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# How does exercise treatment compare with antihypertensive medications? A network meta-analysis of 391 RCTs assessing exercise and medication effects on systolic blood pressure

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## **Conflicts of interest:**

None.

### **What is already known?**

- Exercise interventions are effective in lowering systolic blood pressure.

### **What are the new findings?**

- Across all populations, individuals who receive antihypertensive medications tend to achieve greater reductions in SBP than those who adopt structured exercise regimens.
- In populations with hypertension, different types of exercise interventions appear equally effective as most antihypertensive medications.
- Structured exercise has not been evaluated as extensively as antihypertensive medications.

## Abstract

*Objective:* To compare the effect of exercise regimens and medications on systolic blood pressure (SBP).

*Data sources:* Medline (via Pubmed) and the Cochrane Library.

*Eligibility criteria:* Randomized controlled trials (RCTs) of angiotensin convertase enzyme inhibitors (ACE-I), angiotensin-2 receptor blockers (ARB), beta-blockers, calcium channel blockers (CCBs), and diuretics were identified from existing Cochrane reviews. A previously published meta-analysis of exercise interventions was updated to identify recent RCTs that tested the SBP-lowering effects of endurance, dynamic resistance, isometric resistance, and combined endurance and resistance exercise interventions (up to September 2018).

*Design:* Random-effects network meta-analysis.

*Outcome:* Difference in mean change from baseline SBP between comparator treatments (change from baseline in one group minus that in the other group) and its 95% credible interval (95% CrI), measured in millimeter mercury (mmHg).

*Results:* We included a total of 391 RCTs, 197 of which evaluated exercise interventions (10,461 participants) and 194 evaluated antihypertensive medications (29,281 participants). No RCTs compared directly exercise against medications. While all medication trials included hypertensive populations, only 56 exercise trials included hypertensive participants ( $\geq 140$  mm Hg), corresponding to 3,508 individuals. In a 10% random sample, risk of bias was higher in exercise RCTs, primarily due to lack of blinding and incomplete outcome data. In analyses that combined all populations, antihypertensive medications achieved higher reductions in baseline SBP compared to exercise interventions (mean difference: -3.96 mmHg, 95% CrI: -5.02 to -2.91). Compared to control, all types of exercise (including combination of endurance and resistance) and all classes of antihypertensive medications were effective in lowering baseline SBP. Among hypertensive populations, there were no detectable differences in the SBP-lowering effects of ACE-I, ARB, beta-blocker, and diuretic medications when compared to endurance or dynamic resistance exercise. There was no detectable inconsistency between direct and indirect comparisons. Although there was evidence of small-study effects, this affected both medication and exercise trials.

*Conclusions:* The effect of exercise interventions on SBP remains under-studied, especially among hypertensive populations. Our findings confirm modest but consistent reductions in SBP in many studied exercise interventions across all populations but individuals receiving medications generally achieved greater reductions than those following structured exercise regimens. Assuming equally reliable estimates, the SBP-lowering effect of exercise among hypertensive populations appears similar to that of commonly used antihypertensive

medications. Generalisability of these findings to real-world clinical settings should be further evaluated.

## Introduction

High systolic blood pressure (SBP) is a major modifiable risk factor for cardiovascular disease.<sup>1</sup> Individuals with high SBP are at elevated risk of cardiovascular disease and death<sup>2-4</sup> and high SBP is the leading cause of death and disability around the world.<sup>5</sup> Over the past half century, several classes of pharmacological treatment options have received approval to be prescribed for blood pressure-lowering.<sup>6</sup> The mortality and morbidity benefits of these antihypertensive medication options have been extensively documented in randomized controlled trials (RCTs) and meta-analyses.<sup>7,8</sup>

As the burden of cardiovascular disease continues to rise,<sup>9</sup> the use of medications targeting high blood pressure is sharply increasing.<sup>10</sup> In England, the number of adults taking blood pressure-lowering medications increased by approximately 50% from 2006 to 2016.<sup>11</sup> This upward trend will likely increase, as recent changes to major clinical practice guidelines developed by prominent organisations such as the American Heart Association and the American College of Cardiology (AHA/ACC) have lowered the SBP threshold for the definition of hypertension.<sup>12</sup> These changes are expected to markedly increase the number of people labelled as having hypertension and treated with medications.<sup>13,14</sup>

Such an increase may lead to inadvertent adverse events at the population level, as the number of people taking multiple medications continues to rise;<sup>15</sup> polypharmacy represents a major risk factor for drug-related morbidity and mortality.<sup>16</sup> Prescription drugs also contribute to rising health care expenditures. Spending on medications accounts for about 18% of total health spending on average across European countries.<sup>17</sup> Recent increases in medication-related costs have prompted significant policy and clinical attention to the comparative effectiveness of new and existing medications.<sup>18</sup> Meanwhile, relatively little attention has been given to promote wider adoption of non-pharmacological interventions such as exercise.

Exercise interventions have indisputable benefits for cardiovascular disease and beyond.<sup>19,20</sup> According to a pooled analysis of observational cohort studies, men and women with high levels of leisure time physical activity had a 24% and 27% lower risk of cardiovascular disease, respectively, than men and women with low levels of physical activity.<sup>21</sup> In addition, previous meta-analyses of RCTs showed that exercise is effective in improving established cardiovascular risk factors: exercise interventions reduce waist circumference,<sup>22</sup> improve HbA1c,<sup>23</sup> lower serum triglycerides,<sup>24</sup> and increase high-density lipoprotein.<sup>25</sup>

Exercise also has well-documented benefits in lowering SBP.<sup>26</sup> In a previous meta-analysis of 93 RCTs conducted among 5,223 healthy adults, SBP was reduced after endurance, dynamic resistance and isometric resistance exercise regimens.<sup>27</sup> Although recent AHA/ACC guidelines emphasize the role of lifestyle interventions, including exercise, in the management and treatment of hypertension, they consider pharmacological and non-

pharmacological interventions in isolation.<sup>12</sup> It would be very important to evaluate the comparative SBP-lowering effects of exercise and medication interventions.

