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The effect of exercise training on cutaneous microvascular reactivity: A systematic review and meta-analysis.

Abstract

Objective: This study aimed to review the efficacy of exercise training (ET) for improving cutaneous microvascular reactivity (CMR) in response to local stimulus in human adults.

Design: Systematic review with meta-analysis.

Method: A systematic search of Medline, Cinahl, AMED, Web of Science, Scopus, and Embase was conducted up to June 2015. Included studies were controlled trials assessing the effect of an ET intervention on CMR as instigated by local stimulus such as local heating, iontophoresis and post-occlusive reactive hyperaemia. Studies where the control was only measured at baseline or which included participants with vasospastic disorders were excluded. Two authors independently reviewed and selected relevant controlled trials and extracted data. Quality was assessed using the Downs and Black Checklist.

Results: Seven trials were included, with six showing a benefit of ET but only two reaching statistical significance with Effect Size (ES) ranging from -0.14 to 1.03. The meta-analysis revealed that aerobic exercise had a moderate statistically significant effect on improving CMR (ES = 0.43, 95% CI: 0.08 to 0.78, $p = 0.015$).

Conclusions: Individual studies employing an ET intervention have tended to have small sample sizes and hence lacked sufficient power to detect clinically meaningful benefits to CMR. Pooled analysis revealed a clear benefit of ET on improving CMR in older and previously inactive adult cohorts. ET may provide a cost-effective option for improving CMR in adults and may be of benefit to those with cardiovascular disease and metabolic disorders such as diabetes.

Keywords: Exercise, microcirculation, physical activity, vasodilation

Abbreviations: CMR, cutaneous microvascular reactivity; CVC, cutaneous vascular conductance; ES, effect size; ET, exercise training; LDF, laser-Doppler flowmetry; MAP, mean arterial pressure;

NAFLD, nonalcoholic fatty liver disease; PF, peak flux; PORH, post-occlusive reactive hyperaemia;
RF, resting flux; UTD, unable to determine; VO₂max, maximal oxygen consumption

Introduction

Chronically impaired CMR is characterised by dysfunction of vasodilatory capacity and is associated with development of heat-related illnesses through impaired temperature regulation, increased risk of skin ulceration, and, a reduction in wound healing capacity in the periphery¹⁻⁵. Chronic impairment in CMR occurs as part of the normal aging process^{6,7} and in conjunction with chronic diseases, including those affecting the cardiovascular system^{8,9}.

Whilst the mechanisms underlying CMR are not fully understood, it is associated with a number of chronic disease states and appears to contribute to morbidity and mortality, specifically through its role in heat-related illness as well as impaired cutaneous tissue viability and increased susceptibility to infection^{10,11}. Cardiovascular disease produces impairment in CMR, with research demonstrating an impaired hyperaemic response to occlusion^{12,13}. In the presence of hypertension there is structural and functional alteration with a reduction in the number of capillaries in the skin and concomitant decrease in the number of perfused vessels^{14,15}. CMR is also impaired by diabetes-related microvascular disease, causing structural and functional impairment of endothelium-dependent and -independent vasodilation as well as altered neurological function in the periphery via a diminishing nerve-axon reflex-related microvascular reactivity^{2,16}. Furthermore, sympathetic denervation and autonomic neuropathy, common in people with diabetes, are proposed to contribute to shunting of blood away from nutritional capillaries resulting in ischemia^{17,18}.

Exercise training (ET) has been shown to improve aspects of CMR including endothelial-dependent responsiveness to vasodilator stimulus¹⁹, while trained distance runners have demonstrated enhanced endothelial-dependent cutaneous vasodilation compared with controls who perform only some regular physical activity²⁰. From the available data it appears that there is a positive association between self-reported physical activity level and higher resting skin blood flow in healthy populations²¹⁻²⁴.

Furthermore, acute bouts of exercise have been shown to cause a transient increase in CMR in healthy

people and in those with diabetes^{1 20}. Both acute exercise and ET are suggested to improve CMR through increased cardiac output⁶ and an increase in the bioavailability of nitric oxide and other vasoactive substances⁴. Several cohort studies have demonstrated that ET may produce sustained improvements in both resting skin blood flow and vasodilatory capacity of skin capillaries^{25 26} suggesting that ET may be an effective intervention for the prevention and treatment of impaired CMR and associated complications.

The aim of this study was to conduct a systematic review with meta-analysis of the pooled data from controlled human adult trials to assess the efficacy of ET interventions on CMR. We hypothesized that, when compared with a non-exercise control condition, interventions involving ET would improve CMR.

Methods

Initial electronic database searches and subsequent determination of relevance based on title and abstract was conducted independently by two researchers (SL and VC). Databases searched up to March 2016 were: Medline (Ovid), Cinahl (EBSCO Host), AMED (Ovid), Web of Science (ISI Web of Knowledge), Scopus, and Embase. Keyword phrases used in different combinations were: skin perfusion, tissue perfusion, cutaneous, blood flow, haemodynamics, reactivity, exercise, aerobic training, endurance training, physical endurance, physical exertion, strength training, weight training, resistance training, progressive resistance and weight lifting. Reference lists of included papers were searched manually for potentially eligible papers. Controlled trials were reviewed while uncontrolled trials and cross-sectional studies were excluded from analysis. To be considered a suitable control, the group needed to differ only in exercise (non-exercise control). Manuscripts were not excluded based on language however all manuscripts retrieved were published in English.

