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SYSTEMATIC REVIEW

The Impact of High-Intensity Interval Training Versus Moderate-Intensity Continuous Training on Vascular Function: a Systematic Review and Meta-Analysis

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Abstract

Background Vascular dysfunction is a precursor to the atherosclerotic cascade, significantly increasing susceptibility to cardiovascular events such as myocardial infarction or stroke. Previous studies have revealed a strong relationship between vascular function and cardiorespiratory fitness (CRF). Thus, since high-intensity interval training (HIIT) is a potent method of improving CRF, several small randomized trials have investigated the impact on vascular function of HIIT relative to moderate-intensity continuous training (MICT).

Objective The aim of this study was to systematically review the evidence and quantify the impact on vascular function of HIIT compared with MICT.

Methods Three electronic databases (PubMed, Embase, and MEDLINE) were searched (until May 2014) for randomized trials comparing the effect of at least 2 weeks of HIIT and MICT on vascular function. HIIT protocols involved predominantly aerobic exercise at a high intensity, interspersed with active or passive recovery periods. We performed a meta-analysis to compare the mean difference in the change in vascular function assessed via brachial artery flow-mediated dilation (FMD) from baseline to post-intervention between HIIT and MICT. The impact of HIIT versus MICT on CRF, traditional cardiovascular disease (CVD) risk factors, and biomarkers associated with vascular function (oxidative stress, inflammation, and insulin resistance) was also reviewed across included studies.

Results Seven randomized trials, including 182 patients, met the eligibility criteria and were included in the meta-analysis. A commonly used HIIT prescription was four intervals of 4 min (4 × 4 HIIT) at 85–95 % of maximum or peak heart rate ($HR_{max/peak}$), interspersed with 3 min of active recovery at 60–70 % $HR_{max/peak}$, three times per week for 12–16 weeks. Brachial artery FMD improved by 4.31 and 2.15 % following HIIT and MICT, respectively. This resulted in a significant ($p < 0.05$) mean difference of 2.26 %. HIIT also had a greater tendency than MICT to induce positive effects on secondary outcome measures, including CRF, traditional CVD risk factors, oxidative stress, inflammation, and insulin sensitivity.

Conclusion HIIT is more effective at improving brachial artery vascular function than MICT, perhaps due to its tendency to positively influence CRF, traditional CVD risk factors, oxidative stress, inflammation, and insulin sensitivity. However, the variability in the secondary outcome measures, coupled with the small sample sizes in these studies, limits this finding. Nonetheless, this review suggests that 4 × 4 HIIT, three times per week for at least 12 weeks, is a powerful form of exercise to enhance vascular function.

Key Points

High-intensity interval training (HIIT) is a more potent stimulus than moderate-intensity continuous training (MICT) in enhancing vascular function.

HIIT has a greater positive influence on cardiorespiratory fitness (CRF) and biomarkers associated with vascular function than MICT.

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1 Introduction

The endothelium is an important regulator of vascular homeostasis [1], and its dysfunction is a precursor of atherosclerosis [2]. Vascular function is the ability of the endothelial and smooth muscle cells to release and respond to molecules responsible for maintaining a relaxed vascular tone [3]. Nitric oxide (NO) is considered to be the most important molecule required to maintain vascular function among other substances produced by endothelial cells such as prostacyclin, hyperpolarizing factors, and C-type natriuretic peptide [4]. This is because NO is not only a potent vasodilator, but also functions to prevent smooth muscle cell proliferation, and to inhibit production of pro-inflammatory factors and adhesion molecules [5].

Vascular function is usually assessed as the ability of the vessels to dilate in response to a stimulant (e.g. acetylcholine) or shear stress stimulus primarily evoking NO production [6]. The change in coronary artery diameter in response to acetylcholine infusion is considered to be the 'gold standard' measure of vascular function [7]. However, due to the invasive nature of this procedure, a measure involving the examination of flow-mediated dilation (FMD) of the brachial conduit artery via ultrasound imaging was introduced [8]. This technique is based on the principle that an increase in blood flow due to reactive hyperemia could enhance shear stress-induced NO production [6]. This surrogate measure correlates well with results acquired from the more invasive test of the coronary artery endothelial-dependent function [9]. Shear stress is a mechanical stimulus to the activation of potassium channels that could in turn facilitate calcium influx into the endothelial cells. The increase in intracellular calcium activates endothelial nitric oxide synthase (eNOS), promoting NO bioavailability [10]. NO diffuses into the vascular smooth muscle cells to activate different enzymes and kinases responsible for vessel relaxation and thus vasodilation. Therefore, to ensure that this brachial artery FMD test solely reflects abnormality at the level of the endothelium, brachial artery diameter in response to an exogenous NO producer [e.g., glyceryl trinitrate (GTN)] is also assessed to directly examine the reactivity of the underlying smooth muscle cells [7].

Traditional cardiovascular disease (CVD) risk factors such as obesity, dyslipidemia, hyperglycemia, and hypertension [11], which could all be exacerbated by increased levels of insulin resistance and oxidative stress, contribute to vascular homeostasis perturbation due to a direct effect on NO bioavailability [12]. Exercise training has been shown to be a therapeutic strategy towards vascular function improvement in different clinical populations, concurrently reducing overall mortality [13–22]. It has been reported that the positive impact of exercise on traditional CVD risk factors does not completely explain its protective role against CVD onset [23]. Instead, it was suggested that the ability of exercise to restore vascular homeostasis through enhancement in shear stress-induced NO bioavailability may be another important mechanism explaining the protective role of exercise against CVD development [24, 25].

A recent meta-analysis incorporating four randomized trials [26–29] found improved pre- to post-exercise training brachial artery FMD values in 217 patients with type 2 diabetes (T2DM) compared with control groups (mean difference 2.23 %, $p < 0.0001$), with no change in vascular-independent dilation [30]. However, the exercise prescription (ExRx) parameters utilized (type, intensity, and program duration) varied considerably across studies. The ExRx included strength training, resistance-band training, continuous aerobic training, and circuit training, with mean exercise parameters of 3.6 sessions per week (3–5 sessions per week), 67.5 min per session at 74.4 % of maximum heart rate (HR_{max}) (60–90 % HR_{max}) for 14 weeks (8–26 weeks). Thus, more studies are warranted in order to effectively titrate ExRx to promote optimal vascular function enhancement. Several small randomized trials utilizing high-intensity interval training (HIIT), characterized by brief intermittent bouts of high-intensity aerobic exercise have emerged over recent years, and revealed impressive effects on vascular function relative to moderate-intensity continuous training (MICT) in clinical patients [31–37]. Therefore, the aim of this present study was to conduct a systematic review and meta-analysis to better compare the impact of two different types of aerobic exercise (HIIT vs. MICT) on vascular function. The secondary aim of this study was to review the effect of HIIT versus MICT on biomarkers associated with vascular function encompassing traditional and novel CVD risk factors.