In a previous meta-epidemiological study, we evaluated the comparative effectiveness of pharmacological and non-pharmacological interventions on mortality.<sup>28</sup> We found structured exercise interventions to be equally effective as several frequently used medications in terms of their mortality benefits in the secondary prevention of coronary heart disease, rehabilitation after stroke, treatment of heart failure, and prevention of diabetes. However, the amount of evidence on the mortality benefits of exercise was considerably smaller than that on medications. In addition, there was a paucity of available information on the ‘formulation’ and ‘dose’ of different types of exercise interventions and also on the characteristics of people that stood to benefit from such interventions.

In this study, we set out to perform a network meta-analysis to systematically compare the SBP-lowering effects of exercise and medications. Our objective was to evaluate how different types and intensities of exercise fared against different classes and doses of antihypertensive medications in terms of lowering baseline SBP levels. In addition, we assessed the comparative SBP-lowering effects of exercise and medications specifically among hypertensive populations.

## **Methods**

### *Identification of available evidence*

As previously,<sup>28</sup> we identified the relevant body of evidence in three steps. First, one researcher (HN) searched Medline via Pubmed for the most recently published comprehensive meta-analyses of RCTs evaluating the effectiveness of exercise interventions on lowering SBP (*see search strategy in Appendix 1*).

Second, one researcher (HN up to August 2017 and MSK from August 2017 to September 2018) searched Medline via Pubmed to identify recently published RCTs of exercise interventions aimed at lowering SBP that were published after the end date of electronic database search in the meta-analyses identified in step one (*see search strategy in Appendix 2*). Accordingly, our search covered the period from February 2012 to September 2018. Two researchers (SAS and HN, up to August 2017) and one researcher (MSK, from August 2017 to September 2018) screened identified titles and abstracts according to prespecified eligibility criteria. Participants of interest included adults (with or without hypertension) with no cardiovascular disease, cerebrovascular disease, diabetes, or other chronic conditions such as cancer. Eligible interventions were any form of structured exercise of any frequency, duration or intensity. Eligible comparator interventions included usual practice (no exercise), other exercise regimens, or medications. Studies were included if they lasted at least four weeks and reported SBP at baseline and follow-up (or change from baseline) for intervention and comparator arms or the difference in means between the two arms. One researcher (MB) contacted the corresponding authors of recently published RCTs to obtain missing

outcome data in the papers. Following title and abstract screening, three researchers (MB, MSK and HN) reviewed potentially relevant full text articles to determine study eligibility. Disagreements were resolved by consensus.

Third, one researcher (MSK) searched the Cochrane Library to identify published meta-analyses of RCTs of prescription medications aimed at lowering SBP with similar participant populations to those in the meta-analyses of exercise trials (i.e., adults in whom the blood-pressure lowering effect of an intervention can be observed, excluding individuals with other conditions potentially causing hypertension, such as renal failure). Comparators in eligible medication trials included placebo, other medications, doses, or usual care. The list of relevant medication classes was identified using the clinical practice guidelines developed by the National Institute for Health and Care Excellence (NICE)<sup>29</sup> and European Society of Hypertension/European Society of Cardiology (ESH/ESC).<sup>30</sup> We also used the British National Formulary (BNF) to determine the eligible doses of individual antihypertensive medications.<sup>31</sup> Only trial arms of RCTs of medications from guideline-recommended medication classes and BNF-approved doses were eligible for inclusion in our review. We did not run additional searches to update the list of medication RCTs included in previous meta-analyses, since they were deemed to be sufficiently up-to-date and, in contrast to exercise trials, the amount of evidence for medication trials was already very large.

#### *Data extraction*

We adopted a 2-tiered data extraction strategy. For eligible RCTs of medications, we relied on the information reported in the published Cochrane meta-analyses. We divided the sample of RCTs and two researchers (MSK and MB) extracted information on author name, trial reference, publication year, interventions (including dose), comparators, sample size (total number of randomly assigned participants or total number of participants with outcome measurement) per trial arm, and outcome data.

For eligible RCTs of exercise interventions, we carried out primary data collection from each publication. In addition to the data items captured from medication RCTs, we collected detailed information on the characteristics of participants (e.g., mean age, proportion female) and interventions (type, intensity, frequency, duration). In terms of outcome data, we focused on SBP, as it has been consistently associated with cardiovascular risk in epidemiological and experimental studies.<sup>12</sup> SBP is also more commonly reported than diastolic blood pressure.<sup>27</sup> We set out to extract the mean change from baseline SBP levels and its standard deviation in each trial arm. When the mean change from baseline was not available, we obtained the mean and standard deviation of SBP levels at baseline and follow-up in each arm and thus calculated the mean change from baseline for each study.

Data on the standard deviation of change from baseline SBP were rarely available. We therefore relied on standard errors, 95% confidence intervals, p-values, or t statistics to calculate standard deviations, as recommended by the Cochrane Handbook.<sup>32</sup> When no information was available to calculate standard deviations, we imputed missing values by



using a correlation coefficient of 0.8 between baseline and follow-up SBP. We tested the sensitivity of our findings to different correlation coefficients and confirmed the consistency of results across different sets of analyses (*see Appendix 4*). Two researchers extracted outcome data (SAS & MB up to August 2017 and HN & MSK from August 2017 to September 2018) and another researcher independently appraised the accuracy of the information.