Inclusion and exclusion criteria were determined a priori by two researchers (SL, VC) with disagreements resolved by a third researcher (NJ). Included studies were controlled trials and employed ET interventions involving three exercise sessions or more. This cut-off was established to differentiate studies examining the acute effects of exercise from those examining training adaptations. Trials involving supervised or unsupervised aerobic or resistance ET in male and/or female adults

(mean age of 18 or over) were included. Studies involving dietary control/intervention were included only if the diet was the same between the ET and control groups thus allowing the independent effect of ET to be measured. Included trials used local stimulus to assess CMR. This included studies utilising post-occlusive reactive hyperaemia (PORH), which uses occlusion as a local stimulus. Studies were excluded if they included participants diagnosed with vasospastic disorders or connective tissue disease due to pathology-specific skin blood flow response. Furthermore, studies were excluded if the control group was only measured at baseline.

The outcome measure used in this review was change in CMR. For primary studies, data on participant characteristics, ET and control interventions (mode of exercise, exercise frequency, exercise intensity, session duration and intervention duration), and blood flow measurements were extracted by two researchers (SL and VC) independently with disagreements resolved by a third researcher (MB). In cases where journal articles contained insufficient information, attempts were made to contact authors to obtain missing details.

The between-trial standardized mean difference, or effect size (ES), and 95% confidence intervals (CI) were calculated. The ES was used to standardize changes of CMR. Effect sizes were calculated as Cohen's d and then converted to Hedge's g ²⁷ which provided a less biased estimate of the treatment effect²⁸ i.e. $G = \left[1 - \frac{3}{4df-1}\right] \bar{d}$.

The pooled estimate of the effect of exercise on CMR, using ES, was obtained by random-effects model using the DerSimonian and Laird method²⁹. This involved adding the constant T^2 to the inverse variance weighting to account for likely variance in true effects due to the differing study conditions. Heterogeneity was then assessed using the Q statistic, I^2 and T^2 . Finally, we examined potential publication bias using a funnel plot and appropriate diagnostics, Egger's and Begg's test of asymmetry^{30 31}. All analyses and calculations were performed with STATA version 12.1, R version 2.15.2 and Microsoft Excel 2010.

Study quality was assessed by two researchers (SL and VC) using a modified Downs & Black

checklist³². Where reviewers disagreed, specific criteria were discussed with a third reviewer (MB) until consensus was reached. If consensus could not be reached on an item then this was reported as unable to determine (UTD).

Results

The original search yielded 46,223 articles. A further eight articles were found from reference lists of articles retrieved. After removal of duplicates and elimination of papers based on the eligibility criteria, seven studies remained. The process of article selection is detailed in *Figure 1*.

A total of 245 individuals (102 male; 64 female; 79 gender unreported) participated in the seven trials. One study recruited male participants exclusively³³, and six studies recruited both males and females³⁴⁻³⁹. The mean age of participants ranged from 25-75 (years). The mean mass and height of participants ranged from 65 to 91kg and 149 to 180cm, respectively. Mass was not reported in one study³⁸ while four studies did not report height^{34 36 38 39}. Studies described the participants as older inactive³⁴; overweight, inactive individuals with grade-one essential hypertension³⁸; individuals with type 2 diabetes^{36 37}; post-surgical varicose veins patients³⁵; individuals with nonalcoholic fatty liver disease (NAFLD)³⁹ and healthy³³. Middlebrooke and associates reported that seven participants dropped out; three for health reasons, two due to time constraints and two for no reported reason³⁶. Pugh and associates reported that two individuals were lost to follow-up as one declined the post-intervention assessments and one did not maintain habitual diet³⁹. Three participants were excluded from the study by Mitranun and colleagues as they failed to complete at least 80% of the training³⁷. None of the studies reported an intention to treat analysis.

Five studies were randomised controlled trials^{34-37 39}, and two studies were controlled trials which did not stipulate random allocation to groups^{33 38}. Comprehensive ET intervention characteristics are detailed in *Table 1*. The seven studies employed aerobic ET as the intervention. One study also contained an aerobic interval training group³⁷. One study grouped participants who had been allocated to the aerobic ET intervention and had increased their fitness (VO_{2max}) versus those who did not respond. This study also reported data from a resistance ET intervention³³.

Three studies reported that the ET intervention was supervised^{35 37 39}. Pasqualini and colleagues reported supervision for the initial two weeks followed by one supervised session per week for a further six weeks³⁸. Thomas et al, reported that three of the four weekly sessions were supervised³³ while both Black et al, and Middlebrooke et al, reported that two of the three weekly exercise sessions were supervised, with compliance assessed by telephone and regional site visits³⁴ and one of the three sessions performed at home³⁶.

Six studies employed laser-Doppler flowmetry (LDF) techniques to quantify changes to CMR^{33-35 37-39} and one study utilised laser-Doppler perfusion imaging³⁶. Methods of stimulating CMR for LDF measures varied and included: localised heating to 42°C^{33 34 36 39}, PORH^{37 38}, and iontophoresis or microdialysis with Acetylcholine (ACh) or Sodium Nitroprusside³³⁻³⁶.

Four of the studies attempted to control for environmental temperature of the test site, reporting room temperatures between 22-24°C^{34-36 38} with four studies specifically mentioning a period of acclimatisation ranging from 15-90 minutes^{34 35 37 39}. Three studies requested participants refrain from strenuous exercise for 24 hours preceding the measurements^{35 36 39} while one study performed post-test measures 48-72 hours after the last bout of ET to avoid measuring effects of acute exercise³⁷.

