Isometric exercise versus high intensity interval training for the management of blood pressure: A systematic review and meta-analysis.

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Running Title: IET vs HIIT in the management of blood pressure

Key Words: Isometric exercise training, high intensity interval training, blood pressure, hypertension

Abstract

Objective: We aimed to compare the efficacy of isometric exercise training (IET) versus high-intensity interval training (HIIT) in the management of resting blood pressure (BP).

Design: Systematic review and meta-analysis.

Data sources: PubMed (MEDLINE), the Cochrane library and SPORTDiscus were systematically searched.

Eligibility criteria: RCT's published between January 1st, 2000 and September 1st, 2020. Research trials reporting the effects of IET or HIIT on resting BP following a short-term intervention (2-12 weeks).

Results: IET produced significantly greater reductions in resting BP compared to HIIT with systolic, diastolic and mean BP effect sizes of 8.50mmHg vs 2.86mmHg (Q=17.10, $p<0.001$), 4.07mmHg vs 2.48mmHg (Q=4.71, p=0.03) and 6.46mmHg vs 3.15mmHg (Q=4.21, p=0.04) respectively. However, HIIT reduced resting heart rate significantly more than IET (3.17bpm vs 1.34bpm, Q=7.63, p=0.006).

Conclusion: While both modes are efficacious, IET appears to be the superior mode of exercise in the management of resting BP. However, HIIT is more effective in reducing resting heart rate. ~~Future research, ideally employing a sham-design protocol, is needed to establish the mechanistic underpinnings behind such differences in BP reducing effects.~~

Introduction

As the leading modifiable risk factor for mortality, arterial hypertension remains a global problem with important implications for cardiovascular health [1]. Although largely efficacious, anti-hypertensive medication has a number of substantial limitations including adverse side effects [2], considerable economic strain [3] and poor adherence rates, typically reported at less than 50% 1 year following prescription [4]. Additionally, current exercise guidance is unlikely to benefit long-term cardiovascular risk [5] due to poor global adherence [6]. Therefore, establishing novel lifestyle approaches to the management of hypertension is pivotal.

In recent years, isometric exercise training (IET) and high intensity interval training (HIIT) have emerged as convenient and highly time-efficient modes of exercise, which can produce clinically significant reductions in resting clinic and ambulatory blood pressure (BP) following short-term interventions [7–10]. This is crucial as behavioural psychology research has identified perceived lack of time and motivation as the most common barriers to the adoption of physical activity [11]. Importantly, both IET and HIIT interventions have previously been shown to produce a magnitude of BP reduction similar to, or greater than the current recommended international physical activity guidelines [12,13]. Thus, given the efficacy and potential for greater adoption and adherence, these novel exercise modes may have significant clinical utility in the control of arterial BP.

Despite this, no research to date has attempted to compare the anti-hypertensive efficacy of these two distinct exercise modes. Furthermore, previous investigations have only examined the efficacy of HIIT against moderate intensity continuous training or as a sub-group to separate primary analyses, resulting in the omission of a plethora of comprehensive trials and thus an insufficient understanding of the overall effects of HIIT on BP. Additionally, several new IET studies have been published since the latest meta-analysis [14], many of which utilise a lower-body methodology, establishing a need for a lower vs upper body IET analysis. Therefore, we aimed to perform an independent meta-analysis on randomised-controlled trials investigating the effects of IET on BP, with subgroup analysis of the implemented IET method. Separately, we also aimed to perform an independent meta-analysis measuring the effects of HIIT on BP. Finally, following both independent analyses, we performed a meta-analytic comparison to measure the efficacy of IET versus HIIT in the management of BP.

Methods

Search strategy

This systematic review and meta-analysis was performed in accordance with the PRISMA guidelines. To identify potential studies, a systematic search was performed using PubMed (MEDLINE), the Cochrane library and SPORTDiscus for research trials reporting on the effects of IET or HIIT on BP. The search strategy was developed by a research librarian experienced in scientific database searching and included MeSH terms, key words, and word variants. The IET key Boolean search terms included: “Isometric training” OR “Isometric Exercise” OR “Static contraction” OR “Exercise training” AND “Blood pressure” OR Hypertension. The HIIT key Boolean search terms included: “High intensity interval training” OR HIIT OR “anaerobic training” OR “Sprint training” OR “Exercise training” AND “Blood pressure” OR Hypertension. Journal articles written in English and published between the 1st January 2000 and 1st September 2020 were considered. Where possible, corresponding study authors were contacted to ascertain whether non-published data was available or in the pre-print stage, and studies found through the systematic protocol were screened for exterior citations and their respective reference lists searched for eligible studies.