#### *Categorization of available evidence*

Exercise was defined as a subset of physical activity that is structured and repetitive with the objective of improving or maintaining physical fitness.<sup>33</sup> We divided exercise interventions into four major categories: (1) endurance, (2) dynamic resistance, (3) isometric resistance, and (4) a combination of endurance and dynamic resistance.<sup>27</sup> Endurance exercise included interventions aimed at increasing heart rate and energy expenditure. Examples of endurance exercise included walking, jogging, running, cycling, and swimming. Interval training was considered as endurance exercise. We labeled exercise interventions as resistance training if they were aimed at increasing muscular strength and power. Strength training with dumbbells was a typical form of resistance exercise. We categorized exercise interventions as isometric exercise if they involved sustained contraction against an immovable load.

Intensity of exercise interventions was categorized into low, moderate, and high using the classification developed by the American College of Sports Medicine.<sup>34</sup> The majority of exercise RCTs reported relevant information such as percent of heart rate reserve (% HRR), percent of maximal heart rate (% HR<sub>max</sub>), percent of maximal oxygen uptake (% VO<sub>2 max</sub>), or percent of one repetition maximum (% 1RM) to categorize the relative or absolute intensity of exercise interventions. In cases where such information was not available, we relied on the study authors' reporting to determine the intensity of physical activity (n=9).

Individual medications were categorized into the following antihypertensive medication classes: angiotensin convertase enzyme inhibitors (ACE-I), angiotensin-2 receptor blockers (ARB), beta-blockers, calcium channel blockers (CCB), and diuretics. Medications were also divided into low and high doses according to the BNF, assigning them to "low" if at or below the mid-point of recommended doses in the BNF and "high" if above the mid-point of recommended doses.

We categorized exercise trials according to the study-level mean baseline SBP of the participant population. While the RCTs of antihypertensive medications included only hypertensive participants (with baseline SBP at or above 140 mmHg), exercise trials had more variable inclusion criteria. In our primary analysis, participant populations were labeled as "hypertensive" if exercise trials included adults with mean baseline SBP of at least 140 mmHg, which was consistent with the original definition of hypertension until the changes introduced by the 2017 AHA/ACC guidelines.

We also considered additional cut-offs to define hypertension in two sensitivity analyses. In the first set of sensitivity analyses, we labeled populations in exercise RCTs as hypertensive if they had average SBP of at least 130 mmHg, which corresponds to the new blood pressure threshold to define hypertension in the 2017 AHA/ACC guidelines.<sup>12</sup> In the second set of sensitivity analyses, we tested a cut-off of 150 mmHg for mean SBP in exercise trials, as this more closely matched the mean SBP of the trial populations in medication trials.

#### *Risk of bias assessment*

We used the Cochrane risk of bias tool to evaluate the internal validity of results in a 10% random sample of medication (n=20) and exercise RCTs (n=20) (*Appendix 5*).<sup>35</sup> Two researchers (HN and MB) reviewed the publications of selected trials to determine whether the investigators used appropriate methods to (1) generate a random allocation sequence (selection bias), (2) conceal the sequence of treatment allocation from trial investigators and participants before the trial (selection bias), (3) mask participants and investigators from knowledge of treatment allocation during the trial (performance bias and detection bias), and (4) deal with missing outcome data (attrition bias). We consistently rated the selective outcome reporting domain as “unclear”, as there was inadequate information available in the trials to evaluate planned vs. reported outcomes.

#### *Statistical analysis*

We first qualitatively synthesized included trials and described the types of direct and indirect comparisons and their relative contributions to the overall body of evidence available. We then developed network diagrams to visualize the relative amount of available evidence on exercise and medications.<sup>36</sup> Nodes represented different exercise and medications and lines connecting the nodes represented the direct head-to-head comparisons between interventions. In network diagrams, the size of each node and the thickness of each line connecting the nodes were proportional to the number of participants. All network diagrams were generated using Stata version 15.<sup>37</sup>

To estimate the comparative effectiveness of exercise and medications on SBP-lowering, we performed network meta-analyses.<sup>38</sup> Such analyses allow for comparing treatments that have not been directly compared to each other in head-to-head studies.<sup>39</sup> They can also combine evidence obtained from direct and indirect comparisons, thereby improving the precision of treatment effect estimates.<sup>40,41</sup> Similar to pair-wise meta-analyses, network meta-analyses preserve the random allocation of participants to different arms within each trial, however, they compare multiple interventions by combining all available comparisons between treatments across trials, utilizing the totality of the available evidence.<sup>42</sup>

Study-level treatment effects were combined using Bayesian Markov chain Monte Carlo methods in WinBUGS version 1.4.3.<sup>43</sup> We used the model developed by Dias and colleagues for the NICE Decision Support Unit.<sup>44-46</sup> Our base-case model assumed that the mean change from baseline in SBP per trial arm had a normal distribution. The relative effects

across trials making different comparisons were linked using the identity function. This model took into account the correlations between treatment effects within multi-arm trials.

We used a random-effects model to perform the network meta-analyses, allowing for between-study heterogeneity.<sup>47</sup> Our models therefore assumed that trial-specific treatment effects were drawn from a normal distribution, with a mean that was specific for each treatment comparison, and a common variance that was shared by all comparisons. We reported the mean treatment effect with 95% credible intervals (95% CrI) of every intervention relative to control and other interventions and the estimated between-study heterogeneity standard deviation with its 95% CrI.

To test the consistency assumption of the network meta-analysis, we compared the fit of the base-case model to that of an inconsistency model.<sup>48,49</sup> The latter model does not assume consistency between direct and indirect evidence and instead estimated independent mean treatment effects.<sup>50</sup> We also examined each data point's contribution to the residual deviance and compared the estimated between-study heterogeneity in each model. We assessed any improvements in fit or reductions in between-study heterogeneity in the inconsistency model, which would suggest potential inconsistency (*see Appendix 6*). We plotted the findings of this secondary analysis side-by-side with our base-case model that assumed consistency to compare the results of the two models. We visually inspected the findings and assessed for systematic differences from those obtained from our primary analyses (*see Appendix 6*).