Abstinence from caffeine^{35 36 39}, alcohol^{34 39} and smoking^{35 36} was requested of participants in some of the studies with timeframes ranging from two to 24 hours prior to testing. Overnight fasting was requested of participants in four studies^{34 36 37 39}. Skin temperature was continuously monitored in two of the studies^{33 36}. The females recruited in one study were post-menopausal³⁷. Lastly, many participants were excluded from participating in individual studies due to a range of factors influencing thermoregulation or CMR. These include history of smoking^{33 34 38 39}, medication use, particularly vasodilators^{33-35 38}, and medical conditions including cardiovascular disease, diabetes and Raynaud's disease^{33-36 38 39}.

Three studies^{33 34 39} expressed CMR as cutaneous vascular conductance (%CVC_{max}). The equation to determine the %CVC_{max} was described as laser-Doppler flux/mean arterial pressure (LDF/MAP). LDF measures were expressed as arbitrary flux units and MAP expressed as mmHg. One study reported the

peak flux (PF) only ³⁵. One study reported the peak responses and area under the (V/time) curve, where V is the peak response ³⁶. One study reported baseline resting flux (RF), PF, RF/PF, and area under the curve PORH ³⁸, and one study reported RF, PF, and (PF-RF)/(RFx100) ³⁷.

Methodological quality was appraised using the Downs and Black checklist ³². Hypotheses, main outcomes and interventions were detailed in all of the studies. Participant characteristics for the ET arm of one study were not clearly described ³⁴. Two studies did not clearly report main findings or variability estimates ^{34 35}. All studies used accurate measures and appropriate statistical tests. All potential confounders were accounted for and there were no adverse events. Middlebrooke et al, Mitranun et al, and Pugh et al, reported seven ³⁶, three ³⁷ and two ³⁹ drop-outs, respectively, while no other studies reported losses to follow-up. Five studies specifically mention random allocation of participants to a control or intervention group ^{34-37 39}. There were no reported attempts in any studies to blind the participants to the intervention they received or attempts to blind those measuring the main outcomes. Lastly, three studies reported sufficient power to detect a clinically important effect ^{36 37 39}.

Seven studies provided sufficient data to enable calculation of mean differences, ES and 95% confidence intervals (95% CI) for CMR, *Figure 2*. The ES were calculated using the post-test scores at 12 weeks or for trials in which data was collected at multiple time-points we used the data collected at or closest to 12 weeks. For missing information, we calculated ES or pooled variances from the appropriate test statistics *t* or *F*. If test statistic values were not provided, we calculated these using the upper significance boundary such as using $p = 0.05$ for $p < 0.05$. For studies where multiple methods of assessing CMR were employed ^{34 36}, local heating measures were used as this was the most common method. For the trials by Mitranun et al, and Thomas et al, results from the aerobic exercise intervention were used as this was consistent with other trials in the meta-analysis ^{33 37}. In the latter of these two, results for the aerobic ET group were reported as four groups - young and older participants who increased their VO_{2max} by 5% after aerobic ET (responders) and those that did not. However, as the pooled results of these groups could not be retrieved, only the results from the older responders were included.

Six of the seven studies showed an increase in CMR in the aerobic ET intervention group compared with the non-exercise control group with ES ranging from -0.14 to 1.03, *Figure 2*. Two studies demonstrated a large statistically significant effect of ET on CMR^{34 35}. Another study also demonstrated a large ES though this was not statistically significant³⁹. Similarly, studies by Thomas et al, Mitranun et al, and Pasqualini et al, displayed non-significant small³³ and moderate^{37 38} ES, respectively. The study by Middlebrooke et al, demonstrated no increase in CMR following ET³⁶.

The meta-analysis revealed that aerobic exercise had a moderate, but statistically significant effect on improving CMR (ES = 0.43, 95% CI: 0.08 to 0.78, $p = 0.015$) *Figure 2*. However, the lower confidence bound of 0.08 was quite small, suggesting it is possible that the difference between ET and control groups was trivial. The ES though was quite robust given the consistency of the ES of six of the seven studies. In particular, there was no significant heterogeneity present ($I^2 = 27.4\%$, $\tau^2 = 0.059$, $p = 0.219$) indicating the variability in effect estimates is likely to be due to sampling error rather than heterogeneity between studies. Risk of publication bias was found to be low. The funnel plot showed the studies to be randomly scattered around the summary ES = 0.43 with no obvious asymmetry present. This is further confirmed by the results of Egger's Test ($p = 0.074$) and Begg's Test ($p = 0.368$). It is unlikely that our results are an artefact of publication bias.

Discussion

This systematic review with meta-analysis assessed the effect of ET on CMR in human adults. The review included five randomised controlled trials and two controlled trials with a total of 245 participants. Although the studies we identified in this review employed controlled designs and observed a tendency for benefit with ET, the majority failed to reach statistical significance^{33 36-39}. By performing a meta-analysis of the combined data we were able to demonstrate a moderate but statistically significant effect in favour of ET compared with non-exercise control for improving CMR. These findings, shown in a mixed population of adults who were primarily inactive previously, build on previous cross-sectional research which has suggested that higher self-reported general physical activity level is associated with an increase in resting skin blood flow, and improvement in CMR to a maximal bout of exercise^{1 3}. Similarly, in cross-sectional studies, physically trained young and older

adults have also been shown to have a greater skin vasodilatory capacity than inactive subjects^{20 23 24} suggesting that ET may improve CMR. It has been proposed that shear stress associated with increased blood volume is a mechanism for improving vascular adaptations in skeletal muscle⁴⁰ and that increased blood volume may trigger cutaneous vascular adaptations⁴¹. This increased blood volume may be brought about by the thermal strain produced through ET⁴² and supports the results of this meta-analysis. Notably, the ET used in the included studies differed in type, duration and intensity, therefore the results of the meta-analysis demonstrate a global effect of exercise only and inferences about specific types of exercise programs cannot be made.

