in different settings such as a hospital gyms (27, 40, 43-45),
8 217 fitness/exercise centres (28, 29, 41), at home (40, 45), or in public gyms (42) or parks (46).
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15 219 *Effects of physical activity on vascular function*

16 220 Microvascular function

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18 221 Microvascular function was assessed in 4 studies (5 trials) via the evaluation of the
19 222 responses of forearm skin blood flow or vascular conductance to ACh (endothelium-dependent)
20 223 or SNP (endothelium-independent) iontophoresis (Table 1). Metsios *et al.* (40) reported increases
21 224 in the skin blood flow response to ACh and SNP after 24 weeks of combined MIIT and RT in RA
22 225 patients. In this same population, 12 weeks of MIIT promoted an increase in skin blood flow
23 226 responses to SNP, but not to ACh (45). In patients with lcSSc, Mitropoulos *et al.* (29) reported
24 227 increased maximal forearm cutaneous vascular conductance in response to ACh after 12 weeks of
25 228 upper-limb HIIT, however no benefits were observed after lower limb HIIT. Neither upper- or
26 229 lower-limb training were able to improve microvascular responses to SNP. A latter study from the
27 230 same group (28) observed that 12 weeks of combined HIIT and RT increased maximal forearm
28 231 cutaneous vascular conductance in response to SNP, but not to ACh (Supplementary Table S2).
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38 232 Overall, the meta-analysis revealed a large significant improvement in microvascular
39 233 function responses to ACh in the PA group compared with the control group (Figure 3; [g=0.92;
40 234 IC95%, 0.42 to 1.42]). On the other hand, no significant differences were found between PA and
41 235 control groups in the microvascular responses to SNP (Figure 3; [g=1.62; IC95%, -0.27 to 3.51]).
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46 237 Macrovascular function

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48 238 Macrovascular function was assessed in 5 studies (5 trials) through the evaluation of
49 239 FMD% (endothelium-dependent) and in 3 studies (3 trials) using the GTN% (endothelium
50 240 independent) (Table 1). Van Zanten *et al.* (45) and Metsios *et al.* (40) reported increases in both
51 241 FMD% and GTN% after 12 weeks of MIIT and 24 weeks of combined MIIT and RT, respectively,
52 242 in RA patients. A study employing 1 day/week of Tai-Chi for 12 weeks also verified an increase
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243 in FMD% in RA patients (44). Reis-Neto (46) observed increase in FMD% and no changes in
244 GTN% after 16 weeks of moderate-intensity walking in a public park in patients with SLE. On the
245 other hand, Misse *et al.* (43) did not observe increase in FMD% after 12 weeks of combined
246 aerobic and RT in patients with SAM (Supplementary Table S2).

247 Overall, the meta-analysis revealed a large significant increase in FMD% (Figure 4 [$g =$
248 0.94 ; IC95%, 0.56 to 1.32]) and a moderate increase in GTN% (Figure 4 [$g = 0.53$; IC95%, 0.09
249 to 0.98]) favoring the intervention group. On average, FMD% increased 5.07% after the PA
250 interventions (1.26 to 8.88) (Supplementary Figure S1).

251 Macrovascular structure

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

261 Overall, the meta-analysis revealed no significant effects of PA on PWV (Figure 5 [$g = -$
262 0.41 ; IC95%, -1.13 to 0.32]).

263 *Adherence and safety*

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

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

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3 273 not clear if this was related to the intervention. Four studies did not report data on the safety of the
4 274 PA interventions (42, 44-46).

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6 275 Group mean disease activity measured using disease-specific tools was reported to be
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8 276 unchanged by the PA intervention in 4 studies (42, 44-46) and to be reduced in 2 (40, 41).
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10 277 Individual data on disease activity was reported by two studies only (41, 43). In one of them (41),
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12 278 2 participants (out of 10) had a slight increase in their disease activity, while the others either
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14 279 decreased or did not change their disease activity. Four studies did not report data on the effects
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16 280 of the interventions on disease activity (27-29).

17 281

18 282 **DISCUSSION**

19
20 283 Our systematic review and meta-analysis summarised the evidence on the effectiveness of
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22 284 PA on vascular function and structure in ARDs. Although limited by the reduced number and low
23
24 285 quality of the studies, data reviewed herein demonstrated a beneficial effect of PA on micro- and
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26 286 macrovascular function in ARDs. However, results from available studies observed no effect of
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28 287 PA on macrovascular structure. Furthermore, where this is reported, evidence suggests that PA is
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30 288 safe and well adhered to by individuals with ARDs.

