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Long-Term Aerobic Exercise Improves Vascular Function in Old Age: A Systematic Review, Meta-Analysis and Meta Regression of Observational and Interventional Studies

Amy Campbell¹, Fergal Grace², Louise Ritchie¹, Alexander Beaumont³, Nick Sculthorpe^{1*}

¹University of the West of Scotland, United Kingdom, ²Federation University, Australia, ³York St John University, United Kingdom

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Author contribution statement

The literature search and selection of studies was performed by authors AC and AB. Data analysis was performed by NS, AC, and AB. Interpretation of data was performed by NS, FG, LR and AC. Manuscript preparation and revision was undertaken by all authors

Keywords

Exercise, Flow mediated dilatation (FMD), vascular health, Ageing, Study quality, Meta regression

Abstract

Word count: 277

There is an emerging body of literature relating to the effectiveness of frequent aerobic exercise as a prophylactic for age-associated dysfunction of large arteries, yet systematic evaluation and precise estimate of this effect is unknown. We conducted a systematic review and meta-analysis of controlled studies examining flow mediated dilatation (FMD) of athletic older persons and otherwise healthy sedentary counterparts to (i) compare FMD as a determinant of endothelial function between athletes and sedentary (ii) summarise the effect of exercise training on FMD in studies of sedentary ageing persons. Studies were identified from systematic search of major electronic databases from inception to January 2018. Study quality was assessed before conducting a random effects meta-analysis to calculate a pooled ES (mean difference) with 95% CI's. Thirteen studies [10 cross-sectional (n=485); 4 intervention (n=125)] with age ranges from 62-75 years underwent quantitative pooling of data. Older athletes had more favourable FMD compared with sedentary controls (2.1%; CI: 1.4%, 2.8%; $P < 0.001$). There was no significant improvement in the vascular function of sedentary cohorts following a period of exercise training (0.7%; CI: -0.675%, 2.09%; $P = 0.316$). However, there was a significant increase in baseline diameter from pre to post intervention (0.098%; CI: 0.066%, 0.130%; $P < 0.001$). In addition, there was no significant difference in endothelial independent vasodilation between the trained and sedentary older adults (1.57%; CI: -0.13%, 3.27%; $P = 0.07$) or from pre to post exercise intervention (1.48%; CI: -1.34%, 4.3%; $P = 0.3$). In conclusion, long-term aerobic exercise appears to attenuate the decline in endothelial vascular function, a benefit which is maintained during chronological ageing. However, currently there is not enough evidence to suggest that exercise interventions improve vascular function in previously sedentary healthy older adults.

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Data availability statement

Generated Statement: No datasets were generated or analyzed for this study.

1 **Long-Term Aerobic Exercise Improves Vascular Function in Old**
2 **Age: A Systematic Review, Meta-Analysis and Meta Regression of**
3 **Observational and Interventional Studies**

4 Amy Campbell ^a, Fergal Grace ^b, Louise Ritchie ^a, Alexander Beaumont ^c and Nicholas
5 Sculthorpe ^{a*}

6 ^a Institute of Clinical Exercise & Health Sciences, School of Health and Life Sciences,
7 University of the West of Scotland, Hamilton, UK

8 ^b School of Health Science & Psychology, Faculty of Health, Federation University Australia,
9 Ballarat, VIC, Australia.

10 ^c School of Sport, York St John University, UK
11
12
13

14 * Correspondence:

15 Prof. N Sculthorpe

16 nicholas.sculthorpe@uws.ac.uk
17
18

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33 **Keywords: vascular ageing, vascular function, flow mediated dilation, healthy older**
34 **adults, exercise**

35

36 **Abstract**

37

38 There is an emerging body of literature relating to the effectiveness of frequent aerobic
39 exercise as a prophylactic for age-associated dysfunction of large arteries, yet systematic
40 evaluation and precise estimate of this effect is unknown.

41 We conducted a systematic review and meta-analysis of controlled studies examining
42 flow mediated dilatation (FMD) of athletic older persons and otherwise healthy sedentary
43 counterparts to (i) compare FMD as a determinant of endothelial function between athletes and
44 sedentary individuals and, (ii) summarise the effect of exercise training on FMD in studies of
45 sedentary ageing persons. Studies were identified from systematic search of major electronic
46 databases from inception to January 2018. Study quality was assessed before conducting a
47 random effects meta-analysis to calculate a pooled ES (mean difference) with 95% CI's.
48 Thirteen studies [4 interventional (n=125); 10 cross-sectional (including one study from the
49 interventional analysis; n=485)] with age ranges from 62-75 years underwent quantitative
50 pooling of data. The majority of study participants were male.

51 Older athletes had more favourable FMD compared with sedentary controls (2.1%; CI:
52 1.4%, 2.8%; P<0.001). There was no significant improvement in the vascular function of
53 sedentary cohorts following a period of exercise training (0.7%; CI: -0.675%, 2.09%; P=0.316).
54 However, there was a significant increase in baseline diameter from pre to post intervention
55 (0.1mm; CI: 0.07mm, 0.13mm; P<0.001). In addition, there was no significant difference in
56 endothelial independent vasodilation between the trained and sedentary older adults (1.57%;
57 CI: -0.13%, 3.27%; P=0.07), or from pre to post exercise intervention (1.48%; CI: -1.34%,
58 4.3%; P=0.3).

59 In conclusion, long-term aerobic exercise appears to attenuate the decline in endothelial
60 vascular function, a benefit which is maintained during chronological ageing. However,
61 currently there is not enough evidence to suggest that exercise interventions improve vascular
62 function in previously sedentary healthy older adults.

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74 1. Introduction

75 **Impaired vascular function as a result of ageing** occurs due to the coalition of
76 environment, oxidative stress and inflammation (Donato et al., 2007; Seals et al., 2011). These
77 factors result in reduced nitric oxide (NO) bioavailability, causing a failure of the vasculature
78 to dilate in response to increases in shear stress during hyperaemia (Taddei et al., 2000, 2001;
79 Virdis et al., 2010). **Furthermore, vascular structure is also compromised with age as wall**
80 **stiffness increases, reducing flexibility.** **Therefore, vascular dysfunction** promotes
81 cardiovascular disease (CVD) risk and contributes both to a reduction in health span and overall
82 life expectancy (Roger et al., 2012). Given this premise there is an increasingly important but
83 unmet need for interventions which aim to reduce inflammation and oxidative stress, while
84 developing an environment conducive to vascular function (Seals et al., 2009).

85 Modifiable lifestyle factors, such as increased physical activity (PA) and/or exercise
86 have been advocated to reduce vascular impairment and restore NO dependent vasodilatation,
87 even in apparently healthy older cohorts (Grace et al., 2015; Taddei et al., 2000). Multiple
88 lines of evidence, including both human and pre-clinical models demonstrate that those
89 individuals who are regularly active enjoy superior vascular function, with lower levels of
90 systemic inflammation and oxidative stress (Eskurza et al., 2004; Grace et al., 2015;
91 Lesniewski et al., 2013; Seals, 2014a). Despite this more than 1 in 4 of all adults¹, and 85 to
92 90% of older adults in developed countries fail to meet the PA guidelines to maintain
93 cardiovascular health (Sparling et al., 2015). This represents a contemporary challenge for
94 researchers and healthcare providers to provide evidence-based strategies to improve
95 engagement with PA, and to improve vascular function in older adults as a primary therapeutic
96 target².

97 Vascular function, **or specifically endothelial function**, is commonly assessed non-invasively
98 using the flow mediated dilation (FMD) technique. As cardiovascular events can be
99 independently predicted by endothelial compliance, FMD has emerged as a conventional
100 method to determine vascular function (Inaba et al., 2010). **Although assessment of whole**
101 **vascular function includes measures of arterial stiffness, FMD is specific to measuring**
102 **endothelial function whereby endothelial NO contributes to the vasodilation of vessels after a**
103 **temporary occlusion of blood flow** (Green et al., 2014). However, there are few systematic
104 interrogations of literature examining vascular function of healthy older adults, and those that
105 have been performed, while well executed, have key limitations. For example, (Ashor et al.,
106 2015) and (Early et al., 2017) reported that exercise training improved vascular function in
107 healthy and diseased cohorts, but in both cases, data pooling mixed young and old participants,
108 preventing direct assessment of the effect of exercise on vascular function exclusively in older
109 individuals. Moreover, since disease may superimpose additional vascular dysfunction on top
110 of ageing alone, it is unclear whether exercise improves vascular function due to direct effects
111 of disease, on age *per se*, or a combination of the two. A further review by (Montero et al.,

¹ The World Health Organization (2017). The World Health Organization Physical Activity Fact Sheet. Available at: <http://www.who.int/mediacentre/factsheets/fs385/en/>.

² The World Health Organization (2010). Global Recommendations on Physical Activity for Health. Available at: http://apps.who.int/iris/bitstream/10665/44399/1/9789241599979_eng.pdf.