The majority of studies included in this review reported improved CMR after eight to 26 weeks of aerobic ET performed two to five times weekly for a duration of 30-60 minutes at light to moderate intensity. The largest improvements to CMR were found in older cohorts of inactive³⁴ and post-surgical varicose veins participants³⁵. Lesser improvements were also reported in adults with NAFLD³⁹, type-2 diabetes³⁷, overweight adults³⁸, and older adults³³. No improvements were found in a second adult diabetes cohort³⁶. Studies included in this review measured CMR at the forearm^{33 34 36-39}, and gaiter region of the leg³⁵. Previous research has demonstrated that despite differences in structural and microvascular characteristics and innervation between glabrous and non-glabrous skin, improvement in CMR in response to ET can occur in both skin types^{43 44}. Our meta-analysis supports improved CMR in non-glabrous skin with exercise training. Based on previous research these results may also be applicable to glabrous skin.

Only one trial failed to show any effect of ET on CMR³⁶. The ET group in the study by Middlebrooke and colleagues in people with Type 2 diabetes did not display significantly greater CMR than the control group. The authors suggested the lack of significant improvement in CMR may have been due to the short mean duration of diabetes, early intervention with pharmacological management and good control of blood glucose levels as evidenced by the mean HbA_{1C} of less than 7% in the intervention group³⁶. These factors may have reduced the incidence and severity of microvascular dysfunction in this cohort leading to the lack of effect of ET.

Based on the controlled trials to date, evidence of the effectiveness of ET for diabetes-related microvascular disease is conflicting and warrants further investigation. Overall prevalence of diabetes-related microvascular disease is high, with disturbances of endothelial-dependent and -independent microvascular function reported to typically occur three years after onset of Type 1 diabetes⁴⁵ and may be present at diagnosis of Type 2 diabetes⁴⁶⁻⁴⁸. It has also been shown to affect approximately 20% of people with diabetes in the absence of detectable macrovascular changes^{49 50}, suggesting treatment needs to target microvascular function. In the foot, this microvascular disease is associated with localised tissue hypoxia, reduced vasodilatory capacity of the endothelium, and the development of peripheral neuropathy resulting in delayed wound healing and an increased risk of infection and ulceration^{16 49}.

ET has previously been demonstrated to have therapeutic benefits for older adults, as well as those with hypertension and impaired fasting glucose, by reducing the risk of cardiovascular events and improving endothelial macrovascular function⁵¹⁻⁵³. ET may also be a potential mechanism for improving CMR and therefore has implications for a number of patient populations at risk of microvascular dysfunction, particularly in association with ageing and chronic disease. However, our review has demonstrated relatively few controlled trials have been conducted and although most participants included in our meta-analysis were at risk of microvascular dysfunction or related co-morbidities, there is currently insufficient data to determine the effectiveness of ET in specific patient cohorts. Furthermore, while our meta-analysis suggests that ET may be a mechanism to improve impaired CMR, the mechanisms underlying these vascular changes requires further investigation.

Limitations of included studies

Two of the trials in this review did not have random allocation to groups and none of the studies clearly stated whether assessors or participants were blinded. Studies involving ET interventions compared to a non-exercise control group naturally have difficulties concealing the group to which the participant is assigned, randomly or otherwise. The intervention characteristics were not identical across the included studies and thus we were unable to perform any sub-analyses regarding specific exercise intensity, duration, modality or timeframe. Additionally, there was a tendency within the

studies to recruit male participants with 61% of participants being male and 39% female, though 32% of included participants had gender not reported. It is unlikely that female gender influenced response to ET as two studies that contained a high proportion of female participants demonstrated statistically significant increases in CMR^{34 35}. It should be noted that some studies used multiple measures of stimulating CMR and for these studies this review only analysed results from methods that were in common³⁴⁻³⁶.

Review limitations

While we performed an exhaustive search for relevant literature, the large number of articles retrieved from database searches may have led to accidental omissions of significant research. Authors were only contacted where information from included articles were missing. Furthermore, strict exclusion criteria meant that multiple studies were not included as they were not controlled trials and in one study we have only analysed the data from participants who had responded to ET (increased VO_{2max} by 5%) which may have led to an overestimation of the effect of the intervention.

Though pre- and post-test measurements of CMR are consistently conducted on different days there is some research suggesting that laser-Doppler measurement conducted on different days can be reliable⁵⁴. As mentioned, included studies assessed CMR in response to local stimulus and it should be noted that we have included PORH in this category as though its mechanism is complex and perhaps not well understood⁵⁵ it has been reported as a measure of endothelial function^{43 56}. Furthermore, while we were able to calculate ES as a measure of change, the results of the meta-analysis need to be viewed in light of the heterogeneity of the studies in regards to population and measurement technique.

These aside, the overarching limitation to the results of this systematic review and meta-analysis is the lack of available high-level evidence investigating the effect of ET on CMR. Furthermore, there is little data focussing on pathologies specifically associated with development of microvascular disease such as diabetes and cardiovascular disease. Extensive investigation is required to determine the effect of ET on CMR in populations known to suffer microvascular disease and, in addition, to identify the most effective dose and intensity of ET.

Conclusions

Available evidence suggests that ET moderately improves CMR. However, this finding is based on the small number of controlled human trials, limited by small samples sizes and varying methodological quality. More studies are required targeting at-risk populations such as people with diabetes.

Investigation of non-traditional exercise therapies such as resistance training and high-intensity interval training on CMR are also required.

Practical implications

- Based on the results of this review, we suggest that ET be considered as a means of improving CMR in people with microvascular disease as well as healthy but physically inactive adults. We would not expect further improvement to CMR in healthy adults who are physically active.