We compared the SBP-lowering effects of exercise and antihypertensive medications in three sets of analyses: (1) all exercise interventions vs. all antihypertensive medications; (2) different types of exercise interventions vs. different classes of medications; and (3) different intensities of exercise interventions vs. different doses of medications. We then repeated these analyses and compared the antihypertensive RCTs to a subset of exercise trials that only included hypertensive populations.

We evaluated small-study effects by extending the regression-based approach proposed by Moreno and colleagues.<sup>51–53</sup> We regressed the treatment effects against their standard errors and predicted the pooled effect size for an ideal study of infinite size (i.e., with zero standard error), assuming that smaller studies would be more biased than larger studies.<sup>54</sup> This meta-regression allowed for a different mean bias according to type of comparison (i.e., mean bias due to small-study effects was assumed to be different for RCTs evaluating the effect of exercise vs. control and medications vs. control).<sup>55</sup>

We adopted non-informative prior distributions for treatment effects (normal (0, 10,000)) and the between-trial variance (uniform (0, 10)). Our analyses employed a long burn-in period (50,000 iterations) and follow-up period (100,000 iterations) to allow for convergence. We ran three chains with different sets of initial values. We visually inspected trace plots for key parameters for each analysis to assess convergence in terms of stability.

## Results

### *Evidence base for medications*

Using the Cochrane Library, we initially identified 14 potentially relevant meta-analyses of medication therapies aimed at lowering baseline SBP (**Figure 1**). Of these, we selected the most comprehensive meta-analyses within each medication class recommended by the NICE and ESH/ESC guidelines as first-line therapy for hypertension.<sup>56–63</sup> In total, these meta-analyses included 316 RCTs. We excluded the trials and trial arms of medications and medication dosages that were not indicated in the BNF. After these exclusions, we included 194 medication RCTs, corresponding to 57 trials of ACE-inhibitors, 36 studies of ARBs, 63 studies of beta-blockers, 9 studies of CCBs, and 46 studies of diuretics. 17 RCTs compared one medication class to another.

### *Evidence base for exercise interventions*

Of 47 potentially relevant reviews of exercise interventions identified from Medline, we considered the meta-analysis conducted by Cornelissen and Smart to be the most comprehensive in terms of its study identification, selection, review, and synthesis methods.<sup>27</sup> This analysis relied on 93 RCTs published up to February 2012. We subsequently updated this review and identified 2,619 potentially relevant titles and abstracts published until September 2018 (**Figure 1**). We excluded 2,317 records that were irrelevant. Of 302 full-text articles, we included an additional 107 RCTs. In total, we ultimately included 197 RCTs of exercise interventions (*see Appendix 3 for trial characteristics*). 115 of these evaluated endurance training interventions including walking, running, cycling, or aquatic exercises; 30 RCTs evaluated dynamic resistance interventions; 10 evaluated isometric resistance exercises; and 12 tested endurance and resistance training regimens in combination. The remaining 30 RCTs compared one type of exercise intervention to another. No RCTs compared directly exercise against medications.

### *Characteristics of exercise and medication RCTs*

RCTs of exercise interventions included substantially fewer participants; average sample size in exercise RCTs was 53 (range: 15-464) compared to 139 in RCTs of beta-blockers (7-1092), 174 in studies of ACE-inhibitors (14-625), 188 for diuretics (24-2776), 185 for CCBs (15-397), and 292 for ARBs (40-1369). Mean age ranged from 50.4 for exercise trials to 55.0 for ARB and diuretics trials. On average, a higher proportion of participants were women in RCTs of exercise interventions (61%) compared to the proportion of women participants in RCTs of medications (ranging from 39% for ARBs to 47% for beta-blockers). While the mean SBP at baseline was 132 mmHg for participants in the RCTs of exercise interventions, it was consistently over 150 mmHg in medication RCTs (**Table 1**).

### *Distribution of participants in exercise and medication RCTs*

In total, 39,742 participants were included in RCTs testing the SBP-lowering effects of medications and exercise interventions. While 29,281 participants were included in medication trials, 10,461 were included in exercise RCTs (**Figure 2a**). On average, trials of

individual medication classes had more participants than those included in the RCTs of different types of exercise (**Figure 2b**). The majority of participants included in exercise RCTs were in trials evaluating the effect of endurance training, as compared to control or other exercise interventions (n=8,174). Relatively more participants were included in trials evaluating moderate-intensity exercise alone (n=4,675) compared to those testing low and high-intensity interventions (**Figure 2c**). 56 exercise trials included hypertensive participants ( $\geq 140$  mmHg), corresponding to 3,508 individuals (**Figure 3**). A total of 6,046 and 1,828 participants were included in exercise RCTs with hypertensive populations when using a cutoff of 130 mmHg and 150 mmHg for mean baseline SBP, respectively.

#### *Risk of bias*

**Figure 4** and **Appendix 5** summarize the risk of bias in a 10% random sample of exercise and medication RCTs. 17/20 exercise RCTs were judged to be at high risk of performance and detection bias due to lack of blinding while only 1 medication RCT was at high risk of bias on this domain. Risk of attrition bias was also higher in exercise trials (5/20) compared to that in medication trials (0/20). Inadequate reporting complicated our assessments for selection bias with the majority of both exercise and medication trials rated at unclear risk of bias.

