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

Hypertension 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

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24-hour ABP set at 125/75 and 130/80 mm Hg in the United States and European guidelines, respectively. Particularly, an increased 24-hour and nighttime ABP is associated with a high cardiovascular disease risk—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.” 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.

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, although unfortunately physical inactivity is reaching pandemic proportions. 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. Furthermore, exercise has minimal side effects compared with drugs. 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) 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, 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. However, other studies not included in the aforementioned meta-analysis have assessed the effects on ABP of aerobic, RT, or multi-component exercise training 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).

**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.

**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.\textsuperscript{13,43} No inclusion/exclusion criteria were documented—BP-lowering effect of diet-induced weight loss per se.\textsuperscript{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\textsuperscript{22–24,33} and we contacted the authors of 1 study because the values could not be extracted from figures.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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\textsuperscript{47,48} (eg, 0.79 for 24-hour DBP and 0.82 for 24-hour SBP for both sexes in repeated-days measurements\textsuperscript{49}). 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\textsuperscript{20,21,24,26,28–33,44} participants were taking antihypertensive drugs during the intervention, whereas in the other 4 studies\textsuperscript{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,\textsuperscript{22–24,26,28–34,44,49} 3 studies\textsuperscript{26,28,32} included both supervised and non-supervised exercise, and 2 included only non-supervised exercise.\textsuperscript{20,24} Different modalities of exercise were used, notably moderate-intensity continuous training\textsuperscript{20–24,44,49} or aerobic interval training for aerobic exercise,\textsuperscript{29–31,49} RT\textsuperscript{21,23,26,32} (consisting of only isometric handgrip training in 2 studies),\textsuperscript{26,32} or a combination of both aerobic and RT\textsuperscript{24,28,33,34} (ie, multicomponent exercise training, which was performed on a heated [30°C–32°C] swimming pool in 1 study).\textsuperscript{35} On the other hand, 7 studies\textsuperscript{22,23,28,29,33,44} 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,\textsuperscript{20–24,26,28–34,44,49} and 2 were deemed to have a high quality.\textsuperscript{20,26}
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 (I²=0% for both) and no signs of publication 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). A moderate heterogeneity was found for the effects on SBP (I²=53.0%) but not on DBP (I²=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\(^a\)        | 1. CT: n=24 (66 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       |
|                            | 2. CG: n=21 (70 y)                                                                 | 2. Total duration: 12 wk 3. Frequency: 3 sessions/wk 4. Duration per session: 20 min 5. Intensity: 60%–80% of MHR |                                                                                                 |                                             |                                             |
|                            |                                                                                   | 3. RT: n=16 (67 y) 4. CG: n=15 (66 y)                                                 |                                                                                                 |                                             |                                             |
|                            |                                                                                   | 1. MICT: 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 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       |
|                            |                                                                                   | 2. CG: n=23 (45 y) 3. CG: n=24                                                      |                                                                                                 |                                             |                                             |
|                            |                                                                                   | 1. MICT: n=15 (67 y) 2. MICT: n=15 (68 y) 3. RT: n=16 (67 y) 4. CG: n=15 (66 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 |
|                            |                                                                                   | 2. CG: n=21 (47 y) 3. CG: n=24                                                      |                                                                                                 |                                             |                                             |
|                            |                                                                                   | 1. Modality: ET (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 VO \(_{2}\)max | 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 |
|                            |                                                                                   | 2. CG: n=23 (45 y) 3. CG: n=24                                                      |                                                                                                 |                                             |                                             |
|                            |                                                                                   | 1. Modality: ET: n=41 (54 y) RT+flexibility: n=35 (46 y) CG: n=23 (45 y) |                                                                                                 |                                             |                                             |
|                            |                                                                                   | 1. Modality: MICT 2. Total duration: 6 mo 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 SBP/DBP with ET, but not with MT |
|                            |                                                                                   | 2. CG: n=20 (50 y) 3. 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: 30–36 min, including intervals of 3–15 min interspersed with 3-min walking intervals 5. Intensity: 70% of MVC | 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     |
|                            |                                                                                   | 3. CG: n=20 (50 y) 4. CG: n=20 (50 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 (defined as office SBP/DBP ≥140/90 mm Hg) with or regular use of 3 anti-hypertensive drugs of different classes or a BP that is controlled with >4 anti-hypertensive drugs) | Yes                                         | 2. The effects on nighttime SBP and DBP did not reach statistical significance |
|                            |                                                                                   | 2. CG: n=26 (67 y) 3. CG: n=26 (67 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: 30–36 min, including intervals of 3–15 min interspersed with 3-min walking intervals 5. Intensity: 70% of MVC | “Use of anti-hypertensive medications” | Yes                                         | 1. No significant changes in ABP          |
|                            |                                                                                   | 3. CG: n=24Age range, 58–61 y 4. CG: n=24Age 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 | 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 |
|                            |                                                                                   | 2. Supervised IT: n=24 3. Supervised IT: n=24 |                                                                                                 |                                             |                                             |
|                            |                                                                                   | 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 | 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          |
|                            |                                                                                   | 2. CG: n=16 (52 y) 3. CG: n=16 (52 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          |
|                            |                                                                                   | 2. CG: n=13 3. CG: n=13 Age range, 45–50 y                                           |                                                                                                 |                                             |                                             |