- ET may have potential as a pre-surgical tool to enable faster healing of cutaneous wounds. Similarly, ET may hold clinical utility for timely wound healing in suitable patients. Research is warranted into the effect of ET on other forms of microvascular disease such as neuropathy and retinopathy.

- Though the review highlights the need for further trials with regards to cutaneous outcomes, the large array of other health benefits of ET as well as its inherent affordability leads us to advocate its utilisation as a general health and rehabilitation tool.

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Figure legends

Figure 1: PRISMA flow diagram detailing the search strategy for article inclusion (Abbreviations: n = number, CMR = cutaneous microvascular reactivity)

Figure 2: Forest plot displaying a random-effects meta-analysis of the effect of exercise training on cutaneous microvascular reactivity (Abbreviations: ES = effect size, CI = confidence interval)

Table 1 Participant characteristics

Reference	Participants	Age	% Male	% Female	Disease status	BMI	Mass (Kg)	Height (cm)
Black et al, (2008)	AE: 16	NR	50	50	Older sedentary			NR
	- LH: 8					LH: 30±2	LH: 88±7	
	- ACh: 8					ACh: 30±2	ACh: 82±4	
Klonizakis et al, (2009)	C: 9	NR	NR	NR	Older sedentary	NR	NR	NR
	AE: 8	57±9	14	86	Post-surgical varicose veins	NR	71.8±12.2	168.2±5.0
	C: 8	51±3	14	86	Post-surgical varicose veins	NR	81.4±3.7	166.2±3.1
Middlebrooke et al, (2006)	AE: 22	61.8±7.7	NR	NR	Type 2 diabetes (7 SN)	31.8±4.0	90.7±13.5	NR
	C: 30	64.6±6.8	NR	NR	Type 2 diabetes (11 SN)	29.9±5.4	87.5±17.5	NR
	AE: 14	61.7±2.7	36	64	Type 2 diabetes	29.4±0.7	65.8±3.1	149±5
Mitranun et al, (2014)	IT: 14	61.2±2.8	36	64	Type 2 diabetes	29.6±0.5	66.5±3.7	149±4
	C: 15	60.9±2.4	33	67	Type 2 diabetes	29.7±0.4	67.7±3.2	152±5
	AE: 24	44±6	75	25	Grade 1 essential HT, overweight, sedentary.	28±3	NR	NR
Pasqualini et al, (2009)	C: 24	43±8	66	34	Grade 1 essential HT, overweight, sedentary.	29±4	NR	NR
	AE: 6	45±5	NR	NR	NAFLD	31±1	93	NR
	C: 5	51±3	NR	NR	NAFLD	30±21	84	NR
Thomas et al, (1999)	YA5%: 5	25 ± 1	100	0	Healthy	NR	77.1±7.3	176±2
	YA: 3	29±1	100	0	Healthy	NR	80.5±8.7	179±2
	YR: 7	24±1	100	0	Healthy	NR	79.2±7.1	173±5
	YC: 7	26±1	100	0	Healthy	NR	80.3±3.7	175±2
	OA5%: 7	69±1	100	0	Older	NR	80.6±3.0	176±2
	OA: 4	67±1	100	0	Older	NR	81.2±6.4	175±1
	OR:3	67±1	100	0	Older	NR	91.5±2.6	180±1
	OC: 7	68±1	100	0	Older	NR	84.1±4.3	177±1

All data reported as means ± SD. ACh = acetylcholine protocol; AE = aerobic exercise group; BMI = body mass index; C = control group; HT = hypertension; IT = Interval training group; LH = local heating protocol; NR = not reported; OA = older aerobic training group; OA5% = older aerobic training group who increased VO_{2max} by 5%; OC = older control group; OR = older resistance training group; SN = sensory neuropathy; YA = young aerobic training group; YA5% = young aerobic training group who increased VO_{2max} by 5%; YC = young control group; YR = young resistance training group.

Table 2 Exercise and Control Interventions

Reference	Mode of Intervention	Frequency of exercise (sessions per week)	Intensity of Exercise	Exercise Duration	Session	Intervention Duration
Black et al, (2008)	C: n= 9;	N/A	N/A	N/A		24 weeks
	AE: n= 16; Treadmill walking, cycling	3/7 for 6 weeks; 5/7 for 18 weeks	30% HRR (12 weeks); 60% HRR (12 weeks)	30min		24 weeks
Klonizakis et al, (2009)	C: n = 8;	N/A	N/A	N/A		8 weeks
	AE: n = 8; treadmill walking	2/7	(‘light’ to ‘somewhat-hard’) using Borg's 6 to 20 RPE scale (Borg, 1998)	40min session: cycles of 2min exercise > 2min rest, for a total exercise time of 20min		8 weeks
Middlebrooke et al, (2006)	C: n=30; standard care	N/A	N/A	N/A		26 weeks
	AE: n=22; light aerobic exercise and stretching	3/7	70-80% MHR	50-60min session: 10-15min warm-up > 30min > 10-15min cool-down		26 weeks
Mitranun et al, (2014)	C: n=15; remain sedentary, do not alter diet	N/A	N/A	N/A		12 weeks
	AE: n=14; treadmill	3/7	<u>P1</u> : warm-up and exercise (50% VO ₂ max)	<u>P1</u> : 30min session: 5min warm-up > 20min exercise > 5min cool-down		2 weeks (of 12)
			<u>P2</u> : warm-up and exercise (60% VO ₂ max)	<u>P2</u> : 30min session: 5min warm-up > 20min exercise > 5min cool-down		4 weeks (of 12)
			<u>P3</u> : warm-up and exercise (65% VO ₂ max)	<u>P3</u> : 40min session: 5min warm-up > 30min exercise > 5min cool-down		6 weeks (of 12)
	IT: n=14; treadmill	3/7	<u>P1</u> : warm-up (50% VO ₂ max), exercise (50% VO ₂ max)	<u>P1</u> : 30min session: 5min warm-up > 20min exercise > 5min cool down		2 weeks (of 12)
			<u>P2</u> : warm-up (50% VO ₂ max), 4 intervals of 1min (80% VO ₂ max) and 4min (50% VO ₂ max)	<u>P2</u> : 30min session: 5min warm-up > 20min exercise > 5min cool-down		4 weeks (of 12)
			<u>P3</u> : warm-up (60% VO ₂ max), 6 intervals	<u>P3</u> : 40min session: 5min warm-up > 30min		6 weeks (of 12)