112 2014) identified that exercise trained adults had displayed superior vascular function compared
113 to their untrained counterparts. However, this review compared trained and untrained adults
114 and did not address the effects of training programmes on vascular function in older adults.
115 Moreover, their inclusion criteria encompassed studies of both middle and old age cohorts.
116 Given that the beneficial effects of exercise may reduce with increasing age, it is difficult to
117 interpret the results of Montero et al., (2014) in an exclusively older population.

118 Consequently, no meta-analysis has assessed the degree to which older (>60 years)
119 trained individuals may have greater indices of vascular function than their untrained
120 counterparts. Equally, there are no meta-analyses assessing the effectiveness of exercise or PA
121 interventions in improving vascular function in similarly aged, but otherwise healthy adults.
122 Unpicking the relationships between vascular function, ageing, and exercise is necessary to
123 enable evidence-based proposals to support health in old age. Therefore, given these gaps in
124 the literature, the aim of this systematic review and meta-analysis was to address the following
125 questions:

- 126 (i) Do longer-term trained older persons have more favourable vascular function,
127 as determined by FMD, than age matched sedentary controls?
 - 128 (ii) Do short-term exercise training interventions improve vascular function in
129 previously sedentary but healthy older individuals?
- 130

131 **2. Methods**

132 The current systematic review and Meta-analysis was conducted in accordance with the
133 2009 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)
134 checklist, and the 2000 Meta-analysis Of Observational Studies in Epidemiology checklist
135 (Moher et al., 2009; Stroup et al., 2000).

136 **2.2 Search strategy**

137 An electronic database search was conducted to identify relevant exercise studies using
138 FMD to determine vascular function of older healthy exercising and sedentary adults.
139 PubMed/MEDLINE (abstract/title), Web of Science (title only) and ScienceDirect
140 (abstract/title/keywords) online databases were searched, and all studies from inception to the
141 date searched (January 2018) were included. The search string included (brachial artery flow
142 mediated dila* OR vasodilation OR vascular function OR vascular reactivity OR vascular
143 health OR endothelial function OR brachial artery) AND (exercise OR train* OR physical
144 activity OR untrain* OR fitness OR program*). Filters were applied to ensure that only records
145 in English with human participants were included in the search results. Reference lists from
146 eligible articles were reviewed to search for additional relevant studies which may not have
147 been present during the database search, before being subsequently screened for potential
148 inclusion into the meta-analysis.

149 **2.3 Inclusion and exclusion criteria**

150 The inclusion criteria consisted of: (1) non-pharmacological studies of male and female
151 human participants; (2) aged 60 years and over, and (3) employing either cross-sectional,
152 cohort or randomised control trial (RCT) study designs. (4) Cross sectional design studies had
153 to have an aged matched control group, while in the aerobic exercise intervention, studies both
154 pre and post intervention (cohort) or RCT designs were included. (5) Studies had to include
155 physically healthy cohorts comprising of sedentary individuals for intervention studies, or
156 regular exercisers and sedentary individuals for cross-sectional studies. (6) Vascular function

157 was determined using endothelium dependent FMD of the brachial artery (BA) using valid
158 ultrasonic techniques and occlusion of the lower arm. (7) Studies must have also been
159 published in English language literature. FMD was used as the main measure of vascular
160 function as it is the most widely used non-invasive assessment of endothelial function, and thus
161 gives an accurate representation of endothelial health. As FMD can predict vascular events
162 within asymptomatic persons, it can identify impairments in vascular function within healthy
163 older adults. There was no limitation imposed on the method of subsequent analysis, thus
164 studies using either fixed post-deflation time points or continuous edge detection methods were
165 included. Other measures of vascular function such as pulse wave velocity (PWV) were not
166 included within the meta-analysis as we were specifically interested at measuring endothelial
167 function, rather than arterial stiffness. However, since arterial diameter has been suggested as
168 a potential confounder when assessing FMD (Atkinson and Batterham, 2015) we included
169 analysis of this structural measure. There were also no limitations regarding the length, duration
170 or intensity of exercise interventions.

171 Studies were excluded if they (i) used pharmacological stimulus, (ii) assessed a single
172 acute exercise bout (iii) assessed resistance interventions only, or (iv) assessed vascular
173 function using a method other than FMD. In addition, (v) studies which occluded the upper
174 arm during the FMD protocol were also excluded as this can cause a greater vasodilatory
175 response after ischemia, possibly from mechanisms other than NO (Berry et al., 2000). As the
176 current study aimed to assess the function of the vascular endothelium as a measure of vascular
177 function, only lower arm occlusion was included as the post occlusion vasodilation is mainly
178 NO mediated, and more representative of endothelium function (Doshi et al., 2001; Green et
179 al., 2011). For example, there is evidence that increases in arterial diameter as a result of
180 hyperaemic shear are abolished in the presence of a selective blockage of NO production within
181 lower arm occlusion, but not upper arm occlusion (Doshi et al., 2001). We therefore excluded
182 studies which occluded the upper arm during the FMD protocol as this method causes a greater
183 ischemic response which may not be exclusively due to NO, and thus endothelial function.
184 Furthermore, including lower arm occlusion also helped to standardise the FMD protocol
185 between the included studies.

186

187 2.4 Study selection

188 The literature search and selection of studies was performed by authors AC and AB.
189 Following an initial screen of titles and abstracts (AC), full scrutiny of potentially eligible
190 studies were independently screened by AC and AB using the specific inclusion criteria. NS
191 arbitrated any disagreements in study inclusion.

192 2.5 Data extraction

193 Data from the final list of eligible studies were extracted and entered into a spreadsheet
194 (Microsoft Excel 2010). Extracted data included the following for all participant groups in
195 each study: (1) participant ages; (2) participant activity status; (3) participant maximum oxygen
196 uptake ($\dot{V}O_{2max}$); (4) sample size; (5) study type; (6) intervention type, frequency, duration and
197 intensity (for interventional studies); (7) relative BA FMD percentage change ($\Delta FMD\%$); (8)
198 BA baseline diameter (mm, when reported); (9) endothelial independent vasodilation (EIDV)
199 (% when measured); (10) supervised and non-supervised interventions; (11) shear rate/stress
200 (when measured) and (12) details of FMD protocols. When studies reported both cross-
201 sectional and interventional data from their analysis, each were screened individually to

202 determine their eligibility. Given the suggestions of morphological adaptations in response to
203 training (Green et al., 2012), we also sought to examine structural changes. Arterial diameter
204 was extracted from studies to determine whether structural adaptations also occurred as a result
205 of exercise. As arterial hyperaemic response is influenced by baseline diameter, extracting
206 arterial diameter may help to understand why some studies show an increase in FMD or not.

207 Δ FMD% data were extracted as the main outcome variable. If not reported, Δ FMD%
208 was calculated as: [(post occlusive peak BA diameter – baseline BA diameter)/
209 (baseline BA diameter) * 100], where post-occlusive diameter was the peak artery diameter
210 which occurred following cuff deflation, and baseline was the diameter determined at rest. All
211 data were entered as mean \pm standard deviation (SD). When studies reported standard error of
212 the mean (SEM), conversion to SD was performed using the equation $SD = SEM * \sqrt{N}$,
213 where N was the number of participants. Authors of several eligible studies were contacted by
214 email when data were not available from the text, figures or tables. Where authors failed to
215 respond, mean and standard deviation were extracted from graphs using the calibrated
216 measuring function within the software 'ImageJ' (Image Processing and Analysis in Java,
217 Maryland, USA) (Abramoff et al., 2004).

218 2.6 Study quality assessment

219 Appraisal of study quality was undertaken using an assessment tools established by the
220 National Heart, Lung and Blood Institute (NHLBI, Bethesda, MD). Individual quality
221 assessment tools specific to the RCT³, cohort⁴ and cross-sectional study designs⁵ were used
222 and subsequently classified as good, fair, or poor.

223 2.7 Statistical analysis

224 All study data were analysed using the Comprehensive Meta-Analysis software
225 (Biostat: V 2.2.064, Englewood, NJ, USA). Data were entered in accordance with the research
226 questions: (1) Δ FMD% of sedentary participants compared with those who were long-term
227 trained; and (2) pre and post Δ FMD% of previously sedentary participants who had completed
228 an exercise intervention.

229 The meta-analysis calculated the mean difference (MD) of BA Δ FMD%, BA diameter
230 (mm) and BA EIDV (%), between the long-term trained versus sedentary participants (question
231 1) and pre to post intervention in sedentary participants (question 2). A meta-analysis
232 comparing the Δ FMD% of supervised and non-supervised interventions was also included
233 within the analysis. Pooled data were analysed using a random effects model, and differences
234 in means in a positive direction represented an increase in FMD, baseline diameter and EIDV
235 in favour of exercise, whereas a negative direction indicated a decrease. Between study
236 heterogeneity was calculated for each study question, and reported as Cochran's Q and I², with
237 variability of measurement characterised as low, medium or high as 25%, 50% and 75%,

³ Quality Assessment of Controlled Intervention Studies (2014). *Natl. Heart Lung Blood Inst.* Available at: <https://www.nhlbi.nih.gov/health-pro/guidelines/in-develop/cardiovascular-risk-reduction/tools/rct>.