(Continued)
There was no sign of publication bias 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 There was no sign of heterogeneity (I²=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 participants 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=0.484; 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=0.84). Regarding the studies in untreated patients, 2 studies22,45 found significant benefits on daytime ABP, of which one49 also reported significant benefits for both

| Study | Participants (Sample Size and Mean Age) | Exercise Intervention | Criteria to Define Hypertension | Antihypertensive Treatment | Main Effects on ABP |
|-------|----------------------------------------|-----------------------|---------------------------------|--------------------------|---------------------|
| Lima et al24 | 1. MICT: n=18  2. CT: n=15  3. CG: n=14  Age range, =67–69 y | 1. Modality: MICT (fresedmill), 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 antihypertensive 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 al29 | 1. HIIT: n=31 (=52 y)  2. MICT: n=23 (=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 al32 | 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 al33 | 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 al32 | 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 al31 | 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 |

1IRM 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 VO2max, maximal oxygen uptake.

Table 1. Continued

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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 training24,28,33,34 on any ABP measure (Table 4). When separately analyzing the 2 studies (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 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 (≈ −3.3 mm Hg) but not nighttime ABP.40 Another meta-analysis reported a significant reduction of daytime (≈ −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 (≈ −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
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 guidelines3 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 drugs15 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 study49 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.

