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REVIEW ARTICLE

The effectiveness and safety of isometric resistance training for adults with high blood pressure: a systematic review and meta-analysis

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Abstract

High blood pressure (BP) is a global health challenge. Isometric resistance training (IRT) has demonstrated antihypertensive effects, but safety data are not available, thereby limiting its recommendation for clinical use. We conducted a systematic review of randomized controlled trials comparing IRT to controls in adults with elevated BP (systolic ≥130 mmHg/diastolic ≥85 mmHg). This review provides an update to office BP estimations and is the first to investigate 24-h ambulatory BP, central BP, and safety. Data were analyzed using a random-effects meta-analysis. We assessed the risk of bias with the Cochrane risk of bias tool and the quality of evidence with GRADE. Twenty-four trials were included ($n = 1143$; age = 56 ± 9 years, 56% female). IRT resulted in clinically meaningful reductions in office systolic (–6.97 mmHg, 95% CI –8.77 to –5.18, $p < 0.0001$) and office diastolic BP (–3.86 mmHg, 95% CI –5.31 to –2.41, $p < 0.0001$). Novel findings included reductions in central systolic (–7.48 mmHg, 95% CI –14.89 to –0.07, $p = 0.035$), central diastolic (–3.75 mmHg, 95% CI –6.38 to –1.12, $p = 0.005$), and 24-h diastolic (–2.39 mmHg, 95% CI –4.28 to –0.40, $p = 0.02$) but not 24-h systolic BP (–2.77 mmHg, 95% CI –6.80 to 1.25, $p = 0.18$). These results are very low/low certainty with high heterogeneity. There was no significant increase in the risk of IRT, risk ratio (1.12, 95% CI 0.47 to 2.68, $p = 0.8$), or the risk difference (1.02, 95% CI 1.00 to 1.03, $p = 0.13$). This means that there is one adverse event per 38,444 bouts of IRT. IRT appears safe and may cause clinically relevant reductions in BP (office, central BP, and 24-h diastolic). High-quality trials are required to improve confidence in these findings. PROSPERO (CRD42020201888); OSF (https://doi.org/10.17605/OSF.IO/H58BZ).

Keywords Blood pressure · Isometric resistance training · Exercise · Safety

Introduction

High blood pressure (BP) affects 1.13 billion people worldwide and is the leading risk factor globally for mortality, accounting for 10.8 million deaths in 2019 [1, 2]. Due to the widespread impact of an elevated BP [2], there is a clear need for strategies to reduce its prevalence and severity. Exercise is one such strategy. Both aerobic and dynamic resistance exercise appear effective at reducing BP [3], and for people with hypertension, potentially to a similar extent as common antihypertensive medications [4]. Isometric resistance training (IRT) is an emerging mode of exercise demonstrating effectiveness in reducing office BP [5–7]. However, no previous review has investigated the safety of IRT in people with high BP or its effect on central and 24-h ambulatory BP, limiting its clinical applications [6–10].

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IRT is defined as a muscular contraction against an immovable load (i.e., there is no change in muscle length). The benefits of IRT over other modes of exercise include its simplicity to prescribe and administer, it can be undertaken even if participants have functional limitations, and it is time efficient (usually <15 min/session) [11]. It is most commonly undertaken by squeezing a handgrip device, or less commonly by pushing against a leg dynamometer (usually in knee extension) or while performing a "wall sit" [12, 13].

In addition to its effectiveness, the safety of an intervention is vital to its recommendation in clinical practice. The utility of IRT to lower BP in people with hypertension was noted as far back as 1973 [14], but it has been disadvised due to an acutely exaggerated BP elevation during exercise [15] and is currently not recommended by many major hypertension guidelines [16–18]. Despite its apparent safety during a single bout [19, 20], the safety of regular IRT over weeks to months remains unknown and this is crucial to understand before confidently prescribing it to patients. Moreover, previous systematic reviews of IRT have stated that adverse events have not been reported [6, 9], but this does not indicate that no adverse events occurred [21]. Rather, this may be an artifact of poor adverse event reporting, as is common in studies of exercise [22]. IRT appears effective and may indeed be safe; however, until sufficient evidence of safety is demonstrated, it may remain underutilized by clinicians and not mentioned in the hypertension management guidelines.

There has been extensive study on the effect of IRT on office BP in previous systematic reviews and meta-analyses [3–10, 23, 24], although all have several important limitations. The primary limitation of these previous studies is their small sample size, with an average of 230 participants (range = 66–492). There have been several large trials ($n > 100$) [25, 26] that have not been included in these reviews; thus, the estimates of the effect of IRT on office BP should be updated. Furthermore, no previous reviews have investigated its safety or its effect on central or 24-h ambulatory BP, two important measures of BP.

Another limitation of the previous IRT reviews is that none have assessed the completeness of exercise intervention reporting, for example, by using the Consensus on Exercise Reporting Template (CERT) or the Template for Intervention Description and Replication [27, 28]. CERT is designed to aid researchers in accurately reporting interventions to promote the translation of evidence to clinical practice [28]. The Grading of Recommendations, Assessment, Development and Evaluations (GRADE) framework was developed to provide a systematic approach for making clinical practice recommendations [29]. To date, only two reviews of IRT [5, 30] have used GRADE. Therefore, due to the limited evaluation of the quality of evidence, the certainty of the findings from previous IRT reviews is undetermined.

