SYSTEMATIC REVIEW AND META-ANALYSIS

Exercise Reduces Ambulatory Blood Pressure in Patients With Hypertension: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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BACKGROUND: Although exercise training reduces office blood pressure (BP), scarcer evidence is available on whether these benefits also apply to ambulatory blood pressure (ABP), which is a stronger predictor of cardiovascular disease and mortality. The present study aims to assess the effects of exercise training on ABP in patients with hypertension based on evidence from randomized controlled trials.

METHODS AND RESULTS: A systematic search of randomized controlled trials on the aforementioned topic was conducted in PubMed and Scopus (since inception to April 1, 2020). The mean difference between interventions (along with 95% CI) for systolic BP and diastolic BP was assessed using a random-effects model. Sub-analyses were performed attending to (1) whether participants were taking antihypertensive drugs and (2) exercise modalities. Fifteen studies (including 910 participants with hypertension) met the inclusion criteria. Interventions lasted 8 to 24 weeks (3–5 sessions/week). Exercise significantly reduced 24-hour (systolic BP, –5.4 mm Hg; [95% CI, –9.2 to –1.6]; diastolic BP, –3.0 mm Hg [–5.4 to –0.6]), daytime (systolic BP, –4.5 mm Hg [–6.6 to –2.3]; diastolic BP, –3.2 mm Hg [–4.8 to –1.5]), and nighttime ABP (systolic BP, –4.7 mm Hg [–8.4 to –1.0]; diastolic BP, –3.1 mm Hg [–5.3 to –0.9]). In separate analyses, exercise benefits on all ABP measures were significant for patients taking medication (all *P*<0.05) but not for untreated patients (although differences between medicated and non-medicated patients were not significant), and only aerobic exercise provided significant benefits (*P*<0.05).

CONCLUSIONS: Aerobic exercise is an effective coadjuvant treatment for reducing ABP in medicated patients with hypertension.

Key Words: blood pressure ■ cardiovascular risk ■ hypertension ■ physical activity

H ypertension is the major cause of premature death worldwide, which is associated with an estimated global direct medical cost of $370 billion/year.[1] This condition has been traditionally identified by assessing blood pressure (BP) in a clinical setting (ie, office [or "clinic"] BP) and medical treatment adjusted accordingly. The 2017 American College of Cardiology/American Heart Association proposed office BP of ≥130/80 mm Hg as a new threshold for diagnosis of hypertension,[2] whereas the 2018 European Society of Cardiology/European Society of Hypertension maintained an office BP threshold of ≥140/90 mm Hg to define hypertension, similar to previous guidelines.[3] Yet, monitoring of BP at regular intervals during normal day life (ie, ambulatory BP [ABP]) has emerged as a stronger predictor of cardiovascular disease and mortality,[4–8] with threshold criteria to define hypertension based on

CLINICAL PERSPECTIVE

What Is New?

- Exercise interventions significantly reduce 24-hour ambulatory blood pressure in patients with hypertension, with decreases in both daytime and nighttime ambulatory blood pressure.

What Are the Clinical Implications?

- Aerobic exercise is an effective coadjuvant treatment for reducing ambulatory blood pressure in patients with hypertension.

Nonstandard Abbreviations and Acronyms

AIT	aerobic interval training
MICT	moderate-intensity continuous training
RT	resistance training

24-hour ABP set at 125/75 and 130/80 mm Hg in the United States[2] and European guidelines,[3] respectively. Particularly, an increased 24-hour and nighttime ABP is associated with a high cardiovascular disease risk[9]—even if office BP is apparently well controlled (ie, systolic BP [SBP]/diastolic BP [DBP] <130/80 mm Hg), leading to a prevalent and especially unfavorable hypertension phenotype, the so-called "masked uncontrolled hypertension".[10] For this reason, assessment of ABP rather than—or at least together with—office BP is currently proposed for the diagnosis and control of hypertension.[11,12]

Given the high prevalence and negative consequences of hypertension, strategies other than drug treatment are needed for the management of this condition. In this context, a main lifestyle intervention is physical exercise,[13] although unfortunately physical inactivity is reaching pandemic proportions.[14] Tailored exercise has been shown not only to reduce office BP in individuals with hypertension, but also to be as effective as most antihypertensive drugs for office BP reduction.[15,16] Furthermore, exercise has minimal side effects compared with drugs.[13,17] However, scarcer evidence is available on the effects of exercise on ABP. To the best of our knowledge, the largest meta-analysis to date on this topic (including 37 studies published until 2015)[18] assessed the pre-post effects of exercise training. Yet, there was no comparison with a control group, individuals with hypertension and normotension were assessed together, and some of the included studies combined an exercise intervention with a weight-loss diet. Moreover, although meta-analytical evidence supports the effectiveness of different exercise modalities (endurance ["aerobic"], resistance training [RT], or a combination thereof) to reduce office BP,[15,16] the evidence is also scarcer on their effects on ABP.

A recent meta-analysis including only 2 studies reported that aerobic training significantly reduces ABP.[19] However, other studies not included in the aforementioned meta-analysis[19] have assessed the effects on ABP of aerobic,[20–31] RT,[21,23,26,32] or multi-component exercise training[24,28,33,34] and there is no meta-analytical evidence pooling the effects of these different exercise modalities based on evidence from randomized controlled trials (RCTs).

It was therefore the aim of this study to assess the effects of different modalities of exercise training on ABP in individuals with hypertension pooling evidence from RCTs.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request. The conduct and reporting of the current systematic review and meta-analysis conform to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (Figure S1).[35]

Data Sources and Search Strategies

Two authors (G.S.L. and P.L.V.) independently conducted a systematic search (first by title and abstract, and then by full-text) in the electronic databases PubMed and Scopus (with no restriction on initial date to April 1, 2020) using the following search strategy: (exercise OR "physical activity" OR training) AND ("ambulatory blood pressure" OR "ambulatory BP" OR "ambulatory SBP" OR "ambulatory DBP" OR "24-hour blood pressure" OR "24-hour BP" OR "24-h blood pressure" OR "24-h BP" OR "daytime blood pressure" OR "day-time blood pressure" OR "daytime BP"). The search was supplemented by a manual review of reference lists from relevant publications to find additional studies on the subject.[18,19,25,36–42]

Study Selection

Studies were eligible for inclusion if they met each of the following criteria: (1) RCT design; (2) participants aged ≥18 years; (3) included a physical exercise intervention; (4) all participants reported to be hypertensive and/or to be on antihypertensive medication; and (5) assessed ABP before and upon completion of the intervention. Studies were excluded if: (1) they assessed the acute—but not the chronic—effects of physical exercise on ABP; (2) had a cross-over design; and (3) the exercise intervention was combined

with a hypocaloric diet. The latter exclusion criterion was meant to avoid the confounding—and well-documented—BP-lowering effect of diet-induced weight loss per se.[13,43] No inclusion/exclusion criteria were set on the intensity or duration of exercise training sessions.

Data Extraction

Two reviewers (G.S.L. and P.L.V.) independently extracted the following data from each study: number of participants within each group, participants' and exercise intervention characteristics, end points, and results. Data were extracted as mean and SD. A specific software (WebPlotDigitizer 4.2, San Francisco, CA) was used to extract data when provided as a figure[22–24,33] and we contacted the authors of 1 study because the values could not be extracted from figures.[44]

Quality Assessment

Two authors (G.S.L. and P.L.V.) independently assessed the methodological quality of the included studies with the PEDro scale.[45] A 0 to 10 total score was determined by counting the number of criteria satisfied by each study. Study quality was rated as poor (PEDro score ≤3), fair (4–5), or high (>5). All studies were used for data synthesis independently of their methodological quality.

Statistical Analysis

A meta-analysis was performed to assess the mean difference in the change (post- minus pre-intervention data, in mm Hg) between the control and intervention groups along with 95% CI. Given the existing differences between studies in terms of participants' characteristics and exercise interventions (modality, intensity, or duration), as well as our intent to generalize the results beyond the included studies, a random effects model was used.[46] No information was available from any of the meta-analyzed studies for the correlation between pre- and post-intervention data. We therefore decided to use a conservative correlation Pearson coefficient (r) value of 0.7 between pre- and post-intervention data, which is lower than most average correlation coefficients reported for ABP reliability measures[47,48] (eg, 0.79 for 24-hour DBP and 0.82 for 24-hour SBP for both sexes in repeated-days measurements[48]). Sensitivity analyses with an r-value of 0.2 and 0.5 were then performed when a significant result was found to estimate the worst-case scenario. Egger test was used to determine the presence of publication bias, and the I^2 statistic was used to assess heterogeneity across studies. Sub-analyses were performed attending to (1) whether participants were on anti-hypertensive medication or not and (2) exercise modality. Meta-regression analyses were conducted using the random-effects model (method of moments) to assess the association between the magnitude of the effect (mm Hg) and the duration of studies (weeks). All statistical analyses were performed using the statistical software package Comprehensive Meta-analysis 2.0 (Biostat; Englewood, NJ) setting the level of significance at 0.05.

RESULTS

Study Characteristics

From the retrieved studies, 15 (including 910 participants) were included in the systematic review (Figure 1). All studies were conducted in patients with hypertension aged 45 to 70 years and with a weighted average 24-hour ABP of 132±4 (SBP) and 79±2 mm Hg (DBP) at baseline. In 11 studies[20,21,24,26,28–33,44] participants were taking antihypertensive drugs during the intervention, whereas in the other 4 studies[22,23,34,49] they had refrained from taking their usual medication before the start of the intervention (usual "washout" period before enrolling in the intervention of 2–6 weeks). The characteristics of the included studies are summarized in Table 1.

Exercise interventions lasted between 8 and 24 weeks and included 3 to 5 sessions per week (≈24–60 minutes per session). Exercise sessions were supervised in 13 studies,[22–24,26,28–34,44,49] 3 studies[26,28,32] included both supervised and non-supervised exercise, and 2 included only non-supervised exercise.[20,24] Different modalities of exercise were used, notably moderate-intensity continuous training[20–24,44,49] or aerobic interval training for aerobic exercise,[29–31,49] RT[21,23,26,32] (consisting of only isometric handgrip training in 2 studies),[26,32] or a combination of both aerobic and RT[24,28,33,34] (ie, multicomponent exercise training, which was performed on a heated [30°C–32°C] swimming pool in 1 study).[33] On the other hand, 7 studies[22,23,26,28,29,33,44] reported the adherence rate to the exercise interventions, which ranged from 61% to 100% (weighted average 81%).