#### *Comparative effects on SBP*

Across all populations, antihypertensive medications (mean difference: -8.80 mmHg, 95% CrI: -9.58 to -8.02) and exercise interventions (-4.84, 95% CrI: -5.55 to -4.13) were both effective in lowering SBP from baseline as compared to control (**Figure 5a**). Populations receiving medications achieved greater reductions in SBP compared to those participating in physical activity interventions (-3.96, 95% CrI: -5.02 to -2.91).

Compared to control, all types of exercise (endurance: -4.88, 95% CrI: -5.69 to -4.06; resistance: -3.50, 95% CrI: -4.91 to -2.09; isometric: -5.65, 95% CrI: -8.21 to -3.13; and combination of endurance and resistance: -6.49, 95% CrI: -8.17 to -4.82) and all classes of antihypertensive medications (ACE-I: -7.33, 95% CrI: -8.75 to -5.91; ARB: -8.14, 95% CrI: -9.62 to -6.69; CCB: -10.58, 95% CrI: -12.03 to -9.14; and diuretic: -8.06, 95% CrI: -9.48 to -6.64) were effective in lowering baseline SBP (**Figure 5b**).

Overall, different types of structured exercise interventions achieved similar reductions from baseline (**Table 2**). One exception was the combination of endurance and resistance training, which was more effective in reducing baseline SBP than dynamic resistance alone (-2.99, 95% CrI: -5.04 to -0.93). While different classes of antihypertensive medications were generally more effective than different types of exercise interventions, most medication classes (ACE-I, ARB, and diuretic) did not differ beyond chance from isometric resistance and combination of endurance and dynamic resistance exercises.

Participants in low- (-4.60, 95% CrI: -6.51 to -2.69), moderate- (-5.41, 95% CrI: -6.37 to -4.46), and high-intensity (-3.87, 95% CrI: -5.11 to -2.65) exercise groups achieved greater

reductions in baseline SBP than those in control groups (**Figure 5c**). Similarly, low- and high-dose medications were more effective than control, lowering baseline SBP by 8.29 mmHg (95% CrI: -9.13 to -7.46) and 10.71 mmHg (95% CrI: -11.94 to -9.46), respectively. While a dose gradient was seen for medications, there was substantial uncertainty for effects of different exercise intensities.

There was no detectable evidence of inconsistency in the network meta-analyses (**Appendix 6**). In our small-study effects analysis, we found some evidence that smaller studies reported different results than those in larger studies for both exercise and medication interventions (**Appendix 7**). We observed similar model fit with both models according to total residual deviance and deviance information criterion. The estimated mean bias for exercise vs. control was -1.09 (95% CrI: -1.89 to -0.34) and -1.75 (95% CrI: -2.61 to -0.72) for medications vs. control; however, there was no meaningful reduction in between-study heterogeneity when we adjusted for small-study effects, suggesting that this adjustment did not necessarily explain the observed differences in effects across studies. Since the base-case model fitted well, inferences about observed improvements to model fit or lack thereof may be spurious. Regardless, models adjusted for small-study effects tended to produce smaller treatment effect estimates for both exercise and medication interventions. **Appendix 7** compares the base-case results with predicted effect size for an ideal study of infinite size for each intervention.

#### *Comparative effects on SBP among hypertensive populations ( $\geq 140$ mmHg)*

Compared to control, exercise reduced SBP by 8.96 mmHg (95% CrI: -10.27 to -7.64) among hypertensive populations ( $\geq 140$  mmHg) (**Figure 5a**). We did not observe a difference between the SBP-lowering effects of medications and exercise (0.18, 95% CrI: -1.35 to 1.68).

SBP was reduced (compared to control) by endurance (-8.69, 95% CrI: -10.13 to -7.25), dynamic resistance (-7.23, 95% CrI: -10.58 to -3.87), and their combination (-13.51, 95% CrI: -16.55 to -10.45), while the 95% CrI included the null for isometric resistance (-4.92, 95% CrI: -10.28 to 0.38) (**Figure 5b**). Overall, different types of exercise interventions appeared similar to medication interventions in terms of their SBP-lowering effects (**Table 2**).

Hypertensive populations participating in moderate- and high-intensity exercise interventions achieved greater reductions in SBP compared to those in control groups (**Figure 5c**). There were no detectable differences between different intensities of exercise and different doses of medication interventions, however these analyses should be interpreted with caution given the wide 95% CrIs.

#### *Sensitivity analyses with different hypertension cut-offs*

**Figure 6 and Appendix 8** show the findings of sensitivity analyses comparing the SBP-lowering effects of exercise and medication interventions at different hypertension cut-offs. Overall, exercise interventions appeared more effective as we restricted the sample of

exercise trials included in the analysis to those with more hypertensive populations. For example, endurance interventions, compared to control, reduced baseline SBP by 4.88 (95% CrI: (-5.69, -4.06) in the base-case analysis; respective reductions were 6.84 (-7.90 to -5.76) in trials with  $\geq 130$  mmHg; 8.70 (-10.13 to -7.25) with  $\geq 140$  mmHg, and 10.74 (-12.70 to -8.77) with  $\geq 150$  mmHg. There was substantial uncertainty in relative treatment effects when using a cut-off of  $\geq 150$  mmHg.

## Discussion

In this study, we compared the SBP-lowering effects of commonly used antihypertensive medications and exercise interventions. We found that structured exercise was often evaluated in fewer and smaller trials than medications. While the number of participants included in exercise trials accounted for approximately one quarter of the total in medication trials, only one tenth of the overall hypertensive population (using a 140 mmHg cut-off) came from the exercise trials. Our analyses that synthesized the results of 391 RCTs including 39,742 participants showed that individuals receiving medications achieved greater reductions in SBP than those following structured exercise regimens. However, different types of exercise interventions appeared equally effective as most antihypertensive medications when we limited our analyses to trials in populations with high SBP. The effectiveness of exercise increased as we adopted higher SBP cut-offs to define hypertension.