⁴ Quality Assessment Tool for Before-After (Pre-Post) Studies With No Control Group (2014). *Natl. Heart Lung Blood Inst.* Available at: <https://www.nhlbi.nih.gov/health-pro/guidelines/in-develop/cardiovascular-risk-reduction/tools/before-after>

⁵ Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies (2014). *Natl. Heart Lung Blood Inst.* Available at: <https://www.nhlbi.nih.gov/health-pro/guidelines/in-develop/cardiovascular-risk-reduction/tools/cohort>

238 respectively (Higgins et al., 2003). A method of moments mixed effects meta-regression was
239 conducted to determine if age significantly moderated the effect on Δ FMD%. Publication bias
240 was assessed by Egger's regression. All data are presented as mean \pm SD, and a P-value of
241 ≤ 0.05 identified statistical significance.

242 3. Results

243 3.1 Study selection

244 Following the literature search from all three databases, 3199 records were identified
245 after the removal of duplicates. Based on title and abstract, 3132 records were excluded,
246 primarily due to the inclusion of participant morbidity. With the inclusion of 1 study from an
247 external source following reference list examination, full texts of the remaining 68 articles were
248 screened in accordance with the study inclusion and exclusion criteria. Fifty-five studies were
249 excluded for the following reasons: non-reporting of scaling used in FMD analysis (n=1);
250 occlusion of the upper arm during the FMD protocol (n=3); no intervention group (n=1); no
251 sedentary group (n=2); participants were under 60 years of age (n=11); participants were
252 unhealthy (n=2); FMD was not used (n=6); BA FMD was not performed (n=1); conference
253 abstract only (n=26) and no full text available (n=2). Consequently, 13 studies were deemed
254 eligible for analysis. One study consisted of both an intervention and a cross-sectional design
255 and analysis, however only the cross-sectional section met all inclusion criteria (Pierce et al.,
256 2011b). Additionally, one of the interventional studies contained both baseline and post
257 intervention data and was therefore included in both comparisons (Grace et al., 2015). As a
258 result the overall analysis contained 10 cross-sectional (DeVan et al., 2013; Eskurza et al.,
259 2004, 2005b; Franzoni et al., 2005; Galetta et al., 2006; Grace et al., 2015; Jensen-Urstad et
260 al., 1999; Pierce et al., 2011a, 2011b; Walker et al., 2009) and 4 interventional studies (Grace
261 et al., 2015; Klonizakis et al., 2014; Suboc et al., 2014; Thijssen et al., 2007) (Figure 1). The
262 included studies were believed to be mainly of 'good' quality as measured using the National
263 Heart, Lung and Blood Institute study quality assessment criteria (Tables 3-5).

264 The cross-sectional and interventional analyses were found to have moderate and low
265 heterogeneity ($I^2=63.6\%$; $P=0.003$ and $I^2=47.4$ respectively). To compensate for the
266 heterogeneity identified, the meta-analysis was conducted using random effect models, as
267 recommended by the Cochrane guidelines (Higgins and Green, 2011).

268 3.2 Question 1: Cross-sectional study analysis

269 The 10 cross-sectional studies included 485 participants (210 long-term trained and 275
270 sedentary) (DeVan et al., 2013; Eskurza et al., 2004, 2005a; Franzoni et al., 2005; Galetta et
271 al., 2006; Grace et al., 2015; Jensen-Urstad et al., 1999; Pierce et al., 2011a, 2011b; Walker et
272 al., 2009). Ages ranged from 62 to 75 years in the sedentary participants (mean of 65 years)
273 and from 61 to 75 years in the long-term trained participants (mean of 65 years). Cohort sizes
274 ranged from n=9 to n=65 participants in the long-term trained and n=9 to n=102 in the
275 sedentary groups. Seven of the long-term trained groups and 5 of the sedentary groups
276 contained less than 20 participants (Eskurza et al., 2005b; Franzoni et al., 2005; Grace et al.,
277 2015; Jensen-Urstad et al., 1999; Pierce et al., 2011a; Walker et al., 2009). Two of the 10
278 studies contained both male and female participants (DeVan et al., 2013; Pierce et al., 2011b).
279 Studies with both males and females were included as it has previously been identified that
280 post-menopausal females display a similar BA FMD compared to males of the same age
281 (Jensen-Urstad and Johansson, 2001). Additionally, as only one study presented male and
282 female data individually, results for each sex were analysed together. Long-termed trained
283 participants consisted of endurance runners, swimmers and cyclists who trained at least three
284 times per week and with regular exercise participation between 2 and 37 years.

285 Studies described cuff occlusion pressures to range from 40mmHg above systolic blood
286 pressure to 300mmHg and remained inflated between 4 and 5min. Δ FMD% was analysed from
287 all 10 cross-sectional studies and ranged from $4.8 \pm 5\%$ to $7 \pm 1.8\%$ in the long-term trained
288 participants and $1.1 \pm 2.1\%$ to $5.3 \pm 2.2\%$ in sedentary participants. Δ FMD% values
289 normalised for shear stress were reported in one study (Eskurza et al., 2005b), and for
290 hyperaemic shear in one other (Eskurza et al., 2004). All 10 cross-sectional studies reported
291 mean baseline BA diameter data, whereas only 9 studies reported EIDV data.

292 Data pooling from the meta-analysis indicated that Δ FMD% was significantly greater
293 in long-term trained, versus sedentary older adults (MD: 2.1%, 95% CI: 1.4%, 2.8%; $P < 0.001$;
294 Figure 2). Moderate heterogeneity was observed between the 10 cross-sectional studies ($I^2 =$
295 63.6%; $P = 0.003$). Egger's regression determined that there was a low risk of publication bias
296 ($P = 0.7$). The meta-regression found no significant effect of age on Δ FMD% ($P = 0.08$; Table
297 8). Data pooling identified that EIDV was not significantly different between the trained and
298 untrained participants (MD: 1.57%; 95% CI: -0.132%, 3.274%; $P = 0.07$; Figure 4), and baseline
299 diameter of the BA was also similar between the two groups (MD: -0.1mm; 95% CI: -0.09mm,
300 0.29mm; $P = 0.31$; Figure 3).

301

302 **3.3 Question 2: Intervention study analysis**

303 The 4 intervention studies consisted of 3 cohort designs (Grace et al., 2015; Klonizakis
304 et al., 2014; Thijssen et al., 2007) and one RCT (Suboc et al., 2014). Included in the 4 studies
305 were 125 sedentary participants. Sample sizes ranged from 8 to 77 participants, where two of
306 the studies contained less than 20 participants (Klonizakis et al., 2014; Thijssen et al., 2007).
307 The ages of participants ranged from 62 ± 7 to 70 ± 1 years, with a mean age of 65 years. One
308 of the studies contained both male and female participants (Suboc et al., 2014), and one study
309 recruited only postmenopausal females (Klonizakis et al., 2014). Again, as the study
310 containing both males and females did not present their results separately, data for each sex
311 was analysed together.

312 Cuff inflation during the FMD protocol ranged from 50mmHg above systolic blood
313 pressure to approximately 220mmHg for a 5min period. The duration of study interventions
314 lasted between approximately 9 to 84 sessions from 2 to 12 weeks, with 3 of the studies
315 including exercise interventions of a moderate to high intensity. One of the cohort studies
316 included two separate interventions - one consisting of high intensity, and the other a moderate
317 intensity intervention (Klonizakis et al., 2014). Frequency of interventions ranged from once
318 every 5 days to 7 days per week and lasting between 20min to one hour per day.

319 For the cohort studies Δ FMD% was calculated from baseline and post measures, while
320 post intervention and control values were analysed in the RCT study. Δ FMD% ranged from
321 $3.4 \pm 1.5\%$ and $8.9 \pm 7.9\%$ pre-intervention to $5.4 \pm 1.4\%$ and $7 \pm 4.3\%$ post intervention. All
322 four of the studies reported baseline BA diameter data, whilst only two studies reported data
323 for EIDV.

324 The meta-analysis suggests that there was no significant improvement in Δ FMD% after
325 the exercise interventions in previously sedentary older adults (MD: 0.707%, 95% CI: -0.68%,
326 2.1%; $P = 0.316$; Figure 2). Heterogeneity of the 5 intervention studies were calculated as low
327 ($I^2 = 47.4\%$, $P = 0.107$, and Egger's regression determined that some publication bias may be
328 present ($P = 0.047$). The meta-analysis identified that there was no increase in EIDV from pre
329 to post intervention (MD: 1.48%; 95% CI: -1.3%, 4.3%; $P = 0.303$; Figure 4), however there
330 was a significant increase in BA baseline diameter post intervention (MD: 0.1mm; 95% CI:

331 0.07mm, 0.13mm $P < 0.001$; Figure 3). Finally, $\Delta\text{FMD}\%$ was not affected by whether the
332 interventions were supervised or non-supervised (heterogeneity $p = 0.927$; Figure 5).