### 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 (−10.2 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).
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)<sup>21</sup> | -1.50               | -8.19       | 5.19        | 0.660   | 3.87           |
| Bertani et al (2018) (AIT)<sup>21</sup>  | -1.90               | -9.02       | 5.22        | 0.601   | 3.69           |
| Bertani et al (2018) (RT)<sup>21</sup>   | -7.30               | -13.53      | -1.07       | 0.022   | 4.08           |
| Blumenhals et al (1991) (MCT)<sup>23</sup> | -1.10               | -1.75       | -0.45       | 0.001   | 6.17           |
| Blumenhals et al (1991) (RT)<sup>23</sup> | 2.00                | 1.35        | 2.65        | 0.000   | 6.17           |
| Blumenhals et al (2000) (MCT)<sup>22</sup> | 4.30                | 3.41        | 5.19        | 0.000   | 6.14           |
| Brito et al (2019) (morning MCT)<sup>44</sup> | 5.00                | 0.23        | 9.77        | 0.040   | 4.75           |
| Brito et al (2019) (evening MCT)<sup>44</sup> | 4.00                | 0.56        | 7.44        | 0.023   | 5.36           |
| Dimeo et al (2012) (AIT)<sup>30</sup>   | 9.00                | 3.25        | 14.75       | 0.002   | 4.30           |
| Farah et al (2018) (home-based RT)<sup>26</sup> | -4.00               | -5.83       | -2.17       | 0.000   | 5.94           |
| Farah et al (2018) (supervised RT)<sup>26</sup> | -1.00               | -3.35       | 1.35        | 0.405   | 5.78           |
| Guimaraes et al (2010) (combined + MCT)<sup>28</sup> | 1.00                | -4.56       | 6.56        | 0.724   | 4.38           |
| Guimaraes et al (2010) (combined + AT)<sup>28</sup> | 2.00                | -3.35       | 7.35        | 0.464   | 4.48           |
| Guimaraes et al (2014) (combined + MCT)<sup>33</sup> | 25.78               | 22.41       | 29.15       | 0.000   | 5.39           |
| Lima et al (2017) (Combined + MCT)<sup>24</sup> | 12.50               | 6.38        | 18.62       | 0.000   | 4.13           |
| Lima et al (2017) (MCT)<sup>24</sup>     | 9.80                | 2.59        | 17.81       | 0.008   | 3.85           |
| Molmen-Hansen et al (2011) (AT)<sup>49</sup> | 12.50               | 6.59        | 18.41       | 0.000   | 4.22           |
| Molmen-Hansen et al (2011) (MCT)<sup>49</sup> | 4.50                | -1.60       | 10.60       | 0.148   | 4.14           |
| Pagonas et al (2014) (AT)<sup>29</sup>    | 7.30                | 2.98        | 11.62       | 0.001   | 4.96           |
| Stiller-Moldovan et al (2012) (RT)<sup>32</sup> | 3.40                | -3.41       | 10.21       | 0.328   | 3.82           |
| Westhoff et al (2007) (AT)<sup>31</sup>  | 9.60                | 4.44        | 14.76       | 0.000   | 4.57           |
|                            | 4.48                | 2.33        | 6.63        | 0.000   | 4.57           |

### B: Daytime DBP

| Study name               | Difference in means | Lower limit | Upper limit | p-Value | Relative weight |
|--------------------------|---------------------|-------------|-------------|---------|----------------|
| Bertani et al (2018) (MCT)<sup>21</sup> | 0.60                | -4.98       | 6.18        | 0.833   | 3.58           |
| Bertani et al (2018) (AIT)<sup>21</sup>  | -0.10               | -6.29       | 6.09        | 0.975   | 3.26           |
| Bertani et al (2018) (RT)<sup>21</sup>   | -4.00               | -9.67       | 1.67        | 0.167   | 3.52           |
| Blumenhals et al (1991) (MCT)<sup>23</sup> | 0.00                | -0.89       | 0.69        | 1.000   | 6.02           |
| Blumenhals et al (1991) (RT)<sup>23</sup> | 1.80                | 1.14        | 2.46        | 0.000   | 6.03           |
| Blumenhals et al (2000) (MCT)<sup>23</sup> | 3.40                | 2.81        | 4.19        | 0.000   | 6.00           |
| Brito et al (2019) (morning MCT)<sup>44</sup> | 5.00                | 1.57        | 8.43        | 0.004   | 4.81           |
| Brito et al (2019) (evening MCT)<sup>44</sup> | 4.00                | 1.18        | 6.82        | 0.006   | 5.16           |
| Dimeo et al (2012) (AT)<sup>30</sup>   | 4.50                | 0.41        | 8.59        | 0.001   | 4.42           |
| Farah et al (2018) (home-based RT)<sup>26</sup> | -2.00               | -3.44       | -0.56       | 0.007   | 5.81           |
| Farah et al (2018) (supervised RT)<sup>26</sup> | 1.00                | -0.80       | 2.80        | 0.275   | 5.67           |
| Guimaraes et al (2010) (combined + MCT)<sup>28</sup> | 2.00                | -3.35       | 7.35        | 0.464   | 3.70           |
| Guimaraes et al (2010) (combined + AT)<sup>28</sup> | 3.00                | -1.37       | 7.17        | 0.178   | 4.25           |
| Guimaraes et al (2014) (combined + MCT)<sup>33</sup> | 16.13               | 14.19       | 18.07       | 0.000   | 5.61           |
| Lima et al (2017) (Combined + MCT)<sup>24</sup> | 2.30                | -1.47       | 6.07        | 0.232   | 4.61           |
| Lima et al (2017) (MCT)<sup>24</sup>     | 6.30                | 2.33        | 10.27       | 0.002   | 4.49           |
| Molmen-Hansen et al (2011) (AT)<sup>49</sup> | 7.00                | 3.11        | 10.89       | 0.000   | 4.54           |
| Molmen-Hansen et al (2011) (MCT)<sup>49</sup> | 2.50                | -1.13       | 6.13        | 0.176   | 4.69           |
| Pagonas et al (2014) (AT)<sup>29</sup>    | 3.80                | 0.98        | 6.64        | 0.009   | 5.15           |
| Stiller-Moldovan et al (2012) (RT)<sup>32</sup> | 0.60                | -4.62       | 5.82        | 0.822   | 3.77           |
| Westhoff et al (2007) (AT)<sup>31</sup>  | 4.50                | 1.23        | 7.77        | 0.007   | 4.90           |
|                            | 3.15                | 1.50        | 4.79        | 0.000   | 4.90           |

