Updated systematic review and meta-analysis on the role of isometric resistance training for resting blood pressure management in adults

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Background and method: This meta-analysis sought to: quantify the effects of isometric resistance training (IRT) on the magnitude of change in systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP) and resting heart rate in adults; and examine whether the magnitude of change in SBP, DBP, MAP and heart rate was different with respect to the patient demographic characteristics and IRT parameters. To be included in the meta-analysis, studies had to be randomized controlled trials lasting 2 or more weeks, investigating the effects of IRT on blood pressure in adults. The methodological quality of the studies selected was evaluated using the PEDro scale. For each main outcome measure, an average effect size and its respective 95% confidence intervals were calculated.

Results: A total of 16 articles (492 participants) fulfilled the selection criteria (mean quality score in the PEDro scale of 5.9). Compared with control groups, IRT groups showed statistically significant (P<0.05) and clinically relevant (>2mmHg) positive effects on the SBP (-5.23mmHg) and MAP (-2.9mmHg). IRT groups also showed statistically significant, but not clinically relevant reduction in DBP (-1.64mmHg). Furthermore, IRT groups did not report any statistically significant and clinically relevant (>5bpm) effect on resting heart rate (-0.08bpm).

Conclusion: The analysis of moderator variables showed that none of them exhibited a statistically significant relationship with the positive effects of IRT for lowering blood pressure. Therefore, IRT may be considered an appropriate nonpharmacologic treatment for lowering SBP and MAP.

Keywords: adults, blood pressure, hypertension, isometric exercise training, treatment

Abbreviations: AHA, American Heart Association; b_j, regression coefficient for the predictor variable; BP, blood pressure; CI, confidence interval; D+, effect size; DBP, diastolic blood pressure; DRT, dynamic resistance training; ICC, intra-class correlation coefficient; IRT, isometric resistance training; k, number of studies; MAP, mean arterial pressure; MVC, maximal voluntary contraction; Q_E, statistic for testing the model misspecification; Q_R, statistic for testing the statistical significance of the predictor variable; R^2, proportion of variance explained by the predictor variable; RCTs, randomized control trials; SBP, systolic blood pressure; SDC, supplemental digital content; SD, standard deviation; SE, standard error

INTRODUCTION

Increasing levels of physical activity has been recommended as a nonpharmacological therapy, as part of a global lifestyle modification strategy, for populations at high risk of developing hypertension and those with controlled hypertension [1,2]. Thus, the general health recommendation (class I, level B evidence) for lowering blood pressure (BP) is to perform moderate to high-intensity physical activity for at least 30min on most days per week and to achieve a total of at least 150min per week [2,3]. At present, and based on their documented efficacy in lowering BP, aerobic training (e.g. speed walking, jogging, dancing, cycling, swimming, etc.) and/or dynamic resistance training (DRT) (i.e. weight lifting and circuit training) have been considered the gold-standard methodologies for increasing levels of physical activity. It has been reported that aerobic training causes reductions in systolic BP (SBP) and diastolic BP (DBP) of about 3–6mmHg, whereas DRT can reduce resting SBP by 2–3mmHg [2,4–9].

Adherence to aerobic training and DRT has, however, not always been optimum as some patients are unwilling or unable to adopt the aforementioned lifestyle changes [10]. In this sense, both training modalities commonly require access to a fitness centre or suitable equipment. Furthermore, most individuals with hypertension or at high risk of developing hypertension (approximately two out of every three cases) present associated comorbidities (i.e. obesity, arthritis, diabetes, lung disease, etc.) and have a low level of physical fitness (<20th percentile) [11]. Consequently, for these patients, it would be advisable that the aerobic training and DRT sessions were designed by a certified professional (i.e. personal trainer) that takes their individual characteristics and limitations into account. As these two constraints imply an economic cost, the individual may choose to avoid these types of interventions.

Literature review [4] and meta-analyses [12–14] have indicated that low to moderate intensity isometric resistance training (IRT) (i.e. exercises that involve static contraction of muscles without joint movement such as isometric handgrip contractions) might be a useful non-pharmacological therapy for the prevention and management of hypertension, at least during early stages where dropping out rates are usually high. This statement has been based on the following four main points: their great efficacy for lowering resting SBP (~5mmHg) and DBP (~4mmHg); the relatively inexpensive equipment needed (e.g. a handgrip device) that allows to perform the exercises anywhere; the lower level of cardiovascular stress elicited; and it is less time-consuming than other training methodologies (each IRT session lasts 8–12min approximately).

Despite recent meta-analyses by Carlson et al. [13] and Inder et al. [14] on the topic of the efficacy of IRT for BP management, there has been a rapid increase in publication of isometric resistance training trials over the past 3 years that necessitates an update. Furthermore, the application of more robust statistical methods to analyse the data available might contribute to establish more accurate estimations of the true effects of IRT on the main BP outcomes. As an example, the use of less demanding cut-off scores for the I^2 index (e.g. >50%) when justifying the selection of random effects models to calculate the effect sizes and their confidence intervals (CIs) may allow a better management of the within-study and between-studies variances (i.e. heterogeneity) [15]. Furthermore, the implementation of the trim-and-fill method provides quantitative and powerful statistics for assessing the possible existence of publication bias as it does not require the subjective interpretation of the funnel plot and it also provides an adjustment of the effect sizes if it is needed. Finally, the application of regression-based techniques (meta-regressions) has been suggested as a

more effective approach for adjusting the influence of continuous moderators (e.g. age, length of the intervention program, dose or intensity of the intervention) on the effect sizes in contrast to the standard meta-analytic techniques that usually require dichotomization using arbitrary cut-off scores.

Therefore, the main purposes of the current study were as follows: to conduct a meta-analysis quantifying the effects of IRT on the magnitude of change in SBP, DBP, mean arterial pressure (MAP) and resting heart rate in adults; to examine whether the magnitude of change in SBP, DBP, MAP and heart rate was different with respect to the patient demographic characteristics (age, sex, BP status) and IRT parameters (length of the program, extremity used for carrying out the exercises, type of exercises, intensity).

METHOD

To accomplish our objectives, a systematic review and a meta-analysis were carried out in accordance with the recommendations and criteria outlined in the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement [16].

Study selection

To be included in the meta-analysis, the studies had to fulfil the following criteria: the study had to be a randomized controlled trial (RCT), lasting 2 or more weeks, which analysed the effects of IRT; the participants in the study had to be adults (aged ≥18 years); the minimum sample size in the post-test had to be of five participants per group; the study had to report enough statistical data to calculate the effect sizes; the study had to be published or carried out before January 2018; and the study could be written in English or Spanish. Animal studies, review articles, acute exercise studies and non-RCTs were excluded.

Search strategy

Potential studies were identified by combined search processes, clearly planned and ordered. Firstly, the following electronic databases were consulted: PubMed, Scopus and the Cochrane Library with the following search terms included in Boolean search strategies: (’hypertension’ OR ‘hypertensive’ OR ‘normotensive’ OR ‘normotension’) AND blood pressure AND (’isometric exercise’ OR ‘isometric physical activity’ OR ‘isometric physical exercise’ OR ‘isometric strength’). By using filter criteria of the respective databases, the search was limited to publication dates (to 12/31/2017), human species, ages (adult: 18þyears), and English and Spanish languages. Secondly, several specialized electronic journals were also consulted, including: Journal of Hypertension, Mayo Foundation for Medical Education and Research, Hypertension Research Journal and The Japanese Society of Hypertension. Finally, the reference lists of the studies recovered were also consulted. Two reviewers independently: a) screened the title and abstract of each reference to locate potentially relevant studies and, once full-text of the screened documents were obtained, b) reviewed them in detail to identify articles that met the selection criteria. A third external reviewer was consulted to resolve discrepancies.

Data extraction and quality assessment

With the aim of guaranteeing the maximum objectivity possible, a codebook was produced that specified the standards followed in coding each of the characteristics of the studies. The moderator

variables of the studies selected were coded and grouped into three categories according to Lipsey [17] recommendations: substantive (participants, context and treatment), methodological and extrinsic variables. SDC 1 (http://links.lww.com/HJH/B50) displays a brief description of the moderator variables coded separately by category.

The outcome measures were SBP, DBP, MAP (which was calculated following the method described in Inder et al. [14]) and heart rate.

The methodological quality of the studies selected was evaluated using the Physiotherapy Evidence Database Scale (PEDro) [18]. The PEDro scale has demonstrated being reliable in clinical and randomized trials [19,20], and has been used in several intervention meta-analyses [13,21,22]. A total score out of 10 is derived for each study, adding the criteria that are satisfied. A PEDro score ranging from 6 to 10 is indicative of high quality, whereas scores of 4–5 indicate fair quality and scores 3 or less indicate poor quality [23].