2 Methods

Three electronic databases (PubMed, Embase, and MEDLINE) were searched for eligible studies conducted from the earliest available date to May 2014 by an independent researcher. The following keywords were used in the searches in conjunction with Medical Subject Heading (MeSH) terms, including endothelium, vascular endothelium, vasodilation, nitric oxide, vascular function, and their related terms: (1) high-intensity training/exercise; (2) interval training/exercise; (3) high-intensity interval training/exercise; and (4) aerobic interval training/exercise. The reference list of articles retrieved was also manually searched for eligible studies.

2.1 Inclusion Criteria

Only randomized trials conducted in humans and published in English were considered for this study. The following criteria had to be met in order to be included in the analysis: (1) vascular function had to be evaluated at pre- and post-training intervention; (2) the exercise intervention duration had to be at least 2 weeks; (3) the HIIT protocol had to involve performance of predominantly aerobic exercise at a high intensity (vs. all-out sprinting) and separated by active (at low-moderate intensity) or passive recovery periods; (4) the study had to include a comparator MICT group; and (5) vascular function had to be evaluated via FMD of the brachial artery. Studies that also used another intervention (e.g., diet) that may have impacted on vascular function were excluded. When the same data were presented in multiple publications, the first published study was used for the analysis. Two authors [32, 35] were contacted to obtain complete FMD data.

2.2 Procedural Quality Assessment of Included Studies

The quality of methods reported in each included study was evaluated through consensus of two reviewers, using the PEDro Scale [38] (Table 1). If consensus was not achieved, another reviewer was consulted. A PEDro score of at least 6 was required for inclusion into this study to limit analytical bias of this review.

2.3 Data Synthesis and Analysis

The meta-analysis was conducted using Review Manager software (RevMan 5; Cochrane Collaboration, Oxford, UK). The effect size of the change in mean difference of the relative brachial artery FMD from pre- to post-intervention between groups (HIIT vs. MICT) in each study was calculated and pooled using the random-effects model. Heterogeneity of included trials was assessed with the I^2 statistic and the chi-squared test for heterogeneity. Inverse variance weighting was used to compensate for heterogeneity of sample sizes between studies. The mean difference in post-intervention change in FMD between HIIT and MICT, expressed as a percentage, was calculated as follows: ($\sum$weighted mean/$\sum$product of weighted mean and effect size) $\times$ 100.

3 Results

Of the 283 trials retrieved in the initial search after duplicates were removed, seven trials met the inclusion criteria. These trials included 182 participants with heart failure, hypertension, metabolic syndrome (MetS), coronary artery disease (CAD), T2DM, and post-menopausal women and obese adults (Fig. 1).

3.1 Quality Assessment of Study Methodology

The quality of the trials included was considered to be moderate, with a mean PEDro score of 7.29 out of 10 [standard deviation (SD) 0.76], with a range of 6–8 (Table 1). None of the studies reported the allocation-concealment process. Furthermore, only two studies [33, 34] provided a sample size explanation. 'Intention-to-treat' analysis was used in all included studies.

Table 1 PEDro scores for included studies: total score out of 10

References	Random allocation	Groups similar at BL	Concealed allocation	Assessor blinding	Sample size calculation explained	BG statistical difference reported for PO	Point and variability measures reported	<15 % dropouts	Eligibility criteria specified	ITT analysis	Total PEDro score
Klonizakis et al. [37]	1	1	1	0	0	1	1	1	1	1	8
Wisloff et al. [32]	1	1	0	0	0	1	1	1	1	1	7
Tjonna et al. [34]	1	1	0	0	1	1	1	1	1	1	8
Schjerve et al. [35]	1	1	0	1	0	1	1	0	1	1	7
Molmen-Hansen et al. [33]	1	1	0	1	1	1	1	0	1	1	8
Currie et al. [31]	1	1	0	0	0	1	1	1	1	0	6
Mitranun et al. [36]	1	1	0	0	0	1	1	1	1	1	7

BG between-group, *BL* baseline, *ITT* intention-to-treat, *PO* primary outcome

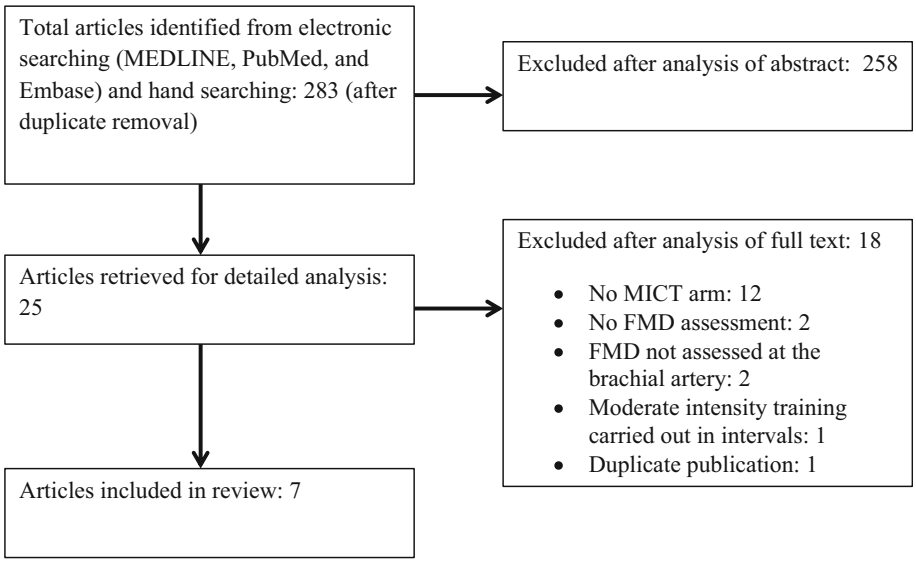

Fig. 1 Flow diagram of systematic search. *FMD* flow-mediated dilation, *MICT* moderate-intensity continuous training

3.2 Vascular Function

All participants in the included studies had impaired vascular function prior to the exercise interventions (Table 2). Endothelial-dependent and -independent functions of the brachial artery were assessed via FMD and administration of GTN according to the current guidelines [6, 39], respectively. One study did not evaluate vascular-independent function [36]. During the brachial FMD procedure, reactive hyperemia was induced by inflating a cuff at 200–250 or 50 mmHg above systolic blood pressure (SBP) at either the upper arm [32, 34, 35] or the forearm [31, 36, 37] and by deflating the cuff after 5 min of occlusion. Cuff placement and pressure used to produce brachial artery occlusion was not reported in one of the studies [33]. The range of GTN dose administered sublingually to assess vascular-independent dilation in included studies was 0.4 mg [31, 37] to 0.5 mg [32, 33, 35], and was not reported in one study [34]. All trials expressed vascular-dependent and -independent functions as an increase in brachial artery diameter from baseline to maximum dilation after 1 min of cuff release or 4 min following GTN administration, respectively. These were calculated as a percentage change from baseline to maximum dilation (relative FMD) in accordance with the following equation: [(maximum diameter−baseline diameter)/baseline diameter] × 100. Five of the seven trials reported resting brachial diameter and found no significant change from baseline to post-intervention [31, 34–37]. Studies that evaluated shear rate [34–36] or shear rate area under the curve (AUC) [31] found no change from baseline to post HIIT or MICT. Shear rate was calculated as blood flow velocity (cm/s) divided by brachial diameter (cm) according to Pyke and Tschakovsky [40].