No study reported any type of adverse event related to the exercise sessions (eg, no musculoskeletal injury or excessive hypertensive/hypotensive response).

Quality Assessment and Publication Bias

The quality of the included studies was overall fair (median PEDro score=4.8 [range, 4–6]; Table 2). Thirteen studies showed fair methodological quality,[20–24,26,28–34,44,49] and 2 were deemed to have a high quality.[20,26]
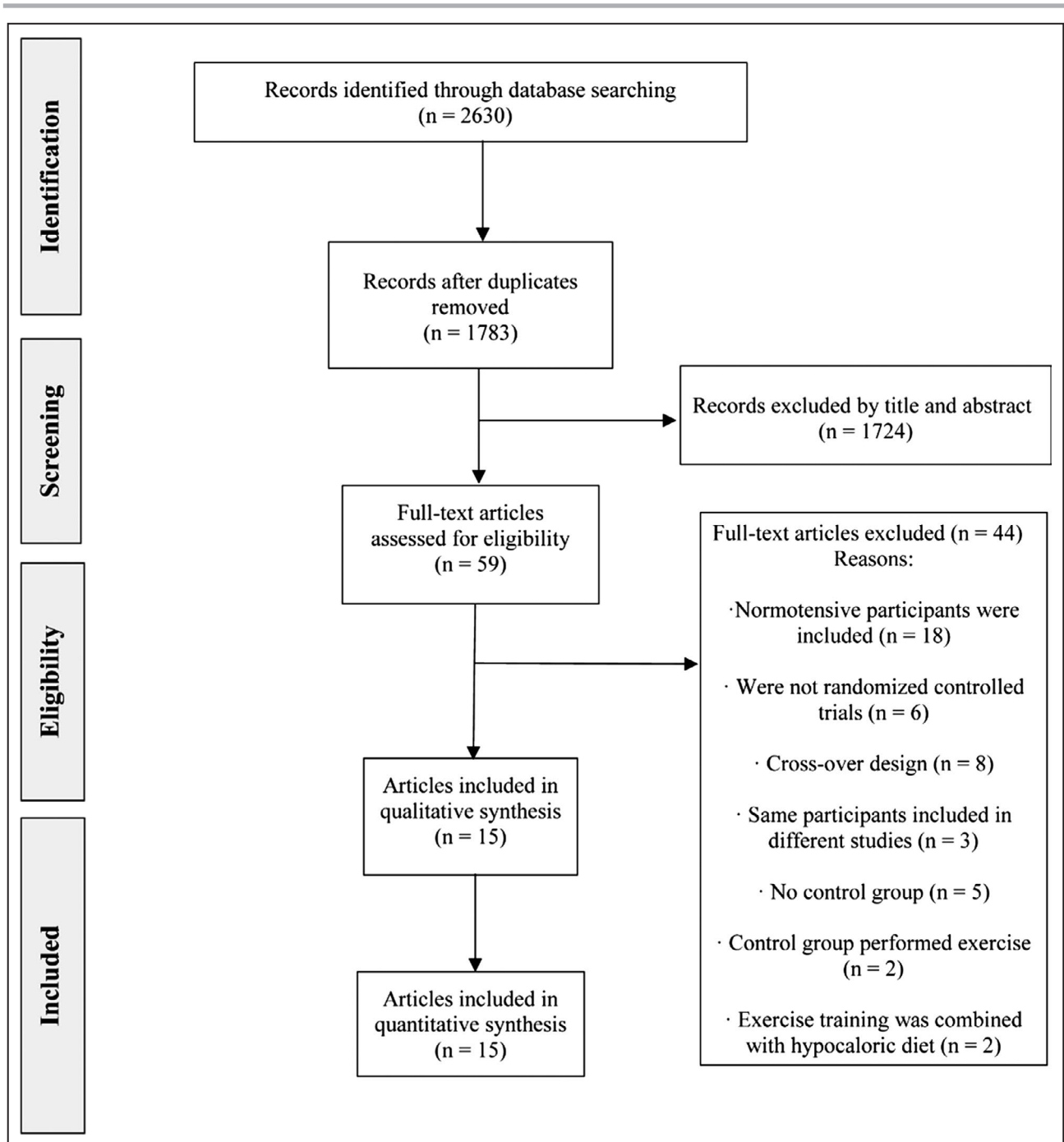
Figure 1. Flowchart of literature search.

Synthesis

The pooled effects of exercise interventions on ABP are summarized in Table 3. The pooled analysis of the 12 studies (n=582 participants) that assessed the effects of exercise on 24-hour ABP showed a significant reduction in both SBP and DBP (Figure 2).[†] No heterogeneity (I^2=0% for both) and no signs of publication

[†]References 20,21,23,24,26,28,30–34,44.

bias (P=0.231 and 0.319 for SBP and DBP, respectively) were observed, and the effect remained significant in sensitivity analyses ($P<0.05$).

Thirteen studies (n=711 participants) assessed the effects of exercise on daytime ABP, with pooled analysis showing a significant reduction in SBP and DBP (Figure 3).[21,23,24,26,28–33,44,49] A moderate heterogeneity was found for the effects on SBP (I^2=53.0%) but not on DBP (I^2=13.5%), and no sign

Table 1. Main Characteristics of the Included Studies

Study	Participants (Sample Size and Mean Age)	Exercise Intervention	Criteria to Define Hypertension	Antihypertensive Treatment	Main Effects on ABP
Barroso et al[34]	1. CT: n=24 (≈66 y) 2. CG: n=21 (≈70 y)	1. Modality: RT+MICT 2. Total duration: 6 mo 3. Frequency: 3 sessions/wk 4. Duration per session: 60 min 5. Intensity: 60%–75% of MHR 50%–60% of 1RM)	Office SBP/DBP ≥140/90 mm Hg after no drug treatment for ≥2 wk	No (drug washout before the study of 2 wk)	1. No significant changes in 24-h ABP
Bertani et al[21]	1. MICT: n=15 (≈67 y) 2. AIT: n=15 (≈68 y) 3. RT: n=16 (≈67 y) 4. CG: n=15 (≈66 y)	1. Modality: MICT, AIT, RT 2. Total duration: 12 wk 3. Frequency: 3 sessions/wk 4. Duration per session: MICT, 20 min. AIT, alternating high and low-intensity each 2 min for 20 min RT, 2 sets of 6–10 repetitions for 9 exercises 5. Intensity: MICT: 70% of MHR AIT: 60%–80% of MHR RT: 75% of 1RM	"Hypertensives taking medication" (no other specification)	Yes	1. No significant changes in 24-h ABP
Blumenthal et al[22]	ET: n=54 (≈46 y) CG: n=24 (≈47 y)	1. Modality: MICT 2. Total duration: 6 mo 3. Frequency: 3–4 times/wk 4. Duration per session: 35 min 5. Intensity: 70%–85% of HRR	"Unmedicated high normal BP" or stage 1–2 hypertension (mean office SBP 130–180 mm Hg and/or mean office DBP 85–110 mm Hg)	No (drug washout before the study for at least 6 wk)	1. Significant reduction in daytime SBP/DBP
Blumenthal et al[23]	ET: n=41 (≈54 y) RT+flexibility: n=35 (≈46 y) CG: n=23 (≈45 y)	1. Modality MICT; RT (weight circuit)+flexibility 2. Total duration: 4 mo 3. Frequency: 2–3 times/wk 4. Duration per session: 35–50 min 5. Intensity: 70% of VO₂max	Office SBP 140–180 mm Hg or office DBP 90–105 mm Hg	No (drug washout before the study of 4 wk)	1. No significant changes in daytime ABP
Brito et al[44]	ET: n=15 (≈51 y) MT: n=15 (≈49 y) CG: n=20 (≈50 y)	1. Modality: MICT (either in the morning [MT] or the evening [ET]) 2. Total duration: 10 wk 3. Frequency: 3 sessions/wk 4. Duration per session: 30–45 min 5. Intensity: increasing from ≈100% of anaerobic threshold to 90% of RCP	Office SBP <160 mm Hg and office DBP <105 mm Hg while receiving anti-hypertensive drugs for ≥4 mo	Yes	1. Significant reduction in 24-h and daytime DBP with ET, but not with MT
Dimeo et al[30]	1. AIT: n=24 (≈62 y) 2. CG: n=26 (≈67 y)	1. Modality: AIT 2. Total duration: 8–12 wk 3. Frequency: 3 sessions/wk 4. Duration per session: 30–36 min, including intervals of 3–15 min interspersed with 3-min walking intervals 5. Intensity: aerobic threshold	RH (ie, defined as office SBP/DBP ≥140/90 mm Hg in spite of concurrent use of 3 anti-hypertensive drugs of different classes or a BP that is controlled with ≥4 anti-hypertensive drugs)	Yes	1. AIT reduced daytime and 24-h SBP/DBP 2. The effects on nighttime SBP and DBP did not reach statistical significance
Farah et al[26]	1. Home-based IT: n=24 2. Supervised IT: n=24 3. CG: n=24 Age range, ≈58–61 y	1. Modality: RT (handgrip exercise) 2. Total duration: 12 wk 3. Frequency: 3 sessions/wk 4. Duration per session: four 2-min contractions interspersed with 1-min rests 5. Intensity: 30% of MVC	"Use of anti-hypertensive medications"	Yes	1. No significant changes in ABP
Guimaraes et al[33]	1. CT: n=16 (≈55 y) 2. CG: n=16 (≈52 y)	1. Modality: CT (callisthenic exercises+walking in a heated [30°C–32°C] swimming pool 2. Total duration: 12 wk 3. Frequency: 3 sessions/wk 4. Duration per session: 50 min 5. Intensity: 11–13 Borg Scale	RH for >5 y with unchanged or regular use of 3 anti-hypertensive drugs in the past 3 mo, with an office SBP/DBP ≥140/90 mm Hg	Yes	1. CT reduced 24-h, daytime, and nighttime SBP/DBP
Guimaraes et al[28]	1. CT+AIT: n=26 2. CT+MICT: n=26 3. CG: n=13 Age range, ≈45–50 y	1. Modality: CT (MICT or AIT+RT) 2. Total duration: 16 wk 3. Frequency: 3 sessions/wk 4. Duration per session: 60 min (40 min of aerobic training+20 min of RT) 5. Intensity: MICT, 60% of HRR AIT: alternating 2 min at 50% and 1 min at 80% of HRR RT: submaximal strength training	Hypertensive subjects on anti-hypertensive medication with "controlled" office BP (SBP <140 mm Hg and DBP <90 mm Hg)	Yes	1. No significant changes in ABP

