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The Influence of Modality on the Antihypertensive Effects of Exercise: A Meta-Analysis

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Background: Over 80 million adults in the United States have hypertension (~33%); of those, less than half are adequately controlled. Regular participation in exercise is one of the most important modifiable risk factor in the prevention, treatment, and control of hypertension. The antihypertensive effects of exercise have been studied extensively, concluding that aerobic exercise training (AET) and dynamic resistance training (RT) lowers blood pressure (BP) 5-7 and 2-3 mmHg among adults with hypertension. Nonetheless, BP reductions with AET and RT (~1-9 and ~0-6 mmHg) vary widely, highlighting the significant variability in the training response. Patient and exercise characteristics may explain these differences; however, what patient profile and exercise features elicits optimal BP benefit remains unclear. Therefore, we performed two high-quality meta-analyses that adhered to contemporary standards to determine the effectiveness of AET and RT as stand-alone antihypertensive therapy and identify what patient profile and exercise 'dose' elicited optimal antihypertensive therapy. **Methods:** Electronic databases identified 84 and 64 controlled AET (105 interventions) and RT (71 interventions) trials that involved adults ≥19yr and reported BP pre- and post-intervention. Analyses followed random-effects assumptions. **Results:** Participants were White, middle-aged, overweight adults with prehypertension. Moderate-to-vigorous intensity AET and moderate-intensity RT performed ~3-4 $d \cdot wk^{-1}$ for 14-18 wks reduced systolic BP (SBP)/diastolic BP (DBP) ~4/3 mmHg and ~3/2 mmHg versus controls (*ps*<0.01). Greater BP reductions occurred among AET and RT samples with higher resting BP: ~7/6 and ~6/5 mmHg for hypertension, ~5/4 and ~3/3 mmHg for prehypertension, ~3/1 and ~0/1 mmHg for normal BP (*ps*≤0.03). For AET, BP was reduced to the greatest extent among non-White samples with hypertension that achieved the largest fitness gains and performed the highest volumes of AET (-12.0/-12.2 mmHg), twice the

magnitude observed for White samples (-6.8/-6.3 mmHg). Similarly, dynamic RT reduced BP to the greatest extent among non-White samples with hypertension (-14.3/-10.3 mmHg), reductions approximately twice the magnitude previously reported following AET. **Discussion:** These results highlight the critical need for more precise exercise prescriptions that maximize the effectiveness of AET and RT as viable stand-alone or combined antihypertensive therapeutic exercise options among racially/ethnically diverse samples with hypertension.

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Chapter 1

Introduction

1.1 Background and Significance

Cardiovascular disease (CVD) causes 17.3 million global deaths annually, which represents approximately one-third (~30%) deaths worldwide [1, 2]. CVD-mortality follows a similar pattern in the United States (US). It is responsible for one of every three US deaths (~76 million) making it one of the leading causes of mortality [2]. In 2013, over 40% of all CVD-related deaths were attributed to high blood pressure (BP) [2]. In addition to hypertension, approximately 85% of US adults have at least one other CVD risk factor [3].

Hypertension is a major risk factor for CVD [2]. Hypertension leads to an estimated 9.4 million annual deaths worldwide, which is about as many deaths that result from all infectious diseases combined [1]. Nearly ~33% (80 million) of US adults currently have hypertension (systolic BP [SBP] ≥140 mmHg or diastolic [DBP] ≥90 mmHg) [2]; ~6% higher than the Healthy People 2020 goal of 26.9% of US adults with hypertension [4, 5]. By 2030, this number is projected to reach 41.1%, an increase in hypertension prevalence of 8.4% [2, 4]. Another 68 million US adults (~36.3%) have prehypertension (SBP 120-139 mmHg or DBP 80-89 mmHg) [2], and are at increased risk for developing hypertension, incident stroke, myocardial infarction, and CVD [2, 6]. If prehypertension is left untreated it will progress rapidly to hypertension [2, 7]. The residual lifetime risk for developing hypertension is 90%, making it one of the most prevalent, modifiable, and costly CVD risk factors [2]. In 2011, the direct and indirect cost of hypertension totaled $46.4 billion. Based on the current trends, in 2030 these costs are expected to reach ~$274 billion in total medical expenditures [2].

Over the last decade (1999-2012), hypertension treatment (77% versus 60%) and control (52% versus 32%) in the US have improved, whereas hypertension prevalence has remained unchanged (30-32%) [4]. Several modifiable risk factors have been identified in the prevention,

treatment, and control of hypertension, an important one being regular participation in exercise [2, 4, 7-10]. Lifestyle-related factors were recently identified as the only modifiable determinants of hypertension [4]; therefore, more intensive efforts should be focused on promoting these strategies to reduce the significant public health burden of hypertension [2].