Study eligibility

Screening was carried out following the exclusion of duplicate articles by two authors (JE and AD) who resolved any confliction via consensus. Studies were initially screened by title and then by abstract for relevance. Studies retained for the next step of evaluation were assessed by full-text and considered if they reported pre-post intervention BP changes following either an IET intervention or a HIIT intervention with a control group and sufficient randomisation. Only studies of intervention groups performing IET individually or HIIT individually with no other concurrent exercise were included; however, research designs utilising moderate intensity continuous training as a control arm were included. HIIT was defined in accordance with the EXPERT tool [15], in which >89% heart rate maximum or >80% VO_2 peak was considered a sufficient intensity. Randomised controlled trials, including cross-over design studies with an intervention duration of 2 to 12 weeks were eligible. Participants were required to be ≥18 years of age with no limitations on health or baseline BP status.

Study quality

Study quality and risk of bias was evaluated using the TESTEX scale [16] which is a 15 point (12 item) system designed for the specific application to exercise science research. Two reviewers (JE and AD) independently scored all eligible articles. When disputes were detected in quality analyses, the reviewers met to discuss any conflicts and a third reviewer was consulted (JOD).

Statistical analysis

Derivation of outcome statistics: Data were extracted from the studies independently by the first author. The key variables were 4 continuous measures of cardiovascular health before and after the study intervention; systolic BP (sBP), diastolic BP (dBP), mean BP (mBP) and heart rate with SDs. Where available we also extracted the exercise intervention duration, percentage of medicated participants, and percentage of hypertensive participants for use in the meta-regression analyses. If these data were not available, efforts were made to contact the authors of the paper to obtain them.

Pooling of results: Data were analysed with the meta [17] packages in the statistical software R 4.0.3 (R Core Team, 2020). Effect sizes were calculated based on the change score (MD) between baseline and follow-up measures to demonstrate the clinical impact of each exercise type. Additionally, it has been suggested (Fu and Holmer 2016) that change score provides a greater degree of accuracy when the baseline and follow-up scores are highly correlated and SDs are similar, as was the case in our dataset. The MDs with 95% CI's were computed individually for the four outcome measures. The effect sizes were weighted according to the intra-study variability (calculated from reported means and SDs), with larger, more precise studies having a greater weighting on the overall effect size. Separate random-effects meta-analysis were run for each variable using CMA's meta-regression function to establish if any moderator variables influenced the change in BP following IET or HIIT and explain any inter-study variance in outcomes. The moderators assessed independently were: hypertension diagnosis, medication status, TESTEX score, and intervention duration. This yielded the summary measures, significance levels (P), and the between-study heterogeneity (Cochran's Q and I^2) and variability (τ^2).

Exploration of publication bias: Publication bias was assessed via funnel plot inspection, with the expectation that studies would be evenly distributed between both sides of the average effect size, with high-precision studies close to the mean. The individual funnel plots are displayed in the supplementary material (Figure S1). Quantitative assessments of Egger's regression are reported for the four effect sizes alongside the funnel plots.

Exploration of heterogeneity and meta-regression analyses: Heterogeneity of the 3 effect sizes were assessed by Cochran's Q and I^2 values calculated in the random-effects model. Statistical significance for Q was $p<0.01$ and I^2 of 25, 50 and 75% were interpreted as small, medium and large degrees of heterogeneity. In the event of significant levels of heterogeneity in any of the meta-analyses, exploratory meta-regression analyses were conducted to determine how participant and exercise characteristics accounted for heterogeneous effect sizes. The residual plots were inspected for suitability before reporting the R^2 value of the fitted models. In the event of non-random residual plots, further variables were added to the model to capture possible significant interactions. All covariates were analysed separately and then together to assess the individual contribution of each variable. A method of moment's estimator for the between-study covariance matrix in the random effect models meta-regression was used. A sub-group analysis was conducted based on the MD between study exercise-mode, and 2 groups were formed, which were IET and HIIT. On the IET data we performed additional sub-group analyses for the 4 outcome measures on upper vs. lower body IET training.

Sensitivity analysis: We conducted a sensitivity analysis by removing outlying studies using the leave-one-out influence analysis method in the dmetar package [18]. The study by May et al was found to contribute the most to the overall heterogeneity for all 4 outcome measures but did not influence the overall effect size to a large degree and was left in the final analysis.

Results

As presented in Figure 1, our initial search identified 5220 manuscripts (2793 IET and 2427 HIIT). Following all exclusions, 38 studies were analysed (18 IET and 20 HIIT), including 1583 (672 IET and 911 HIIT) participants, of which 612 (268 IET and 344 HIIT) were controls. Study characteristics for the included IET and HIIT articles can be found in Table 1 and Table 2 respectively. Detailed TESTEX scoring for each category and the full reference list of all analysed studies are presented in the supplementary file (Table S1 and Table S2).