31 289 The results of the present review support the notion that PA may counter vascular
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33 290 impairment observed in ARDs (17, 47). More specifically, PA interventions were effective in
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35 291 improving micro- and macrovascular function, with clearer and larger effects observed on
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37 292 endothelium-dependent (FMD% and skin blood flow responses to Ach) as opposed to
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39 293 endothelium-independent (GTN% and skin blood flow responses to SNP) function. This
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41 294 information corroborates previous studies demonstrating that vascular adaptations promoted by
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43 295 PA are largely mediated by its direct effects on the endothelium rather than on smooth muscle
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45 296 vasodilator function (48, 49). Beneficial effects of PA on the endothelium are a consequence of
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47 297 repeated hemodynamic stimulation (e.g., shear stress and transmural pressure), which favors the
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49 298 production of nitric oxide and vascular relaxation (20). As for the clinical impact of these findings,
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51 299 PA yielded a ~5% increase in FMD% (Figure S1), which may be seen as clinically relevant, as
52
53 300 there is an associated reduction in 12-13% in the risk of cardiovascular events for every 1%
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55 301 increase in FMD% (34, 35). Additionally, previous reviews indicated that patients with ARDs
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57 302 present 1-3% reduced FMD% compared to controls (17, 47); therefore, the present review
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59 303 indicates that PA may reverse the endothelial dysfunction observed in these patients.
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3 304 The improvements in both macro- and microvascular endothelial function highlight the
4
5 305 broad effects of PA across the vasculature in this population. These data prove relevant, as a recent
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7 306 study identified that changes in macrovascular and microvascular function may occur at different
8
9 307 stages in the progression of CVD in ARDs, and reflect different and complementary aspects of
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11 308 vascular pathology (12). For instance, in an experimental model of adjuvant-induced arthritis,
12
13 309 endothelial dysfunction in mesenteric arteries (i.e., microvasculature) occurred earlier than
14
15 310 dysfunction in the aorta (i.e., macrovasculature) along the course of the disease. Moreover,
16
17 311 microvascular dysfunction persisted even in the late stage of the disease, while macrovascular
18
19 312 dysfunction returned to pre-disease values when inflammation was resolved (50). Data from cohort
20
21 313 studies further support the different prognostic information provided by markers of micro- and
22
23 314 macrovascular function, as the former seems to be a more powerful predictor of cardiovascular
24
25 315 events in subjects without pre-existing cardiovascular conditions (51, 52), while the latter seems
26
27 316 to be more important in subjects with existing CVD (35). Therefore, PA may beneficially affect
28
29 317 ARD patients with different vascular phenotypes, in different stages of the cardiovascular
30
31 318 continuum and along the course of the diseases.

32
33 319 The results of this review do not support the hypothesis that PA promotes positive changes
34
35 320 in vascular structure in ARDs. Notwithstanding the reduced number of studies, the absence of any
36
37 321 clear effects of PA on vascular structure may be explained by the small duration of most of the
38
39 322 studies' interventions (~12 weeks). Changes in vascular function and structure in response to PA
40
41 323 often follow a distinct time-course, with improvements in function preceding structural remodeling
42
43 324 (20, 32). Therefore, it is likely that longer interventions (>16 weeks) might have elicited more
44
45 325 consistent effects on vascular structure, as reviewed elsewhere (53). It is also possible that
46
47 326 persistent inflammation may cause profound changes in vascular structure (e.g., collagen and
48
49 327 cholesterol deposition, fibrosis, plaque formation) that may be less prone to be reversed by PA
50
51 328 (54). Finally, PA alone may also be a 'weak' intervention to produce consistent changes in vascular
52
53 329 structure. In this respect, previous evidence suggests that multicomponent interventions (e.g., PA,
54
55 330 low-fat diet, smoking cessation and lipid-lowering drugs) with intensive control of cardiovascular
56
57 331 risk factors may be the most effective strategy to produce consistent vascular remodeling in clinical
58
59 332 populations (55, 56), which may also hold true for ARDs.

60
333 Studies included in the present review employed different protocols of PA. Five studies
334 (28, 40-43) used a combination of aerobic training with RT, which is in compliance with public

1
2
3 335 health recommendations for PA in ARDs (57). Exercise intensity ranged from moderate to very
4
5 336 intense, which reveals the feasibility of more intense exercise interventions for this population,
6
7 337 diverging from the previous notion that intense PA could be detrimental to ARDs (58). In fact, 3
8
9 338 studies (28, 29, 41) employed HIIT, which has only in the last two decades been recognised as a
10
11 339 form of therapeutic exercise for clinical populations (59). Two studies (28, 41) also employed
12
13 340 high-intensity dynamic RT, which has been recently advocated as a means to counteract functional
14
15 341 decline in elderly and in population with chronic diseases, including ARDs (60). More importantly,
16
17 342 the studies included in the review reported no serious adverse effects related to all these
18
19 343 interventions, suggesting that PA is safe across a broad range of exercise types, modalities and
20
21 344 intensities in ARDs. This information supports previous findings from studies addressing the
22
23 345 safety of PA to ARDs (61, 62).