### *Comparison with other studies in the literature*

To the best of our knowledge, our study is the first formal evaluation of the comparative effectiveness of exercise and medications on SBP. However, a large number of previous systematic reviews and meta-analyses have examined the SBP-lowering effects of medications<sup>8,64–67</sup> and exercise separately.<sup>27,68–72</sup> Similar to other reviews, our study identified a diverse set of exercise interventions that varied in terms of their formulation, intensity, frequency, and duration. Aerobic endurance was the most frequently studied type of exercise, followed by dynamic resistance.

Our findings differed from the meta-analysis by Cornelissen and Smart in two key ways.<sup>27</sup> First, the magnitude of SBP reduction achieved with resistance training was considerably higher in our study, likely reflecting the large numbers of newer RCTs included in our study evaluating this type of exercise and having favourable results. This was particularly so when we limited our analyses to exercise RCTs with hypertensive populations. Second, we found compelling evidence that combining endurance and dynamic resistance training was effective in reducing SBP. The previous review had insufficient evidence on the effectiveness of combining endurance and dynamic resistance exercise.

### *Implications for policy and practice*

These findings could be used to examine and improve the evidence base supporting exercise recommendations. Current exercise recommendations are primarily based on observational evidence and highly variable across different settings.<sup>73</sup> For example, in the UK, the National

Health Service exercise guidelines for healthy adults 19 to 64 years of age recommend either (1) a combination of at least 150 minutes per week of moderate aerobic activity and strength training on 2 or more days a week or (2) a combination of 75 minutes per week of vigorous endurance activity and strength training on 2 or more days a week.<sup>74</sup> Notably, while the guidelines specify the recommended duration of strength training, they do not specify its optimal volume and intensity. Examining and corroborating the evidence base behind these recommendations is not straightforward using the available exercise RCTs on SBP. For example, only a small subset of studies identified in our review tested the effectiveness of the combination of endurance and dynamic resistance training. Although these types of interventions were often effective, especially in hypertensive populations, their frequency and duration were not consistently reported to determine the optimal formulation and dose of physical activity to maximize its benefit. We also did not observe a dose-response relationship between exercise intensity and SBP reduction.

Recent changes to major practice guidelines developed by ACC/AHA will substantially increase the number of people labelled as having hypertension.<sup>13,14</sup> While our findings support previous calls to prescribe exercise as a treatment option for hypertension,<sup>75,76</sup> relatively little is known about the effectiveness and comparative effectiveness of implementation strategies for optimal exercise uptake.<sup>77–80</sup> Health care systems are therefore ill-equipped to ensure effective adoption of and adherence to exercise prescriptions. Despite the availability of national guidelines promoting exercise, levels of physical activity remain stubbornly low worldwide.<sup>81</sup> For example, an estimated 40% of adults in the Americas and many European countries are physically inactive.<sup>82,83</sup> Given our findings that even low-intensity exercise may be effective in reducing SBP, renewed attention is warranted to identify effective strategies to promote exercise.

While our study suggests that exercise effectively lowers baseline SBP, the generalisability of these findings to real-world settings should be investigated further. Most exercise trials in our study included healthy adults with optimal or mildly elevated blood pressure. When participants had elevated SBP, exercise was often evaluated as an add-on to background antihypertensive therapy. Unlike trial populations in our review, the majority of individuals in actual clinical practice who are eligible for antihypertensive therapy have multiple chronic conditions and receive several medications. Substituting medication therapy with exercise prescriptions in these populations may therefore be challenging.<sup>85</sup> The proportion of such patient populations who can adopt some meaningful amount of exercise is unknown. This is further compounded by the reporting quality of exercise trials. According to a recent analysis, descriptions of exercise interventions in hypertension trials were inadequately detailed for their replication in practice.<sup>84</sup> Nevertheless, our findings can form the basis of evidence-based discussions between patients and their doctors about the SBP-lowering benefits of exercise. Although the effect of exercise is modest among individuals with moderately elevated SBP, providers should still have such discussions with their patients who are newly eligible for antihypertensive therapy as a result of recent changes to ACC/AHA guidelines.



### *Implications for research*

Studies comparing the effectiveness of medications and non-medication interventions are rare. Similar to our previous study,<sup>28</sup> we did not identify any RCTs that directly compared the SBP-lowering effects of antihypertensive medications and structured training programs. To address this gap, future studies should adopt exercise as an active comparator in trials of interventions aimed at preventing, managing, or treating cardiovascular diseases.

Pharmaceutical companies, which in recent years have sponsored the majority of clinical studies, currently have little incentive to design studies that compare their products to non-medication alternatives.<sup>86</sup> Encouraging sponsors to include established non-pharmacological alternatives in head-to-head trials will require buy-in from drug licensing agencies such as the Food and Drug Administration and European Medicines Agency, health technology assessment bodies such as NICE, research funders such as the National Institutes of Health in the US and National Institute for Health Research in the UK, and research ethics committees.

In the absence of head-to-head RCTs that directly compare exercise and drug interventions, network meta-analyses can rely on existing studies and generate valuable evidence to inform policy and practice.<sup>87</sup> Network meta-analyses that compare the benefits and harms of multiple interventions are increasingly common in the medical literature.<sup>88,89</sup> However, most consider pharmacological or non-pharmacological interventions separately. Combining these bodies of literature in network meta-analyses could identify areas where exercise interventions should be considered as viable alternatives to medications. In areas where evidence is inconclusive or biased, network meta-analyses could help inform the design of future head-to-head RCTs.<sup>90</sup>

### *Limitations*

This study had several limitations. First, our electronic searches were conducted in Medline and did not cover other relevant bibliographic databases. Therefore, we may have missed relevant RCTs of exercise interventions if they were published in journals not indexed in Medline. Still, our review covered almost twice as many RCTs as those included in the most comprehensive systematic review to date.