333 4. Discussion

334 This systematic review and meta-analysis set out to determine the effects of short and
335 long-term exercise training on vascular function and has 2 main findings. First, pooled data
336 from cross-sectional studies demonstrate that long-term trained healthy older adults have
337 superior vascular function compared with their sedentary but otherwise healthy counterparts;
338 and second that FMD may not improve in sedentary individuals who undertake shorter-term
339 aerobic exercise interventions although there may be an increase in arterial diameter. These
340 data are the first pooled synthesis of controlled observational and interventional studies using
341 healthy older cohorts. The current meta-analysis also allows some comparison between
342 observational and interventional studies since we used the same inclusion and exclusion criteria
343 for studies in both comparisons. Moreover, since all participants were apparently healthy and
344 not taking any medication, the results may provide some insight into the effect of short and
345 long-term training on ageing *per se* rather than on ageing in combination with comorbidities.
346 The current study therefore differs from previous meta-analyses which combined healthy and
347 diseased participants, or mixed middle aged and older participants together in their analysis
348 (Ashor et al., 2015; Early et al., 2017; Montero et al., 2014). Therefore, to our knowledge the
349 current study is the first meta-analysis to identify vascular function exclusively in healthy
350 adults aged 60 years and over who are either endurance trained or untrained, or who have
351 completed an endurance intervention having previously been sedentary.

352 4.1 Question 1 – Do long-term trained older individuals demonstrate superior vascular 353 function, as determined by FMD, than age matched sedentary controls?

354 As outlined above, the meta-analysis indicated that endurance exercise training is
355 associated with improved vascular function, despite considerable differences in study designs.
356 Indeed, within these 10 studies there was a wide range in prior exercise experience, with trained
357 cohorts ranging from a minimum of 2 years training through to life-long exercisers and which
358 may have contributed to the heterogeneity in this comparison.

359 Nevertheless, the data indicates that exercise provides a protective mechanism in long-
360 term trained participants, who experience a slower deterioration of vascular function, compared
361 with sedentary but otherwise healthy older adults. While the protective mechanism of exercise
362 remains to be fully elucidated it is widely believed that the hyperaemic effects of exercise, and
363 the repeated exposure of the endothelium to bouts of increased shear stress, act to reduce the
364 deleterious effects inflammation and oxidative stress (Tinken et al., 2010). The combination
365 of these effects enhances the bioavailability of NO, increasing vasodilation during the
366 hyperaemic response following an ischaemic stimulus (Taddei et al., 2000). From the data
367 presented it appears that the vasculature of healthy older long-term trained adults may be
368 exposed to these physiological mechanisms at a level which preserves vascular function
369 relative to their sedentary counterparts.

370 Previous work has suggested that trained individuals have shown to exhibit wider
371 peripheral artery diameters when compared to untrained individuals. Often referred to as the
372 athletes artery, it is thought to represent arterial remodelling in response to repeated bouts of
373 shear stress which occur during exercise. It is hypothesised that a widened vessel requires less
374 vasodilation during periods of reactive hyperaemia, resulting in reduced dilatation during FMD
375 (Green et al., 2012, 2013). However, the analysis of long-term trained athletes, in whom any
376 such adaptation may be greatest fails to support this concept since arterial diameters of the

377 trained individuals did not differ significantly from the sedentary cohort. Although allometric
378 scaling of the data would have been beneficial, a lack of anthropometric data within the studies
379 meant that scaling was not possible. Nevertheless, the present meta-analysis identified that the
380 trained group had a greater vascular function compared to the untrained group, whilst both
381 displaying a similar baseline artery diameter (Figure 3). These findings agree with a meta-
382 analysis by (Montero et al., 2014) who identified that masters athletes BA diameters were
383 similar to untrained controls, whilst FMD was also significantly greater.

384 The meta-regression aimed to identify if increasing age reduced the improvement in
385 FMD seen in trained individuals compared to sedentary controls. In this case the lack of a
386 significant association indicated that the difference between the two cohorts was not reduced
387 with advancing age. Therefore, the present findings underline the notion that exercise can
388 support vascular function, well into the eighth decade (Grace et al., 2015). It is also notable,
389 that most (DeVan et al., 2013; Pierce et al., 2011a; Walker et al., 2009), but not all (Franzoni
390 et al., 2005), previous work has demonstrated that the vascular function of healthy young
391 untrained adults is greater than older trained adults. These data suggest that, even in well
392 trained individuals, there may be some unavoidable decrement in vascular function with age. In
393 addition, the range in mean ages of the included observational studies was relatively narrow
394 (62 to 75 years); future research should attempt to determine if improvements in vascular
395 function is maintained in those who participate in long-term endurance exercise.

396 **4.2 Question 2 – Do exercise training interventions improve vascular function in** 397 **previously sedentary healthy older persons?**

398 The results of observational studies support the use of exercise to ameliorate the age
399 related decline in vascular function. However, as is the case in all observational studies, the
400 inability to directly link the main outcome (i.e. FMD) to the exposure of interest (i.e. exercise
401 training) limits the confidence that may be placed in conclusions from such studies (Higgins
402 and Green, 2011). In an attempt to overcome this, the present review further assessed the
403 effectiveness of prospective aerobic intervention studies with otherwise sedentary participants.

404 Data pooling indicated that the short term training programmes within the included
405 studies (2 to 12 weeks) did not significantly improve vascular function. This finding is at odds
406 with the results of the cross-sectional assessment of endurance trained participants and controls
407 reported above. However, the training interventions were associated with a significant increase
408 in diameter of the BA at baseline (i.e. immediately prior to cuff inflation; Figure 3). Since
409 included studies were not mechanistic in nature, assessing the lack of effect is speculative.
410 For example, it may be that in this age group the recovery of vascular function is slow and
411 vascular remodelling (i.e. 'the athlete's artery') becomes a primary method of adaptation (Green
412 et al. 2012). Similarly, it may be that since most studies used cycling exercise, early adaptation
413 is focussed on the most active vascular beds of the lower limbs, and assessment of brachial
414 arterial function is insufficiently sensitive (Thijssen et al., 2007).

415 Alternatively, there may not be any vascular dysfunction, and the lack of effect on FMD
416 is a result of the increased baseline diameter which aids total blood flow. Indeed increased
417 shear stress, as a result of an exercise has been suggested to cause systemic arterial remodelling
418 (Maiorana et al., 2011). It is noteworthy that long-term training improved FMD without
419 morphological changes (rationale 1), while short term training increased baseline diameter
420 without improving FMD. Given the interventions were between 2 and 12 weeks, and that
421 vascular remodelling may occur within that time frame (Tinken et al., 2008), it is possible that
422 this is responsible for increased baseline diameter within short term interventions. However,
423 the majority of the interventional studies only measured vascular function before and after the

424 **exercise intervention**. The ‘pre-post’ nature of FMD assessments means that it is possible that
425 improvements were missed by the time post measures were performed. Indeed, future work
426 should assess the presence (or otherwise) of changes in vascular function throughout the time
427 course of training interventions. However, it is also worth noting that there was no
428 improvement in vascular function after 2 weeks of either continuous or high intensity training
429 within the study by Klonizakis et al., (2014), suggesting that relatively fast improvements in
430 vascular function may not always occur.

431 It is also worth noting several limitations of the literature pertaining to interventions in
432 this age group. There were a relatively small number of interventional studies which met the
433 inclusion criteria, meaning that again there was a relatively limited age range of (62 to 70
434 years). Moreover although the studies included within the meta-analysis were endurance
435 based, the 4 included studies consisted of low, moderate and high exercise intensities, and
436 ranged between 2 and 12 weeks, all of which may have contributed to the moderate
437 heterogeneity of the pooled data. Future analyses may benefit from analysing intensity zones
438 as these may affect vascular function differently (Ashor et al., 2015; Early et al., 2017; Ramos
439 et al., 2015), and the greatest effect in the available literature was observed following high
440 intensity interval training (Grace et al., 2015). However, due to the limited number of studies
441 included within the current analysis, it was not possible to categorise studies based on their
442 intensities.

443 However, the lack of improvements in vascular function following exercise
444 interventions, there are a number of other physiological advantages of exercise such as
445 increased muscle strength and power (Reid and Fielding, 2012), as well as a reduction in other
446 risk factors involved in ageing (Barnes, 2015; Seals, 2014b). It therefore seems prudent to
447 advise older adults who begin exercising to remain active indefinitely in order to enjoy other
448 health benefits associated with PA and exercise; not least as detraining may reverse potential
449 improvements in various physiological factors (Pullin et al., 2004).