To assess the inter-coder reliability of the coding process, two researchers coded all the selected studies (including methodological quality assessment). For the quantitative moderator variables, intra-class correlation coefficients (ICCs) were calculated, whereas for the qualitative moderator variables, Cohen's kappa coefficients were applied. On average, the ICC was 0.994 (range 0.98–1.0) and the kappa coefficient was 0.989 (range 0.77–1.0), which can be considered highly satisfactory, as proposed by Orwin and Vevea [24]. The inconsistencies between the two coders were resolved by consensus or by consulting with athird reviewer. When the inconsistencies were due to ambiguity in the coding book, this was corrected. The codebook can be obtained from the corresponding author upon request.

Statistical analysis

All outcomes were reported as means and standard deviations (SDs). For each of the four outcome measures (SBP, DBP, MAP and heart rate), an effect size was calculated as the average difference between the post-test and pretest change scores of the experimental and control groups: $D = (m^{E}_{Post} - m^{E}_{Pre}) - (m^{C}_{Post} - m^{C}_{Pre})$ [25]. Negative *D* values indicated a better result for the IRT group than for the control one. For the assessment of the reliability of the effect size calculations, the same random sample of studies used in the coding reliability study was subjected to a double process of effect size calculations, obtaining excellent intercoder reliability, with intra-class correlations of over 0.90.

Separate meta-analyses were performed for each outcome measure. For each one of them, an average effect size (D_+) and a 95% CI was calculated by assuming a random effects model, with the inverse variance as the weighting factor [26]. Heterogeneity of the effect sizes across studies was assessed by means of Cochrane Q statistic and the I^2 index. A forest plot was also constructed for each meta-analysis. Lack of homogeneity was considered for Cochrane Q tests with $P < 0.10$ and/or for I^2 indices at least 50%. Funnel plots were constructed and the trim-and-fill method [27] was applied to assess whether publication bias might be a threat to the validity of the meta-analytic results.

Magnitude-based inferences about the true IRT net effects on each main outcome measure (i.e. SBP, DBP, MAP and heart rate) were estimated by expressing the probabilities that the true value of the meta-analysed effect was trivial, beneficial or harmful in relation to predetermined threshold values

for benefit and harm (i.e. smallest worthwhile clinical changes). Probabilities were then used to make a qualitative probabilistic inference about the effects [28].

Clinical [29,30] and observational [31] studies have suggested that a reduction of BP by 1–3mmHg could have a substantial impact on cardiovascular disease incidence. For example, Hardy et al. [30] reported that a 1mmHg population-wide SBP reduction was associated with 20.3 and 13.3 fewer heart failure events per 100000 person-years in African Americans and whites, respectively. Thus, and giving their clinical implications, a reduction of 2mmHg (an intermediate value between 1 and 3mmHg) were considered the smallest substantial changes for BP outcomes (SBP, DBP and MAP). Although elevated heart rate values are associated with an increased risk for cardiovascular disease [32,33], the impact of specific reductions in this variable on the likelihood of sustaining a cardiovascular disease has not been estimated yet (from the authors' knowledge). Consequently, in the absence of robust anchors for the smallest worthwhile clinical reductions for heart rate, our inferences were based on the results reported by Paul et al. [34] that showed that an increase in heart rate of above 5bpm over time was associated with mortality in hypertensive patients. An effect was deemed unclear if its CI overlapped the thresholds for substantiveness, that is, if the effect could be substantial in both a positive and negative sense. Otherwise, the effect was clear and deemed to have the magnitude of the largest observed likelihood value. This was qualified with a probabilistic term using the following scale: less than 0.5%, most unlikely;0.5–5%,veryunlikely;morethan5–25%,unlikely; more than 25–75%, possible; more than 75–95%, likely; more than 95–99.5%, very likely; and more than 99.5%, most likely [35]. The present study considered a 'substantial' main effect when a change was noted in BP outcomes and heart rate that had reported a probability of the worthwhile differences of 'likely' or higher (>75% positive or negative).

The influence of qualitative moderator variables [i.e. sex (male, female, mixed), clinical status (normotensive vs. hypertensive), extremity used for carrying out the exercises (upper vs. lower) and type of exercise (unilateral vs. bilateral)] on the effect sizes was performed by means of analyses of variance (ANOVAs) and assuming a mixed-effects model. To make direct comparisons with the analysis of moderator results reported by Inder et al. [14], the continuous variables of weeks of interventions and age were also dichotomized using the same cut-off scores. Mixed-effects meta-regressions were also applied to test the influence of continuous moderators on the effect sizes, such as the PEDro score, number of weeks of intervention, intensity of the intervention, average percentage of males in the two groups, difference between the male percentages in the two groups, average age of the two groups and mean difference between the age of the two groups. Q_B and Q_w for ANOVAs, and Q_R and Q_E statistics for meta-regressions were calculated to test the statistical significance of each moderator variable and to assess the model misspecification, respectively. In addition, an estimate of the proportion of variance accounted for by the moderator was calculated by means of $R^2 = 1 - T^2_{RES}/T^2_{TOTAL}$, with T^2_{RES} and T^2_{TOTAL} being the residual and total heterogeneity variance estimates, respectively [36]. Calculations for the intra-group inferences were made with the spreadsheet designed by Hopkins [28]. The forest plots were carried out with the Review Manager (RevMan) software package (version 5.3 for OSX, The Nordic Cochrane Centre, The Cochrane Collaboration, 2014, Copenhagen, Denmark). The funnel plots with the trim-and-fill method and the ANOVAs and meta-regressions were obtained from the package Comprehensive Meta-analysis 3.3 [37]. The PRISMA checklist [38] was used to check the reporting quality of the meta-analysis.

RESULTS

Study selection

A total of 893 references were identified with all search strategies, from which 312 were excluded in the first screening as duplicates (approximately35%). Four hundred and sixty-eight studies (approximately 52%) were eliminated after reading the title and abstract. Another 14 studies did not apply isometric exercises (about 2%), 71 did not methodologically comply with the established criteria (close to 8%) and 2 other studies were excluded because of data duplication.

The searching process enabled us to identify 16 articles (21 intervention groups as five studies had more than one intervention group, and 17 control groups as one study had two control groups) that met the selection criteria [39–54]. Figure 1 shows the flow chart of the selection process of the studies.