24 346 Data on adherence is also encouraging as it was reported to be above 75% across all studies
25
26 347 that reported this variable, which is in agreement with previous studies specifically designed to
27
28 348 assess adherence to PA interventions in ARDs (63, 64). However, it must be highlighted that most
29
30 349 interventions included in this review were fully supervised and conducted in specialised exercise
31
32 350 facilities (e.g., hospital gym and fitness centres). While intense monitoring by health professionals
33
34 351 may be the most effective way to encourage adherence, it does not represent the real-world exercise
35
36 352 setting for most of these patients. Interestingly, 2 studies (40, 45) employed a mixed monitoring
37
38 353 approach with two supervised centre-based PA sessions and one unsupervised home-based
39
40 354 session, also reporting good adherence (88% (24)) and benefits on vascular function. Future studies
41
42 355 should examine the feasibility and effectiveness of even less controlled interventions (e.g., full
43
44 356 time home-based PA, web-based or mHealth PA programmes), with the intent to subsidise public
45
46 357 health initiatives that may be directly applied to this population.

47 358

48 359 *Risk of bias*

49 360 The generalisability of the present review findings are limited by the quality of the studies
50
51 361 composing the review. In this regard, it should be noted that only 3 studies were RCTs, and one of
52
53 362 them (29) did not provide specific information about the randomisation process. Another aspect
54
55 363 that affected the overall risk of bias is the inherent difficulty to blind the participants and those
56
57 364 delivering the intervention to group allocation, which may have caused results to be impacted by
58
59 365 the expectations about the intervention, both by the participant and the intervention team. In this
60

1
2
3 366 scenario, additional effort must be given to blind the remaining personnel involved in the conduct
4
5 367 of the study, such as testing staff and outcome assessors. In fact, some of the vascular outcomes in
6
7 368 the present review present a degree of operator dependence for data analysis (65). Therefore,
8
9 369 absence of blinding of testing staff and, especially, data analysts may be considered an important
10
11 370 limitation of these studies. In the present review, only 4 studies reported that data assessors were
12
13 371 blinded for group assignment (27, 40, 41, 44). Overall, the high-risk of bias presented in all, but
14
15 372 one, of the studies included in this review highlight the incipience of this study area and points to
16
17 373 the urgent need of well-designed RCTs.
18

19 375 *Limitations*

20
21 376 This review is not without limitations. Firstly, due to the limited number of studies and
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23 377 diseases included in the review, the results reported herein should not be generalized to all ARDs,
24
25 378 therefore they should be interpreted with caution. For the same reason, it was not possible to
26
27 379 perform sensitivity and meta-regression analyses to test the robustness of the observed outcomes
28
29 380 and the potential effects of moderators on the study results. For instance, the vascular responses to
30
31 381 PA may vary across different ARDs and protocols of PA, however the reduced number of studies
32
33 382 precludes subgroup analyses. Secondly, the included studies presented relatively small sample
34
35 383 sizes and follow-up periods. As the ultimate goal of PA is to reduce the number of clinically overt
36
37 384 cardiovascular events in ARDs, future studies should investigate the effects of long-term
38
39 385 interventions on the occurrence of cardiovascular events using adequately powered sample sizes.
40
41 386 Thirdly, we included SpA (including PsA and AS) as ARDs. In fact, these diseases are better
42
43 387 classified as autoinflammatory rather than autoimmune diseases, as they are not associated with
44
45 388 the production of autoantibodies (66). However, these are chronic inflammatory musculoskeletal
46
47 389 conditions and previous studies have included them among the ARDs (2, 67). Therefore, in order
48
49 390 to preserve the original search strategy, we decided to maintain SpA in the study review. Fourth,
50
51 391 as considered in this review, arterial stiffness is largely determined by aspects of the vascular
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53 392 structure, such as collagen/elastin ratio and smooth muscle cell hypertrophy (68); however, factors
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55 393 related to vascular function (e.g., smooth muscle tone, sympathetic activity) may also effect arterial
56
57 394 stiffness (69), therefore arterial stiffness is sometimes seen as a marker of both vascular function
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59 395 and structure. Finally, we only searched and selected papers written in English, which may have
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61 396 caused some selection bias.

397

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.

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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.