Overall, IRT appears to be effective in reducing BP, but the previous reviews were limited to small samples of small studies ($n < 100$), did not fully describe the IRT interventions, did not adequately assess safety, and insufficiently evaluated the certainty of the evidence by using GRADE [3–10, 23, 24]. The primary aim of this systematic review was to update estimates for the effectiveness of IRT for lowering office BP in people with elevated BP or hypertension and to provide novel data about central and 24-h ambulatory BP and safety. We hypothesized that IRT would lower BP more than in the control and would do so with relatively few adverse events.

Methods

This study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) [31], Transparency and Openness Promotion [32], and A Measurement Tool to Assess Systematic Reviews 2 [33] guidelines. The protocol was preregistered on the Open Science Framework (OSF) (https://doi.org/10.17605/OSF.IO/H58BZ) and PROSPERO (CRD42020201888) prior to conducting the searches. The data and code used for this review are available on OSF, and a full description of the methods can be found in Supplementary Material 1. Deviations from the protocol, with the reasons, are stated as such.

Eligibility criteria

Study design

We included randomized controlled trials, including crossover trials written in any language. There were no restrictions on publication status, as unpublished data may result in meaningful differences in the outcomes of systematic reviews [34]. Publication bias or selective omission of data is of particular concern regarding adverse events, which have been shown to be significantly higher in unpublished studies [35].

Participants

We included trials examining adults with a mean office BP classed as high-normal (SBP 130–139 mmHg or DBP 85–89 mmHg), grade 1 hypertension (SBP 140–159 mmHg or DBP 90–99 mmHg), or grade 2 hypertension (SBP ≥160 mmHg or DBP ≥100 mmHg) according to the International Society of Hypertension guidelines [17].

Interventions

We included trials that examined IRT, defined as exercises involving muscular contraction against an immovable resistance or a load with a negligible change in the length of the muscles involved [13]. Trials were included if IRT was performed for at least 3 weeks, the minimum duration believed to produce an effect on BP [9], without restrictions on the frequency, volume, or intensity of the IRT prescribed.

Comparators

We included the following comparators: aerobic exercise, dynamic resistance exercise, and nonexercise controls, including lifestyle modification (e.g., advice to be physically active), nonexercise control, or sham isometric exercise.

Outcomes

The primary outcome was the mean difference in BP change scores between the IRT and control groups. BP included systolic and diastolic pressures, measured in the office (brachial), central, or 24-h ambulatory BP, which we analyzed as separate outcomes.

The secondary outcome was safety. Safety was expressed as the number of participants who experienced an adverse or serious adverse event, either during or after the exercise. Adverse events and serious adverse events were defined according to the Food and Drug Administration [36].

Searches

We searched electronic databases of published and unpublished literature up to August 2020, including MEDLINE, EMBASE, Cumulative Index to Nursing and Allied Health Literature, Physiotherapy Evidence Database, SPORTDiscus, Cochrane Register of Controlled Trials, ClinicalTrials.gov, Australian New Zealand Clinical Trials Registry, and European Union Clinical Trial Registry. The full list of the search strategies and databases searched are available in Supplementary Material 2. We also searched previous systematic reviews and conducted forward and backward citation tracking of the included studies to identify additional relevant articles.

Two reviewers (HJH, MDJ) independently conducted two stages of eligibility screening in duplicate: (i) title and abstract; (ii) full text. Disagreements were resolved through discussion with a third reviewer (BJP) when required.

Data extraction

Descriptive data and the results from the included studies were extracted independently and in duplicate by the authors (HJH, MDJ, KAM, MAW) into a standardized document, with disagreements resolved through discussion. When data were only presented in figures, we extracted them using WebPlotDigitizer [37]. If the studies did not report outcomes of interest (e.g., adverse events), the authors were contacted up to three times requesting the relevant data. If no reply was received within 6 weeks, the data were considered unobtainable.

For each outcome, we prioritized extracting the mean change and the SD of change (SD_{change}) for the intervention and control groups. We transformed the standard error and 95% confidence intervals (CI) using the methods outlined by the Cochrane Collaboration [38]. If the mean change and SD_{change} were not reported, we calculated them from the baseline and postintervention values based on the recommendations from the Cochrane Collaboration [38].

Risk of bias in the individual studies

We used the Cochrane risk of bias tool to assess the risk of bias [39]. Each trial was appraised independently and in duplicate by two authors (HJH, MDJ, KAM, MAW), and disagreements were resolved through discussion. The domains assessed included selection, performance, attrition, detection, reporting, and other sources of bias. The overall risk of bias for each trial was determined to be "high," "some concerns," or "low" (Supplementary Material 3) [39].

Data analysis

Random-effect meta-analyses were conducted by two authors (HJH, MAW) using the metafor package in R [40]. The effects of IRT on BP compared to a nonexercising control and aerobic exercise were summarized separately using the mean difference and 95% CI. Safety was determined using the risk ratio (RR) and risk difference (RD) with a 95% CI. Heterogeneity was quantified using Cochran's Q, τ^2, the I^2 statistic and 95% prediction intervals. A clinically important difference in SBP was determined to be 5 mmHg based on expert consultation (AES) and 2 mmHg for DBP based on previous research [41]. Funnel plots were produced with metafor to assess publication bias/data dredging [42]. Extended funnel plots were constructed using the extfunnel package in R to determine the impact of the results of a future study on the pooled effect observed in this review [43]. We conducted several prespecified subanalyses, including medication status and type of exercise and BP classification. A study was deemed to have "medicated" participants if >80% of participants were medicated. This was an arbitrary cutoff based on expert consultation (AES). An exploratory post hoc subanalysis of age (< or ≥65 years old) was also conducted.