450 Additionally, the meta-analysis identified that EIDV did not change significantly in
451 either the trained versus untrained participants in the cross-sectional analysis, or pre versus post
452 training within the interventional analysis, however combined pooling suggested a small effect.
453 As EIDV is commonly used as a control test to assess whether improvements in FMD are
454 mainly NO mediated, these data suggest that improvements in trained participants FMD may
455 be due to exercise induced improvements of the vascular endothelium, rather than alterations
456 in vascular smooth muscle within the tunica media (Maruhashi et al., 2013). Conversely, the
457 previously sedentary participants who completed an exercise intervention found no overall
458 improvements in either endothelial function, or vascular smooth muscle cell function.

459

460 **4.3 Study quality**

461 The quality of most studies was determined as ‘good’ (see tables 3-5); however, some
462 limitations were noted. Firstly, the majority of both observational and cohort studies recruited
463 only a small number of participants (less than 20 participants per group) which increases the
464 chances of type 2 error, while also increasing the risk of finding a disproportionately large
465 effect size (Button et al., 2013). Furthermore, the current meta-analysis only identified a single
466 RCT from the literature which met the study’s inclusion criteria. Given that RCTs are widely
467 considered the most internally valid design to determine cause and effect (Evans, 2003), future
468 studies should investigate the use of this approach. Furthermore, few studies reported that
469 outcome assessors were blind to the participant’s group allocation during assessment of FMD,
470 increasing the risk of performance bias (Higgins and Green, 2011).

471 Moreover, while the included intervention studies performed outcome assessments at
472 the cessation of the training programme, no studies included a sufficient follow-up to allow for
473 determination of the longevity of any beneficial effect. Although FMD is a useful predictor
474 of vascular endothelial function, longer follow-up periods would be useful to identify whether
475 improvements in FMD from exercise translates into a decreased incidence of vascular disease
476 and mortality. Additionally, there is also the need for more comprehensive reporting of
477 participant characteristics, including confirmation of medical history, training status, training
478 frequency and duration (e.g. mins per week), and intensity as many studies lack sufficient
479 detail.

480 **4.4 Strengths and limitations**

481 This is the first systematic review and meta- analysis to focus on the effects of exercise
482 on vascular function via FMD in healthy older adults using both cross-sectional and
483 interventional studies; however, a number of limitations should be noted. Firstly, although
484 FMD measurement protocols were similar between studies, some minor differences in
485 protocols were evident. Studies measured post occlusion BA diameter for different durations,
486 ranging from 90 seconds to 10 minutes after cuff deflation. In addition to differences in
487 methodology, there were also a wide range of baseline Δ FMD% values in intervention studies
488 ($3.4 \pm 1.5\%$ to $8.9 \pm 4.9\%$). Furthermore, only a small number of studies normalised FMD
489 values for hyperaemic stimulus (Eskurza et al., 2004, 2005a). Therefore, the varied protocols
490 and lack of FMD normalisation by shear may have all contributed to the differences between
491 the studies. Additionally, despite the majority of the cross-sectional studies including EIDV
492 within their analysis, only 2 of the 4 interventional studies reported EIDV data. This therefore
493 reduces the confidence that any improvements in FMD were mediated by only the endothelium,
494 and not by vascular smooth muscle cells. Also, for the purposes of this analysis we defined
495 vascular function as brachial artery FMD response. However, it is plausible that analysis of
496 micro-vascular function, different regions of the vascular system, or analysis of other measures
497 of vascular health (e.g. pulse wave analysis, or pulse wave velocity) may provide different
498 results.

499 Moreover, although the interventional studies were specifically aerobic in nature, the
500 intensities of the exercises differed considerably. For example, (Suboc et al., 2014) conducted
501 a walking intervention, which was of relatively low intensity, whereas (Klonizakis et al., 2014)
502 documented a high intensity protocol requiring participants to work at 100% of their peak
503 power output. However, due to the lack of interventional studies meeting the inclusion criteria,
504 all 4 studies had to be analysed together. A greater number of interventional studies are
505 therefore required within this specific cohort to investigate whether varying exercise intensities
506 would influence vascular improvements differently. Additionally, within the cross-sectional
507 studies the lack of detail, and the use of qualitative descriptors of training intensity in the trained
508 older individuals (e.g. 'vigorous exercise') makes more detailed comparison of the effects of
509 long-term training in this cohort difficult. Furthermore, although there were no differences in
510 Δ FMD% between supervised and non-supervised interventions, only one non-supervised
511 intervention was included in the meta-analysis. Therefore, until further non-supervised
512 interventional protocols meeting the inclusion criteria become available, this result should be
513 interpreted with caution.

514 All of the studies included within the meta-analysis assessed vascular function of the
515 BA via FMD, despite the interventions and longer-term exercise routines consisting primarily
516 of lower-limb exercise. However, it has previously been identified that cycling can
517 significantly improve vascular function of the non-exercising upper limbs (Birk et al., 2012).
518 Although (Birk et al., 2012) assessed only young male participants, their results suggest that

519 lower-limb exercise can cause systemic adaptations to vascular function, which is likely caused
520 by increases in shear stress. Therefore, it seems likely that the improvement in BA vascular
521 function identified within the cross-sectional studies is due to systemic vascular adaptations
522 from many years of lower-limb exercise training.

523 Additionally, it has been previously shown that vascular function in older females
524 decreases at a faster rate than in males (Celermajer et al., 1994). As the current systematic
525 review and meta-analysis included both male and female participants, it is possible that our
526 results could have differed if males and females were analysed separately. However, there
527 were too few studies containing female participants to split the analysis by sex. Furthermore,
528 it has been previously found that oestrogen may be required to induce the benefits of endurance
529 exercise on vascular function, potentially by increasing NO bioavailability further (Moreau et
530 al., 2013). As the females included in the meta-analysis were post-menopausal and not
531 receiving oestrogen supplementation, perhaps intake of the hormone after menopause
532 alongside aerobic exercise may have helped to improve vascular function further. However,
533 as the majority of the cross-sectional participants within the current meta-analysis were male,
534 the results from the cross-sectional analysis may better represent the male population. Future
535 studies may wish, where possible, to report male and female results separately, and to further
536 report the menstrual status of female participants.

537 **5. Conclusion**

538 In summary, the current systematic review and meta-analysis identifies that aerobic
539 exercise training during advancing age can maintain healthy vascular function compared with
540 otherwise healthy sedentary peers. These findings emphasise the importance of remaining
541 active throughout the life-span. However, currently there is not enough evidence to suggest
542 that aerobic exercise interventions ranging from 2 to 12 weeks can improve vascular function
543 in previously sedentary older adults. Nonetheless, sedentary older individuals should still be
544 encouraged to become active until more evidence becomes available.

545 **Author contributions**

546 The literature search and selection of studies was performed by authors AC and AB.
547 Following an initial screen of titles and abstracts (AC), full scrutiny of potentially eligible
548 studies were independently screened by AC and AB using the specific inclusion criteria. NS
549 arbitrated any disagreements in study inclusion. Study quality assessment was performed by
550 AC.

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553

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Table 1. Cross-sectional Studies Characteristics. Study characteristics of cross-sectional studies within question 1 (↑ identifies that a significant increase in FMD% change occurred ($P \leq 0.05$) and → identifies no change ($P > 0.05$)). N = number of participants; % Male = percentage of male participants; $\dot{V}O_{2max}$ = maximum aerobic capacity; FMD% change = flow mediated dilation percentage change; PA = physical activity). Values are displayed as mean \pm SD

Study	Training Status	N	Age (years)	% Male	Physical Activity Levels	$\dot{V}O_{2max}$ (ml.kg.min ⁻¹)	FMD % Change	Overall Findings	Study Quality
DeVan et al. (2013)	Trained	23	62 \pm 4	91	>45min day ⁻¹ , \geq 5days week ⁻¹ for previous 2 years.	($\dot{V}O_{2peak}$): 42 \pm 9.6	6.4 \pm 1.7	↑ Trained	Fair
	Sedentary	35	62 \pm 5	86	<30min day ⁻¹ , \leq 2days per week for previous 2 years.	($\dot{V}O_{2peak}$): 31 \pm 5.9	5.3 \pm 2.2		
Eskurza et al. (2005)	Trained	12	66 \pm 4	100	>3 sessions week ⁻¹ of vigorous endurance exercise >2 years.	41.3 \pm 4.2	5.9 \pm 1.7	↑ Trained	Good
	Sedentary	9	62 \pm 6	100	No regular PA >2 years.	29.1 \pm 6.3	3.9 \pm 2.1		
Franzoni et al. (2005)	Trained	16	64 \pm 6	100	$\dot{V}O_{2max}$ >50ml.kg.min ⁻¹ . Vigorous endurance exercise >5 times week ⁻¹ & participate in national & international road-running races. Training for 37 \pm 5 years.	54.7 \pm 3.7	5.3 \pm 3.2	↑ Trained	Good
	Sedentary	16	64 \pm 4	100	$\dot{V}O_{2max}$ <45 ml.kg.min ⁻¹	28 \pm 5.9	2.3 \pm 1		
Galetta et al. (2006)	Trained	30	65 \pm 5	100	$\dot{V}O_{2max}$ >40 ml.kg.min ⁻¹ Competitive endurance runners since 40 years. 1-2hour day ⁻¹ for 5 days (3 days long distance running & 2 days walk-weight training) or 5-10km weekly or 20km once every 2 weeks.	45.7 \pm 3.7	6.2 \pm 2	↑ Trained	Good
	Sedentary	28	66 \pm 6	100	$\dot{V}O_{2max}$ <35 ml.kg.min ⁻¹ and no regular exercise	28 \pm 5.9	2.4 \pm 1.5		