428 **REFERENCES**

- 429 1. Goldblatt F, O'Neill SG. Clinical aspects of autoimmune rheumatic diseases. *Lancet* (London, England). 2013;382(9894):797-808.
- 431 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.
- 434 3. Oliver JE, Silman AJ. Why are women predisposed to autoimmune rheumatic diseases? *Arthritis research & therapy*. 2009;11(5):252.
- 436 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.
- 439 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.
- 442 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.
- 444 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.
- 447 8. Ahlehoff O, Gislason GH, Charlott 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.
- 450 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.
- 453 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.
- 456 11. Skeoch S, Bruce IN. Atherosclerosis in rheumatoid arthritis: is it all about inflammation? *Nat Rev Rheumatol*. 2015;11(7):390-400.
- 458 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.
- 460 13. Liu Y, Kaplan MJ. Cardiovascular disease in systemic lupus erythematosus: an update. *Current opinion in rheumatology*. 2018;30(5):441-8.
- 462 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.
- 465 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.
- 468 16. Lüscher TF, Barton M. Biology of the endothelium. *Clinical cardiology*. 1997;20(11 Suppl 2):II.
- 469 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.
- 472 18. Palombo C, Kozakova M. Arterial stiffness, atherosclerosis and cardiovascular risk: Pathophysiologic mechanisms and emerging clinical indications. *Vascular pharmacology*. 2016;77:1-7.

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, Mulooly 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, Lasasosa-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).

- 1
2
3 522 36. Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for
4 523 assessing risk of bias in randomised trials. *BMJ (Clinical research ed)*. 2019;366:l4898.
- 5 524 37. Hedges LV, Pigott TD. The power of statistical tests in meta-analysis. *Psychological methods*.
6 525 2001;6(3):203-17.
- 7 526 38. Cohen J. *Statistical power analysis for the behavioral sciences*: Academic press; 2013.
- 8 527 39. Viechtbauer W. Bias and Efficiency of Meta-Analytic Variance Estimators in the Random-Effects
9 528 Model. *Journal of Educational and Behavioral Statistics*. 2005;30(3):261-93.
- 10 529 40. Metsios GS, Stavropoulos-Kalinoglou A, Veldhuijzen van Zanten JJ, Nightingale P, Sandoo A,
11 530 Dimitroulas T, et al. Individualised exercise improves endothelial function in patients with rheumatoid
12 531 arthritis. *Ann Rheum Dis*. 2014;73(4):748-51.
- 13 532 41. Sveaas SH, Berg IJ, Provan SA, Semb AG, Hagen KB, Vøllestad N, et al. Efficacy of high intensity
14 533 exercise on disease activity and cardiovascular risk in active axial spondyloarthritis: a randomized
15 534 controlled pilot study. *PLoS ONE*. 2014;9(9):e108688.
- 16 535 42. Sarajlic P, Fridén C, Lund LH, Manouras A, Venkateshvaran A, Larsson SC. Enhanced ventricular-
17 536 arterial coupling during a 2-year physical activity programme in patients with rheumatoid arthritis: a
18 537 prospective substudy of the physical activity in rheumatoid arthritis 2010 trial. 2018;284(6):664-73.
- 19 538 43. Misse R, Borges I, Santos A, Sales de Oliveira D, Souza J, Gualano B, et al. Effects of Exercise
20 539 Training on Endothelial Function, Arterial Structure, and Physical Conditioning in Patients with Systemic
21 540 Autoimmune Myopathies: A Case Series Study. *Open Journal of Rheumatology and Autoimmune*
22 541 *Diseases*. 2019:57-68.
- 23 542 44. Shin JH, Lee Y, Kim SG, Choi BY, Lee HS, Bang SY. The beneficial effects of Tai Chi exercise on
24 543 endothelial function and arterial stiffness in elderly women with rheumatoid arthritis. *Arthritis research*
25 544 *& therapy*. 2015;17:380.
- 26 545 45. Veldhuijzen van Zanten J, Sandoo A. Comparison of the effects of exercise and anti-TNF
27 546 treatment on cardiovascular health in rheumatoid arthritis: results from two controlled trials.
28 547 2019;39(2):219-25.
- 29 548 46. dos Reis-Neto ET, da Silva AE, Monteiro CM, de Camargo LM, Sato EI. Supervised physical
30 549 exercise improves endothelial function in patients with systemic lupus erythematosus. *Rheumatology*
31 550 *(Oxford, England)*. 2013;52(12):2187-95.
- 32 551 47. Mak A, Kow NY, Schwarz H, Gong L, Tay SH, Ling LH. Endothelial dysfunction in systemic lupus
33 552 erythematosus - a case-control study and an updated meta-analysis and meta-regression. *Scientific*
34 553 *reports*. 2017;7(1):7320.
- 35 554 48. Tinken TM, Thijssen DH, Hopkins N, Dawson EA, Cable NT, Green DJ. Shear stress mediates
36 555 endothelial adaptations to exercise training in humans. *Hypertension (Dallas, Tex : 1979)*.
37 556 2010;55(2):312-8.
- 38 557 49. Hambrecht R, Wolf A, Gielen S, Linke A, Hofer J, Erbs S, et al. Effect of exercise on coronary
39 558 endothelial function in patients with coronary artery disease. *The New England journal of medicine*.
40 559 2000;342(7):454-60.
- 41 560 50. Totoson P, Maguin-Gaté K, Nappey M, Prati C, Wendling D, Demougeot C. Microvascular
42 561 abnormalities in adjuvant-induced arthritis: relationship to macrovascular endothelial function and
43 562 markers of endothelial activation. *Arthritis & rheumatology (Hoboken, NJ)*. 2015;67(5):1203-13.
- 44 563 51. Anderson TJ, Charbonneau F, Title LM, Buithieu J, Rose MS, Conradson H, et al. Microvascular
45 564 function predicts cardiovascular events in primary prevention: long-term results from the Firefighters
46 565 and Their Endothelium (FATE) study. *Circulation*. 2011;123(2):163-9.
- 47 566 52. Lind L, Berglund L, Larsson A, Sundström J. Endothelial Function in Resistance and Conduit
48 567 Arteries and 5-Year Risk of Cardiovascular Disease. *Circulation*. 2011;123(14):1545-51.
- 49
50
51
52
53
54
55
56
57
58
59
60