Isometric exercise training

IET significantly reduced sBP and dBP by a mean difference of 8.50mmHg (95% CI= 6.49-10.52, $p<0.001$) and 4.07mmHg (95% CI= 3.04-5.10, $p<0.001$) respectively, with no significant changes observed in the control group. mBP also significantly decreased following IET by 6.46mmHg (95% CI= 4.18-8.74, $p<0.001$) with no significant change in the control group. There were significant differences between groups for all BP variables (all $p<0.001$). IET also had a significant effect on RHR by a mean difference of 1.34bpm (95% CI= 0.24-2.44, $p=0.0169$) with no changes in the control group and a significant between-groups effect ($p=0.006$). The subgroup analyses for the effect of upper vs. lower body isometric training were not significant for any of the four outcome measures (sBP, dBP, mBP and RHR).

There was significant heterogeneity between studies in the IET sBP (I^2=78%), dBP (I^2=52%) and mBP arms (I^2=84%), as well as the dBP control group (I^2=0.47). The Egger's regression test was performed, which was only significant for dBP in the IET trials (P= 0.04) (Figure S1).

High intensity interval training

HIIT significantly reduced sBP and dBP by a mean difference of 2.86mmHg (95% CI= 1.11-4.62, $p=0.0014$) and 2.48mmHg (95% CI= 1.49-3.48, $p<0.001$) respectively, with no significant sBP change observed in the control group, but a statistically significant increase in dBP (MD: 0.50, 95% CI= -0.961-0.041, p=0.03). mBP also borderline-significantly decreased with wide confidence intervals following HIIT by 3.15 (95% CI= 0.96- 5.34, p=0.0049) with no significant change in the control group. There were significant differences between groups for dBP (p<0.001) and mBP (p=0.038), with a non-significant difference for sBP due to wide confidence intervals (MD: 1.03, 95% CI= -0.170-2.224, p=0.09). HIIT also had a significant effect on RHR by a mean difference of 3.17bpm (95% CI= 2.49-3.85, p<0.001) with no changes in the control group and a significant between-groups effect.

There was significant heterogeneity between studies in the HIIT sBP (I^2=52%), dBP (I^2=34%) and mBP arms (I^2=47%), with no significant heterogeneity in the control group. Eggers test (1997) for publication bias was significant for asymmetry in sBP in the HIIT trials (P =0.02) (Figure S2).

Isometric exercise training vs high intensity interval training

There was a significant treatment difference between IET and HIIT trials for all variables. IET produced significantly greater reductions in resting BP compared to HIIT in sBP (MD: 5.29, 95%CI = 3.97, 6.61, Q = 17.1, p<0.01, I^2 = 86%), dBP (MD: 3.25, 95%CI = 2.53, 3.96, Q = 4.71, p=0.03, I^2 = 70%) and MAP ((MD: 4.63, 95%CI = 3.09, 6.17, Q = 4.54, P=0.03, I^2 = 83%). However, HIIT reduced RHR to a significantly greater extent than IET (MD: 2.45, 95%CI = 1.78, 3.11, Q=6.01, p=0.01, I^2 =22%).

Meta-regression

There was no statistical significance for the moderator variables: hypertension diagnosis, medication status and intervention duration. As such, TESTEX score was the only statistically significant moderator, which explained a significant proportion of the dBP inter-study variance in the HIIT trials only (R^2 = 75.41, P = 0.014, 95% CI= 0.137-1.205) (Figure S3).

Discussion

The aim of this study was to perform a meta-analytic comparison of randomised controlled trials to directly compare the efficacy of IET versus HIIT in the management of BP. While the findings of our analysis support both IET and HIIT as efficacious modalities in reducing resting sBP, dBP and mBP, this novel comparison reported a statistically significant between-treatment difference, with reductions of a greater magnitude in all BP measures following IET compared to HIIT. However, resting heart rate (RHR) was reduced to a significantly greater extent following HIIT compared to IET.

IET demonstrated significant sBP, dBP and mBP reductions of -8.5, -4.07 and -6.46 mmHg respectively. Importantly, these reductions are clinically significant and of a similar, or greater magnitude to the reductions commonly observed following standard anti-hypertensive pharmacotherapy [19]. Although the lower limit confidence intervals were below what is generally accepted as clinically significant, HIIT produced significant reductions of -2.86, -2.48 and -3.15 in sBP, dBP and mBP respectively. While not to the same magnitude as IET, these HIIT reductions are certainly comparable to the effects typically seen following traditional moderate intensity aerobic exercise [20] which is currently recognised as the recommended modality for the management of BP in international guidelines [21]. Indeed, a previous meta-analysis [20] reported reductions in resting sBP and dBP by -3.84 and -2.58 mmHg following traditional aerobic exercise, thus demonstrating the comparative efficacy of these modes and highlighting IET as unequivocally superior. Ultimately, the presented anti-hypertensive effects of both IET and HIIT are associated with a reduced risk of cardiovascular disease and all-cause mortality, therefore providing imperative clinical implications regarding the optimal control of BP [22,23].