Both HIIT and MICT improved FMD in six of seven studies. The one study that found no effect only used a 2-week training period [37]. Trials ($n = 4$) that used the 4 × 4 HIIT protocol (four intervals for 4 min at 85–95 % $HR_{max/peak}$) with 3 min active recovery (50–70 % $HR_{max/peak}$) for 12–16 weeks (three times per week) were found to significantly enhance vascular-dependent function more than MICT [32–35]. Studies that incorporated HIIT with a shorter interval duration but with a greater number of bouts [4–10 × 1 min at 80–85 % peak oxygen uptake (VO_{2peak}), 4 min active recovery at 50–60 % VO_{2peak}] revealed either superior [36] or no significant difference [31] in brachial artery FMD relative to an isocaloric MICT after 12 weeks (three times per week). Furthermore, no significant difference was found in the change in GTN-mediated brachial artery dilation following either HIIT or MICT [31–35, 37]. When all data from the included studies were collated, the meta-analysis revealed that post-intervention change in FMD was significantly greater following HIIT than following MICT (mean difference 2.26 %, $p < 0.05$) (Fig. 2). The average relative FMD value increased from 5.14 to 9.45 % and from 5.12 to 7.27 % after 2–16 weeks (three times per week) of HIIT and MICT, respectively. However, substantial heterogeneity was detected between studies as evidenced by $I^2 = 68$ %. It is also noteworthy that four studies were conducted in the same laboratory [32–35]. Moreover, the study by Klonizakis et al. [37] could be considered an outlier in terms of the average program duration compared with other studies included in this meta-analysis (see Table 2). When this study was deleted from the analysis, the mean difference in post-intervention change in FMD between HIIT and MICT increased from 2.26 to 2.45 %.

Table 2 Description of studies

References	Participant characteristics	HIIT and MICT program duration, type, and frequency	Exercise intervention	HIIT outcomes relative to MICT
Wisloff et al. [32]	18 post-infarction HF pts. HIIT ($n = 9$; age 76.5 ± 9 y; VO_{2max} 13 ± 1.6 ml/kg/min); MICT ($n = 9$; age 74.4 ± 12 y; VO_{2max} 13 ± 1.1 ml/kg/min)	12 wks uphill treadmill walking; supervised 2×/wk; unsupervised 1×/wk (home-based)	HIIT: 4 × 4-min intervals at 90–95 % HR_{peak}, interspersed by 3 min active recovery at 50–70 % HR_{peak} MICT (iso-caloric with HIIT): 47 min at 70–75 % HR_{peak}	↑ FMD (pre vs. post; HIIT 3.49 ± 1.95 vs. 11.58 ± 1.5 %; MICT 3.73 ± 2.42 vs. 8.34 ± 1.7 %); NC in GTN-mediated dilation, SBP, DBP, TC, TG, HDL, glucose, IGF-1, and endothelin-1; ↑ VO_{2peak}, PGC-1α (NC in MICT group), and maximal Ca^{2+} re-uptake (NC in MICT group)
Molmen-Hansen et al. [33]	48 hypertensive pts: essential HTN stage 1–2 (SBP 140–179 and/or DBP 90–109 mmHg); HIIT ($n = 31$; age 52.5 ± 7.4 y; VO_{2max} 36.3 ± 8.8 ml/kg/min); MICT ($n = 28$; age 53.6 ± 6.5 y; VO_{2max} 34 ± 7 ml/kg/min)	12 wks uphill treadmill walking/running; supervised 3×/wk	HIIT: 4 × 4-min intervals at 90–95 % HR_{max}, separated by 3 min active recovery at 60–70 % HR_{max} MICT (iso-caloric with HIIT): 47 min at 70 % HR_{max}	↑ FMD (pre vs. post; HIIT 6.49 ± 3.71 vs. 10.66 ± 5 %; MICT 6.50 ± 5.01 vs. 7.11 ± 5.10 %); NC in GTN-mediated dilation; ↑ VO_{2max}; ↓ ASBP, ADBP
Tjonna et al. [34]	22 MetS pts (WHO criteria). HIIT ($n = 12$; age 55.3 ± 13.2 y; VO_{2max} 33.6 ± 2.5 ml/kg/min); MICT ($n = 10$; age 52 ± 10.6 y; VO_{2max} 36 ± 3.2 ml/kg/min)	16 wks uphill treadmill walking/running; supervised 2×/wk; unsupervised 1×/wk (home-based)	HIIT: 4 × 4-min intervals at 90 % HR_{max}, separated by 3 min active recovery at 70 % HR_{max} MICT (iso-caloric with HIIT): 47 min at 70 % HR_{max}	↑ FMD (pre vs. post; HIIT 5.27 ± 2.24 vs. 14.23 ± 1.51 %; MICT 4.50 ± 3.46 vs. 9.19 ± 1.25 %); NC in GTN-mediated dilation; ↑ VO_{2max}; ↔ SBP; ↔DBP; ↑ HDL (NC in MICT group); NC in TG, TC, LDL; ↔ shear rate; ↑ insulin sensitivity; ↔ waist circumference; NC in WHR; ↑ PGC-1α (NC in MICT group); ↑ maximal Ca^{2+} re-uptake (NC in MICT group)
Currie et al. [31]	21 pts with CAD. HIIT ($n = 11$; age 62 ± 11 y; VO_{2peak} 19.8 ± 23.7 ml/kg/min); MICT ($n = 10$; age 68 ± 8 y; VO_{2peak} 18.7 ± 5.7 ml/kg/min)	12 wks cycling exercise; supervised 2×/wk; unsupervised 1×/wk	HIIT: 10 × 1-min intervals at 80–104 % PPO, interspersed by 1 min active recovery at 10 % PPO MICT (not iso-caloric with HIIT—was according to the CACR exercise guideline): 30–50 min at 51–65 % PPO	↔ FMD (pre vs. post; HIIT 4.60 ± 3.60 vs. 6.10 ± 3.40 %; MICT 4.40 ± 2.60 vs. 5.90 ± 3.60 %); NC in GTN-mediated dilation; ↔ VO_{2peak}; NC in SBP; ↔ DBP; ↔ shear rate