Second, we did not update the list of studies included in the previously published meta-analyses of antihypertensive medications, which were published from 2008 to 2016. However, it is unlikely that we missed additional RCTs of medications, as the majority of antihypertensive medications are off patent and there is no longer an active research agenda evaluating their SBP-lowering effects.

Third, we relied on indirect evidence to determine the comparative SBP-lowering effects of exercise and medications. Such indirect comparisons could be biased if there is an imbalance in the distribution of unmeasured or unknown relative treatment modifiers across trials comparing different interventions.<sup>91</sup> We summarised results from substantially

heterogeneous RCTs from different settings and time periods. Trials included diverse participant populations, intervention definitions, comparators, and outcome measurements. Findings of our network meta-analyses should hence be interpreted with caution.<sup>92</sup> Transitivity may be tenuous given the typically different levels of SBP in medication vs. exercise trials. However, when we tried to match trial populations more closely, the gap between medication and exercise in efficacy diminished. As we limited our analyses to more hypertensive populations, exercise interventions appeared more effective.

Fourth, while we obtained clinically relevant relative treatment effects for antihypertensive medications, we may have underestimated the magnitude of SBP-lowering associated with exercise interventions. We excluded trials of medications and dosages that were considered to be ineffective or suboptimal by the BNF even though we did not exclude any exercise trials on this basis, as there is no equivalent body that is responsible for evaluating the effectiveness of structured exercise interventions and determining their suitability as treatment options in clinical practice.

Fifth, our review shares the limitations of the studies on which it is based. Although we did not formally evaluate the internal validity of all included RCTs, we conducted a risk of bias assessment in a 10% random sample. Both exercise and medication trials had limitations in their reporting, which severely limited our accurate evaluation. We considered exercise trials to be at higher risk of performance and detection bias as compared to medication trials, primarily due to lack of blinding of investigators and participants in exercise trials. This may have greater implications on the reliability of estimates from exercise trials given the semi-objective nature of SBP-lowering. However, a recent meta-epidemiological study found no significant association between treatment effects and adequate blinding in physical therapy trials.<sup>93</sup> In contrast to the findings of a recent comprehensive review that showed a different level of reporting bias between meta-analyses of pharmacological and non-pharmacological interventions,<sup>94</sup> we observed a similar relationship between trial size and magnitude of effect for both exercise and medications. Small-study effects may reflect publication bias, differential presence of quality issues in smaller trials, but also many other factors.<sup>95</sup> Although exercise trials tended to be smaller, antihypertensive medication trials were not immune to small-study effects, which could explain our findings.

Exercise trials had several other methodological drawbacks. The majority of exercise trials included healthy adults with optimal blood pressure at baseline; reduction in blood pressure may be larger when the starting point is higher. Also, unlike antihypertensive medication trials, most exercise trials evaluated SBP only as secondary or tertiary outcomes; sample sizes were often too small to adequately control for confounding and produce reliable estimates of treatment effects; the composition of control arms was heterogeneous (e.g., some trials included exercise as an add-on to background antihypertensive therapy while others did not allow for such therapy); and the methods used to measure SBP varied considerably across trials (e.g., ranging from office-based measurement to ambulatory measurement). Similar to the findings of a recent analysis, reporting of harms associated with exercise interventions

was rare and inconsistent.<sup>95</sup> Taken together, these variations highlight the need for a more standardised approach to the design, conduct, analysis, and reporting of exercise trials. Whether the reliability of estimates from exercise trials is similar to those from trials of antihypertensive medications should be evaluated in the future.

### *Conclusions*

The effect of exercise interventions on SBP remains under-studied in relation to commonly used medications, especially among hypertensive populations. Many studied types and intensities of exercise interventions demonstrate modest but consistent reductions in SBP across diverse populations and settings. The SBP-lowering effects of exercise among hypertensive populations appear similar to that of commonly used antihypertensive medications but this is tempered by the observed differences in study population characteristics.

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**Table 1.** Overall characteristics of available evidence from randomized controlled trials on exercise and drug interventions.

	Endurance	Dynamic resistance	Isometric Resistance	Combination exercise***	ACE-I	ARB	Beta-blockers	CCB	Diuretic
Number of trials*	135	48	12	31	57	36	63	9	46
Mean age in years	50.8	48.5	51.9	54.0	54.4	55.0	52.1	52.3	55.0
Proportion female	59%	60%	47%	75.4%	41%	39%	47%	N/A**	43%
Mean baseline SBP (mm Hg)	134	125	129	135	157	156	160	N/A**	158
Mean enrolment (range)	58 (15-464)	35 (15-96)	30 (15-48)	65 (16-387)	174 (14-625)	292 (40-1369)	139 (7-1092)	185 (15-397)	188 (24-2776)
Years covered	1976-2018	1987-2018	1992-2018	2001-2017	1983-2002	1995-2004	1968-2008	1988-2003	1978-2009

\* Number of trials does not add up to total number of RCTs included in the analysis, as some RCTs included more than one class of antihypertensive drugs or one type of exercise interventions.

\*\*N/A: not sufficient information reported in meta-analysis report and supplementary material.

\*\*\* Combination of endurance exercise and dynamic resistance training.

**Table 2.** Findings of network meta-analyses. Change from baseline systolic blood pressure (mmHg) achieved when comparing different types of exercise vs. classes of drugs. Lower diagonal shows results of the analysis that pools trials across all populations. Upper diagonal (in grey) shows the results of the analysis focusing on hypertensive populations ( $\geq 140$  mmHg).