The mechanistic underpinnings behind the anti-hypertensive effects of IET and HIIT are highly complex and still largely unknown, but are likely to share some homogenous physiological processes [24,25]. Despite the significant reductions in RHR observed in our analysis, both interventions have often been shown to reduce BP with only small or no changes in CO [8,10]. This suggests that BP is reduced following either intervention primarily via changes in total peripheral resistance. As such, both modes have been linked with enhanced shear stress as a mechanical stimulus to facilitate increases in endothelial intracellular calcium via potassium channel activation, ultimately promoting endothelial nitric oxide synthase and thus nitric oxide bioavailability [26]. While this mechanism is conceptually consistent across both modes, the stimulating process of flow mediated dilation (FMD) differs between IET and HIIT within an acute setting [25,27,28], which although speculative, may be implicit in determining the observed differences in magnitude of BP reduction. Specifically, IET acutely produces such a mechanical response via contraction-induced occlusion of the relevant vasculature, thus causing reactive hyperaemia on relaxation to produce such mechanism, which has been demonstrated to translate into chronic FMD changes adjacent to significant improvements in BP [29]. Conversely, HIIT simply invokes standard exercise hyperaemia, and despite the considerable stress placed on the relevant skeletal muscles with such workload intensity, current evidence indicates that the shear rate following HIIT is no greater than that of traditional aerobic exercise, thus potentially limiting the anti-hypertensive effects [26,30]. However, the mechanistic rationale behind such differences in BP reducing effects between both modes is not understood and requires future investigation.

Interestingly, we found no significant differences for any of the measured parameters between upper (handgrip) and lower (wall-squat and leg-extension) body IET modes. While handgrip remains the traditionally investigated IET mode, more recent data has demonstrated lower-body IET to achieve reductions to a much larger magnitude [8]. Such differences have been mechanistically attributed to the larger muscle mass involvement in lower body IET, generating a greater occlusion-response stimulus and thus enhancing the metabolic and autonomic regulatory adaptations [8,27]. To what extent the lack of differences observed in the present analysis is owing to the disparity in published trials between IET modes is unknown, with future lower body IET research warranted before definitive conclusions on the optimal application of IET can be made. Furthermore, we also found no significant effects of medication and hypertension status on BP or RHR changes following IET or HIIT. Similarly, this finding may also be somewhat attributable to methodological limitations, with many studies failing to report exact participant characteristic data on medication or hypertension status, as well as the role of different medications and varying severities of hypertension increasing the complexity of this analysis.

Separately, both modes also show significant reductions in RHR with a significantly greater magnitude of change following HIIT compared to IET, perhaps indicating a more prominent role of RHR in the observed BP changes following HIIT than IET. Given the strong association between RHR and cardiovascular and all-cause mortality [31], these findings may be of clinical importance. Both IET and HIIT have been shown to produce significant improvements in cardiac autonomic regulation and baroreceptor sensitivity [8,10], which as well as mechanistically contributing to the observed BP changes, are likely to be implicit in these RHR reductions. Additionally, previous investigations from our lab in HIIT [10] and acute IET [32] have demonstrated significant improvements in cardiac function and mechanics following both interventions, providing potential mechanistic implications for such RHR changes. In speculating the differences in the magnitude of RHR change, it is well-established that, despite being an anaerobic modality in nature, HIIT may induce significant peripheral and haematological adaptations that are generally associated with traditional aerobic exercise, such as increased skeletal muscle mitochondrial content [33,34], capillary density [35] and plasma and blood volume [36], thus contributing to enhanced arteriovenous oxygen difference and stroke volume, resulting in vagally-mediated reductions in resting RHR to a greater extent [25]. Conversely, such physiological changes are not generally associated with IET.

Aside from RHR, these physiological adaptations raise an important point in distinguishing the appropriate application of either modality. In particular, these HIIT-induced adaptations may directly contribute to functional capacity and therefore have significant implications for clinical prognosis as one of the strongest predictors of outcome [37]. Thus, it may be speculated that, while IET is superior in the management of resting BP, especially in hypertensive populations, HIIT may provide wider physiological advantages and greater clinical implications in individuals without hypertension, making it the preferred modality for the maintenance of general health. Therefore, since both modes may have different physiological advantages, future research should explore the application of both IET and HIIT in combination versus single-mode exercise training.