Table 2 continued

References	Participant characteristics	HIIT and MICT program duration, type, and frequency	Exercise intervention	HIIT outcomes relative to MICT
Schjerve et al. [35]	27 obese adults. HIIT ($n = 14$; age 46.9 ± 2.2 y; VO_{2max} 23.6 ± 1.3 ml/kg/min); MICT ($n = 13$; age 44.4 ± 2.1 y; VO_{2max} 25.1 ± 1.4 ml/kg/min)	12 wks treadmill walking or running; supervised 2×/wk; unsupervised 1×/wk (at home or in the gym)	HIIT: 4 × 4-min intervals at 85–95 % HR_{max} interspersed by 3 min of active recovery at 50–60 % HR_{max} MICT (iso-caloric with HIIT): 47 min at 60–70 % HR_{max}	↑ FMD (pre vs. post; HIIT 2.64 ± 3.54 vs. 9.71 ± 1.20 %; MICT 3.00 ± 3.16 vs. 7.27 ± 1.27 %); NC in GTN-mediated dilation; ↑ VO_{2max}; NC in SBP; ↓ DBP; NC in HDL and TC; ↔ shear rate; NC in insulin sensitivity; ↔ body fat %; NC in WHR; ↑ PGC-1α (NC in MICT group) ↑ maximal Ca^{2+} re-uptake (NC in MICT group)
Mitranun et al. [36]	28 T2DM adults. HIIT ($n = 14$; age 61.2 ± 2.8 y; VO_{2max} 24.2 ± 1.6 ml/kg/min); MICT ($n = 14$; age 61.7 ± 2.7 y; VO_{2max} 23.8 ± 1.0 ml/kg/min)	12 wks treadmill walking; supervised 3×/wk	HIIT: 4–6 × 1-min intervals at 80–85 % VO_{2peak}, separated by 4 min of active recovery at 50–60 % VO_{2peak} MICT (iso-caloric with HIIT): 30 min at 60–65 % VO_{2peak}	↑ FMD (pre vs. post; HIIT 5.40 ± 1.10 vs. 7.40 ± 0.90 %; MICT 4.80 ± 1.60 vs. 6.10 ± 1.80 %); ↑ VO_{2max}; ↓ SBP; NC in DBP; ↑ TC (NC in MICT group); ↑ HDL; ↔ LDL; NC in TG; ↔ shear rate; ↔ insulin sensitivity; ↔ WHR
Klonizakis et al. [37]	18 postmenopausal women, age 55–85 y. HIIT ($n = 11$; VO_{2max} 20.4 ± 3.4 ml/kg/min); MICT ($n = 14$; VO_{2max} 25 ± 7.4 ml/kg/min)	2 wks cycling exercise; supervised 3×/wk	HIIT: 10 × 1-min intervals at 100 % PPO, separated by 1 min active recovery (intensity NR) MICT (iso-caloric with HIIT): 40 min at 65 % PPO	NC in FMD (pre vs. post; HIIT 8.10 ± 7.20 vs. 6.50 ± 3.70 %; MICT 8.90 ± 7.90 vs. 7.00 ± 4.30 %); NC in GTN-mediated dilation; ↑ VO_{2peak} (NC in MICT group); NC in SBP or DBP

Values in column 2 are presented as mean ± standard deviation

ADBP ambulatory diastolic blood pressure, *ASBP* ambulatory systolic blood pressure, Ca^{2+} calcium ion, *CACR* Canadian Association of Cardiac Rehabilitation, *CAD* coronary artery disease, *DBP* diastolic blood pressure, *FMD* flow-mediated dilation, *GTN* glyceryl trinitrate, *HDL* high-density lipoprotein, *HF* heart failure, *HIIT* high-intensity interval training, $HR_{peak/max}$ peak or maximum heart rate, *HTN* hypertension, *IGF* insulin growth factor, *LDL* low-density lipoprotein, *MetS* metabolic syndrome, *MICT* moderate-intensity continuous training, *NC* no change, *NR* not reported, *PGC* peroxisome proliferator-activated receptor-gamma coactivator, *PPO* peak power output, *pts* patients, *SBP* systolic blood pressure, *TC* total cholesterol, *TG* triglyceride, *T2DM* type 2 diabetes mellitus, $VO_{2max/peak}$ maximum or peak oxygen uptake, *WHO* World Health Organisation, *WHR* waist-to-hip ratio, *wk(s)* week(s), *y* year, ↑ indicates that change was significantly greater following HIIT than following MICT, ↓ indicates that change was significantly lower following HIIT than following MICT, ↔ indicates significant within-group difference, but not between groups

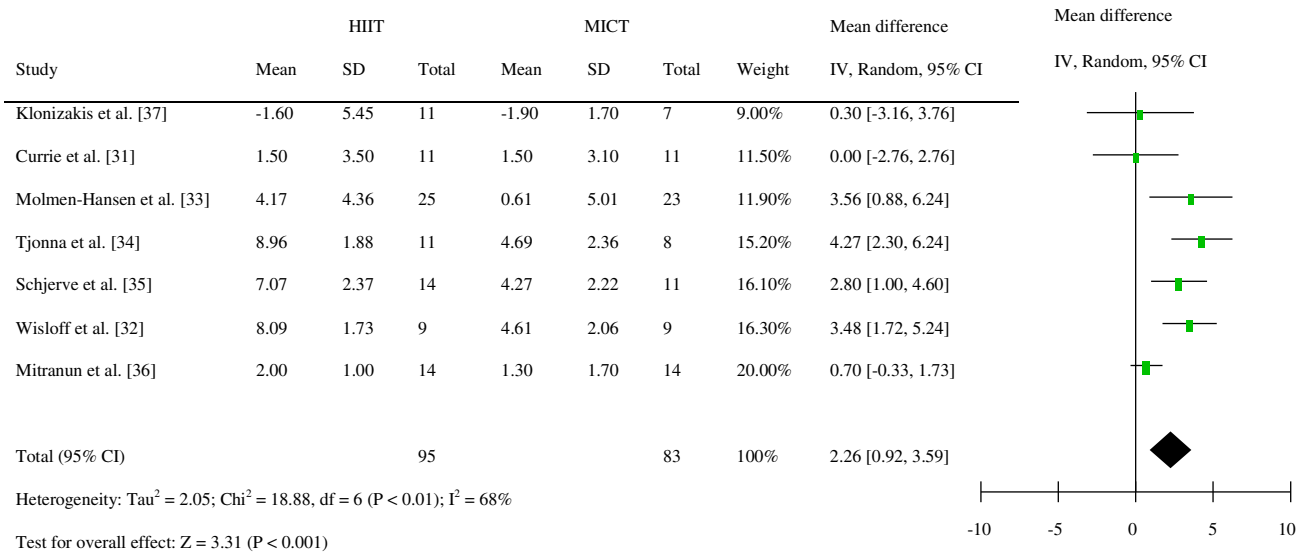

Fig. 2 Forest plot of mean difference in relative flow-mediated dilation of studies included. *CI* confidence interval, *HIIT* high-intensity interval training, *IV* inverse-variance, *MICT* moderate-intensity continuous training, *SD* standard deviation