-	Endurance	Resistance	Isometric	Combination*	ACE-I	ARB	Beta-blocker	CCB	Diuretic
Endurance	-	1.46 (-2.05, 4.99)	3.77 (-1.73, 9.21)	-4.81 (-7.99, -1.61)	1.35 (-0.64, 3.31)	0.55 (-1.45, 2.55)	-1.81 (-3.82, 0.186)	-3.70 (-7.64, 0.27)	0.66 (-1.33, 2.66)
Resistance	1.37 (-0.15, 2.92)	-	2.32 (-4.02, 8.61)	-6.26 (-10.67, -1.90)	-0.11 (-3.73, 3.50)	-0.90 (-4.52, 2.71)	-3.27 (-6.91, 0.33)	-5.15 (-10.16, -0.20)	-0.78 (-4.41, 2.83)
Isometric	-0.76 (-3.40, 1.86)	-2.15 (-5.04, 0.75)	-	-8.58 (-14.68, -2.45)	-2.42 (-7.89, 3.08)	-3.21 (-8.70, 2.31)	-5.59 (-11.04, -0.05)	-7.48 (-13.91, -0.96)	-3.11 (-8.55, 2.441)
Combination*	-1.61 (-3.34, 0.12)	-2.98 (-5.04, -0.93)	-0.84 (-3.85, 2.13)	-	6.16 (2.81, 9.48)	5.37 (2.03, 8.70)	3.00 (-0.38, 6.32)	1.11 (-3.66, 5.86)	5.48 (2.13, 8.82)
ACE-I	-2.45 (-4.07, -0.82)	-3.83 (-5.83, -1.83)	-1.67 (-4.57, 1.20)	-0.83 (-3.03, 1.35)	-	-0.78 (-2.60, 1.02)	-3.16 (-5.12, -1.21)	-5.04 (-8.98, -1.13)	-0.67 (-2.50, 1.14)
ARB	-3.26 (-4.96, -1.60)	-4.64 (-6.65, -2.61)	-2.49 (-5.42, 0.43)	-1.64 (-3.89, 0.57)	-0.81 (-2.72, 1.07)	-	-2.37 (-4.34, -0.41)	-4.25 (-8.18, -0.33)	0.11 (-1.68, 1.89)
Beta-blocker	-5.70 (-7.36, -4.04)	-7.07 (-9.11, -5.08)	-4.93 (-7.83, -2.01)	-4.09 (-6.28, -1.88)	-3.24 (-5.27, -1.24)	-2.43 (-4.50, -0.36)	-	-1.88 (-5.84, 2.06)	2.48 (0.54, 4.45)
CCB	-7.46 (-11.36, -3.57)	-8.85 (-12.90, -4.80)	-6.70 (-11.26, -2.10)	-5.85 (-10.05, -1.73)	-5.01 (-9.09, -0.97)	-4.20 (-8.30, -0.10)	-1.75 (-5.79, 2.31)	-	4.36 (0.44, 8.29)
Diuretic	-3.17 (-4.81, -1.53)	-4.55 (-6.56, -2.57)	-2.40 (-5.31, 0.49)	-1.56 (-3.78, 0.64)	-0.72 (-2.60, 1.16)	0.09 (-1.77, 1.92)	2.52 (0.50, 4.54)	4.29 (0.27, 8.32)	-

Lower diagonal: mean difference in change from baseline and 95% CrIs from base-case analysis. Negative values favor the row defining treatment, positive values favor the column defining treatment.

Upper diagonal: mean difference in change from baseline and 95% CrIs from sensitivity analysis. Negative values favour the column defining treatment, positive values favour the row defining treatment.

\* Combination of endurance and dynamic resistance exercise.

## Figure legends

**Figure 1.** Flow diagram of study identification and selection.

**Figure 2.** Available evidence comparing **(a)** exercise vs. drugs; **(b)** different types of exercise vs. classes of drugs; and **(c)** different intensities of exercise vs. doses of drugs. The nodes represent different interventions and the lines connecting the nodes represent direct head-to-head randomized controlled trials comparing the interventions. The size of the node and the thickness of the line connecting the nodes are proportional to the number of participants. Combination refers to a combination of endurance exercise and dynamic resistance. Control refers to no exercise.

**Figure 3.** Available evidence in hypertensive populations comparing **(a)** exercise vs. drugs; **(b)** different types of exercise vs. classes of drugs; and **(c)** different intensities of exercise vs. doses of drugs. Combination refers to a combination of endurance exercise and dynamic resistance. Control refers to no exercise.

**Figure 4.** Risk of bias assessment of a 10% random selection of exercise and drug RCTs.

**Figure 5.** Findings of network meta-analyses. Change from baseline systolic blood pressure (mmHg) and 95% CrI achieved with exercise and drug interventions as compared to control (no exercise): **(a)** exercise and drugs; **(b)** different types of exercise and classes of drugs; and **(c)** different intensities of exercise and doses of drugs. Findings of analyses pooling trials from all populations are shown in black; findings of analyses restricting exercise trials to those with mean systolic blood pressure  $\geq 140$  mmHg are shown in white. Combination refers to a combination of endurance exercise and dynamic training.

**Figure 6.** Findings of sensitivity network meta-analyses. Change from baseline SBP (mmHg) and 95% CrI achieved with different types of exercise and drug interventions as compared to control (no exercise) using different mean SBP cut-offs. Findings of analyses pooling trials from all populations are shown in **black**; findings of analyses restricting exercise trials to those with mean SBP  $\geq 130$  mmHg are shown in **grey**;  $\geq 140$  mmHg are shown in **white**; and  $\geq 150$  mmHg are shown in **stripes**. Combination refers to a combination of endurance exercise and dynamic training.