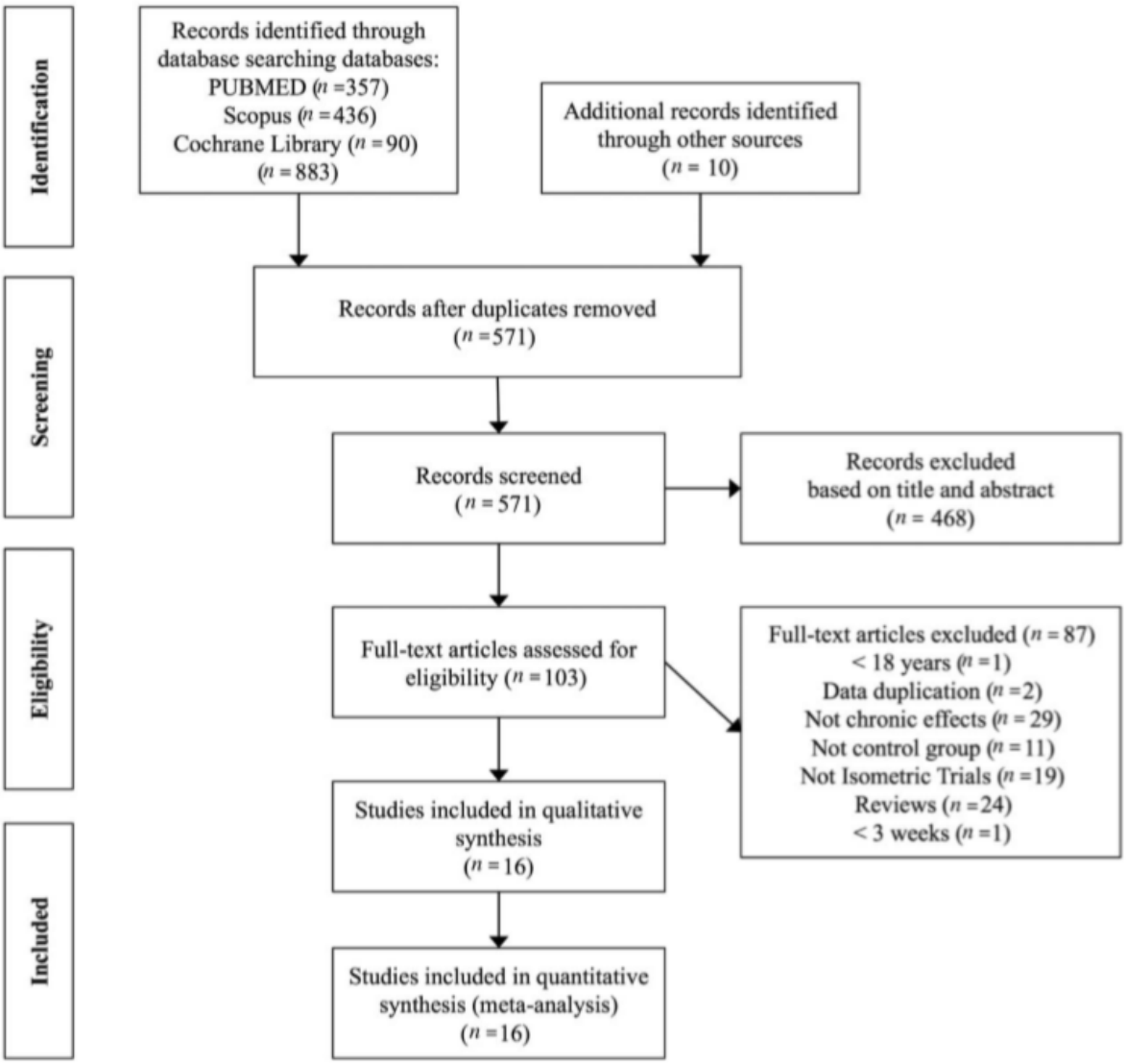

Figure 1 Flow chart of the selection of studies for the meta-analysis.

Descriptive characteristics of the studies

The main characteristics of each of the integrated studies are present in Table 1. The studies selected were carried out between 1992 and 2017. Five studies were carried out in Canada, six in the United Kingdom, three in the United States of America, one in Australia and one in Germany. The total sample size was of 492 participants, 266 pertaining to the treatment groups and 226 to the control groups. In relation to the clinical status of the participants, seven studies were carried out with pre or hypertensive participants and nine studies were performed with normotensive participants. Five trials included only men, one study was restricted to women only, whereas eight trials included both men and women. Two studies did not inform about the sex of the participants. The mean age of participants in the samples was 40.4 ± 5.2 years, and the mean percentage of men was 60% approximately.

Table 1 Characteristics of the studies included in the meta-analysis

Reference Country	**Participants**	**Length (weeks)**	**Frequency (days/week)**	**Exercise training characteristic**	**Outcome**
Badrov et al. (2013b) [39], Canada	CG: 9 F EG 1: 12 F EG 2: 11 F Normotensive	8	EG1: 3d EG2: 5d	4 x 2 min non-dominant isometric handgrip contractions at 30% MVC, separated by 4 min of rest.	Significant reductions in SBP were observed in both EGs (6 mmHg) compared to control group.
Badrov et al. (2013a) [40], Canada	CG: 7 M and 5 F EG: 6 M and 6 F Hypertensive	10	3	4 x 2 min bilateral isometric handgrip contractions at 30% MVC, separated by 4 min of rest.	The EG obtained a significant reduction in resting SBP (8 mmHg), DBP (5 mmHg), and MAP (6 mmHg).
Baross et al. (2012) [41], United Kingdom	CG: 10 M EG 1: 10 M EG 2: 10 M Pre-hypertensive patients	8	3	EG1: 4 x 2 min bilateral leg extension isometric contractions at 14% MVC, separated by 2 min of rest. EG2: 4 x 2 min bilateral leg extension isometric contractions at 8% MVC, separated by 2 min of rest.	Only significant reductions were observed in high intensity EG1 in SBP (10.8 mmHg), MAP (4.7 mmHg) and HR (4.8 BPM).
Baross et al. (2013) [54], United Kingdom	CG: 10 M EG: 10 M Pre-hypertensive patients	8	3	4 x 2 min bilateral leg extension isometric contractions at 85% HR, separated by 2 min of rest.	The EG obtained a significant reduction in resting SBP (11 mmHg) and MAP (5 mmHg).
Carlson et al. (2016) [42], Australia	CG: 8 M and 12 F EG: 6 M and 12 F Pre-hypertensives	8	3	EG: 4 x 2 min nondominant isometric handgrip contractions at 30% MVC, separated by 3 min of rest. CG: 4 x 2 min non-dominant isometric handgrip contractions at 5% MVC, separated by 3 min of rest.	The EG obtained a significant reduction in SBP (7 mmHg) and MAP (4 mmHg). No changes in DBP and HR in any group.
Devereux et al (2011) [43], United Kingdom	CG: 13 M EG: 13 M Normotensive patients	4	3	4 x 2 min bilateral leg extension isometric contractions at 95% HR, separated by 3 min of rest.	The EG obtained a significant reduction in resting SBP (4.9 mmHg), DBP (2.8 mmHg) and MAP (2.6 mmHg) compared with CG.
Gill et al. (2015) [44], United States of America	CG: 4 M and 14 F EG1: 4 M and 4 F EG2: 2 M and 7 F Normotensive patients	3	3	EG1: 4 x 2 min bilateral leg extension isometric contractions at 23% MVC, separated by 3 min of rest. EG2: 4 x 2 min bilateral leg extension isometric contractions	The EG2 showed significant reductions in SBP (3.6 mmHg), DBP (4 mmHg) and MAP (3.9 mmHg) compared to EG1 and CG. Neither EG1 nor CG showed changes in any variable.

				at 34% MVC, separated by 3 min of rest.	
Howden et al. (2002) [45], United Kingdom	CG1: 6 M and 2 F CG1: 5 M and 3 F EG1: 7 M and 2 F EG2: 6 M and 2 F Normotensive patients	5	3	EG1: 4 x 2 min bilateral leg extension isometric contractions at 20% MVC, separated by 3 min of rest. EG2: 4 x 2 min bilateral arm flexion isometric contractions at 30% MVC, separated by 3 min of rest.	Resting SBP was significantly reduced after both leg (10 mmHg) and arm (12.4 mmHg) isometric exercise training, compared to controls. Resting DBP did not change in any group.
Millar et al. (2008) [46], Canada	CG: 7 M and 17 F EG: 14 M and 11 F Normotensive patients	8	3	4 x 2 min alternating bilateral isometric handgrip contractions at 35% MVC, separated by 1 min of rest.	The EG demonstrated significant reductions in resting SBP (10 mmHg) and DBP (3 mmHg).
Pagonas et al. (2017) [47], Germany	CG: 10 M and 13 F EG: 9 M and 15 F Hypertensive patients	12	5	EG: 2 x 2 min alternating bilateral isometric handgrip contractions at 30% MVC, separated by 1 min of rest. CG: 2 x 2 min alternating bilateral isometric handgrip contractions at 5% MVC, separated by 1 min of rest.	Isometric handgrip training did not reduce blood pressure in hypertensive patients.
Ray and Carrasco (2000) [48], United States of America	CG: 8 EG: 9 Normotensive patients	5	4	4 x 3 min dominant isometric handgrip contractions at 30% MVC, separated by 5 min of rest.	In the trained group, resting DBP and MAP significantly decreased (5 and 4 mmHg, respectively), whereas SBP and HR did not significantly change.
Stiller-Moldovan et al. (2012) [49], Canada	CG: 6 M and 3 F EG: 7 M and 4 F Hypertensive patients	8	3	4 x 2 min alternating bilateral isometric handgrip contractions at 30% MVC, separated by 1 min of rest.	No significant changes in resting SBP, DBP, or HR were observed in either the EG or in the CG.
Taylor et al. (2003) [50], Canada	CG: 5 M and 3 F EG: 5 M and 4 F Hypertensive patients	10	3	4 x 2 min alternating bilateral isometric handgrip contractions at 30% MVC, separated by 1 min of rest.	The EG obtained a significant reduction in SBP (10 mmHg) and MAP (11 mmHg). No changes in DBP and HR.
Wiles et al. (2010) [51], United Kingdom	CG: 11 M EG1: 11 M EG2: 11 M Normotensive patients	8	3	EG1: 4 x 2 min bilateral isometric contractions at 21% MVC, separated by 2 min of rest. EG2: 4 x 2 min bilateral isometric contractions at 10% MVC, separated by 2 min of rest.	SBP, DBP and MAP were reduced significantly in EGs after training (5.2, 2.6, and 2.5 mmHg; 3.7, 2.5 and 2.6 mmHg, respectively).
Wiles et al (2017) [52], United Kingdom	CG: 28 M EG: 28 M Normotensive patients	4	3	4 x 2 min bilateral leg extension isometric contractions at 95% HR, separated by 2 min of rest.	Significant reductions in resting BP (4 mmHg), DBP (3 mmHg), and MAP (3 mmHg) compared to the control condition.
Wiley et al (1992) [53], United States of America	CG: 8 EG: 7 Normotensive patients	8	3	EG: 4 x 2 min dominant isometric handgrip contractions at 30% MVC, separated by 3 min of rest.	The EG reduced significantly SBP (12.7 mmHg) and DBP (14.9 mmHg).