1.2 Exercise Recommendations for Hypertension: The ***F***requency, ***I***ntensity, ***T***ime and ***T***ype of the Exercise Prescription

Many randomized control trials (RCTs) have investigated the antihypertensive effects of exercise, and in turn, over 33 meta-analyses have been published to date [11, 12]. Collectively, these meta-analyses concluded that aerobic training (AET) lowers blood pressure (BP) 5-7 mmHg [9, 13, 14], while dynamic resistance training (RT) lowers BP 2-3 mmHg [9, 14-17] among adults with hypertension. Accordingly, the American College of Sports Medicine (ACSM) [9] and other professional organizations and committees [8, 10, 18-20] recommend 30-60 minutes of moderate intensity (i.e., 40% to <60% maximal oxygen consumption) AET on most days of the week [8-10, 18, 20] supplemented by moderate-intensity dynamic RT on ≥2 days·week^{-1} [8, 9, 20] for the prevention, treatment, and control of hypertension.

1.3 The Meta-Analytic Evidence Regarding the Antihypertensive Effects of Exercise

Despite the general consensus that exercise, particularly AET, lowers resting BP, a more recent and critical review of this literature revealed considerable variability in the magnitude of the BP reductions following both AET (i.e., 1-9 mmHg) [12] and dynamic RT (i.e., 0-6 mmHg) [9, 16, 21, 22] for reasons that are not clear [8, 12]. Investigators conducting RCTs often report aggregate-level data with standard deviations exceeding the mean BP change of the sample [23]. Furthermore, ~20-25% of individuals do not lower BP with exercise [24, 25], highlighting the significant inter-variability in the BP response to exercise training [9, 26, 27].

Reasons for inter- and intra-individual variability are not well understood but may be partially attributable to differences in baseline sample and exercise intervention characteristics such

as the *F*requency, *I*ntensity, *T*ime or *T*ype or FITT of the exercise prescription (Ex R_x). Nonetheless, few meta-analyses have documented significant moderation patterns pertaining to these characteristics with the exception of resting BP or BP status (i.e., normal, prehypertension and hypertension) [13, 28-40]. The absence of moderation patterns in the exercise and hypertension literature may be attributed to earlier meta-analyses [29, 36-38, 41, 42] being underpowered to perform moderator analysis due small samples (<10 trials), or because meta-analyses have used statistical approaches that lack the sensitivity to detect exercise-related changes in BP.

More recent meta-analyses [13, 28, 30, 31, 43, 44] with a greater number of included trials (≥28 trials) do not bear this limitation. In addition, the authors of more recent meta-analyses have also had access to standard reporting guidelines [45-47] and to more sophisticated meta-analytic techniques to estimate the exercise-related changes in BP. Theoretically, more recent meta-analyses should be able to calculate and combine effect size estimates from different studies more precisely and investigate heterogeneity to a greater extent [47-49]. Conventional meta-analytic techniques, such as meta-regression, and more complex analyses using multiple moderator models and the moving constant technique should be able to more accurately quantify the influence of sample and FITT characteristics and their interaction on resting BP [11, 50-55]. Furthermore, the moving constant technique can be used to estimate BP effects at different moderator levels to provide greater clinical translation [54].

It is clear that the science of meta-analysis has continued to grow and become more advanced [48, 49]. Taken together, it is reasonable to assume carefully conducted meta-analyses that pursue higher quality methods (e.g., *P*referred *R*eporting *I*tems for *S*ystematic *R*eviews and *M*eta-analyses or PRISMA [56]) should be able to identify what sample characteristics and ‘dose’ of exercise yields the greatest antihypertensive benefits. Yet, the majority of meta-analyses evaluating the antihypertensive effects of exercise still fail to fulfill the requirements of the PRISMA reporting checklist [11, 56-58] which in turn, threatens the validity and clinical translation of their findings.

1.3.1 Reporting Standards for Meta-Analyses

Systematic reviews and meta-analyses often serve as pillars of scientific statements, exercise recommendations, and clinical guidelines [56-58]. Therefore, progressively more rigorous standard reporting practices have been published to improve the overall quality of meta-analyses, focusing on the consistency and transparency of reporting procedures [45, 46, 59-62]. The *QU*ality *O*f *R*eporting *O*f *M*eta-analyses (QUOROM) statement was first published in 1999 [45], and has been updated twice since then: with the PRISMA Statement in 2009 [46], and more recently with the 2015 PRISMA-P Statement [56, 63].