3.3 Cardiorespiratory Fitness

All studies also evaluated cardiorespiratory fitness (CRF) as either maximum oxygen uptake (VO_{2max}) [33–36] or VO_{2peak} [31, 32, 37]. In five studies that included different clinical patients [32–36], CRF improved at a greater extent following 12 weeks of HIIT (three times per week) compared with MICT (14–46 vs. 5–16 %, respectively) (Table 2). However, Currie et al. [31] reported no significant difference in CRF improvement between HIIT and MICT (24 vs. 19 %, respectively). The HIIT prescription (HIIT-Rx) used in this study consisted of shorter intervals and recovery periods; however, the number of interval repetitions was greater when compared with HIIT protocols employed in other studies [ten intervals for 1 min at 80–104 % of peak power output (PPO), 1 min active recovery at 10 % PPO]. Moreover, a study that only used a 2-week exercise program revealed no change in CRF [37].

3.4 Blood Pressure

BP was also evaluated by all studies in this review, with variable findings. The method of BP measurement was relatively homogenous in four studies [31, 34, 35, 37]. BP was measured at a seated position after 5 [34, 35], 10 [31] or 15 min [37] of rest in a quiet room. Some studies measured BP multiple times for each participant, with the first reading considered a calibration measure and the subsequent measures averaged and recorded [31, 34, 35]. The rest of the studies included either failed to report how BP was measured [32, 36] or monitored BP for 24 h [33]. Two studies that compared the impact of a similar HIIT-Rx (4 × 4 min; 12 weeks; three times per week) and MICT showed no change in SBP following both types of training [32, 35]. However, in the same studies, this HIIT-Rx had a different impact on diastolic BP (DBP), revealing either no change [32] or lower significant reduction compared with MICT (7 vs. 9 %, respectively) [35]. Furthermore, a study that utilized a shorter interval duration but greater interval bout frequency (ten × 1 min HIIT; 12 weeks; three times per week) also found no change in SBP but revealed a significant reduction in DBP (HIIT vs. MICT 2 vs. 7 mmHg) after a 12-week program, although there were no significance between-group differences [31]. The opposite was found in a study that used a similar HIIT-Rx (4–6 × 1 min; 12 weeks, three times week), wherein SBP dropped significantly only in the HIIT group (12 mmHg), with no change in DBP [36]. Molmen-Hansen et al. [33] carried out a more comprehensive study that investigated the effect of HIIT on 24-h ambulatory BP. This study revealed that 4 × 4 HIIT (12 weeks, three times per week) could significantly reduce ambulatory SBP (ASBP) more than could MICT (HIIT vs. MICT 12 vs. 4.5 mmHg). However, there was no difference in effect between either types of training on ambulatory DBP (ADBP) (HIIT vs. MICT 8 vs. 3.5 mmHg). This was supported by a study conducted by Tjonna et al. [34], who found significant reductions in SBP following HIIT (4 × 4 HIIT, 12 weeks, three times per week) and MICT (HIIT vs. MICT; 9 vs. 10 mmHg). However, a significant reduction in DBP was only evident in the HIIT group (HIIT vs. MICT 6 vs. 6 mmHg). Furthermore, Klonizakis et al. [37] found no significant difference in BP following only 2 weeks of either HIIT (10 × 1 min at 100 % PPO, 1 min active

recovery, three times per week) or MICT, but reported a trend towards a reduction in SBP (–7 mmHg; $p = 0.073$) and DBP (–3 mmHg; $p = 0.086$) from pre- to post-intervention, respectively.

3.5 Lipid Profile

In all studies that incorporated a 4 × 4 HIIT-Rx and an iso-caloric MICT (12–16 weeks, three times per week) [32, 34, 35], no change in total cholesterol (TC) was found. However, 4–6 × one HIIT for an intervention of similar duration and frequency (12 weeks, three times per week) significantly reduced TC [36]. In these studies [32, 34, 36], no significant changes in plasma triglyceride (TG) levels were reported following either type of training. Furthermore, high-density lipoprotein cholesterol (HDL-C) has only been shown to significantly increase in patients with MetS [34] and T2DM [36]. No significant changes in HDL-C concentrations were found in the other studies [32, 35] following HIIT or MICT. However, Wisloff et al. [32] reported that there was a trend for HIIT to promote positive influences on lipid profiles in heart failure patients (pre vs. post: TG 2.1 ± 1.2 vs. 1.7 ± 7 mmol/l, $p = 0.11$; HDL 1.2 ± 0.4 vs. 1.3 ± 0.3 mmol/l, $p = 0.20$).

3.6 Oxidative Stress

In the study by Wisloff et al. [32], HIIT was found to induce a significant enhancement in antioxidant status compared with an iso-caloric MICT in heart failure patients. In agreement with this finding, Mitranun et al. [36] revealed an increase in glutathione peroxidase only following HIIT. These results were supported by studies that showed a significantly greater increase in NO bioavailability following HIIT compared with an MICT protocol [34, 36]. Furthermore, in line with these findings, studies included have also shown a significantly greater reduction in plasma levels of oxidized low-density lipoprotein (LDL) following HIIT relative to an iso-caloric MICT [32, 34]. In contrast, Schjerve et al. [35] found no change in antioxidant status following either type of training, but found a significant reduction in oxidized LDL cholesterol (LDL-C) following MICT in obese adults.

3.7 Insulin Sensitivity

Three of the studies also measured insulin sensitivity as assessed by an oral glucose tolerance test (OGTT) [35] and homeostatic model assessment–insulin resistance (HOMA-IR) [34, 36]. No changes in glucose and C-peptide concentrations were derived from the OGTT in obese individuals following either type of training [35]. However, following 12 weeks (three times per week) of 4–6 × 1 HIIT and 4 × 4 HIIT, insulin sensitivity determined via HOMA-IR was shown to improve, either similarly [36], or at a greater magnitude [34] relative to MICT in patients with T2DM and MetS, respectively. Mitranun et al. [36] also revealed a significant decrease in glycated hemoglobin (HbA_{1c}) levels only in the HIIT group. In contrast, Schjerve et al. [35] found no change in HbA_{1c} following either type of training with a similar exercise program duration and frequency (12 weeks, three times per week) but with a different HIIT protocol (4 × 4 HIIT). Schjerve et al. [35] utilized an HIIT protocol with much longer bouts of high-intensity exercise (4 min) than that of Mitranun et al. [36], which only used 1-min bouts with similar recovery duration (4 min).