CG, control group; DBP, diastolic blood pressure; EG, experimental group; F, female; HR, heart rate; M, male; MAP, mean arterial pressure; MVC, maximal voluntary contraction; SBP, systolic blood pressure.

Collectively, the length of the IRT programmes ranged from 3 to 12 weeks. The study training sessions per week ranged from three to five, and intensity ranged from 5 to 35% of one-repetition maximum. Nine studies used upper-extremity exercises (handgrip) and seven studies used lower-extremity exercises (leg press, squats).

Quality of the selected studies

The quality scores of each study are displayed in SDC 2 (http://links.lww.com/HJH/B50).The mean score obtained with the quality scale (range 0–10) was 5.9 (minimum 4, maximum 8) (higher score indicates better quality). Ten (62.5%) studies clearly stated eligibility criteria, all studies were randomized and 14 (87.5%) studies matched intervention groups at baseline for BP, although groups were also well matched for age and sex. Blinding of outcome assessment was performed in one study, but neither of the studies selected specifically reported that the observers were blinded to treatment allocation. However, 14 (87.5%) studies clearly reported that more than 85% of participants had complied with the intervention, and all studies completed an intent-to-treat analysis, between-group analyses and provided point estimates for effect size.

Effect sizes

Primary outcomes

Figures 2–5 show the main results and forest plots for each of the four meta-analyses carried out. Compared with control groups, experimental (IRT interventions) groups showed most likely (>99% of probability) and likely (>75 – 95% of probability) positive effects on SBP [D_+ = -6.00mmHg (95% CI -7.75 to -4.26); see Fig. 2], DBP [D_+ = -2.75mmHg (95% CI -3.78 to -1.72); see Fig. 3] and MAP [D_+ = -3.20mmHg (95% CI -4.69 to -1.71); see Fig. 4]. However, no main effects (>75–95% of probability) were observed between controls versus experimental groups for heart rate [D_+ = -0.75bpm (95% CI -1.83 to 0.34); see Fig. 5]. In the four meta-analyses, the effect sizes exhibited a large heterogeneity (based on the Q statistics and the I^2 indices; see Figs. 2–5), supporting our decision of applying random-effects models.

Analysis of moderator variables

Tables 2 and 3 display the results of the ANOVAs and meta-regressions, respectively, to examine the influence of qualitative and continuous moderator variables on the effect sizes.

As Table 2 shows, none of the qualitative moderators exhibited a statistically significant relationship with the effect sizes. Only the clinical status approached statistical significance on the effect sizes for DBP (P = 0.060, R^2 = 0.17), with the normotensive samples presenting a better benefit, and statistically significant, from IRT (D_+ = -3.59mmHg) than the hypertensive ones (D_+ = -1.15mmHg), the last not reaching statistical significance. Furthermore, the intra-group analyses of the different categories belonging to each moderator variable showed statistically significant (P<0.05) and clinically relevant (with a probability >70%) positive effects on SBP, DBP (with the exception of the categories female, hypertensive and unilateral belonging to the sex, clinical status and type of

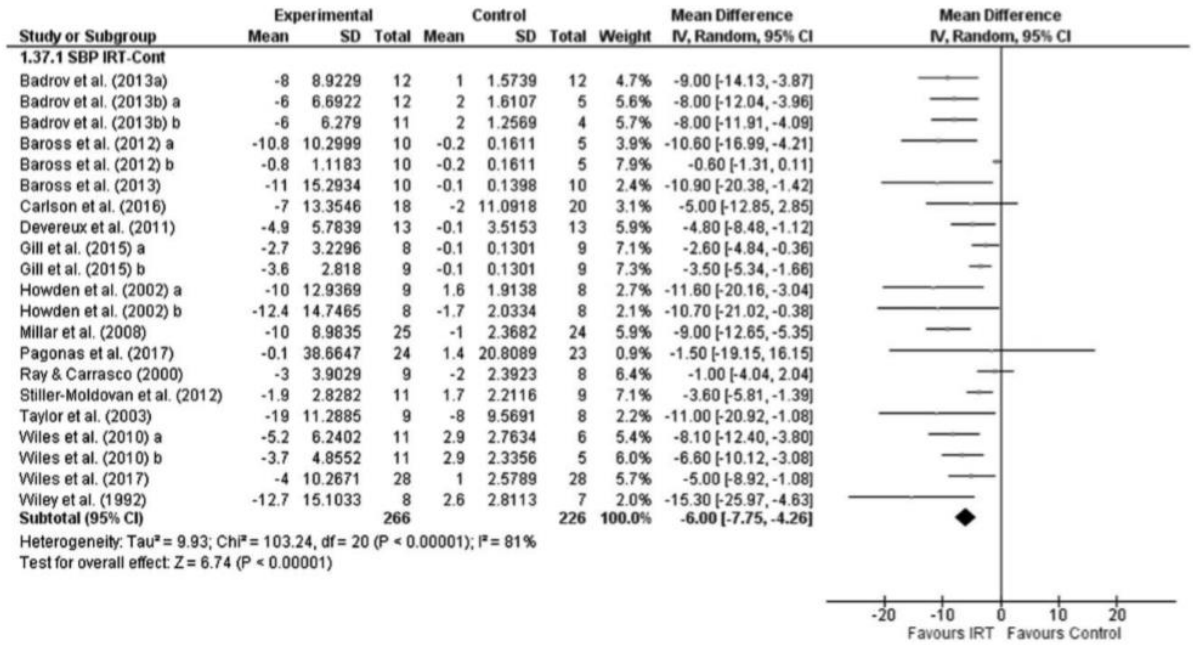

Figure 2 Forest plot systolic blood pressure.

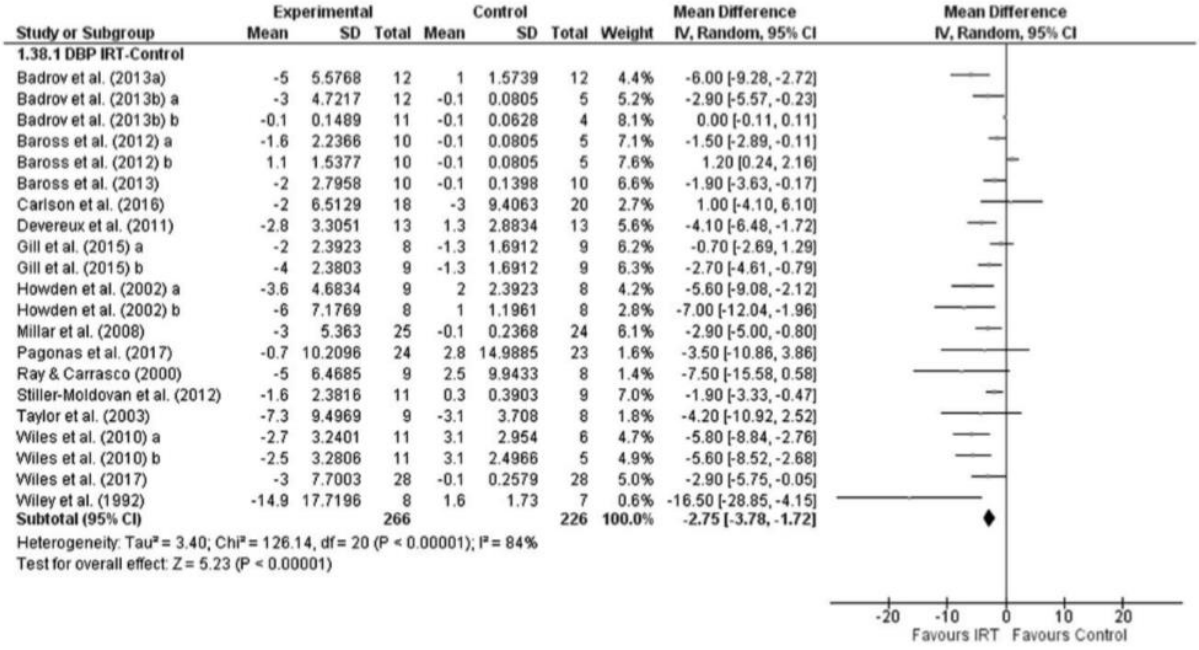

Figure 3 Forest plot diastolic blood pressure.