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.
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...
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.\textsuperscript{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.\textsuperscript{13}

It must be noted that a limited number of studies\textsuperscript{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,\textsuperscript{21,23} whereas in others they consisted solely of isometric handgrip exercise.\textsuperscript{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,\textsuperscript{54,55} a recent meta-analysis found that the ABP-lowering effect of isometric RT among individuals with hypertension did not reach statistical significance.\textsuperscript{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).\textsuperscript{56} Because no benefits

| Exercise Type | Outcome | Studies (Participants) | Mean Difference (mm Hg, 95% CI) | P Value |
|---------------|---------|------------------------|---------------------------------|---------|
| 24-h ABP      | SBP     | 7 (n=373)              | −5.5 (−8.1 to −2.8)             | <0.001* |
|               |         |                        | −3.8 (−4.9 to −2.6)             | <0.001* |
|               | DBP     | 3 (n=99)               | 0.5 (−1.1 to 2.1)               | 0.573   |
|               |         | 2 (n=68)               | 0.2 (−1.2 to 1.6)               | 0.784   |
|               |         | 4 (n=139)              | −9.6 (−20.7 to 1.5)             | 0.091   |
| Daytime ABP   | SBP     | 9 (n=507)              | −5.0 (−7.6 to −2.3)             | <0.001* |
|               |         |                        | −3.5 (−5.1 to −1.9)             | <0.001* |
|               | DBP     | 4 (n=152)              | 1.3 (−2.2 to 4.8)               | 0.471   |
|               |         | 2 (n=68)               | 1.7 (−1.5 to 4.8)               | 0.309   |
|               |         | 2 (n=84)               | 2.1 (−6.9 to 11.2)              | 0.644   |
|               |         | 3 (n=104)              | −10.4 (−23.7 to 2.9)            | 0.125   |
|               |         |                        | −6.0 (−14.7 to 2.7)             | 0.178   |
| Nighttime ABP | SBP     | 7 (n=367)              | −3.8 (−6.4 to −1.3)             | 0.003*  |
|               |         |                        | −2.9 (−4.1 to −1.6)             | <0.001* |
|               | DBP     | 3 (n=99)               | −3.7 (−6.4 to −0.9)             | 0.009*  |
|               |         | 2 (n=68)               | −2.8 (−9.2 to 3.6)              | 0.398   |
|               |         | 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).
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).37,58 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 year60 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.

ARTICLE INFORMATION

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Disclosures

None.

Supplementary Material

Figure S1

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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., I²) 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                  |

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