Table 1.   Continued

Study	Participants (Sample Size and Mean Age)	Exercise Intervention	Criteria to Define Hypertension	Antihypertensive Treatment	Main Effects on ABP
Lima et al[24]	1. MICT: n=15 2. CT: n=15 3. CG: n=14 Age range, ≈67–69 y	1. Modality: MICT (treadmill). CT (MICT+RT) 2. Total duration: 10 wk 3. Frequency: 3 sessions/wk 4. Duration per session: MICT=20–30 min; CT=same as MICT plus 9 RT exercises (15–20 repetitions, with 1-min rests). 5. Intensity: MICT (NS); RT=50–60% of 1RM	People regularly using anti-hypertensive medication (hydrochlorothiazide, ACE inhibitors or ARB), with office SBP <160 mm Hg and office DBP <105 mm Hg)	Yes	1. MICT and CT had a similar significant lowering effect on 24-h, daytime, and nighttime SBP/DBP
Molmen - Hansen et al[49]	1. HIIT: n=31 (≈52 y) 2. MICT: n=28 (≈53 y) 3. CG: n=29 (≈51 y)	1. Modality: AIT, MICT 2. Total duration: 12 wk 3. Frequency: 3 sessions/wk 4. Duration per session: MICT (47 min/session). AIT (37 min/session) 5. Intensity: MICT (70% of MHR). AIT 4×4 min intervals 85%–90% of MHR, with 3 min at 60%–70% of MHR	Essential hypertension stage 1–2, defined as office SBP 140–179 mm Hg and/or office DBP 90–109 mm Hg	No (drug washout before the study of 4 wk)	1. All training groups showed reductions in 24-h BP 2. Daytime SBP/DBP was reduced in both training groups 3. Nighttime SBP/DBP was reduced in HIIT group
Motlagh et al[20]	1. MICT: n=39 (≈54 y) 2. CG: n=39 (≈53 y)	1. Modality: MICT 2. Total duration: 12 wk 3. Frequency: 5 sessions/wk 4. Duration per session: 30 min 5. Intensity: 40%–60% of MHR	Diagnosed with primary hypertension, with an office SBP <170 mm Hg and taking ≥1 anti-hypertensive medication	Yes	1. MICT reduced 24-h SBP and DBP
Pagonas et al[29]	1. AIT: n=36 (≈65 y) 2. CG: n=36 (≈67 y)	1. Modality: AIT 2. Total duration: 8- to 12-wk 3. Frequency: 3 sessions/wk 4. Duration per session: 30–36 min including intervals of varying duration 5. Intensity: aerobic threshold	Patients under anti-hypertension treatment with ≥1 anti-hypertensive drug and/or office SBP/DBP ≥140/90 mm Hg	Yes	1. AIT reduced daytime SBP and DBP 2. No effects on nighttime SBP or DBP
Stiller-Moldovan et al[32]	1. RT: n=13 2. CG: n=12 Age range, ≈60–62 y	1. Modality: RT (handgrip exercise) 2. Total duration: 8 wk 3. Frequency: 3 sessions/wk 4. Duration per session: four 2-min contractions interspersed with 1-min rests 5. Intensity: 30% of MVC	Individuals medicated for hypertension for ≥4 mo	Yes	1. No significant changes in ABP
Westhoff et al[31]	1. AIT: n=24 (≈67 y) 2. CG: n=27 (≈68 y)	1. Modality: AIT 2. Total duration: 12 wk 3. Frequency: 3 sessions/wk 4. Duration per session: 30–36 min including intervals of varying duration 5. Intensity: aerobic threshold	Current anti-hypertension treatment, ambulatory DBP ≤90 mm Hg	Yes	1. AIT reduced 24-h SBP and DBP 2. AIT reduced daytime and nighttime SBP/DBP

1RM indicates one maximum repetition; ABP, ambulatory blood pressure; ACE, angiotensin-converting enzyme; AIT, aerobic interval training; ARB, angiotensin receptor blockers; BP, blood pressure; CG, control group; CT, combined training; DBP, diastolic blood pressure; ET, evening training; HIIT, high-intensity interval training; HRR, heart rate reserve; IT, isometric handgrip training; MT, morning training; MHR, maximum heart rate; MICT, moderate-intensity continuous training; MVC, maximal voluntary contraction; RCP, respiratory compensation point; RH, resistant hypertension; RHR, reserve heart rate; RT, resistance training; SBP, systolic blood pressure; and VO$_2$max, maximal oxygen uptake.

of publication bias was observed for any of these 2 measures (P=0.072 and 0.156, respectively). The effect remained significant in sensitivity analyses (P<0.05).

Eleven studies (n=587 participants) assessed exercise training effects on nighttime ABP, with pooled analysis indicating a significant reduction in SBP and DBP (Figure 4).[21,24,26,28–33,44,49] There was no sign of heterogeneity (I^2=0% for both measures) or publication bias (P=0.221 and 0.110 for SBP and DBP, respectively), and effects remained significant in sensitivity analyses (P<0.05).

Exercise benefits on 24-hour, daytime and nighttime ABP were significant in separate analyses of patients on medication during the study,[20,21,24,26,28–33,44] but not of those who were untreated (Table 3).[22,23,34,49] However, differences between medicated and non-medicated patients did not reach statistical significance for any of the ABP measures (24 hour SBP: 2.97 mm Hg, 95% CI −7.75 to 13.69, P=0.587; 24 hour DBP: 0.99 mm Hg, 95% CI −5.77 to 7.75, P=0.774; daytime SBP: −0.83 mm Hg, 95% CI −5.82 to 4.16, P=0.746; daytime DBP: −0.54 mm Hg, 95% CI −4.31 to 3.23, P=0.779; nighttime SBP: −5.27 mm Hg, 95% CI −17.21 to 6.67, P=0.387; nighttime DBP: −0.53 mm Hg, 95% CI −1.48 to 0.42, P=0.484). Regarding the studies in untreated patients, 2 studies[22,49] found significant benefits on daytime ABP, of which one[49] also reported significant benefits for both

Table 2. Methodological Quality of the Included Studies

Study	1	2	3	4	5	6	7	8	9	10	11	Total Score*
Barroso et al[34]	+	+	−	+	−	−	−	+	−	+	+	5
Bertani et al[21]	+	+	−	−	−	−	−	+	−	+	+	4
Blumenthal et al[22]	+	+	−	+	−	−	−	−	+	+	+	5
Blumenthal et al[23]	+	+	−	+	−	−	−	+	−	+	+	5
Brito et al[44]	+	+	−	+	−	−	−	+	−	+	+	5
Dimeo et al[30]	+	+	−	+	−	−	−	+	−	+	+	5
Farah et al[26]	+	+	+	+	−	−	+	−	−	+	+	6
Guimaraes et al[33]	+	+	−	+	−	−	+	−	−	+	+	5
Guimaraes et al[28]	+	+	−	+	−	−	+	−	−	+	+	5
Lima et al[24]	+	+	−	+	−	−	−	+	−	+	+	5
Molmen-Hansen et al[49]	+	+	−	+	−	−	−	−	−	+	+	4
Motlagh et al[20]	+	+	+	+	−	−	−	−	+	+	+	6
Pagonas et al[29]	+	+	−	+	−	−	−	+	−	+	+	5
Stiller-Moldovan et al[32]	+	+	+	+	−	−	−	−	−	−	+	4
Westhoff et al[31]	+	+	−	−	−	−	−	+	−	+	+	4

Column numbers correspond to the following criteria on the PEDro scale: (1) eligibility criteria were specified; (2) subjects were randomly allocated to groups; (3) allocation was concealed; (4) groups were similar at baseline; (5) subjects were blinded; (6) therapists who administered the treatment were blinded; (7) assessors were blinded; (8) measures of key outcomes were obtained from >85% of subjects; (9) data were analyzed by intention to treat; (10) statistical comparisons between groups were conducted; (11) point measures and measures of variability were provided.

*Total score from item 2.

nighttime and 24-hour ABP. However, the remaining 2 studies found no benefits on any ABP marker.[23,34]

Exercise benefits on all ABP measures could be separately confirmed for aerobic exercise,[20–24,29–31,44,49] whereas no significant benefits were observed for RT interventions combining both handgrip strength and whole-body (or "large muscle mass") exercises,[21,23,26,32] or multicomponent training[24,28,33,34] on any ABP measure (Table 4). When separately analyzing the 2 studies[26,32] (3 interventions in total) that included only isometric handgrip exercise, no differences were found for any ABP measure (all $P>0.05$, Table 4). The same result was found when separately analyzing the 2 studies[21,23] that assessed the effects of whole-body RT on daytime ABP ($P>0.05$). Two of the four studies that included a multicomponent training intervention reported benefits on at least one ABP measure.[24,33]

Meta-regression analyses showed no consistent association between the magnitude of the effect and the duration of exercise intervention. Thus, a direct association was found between intervention duration and magnitude of the reduction in daytime SBP (−0.2 mm Hg per each additional week of exercise, 95% CI, −0.3 to −0.1; $P<0.001$) but an inverse association was found for the reduction of nighttime SBP (+1.2 mm Hg per week, 95% CI, 0.4–1.9; $P=0.002$) and DBP (+0.6 mm Hg per week, 95% CI, 0.0–1.1; $P=0.047$). No association was found for the remainder of ABP measures.