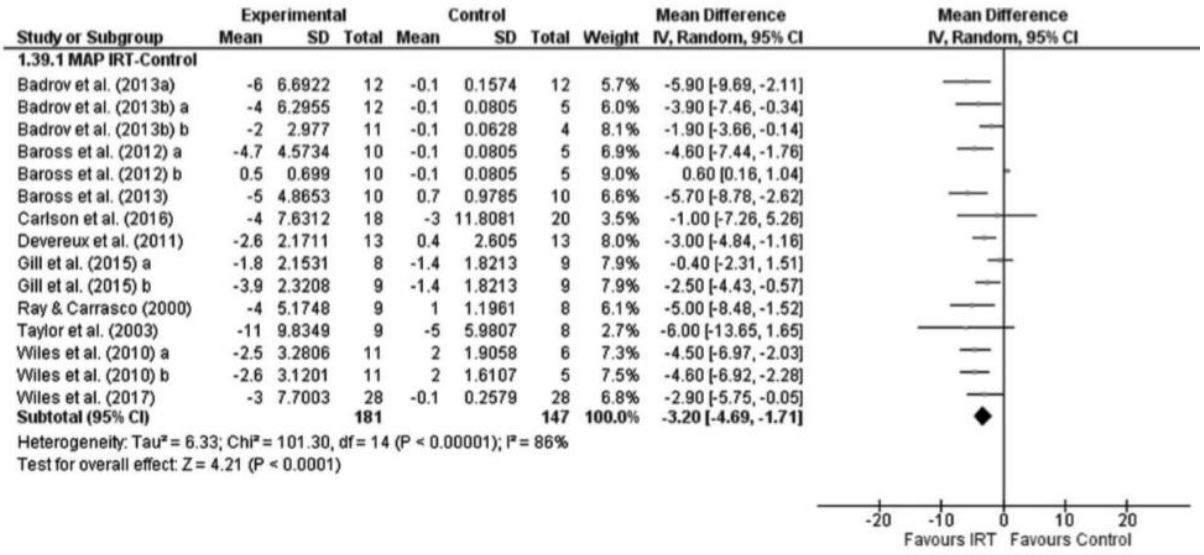

Figure 4 Forest plot mean arterial pressure.

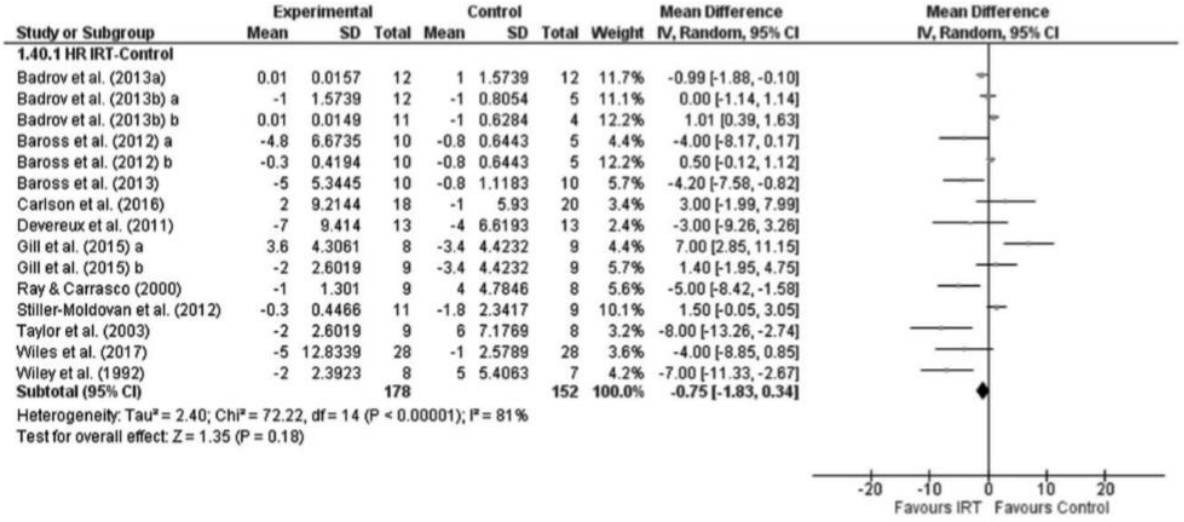

Figure 5 Forest plot heart rate.

exercise moderator variables, respectively) and MAP (with the exception of the categories female and mixed and unilateral belonging to the sex and type of exercise moderator variables, respectively) outcomes. However, and for the heart rate, the intra-group analyses showed no significant main effects for any category of the moderator variables.

With regards to the continuous moderators (Table 3), no statistically significant relationships were found for SBP, DBP and MAP effect sizes. For heart rate effect sizes, the PEDro score showed a positive, statistically significant relationship (P = 0.003; R^2 = 0.34), with the larger PEDro scores being associated to the lower effect sizes. In addition, the percentage of men in the sample presented a negative, statistically significant relationship with the effect sizes (P = 0.038; R^2 = 0.14), with better effect sizes as the proportion of men decreased. The difference between the percentages of men in

the IRT and control groups also exhibited a statistically significant relationship with the effect sizes (P = 0.003; R^2 = 0.35), but this finding was due to the influence of an outlier that presented a very large percentage difference in comparison to those of the other studies (27.7% in the study by Gill et al. [44]). In fact, no statistical significance was found when this study was removed from the analysis (P = 0.541; R^2 = 0.00).

Publication bias

Funnel plots with the trim-and-fill method for imputed missing values were constructed for SBP, DBP, MAP and heart rate (see Appendices 3, 4, 5 and 6). For SBP (SDC 3, http://links.lww.com/HJH/B50), five effect sizes were imputed to symmetrize the funnel plot, leading to an average effect size D_+ = -5.23mmHg (95% CI -6.85 and -3.60), which was statistically significant but lower than the original mean effect (D_+ = -6.00mmHg), this last one exhibiting an overestimation of about 14.7%. For DBP (SDC 4, http://links.lww.com/HJH/B50), seven effect sizes were imputed to symmetrize the funnel plot, obtaining an average effect size statistically significant (D_+ = -1.64mmHg, 95% CI -2.57 and -0.71), and indicating that the original mean effect (D_+ = -2.75mmHg) overestimated the true effect by about 67.7%. For MAP (SDC 5, http://links.lww.com/HJH/B50), two effect sizes were imputed to symmetrize the funnel plot, leading to a statistically significant average effect size (D_+ = -2.90mmHg, 95% CI -4.34 and -1.54), and implying that the original mean effect (D_+ = -3.20mmHg) overestimated the true effect by 10.3%. For heart rate (SDC 6, http://links.lww.com/HJH/B50), three effect sizes were imputed to symmetrize the funnel plot, giving an average effect size (D_+ = -0.08, 95% CI -1.04, 1.21), which was practically null and did not reach statistical significance. Table 4 summarizes the real effects of the IRT (including the magnitude-based inference analysis) on the primary outcomes.

All statistical analyses were accomplished under a random-effects model, and the trim-and-fill method was also applied to each of them.