Johnson and colleagues [11] recently reviewed the methodological quality of 33 published meta-analyses that examined the effects of exercise on BP. They found more recent meta-analyses achieved higher quality scores, but none completely satisfied contemporary quality standards [11]. The majority of meta-analyses did not provide adequate information related to their search methods or duplicate efforts for study selection and data extraction. Further, few meta-analyses documented the scientific quality of included trials, how study quality interacted with their findings, or discussed the scientific quality of the included studies in relation to their conclusions [11, 55, 61, 64]. Departure from these contemporary reporting standards [47, 56, 63] may contribute further to the poor understanding of how important moderators, in particular the sample clinical characteristics, the 'dose' of exercise (i.e., FITT of the Ex R_x), and other study features influence the antihypertensive effects of exercise.

1.4 The Blood Pressure Response to Aerobic Exercise Training

Approximately 27 meta-analyses have examined the effects of AET on resting BP [11]. Given the volume of data, the ACSM classified the BP lowering effects of AET as Category *A* level of evidence, meaning there was "overwhelming data from RCTs provided a consistent pattern of findings regarding the effects of AET on resting BP" [9]. On average, the participants in these meta-analyses were White, middle-aged men and women with prehypertension who performed AET 3

days·week^{-1} for 40 min·session^{-1} at 65% of maximal oxygen consumption (VO_{2max}) for 16 weeks. This dose of aerobic exercise reduced BP 2-3 mmHg among samples with normal BP and 5-7 mmHg among samples with hypertension [9].

Although these meta-analyses confirmed that the greatest antihypertensive benefits are experienced by samples with higher baseline BP, they have not consistently identified other moderation patterns, nor have they completely satisfied contemporary quality standards [11, 46, 64]. Only three meta-analyses to date reported that race/ethnicity [44], age [65], sex/gender [31], and aspects of the FIT [14, 65] influenced the BP reductions following AET. Whelton and colleagues [44] found that AET reduced resting SBP/DBP to greater levels among Asian (6/7 mmHg) and Black (11/3 mmHg) compared to White samples (3/3 mmHg, $p<0.05$), while Hayashino and colleagues [65] observed that AET reduced SBP to greater levels among adults aged ≥60 yrs (~5 mmHg) than <60 yrs (~1 mmHg); and Cornelissen and Smart [31] found that AET was more effective at lowering resting BP among samples involving all men (3-5 mmHg) than all women (~1 mmHg).

In addition, Hayashino et al. [65] and Cornelissen et al. [31] identified FIT characteristics that maximized the BP reductions following AET but with conflicting results. Hayashino et al. [65] reported that greater reductions in BP occurred with longer duration (≥45 min·session^{-1}) AET (~4 mmHg); whereas Cornelissen et al. [31] found shorter duration (30-45 min·session^{-1}) AET to be more effective (~3-4 mmHg). In addition, Cornelissen and Smart [31] also reported that AET performed at moderate-to-vigorous than low intensity and <210 min·week^{-1} than ≥210 min·week^{-1} of AET elicited the greatest BP reductions. Unfortunately, meta-analyses have not routinely identified moderator patterns, and in the few instances that they have, they are not consistent across meta-analyses [9, 11, 12, 24, 26] and in some cases they conflict [14, 65]. Collectively, these limitations highlight the paucity of evidence to support a more personalized approach to the Ex R_x for adults with hypertension.

To date, few meta-analyses have attempted to quantify the level of heterogeneity among included trials, and rarely have they been able to explain BP variability through moderator analysis [31, 44, 65]. The inability of meta-analyses to explain inconsistencies in the BP response following AET may be attributed to the poor reporting of sample and FIT characteristics in the literature itself, or the limited statistical methods that have been used to investigate heterogeneity. The majority of meta-analyses have performed moderator analysis using subgroups despite the availability of conventional meta-analytic techniques (i.e., meta-regression) and more sophisticated approaches that involve multiple moderator models [53, 66]. Subgroup analysis, a statistical procedure similar to analysis of variance (i.e., ANOVA), is most appropriate for research questions focused on analyzing the differences among group means, which may have lacked the sensitivity and precision needed to detect exercise-related changes in BP [67, 68]. Unlike meta-regression, subgroup analysis does not allow for multiple moderators to be examined together [69], and furthermore, it is not suitable for more complex moderator analysis involving the moving constant technique [54]. The moving constant technique can estimate BP changes at levels of individual moderators (i.e., sample and FIT characteristics), to enhance the clinical translation of the findings [54].

In sum, the limitations stated above have precluded a comprehensive meta-analytic investigation of the antihypertensive effects of AET. Meta-analyzing *all of the available literature* using more sophisticated meta-analytic techniques, such as meta-regression and the moving constant technique, will allow for increased precision in estimating the effect of how sample and FIT characteristics, and their interactions modulate the BP response to AET.