When IRT was compared to aerobic exercise, positive values indicate a reduction in BP favoring aerobic exercise.

Confidence in the cumulative evidence

Two reviewers (MDJ, HJH) assessed the quality of the evidence and the strength of recommendations using GRADE [29]. The quality of evidence was downgraded for risk of bias, inconsistency, indirectness, imprecision, and publication bias (see Supplementary Table 4 for details).

Results

Deviations from the protocol

There were several deviations from the protocol [44]:

> We did not examine the impact of different exercise prescriptive parameters (i.e., the frequency or intensity of IRT) or further subgroup the exercise types into unilateral or bilateral due to a lack of variation in the prescriptions. We did not conduct sensitivity analyses by removing studies at high risk of bias because all of the studies were classified as high risk.
> We conducted a post hoc sensitivity analysis by removing the studies where the mean age of the participants was <65 to identify the effect of IRT in older adults; this age cutoff was chosen based on previous guidelines [18].

Search results

Figure 1 outlines the literature search. We screened 8018 records by title/abstract, and citation tracking identified 801 additional articles. Three eligible trials were unable to contribute to the meta-analysis due to a lack of data (two registered clinical trials on hold [45, 46] and one trial protocol [47]). Two included trials were unpublished [48, 49]. Two included trials [50, 51] were published in a non-English language (Thai and Korean) and were translated using Google Translate [52]. We have listed the reasons for the exclusion of the full-text articles in Supplementary Material 5.

Characteristics of the included studies and participants

Twenty-four trials randomizing 1286 participants were included in the quantitative synthesis of office BP. The sample sizes of the included trials were typically small (median $n = 25$, range 8–400, interquartile range 22). More women ($n = 677$, 56%) were included than men ($n = 541$, 44%), with two studies not disaggregating data by sex ($n = 68$). The mean duration of IRT was 9.8 weeks, with a mean frequency of 3.2 sessions per week and an average session duration of 14.75 min. Twenty-one of the 24 trials used handgrip exercises for the IRT. The most frequent prescription of IRT was 4×2 min of IRT at 30% maximal voluntary contraction ($n = 25$). There were 88 dropouts in total, 48 in the IRT and 40 in the control group (median $n = 1$, range 0–33). The comparators included nonexercise ($n = 20$), sham IRT ($n = 4$), and lifestyle modifications ($n = 4$, including education about the physical activity guidelines). The majority ($n = 19$) of trials [11, 12, 25, 26, 46, 48–51, 53–65] used a digital oscillometric device to measure BP, two trials [66, 67] used a finger plethysmograph and two trials [68, 69] used mercury sphygmomanometers. One trial registry record [48] did not report their method of BP measurement. Twenty-one studies (88%) [11, 12, 25, 26, 49, 53–55, 57–69] reported standardized testing procedures for the determination of BP. Three studies directly compared IRT to aerobic exercise [11, 51, 63], and one ongoing trial compared IRT to dynamic resistance exercise [48]. The intervention characteristics are described in Supplementary Table 6, and the participant characteristics are outlined in Supplementary Table 7. We transformed the endpoint data into change scores in 73% of the comparisons ($n = 33$), calculating the SD_{change} using the methods outlined above.

Author contacts

Twenty-one authors of 24 trials were contacted, with 10 authors responding (48%). Adverse event data were provided for ten comparisons [12, 25, 26, 48, 49, 51, 54, 55, 57, 58, 60, 65], and two authors provided unpublished data [48, 49] for inclusion in the quantitative synthesis.

Risk of bias and GRADE assessment

All included trials were deemed to be at a high risk of bias, with only two studies having no domain rated as "high risk," but they were both deemed as having "some concerns" in multiple domains (Supplementary Material 8). The primary limitation across the studies was a lack of blinding of the participants and personnel ($n = 20$), followed by selective reporting ($n = 8$). A description of the sources of the individual trial funding is available in Supplementary Table 9.

Table 1 summarizes the results of the GRADE assessment. The evidence was very low quality for all outcomes except central DBP and adverse events, which were rated as low quality (Supplementary Table 10). The evidence was downgraded due to a high risk of bias and inconsistency.