Limitations

As a primary limitation, we found significant heterogeneity for all BP outcomes in both interventions. Attributing this variance to methodological differences, our meta-regression accounted for hypertension diagnosis, medication status and intervention duration, but found no statistical significance for these moderators. Risk of bias TESTEX score explained a significant proportion of the HIIT dBP inter-study variance only. Nonetheless, random-effects models were applied to account for such heterogeneity. The Eggers plots showed significant publication bias for sBP in the IET trials and dBP in the HIIT trials, suggesting studies that found no significant reductions in BP following either intervention may not have been published. Furthermore, the participants and investigators would have been aware of group allocation, as assessed in the TEXTEX scale. Thus, future IET and HIIT research should attempt to employ a sham-design methodology to blind the participants to their group allocation. It should also be considered that the present within-group analyses are subject to various biases, such as regression to the mean. We also applied an English language filter to our search, which carries the risk of introducing selection bias. Finally, this analysis did not compare IET or HIIT against MICT, which remains the most commonly applied mode, thus limiting the wider interpretations of the present results.

Clinical Implications

Hypertension remains the leading risk factor for cardiovascular disease and all-cause mortality worldwide [1]. Given the widely documented limitations that come with medication usage, it is crucial that effective non-pharmacological / lifestyle treatment options are established. IET and HIIT are short duration, highly time-efficient modes which have been shown to produce clinically significant reductions in resting BP at a magnitude superior to that of traditional exercise training modalities [7,9]. This study demonstrates the efficacy of both interventions in the management of BP, highlighting IET as the superior mode in reducing BP, while HIIT remains more efficacious in reducing RHR. Specifically, at a magnitude of 8.5mmHg sBP and 4mmHg dBP, IET may produce reductions in BP to a greater extent than that typically achieved with standard dose anti-hypertensive monotherapy [38]. While less effective for BP, HIIT may induce wider cardiovascular adaptations, making it the preferred mode in the general maintenance of health.

Conclusion

Both IET and HIIT are efficacious modes in the management of resting BP. IET appears the superior mode, producing a greater magnitude of BP reduction when compared to HIIT.

However, HIIT remains a more effective mode in reducing RHR. Future research, ideally employing a sham-design protocol, is needed to establish the mechanistic underpinnings behind such differences in BP reducing effects and to explore the efficacy of both modes applied in combination.

Competing interests: None

Contributorship: JE, AD and JO'D contributed to the conception and design of the study. JE and AD contributed equally to this work. JE, AD and JO'D contributed to the development of the search strategy. JE and AD conducted the systematic review. JE, AD and JO'D completed the acquisition of data. JE, AD, JD and JO'D performed the data analysis. All authors assisted with the interpretation. JE and JO'D were the principal writers of the manuscript. All authors contributed to the drafting and revision of the final article. All authors approved the final submitted version of the manuscript.

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Table 1. IET study characteristics.

Study	Country	Duration (weeks)	Participants	Hypertension	Medication	Withdrawal (N. of participants)	Training Frequency	Exercise Mode	Exercise Training Characteristics	TESTEX score
Baddeley-White et al (2019)	UK	4	n=23 (13 Male &10 Female) 23 <50 years	NTN	Medicated= 0	None	3 x per week	Isoball rugby handgrip/ zona plus handgrip	4 x 2 min, 1 min rest interval, 30%MVC, (n=7 isoball, n=8 zona, n=8 control).	7
Badrov et al (2013a)	Canada	8	n=36 (36 Female) 36 <50 years	NTN	Medicated= 0	IET= 1 Control= 3	3/5 x per week	Handgrip	4 x 2 min, 4 min rest intervals, 30% MVC, (n=12 3x per week, n=11 5 x per week, n=9 control).	10
Badrov et al (2013b)	Canada	10	n=24 (13 Male & 11 Female) 24 >50 years	HTN	Medicated= 0	None	3 x per week	Handgrip	4 x 2 min bilateral, 1 min rest interval, 30% MVC, (n=12 IET, n=12 control).	8
Baross et al (2012)	UK	8	n=30 (30 Male) 30 >50 years	Mixed NTN/HTN	Medicated= 0	None	3 x per week	Leg extension (Bilateral)	4 x 2 min, 2 min rest intervals, 14%MVC, (n=10 at 85%HRpeak, n= 10	7