3.8 Inflammation

Two studies assessed inflammation, measured as the concentration of serum or plasma high-sensitivity C-reactive protein (hsCRP) and found no change from baseline after 12 weeks of either HIIT or MICT in heart failure patients [32] and obese adults [35].

3.9 Peroxisome Proliferator-Activated Receptor-Gamma Coactivator-1α

The change in protein levels of peroxisome proliferator-activated receptor-gamma coactivator (PGC)-1α was measured in three studies [32, 34, 35]. PGC-1α is known to be a key activator of metabolic genes stimulating mitochondrial biogenesis and substrate utilization. Studies in this review have shown increased PGC-1α protein of 47–138 % ($p < 0.05$) following 12–16 weeks of HIIT, with no significant change found in the MICT group.

3.10 Body Fat

Two studies evaluated the change in body fat percentage through either dual-energy X-ray absorptiometry [35] or bioelectrical impedance analysis [36]. Both studies showed a significant reduction in body fat percentage (HIIT vs. MICT; Schjerve et al. [35] 2.5 vs. 2.2 %; Mitranun et al. [36] 2.2 vs. 2.6 %) after 12 weeks (three times per week) following both types of exercise, with no significant difference between groups. Waist-to-hip ratio (WHR) was also evaluated in three studies [34–36]. Trials that incorporated the 4 × 4 HIIT-Rx [34, 35] showed no change in WHR after 12–16 weeks of training (three times per week); however, a significant reduction in waist circumference alone was observed in one study [34]. In contrast, HIIT with shorter intervals (4–6 × 1 min intervals) was associated with a significant improvement in WHR in T2DM patients [36].

4 Discussion

The main finding of this meta-analysis is that HIIT was a more potent stimulus in improving endothelial function than was MICT in studies incorporating 182 participants. Moreover, HIIT had the tendency to induce superior positive effects on CRF, traditional CVD risk factors, and biomarkers associated with vascular function relative to MICT. In contrast, neither type of training had a significant impact on GTN-induced vasodilation.

When data from all seven studies were pooled and analysed, HIIT was shown to significantly improve brachial FMD by 2.26 % more than MICT. Since no change in GTN-induced vasodilation was found from pre- to post-intervention in studies included, it could be inferred that FMD enhancement solely reflects restoration of vascular function at the level of the endothelium [7]. A meta-analysis including 14 prospective studies encompassing 5547 participants reported a 13 % reduction in risk of cardiovascular events with a 1 % increase in FMD [41]. The magnitude of FMD improvement found following both types of exercise in the studies included in the present review (pre vs. post; HIIT 5.14 vs. 9.45 %; MICT 5.12 vs. 7.27 %) are therefore deemed to be clinically significant. Moreover, the present review suggests that training at a higher intensity is a better stimulus in enhancing vascular endothelial function. This is inconsistent with results obtained from 26 healthy young men showing increased acetylcholine-mediated vasodilation following 30 min of MICT (50 % $V\mathrm{O}_{2\mathrm{max}}$) performed 5–7 times per week for 12 weeks, with no significant improvement found in the high-intensity continuous training group (75 % $V\mathrm{O}_{2\mathrm{max}}$) [42]. The authors postulated that an exercise intensity threshold exists whereby NO bioavailability may be jeopardized when this point is surpassed in training. This was supported in studies showing increased reactive oxygen species (ROS) production [43] and reduced circulating antioxidants as exercise intensity progressed [44]. However, it is plausible that reduced NO bioavailability affecting vascular function could be avoided by limiting the exercise duration above the proposed intensity threshold. This meta-analysis suggests that a recovery period between short bouts of high-intensity exercise as modelled by the HIIT protocol could avoid adverse effects on the vasculature, evident following high-intensity continuous training [43, 44].

Since FMD and CRF (as determined by $V\mathrm{O}_{2\mathrm{max}}$ or $V\mathrm{O}_{2\mathrm{peak}}$) have been shown to be positively associated [45, 46], the result of this meta-analysis is not surprising given the increased ability of HIIT to enhance CRF in patients with cardiometabolic disorders relative to MICT [47]. Several studies have revealed CRF as an antidote against the ability of traditional CVD risk factors to induce mortality [48, 49], showing a 15 % reduction in all-cause mortality for every 1-metabolic equivalent (MET) increase in CRF [50]. Indeed, it has been suggested that the ability of increased CRF to prevent cardiac events may be partially attributable to its significant effect in maintaining vascular homeostasis, beyond its identified positive impact on traditional CVD risk factors [24].

It has been speculated that the superior ability of HIIT to improve vascular function, relative to MICT, could be due to its ability to provoke a greater blood flow through the vessels supplying oxygen to the working muscles, which could in turn promote greater shear stress-induced NO bioavailability [32, 34]. This is supported by a study conducted by Thijssen et al. [51], which showed a parallel incremental increase in blood flow and shear stress with increasing exercise intensity. In line with this theory, chronic low shear stress evident in sedentary individuals as a consequence of inactivity has been found to increase susceptibility to heightened presence of biomarkers associated with vascular dysfunction such as oxidative stress [52], pro-inflammatory factors [53], cell-adhesion molecules [54], and reduced antioxidant expression [55]. It could be postulated that the repetitive shear stress induced by HIIT could initiate changes at the molecular level that could enable potassium channels of the endothelial cells to become more sensitive to shear stress, thereby promoting a greater activity of eNOS. Shear stress is a mechanical stimulus to the activation of potassium channels, which facilitates calcium influx into the endothelial cells. The increase in intracellular calcium triggers eNOS activation and expression [56], promoting NO production and thus vasodilation [57]. However, no difference in shear rate was found following either type of training in the included studies [31, 34–36]. Furthermore, despite no difference in shear rate found following the exercise interventions, NO bioavailability has been shown to significantly increase only following HIIT [36]. This suggests that there may be other mechanisms by which HIIT could enhance vascular function beyond the current concept of increasing shear stress stimulus.