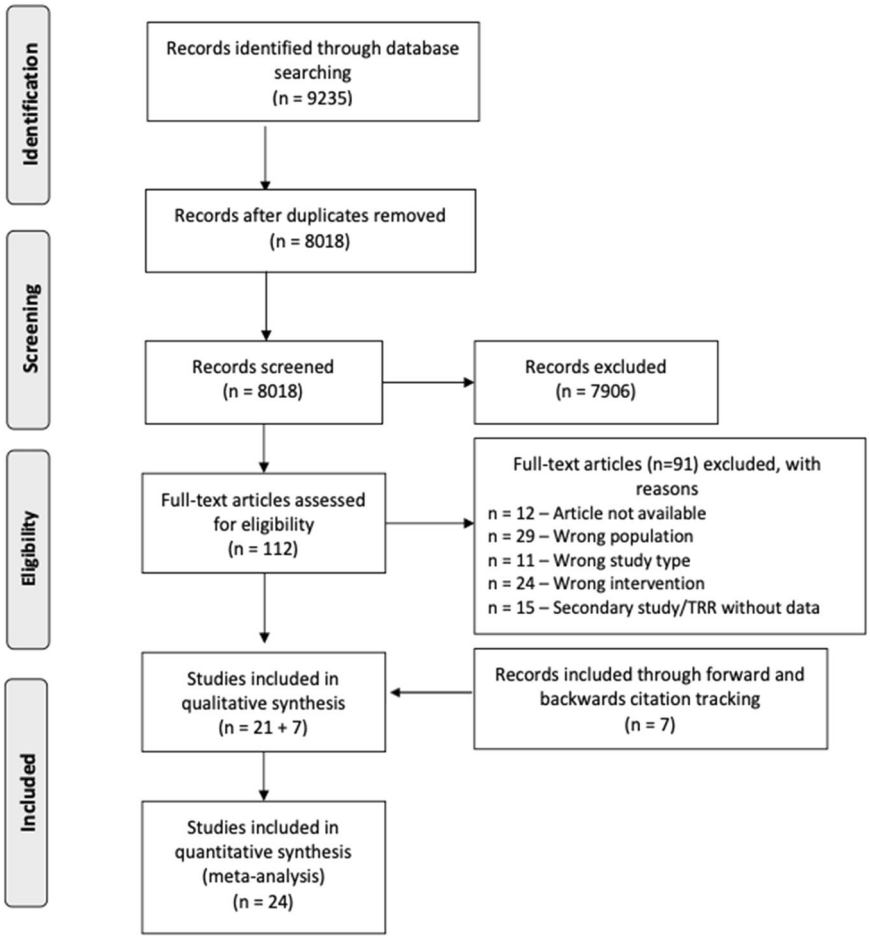

Fig. 1 PRISMA flow diagram of search results

Systolic blood pressure

Twenty-four studies examined the office SBP (Fig. 2). IRT reduced the SBP by –6.97 mmHg (95% CI –8.77 to –5.18, $p < 0.0001$) compared to the control; however, significant heterogeneity was identified ($\tau^2 = 11.26$, $Q = 129.99$, $I^2 = 75.8\%$, $p < 0.0001$). Post hoc analysis stratified by age demonstrated a reduction in SBP in older adults (≥65 years) by –7.17 mmHg (95% CI –10.89 to –3.46, $p < 0.0005$; $I^2 = 46.6\%$, $p = 0.09$) and a reduction of –6.90 mmHg (95% CI –9.01 to –4.80, $p < 0.0001$; $I^2 = 80.4\%$, $p < 0.0001$) in those <65 years old (Fig. 2). When stratified by baseline BP classification (Supplementary Fig. 11), IRT reduced the office SBP in grade 1 hypertension by –6.84 mmHg (95% CI –9.91 to –3.76, $p = 0.0001$; $I^2 = 49.4\%$, $p = 0.06$), and in high-normal BP by –7.05 mmHg (95% CI –9.31 to –4.79, $p < 0.0001$; $I^2 = 79.1\%$, $p < 0.0001$).

Supplementary Fig. 12 displays a sensitivity analysis of the studies ($n = 16$) of unmedicated participants where IRT reduced the SBP by –7.30 mmHg (95% CI –9.64 to –4.96, $p < 0.0001$; $I^2 = 86.4\%$, $p < 0.05$). In unmedicated grade 1 hypertension, IRT reduced the SBP by –8.31 mmHg (95% CI –14.55 to –2.07, $p < 0.01$; $I^2 = 80\%$, $p = 0.01$) and in people with high-normal BP by –7.02 mmHg (95% CI –9.64 to –4.39 $p < 0.0001$; $I^2 = 85.2\%$, $p < 0.0001$). When stratified by the type of exercise (Supplementary Fig. 13), 23 comparisons showed isometric handgrip exercise could reduce the office SBP by –6.45 mmHg (95% CI –8.21 to –4.7, $p < 0.0001$; $I^2 = 60.7\%$, $p < 0.0001$). Isometric leg exercise ($n = 4$) reduced office SBP by –8.68 mmHg (95% CI –14.17 to –3.18, $p = 0.0019$; $I^2 = 87.3\%$, $p < 0.0001$).

Four studies measured the central SBP (Supplementary Fig. 14) and demonstrated a reduction of –7.48 mmHg (95% CI –14.89 to –0.07, $p = 0.048$; $I^2 = 63.8\%$, $p = 0.035$). Seven studies measured the 24-h ambulatory SBP (Supplementary Fig. 15), showing a reduction of –2.74 mmHg (95% CI –6.74 to 1.25, $p = 0.18$; $I^2 = 77.7\%$, $p < 0.0001$).

Diastolic blood pressure

Twenty-four studies examined the office DBP (Fig. 3). IRT reduced the DBP by –3.86 mmHg (95% CI –5.31 to –2.41,

Table 1 Summary of findings

Change in blood pressure associated with IRT intervention compared with nonexercising or sham control				
Population: adults (>18 years old) with high-normal BP or grade 1 hypertension Intervention: IRT Comparison: non-exercising or sham exercise control				
Outcomes	Change (95% CI) after IRT intervention compared to control	Number of participants (comparisons)	Confidence in effect estimate	Comments
Office SBP, MD (95% CI)	–6.97 mmHg** (–8.77 to –5.18)	1143 (27)	⊕◯◯◯ Very low	Rated down –2 for high risk of bias, –1 for inconsistency
Office DBP, MD (95% CI)	–3.86 mmHg** (–5.31 to –2.41)	1139 (27)	⊕◯◯◯ Very low	Rated down –2 for high risk of bias, –1 for inconsistency
Central SBP, MD (95% CI)	–7.48 mmHg* (–14.89 to –0.07)	183 (4)	⊕◯◯◯ Very low	Rated down –2 for high risk of bias, –1 for inconsistency
Central DBP, MD (95% CI)	3.75 mmHg* (–6.38 to –1.12)	161 (3)	⊕⊕◯◯ Low	Rated down –2 for high risk of bias
24-h ambulatory SBP, MD (95% CI)	–2.74 mmHg (–6.74 to 1.25)	223 (8)	⊕◯◯◯ Very low	Rated down –2 for high risk of bias, –1 for inconsistency
24-h ambulatory DBP, MD (95% CI)	–2.39 mmHg* (–4.38 to –0.40)	223 (8)	⊕◯◯◯ Very low	Rated down –2 for high risk of bias, –1 for inconsistency
Adverse events (95% CI)	RR = 1.12 (0.47–2.68); RD = 1.01 (1.00–1.03)	501 (17)	⊕⊕◯◯ low	Rated down –2 for high risk of bias