1.5 The Blood Pressure Response to Dynamic Resistance Training

In the 2004 position stand on exercise and hypertension, the ACSM [9] graded the level of evidence supporting the BP lowering effects of dynamic RT as Category *B,* meaning there were "few randomized trials that existed which are small in size and the results were inconsistent." Thus, the ACSM recommends individuals with hypertension perform dynamic RT as a supplement to AET [9].

At that time, few RCTs had investigated the BP response to dynamic RT and with conflicting results. The BP lowering effects of dynamic RT were diverse, with BP reductions ranging from ~5-14 mmHg for SBP and ~2-8 mmHg for DBP [70-73]. However, there were also trials that did not report BP reductions following dynamic RT [70, 72-75], and trials that observed large BP reductions for both exercise and control groups [70, 72-77]. Furthermore, only two meta-analyses had been conducted on the BP response to RT [37, 42] that included samples of middle-aged, White men with normal BP to prehypertension.

Since then, additional RCTs and meta-analyses have been conducted to examine the BP response to dynamic RT [14-17, 21, 22]. Nonetheless, in contrast to the high-level of evidence supporting the BP-lowering effects of AET [12], there is much weaker evidence supporting the efficacy of RT as a viable therapeutic option to lower BP among adults with hypertension that is primarily based on the findings of six meta-analyses [12, 14-17, 21, 22]. Surprisingly, these meta-analyses included mostly healthy adults with normal BP and prehypertension. Collectively, these meta-analyses concluded that dynamic RT lowers BP by 2-3 mmHg independent of resting BP values [9]. However, two meta-analyses by Kelley et al. [21] and Cornelissen et al. [16] reported larger reductions of 4-6 mmHg, rivaling the magnitude of the reductions reported for individuals with hypertension following AET [9]. Both Kelley et al. [21] and Cornelissen et al. [16] included the smallest number of RT trials (~9) and participants (~259 to 290) compared to the previous meta-analyses, that ranged from 11 [15] to upwards of 28 RT trials [14, 17] with samples sizes of 320 [15] to 1,012 participants [14, 17]. A smaller number of available trials may have resulted in less precision when estimating the BP lowering effects of dynamic RT.

In contrast to AET, meta-analyses investigation the BP response to dynamic RT have yet to identify any moderators of the BP changes following dynamic RT. The absence of moderator variables to date may be attributed to the small number of available trials (~9-25), wide ranges in the FIT of dynamic RT program, and use of subgroup analysis with categorical variables rather than

more sophisticated techniques such as meta-regression with continuous variables to investigate potential moderators. Meta-analysis can be a valuable tool for researchers, especially in small bodies of literature with disparate results [50, 52, 78, 79]. However, the advantages of meta-analysis over the primary literature are only realized if proper statistical approaches are undertaken, and researchers adhere to high quality contemporary standards for conducting and reporting for meta-analyses [11, 56, 61, 64].

Nonetheless, none of the meta-analysis conducted to date have completely satisfied contemporary methodological study quality standards [11, 56, 64], nor have they been able to identify important patient or RT characteristics that modulated the BP response to dynamic RT. Collectively, these observations suggest that the antihypertensive effects of RT may have been underestimated, and they call into question the generalizability of this weak and limited literature to adults with hypertension [11, 12].

1.6 Statement of the Problem

Despite the large number of RCTs and meta-analyses that have examined the BP lowering effects of exercise, little is known about how sample and FITT exercise characteristics may modulate BP changes following exercise. In general the existing literature supports: 1) BP can be reduced following AET and dynamic RT but the magnitude of the BP response varies considerably across trials and modality [12]; 2) sample characteristics may account for some of this variability but meta-analyses have yet to adequately analyze these effects [9, 11, 12, 55]; 3) the 'dose' of exercise or FITT characteristics may also account for some of the variability in the BP response but meta-analyses to date have not consistently found these variables to influence BP changes following exercise training [9, 11, 12]; and last, 4) most meta-analyses have not satisfied contemporary standards [11], most notably, failing to document the study quality of included trials and determine whether quality *independently* or *interactively* influenced their findings [55]. It is possible that low methodological

quality trials have suppressed dose-response patterns and moderator variables, and these patterns will emerge more clearly in higher methodological quality trials.

1.7 Specific Aims and Hypotheses

Therefore, this dissertation proposes to perform two meta-analyses that adhere to high quality, contemporary methodological standards to address the current limitations of the existing literature:

Specific aim 1: To meta-analyze the existing AET literature with high quality methods to determine the effectiveness of AET as an antihypertensive therapy and identify what patient clinical and AET characteristics elicit optimal antihypertensive BP benefit.