- 1
2
3 568 53. Huang C, Wang J, Deng S, She Q, Wu L. The effects of aerobic endurance exercise on pulse wave
4 569 velocity and intima media thickness in adults: A systematic review and meta-analysis. *Scandinavian*
5 570 *journal of medicine & science in sports*. 2016;26(5):478-87.
- 6 571 54. Byrkjeland R, Stensæth KH, Anderssen S, Njerve IU, Arnesen H, Seljeflot I, et al. Effects of
7 572 exercise training on carotid intima-media thickness in patients with type 2 diabetes and coronary artery
8 573 disease. Influence of carotid plaques. *Cardiovascular diabetology*. 2016;15:13.
- 9 574 55. Ornish D, Brown SE, Scherwitz LW, Billings JH, Armstrong WT, Ports TA, et al. Can lifestyle
10 575 changes reverse coronary heart disease? The Lifestyle Heart Trial. *Lancet (London, England)*.
11 576 1990;336(8708):129-33.
- 12 577 56. Kim SH, Lee SJ, Kang ES, Kang S, Hur KY, Lee HJ, et al. Effects of lifestyle modification on
13 578 metabolic parameters and carotid intima-media thickness in patients with type 2 diabetes mellitus.
14 579 *Metabolism*. 2006;55(8):1053-9.
- 15 580 57. Rausch Osthoff AK, Niedermann K, Braun J, Adams J, Brodin N, Dagfinrud H, et al. 2018 EULAR
16 581 recommendations for physical activity in people with inflammatory arthritis and osteoarthritis. *Ann*
17 582 *Rheum Dis*. 2018;77(9):1251-60.
- 18 583 58. Semble EL, Loeser RF, Wise CM. Therapeutic exercise for rheumatoid arthritis and osteoarthritis.
19 584 *Seminars in Arthritis and Rheumatism*. 1990;20(1):32-40.
- 20 585 59. Wisløff U, Støylen A, Loennechen JP, Bruvold M, Rognum Ø, Haram PM, et al. Superior
21 586 cardiovascular effect of aerobic interval training versus moderate continuous training in heart failure
22 587 patients: a randomized study. *Circulation*. 2007;115(24):3086-94.
- 23 588 60. Sveaas SH, Bilberg A, Berg IJ, Provan SA, Rollefstad S, Semb AG, et al. High intensity exercise for
24 589 3 months reduces disease activity in axial spondyloarthritis (axSpA): a multicentre randomised trial of
25 590 100 patients. *British Journal of Sports Medicine*. 2020;54(5):292.
- 26 591 61. de Jong Z, Munneke M, Zwinderman AH, Kroon HM, Jansen A, Runday KH, et al. Is a long-term
27 592 high-intensity exercise program effective and safe in patients with rheumatoid arthritis? Results of a
28 593 randomized controlled trial. *Arthritis and rheumatism*. 2003;48(9):2415-24.
- 29 594 62. Hsieh LF, Chen SC, Chuang CC, Chai HM, Chen WS, He YC. Supervised aerobic exercise is more
30 595 effective than home aerobic exercise in female chinese patients with rheumatoid arthritis. *Journal of*
31 596 *rehabilitation medicine*. 2009;41(5):332-7.
- 32 597 63. Munneke M, de Jong Z, Zwinderman AH, Jansen A, Runday HK, Peter WF, et al. Adherence and
33 598 satisfaction of rheumatoid arthritis patients with a long-term intensive dynamic exercise program (RAPIT
34 599 program). *Arthritis and rheumatism*. 2003;49(5):665-72.
- 35 600 64. Baxter SV, Hale LA, Stebbings S, Gray AR, Smith CM, Treharne GJ. Walking is a Feasible Physical
36 601 Activity for People with Rheumatoid Arthritis: A Feasibility Randomized Controlled Trial. *Musculoskeletal*
37 602 *care*. 2016;14(1):47-56.
- 38 603 65. Thijssen DHJ, Bruno RM, van Mil A, Holder SM, Fata F, Greyling A, et al. Expert consensus and
39 604 evidence-based recommendations for the assessment of flow-mediated dilation in humans. *European*
40 605 *heart journal*. 2019;40(30):2534-47.
- 41 606 66. Generali E, Bose T, Selmi C, Voncken JW, Damoiseaux JGMC. Nature versus nurture in the
42 607 spectrum of rheumatic diseases: Classification of spondyloarthritis as autoimmune or autoinflammatory.
43 608 *Autoimmunity Reviews*. 2018;17(9):935-41.
- 44 609 67. Liu E, Perl A. Pathogenesis and treatment of autoimmune rheumatic diseases. *Current opinion in*
45 610 *rheumatology*. 2019;31(3):307-15.
- 46 611 68. Chen Y, Shen F, Liu J, Yang GY. Arterial stiffness and stroke: de-stiffening strategy, a therapeutic
47 612 target for stroke. *Stroke and vascular neurology*. 2017;2(2):65-72.
- 48 613 69. Holwerda Seth W, Luehrs Rachel E, DuBose L, Collins Michael T, Wooldridge Nealy A, Stroud
49 614 Amy K, et al. Elevated Muscle Sympathetic Nerve Activity Contributes to Central Artery Stiffness in
50 615 Young and Middle-Age/Older Adults. *Hypertension (Dallas, Tex : 1979)*. 2019;73(5):1025-35.
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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, cPWV
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%