Study	Training Status	N	Age (years)	% Male	Physical Activity Levels	$\dot{V}O_{2\max}$ (ml.kg.min ⁻¹)	FMD % Change	Overall Findings	Study Quality
Grace et al. (2015)	Trained	17	61 ± 5	100	Life-long exercisers and completed on average 280min exercise training week ⁻¹ . Most participants were active competing in endurance sports.	39.2 ± 5.6	5.4 ± 1.4	↑ Trained	Good
	Sedentary	22	63 ± 5	100	No formal exercise programme for ≥30years.	27.2 ± 5.2	3.4 ± 1.5		
Jensen-Urstad et al. (1999)	Trained	9	75 ± 3	100	Participants had been and were still among the best in their respective age groups in running since ages of 15-25. Between 3-7 hours strenuous exercise week ⁻¹ .	41 ± 7	4.8 ± 5	↑ Trained	Good
	Sedentary	11	75 ± 2	100	Sedentary or moderately active.	27 ± 5	1.1 ± 2.1		
Pierce et al. (2011a)	Trained	13	62 ± 7	100	Vigorous aerobic exercise (competitive running, cycling and triathlons) ≥ 5days week ⁻¹ for ≥ 45min day ⁻¹ >5 years.	42 ± 3.6	6.3 ± 1.8	↑ Trained	Good
	Sedentary	28	63 ± 5	100	No regular aerobic exercise (<30min day ⁻¹ , <2days week ⁻¹ , ≥2years).	29 ± 5.3	4.9 ± 2.1		
Pierce et al. (2011b)	Trained	65	62 ± 6	69	Vigorous aerobic exercise (competitive running, cycling and triathlons) >5days week ⁻¹ for >45min day ⁻¹ >5 years.	41.5 ± 7.7	6.1 ± 2.9	↑ Trained	Good
	Sedentary	102	62 ± 10	59	No regular aerobic exercise (<30min day ⁻¹ , <2days week ⁻¹ , >2years).	27.4 ± 6.6	4.8 ± 2.3		

Study	Training Status	N	Age (years)	% Male	Physical Activity Levels	$\dot{V}O_{2max}$ (ml.kg.min ⁻¹)	FMD % Change	Overall Findings	Study Quality
Walker et al. (2009)	Trained	16	66 ± 4	100	>3sessions week ⁻¹ vigorous aerobic endurance exercise.	42.8 ± 5.2	6.2 ± 2.6	→	Good
	Sedentary	15	66 ± 4	100	No regular exercise for 2 years	29.9 ± 4.7	4.8 ± 1.6		
Eskurza et al. (2004)	Trained	9	64 ± 6	100	>3sessions week ⁻¹ vigorous aerobic endurance exercise for ≥ 2 years	40 ± 6	7 ± 1.8	↑ Trained	Good
	Sedentary	9	64 ± 6	100	Sedentary (No regular PA) for ≥ 2 years	32 ± 3	4.6 ± 0.6		

Table 2. Interventional Study Characteristics. ↑ identifies a significant increase in FMD% change ($P \leq 0.05$) and → identifies no significant change ($P > 0.05$). N = number of participants; % Male = percentage of male participants; $\dot{V}O_{2\max}$ = maximum aerobic capacity; FMD% change = flow mediated dilation percentage change; PA = physical activity; HRR = heart rate reserve; WR_{\max} = maximum work rate; PP = peak power; HIT = high intensity training; CT = continuous training; ACSM = American College of Sports Medicine; HIIT = high intensity interval training; PED = pedometer; CON = control. Values are displayed as mean \pm SD.

Study	Study Design	N	Age (years)	% Male	Exercise Intervention			Frequency	Study Duration	$\dot{V}O_{2max}$ (ml.kg.min ⁻¹)	FMD % Change	Overall Findings	Study Quality
					Exercise Type	Intensity	Session Duration						
Thijssen et al. (2007)	Cohort	8	70 ± 1	100	Cycling training on an ergometer	65% HRR & gradually increasing by 5% until 85%	20min	3days week ⁻¹	8 weeks	Pre: 30.8 ± 4.8 Post: 33.3 ± 5.5	Pre: 6.9 ± 3.4 Post: 6.4 ± 2.7	→ FMD%	Good
Suboc et al. (2014)	RCT	7 7	PED: 64 ± 7 CON: 62 ± 7	PED: 61 CON: 76	PED (n=36) walking CON (n=41)	Increase PA by 10% weekly above baseline to reach an average of 10,000 steps day ⁻¹	---	Daily	12 weeks	---	Post; CON:6.3 ± 2.7 HIT:6.7 ± 3.9	→ FMD%	Good
Klonizakis et al. (2014)	Cohort	1 8	HIT: 64 ± 7 CT: 64 ± 4	0	HIT (n=11): cycling intervals on ergometer CT (n=7): continuous cycling	HIT: 100%PP & light active recovery intervals at 30W CT: 65% PP	HIIT: 10x1min intervals with 1min recovery between each CT: 40min	3 times week ⁻¹	2 weeks	HIT; Pre: 20.4 ± 3.4 Post: 22.6 ± 3.1 CT; Pre: 25 ± 7.4 Post: 26.7 ± 5.4	HIT; Pre:8.1 ± 7.2 Post:6.5 ± 3.7 CT; Pre: 8.9 ± 7.9 Post: 7 ± 4.3	→ FMD% → FMD%	Good
Grace et al. (2015)	Cohort	2 2	63 ± 5.2	100	Progressive conditioning exercise: ACSM guidelines HIIT: sprints on cycle ergometer.	Conditioning exercise: ACSM guidelines (Chodzko-Zajko et al., 2009) & 50% PP HIIT sprints	Conditioning exercise: 150min week ⁻¹ ≥30min day ⁻¹ (ACSM guidelines (Chodzko-Zajko et al., 2009))	Conditioning : ≥5 days week ⁻¹ (ACSM guidelines (Chodzko-Zajko et al., 2009)) HIIT: once every 5 days	Conditioning: 6 weeks HIIT: 6 weeks	Pre: 27.2 ± 5.2 Post: 32.2 ± 5.6	Pre: 3.4 ± 1.5 Post: 5.4 ± 1.4	↑ FMD%	Good

HIIT: 6x30s
sprints with
3min break
between
each

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Table 3. Cross-Sectional Study Quality. Study quality assessment of the cross-sectional studies included in question 1 developed by the National Heart, Lung and Blood Institute (NHLBI) (Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies, 2014). Y = yes; N = no; NR = not reported.

	Research Question Clear?	Study Population Clear? (including without date and place)	Criteria same within both groups?	Sample size calculation?	Exposure measures clear, reliable and valid? Implemented consistently?	Outcome measures clear, reliable and valid? Implemented consistently?	Blinded assessment of FMD?	Follow-up after baseline 20% or less?	Key potential confounding variables considered?
DeVan et al. (2013)	Y	Y	Y	N	N	N	NR	Y	Y
Eskurza et al. (2005)	Y	Y	Y	N	Y	Y	Y	Y	Y
Franzoni et al. (2005)	Y	Y	Y	N	Y	Y	NR	Y	Y
Galetta et al. (2006) (Galetta et al., 2006)	Y	Y	Y	N	N	Y	NR	Y	Y
Grace et al. (2014)	Y	Y	Y	Y	Y	Y	N	Y	Y
Jensen-Urstand et al. (1999)	Y	Y	Y	N	N	Y	NR	Y	Y
Pierce et al. (2011a)	Y	Y	Y	N	N	Y	Y	Y	Y

	Research Question Clear?	Study Population Clear? (including without date and place)	Criteria same within both groups?	Sample size calculation?	Exposure measures clear, reliable and valid? Implemented consistently?	Outcome measures clear, reliable and valid? Implemented consistently?	Blinded assessment of FMD?	Follow-up after baseline 20% or less?	Key potential confounding variables considered?
Pierce et al. (2011b)	Y	Y	Y	N	Y	Y	Y	Y	Y
Walker et al. (2009)	Y	Y	Y	Y	Y	Y	NR	Y	Y
Eskurza et al. (2004)	Y	Y	Y	N	Y	Y	Y	Y	Y

Table 4. Cohort Study Quality. Study quality assessment of the cohort studies included in question 2 developed by the National Heart, Lung and Blood Institute (NHLBI) (Quality Assessment Tool for Before-After (Pre-Post) Studies With No Control Group, 2014). Y = yes; N = no; NR = not reported; CD = cannot determine.