Hypothesis 1: Patient clinical (i.e., age, body mass index, sex/gender, race/ethnicity, BP medication use, etc.) and AET FIT characteristics will moderate the antihypertensive effects of AET.

Alternative Hypothesis 1: Patient clinical and AET FIT characteristics will not moderate the antihypertensive effects of AET.

Specific aim 2: To meta-analyze the existing dynamic RT literature with high quality methods to determine the effectiveness of RT as stand-alone antihypertensive therapy and identify important moderators (i.e., patient clinical and RT FIT characteristics) of the BP response to provide insight into the optimal dose of RT to lower BP among adults with hypertension.

Hypothesis 2: Patient clinical (i.e., age, body mass index, sex/gender, race/ethnicity, BP medication use, etc.) and RT FIT characteristics will moderate the antihypertensive effects of dynamic RT and provide insight into the optimal dose of RT as stand-alone antihypertensive therapy for adults with hypertension

Alternative Hypothesis 2: Patient clinical and RT FIT characteristics will not moderate the antihypertensive effects of dynamic RT.

1.8 Clinical Significance

In total, over 33 meta-analyses have been published to date [11, 12]. Collectively, these meta-analyses included primarily White middle aged men and women adults with normal BP to stage-1 hypertension and variables related to race/ethnicity and BP medication use were poorly reported. Meta-analyses concluded that exercise training can lower BP among adults with normal to stage-1 hypertension but that the magnitude of BP reductions were specific to modality: AET can lower BP 2-3 mmHg among individuals with normal BP and 5-7 mmHg among individuals with hypertension [9, 13, 14], and dynamic RT can lower BP ~1-3 mmHg, independent of resting BP values [9, 14-17]. It is clear that BP reductions vary widely by modality, however, the influence of sample or FITT characteristics or their interaction on resting BP are still poorly understood [31, 44, 65].

There is little meta-analytic evidence to support that sample characteristics (i.e., age, sex/gender, race/ethnicity, antihypertensive medication use, etc.) influence the BP response to exercise [9]. Therefore the ACSM [9] recommends a generic Ex R_x of primarily aerobic exercise most days of the week supplemented by dynamic RT 2-3 days·week^{-1} to treat, prevent, and control hypertension. However, ~20-25% of individuals do not lower BP with exercise [24, 25], and there is considerable individual variability in this response [9, 23-26]. Reasons for inter- and intra-individual variability are not clear but suggest that an individualized approach to the Ex R_x for individuals with hypertension may provide greater antihypertensive effects than the current recommendations do. Nonetheless, meta-analyses to date have contributed little to our understanding of how important moderators, in particular the sample clinical characteristics, the 'dose' of exercise (or FITT), and other study features influence the antihypertensive effects of exercise. Knowledge of these features can, in turn, better inform exercise guidelines and recommendations regarding the antihypertensive effects of exercise for policy makers, health care providers, and exercise professionals and increase the clinical utility of and adherence to exercise as an antihypertensive lifestyle therapy.

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Chapter 2

The Antihypertensive Effects of Aerobic Exercise Training:

A Meta-Analysis

THE ANTIHYPERTENSIVE EFFECTS OF AEROBIC EXERCISE TRAINING: A META-ANALYSIS

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Abstract

Aerobic exercise training (AET) is recommended as antihypertensive lifestyle therapy because it lowers blood pressure (BP) 5-7 mmHg among most adults with hypertension. Yet due to significant inter-variability in the BP response to AET, it is unclear what types of patient populations would benefit most from AET as antihypertensive therapy. The purpose of our meta-analysis was to identify what patient and exercise features elicit the largest BP benefits. Electronic databases identified 84 controlled AET trials (105 interventions) that involved adults ≥19 yr and reported BP pre- and post-AET. Analyses followed random-effects assumptions. Participants (*n*=3,634) were White (18% non-White), middle-aged (47.9±12.9yr), overweight (27.6±3.3 kg·m^{-2}) adults with prehypertension (systolic BP [SBP]/diastolic BP [DBP]: 130.8±12.7/81.6±9.0 mmHg). AET performed at moderate-to-vigorous intensity (5.9±1.7 metabolic equivalents [MET]) for 44.4±23.7 min·session^{-1}, 3.5±1.1 d·wk^{-1} for 18.3±16.6 wks reduced SBP (d_+=-0.37; 95% *CI*: -0.48, -0.27; -3.5 mmHg) and DBP (d_+= -0.35; 95% *CI*: -0.45, -0.24; -2.7 mmHg) compared to control. Greater BP reductions occurred among samples with higher resting BP: ~7/6 mmHg for hypertension, ~5/4 mmHg for prehypertension, and ~3/1 mmHg for normal BP (*p*=0.033/0.019 SBP/DBP, respectively). Moderate-to-vigorous intensity AET conferred the greatest BP reductions among non-White samples with hypertension that achieved the largest physical fitness gains and performed the highest volumes of AET (-12.0 mmHg, 95% *CI*: -15.1, -8.7/-12.2 mmHg, 95% *CI*: -15.5, -8.9), reductions nearly twice that observed for White samples (-6.8 mmHg, 95% *CI*: -9.4, -4.2/-6.3 mmHg, 95% *CI*: -8.8, -3.7). These results highlight that critical need for more precise exercise prescriptions that maximize the effectiveness of AET as antihypertensive therapy for certain patient populations.