								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.

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.

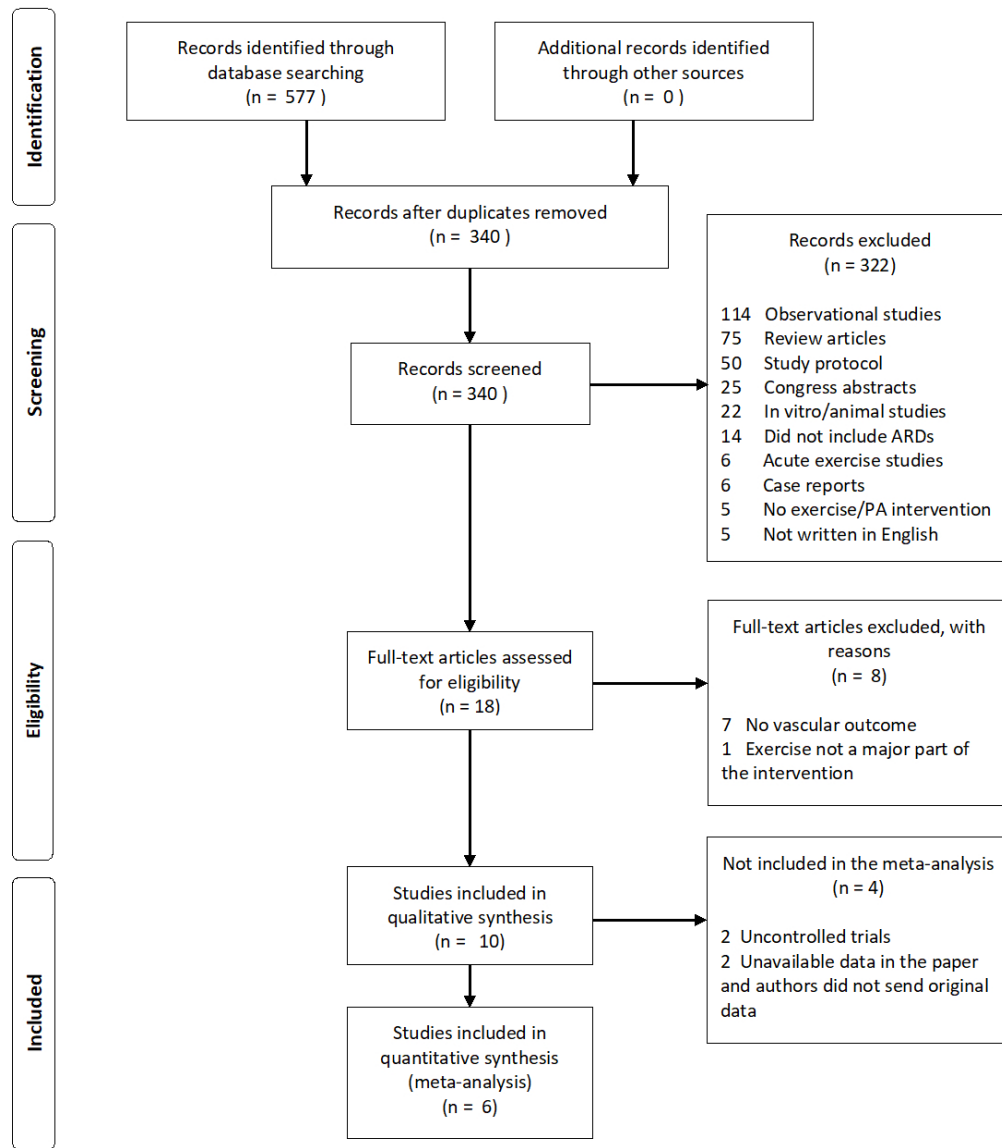


Figure 1. Flow-chart of the systematic review. ARD, autoimmune rheumatic diseases; PA, physical activity.