DISCUSSION

This systematic review and meta-analysis of RCTs found that exercise training interventions result in significant reductions in 24-hour (−5.4 and −3.0 mm Hg for SBP and DBP, respectively), daytime (−4.5 and −3.2 mm Hg), and nighttime ABP (−4.7 and −3.1 mm Hg) among individuals with hypertension. In turn, aerobic exercise appeared as an effective training modality for reducing ABP, whereas RT and multicomponent training showed no overall benefits.

Previous evidence has indicated an overall beneficial effect of exercise training on ABP.[18,19,25,36–38,40–42] For instance, a meta-analysis including both individuals with hypertension and normotension found that physical exercise reduces daytime ($\approx$ −3.3 mm Hg) but not nighttime ABP.[40] Another meta-analysis reported a significant reduction of daytime ($\approx$ −3.2 mm Hg) but not in nighttime ABP when analyzing both individuals with normotension and hypertension, and this effect remained significant in separate analyses for individuals with hypertension only ($\approx$ −3.8 mm Hg).[25] In turn, and in agreement with other studies,[18] the present results suggest that exercise training reduces both daytime and nighttime ABP.

To our knowledge, this is the first meta-analysis that assesses the effects of exercise interventions separately in individuals with hypertension and pooling the results of RCTs, with the latter considered

Table 3.   Summary of Pooled Results

Condition	Studies (Participants)	Outcome	Mean Difference (mm Hg , 95% CI)	P Value
24-h ABP				
Overall	12 (n=582)	SBP	−5.4 (−9.3 to −1.5)	0.006*
		DBP	−3.0 (−5.4 to −0.6)	0.015*
Medicated patients	10 (n=474)	SBP	−4.9 (−9.1 to −0.7)	0.022*
		DBP	−2.8 (−5.5 to −0.1)	0.039*
Non-medicated patients	2 (n=108)	SBP	−7.9 (−17.8 to 2.0)	0.117
		DBP	−3.8 (−10.0 to 2.4)	0.230
Daytime ABP				
Overall	13 (n=711)	SBP	−4.5 (−6.6 to −2.3)	<0.001*
		DBP	−3.2 (−4.8 to −1.5)	<0.001*
Medicated patients	10 (n=468)	SBP	−4.7 (−7.3 to −2.1)	<0.001*
		DBP	−3.3 (−5.3 to −1.3)	0.001*
Non-medicated patients	3 (n=243)	SBP	−3.9 (−8.2 to 0.4)	0.075
		DBP	−2.8 (−6.0 to 0.5)	0.094
Nighttime ABP				
Overall	11 (n=587)	SBP	−4.7 (−8.4 to −1.0)	0.013*
		DBP	−3.1 (−5.3 to −0.9)	0.007*
Medicated patients	10 (n=514)	SBP	−5.2 (−9.2 to −1.3)	0.009*
		DBP	−3.4 (−5.8 to −1.0)	0.005*
Non-medicated patients	1 (n=73)	SBP	0.0 (−11.3 to 11.3)	0.997
		DBP	0.8 (−7.6 to 6.0)	0.818

Mean difference is expressed in mm Hg. ABP indicates ambulatory blood pressure; DBP, diastolic blood pressure; and SBP, systolic blood pressure.
*Significant difference for the comparison between control and exercise groups ($P < 0.05$).

the greatest level of evidence. The present findings are clinically important, particularly given the role of ABP—beyond office BP—as a predictor of cardiovascular disease and mortality.[4–8] Specially relevant are the effects of exercise training on nighttime ABP, with the latter being a better predictor of adverse events in patients with hypertension than daytime ABP.[50] It must also be highlighted that office BP reductions of lower magnitude (−4.9 and −2.8 mm Hg for SBP and DBP, respectively) than those observed here for 24-hour ABP have proven to reduce the risk of stroke and coronary heart disease.[51] In this regard, office BP usually tends to be higher than ABP, and thus the reductions we observed for ABP might correspond with larger reductions of office BP—for instance, in SPRINT (Systolic Blood Pressure Intervention Trial) an intensive medical treatment induced larger reductions in office (−16.0 mm Hg) than in 24-hour SBP (−11.2 mm Hg).[52]

Some controversy exists on whether lifestyle interventions, notably exercise, could be used as a surrogate of pharmacological treatment in patients with hypertension. The European guidelines[3] recommend an optimal lifestyle (including regular exercise) as the only treatment needed for people with grade 1 (mild)—but not for grade 2 or 3—hypertension during the first 3 to 6 months after diagnosis, with

pharmacological treatment added after this period if hypertension is not well controlled. Supporting this recommendation, a recent network meta-analysis concluded that exercise interventions might induce the same lowering effect on office BP—ABP was not assessed—as most anti-hypertensive drugs[15] in patients with hypertension, although the included studies did not directly compare the effects of exercise versus drugs. On the other hand, the reason why in our separate analyses exercise appeared to be effective to decrease ABP in patients on medication but not in their untreated peers might be explained, at least partly, by the relative short duration of most interventions in the latter (ie, consistently ≤6 months)[22,23,34,49] as well as the moderate intensity of the aerobic exercise sessions (ie, usually moderate-intensity continuous training, except for one study[49] using more intense workouts [aerobic interval training]). Further research is thus needed to determine whether longer or more intense aerobic exercise interventions can have a stronger anti-hypertensive effect in the absence of medication. In any case, no significant differences were found between medicated and non-medicated patients for each of the different ABP measures. Studies comparing exercise effects on the 2 types of patients might allow to draw more definite conclusions based on medication status.
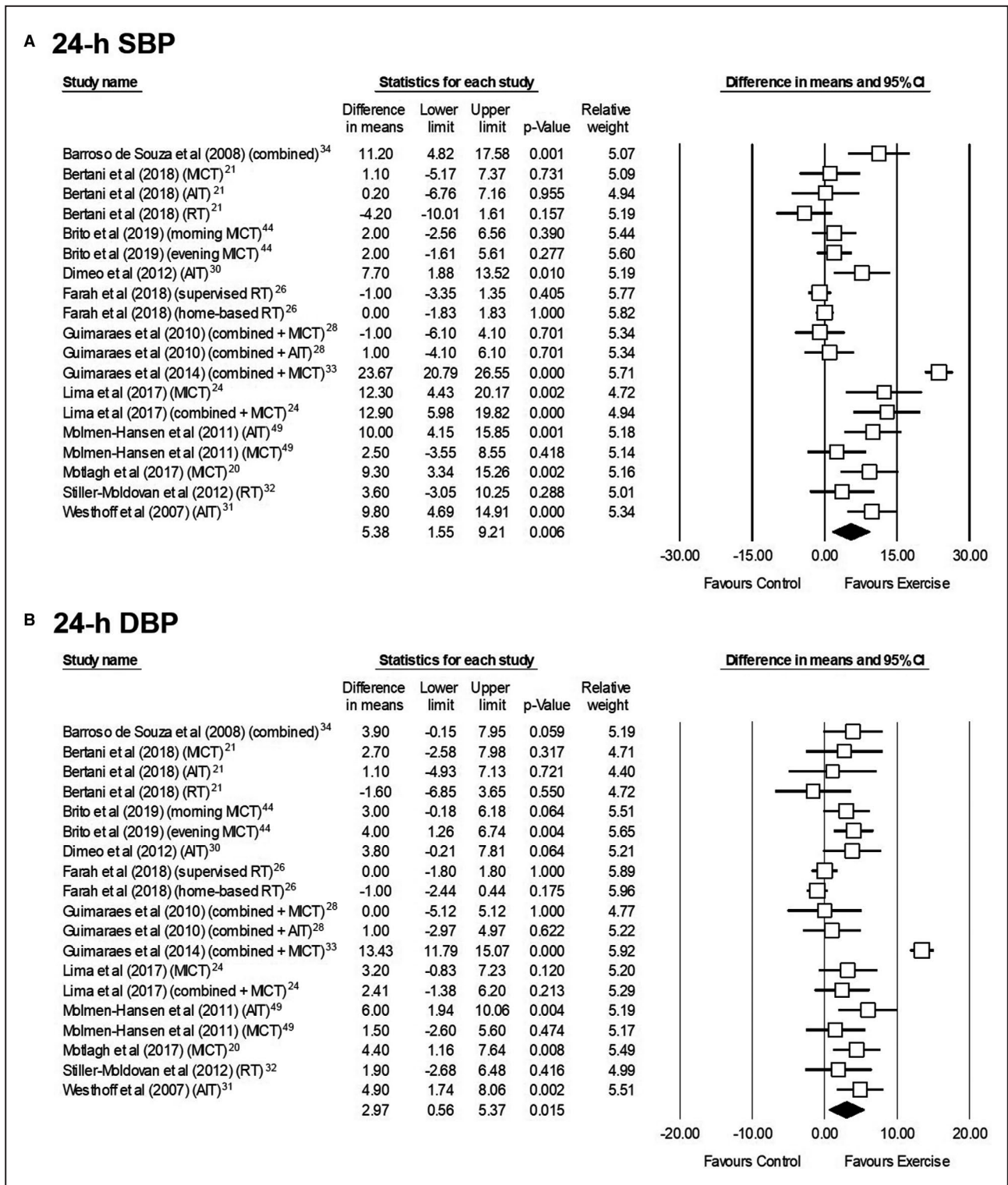
Figure 2. Effects of exercise interventions on 24-hour ambulatory systolic (A) and diastolic ambulatory blood pressure (B) in individuals with hypertension.
AIT indicates aerobic interval training; DBP, diastolic blood pressure; MICT, moderate-intensity continuous training; RT, resistance training; and SBP, systolic blood pressure.