Key words: Blood Pressure; Hypertension; Lifestyle Intervention; Systematic Review

Introduction

Hypertension is the most prevalent, modifiable, and costly cardiovascular disease risk factor (CVD) [1]. Aerobic exercise training (AET) is universally recommended as first line antihypertensive lifestyle therapy due to the strong level of evidence supporting it lowers blood pressure (BP) 5-7 mmHg among most adults with hypertension [2]. Therefore, the American College of Sports Medicine [2] and other professional organizations and committees [3-7] recommend 30-60 minutes of moderate intensity (i.e., 40% to <60% maximal oxygen consumption) AET on most days of the week for the prevention, treatment, and control of hypertension. Nonetheless, the resultant BP reductions from these recommendations range widely from 1-9 mmHg [8], highlighting the significant inter-variability in the BP response to AET [2, 9, 10].

Over 33 meta-analyses have been conducted to summarize the antihypertensive effects of exercise, of which 27 have focused on AET [11]. None of these meta-analyses completely satisfied contemporary quality standards [11-13], and most failed to identify whether patient (i.e., resting BP, race/ethnicity, sex/gender, etc.) or aerobic exercise characteristics (i.e., the *F*requency, *I*ntensity, and *T*ime or FIT) modulated the BP response to AET. Only three meta-analyses to date have reported that race/ethnicity [14], sex/gender [15], age [16], and aspects of the FIT [16, 17] influenced the BP reductions following AET, and these three meta-analyses each found different patterns. For example, Whelton and colleagues [14] found that AET reduced resting systolic BP (SBP)/diastolic BP (DBP) to greater levels among Asian (6/7 mmHg) and Black (11/3 mmHg) compared to White samples (3/3 mmHg, $p<0.05$), while Hayashino and colleagues [16] observed that AET reduced SBP to greater levels among adults aged ≥60 yrs (~5 mmHg) than <60 yrs (~1 mmHg), and Cornelissen and Smart [15] reported that AET reduced BP to a greater extent among samples of all men (~3-5 mmHg) than all women (~1 mmHg). In addition, Hayashino et al. [16] reported greater BP reductions (~4 mmHg) following longer duration (≥45 min·session^{-1}) AET, whereas Cornelissen et al. [15] found shorter duration (30-45 min·session^{-1}) AET elicited greater BP reductions (~3-4 mmHg).

Despite the strong level of evidence to support the antihypertensive effects of AET, there is significant inter- and intra-variability in the magnitude of reported BP reductions that result from AET ranging from 1-9 mmHg [8, 11], and meta-analyses have been unable to identify consistent patterns in what patient and exercise features result in optimal BP benefit. Reasons for these discrepancies are not clear, but may partially reside in the fact the volume of available literature is continually increasing, or the inability of past meta-analyses to adequately explore high levels of heterogeneity that arise from combining trials with widely varying sample and exercise intervention characteristics.

Therefore, we performed a meta-analysis that adhered to high-quality contemporary standards with the primary purpose of identifying what patient clinical and AET characteristics are associated with the greatest antihypertensive therapeutic BP benefit.

Methods

This study fully satisfies the criteria implied by the PRISMA Statement (*P*referred *R*eporting *I*tems for *S*ystematic *R*eview and *M*eta-*A*nalyses) [18, 19] and AMSTAR Methodological Quality Scale (*A*ssessment of *M*ultiple *S*ys*T*em*A*tic *R*eviews) [13, 20].

Inclusion Criteria

Included reports satisfied four *a priori* inclusion criteria: (1) involved adult participants ≥19 yr [21-23]; (2) followed a controlled study design comparing AET to a non-exercise, non-diet control or comparison group; (3) reported pre-and post-intervention BP for the AET and the control/ comparison groups; and (4) reported the FIT of the AET intervention. Trials were excluded if they involved populations with diseases unrelated to CVD (i.e., cancer survivors, substance abusers, human immunodeficiency virus, or AIDS) or if they involved participants using weight loss drugs, diet therapy, or diet modifications.