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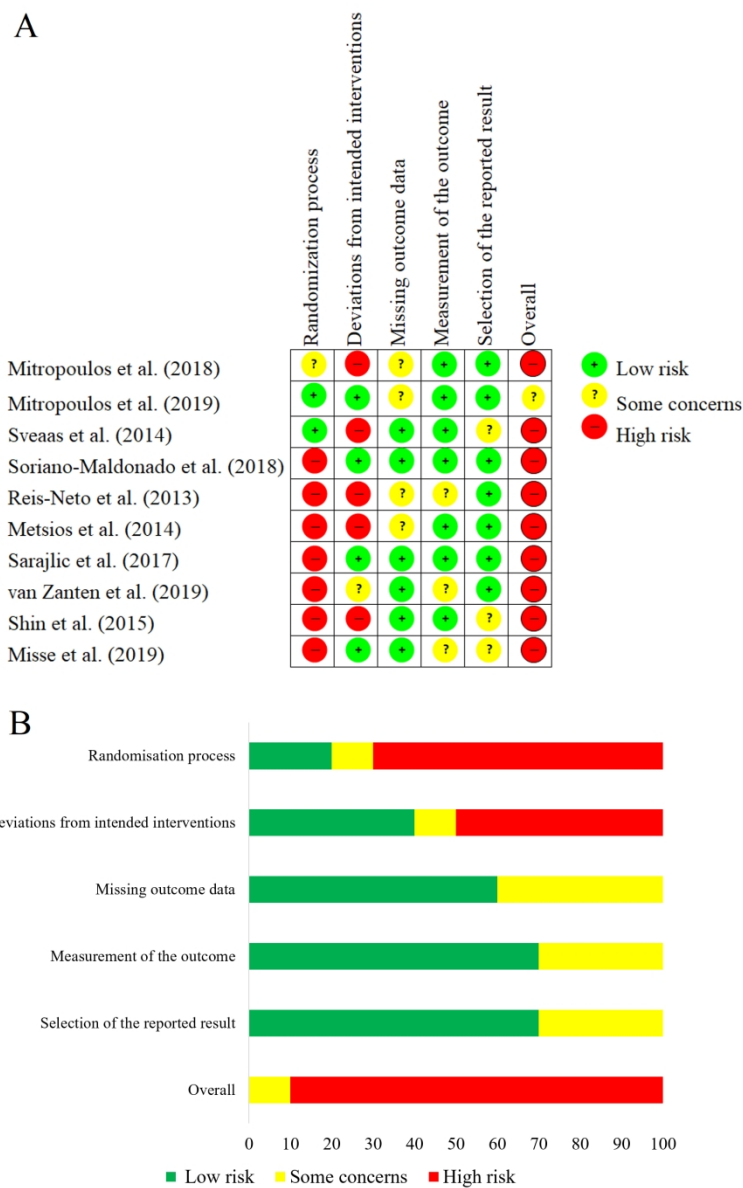


Figure 2. Risk of bias of the included studies. Panel A depicts the risk-of-bias judgement for each study and bias domain. Panel B depicts the overall percentage of 'low risk', 'some concerns' and 'high risk' of bias in each of the bias domain.

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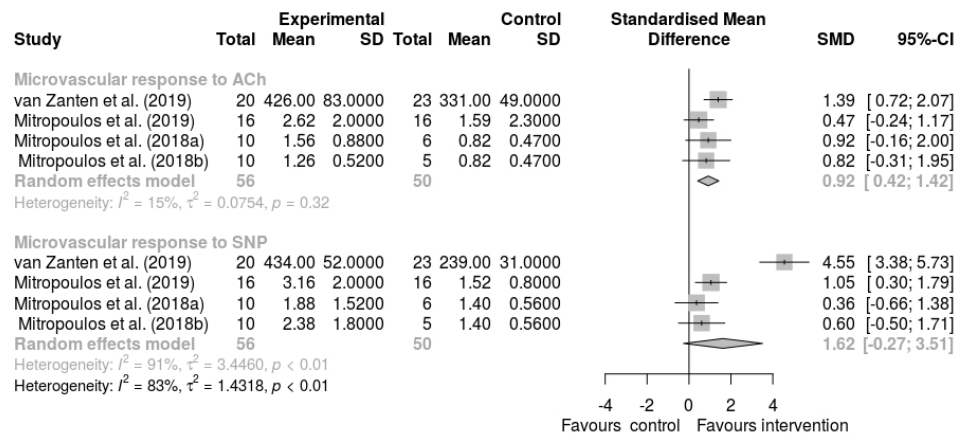