Another major novelty of the present study is the analysis of the effects on ABP of different exercise modalities. Although aerobic exercise is commonly recommended as a first-line antihypertensive lifestyle therapy, dynamic RT or the combination of both aerobic and RT exercise have been reported

A Daytime SBP

Study name	Difference in means	Lower limit	Upper limit	p-Value	Relative weight
Bertani et al (2018) (MCT)[21]	-1.50	-8.19	5.19	0.660	3.87
Bertani et al (2018) (AIT)[21]	-1.90	-9.02	5.22	0.601	3.69
Bertani et al (2018) (RT)[21]	-7.30	-13.53	-1.07	0.022	4.08
Blumenthal et al (1991) (MCT)[23]	-1.10	-1.75	-0.45	0.001	6.17
Blumenthal et al (1991) (RT)[23]	2.00	1.35	2.65	0.000	6.17
Blumenthal et al (2000) (MCT)[22]	4.30	3.41	5.19	0.000	6.14
Brito et al (2019) (morning MCT)[44]	5.00	0.23	9.77	0.040	4.75
Brito et al (2019) (evening MICT)[44]	4.00	0.56	7.44	0.023	5.36
Dimeo et al (2012) (AIT)[30]	9.00	3.25	14.75	0.002	4.30
Farah et al (2018) (home-based RT)[26]	-4.00	-5.83	-2.17	0.000	5.94
Farah et al (2018) (supervised RT)[26]	-1.00	-3.35	1.35	0.405	5.78
Guimaraes et al (2010) (combined + MCT)[28]	1.00	-4.56	6.56	0.724	4.38
Guimaraes et al (2010) (combined + AIT)[28]	2.00	-3.35	7.35	0.464	4.48
Guimaraes et al (2014) (combined + MCT)[33]	25.78	22.41	29.15	0.000	5.39
Lima et al (2017) (Combined + MCT)[24]	12.50	6.38	18.62	0.000	4.13
Lima et al (2017) (MICT)[24]	9.80	2.59	17.01	0.008	3.65
Molmen-Hansen et al (2011) (AIT)[49]	12.50	6.59	18.41	0.000	4.22
Molmen-Hansen et al (2011) (MICT)[49]	4.50	-1.60	10.60	0.148	4.14
Pagonas et al (2014) (AIT)[29]	7.30	2.98	11.62	0.001	4.96
Stiller-Moldovan et al (2012) (RT)[32]	3.40	-3.41	10.21	0.328	3.82
Westhoff et al (2007) (AIT)[31]	9.60	4.44	14.76	0.000	4.57
	4.48	2.33	6.63	0.000	

Difference in means and 95% CI: scale from -30.00 to 30.00. Favours Control / Favours Exercise.

B Daytime DBP

Study name	Difference in means	Lower limit	Upper limit	p-Value	Relative weight
Bertani et al (2018) (MCT)[21]	0.60	-4.98	6.18	0.833	3.58
Bertani et al (2018) (AIT)[21]	-0.10	-6.29	6.09	0.975	3.26
Bertani et al (2018) (RT)[21]	-4.00	-9.67	1.67	0.167	3.52
Blumenthal et al (1991) (MCT)[23]	0.00	-0.69	0.69	1.000	6.02
Blumenthal et al (1991) (RT)[23]	1.80	1.14	2.46	0.000	6.03
Blumenthal et al (2000) (MCT)[22]	3.40	2.61	4.19	0.000	6.00
Brito et al (2019) (morning MCT)[44]	5.00	1.57	8.43	0.004	4.81
Brito et al (2019) (evening MICT)[44]	4.00	1.18	6.82	0.006	5.16
Dimeo et al (2012) (AIT)[30]	4.50	0.41	8.59	0.031	4.42
Farah et al (2018) (home-based RT)[26]	-2.00	-3.44	-0.56	0.007	5.81
Farah et al (2018) (supervised RT)[26]	1.00	-0.80	2.80	0.275	5.67
Guimaraes et al (2010) (combined + MCT)[28]	2.00	-3.35	7.35	0.464	3.70
Guimaraes et al (2010) (combined + AIT)[28]	3.00	-1.37	7.37	0.178	4.25
Guimaraes et al (2014) (combined + MCT)[33]	16.13	14.19	18.07	0.000	5.61
Lima et al (2017) (Combined + MCT)[24]	2.30	-1.47	6.07	0.232	4.61
Lima et al (2017) (MICT)[24]	6.30	2.33	10.27	0.002	4.49
Molmen-Hansen et al (2011) (AIT)[49]	7.00	3.11	10.89	0.000	4.54
Molmen-Hansen et al (2011) (MICT)[49]	2.50	-1.13	6.13	0.176	4.69
Pagonas et al (2014) (AIT)[29]	3.80	0.96	6.64	0.009	5.15
Stiller-Moldovan et al (2012) (RT)[32]	0.60	-4.62	5.82	0.822	3.77
Westhoff et al (2007) (AIT)[31]	4.50	1.23	7.77	0.007	4.90
	3.15	1.50	4.79	0.000	

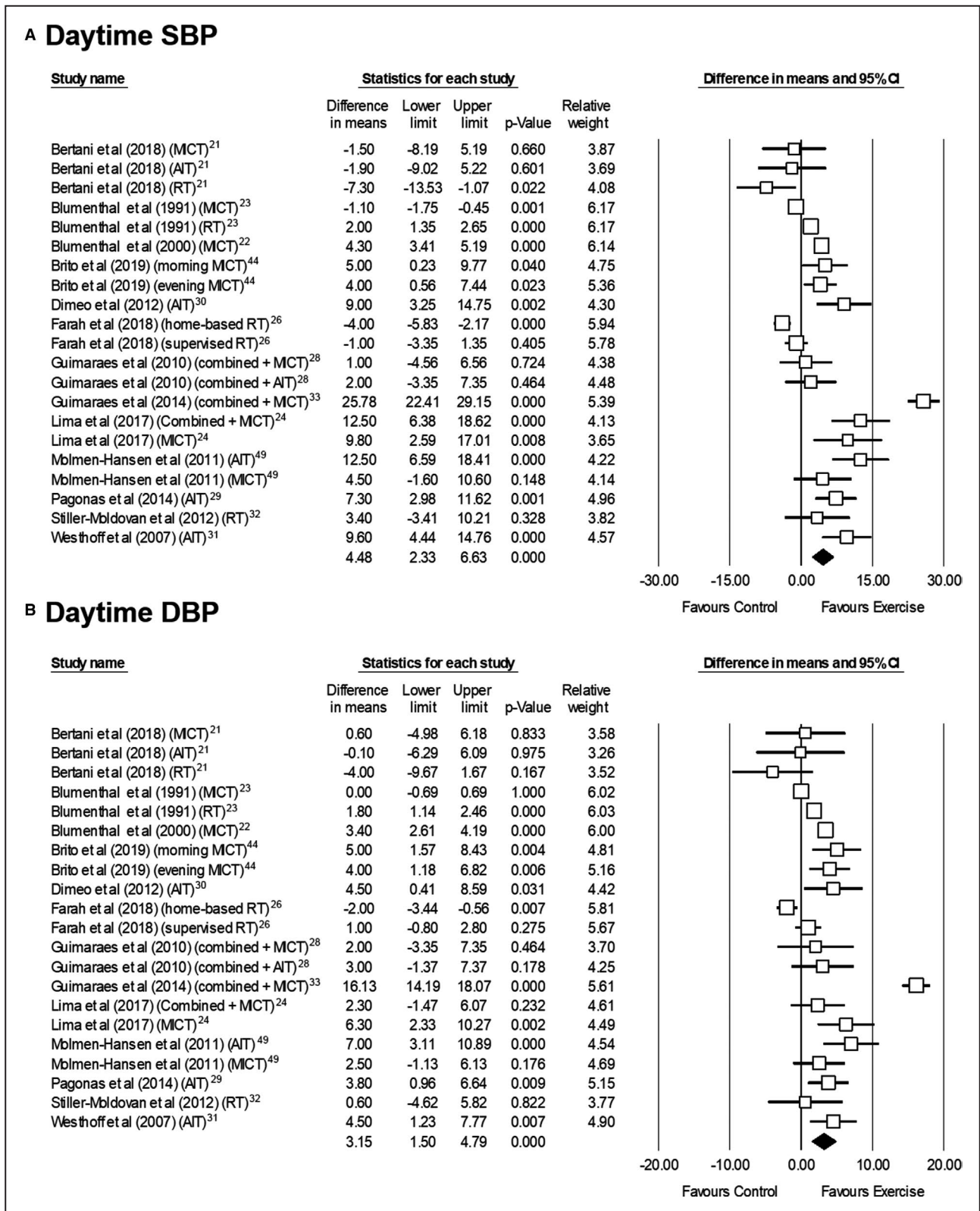Difference in means and 95% CI: scale from -20.00 to 20.00. Favours Control / Favours Exercise.