Table 2 Results of the mixed-effects ANOVAs for the qualitative moderator variables on the effect sizes obtained from systolic blood pressure, diastolic blood pressure, mean arterial pressure and heart rate measures

Moderator variable	*N* (*k*)	D_+ (95% CI)	*P* value	Intra-group inference[c]	ANOVA results
SBP[a]					
Sex					
Male	165 (7)	5.64 (-8.39, -2.89)	0.000059	100/0/0 Most likely worthwhile differences	Q_B (2) = 0.67, P = 0.714 R^2 = 0.01 Q_W (16) = 59.99, P < 0.0001
Female	32 (2)	-8.00 (-12.99, -3.01)	0.00169	100/0/0 Most likely worthwhile differences	
Mixed	263 (10)	-5.98 (-8.54, -3.43)	0.0000044	100/0/0 Most likely worthwhile differences	
Clinical status					
Hypertensive	172 (7)	-4.69 (-7.65, -1.73)	0.00187	99/1/0 Very likely worthwhile differences	Q_B (1) = 0.55, P = 0.458 R^2 = 0.01 Q_W (19) = 56.55, P < 0.0001
Normotensive	296 (13)	-6.02 (-7.89, -4.15)	<0.00000001	100/0/0 Most likely worthwhile differences	
Extremity					
Upper (handgrip)	259 (10)	-6.58 (-9.08, -4.08)	<0.00001	100/0/0 Most likely worthwhile differences	Q_B (1) = 0.50, P = 0.480 R^2 = 0.00 Q_W (19) = 78.20, P < 0.0001
Lower (leg press)	233 (11)	-5.39 (-7.58, -3.20)	<0.00001	100/0/0 Most likely worthwhile differences	
Type of exercise					

Unilateral	102 (5)	-6.26 (-9.91, -2.61)	0.000262	100/0/0 Most likely worthwhile differences	Q_B (1) = 0.03, P = 0.871 R^2 = 0.00 Q_W (19) = 95.01, P < 0.0001
Bilateral	390 (16)	-5.92 (-7.90, -3.94)	0.000000005	100/0/0 Most likely worthwhile differences	
Age					
<45 years	247 (12)	-5.89 (-8.09, -3.69)	0.00000015	100/0/0 Most likely worthwhile differences	Q_B (1) = 0.02, P = 0.892 R^2 = 0.00 Q_W (19) = 76.98, P < 0.0001
≥45 years	245 (9)	-6.14 (-8.95, -3.32)	0.000018	100/0/0 Most likely worthwhile differences	
Weeks of intervention					
<8 weeks	167 (7)	-4.45 (-7.56, -1.33)	0.0051	94/6/1 Likely worthwhile differences	Q_B (1) = 1.76, P = 0.184 R^2 = 0.09 Q_W (19) = 99.42, P < 0.0001
≥8 weeks	325 (14)	-7.10 (-9.48, -1.33)	0.000000005	100/0/0 Most likely worthwhile differences	
DBP[a]					
Sex					
Male	165 (7)	-2.63 (-4.37, -0.89)	0.00308	76/24/0 Likely worthwhile differences	Q_B (2) = 1.13, P = 0.568 R^2 = 0.00 Q_W (16) = 70.17, P < 0.0001
Female	32 (2)	-1.19 (-4.29, 1.91)	0.453	30/65/5 Possibly trivial differences	
Mixed	263 (10)	-3.11 (-4.79, -1.42)	0.00031	90/10/0 Likely worthwhile differences	
Clinical status					
Hypertensive	172 (7)	-1.15 (-3.20, 0.89)	0.268	1/79/20 Likely trivial differences	Q_B (1) = 3.55, P = 0.060 R^2 = 0.17 Q_W (18) = 112.09, P < 0.0001
Normotensive	296 (13)	-3.59 (-5.11, -2.08)	0.0000032	100/0/0 Most likely worthwhile differences	
Extremity					
Upper (handgrip)	259 (10)	-2.83 (-4.71, -0.95)	0.0032	80/20/0 Likely worthwhile differences	Q_B (1) = 0.005, P = 0.945 R^2 = 0.00 Q_W (19) = 106.84, P < 0.0001
Lower (leg press)	233 (11)	-2.91 (-4.43, -1.40)0	0.00017	88/12/0 Likely worthwhile differences	
Type of exercise					
Unilateral	102 (5)	-2.06 (-4.77, 0.66)	0.136	52/48/0 Possibly worthwhile differences	Q_B (1) = 0.41, P = 0.521 R^2 = 0.00 Q_W (19) = 88.14, P < 0.0001
Bilateral	390 (16)	-3.04 (-4.32, -1.76)	0.0000032	94/6/0 Likely worthwhile differences	
Age					
<45 years	247 (12)	-3.70 (-5.34, -2.07)	0.0413	100/0/0 Most likely worthwhile differences	Q_B (1) = 2.03, P = 0.154 R^2 = 0.01 Q_W (19) = 119.64, P < 0.0001
≥45 years	245 (9)	-1.91 (-3.75, -0.07)	0.0000094	46/54/0 Possibly worthwhile differences	
Weeks of intervention					
<8 weeks	164 (7)	-3.50 (-5.23, -1.77)	0.000072	93/7/0 Likely worthwhile differences	Q_B (1) = 1.26, P = 0.934 R^2 = 0.00 Q_W (10) = 77.39, P < 0.0001
≥8 weeks	325 (14)	-2.31 (-3.47, -1.15)	0.0001	70/30/0 Possibly worthwhile differences	
MAP[a]					
Sex					
Male	109 (6)	-3.46 (-5.94, -0.99)	0.00596	84/16/0 Likely worthwhile differences	Q_B (2) = 0.14, P = 0.934 R^2 = 0.00 Q_W (10) = 77.39, P < 0.0001
Female	32 (2)	-2.78 (-7.18, 1.62)	0.215	67/28/5 Possibly worthwhile differences	
Mixed	114 (5)	-2.81 (-5.91, 0.29)	0.0767	71/28/1 Possibly worthwhile differences	
Clinical status					
Hypertensive	105 (5)	-2.71 (-5.07, -0.36)	0.024	72/28/0 Possibly worthwhile differences	Q_B (1) = 0.06, P = 0.811 R^2 = 0.00 Q_W (12) = 43.78, P < 0.0001
Normotensive	199 (9)	-3.06 (-4.59, -1.52)	0.000096	93/7/0 Likely worthwhile differences	
Extremity					
Upper (handgrip)	184 (7)	-3.65 (-5.97, -1.33)	0.0021	93/7/0 Likely worthwhile differences	Q_B (1) = 0.25, P = 0.617 R^2 = 0.00

Lower (leg press)	144 (8)	-2.89 (-4.73, -1.06)	0.0021	83/17/0 Likely worthwhile differences	Q_W (13) = 80.25, P < 0.0001
Type of exercise					
Unilateral	87 (4)	-3.07 (-6.17, 0.03)	0.0524	75/25/0 Likely worthwhile differences	Q_B (1) = 0.01, P = 0.922 R^2 = 0.00 Q_W (13) = 91.15, P < 0.0001
Bilateral	241 (11)	-3.25 (-4.98, -1.52)	0.00023	93/7/0 Likely worthwhile differences	
Age					
<45 years	199 (9)	-3.07 (-4.73, -1.42)	0.000262	91/9/0 Likely worthwhile differences	Q_B (1) = 0.02, P = 0.875 R^2 = 0.00 Q_W (13) = 54.04, P < 0.0001
≥45 years	129 (6)	-3.30 (-5.61, -0.99)	0.0051	87/13/0 Likely worthwhile differences	
Weeks of intervention					
<8 weeks	134 (5)	-2.65 (-5.18, -0.12)	0.05	70/30/0 Possibly worthwhile differences	Q_B (1) = 0.30, P = 0.584 R^2 = 0.00 Q_W (13) = 86.19, P < 0.0001
≥8 weeks	194 (10)	-3.54 (-5.46, -1.61)	0.00032	94/6/0 Likely worthwhile differences	
Heart rate[b]					
Sex					
Male	132 (5)	-2.29 (-4.64, 0.07)	0.0574	0/99/1 Very likely trivial differences	Q_B (2) = 4.11, P = 0.128 R^2 = 0.01 Q_W (10) = 47.59, P < 0.0001
Female	32 (2)	0.52 (-2.27, 3.31)	0.715	0/100/0 Most likely trivial differences	
Mixed	134 (6)	0.76 (-1.27, 2.79)	0.463	0/100/0 Most likely trivial differences	
Clinical status					
Hypertensive	125 (6)	-1.24 (-3.42, 0.94)	0.267	0/100/0 Most likely trivial differences	Q_B (1) = 0.10, P = 0.749 R^2 = 0.00 Q_W (12) = 63.19, P < 0.0001
Normotensive	181 (8)	-0.76 (-2.68, 1.16)	0.4413	0/100/0 Most likely trivial differences	
Extremity					
Upper (handgrip)	163 (8)	-1.12 (-2.74, 0.50)	0.167	0/100/0 Most likely trivial differences	Q_B (1) = 0.19, P = 0.659 R^2 = 0.00 Q_W (13) = 72.09, P < 0.0001
Lower (leg press)	167 (7)	-0.55 (-2.52, 1.42)	0.589	0/100/0 Most likely trivial differences	
Type of exercise					
Unilateral	102 (5)	-1.11 (-3.15, 0.93)	0.285	0/100/0 Most likely trivial differences	Q_B (1) = 0.08, P = 0.773 R^2 = 0.00 Q_W (13) = 70.02, P < 0.0001
Bilateral	228 (10)	-0.73 (-2.26, 0.80)	0.347	0/100/0 Most likely trivial differences	
Age					
<45 years	181 (8)	-0.67 (-2.39, 1.06)	0.448	0/100/ Most likely trivial differences	Q_B (1) = 0.10, P = 0.750 R^2 = 0.00 Q_W (13) = 69.53, P < 0.0001
≥45 years	149 (7)	-1.06 (-2.79, 0.66)	0.227	0/100/0 Most likely trivial differences	
Weeks of intervention					
<8 weeks	134 (5)	-0.48 (-2.82, 1.85)	0.684	0/100/0 Most likely trivial differences	Q_B (1) = 0.07, P = 0.796 R^2 = 0.00 Q_W (13) = 71.60, P < 0.0001
≥8 weeks	181 (10)	-0.83 (-2.07, 0.41)	0.188	0/100/0 Most likely trivial differences	