									at 75%HRpeak, n=10 control).	
Baross et al (2013)	UK	8	n=20 (20 Male) 20 >50 years	NTN	Medicated = 0	None	3 x per week	Leg extension (Bilateral)	4 x 2 min, 2 min rest intervals, (85%HRpeak n=10 exercise group, n=10 control).	7
Cahu Rodrigues et al (2019)	Brazil	12	n=72 (67% Female) (age unknown)	HTN	Medicated= 72	IET=31 Control=8	3 x per week	Handgrip	4 x 2 min, 1 min rest interval, (n=17 30%MVC, n=16 control).	10
Carlson et al (2016)	Australia	8	n=40 (15 Male & 25 Female) 40 >50 years	HTN	Medicated= 26	IET= 2	3 x per week	Handgrip	4 x 2 min, 1 min rest intervals, (n= 18 at 30%MVC, n=20 5%MVC exercise control).	13
Correia et al (2020)	Brazil	8	n=102 (sex unknown)	Pre-HTN	Medicated= 0	IET=21 Control= 2	3 x per week	Handgrip	4 x 2 min, 4 min rest intervals, (n=29 30%MVC, n=50 control).	9

			102 >50 years							
Farah et al (2018)	USA	12	n=72 (75% Female) 48 >50 years	HTN	Medicated= 72	Home IET= 6 Supervised IET= 10 Control= 8	3 x per week	Handgrip	4 x 2 min, 1 min rest intervals, (n=13 at 30%MVC home based, n=14 30%MVC supervised, n=16 non exercise control).	9
Gordon et al (2018)	USA	12	n=22 (sex unknown) 22 <50 years	HTN	Medicated= 20	None	3 x per week	Handgrip	4 x 2 min, 1 min rest intervals, (n=5 30%MVC home based, n=8 30%MVC lab based, n=9 control).	8
Miller et al (2013)	Canada	8	n=23 (18 Male & 5 Female) 23 >50 years	HTN	Medicated= 23	None	3 x per week	Handgrip	4 x 2 min, 1 min rest intervals, (n=13 30%MVC, n=10 control).	7

Okamoto et al (2020)	Japan	8	n=22 (9 Male & 13 Female) 22 >50 years	Pre-HTN	Medicated= 0	None	3 x per week	Handgrip	4 x 2 min, 1 min rest interval. (n=11 30% MVC, n=11 control).	10
Punia et al (2019)	India	8	n=40 (Male & Female) 40 <50 years	HTN	Mixed Medicated & Non-Medicated	None	3 x per week	Handgrip	4 x 2 min, 4 min rest intervals, (n=20 30%MVC, n=20 non-exercise control group).	10
Taylor et al (2003)	Canada	10	n=17 (10 Male & 7 Female) 17 <50 years	HTN	Medicated= 75%	None	3 x per week	Handgrip	4 x 2 min, 1 min rest intervals, (n=9 30%MVC, n=8 non-exercise control group).	7
Taylor et al (2018)	UK	4	n=48 (Male & Female) (age unknown)	HTN	Medicated= 0	None	3 x per week	Wall squat	4 x 2 min, 2 min rest intervals, (n=24 95% HRpeak, n=24 non exercise control).	7
Wiles et al (2009)	UK	8	n=33 (33 Males) 33 <50 years	NTN	Medicated= 0	None	3 x per week	Leg extension (Bilateral)	4 x 2 min, 2 min rest intervals, (n=11 HI-95%HRpeak, n=11	8

									LO-75%HRpeak, n=11 control group).	
Wiles et al (2016)	UK	4	n=28 (28 Male) 28 <50 years	NTN =28	Medicated= 0	None	3 x per week	Wall squat	4 x 2 min, 1 min rest interval, (n=14 95%HRpeak, n=14 non-exercise control).	7
Yamagata et al (2020)	Japan	8	n=20 (sex and age unknown)	NTN= 20	Medicated= 0	None	3 x per week	Handgrip	4 x 2 min, 3 min rest intervals. (n=10 25% MVC Handgrip, n=10 control group).	9

Abbreviations; IET, isometric exercise training, HI, high, HR, heart rate, LO, low, MVC, maximum voluntary contraction, HTN, hypertensive, NTN, normotensive, pre-HTN, pre-hypertensive; RPE, rate of perceived exertion.

Table 2. HIIT study characteristics.