Figure 3. Effects of exercise interventions on daytime ambulatory systolic (A) and diastolic blood pressure (B) in individuals with hypertension.
AIT indicates aerobic interval training; DBP, diastolic blood pressure; MICT, moderate-intensity continuous training; RT, resistance training; and SBP, systolic blood pressure.
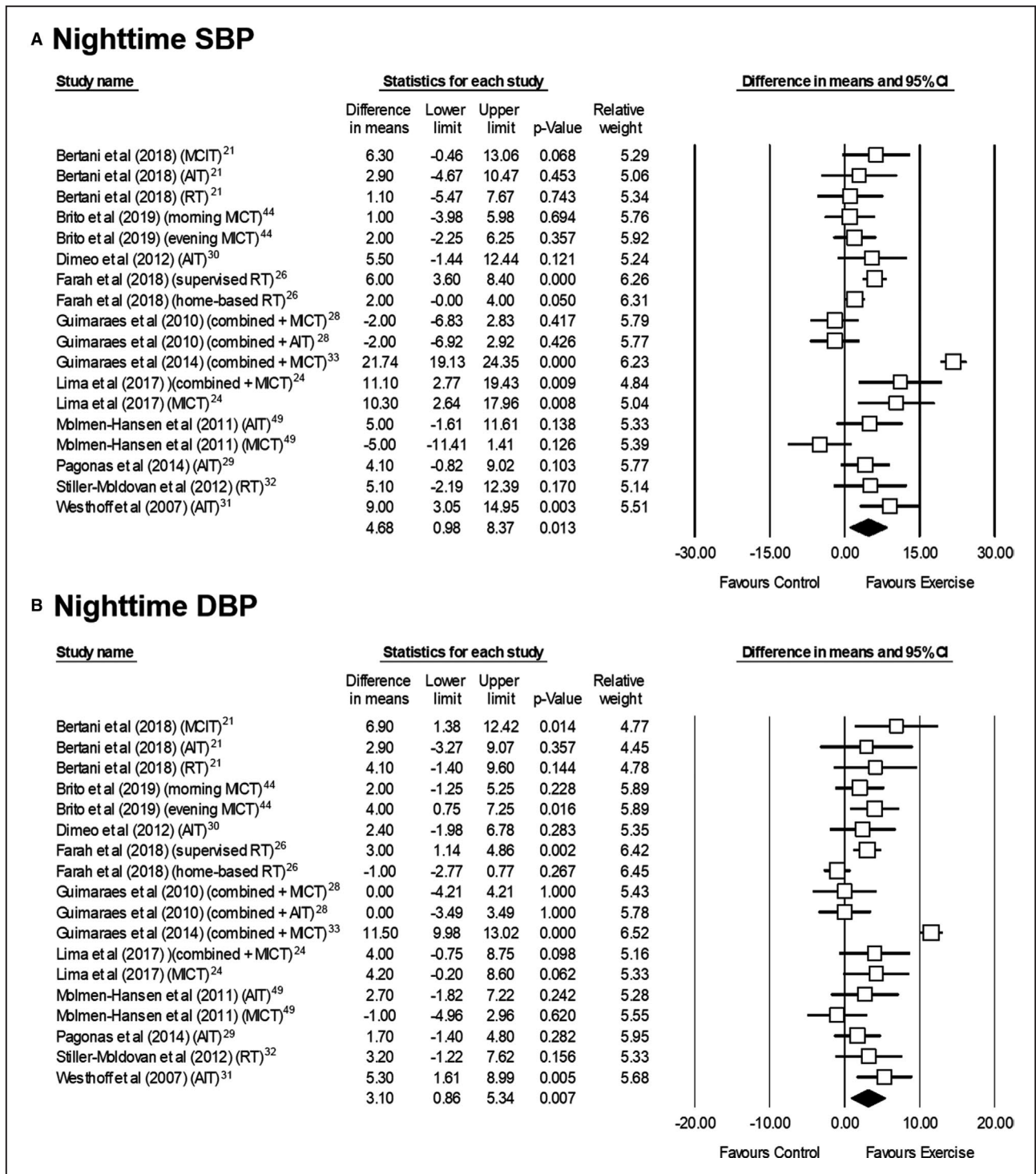
A Nighttime SBP

Study name	Difference in means	Lower limit	Upper limit	p-Value	Relative weight
Bertani et al (2018) (MCIT)[21]	6.30	-0.46	13.06	0.068	5.29
Bertani et al (2018) (AIT)[21]	2.90	-4.67	10.47	0.453	5.06
Bertani et al (2018) (RT)[21]	1.10	-5.47	7.67	0.743	5.34
Brito et al (2019) (morning MICT)[44]	1.00	-3.98	5.98	0.694	5.76
Brito et al (2019) (evening MICT)[44]	2.00	-2.25	6.25	0.357	5.92
Dimeo et al (2012) (AIT)[30]	5.50	-1.44	12.44	0.121	5.24
Farah et al (2018) (supervised RT)[26]	6.00	3.60	8.40	0.000	6.26
Farah et al (2018) (home-based RT)[26]	2.00	-0.00	4.00	0.050	6.31
Guimaraes et al (2010) (combined + MICT)[28]	-2.00	-6.83	2.83	0.417	5.79
Guimaraes et al (2010) (combined + AIT)[28]	-2.00	-6.92	2.92	0.426	5.77
Guimaraes et al (2014) (combined + MICT)[33]	21.74	19.13	24.35	0.000	6.23
Lima et al (2017))(combined + MICT)[24]	11.10	2.77	19.43	0.009	4.84
Lima et al (2017) (MICT)[24]	10.30	2.64	17.96	0.008	5.04
Molmen-Hansen et al (2011) (AIT)[49]	5.00	-1.61	11.61	0.138	5.33
Molmen-Hansen et al (2011) (MICT)[49]	-5.00	-11.41	1.41	0.126	5.39
Pagonas et al (2014) (AIT)[29]	4.10	-0.82	9.02	0.103	5.77
Stiller-Moldovan et al (2012) (RT)[32]	5.10	-2.19	12.39	0.170	5.14
Westhoff et al (2007) (AIT)[31]	9.00	3.05	14.95	0.003	5.51
	4.68	0.98	8.37	0.013	

B Nighttime DBP

Study name	Difference in means	Lower limit	Upper limit	p-Value	Relative weight
Bertani et al (2018) (MCIT)[21]	6.90	1.38	12.42	0.014	4.77
Bertani et al (2018) (AIT)[21]	2.90	-3.27	9.07	0.357	4.45
Bertani et al (2018) (RT)[21]	4.10	-1.40	9.60	0.144	4.78
Brito et al (2019) (morning MICT)[44]	2.00	-1.25	5.25	0.228	5.89
Brito et al (2019) (evening MICT)[44]	4.00	0.75	7.25	0.016	5.89
Dimeo et al (2012) (AIT)[30]	2.40	-1.98	6.78	0.283	5.35
Farah et al (2018) (supervised RT)[26]	3.00	1.14	4.86	0.002	6.42
Farah et al (2018) (home-based RT)[26]	-1.00	-2.77	0.77	0.267	6.45
Guimaraes et al (2010) (combined + MICT)[28]	0.00	-4.21	4.21	1.000	5.43
Guimaraes et al (2010) (combined + AIT)[28]	0.00	-3.49	3.49	1.000	5.78
Guimaraes et al (2014) (combined + MICT)[33]	11.50	9.98	13.02	0.000	6.52
Lima et al (2017))(combined + MICT)[24]	4.00	-0.75	8.75	0.098	5.16
Lima et al (2017) (MICT)[24]	4.20	-0.20	8.60	0.062	5.33
Molmen-Hansen et al (2011) (AIT)[49]	2.70	-1.82	7.22	0.242	5.28
Molmen-Hansen et al (2011) (MICT)[49]	-1.00	-4.96	2.96	0.620	5.55
Pagonas et al (2014) (AIT)[29]	1.70	-1.40	4.80	0.282	5.95
Stiller-Moldovan et al (2012) (RT)[32]	3.20	-1.22	7.62	0.156	5.33
Westhoff et al (2007) (AIT)[31]	5.30	1.61	8.99	0.005	5.68
	3.10	0.86	5.34	0.007	

Figure 4. Effects of exercise interventions on nighttime ambulatory systolic (A) and diastolic blood pressure (B) in individuals with hypertension.
AIT indicates aerobic interval training; DBP, diastolic blood pressure; MICT, moderate-intensity continuous training; RT, resistance training; and SBP, systolic blood pressure.

to elicit similar or even greater reductions in office BP.[16,18,53] In the present meta-analysis, however, only aerobic training showed benefits on all ABP measures, with no significance reached for RT or multicomponent training. In this regard, the numerous biological underpinnings of the exercise benefits on BP at the multisystemic level—loss of adiposity (especially visceral adiposity), increased insulin sensitivity, attenuated oxidative stress and inflammation with subsequent improvements in vascular endothelial

Table 4. Summary of Pooled Results for Each Exercise Modality

Exercise Type	Outcome	Studies (Participants)	Mean Difference (mm Hg, 95% CI)	P Value
24-h ABP				
Aerobic	SBP	7 (n=373)	−5.5 (−8.1 to −2.8)	<0.001*
	DBP		−3.8 (−4.9 to −2.6)	<0.001*
Resistance	SBP	3 (n=99)	0.5 (−1.1 to 2.1)	0.573
	DBP		0.5 (−0.6 to 1.6)	0.349
Handgrip	SBP	2 (n=68)	0.2 (−1.2 to 1.6)	0.784
	DBP		0.5 (−0.7 to 1.6)	0.421
Combined	SBP	4 (n=139)	−9.6 (−20.7 to 1.5)	0.091
	DBP		−4.3 (−10.8 to 2.2)	0.194
Daytime ABP				
Aerobic	SBP	9 (n=507)	−5.0 (−7.6 to −2.3)	<0.001*
	DBP		−3.5 (−5.1 to −1.9)	<0.001*
Resistance	SBP	4 (n=152)	1.3 (−2.2 to 4.8)	0.471
	DBP		0.1 (−2.1 to 2.2)	0.935
Handgrip	SBP	2 (n=68)	1.7 (−1.5 to 4.8)	0.309
	DBP		0.4 (−2.0 to 2.8)	0.754
Whole-body	SBP	2 (n=84)	2.1 (−6.9 to 11.2)	0.644
	DBP		0.4 (−5.1 to 5.9)	0.882
Combined	SBP	3 (n=104)	−10.4 (−23.7 to 2.9)	0.125
	DBP		−6.0 (−14.7 to 2.7)	0.178
Nighttime ABP				
Aerobic	SBP	7 (n=367)	−3.8 (−6.4 to −1.3)	0.003*
	DBP		−2.9 (−4.1 to −1.6)	<0.001*
Resistance	SBP	3 (n=99)	−3.7 (−6.4 to −0.9)	0.009*
	DBP		−1.9 (−4.6 to 0.8)	0.175
Handgrip	SBP	2 (n=68)	−2.8 (−9.2 to 3.6)	0.398
	DBP		−1.5 (−4.6 to 1.6)	0.345
Combined	SBP	3 (n=104)	−7.3 (−21.6 to 7.1)	0.321
	DBP		−4.0 (−11.0 to 2.9)	0.257

Mean difference is expressed in mm Hg. ABP indicates ambulatory blood pressure; DBP, diastolic blood pressure; and SBP, systolic blood pressure.
*Significant difference for the comparison between control and exercise groups (P < 0.05).

function, vascular remodeling with increase in the luminal diameter of conduit and resistance arteries, and improved arterial baroreflex control and thus autonomic balance—have been documented mainly with aerobic training, with scarcer evidence available for other exercise modalities.[13] Interestingly, no other lifestyle intervention (including weight loss) has proven to act on so many potential BP-reducing mechanisms at the multisystemic level as aerobic exercise.[13]

It must be noted that a limited number of studies[21,23,24,26,28,32–34] was available on the effects of exercise modalities other than aerobic training. Moreover, RT interventions included whole-body exercises in some studies,[21,23] whereas in others they consisted solely of isometric handgrip exercise.[26,32] In this context, although some evidence from research on both individuals who were healthy or hypertensive suggests that isometric RT might be as effective as other exercise modalities to reduce office BP,[54,55] a recent meta-analysis found that the ABP-lowering effect of isometric RT among individuals with hypertension did not reach statistical significance.[15] Based on our results, regular aerobic exercise appears as an effective lifestyle intervention for reducing ABP in medicated patients with hypertension, with a minimal dose difficult to establish but possibly corresponding to ≥3 sessions/week, ≥30 min/session, and an intensity of ≈60% to 70% maximum heart rate or peak oxygen uptake for ≥3 months. Thus, these recommendations would be approximately in line with those of the World Health Organization-determined minimum recommendations (ie, ≥150 min/week of moderate-intensity physical activity [eg, walking/brisk walking] or ≥75 min/week of vigorous-intensity physical activity [eg, very brisk walking], or a combination thereof).[56] Because no benefits

were observed in separate analyses for interventions combining both RT and aerobic training, future studies should determine whether RT actually nullifies the beneficial effects of aerobic exercise on ABP. In this regard, the low number of studies available and the heterogeneity among studies in interventions' characteristics can be viewed as a potentially confounding factor. Further research is therefore needed to confirm the effects of exercise modalities other than aerobic exercise (notably whole-body or isometric RT, and combined training)—as well as of different exercise intensities and/or intervention durations.