N is the number of participants whereas the number in parentheses (k) represents the number of studies.
95% CI, 95% confidence interval around D_+; D_+, average mean difference; DBP, diastolic blood pressure; MAP, mean arterial pressure; SBP, systolic blood pressure.
[a]Worthwhile is an absolute change in BP of above 2mmHg for SBP, DBP and MAP.
[b]For heart rate, a worthwhile effect is a change above 5bpm.
[c]If chance of benefit and harm both are above 5%, true effect was assessed as unclear (could be beneficial or harmful). Otherwise, chances of benefit or harm were assessed as follows: below 1%, almost certainly not; 1–5%, very unlikely; above 5–25%, unlikely; above 25–75%, possible; above 75–95%, likely; above 95–99%, very likely; above 99%, almost certain.

Table 3 Results of the mixed-effects meta-regressions for the continuous moderator variables on the effect sizes obtained from systolic blood pressure, diastolic blood pressure, mean arterial pressure and heart rate outcomes

Predictor	***k***	b_j	**SE**	Q_R	***P***	Q_E	R^2
SBP							
PEDro score	21	-0.676	0.929	0.53	0.467	98.96*	0.00
No. of weeks	21	-0.627	0.430	2.13	0.144	100.95*	0.00
Intensity	19	-0.085	0.101	0.72	0.396	55.68*	0.00
Age (mean)	21	-0.020	0.053	0.14	0.713	88.53*	0.00
Age (difference)	21	-0.168	0.492	0.12	0.733	102.62*	0.00
Sex (% male)	19	0.005	0.025	0.04	0.837	68.19*	0.00
Sex (% difference)	19	0.017	0.094	0.03	0.856	93.95*	0.00
DBP							
PEDro score	21	1.045	0.640	2.67	0.102	86.48*	0.02
No. of weeks	21	0.042	0.235	0.03	0.857	108.24*	0.00
Intensity	19	-0.051	0.081	0.39	0.530	117.91*	0.00
Age (mean)	21	0.036	0.035	1.08	0.299	117.66*	0.00
Age (difference)	21	0.343	0.267	1.65	0.199	82.54*	0.00
Sex (% male)	19	-0.014	0.016	0.71	0.400	90.84*	0.00
Sex (% difference)	19	0.017	0.053	0.11	0.743	112.71*	0.00
MAP							
PEDro score	15	0.214	0.788	0.07	0.786	101.15*	0.00
No. of weeks	15	-0.321	0.349	0.85	0.358	91.29*	0.00
Intensity	13	-0.058	0.079	0.54	0.462	41.18*	0.00
Age (mean)	15	-0.022	0.047	0.22	0.641	60.97*	0.00
Age (difference)	15	-0.143	0.513	0.08	0.780	97.54*	0.00
Sex (% male)	14	-0.011	0.021	0.28	0.597	82.31*	0.00
Sex (% difference)	14	0.111	0.097	1.31	0.253	94.30*	0.00
Heart rate							
PEDro score	15	1.934	0.643	9.05	0.003	55.72*	0.34
No. of weeks	15	-0.346	0.271	1.63	0.201	66.97*	0.00
Intensity	13	-0.022	0.083	0.07	0.794	62.18*	0.00
Age (mean)	15	-0.025	0.035	0.50	0.480	67.44*	0.00
Age (difference)	15	-0.363	0.316	1.33	0.250	72.22*	0.00
Sex (% male)	13	-0.032	0.015	4.32	0.038	49.08*	0.14
Sex (% difference)	13	0.208	0.070	8.83	0.003	33.38*	0.35

Age (mean) = mean age (in years) of the experimental and control groups. Age (difference) = difference between the mean age of the experimental and control groups. Sex (% male) = mean percentage of men in the experimental and control groups. Sex (% difference) = difference between the percentage of men in the experimental and control groups.
b_j = regression coefficient for the predictor variable; DBP, diastolic blood pressure; k = number of studies; MAP, mean arterial pressure; Q_E = statistic for testing the model misspecification; Q_R = statistic for testing the statistical significance of the predictor variable; R^2 = proportion of variance explained by the predictor variable; SBP, systolic blood pressure; SE = standard error of b_j.
**P<0.001.*

Table 4 Isometric resistance training effects (adjusted for publication bias) on the primary outcomes.

Outcome	D_+ (95% CI)	I^2	Chances that the true effects were substantial[a] (%)			
			Positive	Trivial	Negative	Qualitative inference[b]
SBP (mmHg)	-5.23 (-6.85, -3.60)	80%	100	0	0	Most likely positive
DBP (mmHg)	-1.64 (-2.57, -0.71)	84%	23.4	76.6	0	Likely trivial
MAP (mmHg)	-2.9 (-4.34, -1.54)	86%	88.0	11.2	0	Likely positive
Heart rate (BPM)	0.08 (-1.04, 1.21)	81%	0	100	0	Most likely trivial

95% CI, 95% confidence interval for D_+; CI, confidence interval around the mean effect size; D_+, average mean difference; DBP, diastolic blood pressure; I^2, heterogeneity index; k, number of studies; k, number of trials; MAP, mean arterial pressure; SBP, systolic blood pressure.
[a]Substantial is an absolute change in BP of above 2mmHg for SBP, DBP and MAP. For heart rate, a substantial effect is a change above 5bpm.

[b]If chance of benefit and harm both are above 5%, true effect was assessed as unclear (could be beneficial or harmful). Otherwise, chances of benefit or harm were assessed as follows: below 1%, almost certainly not; 1–5%, very unlikely; above 5–25%, unlikely; above 25–75%, possible; above 75–95%, likely; above 95–99%, very likely; above 99%, most likely.

DISCUSSION

The primary findings of this systematic review and meta-analysis report that IRT elicits a sufficient stimulus in the cardiovascular function to reduce BP in adults. After having counteracted the influence of the publication bias (using the trim-and-fill method), statistically significant (P<0.05) and clinically relevant (>2mmHg) positive effects on the SBP [-5.23mmHg (95% CI -6.85 to -3.60)] and MAP [-2.9mmHg (95% CI -4.34 to -1.54)] outcomes has been shown after the application of an IRT programme. Although IRT produced a statistically significant reduction in DBP [-1.64mmHg (95% CI -2.57 to -0.71)], the magnitude of the real effect found was not sufficient to exceed the threshold (>2mmHg) for being considered clinically relevant. These reductions in SBP and MAP, larger than 2mmHg, disclosed relevant public health implications for the treatment of the HTA, so that the risk of coronary heart disease and stroke may be reduced up to 6 and 15% respectively [55,56]. Although the mechanisms responsible for these adaptations remain to be fully clarified, improvements in conduit and resistance vessel endothelium-dependent dilation, oxidative stress and autonomic regulation of heart rate and blood pressure have been reported [55]. Furthermore, IRT did not elicit any relevant effect on resting heart rate [-0.75bpm (95% CI -1.83 to 0.34)]. All of these results are based on 16 RCTs that involved 492 participants and with a mean quality score in the PEDro scale of 5.9 (minimum 4, maximum 8). In the scientific literature, a number of randomized trials that analyse the effects of different IRT interventions on BP can be found. However, these randomized trials were excluded from the current systematic review and meta-analysis as they did not contain control groups. Only RCTs that compared the effects of one or more IRT intervention groups with those of a control group (non-intervention) were considered eligible as these studies are considered the most reliable evidence on the effectiveness of interventions because the risk of confounding factors influencing the results (true effects) is minimized or null.