Studies in this review also found a significantly greater enhancement in antioxidant status, indicating decreased oxidative stress and increased NO bioavailability following HIIT compared with MICT in patients with cardiometabolic disorders [32, 34, 36]. Increased oxidative stress is a factor affecting NO bioavailability. The increased presence of ROS leads to a rapid oxidative inactivation of NO into peroxynitrate, which could in turn exacerbate vascular oxidative stress by promoting the 'uncoupling' of eNOS. Uncoupling of eNOS alters its normal function from a NO generator to a superoxide anion-generating enzyme, which further exacerbates vascular dysfunction [58]. The increased flow of electrons via the

electron transport chain in the mitochondria is considered to be an important contributor to increased ROS production (e.g. superoxide anions and hydrogen peroxide) [59]. In contrast, the overexpression of PGC-1α in endothelial cells has been shown to neutralize an enhanced presence of ROS [60]. Although not specifically measured in endothelial cells, HIIT has been reported to enhance PGC-1α abundance more than MICT in the vastus lateralis of patients with cardiometabolic disorders [32, 34, 35]. This is consistent with studies utilizing a considerably smaller HIIT-Rx [10 × 1-min HIIT at ~80 % HR reserve ($HR_{reserve}$), 1 min recovery, three times per week for 2 weeks] in sedentary [61] and T2DM patients [62], showing a significant increase in PGC-1α by 56 % after the training intervention. Assuming that the mechanism of up-regulating the expression of PGC-1α reacts in a similar fashion following higher exercise intensity regardless of the tissue involved, the enhanced vascular function found in the present study could in part be explained by a decrease in ROS and thus enhanced NO availability.

Another mechanism that could explain the superior ability of HIIT to enhance vascular function compared with MICT could be its increased ability to promote enhanced insulin sensitivity. Along with enhanced FMD, Tjonna et al. [34] also reported significantly increased insulin sensitivity measured via HOMA-IR following 4 × 4 HIIT relative to MICT. Insulin also plays a role in regulating vascular homeostasis in addition to its primary function of replenishing glucose reserves in tissues. It promotes vascular homeostasis through its ability to stimulate signaling pathways, which could regulate both NO [phosphoinositide 3-kinase (PI3K)/Akt pathway] and endothelin-1 [mitogen-activated protein kinases (MAPK) pathway] production [12]. In an insulin-resistant state, only the PI3K/Akt pathway is impaired, leading to an imbalance between NO and endothelin-1 bioavailability, and thus vascular dysfunction [63]. Other studies included in this review either showed no change [35] or a similar improvement [36] in insulin sensitivity following either type of training. The inconsistent results could partly be explained by the difference in methods used to measure insulin sensitivity, as well as the time point at which it was measured relative to the last training session between studies. Furthermore, the equivocal results could imply that insulin only plays a small part in regulating vascular homeostasis. This is reflected in studies only showing a small association between insulin sensitivity and vascular dysfunction [64, 65].

Alternatively, discrepancies between results may simply be due to differences in the ExRx employed. Other studies that investigated the impact of HIIT on insulin sensitivity suggest that five to eight 2-min intervals at 80–95 % HR_{max} for at least 12 weeks (three times per week) may be sufficient to improve insulin sensitivity [66, 67] in clinical patients. However, for the same training program duration and frequency (12 weeks, three times per week), it seems that the interval duration should be greater than 2 min at a similar intensity (80–95 % HR_{max}) to surpass the positive effect of MICT on insulin sensitivity [34, 68]. Collectively, these studies suggest that 4 × 4 HIIT may be an optimal form of exercise to induce greater insulin sensitivity and thus vascular function improvement beyond the traditional MICT.

The increased ability of HIIT relative to MICT to enhance vascular function could also be a result of its positive impact on lipid profile. Chronic exposure of the endothelial cells to high concentrations of lipids has been shown to inflict vascular damage [63]. Wisloff et al. [32] reported a tendency for HIIT to promote a positive significant influence on TG and HDL-C levels in heart failure patients. Furthermore, HDL-C has been shown to increase only following HIIT [34] or at a greater level than MICT [36] in MetS and T2DM patients, respectively. The increased level of HDL-C enables faster clearance of LDL-C from the circulation, thereby limiting the available LDL-C that could be engulfed by leukocytes at sites of endothelial cell lesion. This limits the formation of foam cells that are responsible for secreting cytokines and thus inflammation. Cytokines released by foam cells stimulate the production of hsCRP by the liver, which could in turn damage other sites of the endothelial cells, resulting in further aggravation of vascular dysfunction [2]. This notion is inconsistent with included studies that reported no change in hsCRP following either HIIT or MICT in heart failure patients [32] and obese adults [35]. In contrast to these studies, Stensvold et al. [69] has shown a significant decrease in inflammatory markers following a similar HIIT-Rx (4 × 4 min, three times per week, 12 weeks) in patients with MetS. Possible differences in results between these studies employing a similar HIIT-Rx could be that one of the three HIIT sessions prescribed in heart failure patients [32] was home based. However, it was reported that recordings from HR monitors during home-based exercise, in which patients were unable to receive HR feedback, confirmed that they were reaching the prescribed target HR. Therefore, further studies are needed to confirm whether the 4 × 4 HIIT-Rx is indeed a potent stimulus in ameliorating vascular dysfunction and inflammatory markers.

Obesity also contributes to vascular dysfunction, perhaps due to its detrimental effect on metabolic pathways, exacerbating inflammation, insulin resistance, and oxidative stress [70]. Enlarged adipose tissue leads to a mismatch between oxygen demand and blood supply, causing hypoxia [71]. The resultant hypoxia-induced necrosis of adipose tissues attracts leukocytes that eventually form cytokine-secreting macrophages [72, 73], which could in

turn aggravate vascular dysfunction [74]. For example, enhanced vascular function has been shown to be accompanied by a significant reduction in body fat percentage of 2.5 and 2.2 % following HIIT and MICT (group difference $p > 0.05$) in obese [35] and T2DM patients [36], respectively. However, the lack of difference between fat reduction following either type of training despite a greater vascular enhancement following HIIT compared with MICT in both trials suggests that obesity is only a minor contributing factor to vascular dysfunction. This implies that HIIT may be a more potent stimulus in directly influencing other physiological factors (e.g. insulin resistance, oxidative stress, and inflammation) affecting vascular function.