Figure 3. Effects of physical activity on microvascular function. The upper panel presents the responses to ACh (i.e. endothelium-dependent function) and the bottom panel presents the responses to SNP (endothelium-independent function). SMD, standardised mean difference; CI, confidence interval; SD,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

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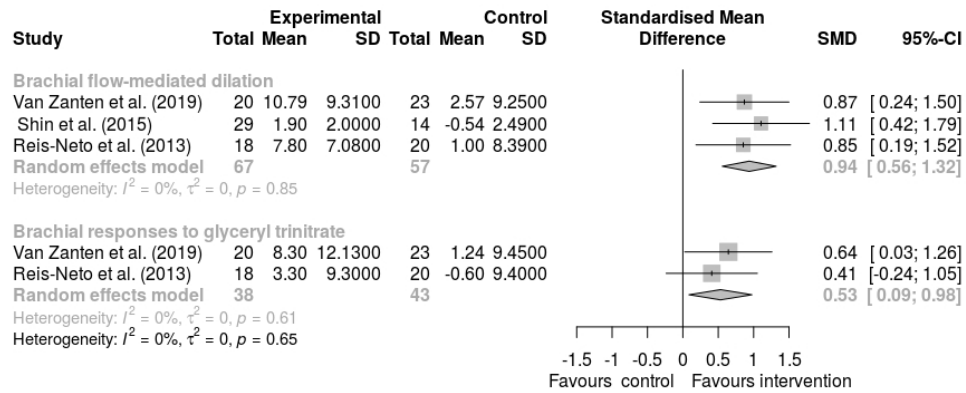


Figure 4. Effects of physical activity on macrovascular function. The upper panel presents the brachial flow-mediated dilation (FMD%; endothelium-dependent function) and the bottom panel presents the brachial artery responses to glyceryl trinitrate (GTN%; endothelium-independent function). SMD, standardized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

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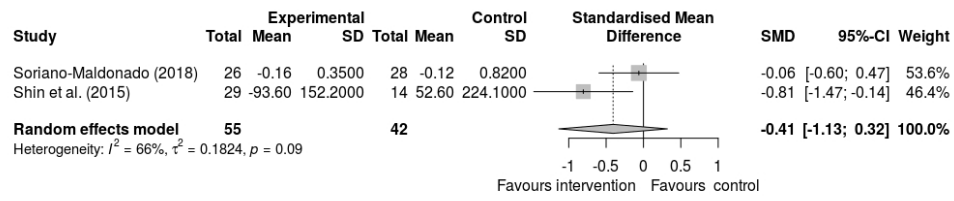


Figure 5. Effects of physical activity on macrovascular structure as assessed by pulse wave velocity analysis. SMD, standardized mean difference; CI, confidence interval; SD, standard deviation.

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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



PRISMA 2009 Checklist

Page 1 of 2

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			



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
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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.

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For Peer Review

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3 **SUPPLEMENTARY MATERIAL**
4

5 **Table S1.** Search strategy.
6

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

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Table S2. 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.

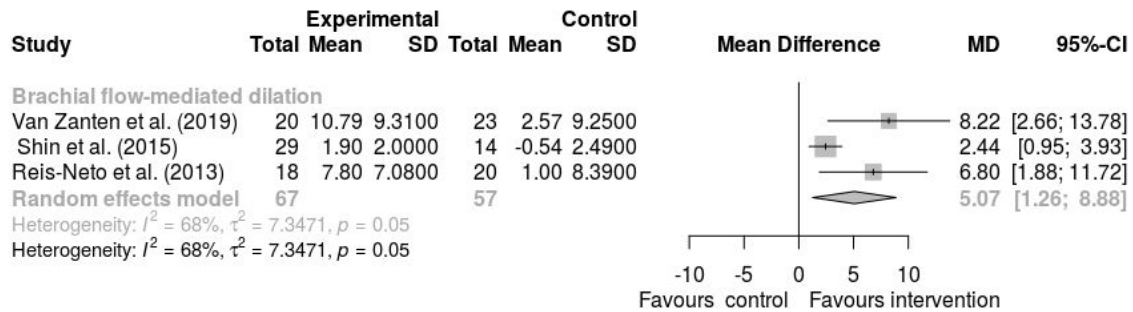


Figure S1. Absolute changes in flow-mediated dilation (FMD%) calculated as mean difference (MD) between intervention and control groups pre-post changes. CI, confidence interval; SD, standard deviation.