The robust methodology that has been used in the current meta-analysis to estimate the true effects of IRT on the main BP outcomes did not allow making direct comparisons with the results found in the previous meta-analyses conducted by Carlson et al. [13] and Inder et al. [14]. In this sense, Carlson et al. [13] and Inder et al. [14] did not apply random-effects models in some of their meta-analyses (despite the fact that a moderate to large heterogeneity was identified) and the effect sizes reported were not adjusted for the possible influence of publication bias using quantitative methods. Leaving aside these methodological differences, in the present meta-analysis, the magnitude of the observed changes in the DBP and MAP outcomes after an IRT intervention was lower than those found in previous meta-analyses [13,14]. For example, for the DBP and MAP outcomes, Inder et al. [14] show an antihypertensive effect size of -3.91mmHg (95% CI -5.68 to -2.14) and -3.67mmHg (95% CI -4.84 to -2.48), respectively. However, the magnitude of the effects of IRT on SBP showed in the present meta-analysis were almost similar to those reported by Inder et al. [14] (-5.20; 95% CI -6.08 to -4.33) and lower than those reported by Carlson et al. [13] (-6.77; 95% CI -7.93 to -5.62). Therefore, the recently published studies have not only increased the statistical power on these analyses but have also reduced the effect sizes of IRT on the main BP outcomes. This decrease has been more substantial for the DBP outcome, and the updated effect of the IRT on DBP may not be clinically relevant and have limited public health implications. Similar to the present meta-analysis, neither Carlson et al. [13] nor Inder et al. [14] found clinically relevant IRT effects on

resting heart rate. Whereas, the effect size found in our meta-analysis for the IRT on SBP is comparable or superior to the ones reported in previous meta-analyses for the aerobic training [6,9,57] and DRT [6,7]. Although the reductions in DBP and MAP elicited by the IRT were smaller than those seen in SBP, the effect sizes are at least comparable with changes observed from the aerobic training and DRT [6,9,57], and DRT [6,7] previously published meta-analysis.

These positive effects of IRT for lowering BP along with the absence of documented side effects, the relative inexpensive and portable equipment needed (e.g. handgrip device) allowing exercise to be performed anywhere, the short duration of the training sessions (each IRT session last 8–12 min approximately) and its low level of cardiovascular stress elicited may lead IRT to become an appropriate nonpharmacological treatment for the prevention and treatment of HTA. These factors are especially true for patients who have no/limited access to a fitness centre, suitable equipment and/or supervision by a certified healthcare professional. Further, it aids those who are unable (for any reason) to reach the current exercise recommendations for blood pressure management in adults, that is, aerobic training of at least 150-min moderate intensity, 75-min vigorous intensity or an equivalent combination of both each week, and also at least 2 days of muscle strengthening [58]. However, it should be noted that for those persons who present associated comorbidities (i.e. obesity, diabetes) and who can be involved in a progressive aerobic training and DRT programme, the IRT should be considered as an adjunct, not an alternative, due to the additional effects that aerobic training and DRT have on body composition and glucose regulation, and also on the cardiovascular and musculoskeletal functions [5,59–61].

The ANOVA findings examining the influence of qualitative moderator variables (i.e. clinical status, sex, extremity used for carrying out the exercises and type of exercise, age and weeks of intervention) on the effect sizes, inform that only the moderator 'clinical status' approached a level of significant difference (in favour of the normotensive category) on the effect size for the DBP outcome (P = 0.060, R^2 = 0.17). Consequently, these findings support the use of IRT, irrespective of the sex and age, not only as non-pharmacology therapy for the treatment of the HTA but also as a preventive measure for those adults described as normotensive. Furthermore, as the extremity variable used for carrying out the exercise and type of exercise appear not to play a role in IRT responsiveness, clinicians and healthcare professionals can include unilateral or bilateral handgrip or leg extension isometric contractions in their IRT programmes. These results are not in agreement with the findings obtained in the meta-analysis conducted by Inder et al. [14]. In this sense, Inder et al. [14] found larger IRT antihypertensive effects (>2mmHg) on MAP in hypertensive [-5.91mmHg (95% CI -7.94 to -3.87)] and male [-4.13mmHg (95% CI -5.08 to -3.18)]) participants in comparison with the normotensive [-3.01mmHg (95% CI -3.73 to -2.29)] and female [-2.29mmHg (95% CI -3.87 to -0.71)] participants. Likewise, Inder et al. [14] reported that the ITRs carried out unilaterally [-8.92mmHg (95% CI -11.22 to -6.61)] and using the upper extremity [-6.88mmHg (95% CI -8.31 to -5.46)] showed larger reductions in SBP in contrast with those IRTs carried out bilaterally [-4.58mmHg (95% CI -5.52 to -3.63)] and using the lower extremity [-4.20mmHg (95% CI -5.30 to -3.09)]. Perhaps the larger number of studies included in the present meta-analysis (16 RCTs vs. 11 RCTs) has allowed a more powerful sub-analysis, and this may explain these discrepancies. However, for the moderators' sex and clinical status, it should be noted that only two (32 participants) and seven (172 participants) cohorts of the nine (197 participants) and 20 (468 participants) cohorts included in their respective subgroup analysis involved female and hypertensive patients, and therefore, these findings should be considered with caution. More

research on the effect of IRT is definitively needed in female and hypertensive populations to make evidence-based recommendations.

Finally, the meta-regressions of the continuous moderator variables revealed that only the variables PEDro score (P = 0.003; R^2 = 0.34) and the percentage of men in the sample (P = 0.038; R^2 = 0.14) showed a statistically significant relationship with the heart rate effect size. As stated before, the limited number of women recruited in the intervention studies in comparison with their counterpart men may explain these results.

Therefore, the findings found in the present meta-analysis do not support the statement reported by Inder et al. [14] that there is an existence of a dose–response relationship, so that the greater the frequency of the IRT, the larger the antihypertensive effects are on BP. The lack of significant interactions between the moderator intensity and the effect sizes of the BP outcomes was expected because most of the studies selected (n = 11) performed isometric contractions at 30–35% maximal voluntary contraction (MVC). However, those studies that have used isometric contractions below 30–35% MVC in their IRT programmes [40,42,50] seem to indicate, that for the leg extension exercise at least, an isometric contraction of 20% MVC is required to achieve clinically relevant reductions in BP outcomes, although isometric contractions at 30–35% might be preferable. If isometric contractions above 30– 35% MVC may produce larger reductions in BP remain unknown as no studies have used such intensities.

Limitations

A number of potential limitations of the present meta-analysis have to be considered. First, there are limitations inherent to the primary literature such as: participants are aware of their allocation to a control or intervention group in IRT studies; and several important scientific criteria have not always been observed (e.g. regular follow-up of the control subjects, assessment of adherence to the training programme, attention to changes in other lifestyle factors and lack of blinded or automated measurements). Second, the small number of studies conducted in female and hypertensive patients make it difficult to quantify any sex-related and clinical status-related differences regarding the hypertensive effect elicited for IRT on the main BP outcomes. Third, all of the selected studies assessed resting BP in laboratory or clinic settings using conventional methods. Although two meta-analyses [5,6] have shown that changes in net daytime ambulatory SBP and DBP in response to aerobic training were reduced to a similar extent as conventional assessment of resting BP, ambulatory monitoring has shown to be a better predictor of target end-organ damage [62], and also cardiovascular outcomes in treated patients with hypertension [63]. Furthermore, ambulatory BP measures might reflect the extent of BP reduction induced by IRT better because of a higher reproducibility over time and an absent or negligible ‘white-coat’ and placebo effect [64]. Finally, another limitation is the evidence of publication bias in some of our meta-analytic results, inviting us to be cautious in interpretation of the results and to take the effect estimates obtained with the trim-and-fill method as more appropriate.

In conclusion, isometric resistance training elicits a sufficient stimulus in the cardiovascular function to reduce BP in adults. In this sense, IRT has shown statistically significant (P<0.05) and clinically relevant (>2mmHg) positive effects on the SBP [-5.23mmHg (95% CI -6.85 to -3.60)] and MAP [-2.9mmHg (95% CI -4.34 to -1.54)] outcomes. Although IRT also produces a statistically significant reduction in DBP [-1.64mmHg (95% CI -2.57 to -0.71)], the magnitude of the real effect found may

not be enough to exceed the threshold for being considered clinically relevant. These hypertensive effects elicited by IRT on BP may be independent of the sex, age and clinical status of the patients. In addition, none of the IRT parameters coded (i.e. length of the programme, extremity used for carrying out the exercises, type of exercises, intensity) appear to have an impact on the different effect sizes calculated. Therefore, IRT may be considered to be a useful non-pharmacologic therapy for the prevention and management of HTA, especially for those patients who do not present associated comorbidities (i.e. obesity, diabetes), and do not have access to a fitness centre or suitable equipment and constant supervision by a certified healthcare professional; and/or are unable (for any reason) to reach the current exercise recommendations for blood pressure management in adults.

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Conflicts of interest

There are no conflicts of interest.

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