SBP systolic blood pressure, *DBP* diastolic blood pressure, *RR* risk ratio, *RD* risk difference

*$p < 0.05$; **$p < 0.0001$

$p < 0.0001$). Significant heterogeneity was identified ($\tau^2 = 7.53$, $Q = 81.46$, $I^2 = 73.3\%$, $p < 0.0001$). Post hoc stratification by age showed a pooled reduction in DBP in older adults (≥65 years) of –3.51 mmHg (95% CI –5.47 to –1.55, $p < 0.0005$; $I^2 = 4.8\%$, $p = 0.6$) and a reduction of –3.79 mmHg (95% CI –5.73 to –1.85, $p < 0.0005$; $I^2 = 82.8\%$, $p < 0.0001$) in those <65 years old. When stratified by baseline BP classification (Supplementary Fig. 16), IRT reduced DBP in grade 1 hypertension by –4.92 mmHg (95% CI –7.13 to –2.71, $p < 0.001$; $I^2 = 55.6\%$, $p = 0.014$) and in high-normal BP by –3.23 mmHg (95% CI –5.13 to –1.33, $p < 0.001$; $I^2 = 73.0\%$, $p = 0.0014$).

Supplementary Fig. 17 displays a sensitivity analysis of studies ($n = 16$) of unmedicated participants where IRT reduced the DBP by –3.90 mmHg (95% CI –5.76 to –2.03, $p = 0.0004$; $I^2 = 79.9\%$, $p < 0.0001$). In those with grade 1 hypertension on medication, IRT reduced the DBP by –5.26 mmHg (95% CI –9.13 to –1.38, $p = 0.0079$; $I^2 = 71\%$, $p = 0.0052$), and in high-normal, medicated individuals, the DBP was reduced by –3.44 mmHg (95% CI –5.57 to –1.30, $p < 0.005$; $I^2 = 77.0\%$, $p = 0.0015$).

When stratified by type of exercise (Supplementary Fig. 18), isometric handgrip exercise ($n = 23$) reduced the DBP by –4.03 mmHg (95% CI –5.67 to –2.39, $p < 0.0001$; $I^2 = 76\%$, $p < 0.0001$), whereas isometric leg exercise ($n = 4$) did not significantly reduce the DBP (–2.99 mmHg (95% CI –6.42 to 0.43, $p = 0.087$; $I^2 = 44.3\%$, $p = 0.16$)).

Two studies of three comparisons measured the central DBP (Supplementary Fig. 19); IRT reduced the central DBP by –3.75 mmHg (95% CI –6.38 to –1.12, $p = 0.005$; $I^2 = 0\%$, $p = 0.63$). Eight studies measured ambulatory DBP (Supplementary Fig. 20); IRT reduced ambulatory DBP by –2.39 mmHg (95% CI –4.38 to –0.40, $p = 0.02$; $I^2 = 51.6\%$, $p = 0.03$).

Effect of IRT on BP compared to aerobic and dynamic resistance exercise

Three studies compared IRT to aerobic exercise. For office SBP (Supplementary Fig. 21), there was no significant difference between IRT and aerobic exercise, with a mean difference of 3.36 mmHg (95% CI –13.94 to 7.22, $p = 0.53$; $I^2 = 83.3\%$, $p = 0.53$) favoring aerobic exercise. Similarly, there was no significant difference in the reduction in office DBP (Supplementary Fig. 22) between IRT and aerobic exercise, with a mean difference of 2.17 mmHg (95% CI –4.80 to 0.45, $p = 0.1$; $I^2 = 0\%$, $p = 0.397$) favoring aerobic exercise.

One ongoing study [48] comparing IRT to dynamic resistance exercise provided the preliminary data of eight participants in each arm, finding no difference between the groups for office SBP (–10 mmHg, 95% CI –20.90 to 0.90, $p = 0.07$) or office DBP (–3 mmHg, 95% CI –10.49 to 4.49, $p = 0.43$).