			of 1min (85% exercise > 5min cool-down VO ₂ max) and 4min (60% VO ₂ max)		
Pasqualini et al, (2009)	C: n = 24; avoid adding salt to food, follow weight-reducing diet if required AE: n = 24; walking and stationary cycling, avoid adding salt to food, follow weight-reducing diet if required	N/A 4/7	N/A Warm-up (65% MHR), exercise (80% MHR), warm-down	N/A 45min session: 10min warm-up > 30min exercise > 5min cool-down	8 weeks 8 weeks
Pugh et al, (2013)	C: n=5; lifestyle and dietary advice AE: Moderate intensity aerobic exercise	N/A 3/7 for 11 weeks 5/7 for 5 weeks	N/A 30% HRR 60% HRR	N/A 30min 45min	16 weeks 16 weeks
Thomas et al, (1999)	C: n = 14; maintain present level of activity AE: n = 19; treadmill, cycle ergometer, rower, and stair climber RE: n = 10; warm-up/ cool-down cycle ergometer > leg extension/flexion, chest press, upper back extension, assisted pull-ups and dips	N/A 4/7 4/7	N/A 60–80% MHR 60% of their 1 RM	N/A 30-60min 40min session: 5min cycle > 30 min RE > 5 min cycle	16 weeks 16 weeks 16 weeks

AE = aerobic exercise group; C = control group; HRR = heart rate reserve; IT = interval training group; MHR = maximal heart rate; n = number of subjects; N/A = not applicable; RE = resistance exercise group; RM = repetition maximum; RPE = ratings of perceived exertion. Weeks not reported as whole weeks are reported as mean ± Standard Deviation

Table 3 Quality Appraisal of included studies

Study	1.Hypothesis stated	2.Main outcomes	3.Participant characteristics	4.Interventions described	5.Principal confounders described	6.Main findings described	7.Variability estimates	8.Adverse events reported	9.Patients lost to follow-up	10.Actual p -value reported	11.Population source stated	12.Participant agreement rate stated	13.Representative facilities/staff	14.Participants blinded	15.Measurees blinded	16. “data-dredging” made clear	17.Follow-up adjusted adequately	18.Statistical tests	19.Compliance reliable	20.Accurate measures	21.Same population recruited	22.Same time recruitment	23.Subjects randomised to intervention	24.Randomisation concealed	25.Adequate confounder adjustments	26.Loss to follow-up considered	27.Sufficient power
Black et al, (2008)	Y	Y	Y	Y	Y	N	N	U	U	N	U	U	Y	U	U	Y	U	Y	Y	Y	U	U	Y	U	Y	U	0
Klonizakis et al, (2009)	Y	Y	Y	Y	Y	N	N	Y	Y	Y	Y	U	U	U	U	Y	Y	Y	Y	Y	Y	U	Y	U	Y	Y	0
Middlebrooke et al, (2006)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	U	U	N	N	Y	Y	Y	Y	Y	Y	Y	Y	U	Y	Y	5
Mitranun et al, (2014)	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	U	Y	U	U	Y	Y	Y	Y	Y	Y	Y	Y	U	Y	Y	5
Pasqualini et al, (2009)	Y	Y	Y	Y	Y	Y	Y	U	Y	N	U	U	U	U	U	Y	Y	Y	Y	Y	U	Y	N	N	Y	Y	0
Pugh et al, (2013)	Y	Y	Y	Y	Y	N	N	N	Y	N	Y	U	Y	N	N	N	Y	Y	Y	Y	Y	U	Y	U	Y	Y	5
Thomas et al, (1999)	Y	Y	Y	Y	Y	Y	Y	U	Y	N	U	U	U	U	U	Y	Y	Y	Y	Y	U	Y	U	U	Y	Y	0

Item numbers refer to items on the *Downs and Black checklist* (1998). N = no, U = unable to determine, Y = yes, 0 = power calculation not provided, 5 = sufficient power calculations provided.