An important question that remains to be solved is the sustainability of exercise benefits on ABP since the longer exercise intervention lasted 6 months,[22,34] and none of the included studies performed a follow-up. Moreover, our meta-regression analysis yielded inconsistent results, with a positive association between BP reduction and intervention length observed for daytime ABP but the opposite trend observed for nighttime ABP—which might be due to the low number of studies available, potential methodological differences between studies, and lack of long-term interventions. In this regard, some research suggests that exercise benefits on office BP might still be observed with long-term interventions (≥12 months).[57,58] However, a meta-analysis concluded that exercise interventions reduce office SBP in the short-middle term (3–6 months) in young adults with prehypertension/hypertension but these benefits are lost at ≥12-month follow-up.[59] Future studies should also consider the levels of physical activity performed by both intervention arms (control and exercise) outside the exercise intervention per se (for instance, by means of accelerometers). Another important question is how exercise compares with antihypertensive medication in terms of patients' adherence. In this context, the average weighted value of 81% found in our meta-analysis for exercise might suggest that adherence to this lifestyle intervention is not necessarily lower compared with drugs. For instance, a retrospective analysis of dosing histories of patients prescribed once a day antihypertensive drugs showed that half of the patients stopped treatment within a year[60] and a non-adherence rate of 28.4% has been reported for newly prescribed medications against hypertension.[61]

Some limitations must be acknowledged, notably the relatively low number of studies included—particularly for those conducted with non-medicated patients with hypertension and for some exercise modalities such as RT or multicomponent training. Moreover, the paucity of studies and the lack of information provided for some variables (eg, exercise intensity relative to well-accepted markers such as maximum oxygen consumption or maximum heart rate) also hindered performing sub-analyses attending to exercise

intensity. In addition, we analyzed studies implementing exercise interventions in individuals with different grades of hypertension (including resistant hypertension) and authors used different BP or medication criteria for patient inclusion. However, many studies had to be excluded due to the strict inclusion criteria we applied (ie, RCTs including only patients with hypertension who were not undergoing a weight-loss diet), which increases in turn the validity of our findings.

CONCLUSIONS

The present findings suggest that exercise training results in significant reductions of all ABP measures (ie, 24-hour, daytime, and nighttime ABP) in individuals with hypertension. Although further evidence is needed to elucidate whether it can replace antihypertensive drugs, exercise training (particularly with aerobic modalities) appears as an effective coadjuvant treatment in hypertension.

REFERENCES

1. Frieden TR, Jaffe MG. Saving 100 million lives by improving global treatment of hypertension and reducing cardiovascular disease risk factors. *J Clin Hypertens*. 2018;20:208–211.

2. Whelton PK, Carey RM, Aronow WS, Casey DE Jr, Collins KJ, Dennison Himmelfarb C, DePalma SM, Gidding S, Jamerson KA, Jones DW, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Hypertension*. 2018;71:1269–1324.

3. Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M, Burnier M, Clement DL, Coca A, de Simone G, Dominiczak A, et al. 2018 ESC/ESH guidelines for the management of arterial hypertension. *Eur Heart J*. 2018;39:3021–3104.

4. Dolan E, Stanton A, Thijs L, Hinedi K, Atkins N, McClory S, Den Hond E, McCormack P, Staessen JA, O'Brien E. Superiority of ambulatory over clinic blood pressure measurement in predicting mortality: the Dublin outcome study. *Hypertension*. 2005;46:156–161.

5. Kikuya M, Ohkubo T, Asayama K, Metoki H, Obara T, Saito S, Hashimoto J, Totsune K, Hoshi H, Satoh H, et al. Ambulatory blood pressure and 10-year risk of cardiovascular and noncardiovascular mortality: the Ohasama study. *Hypertension*. 2005;45:240–245.

6. Hansen TW, Jeppesen J, Rasmussen S, Ibsen H, Torp-Pedersen C. Ambulatory blood pressure and mortality: a population-based study. *Hypertension*. 2005;45:499–504.

7. Fagard RH, Van Den Broeke C, De Cort P. Prognostic significance of blood pressure measured in the office, at home and during ambulatory monitoring in older patients in general practice. *J Hum Hypertens*. 2005;19:801–807.

8. Sega R, Facchetti R, Bombelli M, Cesana G, Corrao G, Grassi G, Mancia G. Prognostic value of ambulatory and home blood pressures compared with office blood pressure in the general population: follow-up results from the Pressioni Arteriose Monitorate e Loro Associazioni (PAMELA) study. *Circulation*. 2005;111:1777–1783.

9. Yang WY, Melgarejo JD, Thijs L, Zhang ZY, Boggia J, Wei FF, Hansen TW, Asayama K, Ohkubo T, Jeppesen J, et al.; International Database on Ambulatory Blood Pressure in Relation to Cardiovascular Outcomes (IDACO) Investigators. Association of Office and Ambulatory blood pressure with mortality and cardiovascular outcomes. *JAMA*. 2019;322:409–420.

10. Ruilope LM, Ruiz-Hurtado G, Barderas MG, de la Cruz JJ, Lucia A, de la Sierra A, Gorostidi M, Vinyoles E, Segura J, Solís J, et al. Frequency and prognosis of treated hypertensive patients according to prior and new blood pressure goals: post hoc analysis of the Spanish ambulatory blood pressure monitoring registry. *Hypertension*. 2019;74:130–136.

11. Segura J, Banegas JR, Ruilope LM. Usefulness of ambulatory blood pressure monitoring (ABPM) in daily clinical practice: data from the Spanish ABPM registry. *Clin Exp Pharmacol Physiol*. 2014;41:30–36.

12. Anstey ED, Muntner P, Bello NA, Pugliese DN, Yano Y, Kronish IM, Reynolds K, Schwartz JE, Shimbo D. Diagnosing masked hypertension using ambulatory blood pressure monitoring, home blood pressure monitoring, or both? *Hypertension*. 2018;72:1200–1207.

13. Valenzuela PL, Carrera-Bastos P, Gálvez BG, Ruiz-Hurtado G, Ordovás JM, Ruilope LM, Lucia A. Lifestyle interventions for the prevention and treatment of hypertension. *Nat Rev Cardiol*. 2020. Oct 9 [epub ahead of print].

14. Guthold R, Stevens GA, Riley LM, Bull FC. Worldwide trends in insufficient physical activity from 2001 to 2016: a pooled analysis of 358 population-based surveys with 1·9 million participants. *Lancet Glob Health*. 2018;6:e1077–e1086.

15. Naci H, Salcher-Konrad M, Dias S, Blum MR, Sahoo SA, Nunan D, Ioannidis JPA. How does exercise treatment compare with antihypertensive medications? A network meta-analysis of 391 randomised controlled trials assessing exercise and medication effects on systolic blood pressure. *Br J Sports Med*. 2019;53:859–869.

16. Pescatello LS, Buchner DM, Jakicic JM, Powell KE, Kraus WE, Bloodgood B, Campbell WW, Dietz S, Dipietro L, George SM, et al.; 2018 PHYSICAL ACTIVITY GUIDELINES ADVISORY COMMITTEE. Physical activity to prevent and treat hypertension: a systematic review. *Med Sci Sports Exerc*. 2019;51:1314–1323.

17. Fiuza-Luces C, Garatachea N, Berger NA, Lucia A. Exercise is the real polypill. *Physiology*. 2013;28:330–358.

18. Sosner P, Guiraud T, Gremeaux V, Arvisais D, Herpin D, Bosquet L. The ambulatory hypotensive effect of aerobic training: a reappraisal through a meta-analysis of selected moderators. *Scand J Med Sci Sport*. 2017;27:327–341.

19. Cao L, Li X, Yan P, Wang X, Li M, Li R, Shi X, Liu X, Yang K. The effectiveness of aerobic exercise for hypertensive population: a systematic review and meta-analysis. *J Clin Hypertens*. 2019;21:868–876.

20. Motlagh Z, Hidarnia A, Kaveh MH, Kojuri J. Effect of theory-based training intervention on physical activity and blood pressure in hypertensive patients: a randomized control trial. *Iran Red Crescent Med J*. 2017;19:e55610.

21. Bertani RF, Campos GO, Perseguin DM, Bonardi JMT, Ferriolli E, Moriguti JC, Lima NKC. Resistance exercise training is more effective than interval aerobic training in reducing blood pressure during sleep in hypertensive elderly patients. *J Strength Cond Res*. 2018;32:2085–2090.

22. Blumenthal JA, Sherwood A, Gullette EC, Babyak M, Waugh R, Georgiades A, Craighead LW, Tweedy D, Feinglos M, Appelbaum M, et al. Exercise and weight loss reduce blood pressure in men and women with mild hypertension: effects on cardiovascular, metabolic, and hemodynamic functioning. *Arch Intern Med*. 2000;160:1947–1958.

23. Blumenthal JA, Siegel WC, Appelbaum M. Failure of exercise to reduce blood pressure in patients with mild hypertension: results of a randomized controlled trial. *JAMA*. 1991;266:2098–2104.