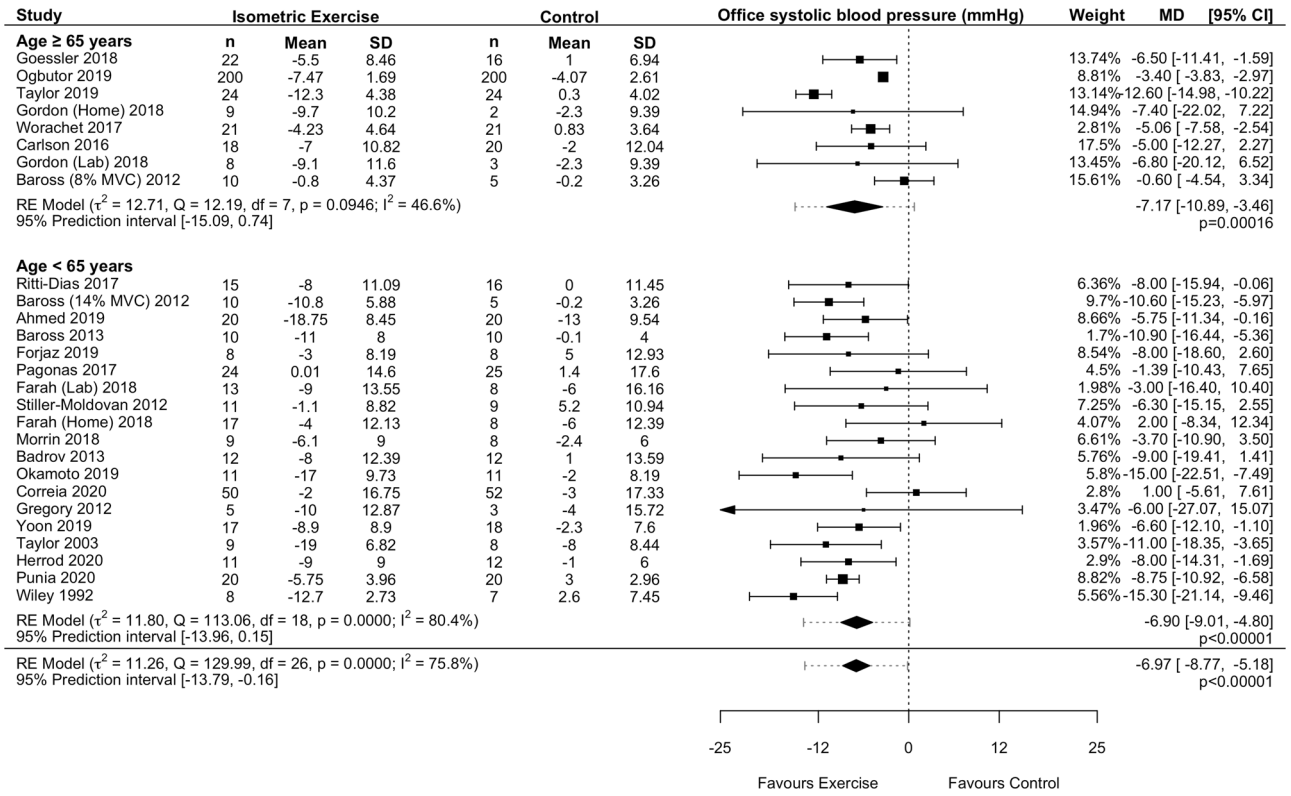

Fig. 2 Isometric resistance training compared to control for office systolic blood pressure, with subanalysis based on age

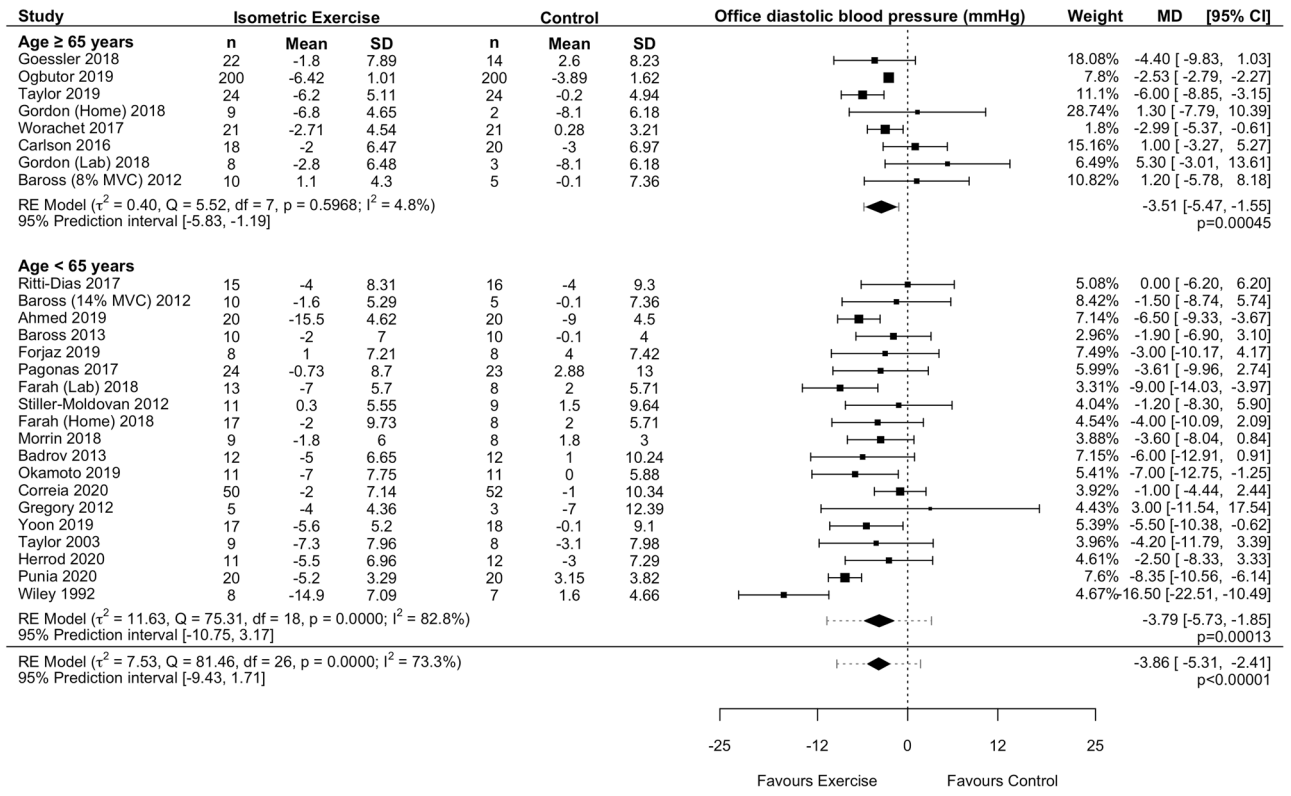

Fig. 3 Isometric resistance training compared to control for office diastolic blood pressure, with subanalysis based on age