Search Strategy

Aided by a medical librarian at the University of Connecticut (JL), we systematically searched several electronic interfaces from their inception until January 31, 2014 using a Boolean search strategy. Potential qualifying reports were retrieved from the following electronic databases: Cumulative Index to Nursing and Allied Health Literature, PubMed (including Medline), Scopus (including EMBASE), SportDiscus, and Web of Science (see Appendix 1 for the complete search strategy). The reference lists of included studies and relevant meta-analyses and reviews were also manually searched for additional reports. After retrieving all potentially qualifying reports, duplicate records were removed, and three investigators (HVM, TUG, LML) screened the sample for inclusion with duplication of effort.

Approximately 2,000 potentially relevant reports were reviewed for eligibility. Of these, we identified 84 controlled trials that satisfied the inclusion criteria (See Appendix 2 for the reference list of included studies). Six trials compared the antihypertensive effects among men versus women [24, 25], pre- versus post-menopausal women [26], and samples with normal BP versus prehypertension [27] and hypertension [28, 29], yielding 90 *independent* AET interventions. Eleven trials compared >1 AET interventions to a *single control group* (i.e., *non-independent* comparisons) that included: lower versus higher AET intensity [30-32], frequency (days·week^{-1}) [33] or duration (min·session^{-1}) [34]; arm versus leg cycle ergometer [35], walking versus fitness [36], and group versus home-based AET performed at various intensities [25], yielding 105 *total* AET interventions (Figure 1 shows the systematic search and selection process for included AET trials).

Data Extraction and Coded Variables

All coded variables were extracted using a standardized coding form and coder manual that was previously developed by a team of experts (LSP, BTJ, TBHM) and pilot tested. Two trained coders (HVM, TUG) independently extracted and entered the study information with high reliability across all dimensions (mean Cohen's κ=0.82 for categorical variables [37]; mean Pearson's r=0.90

for continuous variables); all disagreements were resolved by discussion. Coded variables included: (1) study characteristics (e.g., publication year, study location or region, primary study outcome); (2) experimental study design (e.g., single versus multiple AET interventions, between or within-group design, level of supervision); (3) sample clinical characteristics (e.g., baseline BP, age, race/ethnicity, sex/gender, BP medication use); and (4) features of the AET intervention including the FIT.

Included trials rarely disclosed the race/ethnicity of their study participants (only 18% did) [25, 34, 38-50]. When unreported, we estimated race/ethnicity based on the study location [51]. Samples were considered "White" when the study was conducted in North America, Europe and Australia; "Asian" when conducted in Asian countries; "Hispanic and/or Latino" when conducted in South America; and "Black" when conducted in African countries.

Methodological Study Quality Assessment

Included trials were assessed for methodological study quality using a modified version of the Downs and Black Checklist [52, 53] (see Appendix 3 for the augmented checklist). This instrument [54] is well validated in the health science literature and has been shown to be valid and reliable in assessing RCTs and non-RCTs. The Downs and Black Checklist [54] addresses five subscales of methodological quality: (1) reporting, (2) external validity, (3) bias, (4) confounding, and (5) power, making it one of the most comprehensive extant instruments to evaluate study quality [55]. Methodological study quality score was gauged as the percentage of items satisfied out of a possible 29-point total. A similar approach was used to evaluate each study quality subscale, which provided a summary of the methodological strengths and weaknesses for each study. Consistent with other reviews [52, 53], ranges in overall methodological study quality scores were grouped into three quality levels: low (≤14 points, <50%), moderate (>14 to 23 points, 50-79%), and high (≥24 points, ≥80%). In addition to quantifying the overall quality of the AET literature, we examined how overall study quality (or individual quality items) influenced the BP response to AET independently or interactively [56] with other moderators.

Study Outcomes, Effect Size Calculation, and Moderator Analyses

The standardized mean difference effect size (*d*) was used to quantify the effectiveness of AET as antihypertensive therapy, defined as the magnitude of change in resting SBP and DBP post- versus pre-intervention, correcting for small sample size bias and baseline differences [57, 58]. Whenever possible, multiple comparisons were disaggregated for trials with more than one AET *and* control intervention groups [24-29] and analyzed as individual studies [59] (i.e., *independent* comparisons) (see Appendix 4.1 for effect size estimations). However, several trials compared two [30, 31, 34-36, 45, 60, 61] and three [25, 32] AET interventions to a single control group (i.e., *non-independent* comparisons), to control for the *dependency* among our effect sizes (i.e., multiple AET interventions compared to a single control [62]), we used the within-group effect size estimate for all moderator analyses, i.e., AET and control groups were treated as separate observations (see Appendix 4.2 for effect size estimations). Negative *d* values indicated greater BP reductions were observed at post- compared to pre-intervention; the magnitude of the mean difference can be interpreted as -0.20, -0.50, and -0.80 for small, medium and large reductions in resting BP [63]. Last, we provided the equivalent BP change in mmHg as a supplement to the observed *d* in order to enhance the clinical relevance of our findings (see Appendices 4.3 and 4.4 for the methods used to calculate the raw metric in mmHg).