24. Lima LG, Bonardi JTM, Campos GO, Bertani RF, Scher LML, Moriguti JC, Ferriolli E, Lima NKC. Combined aerobic and resistance training: are there additional benefits for older hypertensive adults? *Clinics*. 2017;72:363–369.

25. Cornelissen VA, Buys R, Smart NA. Endurance exercise beneficially affects ambulatory blood pressure: a systematic review and meta-analysis. *J Hypertens*. 2013;31:639–648.

26. Farah BQ, Rodrigues SLC, Silva GO, Pedrosa RP, Correia MA, Barros MVG, Deminice R, Marinello PC, Smart NA, Vianna LC, et al. Supervised, but not home-based, isometric training improves brachial and central blood pressure in medicated hypertensive patients: a randomized controlled trial. *Front Physiol*. 2018;9:961.

27. Beard JR, Officer A, De Carvalho IA, Sadana R, Pot AM, Michel JP, Lloyd-Sherlock P, Epping-Jordan JE, Peeters GMEEG, Mahanani WR, et al. The World report on ageing and health: a policy framework for healthy ageing. *Lancet*. 2016;387:2145–2154.

28. Guimarães GV, Ciolac EG, Carvalho VO, D'Avila VM, Bortolotto LA, Bocchi EA. Effects of continuous vs. interval exercise training on blood pressure and arterial stiffness in treated hypertension. *Hypertens Res*. 2010;33:627–632.

29. Pagonas N, Dimeo F, Bauer F, Seibert F, Kiziler F, Zidek W, Westhoff TH. The impact of aerobic exercise on blood pressure variability. *J Hum Hypertens*. 2014;28:367–371.

30. Dimeo F, Pagonas N, Seibert F, Arndt R, Zidek W, Westhoff TH. Aerobic exercise reduces blood pressure in resistant hypertension. *Hypertension*. 2012;60:653–658.

31. Westhoff TH, Franke N, Schmidt S, Vallbracht-Israng K, Meissner R, Yildirim H, Schlattmann P, Zidek W, Dimeo F, van der Giet M. Too old to benefit from sports? The cardiovascular effects of exercise training in elderly subjects treated for isolated systolic hypertension. *Kidney Blood Press Res*. 2007;30:240–247.

32. Stiller-Moldovan C, Kenno K, McGowan CL. Effects of isometric handgrip training on blood pressure (resting and 24 h ambulatory) and heart rate variability in medicated hypertensive patients. *Blood Press Monit*. 2012;17:55–61.

33. Guimaraes GV, De Barros Cruz LG, Fernandes-Silva MM, Dorea EL, Bocchi EA. Heated water-based exercise training reduces 24-hour ambulatory blood pressure levels in resistant hypertensive patients: a randomized controlled trial (HEx trial). *Int J Cardiol*. 2014;172:434–441.

34. Barroso WKS, Jardim PCBV, Vitorino PV, Bittencourt A, Miquetichuc F. Influência da atividade física programada na pressão arterial de idosos hipertensos sob tratamento não-farmacológico. *Rev Assoc Med Bras*. 2008;54:328–333.

35. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med*. 2009;6:e1000097.

36. Way KL, Sultana RN, Sabag A, Baker MK, Johnson NA. The effect of high Intensity interval training versus moderate intensity continuous training on arterial stiffness and 24 h blood pressure responses: a systematic review and meta-analysis. *J Sci Med Sport*. 2019;22:385–391.

37. Cornelissen VA, Fagard RH. Effects of endurance training on blood pressure, blood pressure-regulating mechanisms, and cardiovascular risk factors. *Hypertension*. 2005;46:667–675.

38. Fagard RH. Exercise is good for your blood pressure: effects of endurance training and resistance training. *Clin Exp Pharmacol Physiol*. 2006;33:853–856.

39. Pescatello LS, Kulikowich JM. The aftereffects of dynamic exercise on ambulatory blood pressure. *Med Sci Sports Exerc*. 2001;33:1855–1861.

40. Fagard RH, Cornelissen VA. Effect of exercise on blood pressure control in hypertensive patients. *Eur J Prev Cardiol*. 2007;14:12–17.

41. Thompson S, Wiebe N, Padwal RS, Gyenes G, Headley SAE, Radhakrishnan J, Graham M. The effect of exercise on blood pressure in chronic kidney disease: a systematic review and meta-analysis of randomized controlled trials. *PLoS One*. 2019;14:e0211032.

42. Costa EC, Hay JL, Kehler DS, Boreskie KF, Arora RC, Umpierre D, Szwajcer A, Duhamel TA. Effects of high-intensity interval training versus moderate-intensity continuous training on blood pressure in adults with pre- to established hypertension: a systematic review and meta-analysis of randomized trials. *Sport Med*. 2018;48:2127–2142.

43. Neter JE, Stam BE, Kok FJ, Grobbee DE, Geleijnse JM. Influence of weight reduction on blood pressure: a meta-analysis of randomized controlled trials. *Hypertension*. 2003;42:878–884.

44. Brito LC, Peçanha T, Fecchio RY, Rezende RA, Sousa P, Da Silva-Júnior ND, Abreu A, Silva G, Mion-Junior D, Halliwill JR, et al. Morning versus evening aerobic training effects on blood pressure in treated hypertension. *Med Sci Sports Exerc*. 2019;51:653–662.

45. Verhagen AP, De Vet HCW, De Bie RA, Kessels AG, Boers M, Bouter LM, Knipschild PG. The Delphi list: a criteria list for quality assessment of randomized clinical trials for conducting systematic reviews developed by Delphi consensus. *J Clin Epidemiol*. 1998;51:1235–1241.

46. Borenstein M, Hedges LV, Higgins JP, Rothstein HR. A basic introduction to fixed-effect and random-effects models for meta-analysis. *Res Synth Methods*. 2010;1:97–111.

47. Fujiwara T, Hoshide S, Kanegae H, Nishizawa M, Kario K. Reliability of morning, before-dinner, and at-bedtime home blood pressure measurements in patients with hypertension. *J Clin Hypertens (Greenwich)*. 2018;20:315–323.

48. Ash GI, Walker TJ, Olson KM, Stratton JH, Gómez AL, Kraemer WJ, Volek JS, Pescatello LS. Reproducibility of ambulatory blood pressure changes from the initial values on two different days. *Clinics (Sao Paulo)*. 2013;68:1509–1515.

49. Molmen-Hansen HE, Stolen T, Tjonna AE, Aamot IL, Ekeberg IS, Tyldum GA, Wisloff U, Ingul CB, Stoylen A. Aerobic interval training reduces blood pressure and improves myocardial function in hypertensive patients. *Eur J Prev Cardiol*. 2012;19:151–160.

50. Fagard RH, Celis H, Thijs L, Staessen JA, Clement DL, De Buyzere ML, De Bacquer DA. Daytime and nighttime blood pressure as predictors of death and cause-specific cardiovascular events in hypertension. *Hypertension*. 2008;51:55–61.

51. Cook NR, Cohen J, Hebert PR, Taylor JO, Hennekens CH. Implications of small reductions in diastolic blood pressure for primary prevention. *Arch Intern Med*. 1995;155:701–709.

52. Drawz PE, Pajewski NM, Bates JT, Bello NA, Cushman WC, Dwyer JP, Fine LJ, Goff DC Jr, Haley WE, Krousel-Wood M, et al. Effect of intensive versus standard clinic-based hypertension management on ambulatory blood pressure. *Hypertension*. 2017;69:42–50.

53. MacDonald HV, Johnson BT, Huedo-Medina TB, Livingston J, Forsyth KC, Kraemer WJ, Farinatti PT, Pescatello LS. Dynamic resistance training as stand-alone antihypertensive lifestyle therapy: a meta-analysis. *J Am Heart Assoc*. 2016;5:e003231. DOI: 10.1161/JAHA.116.003231.

54. Smart NA, Way D, Carlson D, Millar P, McGowan C, Swaine I, Baross A, Howden R, Ritti-Dias R, Wiles J, et al. Effects of isometric resistance training on resting blood pressure: individual participant data meta-analysis. *J Hypertens*. 2019;37:1927–1938.

55. Jin YZ, Yan S, Yuan WX. Effect of isometric handgrip training on resting blood pressure in adults: a meta-analysis of randomized controlled trials. *J Sports Med Phys Fitness*. 2017;57:154–160.

56. World Health Organization. *WHO Global Recommendations on Physical Activity for Health*. Geneva; 2010. Available at: https://www.who.int/publications/i/item/9789241599979. Accessed July 10, 2020.

57. Cox KL, Burke V, Morton AR, Gillam HF, Beilin LJ, Puddey IB. Long-term effects of exercise on blood pressure and lipids in healthy women aged 40–65 years: the Sedentary Women Exercise Adherence Trial (SWEAT). *J Hypertens*. 2001;19:1733–1743.

58. Seals DR, Reiling MJ. Effect of regular exercise on 24-hour arterial pressure in older hypertensive humans. *Hypertension*. 1991;18:583–592.

59. Williamson W, Foster C, Reid H, Kelly P, Lewandowski AJ, Boardman H, Roberts N, McCartney D, Huckstep O, Newton J, et al. Will exercise advice be sufficient for treatment of young adults with prehypertension and hypertension? A systematic review and meta-analysis. *Hypertension*. 2016;68:78–87.

60. Vrijens B, Vincze G, Kristanto P, Urquhart J, Burnier M. Adherence to prescribed antihypertensive drug treatments: longitudinal study of electronically compiled dosing histories. *BMJ*. 2008;336:1114–1117.

61. Fischer MA, Stedman MR, Lii J, Vogeli C, Shrank WH, Brookhart MA, Weissman JS. Primary medication non-adherence: analysis of 195,930 electronic prescriptions. *J Gen Intern Med*. 2010;25:284–290.

SUPPLEMENTAL MATERIAL

Figure S1. PRISMA 2009 checklist.

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	6
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	N/A
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	6
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6-7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6-7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	7

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	7
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	7
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	7-8, and Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	7-8, and Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Table 2
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	8 and 9, and Figures 2-4
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	8 and 9, and Figures 2-4
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Table 2
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Figures 3-4
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	9-13
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	12
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	13
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	2