Study	Country	Duration (weeks)	Participants	Hypertension	Medication	Withdrawal (N. of participants)	Training Frequency	Exercise Mode	Exercise Training Characteristics	TESTEX score
Amaro-Gahete et al (2019)	Spain	12	n=89 (32 Male and 37 Female) 69 >50 years	Mixed HTN/NTN	Medication not reported	PA= 4 Control= 5 HIIT=5 HIIT+EMS=4	2 x per week	Sloped treadmill and weighted exercises	Walking on an incline, n=17 PA (150min p/w), n=18 HIIT-LI (40-60min p/w at 95%VO^{2}max) and HIIT-SI (16 weighted exercise 6-9 RPE), n=19 HIIT+EMS, (HIIT with electromyostimulation), n=17 non-exercise control.	11
Astorino et al (2012)	USA	2	n=29 (16 Male and 13 Female) 29 <50 years	NTN	Medication not reported	None	3 x per week	Cycling	4 x 30 sec with 5 min rest intervals, n=20 HIIT 7.5% BW all out max, n=9 control.	6
Boutcher et al (2019)	Australia	8	n=40 (40 Female) 40 >50years	NTN	Medication not reported	None	3 x per week	Cycling	8 sec SIT intervals with 12 sec rest intervals for 20 min, n=20 SIT at 80-	9

									85%HRpeak, n=20 non-exercise control.	
Cassidy et al (2019)	UK	12	n=22 (17 Male and 5 Female) 11 >50 years	NTN	Medicated n= 8	None	3 x per week	Cycling	5 x 2 min increasing by 10 sec a week up to 3 min 50 sec by week 12 with 90 sec passive recovery and 60 sec band exercises, n=11 HIIT 16-17 RPE and 80 revolution cadence, n=11 control.	10
Dall et al (2014)	Denmark	12	n=17 (12 Male 5 Female) 17 >18 years	HTN= 81%	Medicated n= 94%	Control= 1	3 x per week	Cycling	4, 2, 1 min intervals for 16 mins, 2 min rest intervals (32 min session), n=8 >80% VO^2 peak, n=8 control 45 min continuous aerobic 60% VO^2max.	10
Edwards et al (2020)	UK	4	n=41 (20 Male 21 Female) Age not stated	NTN	Medicated n= 0	None	3 x per week	Cycling	3 x 30 sec intervals, 2 min rest intervals, n=21 at 7.5%bw, n=20 control group.	8
Gerosa-Neto et al (2019)	Brazil	6	n=46 (46 Male) 46 <50 years	Mixed HTN/NTN	Medication not reported	HIIT= 5 MICT= 5 Control= 18	3 x per week	Treadmill	10 x 1 min intervals, 1 min rest intervals, n=18 HIIT at 100% VO^2max, n=18 MICT.	7

Ghardashi afousi et al (2018)	Iran	12	n=75 (25 Males, 27 Female) 52 >50 years	Mixed HTN/NTN	Medicated n= ˜50%	HIIT= 7 MICT= 8 Control= 8	3 x per week	Cycling	12 x 1.5 min intervals, 2 min rest intervals, n=18 at 85%-90% HRmax and 2 min at 55%-60% HRmax, n=17 42 min at 70% HRmax, n=18 control.	8
Hanssen et al (2017)	Switzerland	12	n=48 (7 Males, 30 Female) 48 <50 years	Mixed HTN/NTN	Medication not reported	HIIT= 3 MICT= 4 Control= 4	2 x per week	Treadmill running	4 x 4 min intervals, 3 min rest intervals, n=13 at 90-95% HRmax, n=12 45 min 70% HRmax, n=12 control.	7
Hallsworth et al (2015)	UK	12	n=28 (all same sex not stated if Male or Female) 23 >50 years	Mixed HTN/NTN	Medication not reported	HIIT= 2 Control= 3	3 x per week	Cycling	5 x 2 min intervals, 3 min rest intervals, increase 10 sec weekly, n=12 HIIT at 16-17 RPE, n= 11 control.	8
Izadi et al (2018)	Iran	6	n=44 (17 Male 13 Female) 44 >50 years	NTN	Medicated n= 44	HIIT= 7 Control= 7	3 x per week	Cycling	10 x 1.5 min intervals, 2 min rest interval (35 min session), n=15 HIIT 90-95% HRR, n=15 control.	8
Jabbour et al (2016)	Canada	6	n=24 (12 Male 12 Female) 24 <50 years	Mixed HTN/NTN	Medication not reported	None	3 x per week	Cycling	6 x 6 sec intervals, 2 min rest intervals, n=12 HIIT at maximal output, n=12 control group.	7