Table 4 Outcomes of exercise interventions for change in cutaneous microvascular reactivity

Reference	Mode (site)	Measurement	Method of stimulating CMR	Pre, mean ($\pm$ SD)	Post, mean ($\pm$ SD)	Change Score
Black et al, (2008)	Laser Doppler (Forearm)	CVC (LDF/MAP); %CVC _{max}	Local heating (42°C) microdialysis	AE:37.1 $\pm$ 6.0 %CVC _{max}	AE:58.1 $\pm$ 6.2 %CVC _{max} (12 weeks)	(P<0.05)*
				C:41.2 $\pm$ 8.8 %CVC _{max}	C:37.8 $\pm$ 7.5 %CVC _{max} (12 weeks)	(P>0.05)
			Ach microdialysis	AE low dose: 4.4 $\pm$ 1.6 %CVC _{max}	AE low dose: 13.7 $\pm$ 3.6 %CVC _{max} (12 weeks)	(P=0.07)
					AE low dose: 9.6 $\pm$ 3.1 %CVC _{max} (24 weeks)	(P=0.08)
				AE mid dose: 13.5 $\pm$ 3.2 %CVC _{max}	AE mid dose: 28.9 $\pm$ 5.3 %CVC _{max} (12 weeks)	(P<0.05)*
					AE mid dose: 27.6 $\pm$ 5.4 %CVC _{max} (24 weeks)	(P<0.05)*
				AE high dose: 45.1 $\pm$ 8.9 %CVC _{max}	AE high dose: 56.1 $\pm$ 3.9 %CVC _{max} (12 weeks)	(P=0.2)
					AE high dose: 55.5 $\pm$ 6.8 %CVC _{max} (24 weeks)	(P=0.3)
				C low dose: -1.7 $\pm$ 3.6 %CVC _{max}	C low dose: 0.7 $\pm$ 2.4 %CVC _{max}	(P>0.05)
				C mid dose: 3.6 $\pm$ 1.2 %CVC _{max}		(P>0.05)

				C high dose: 14.7±6.4 %CVC _{max}	C mid dose: 3.1±1.7 %CVC _{max} (P>0.05)	
					C high dose: 15.5±2.7 %CVC _{max}	
Klonizakis et al, (2009)	Laser Doppler (Gaiter area)	PF (PU)	ACh iontophoresis	AE: - PF to ACh supine: 44±30 - PF to ACh standing: 37±27	- PF to ACh supine: 62±33 - PF to ACh standing: 74±31	(P = 0.03)* (P = 0.08)
			SNP iontophoresis	- PF to SNP supine: 67±48 - PF to SNP standing: 54±31	- PF to SNP supine: 61±33 - PF to SNP standing: 40±23	(P > 0.05) (P > 0.05)
				C: - PF to ACh supine: 35 ± 25 - PF to ACh standing: 41±33	- PF to ACh supine: 30±20 - PF to ACh standing: 45±50	(P > 0.05) (P > 0.05)
			ACh iontophoresis	- PF to SNP supine: 34±25 - PF to SNP standing: 40±33	- PF to SNP supine: 29±21 - PF to SNP standing: 44±49	(P > 0.05) (P > 0.05)
			SNP iontophoresis			
Middlebrooke et al, (2006)	Laser Doppler perfusion imaging (Forearm)	Maximum hyperaemic response; Erythrocyte flux	Local heating (42°C)	AE: 1.42±0.36 C: 1.49±0.43	1.47±0.33 1.52±0.37	(P = 0.85)
			ACh iontophoresis	AE: 1.27±0.44 C: 1.37±0.47	1.44±0.23 1.28±0.37	(P = 0.19)
			SNP iontophoresis	AE: 1.12±0.28 C: 1.09±0.50	1.13±0.40 1.10±0.39	(P = 0.98)
Mitranun et al, (2014)	Laser Doppler (Forearm)	RF (PU); PF (PU); ratio (PF-RF) / RF x 100	Post-occlusive reactive hyperaemia	AE: -RF: 19.2±2.3 -PF: 85.1±12.8 -Ratio: 4.2±0.04 IT: -RF: 19.7±1.9 -PF: 86.1±18.8 -Ratio: 4.5±0.05 C: -RF: 18.8±2.8 -PF: 87.8±14.7 -Ratio: 4.4±0.06	18.1±1.7 91.5±17.4 4.7±0.05 18.4±2.5 93.9±19.5 5.1±0.05 20.1±2.4 89.6±16.4 4.6±0.05	(P>0.05) (P>0.05) (P<0.05 vs pre)* (P>0.05) (P<0.05 vs C)* (P<0.05 vs AE)* (P>0.05) (P>0.05) (P>0.05)
Pasqualini et al, (2009)	Laser Doppler (Forearm)	RF (PU); PF (PU); RF/PF; AuC after	Post-occlusive reactive hyperaemia	AE: - PF: 38.8 ± 19	- PF: 42.2 ± 18	(P>0.05)