4.1 High-Intensity Interval Training Prescription Recommendation Toward Vascular Function Improvement

A specific HIIT-Rx recommendation to attenuate or prevent unfavorable health risk becomes difficult to establish due to several combinations that could result from the manipulation of HIIT components, such as (1) the number of interval bouts, (2) intensity and duration of each bout, (3) type of recovery periods, (4) number of sessions per week, and (5) duration of the program [75]. Four of the included studies conducted by the same group in Norway utilized a long-interval duration HIIT (interval bout duration >2 min) known as the 4 × 4 HIIT protocol [32–35]. This HIIT-Rx consisted of four 4-min bouts of aerobic exercise performed at 90–95 % $HR_{peak/max}$ interspersed with 3 min of active recovery (50–70 % $HR_{peak/max}$), carried out for 12–16 weeks (three times per week). The remaining studies included in this review utilized the short-interval duration HIIT (interval bout duration ≤2 min). This HIIT-Rx consisted of 1-min interval bouts repeated six to ten times at 80–104 % PPO [31, 37] or 80–85 % VO_{2peak} [36] interspersed by 1 min [31, 37] or 4 min [36] of active recovery (10 % PPO/50–60 % VO_{2peak}), performed three times a week for 2 [37] to 12 [31, 36] weeks. In comparison with MICT, this meta-analysis suggests that longer-interval duration HIIT may have a greater capacity to improve vascular function relative to short-duration HIIT (Fig. 2). This promising result could have been driven by the tendency of longer-interval duration HIIT to impose a greater positive influence on CRF, insulin resistance, oxidative stress, inflammation, and traditional CVD risk factors as discussed above.

Recently, Tjonna et al. [76] also compared the impact of differential bouts of longer-interval duration HIIT (1 × 4 vs. 4 × 4) at 90 % HR_{max} on vascular function in healthy men [age 35–45 years; body mass index (BMI) 25–30]. Following 10 weeks (three times per week) of training, no significant change in FMD was found in both HIIT groups (pre vs. post; 1 × 4 HIIT 4.85 vs. 4.35 %; 4 × 4 HIIT 5.62 vs. 4.82 %; $p = 0.75$). The authors suggested that because the participants were already within the normal FMD range for their age at baseline, there was very little potential for further vascular function improvement. Nonetheless, it could be postulated from this study that a single bout of 4-min high-intensity training (1 × 4) three times per week is sufficient to maintain normal vascular function since no significant change in FMD was evident after 10 weeks of training.

4.2 Limitations

It should be noted that most participants included in this review were also receiving medications (Table 3) that are known to improve vascular function [40]. Results from this systematic review and meta-analysis should therefore be interpreted with caution. Nevertheless, Molmen-Hansen et al. [33] showed that training still resulted in a significant

Table 3 Number of participants receiving medications

References	ACEIs		Beta-blocker		Statins		Diuretics		CCBs		Antiplatelets		Anti-hyperglycemics	
	HIIT	MICT	HIIT	MICT	HIIT	MICT	HIIT	MICT	HIIT	MICT	HIIT	MICT	HIIT	MICT
Klonizakis et al. [37]	[a]	[a]	[a]	[a]	NR	NR	NR	NR	[a]	[a]	NR	NR	NR	NR
Wisloff et al. [32]	9/9	9/9	9/9	9/9	9/9	9/9	5/9	4/9	NR	NR	9/9	9/9	NR	NR
Tjonna et al. [34]	2/12	1/10	0/12	1/10	2/12	0/10	NR	NR	1/12	1/10	1/12	0/10	1/12	1/10
Schjerve et al. [35]	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Molmen-Hansen et al. [33]	[b]	[b]	[b]	[b]	NR	NR	NR	NR	[b]	[b]	NR	NR	NR	NR
Currie et al. [31]	5/11	8/11	10/11	7/11	10/11	10/11	2/11	2/11	2/11	0/11	10/11	11/11	NR	NR
Mitranun et al. [36]	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	14/14	14/14

ACEIs angiotensin-converting enzyme inhibitors, *CCBs* calcium-channel blockers, *HIIT* high-intensity interval training, *MICT* moderate-intensity continuous training, *NR* not reported

[a] Patients receiving blood pressure medications were excluded

[b] Blood pressure medications were terminated in a month before inclusion

improvement in vascular function even when a month of washout period from antihypertensive medications was imposed prior to inclusion. It has also been shown that, even when medications taken were relatively homogenous between exercise groups within a study [32, 34], HIIT still had a significantly greater effect on vascular function than MICT. Moreover, it is also known that the time course of vascular function adaptation varies following chronic HIIT or MICT in patients with cardiometabolic disorders [76]. However, three studies in this review failed to specifically report the amount of time between the cessation of the training program and the measurement of vascular function [32, 33, 35]. Nonetheless, these studies reported that vascular function was assessed according to the current exercise guideline, recommending abstinence from exercise and medications for at least 6 h before testing [6, 39].

Another limitation that should be considered in this review is the timing of the assessment of maximal vessel dilation determining the degree of FMD and thus vascular function. It has been reported that assessing peak dilation 1 min after cuff release could lead to an underestimation of true FMD in humans by 25–40 % [77]. However, an optimal timing for the assessment of vessel dilation during FMD has yet to be established. Since all trials included in this review used the same timing criterion for the assessment of FMD, it could be argued that this has minimal impact as a confounding factor towards the overall effect of the exercise interventions on vascular function. The failure to report the method of allocation concealment, the use of small sample sizes, as well as our restricting this review to only English papers could also lead to bias affecting the outcome of this meta-analysis. Moreover, although this review suggests that the greater positive impact of HIIT on vascular function compared with MICT may be its tendency to promote superior impact on CVD risk factors, it could be argued that this is highly speculative since associations between improvement in FMD and different CVD risk factors has not been evaluated in all studies included. However, it should be noted that studies have shown a close association between improved FMD and the following factors: CRF (r 0.54–0.69, $p < 0.05$) [32, 35]; DBP (r −0.4, $p = 0.04$) [35]; and HbA_{1c} (r −0.72) [36]. Finally, since the majority of trials (four of seven) included in this review were conducted by the same group in Norway, results of this meta-analysis should be interpreted with caution until their findings have been replicated by others.

5 Conclusion

This systematic review and meta-analysis found HIIT to be a more potent stimulus in enhancing vascular function, with a capacity to improve brachial artery FMD by 2.26 % more than MICT. This result is consistent with previous studies revealing an inverse relationship between CRF and FMD [45, 46] and with a recent meta-analysis showing a greater ability of HIIT to enhance CRF [47]. The tendency of HIIT to influence physiological factors attenuating traditional CVD risk factors, insulin resistance, oxidative stress, and inflammation could perhaps explain its ability to be a more potent stimulus in enhancing vascular function compared with MICT. However, the variability in findings regarding these secondary outcome measures warrants further investigation to validate effects of HIIT on these factors. Furthermore, given the heterogeneity of studies in the current analysis ($I^2 = 68$ %) coupled with the small sample size ($n = 182$), further research is still warranted to determine an optimal HIIT-Rx to enhance vascular function. Nevertheless, this review suggests that 4 × 4 HIIT, three times per week for at least 12 weeks, is capable of enhancing vascular function more than other prescriptions of HIIT or MICT presented in this review. Large multicenter trials are called upon to assist exercise professionals in titrating ExRx to optimally attenuate vascular dysfunction in these vulnerable individuals.

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