Adverse events

Among the 24 included studies, only 7 (29%) clearly reported adverse events. When all comparisons of IRT and a nonexercising control ($n = 17$) that provided adverse events were pooled (Supplementary Figs 23 and 24), there was no significant increase in risk (RR = 1.12 [95% CI 0.47 to 2.68, $p = 0.800$; $I^2 = 0\%$, $p = 0.99$], RD = 1.01 [95% CI 1.00 to 1.03, $p = 0.113$; $I^2 = 0\%$, $p = 0.99$]). There were seven adverse events in the IRT group and one in the non-exercising control (Supplementary Table 5), equating to one adverse event per 38,444 bouts of IRT. The adverse events were predominantly joint or muscle pain ($n = 6$) and were not severe enough to cause the participants to drop out; one other adverse event occurred in the IRT condition (dyspnea and tachycardia). There were no adverse events reported in the two trials of lower-limb IRT [12, 54]. There were no adverse events in the trials of older adults, with four studies of 84 participants providing adverse event data. There were four events among participants with grade 1 hypertension and four events among people with high-normal BP, showing no difference in risk between the classifications.

Serious adverse events

There were no serious adverse events noted in the IRT or aerobic groups, but there was one myocardial infarction in the dynamic resistance training group in the single study [48] included with a dynamic resistance group of eight participants.

Quality of reporting

The quality of reporting is outlined in Supplementary Fig. 25, and a summary of the CERT findings is presented in Supplementary Table 26.

Publication bias

Funnel plots were produced for all SBP and DBP outcomes. When assessed using conventional funnel plots with Egger's regression test (Supplementary Figs 27 and 28) and contour-enhanced funnel plots (Supplementary Figs 29 and 30), there was no evidence of publication bias for the office BP measures. We refrain from commenting on the results of the other funnel plots due to the small number of studies included ($n < 10$) [38].

Implications of a further trial

Supplementary Fig. 31 illustrates the impact a future trial would have on the pooled effect of IRT on all BP outcomes from this review. These funnel plots indicate that a future trial is unlikely to meaningfully alter the effects found in this study.

Discussion

Our review is the largest review of IRT to date, including more than twice the number of participants than in the largest previous review [6], as well as including two recent, large ($n > 100$) trials [25, 26]. We found that IRT offers significant and clinically relevant reductions in office SBP and DBP compared to the control. This was also true for central BP, whereas the changes in ambulatory BP were smaller and not statistically significant. Our review also provides the only synthesized evidence to date about the safety of IRT, with adverse events seldom occurring and a complete absence of serious adverse events in the IRT condition. However, these findings must be interpreted with caution because they are based on low (central DBP and adverse events) and very low (office and 24-h ambulatory BP and central SBP) quality evidence. Nonetheless, IRT appears to be safe and it may be effective for reducing BP in adults.

Adverse events have been a historic concern regarding the prescription of IRT [15]. In our review, there was no significant increase in the relative or absolute risk of adverse events, and the rare adverse events that did occur were minor. Moreover, there was no increased risk of adverse events in those with a higher baseline BP or in older adults, two groups believed to be at increased risk of adverse events during exercise [70]. The conclusion that IRT may be safe was primarily based on trials that used handgrip exercise (4×2 min) at 30% maximal voluntary contraction. These findings may not generalize to other forms of IRT, IRT with a longer duration, and/or higher intensity contractions. The limited number of lower-limb IRT studies available, which provided adverse event data [12, 54], indicated that IRT is safe with very low rates of adverse events.

The most comprehensive comparative analysis to date of the effectiveness of exercise (aerobic, dynamic resistance, and IRT) or medications for lowering BP was a 2018 network meta-analysis [4]. Interestingly, these reductions in SBP were comparable to those of common antihypertensive medications [4]. In this network meta-analysis, IRT did not significantly reduce BP in those with hypertension –4.68 (95% CI –10.28 to 0.38), although this finding was based on 12 studies of IRT, half the number of studies included in our review. The reductions seen in response to aerobic and dynamic resistance exercise above appear comparable to the reduction due to IRT, –6.84 mmHg (95% CI –9.91 to –3.76), found in our review, reinforced by the findings of no significant differences among IRT, aerobic exercise, and

dynamic resistance exercise in our review. An updated network meta-analysis is needed to rigorously compare the different treatments, including medications, in terms of their effectiveness and safety, especially given the increasing size of this evidence base.

This review provides the first synthesis of the effect of IRT on central BP. Despite the greater sensitivity of central BP to predict structural cardiovascular changes [71], recent evidence suggests that it is not superior to brachial BP for predicting cardiovascular disease risk [72]. Regardless, strategies to reduce central BP are likely of clinical importance. For example, treatments that reduce brachial BP but not central BP do not provide the same risk reduction as treatments that reduce both brachial and central BP [73, 74]. Our results demonstrate that IRT reduces both central and brachial SBP, potentially leading to a greater reduction in cardiovascular risk than interventions that only reduce brachial BP. More studies of the effects of different modes of exercise on central BP are necessary to identify the importance of the reductions in central BP.