		post-occlusive reactive hyperaemia		-RF: 6.6 ± 2.2 - AuC: 876 ± 539 C: - PF: 45.7 ± 22 -RF: 6.20 ± 0.9 - AuC: 1021 ± 611	-RF: 7.6 ± 4.2 - AuC: 1468 ± 925 - PF: 42.4 ± 19 -RF: 7.3 ± 1.6 - AuC: 1091 ± 494	(P>0.05) (P<0.001)* (P>0.05) (P>0.05) (P>0.05)
Pugh et al, (2013)	Laser Doppler (Forearm)	%CVC _{max}	Local heating (42°C)	AE: 63 ± 6 C: 63 ± 4	83 ± 5 64 ± 10	(NR) (NR)
Thomas et al, (1999)	Laser Doppler (Forearm)	CVC (LDF/MAP); %CVC _{max}	Local heating (42°C) at control site	<u>YA5% group</u> Baseline: 20.8 ± 2.9 Threshold: $36.87 \pm 0.09^\circ\text{C}$ Plateau: 63.0 ± 7.6 <u>YA group</u> Baseline: 16.6 ± 4.8 Threshold: $36.95 \pm 0.07^\circ\text{C}$ Plateau: 61.3 ± 5.4 <u>YR group</u> Baseline: 14.2 ± 2.9 Threshold: $36.78 \pm 0.07^\circ\text{C}$ Plateau: 68.5 ± 4.8 <u>YC group</u> Baseline: 17.8 ± 2.0 Threshold: $36.63 \pm 0.08^\circ\text{C}$ Plateau: 75.4 ± 4.3 <u>OA5% group</u> Baseline: 22.6 ± 3.0 Threshold: $36.94 \pm 0.13^\circ\text{C}$ Plateau: 68.7 ± 3.9 <u>OA group</u> Baseline: 22.7 ± 5.4 Threshold: $36.46 \pm 0.12^\circ\text{C}$ Plateau: 57.5 ± 5.6	Baseline: 17.5 ± 4.2 Threshold: $36.74 \pm 0.14^\circ\text{C}$ Plateau: 67.3 ± 6.3 Baseline: 22.9 ± 4.9 Threshold: $36.80 \pm 0.11^\circ\text{C}$ Plateau: 56.1 ± 8.4 Baseline: 18.1 ± 2.6 Threshold: $36.59 \pm 0.10^\circ\text{C}$ Plateau: 61.7 ± 2.7 Baseline: 20.5 ± 1.5 Threshold: $36.80 \pm 0.12^\circ\text{C}$ Plateau: 66.2 ± 1.9 Baseline: 27.6 ± 2.7 Threshold: $36.59 \pm 0.8^\circ\text{C}$ Plateau: 77.7 ± 2.2 Baseline: 21.8 ± 2.6 Threshold: $36.69 \pm 0.04^\circ\text{C}$ Plateau: 68.0 ± 7.5	(P>0.05) (P>0.05) (P>0.05) (P>0.05) (P>0.05) (P>0.05) (P>0.05) (P>0.05) (P>0.05) (P>0.05) (P<0.05)* (P<0.05)* (P>0.05) (P>0.05) (P>0.05)

Local heating (42°C) at Bretylum tosylate treated site:	<u>OR group</u>		
	Baseline: 20.4±1.1	Baseline: 20.1±5.9	(P>0.05)
	Threshold: 36.80±0.10°C	Threshold: 36.92±0.03°C	(P>0.05)
	Plateau: 58.5±3.5	Plateau: 57.1±3.1	(P>0.05)
	<u>OC group</u>		
	Baseline: 25.1±3.7	Baseline: 27.9±4.6	(P>0.05)
	Threshold: 36.70±0.16	Threshold: 36.77±0.06°C	(P>0.05)
	Plateau: 79.5±4.0	Plateau: 76.0±3.6	(P>0.05)
	<u>YA5% group</u>		
	Baseline: 17.7±4.0	Baseline: 11.9±1.9	(P>0.05)
	Threshold: 36.88±0.15°C	Threshold: 36.78±0.15°C	(P>0.05)
	Plateau: 58.0±13.1	Plateau: 56.6±5.5	(P>0.05)
	<u>YA group</u>		
	Baseline: 10.3±1.8	Baseline: 12.7±2.8	(P>0.05)
	Threshold: 36.99±0.09°C	Threshold: 36.92±0.12°C	(P>0.05)
	Plateau: 53.6±0.5	Plateau: 58.1±3.8	(P>0.05)
	<u>YR group</u>		
	Baseline: 10.6±1.9	Baseline: 13.2±2.3	(P>0.05)
	Threshold: 36.74±0.08°C	Threshold: 36.62±0.0.10°C	(P>0.05)
	Plateau: 58.1±3.6	Plateau: 57.1±3.1	(P>0.05)
	<u>YC group</u>		
	Baseline: 15.5±3.2	Baseline: 15.7±2.2	(P>0.05)
	Threshold: 36.80±0.07°C	Threshold: 36.88±0.14°C	(P>0.05)
	Plateau: 63.1±6.8	Plateau: 60.7±4.4	(P>0.05)
	<u>OA5% group</u>		
	Baseline: 22.2±3.2	Baseline: 20.4±3.5	(P>0.05)
	Threshold: 37.04±0.12°C	Threshold: 36.77±0.16°C	(P<0.05)*
	Plateau: 68.8±4.1	Plateau: 61.5±5.1	(P>0.05)
	<u>OA group</u>		
	Baseline: 15.6±5.3	Baseline: 16.1±3.2	(P>0.05)
	Threshold: 36.73±0.21°C	Threshold: 36.90±0.11°C	(P>0.05)

	Plateau: 62.2±7.7	Plateau: 57.5±10.6	(P>0.05)
	<u>OR group</u>		
	Baseline: 12.8±2.4	Baseline: 21.0±2.5	(P>0.05)
	Threshold: 36.87±0.19°C	Threshold: 36.91±0.03°C	(P>0.05)
	Plateau: 51.4±4.0	Plateau: 60.6±0.1	(P>0.05)
	<u>OC group</u>		
	Baseline: 18.1±2.4	Baseline: 17.9±1.0	(P>0.05)
	Threshold: 36.83±0.15°C	Threshold: 36.84±0.1°C	(P>0.05)
	Plateau: 67.9±4.0	Plateau: 73.7±2.9	(P>0.05)

Values are expressed as means ± standard deviation (SD). * indicates (P<0.05). ACh = acetylcholine; AE = aerobic exercise group; AuC = area under the curve; C = control group; IT = Interval training group; NR = not reported; OA = older aerobic training group; OA5% = older aerobic training group who increased VO₂_{max} by 5%; OC = older control group; OR = older resistance training group; PU = perfusion units; SNP = sodium nitroprusside; YA = young aerobic training group; YA5% = young aerobic training group who increased VO₂_{max} by 5%; YC = young control group; YR = young resistance training group.

Figure 1: Flow diagram of the review process

Figure 2: The effect of exercise training on cutaneous microvascular reactivity

Figure 3: Publication bias