	Research Question Clear?	Participant eligibility criteria clear? (without date and names)	Were participants representative of general population of interest?	Were all eligible participants enrolled?	Was sample size sufficient to provide confidence in the findings?	Was the intervention clearly described and delivered consistently?	Outcome measures clear, reliable and valid? Implemented consistently?	Blinded assessment of FMD?	Loss to follow-up after baseline <20%	Did the statistical method examine changes pre and post intervention?
Grace et al. (2015)	Y	Y	Y	Y	Y	Y	Y	NR	Y	Y
Klonizakis et al. (2014) (17)	Y	Y	Y	Y	CD	Y	Y	NR	Y	Y
Thijssen et al. (2007)	Y	Y	Y	Y	Y	Y	Y	NR	Y	Y

Table 5. Randomised Control Trial Study Quality. Study quality assessment of the RCT study included in question 2 developed by the National Heart, Lung and Blood Institute (NHLBI) (Quality Assessment of Controlled Intervention Studies, 2014). RCT = randomised controlled trial; Y = yes; N = no; NR = not reported.

	Described as a RCT?	Was the method of randomisation adequate?	Was the treatment allocation concealed?	Were the investigators blinded?	Were groups similar at baseline on important characteristics that could affect outcomes?	Was overall drop-out rate $\leq 20\%$?	Was the differential drop-out rate at endpoint $\leq 15\%$?	High adherence to intervention protocols?	Were other interventions avoided or similar in the groups?	Outcome measures clear, reliable and valid? Implemented consistently?	Sample size sufficient to detect difference with at least 80% power?	Were outcomes reported or subgroups analysed pre-specified?	Were all randomised participants analysed in the group they were originally assigned?
Suboc et al. (2014)	Y	NR	NR	Y	Y	Y	Y	N	Y	Y	Y	Y	Y

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Table 6. Meta-Regression Analysis. Meta-regressions assessing the effect of age on FMD percentage change

Comparison	Covariate	n	q	df	SE	β	95% CI	P-value
Trained v Sedentary	Age	10	3.17	1	0.12	0.22	0.02%, 0.46%	0.08

Figure Legends

Figure 1. PRISMA flow chart of study selection from the original search on Pubmed, Wed of Science and ScienceDirect.

Figure 2. Forest plot of the meta-analysis with mean differences of FMD percentage change between trained versus sedentary healthy older adults (question 1), and FMD percentage change pre to post exercise intervention in previously sedentary healthy older adults (question 2). Outcomes of question 1, 2 and the moderator analysis are also presented.

Figure 3. Forest plot of the meta-analysis of brachial artery baseline diameter (mm) between trained versus sedentary healthy older adults, and pre to post exercise intervention in previously sedentary healthy older adults. The heterogeneity and moderator analysis are also presented.

Figure 4. Forest plot of the meta-analysis of endothelial independent vasodilation percentage change (EIDV%) between pre to post exercise intervention in previously sedentary healthy older adults, and trained versus sedentary healthy older adults. The heterogeneity and moderator analysis are also presented.

Figure 5. Forest plot of the meta-analysis of brachial artery FMD percentage change within supervised and non-supervised exercise interventions. Heterogeneity and moderator analysis are also presented.

Figure 2.JPEG

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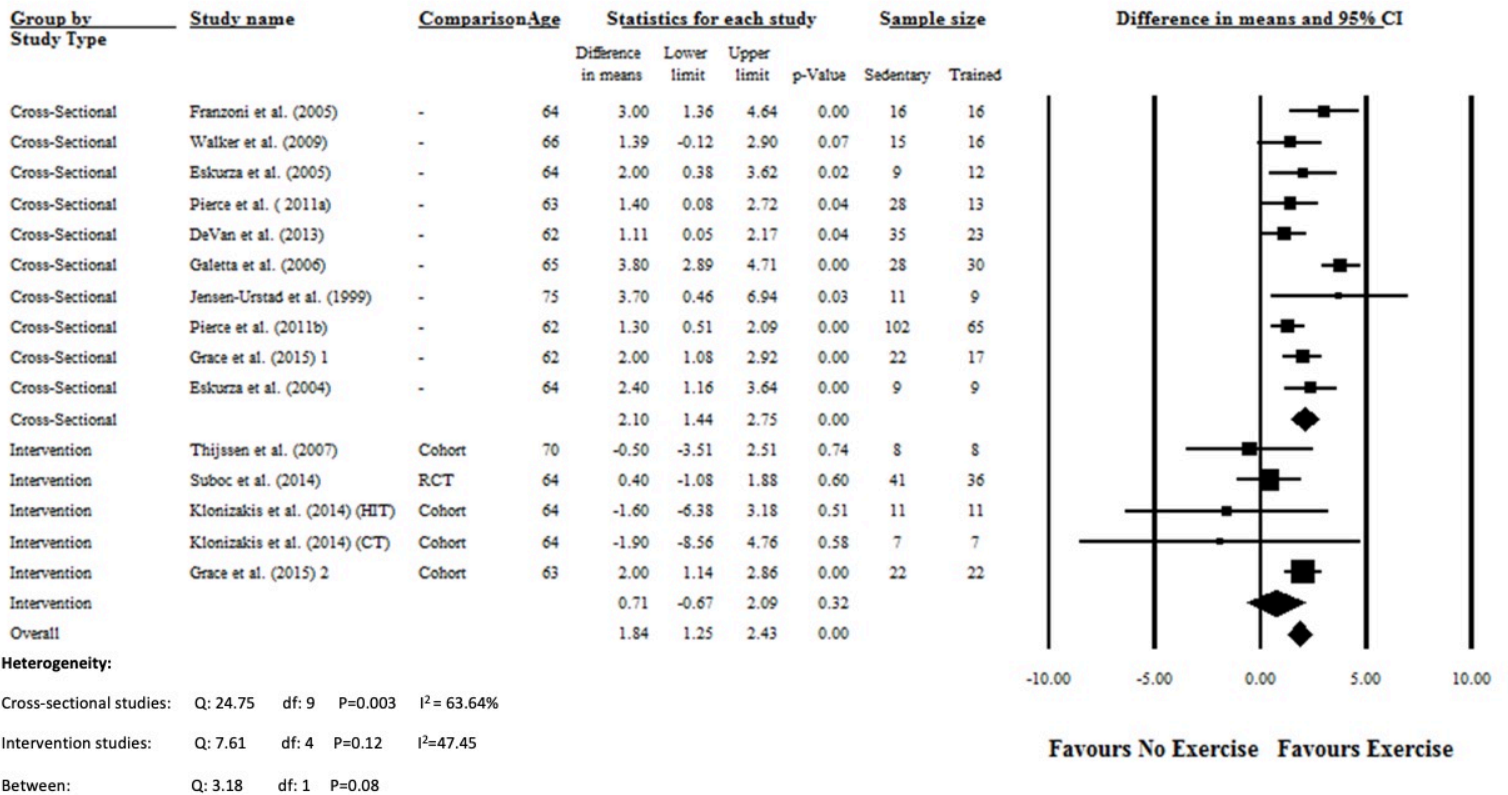