We found that the effect of IRT on office SBP and DBP in older adults and on central DBP for the entire sample had nonsignificant heterogeneity, increasing our confidence in these findings, although it must be acknowledged that these analyses were conducted post hoc. These findings are clinically important, as older adults and those with hypertension are at a higher cardiovascular risk and therefore have more to gain from interventions that lower BP, such as IRT [75]. However, heterogeneity was significant for all of the other analyses, and we were unable to fully explain this heterogeneity.

There have been several reviews of IRT for lowering BP, but only one [5] has evaluated the quality of the evidence using GRADE. Our findings of low (central DBP) and very low-quality evidence (central SBP, ambulatory and office BP) indicate that the true effect of IRT may vary from that presented in this review. Future trials should aim to reduce the risk of bias by blinding participants and outcome assessors, conducting intention-to-treat analyses, concealing allocation, and reducing selective reporting to strengthen confidence in the evidence from such trials.

Further research

Our results demonstrate the safety of IRT within the typical prescription of handgrip exercise for 4 × 2 min holds at 30% maximal voluntary contraction. However, the effectiveness and safety of other modes and doses of IRT are unclear. Thus, future research should explore different prescriptive parameters (dose and intensity) in different populations (e.g., grade 2 hypertension, men, and women) to enhance the generalizability of the findings. For researchers and clinicians to continue to report that IRT is safe and effective, studies must report adverse events, even if to simply state there were none. Only 3 of the 24 studies included in this review used isometric leg exercise training, despite slightly greater reductions in SBP, so this is another area that requires further study. Isometric leg exercise (e.g., a wall sit) is particularly appealing, as it can be done with no equipment, and its intensity can be easily modified by changing the depth of the wall sit, thereby making it accessible to a wide range of participants.

The mechanisms of IRT antihypertensive effects remain elusive [76] and were out of the scope of this review to investigate, although this is an important area of inquiry in the future. Several hypotheses of mechanisms have been proposed, including changes in cardiac autonomic regulation [77], neural regulation of vagal tone [78], vascular adaptations, and oxidative stress [79], although there is no strong evidence for any of these, with trials inadequately powered to identify mechanistic mediators of the antihypertensive effect [76]. Future research should seek to identify the mechanistic pathways by which IRT reduces BP.

The antihypertensive effects of exercise and medication have seldom been compared in a single trial [4], but this was done recently [68]. In their study, Ahmed et al. compared antihypertensive therapy to IRT and antihypertensive therapy in postmenopausal women with hypertension. They found an additive effect of IRT and antihypertensive therapy on reducing SBP (–19 mmHg) and DBP (–15 mmHg) compared to medication alone (SBP: –13 mmHg; DBP: –9 mmHg). Further research into concurrent medication and exercise, including IRT, could assist in the investigation of the mechanisms (due to the potential shared mechanistic targets) and potentially increase the antihypertensive effects of therapy. Thus, replicates of the above study with different medications and exercise interventions in larger, more diverse samples would be useful. Ahmed et al. provide evidence of a more multidisciplinary approach to lowering BP, which is crucial in reducing the global burden of elevated BP. Too frequently, exercise is advertised as an alternative to medication, but little is known about the additive effect of exercise and medical therapy. This may be an interesting focus of future research. Furthermore, medication adherence is important to measure in future trials to ensure that reductions in BP are produced by IRT rather than improved medication adherence resulting from the Hawthorne effect [80].

Limitations

There were several limitations of this review. All included trials were at a high risk of bias, downgrading the quality of

the evidence. The predominant domains that placed the trials at high risk of bias were blinding of the participants and personnel and selective reporting. While these limitations are common in exercise trials [81], they must be addressed in future trials to enhance the quality of evidence. Indeed, innovative methods have been developed to successfully blind participants and personnel to IRT intervention allocation [66], which could be considered in future trials of IRT. We did not investigate any sex differences in response to IRT, as previous research suggests that there is no difference [7].

Perspectives

High BP, a global health concern, is not being addressed adequately [2]. We have shown that IRT appears safe and leads to potentially clinically meaningful reductions in office and central SBP and DBP, especially among older adults. However, the quality of evidence was rated as low (central BP) and very low (office and ambulatory BP), so the true effects may vary. Until higher-quality evidence demonstrates IRT to be equivalent or superior to other modes of exercise or medication and at least as safe, IRT may be recommended as an adjunct treatment for those with high-normal BP or grade 1 hypertension. However, more high-quality research needs to be conducted to increase confidence in the effects demonstrated in this review.

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Author contributions All authors contributed to the protocol. HJH conducted searches, screening and extraction, analysed the data and drafted the initial manuscript. BJP helped conceive the study, provided valuable clinical expertise. MAW designed the meta-analytic code, assisted with screening and extraction as well as providing valuable methodological expertise. KAM assisted with data extraction and provided clinical expertise. NAS and AES provided valuable content expertise and assistance throughout the project. MDJ conceived the study, helped conduct searches, screening and extraction, provided methodological expertise and assisted in drafting the manuscript. All authors provided valuable input when analysing and interpreting the results, approved the final manuscript and provided valuable input in the style and content.

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Compliance with ethical standards

Conflict of interest AES reports speaker honoraria from Takeda, Servier, Novartis, and Omron Healthcare and serves as a scientific advisory for Abbott. All other authors declare that they have no conflicts of interest.

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