Jung et al (2015)	Canada	2	n=32 (5 Male 27 Female) 32 >50 years	Mixed HTN/NTN	Medication not reported	HIIT= 5 Control= 1	5 x per week	Cycling, treadmill, cross-trainer	4 x 1 min intervals, increasing up to 10 x 1 min by day 10, 1 min rest intervals, n=15 HIIT at 90% HRpeak, n=17 control at 60% HRpeak.	10
Lee et al (2019)	USA	8	n=30 (30 Female) 30 >50 years	Mixed HTN/NTN	Medication not reported	None	3 x per week	Cycling	7 x 1 min intervals, 2 min rest intervals (20 min session), n=15 HIIT at 90% peak power output, n=15 control group.	8
May et al (2018)	USA	4	n=90 (82% Female) 90 <50 years	NTN	Medicated n= 0	None	3 x per week	Cycling	10 x 1 min intervals, 1 min rest interval, n=30 HIIT at 90% HRmax, n=30 HRVCB training, n=30 control.	8
O'Driscoll et al (2018)	UK	2	n=44 (44 Female) 44 <50 years	NTN	Medicated n= 0	HIIT= 2 Control= 2	3 x per week	Cycling	3 x 30 sec Wingate intervals, 2 min rest intervals, n=20 HIIT 7.5%bw, n=20 control.	8
Reljic et al (2020)	Germany	12	n=65 (29 Male 36 Female) 65 <50 years	Mixed HTN/NTN	Medicated= mixed, data not reported	n=16	2 x per week	Cycling	5 x 1 min intervals, 1 min rest intervals, n=36 at 80-95%HRmax, n=29 control.	13

Rognmo et al (2004)	Norway	10	n=21 (14 Male 3 Female) 21 >50 years	Mixed HTN/NTN	Medicated= yes, data not reported	HIIT= 3 Control= 1	3 x per week	Incline treadmill	4 x 4 min intervals, 3 min rest intervals, n=8 at 90% HRpeak, n=9 control.	13
Sandstad et al (2015)	Norway	10	n=36 (gender not stated) 36 <50 years	NTN	Medication not reported	HIIT= 6 Control= 3	2 x per week	Cycling	4 min intervals, 3 min rest intervals for 35 min, n= 12 HIIT at 95% HRpeak, n=15 control group.	8
Shepherd et al (2015)	UK	10	n=90 (30 Male 60 Female) 90 <50 years	Mixed HTN/NTN	Medication not reported	None	3 x per week	Cycling	15-60 sec intervals, 45-120 sec rest intervals (8-25 min session), n=46 at > 90% HRmax, n=44 MICT at 70% HRpeak.	11

Abbreviations: HIIT, high intensity interval training; HI, high intensity; LI, low intensity; HR, heart rate; MVC, maximum voluntary contraction; HTN, hypertensive; NTN, normotensive; pre-HTN, pre-hypertensive; RPE, rate of perceived exertion.

Figure Legend:

Figure 1: PRISMA systematic review and meta-analysis flowchart.

Figure 2: Random-effects meta-analysis of the effects of IET versus HIIT in the reduction of sBP.

Figure 3: Random-effects meta-analysis of the effects of IET versus HIIT in the reduction of dBP

What is already known

- Anti-hypertensive pharmacotherapy carries substantial limitations and the current exercise guidelines for the control of resting blood pressure are ineffective limited by poor compliance.
- Isometric exercise training and high-intensity interval training have been shown to improve markers of cardiovascular health.
- Both modalities have promising future clinical utility in the management of resting blood pressure.

What are the new findings

- Compared to HIIT, isometric exercise training is the superior modality in the management of resting blood pressure, with reductions similar to, or greater than that of anti-hypertensive medication.
- While still efficacious in reducing resting blood pressure, high-intensity interval training may achieve wider physiological benefits, with greater reductions in resting heart rate.
- As such, the clinical implementation of isometric exercise training for blood pressure control should be considered, with high-intensity interval training likely preferred for the general maintenance of optimal health.

Fu, R. and H. K. Holmer (2016). "Change score or follow-up score? Choice of mean difference estimates could impact meta-analysis conclusions." Journal of Clinical Epidemiology **76**: 108-117.

Objectives In randomized controlled clinical trials, continuous outcomes are typically measured at both baseline and follow-up, and mean difference could be estimated using the change scores from baseline or the follow-up scores. This study assesses the impact of using change score vs. follow-up score on the conclusions of meta-analyses. Study Design and Setting A total of 63 meta-analyses from six comparative effectiveness reviews were included. The combined mean difference was estimated using a random-effects model, and we also evaluated whether the impact qualitatively varied by alternative random-effects estimates. Results Based on the Dersimonian–Laird (DL) method, using the change vs. the follow-up score

led to five meta-analyses (7.9%) showing discrepancy in conclusions. Based on the profile likelihood (PL) method, nine (14.3%) showed discrepancy in conclusions. Using change score was more likely to show a significant difference in effects between interventions (DL method: 4 of 5; PL method: 7 of 9). A significant difference in baseline scores did not necessarily lead to discrepancies in conclusions. Conclusions Using the change vs. the follow-up score could lead to important discrepancies in conclusions. Sensitivity analyses should be conducted to check the robustness of results to the choice of mean difference estimates.