Figure 3.JPEG

In review

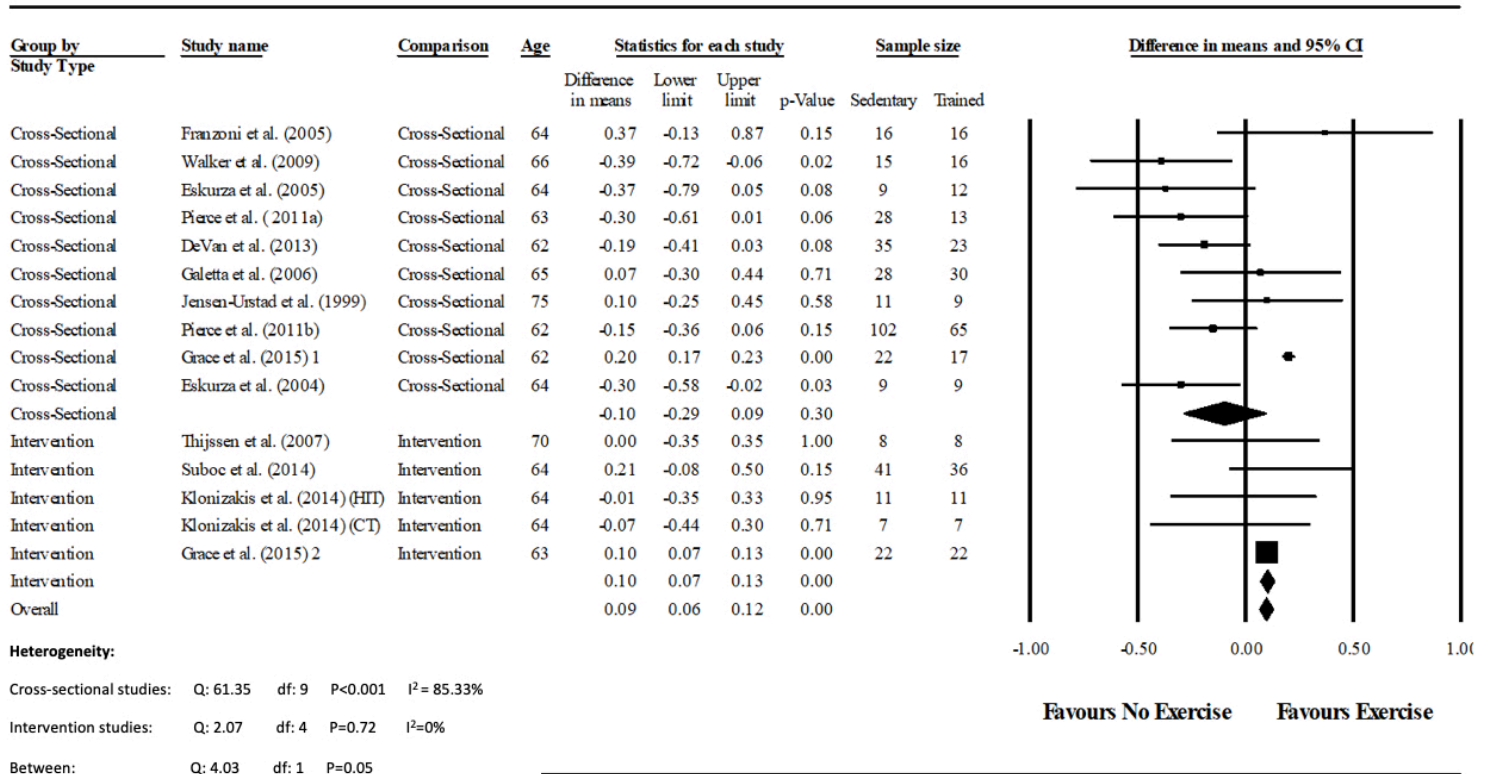


Figure 4.JPEG

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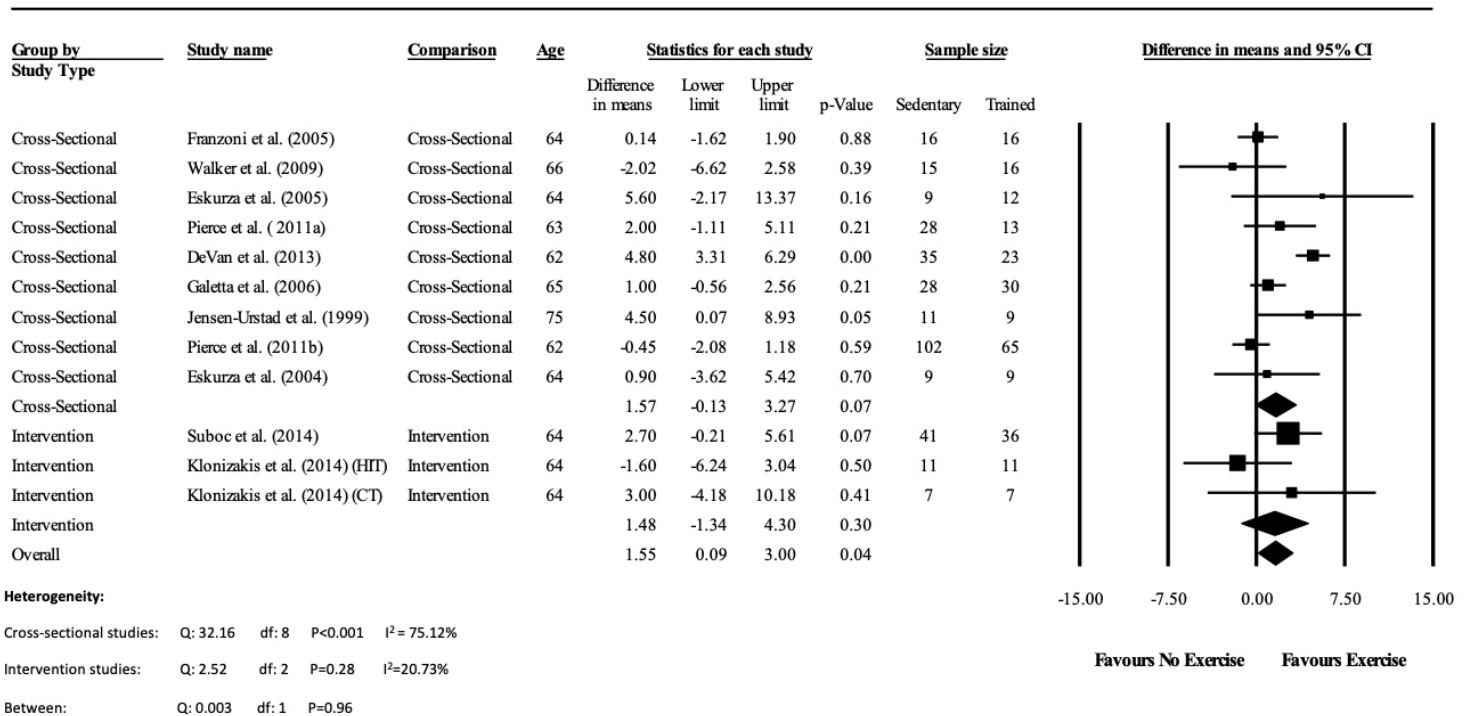


Figure 5.JPEG

In review

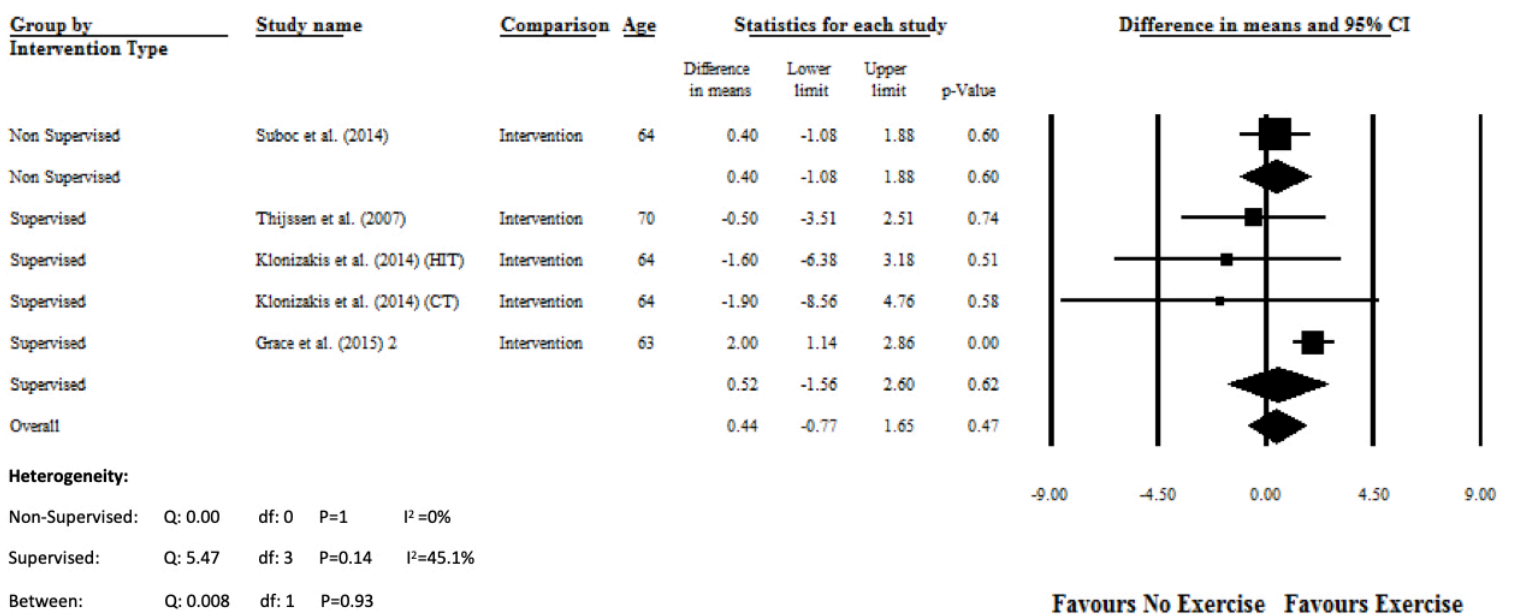


Figure 6.JPEG