We used Stata 13.1 (StataCorp, College Station, TX) [64] with macros for meta-analysis [59] to perform all statistical analyses, incorporating random-effects assumptions. We visually examined funnel plots for any asymmetries in the effect size distribution to identify potential publication or other reporting biases [65], in addition to performing statistical tests of bias using Begg [66] and Egger [67] methods. Publication bias was detected using Begg's (SBP: z=-3.13, p=0.002 and DBP: z=-3.40, p=0.001) but not Egger's (SBP: t=-1.76, p=0.081 and DBP: t=-1.53, p=0.128) tests. After adjusting for suspected publication bias using the Duval and Tweedie trim and fill technique [68], our results remained significant and with high levels of heterogeneity for SBP (Q=358.2, p<0.001;

I^2=66.7%, 95% *CIs*: 59.8%, 72.5%) and DBP (Q=297.2, p<0.001; I^2=63.7%, 95% *CIs*: 55.4%, 70.4%) [69, 70] (see Appendix 11, Figure S1, for the publication bias results, unadjusted and adjusted funnel plots via the trim and fill technique). However, it is important to note that these tests assume a single population of effect sizes and may inaccurately identify publication bias when significant heterogeneity is present [65, 71]. Moreover, asymmetries can also result from other biases, such as clinical heterogeneity and (poor) study quality [67, 72, 73].

Inconsistencies in *d* values were estimated with the I^2 statistic and its confidence intervals (95% *CIs*) [70, 74]. I^2 values range from 0% (homogeneity) to 100% (greater heterogeneity). As I^2 increases, homogeneity is less likely and heterogeneity is more likely; a *CI* that does not include 0% indicates that the hypothesis of homogeneity is rejected, and an inference of heterogeneity is merited [70, 75].

Moderator analyses were used to explain variability in *d*s for SBP and DBP, using weighted regression models with maximum likelihood estimation of the random-effects weights, the inverse of the variance for each *d*. Continuous moderators were mean centered and categorical variables were contrast coded before generating interaction terms or examining multiple moderators simultaneously [56, 76]. Significant moderators identified with bivariate meta-regression analyses were combined in multiple moderator models for SBP and DBP and examined simultaneously to explain unique study variance. In each multiple moderator model, the moving constant technique [76] was used to estimate the magnitude of weighted mean effect sizes ($\hat{d}_+$) and their *CIs* at different levels of interest for individual moderators that represented a range of observations, including minimum and maximum values while statistically controlling for the presence of moderators. For both SBP and DBP, an additive model was generated from the final model that represented the greatest *potential* antihypertensive benefit that could be achieved with AET. Individual moderators and interaction terms were evaluated simultaneously at the level that conferred the greatest BP benefit (i.e., greatest

BP reductions), which in turn, demonstrated the combination of patient and AET characteristics that elicited optimal antihypertensive therapy. Finally, the proportion of between-study variance explained by the model (i.e., Multiple *R*) and the residual unexplained variance (i.e., I^2 Residual) are provided (see Model Summary for Tables 2 and 3). Summary statistics are presented as *M*ean ± standard deviation (*M* ± SD) unless otherwise stated. Two-sided statistical significance was $p<0.05$.

Results

Study Characteristics

AET interventions were published between 1976 and 2013 (2000±9 yr), and conducted in North America (51.4%, *k*=54), Europe (29.5%, *k*=31), Asia (9.5%, *k*=10), Africa (3.8%, *k*=4), Australia (2.9%, *k*=3), and South America (2.9%, *k*=3). Among the trials that reported sex/gender (three trials did not), 16 and 31 trials involved all women (18.4%) or all men (35.6%), respectively; the remaining trials involved samples of mixed sex/gender (46.0%, *k*=40). The majority of AET interventions were RCTs (80%, *k*=84) and received financial support from at least one source (73.3%, *k*=77), yet less than half examined BP as a primary study outcome (46.7%, *k*=49). Most RCTs (84.5%) used a parallel (i.e., between-subject) study design (*k*=71), six interventions [30, 38, 77-79] used a within-subject, cross-over design, and small proportion of RCTs involved a “placebo” comparison group instead of a non-exercise or ‘wait-listed’ control. In total, 10 AET trials used “placebo” or “active control” that included: stretching/flexibility exercises 3 days·wk^{-1} [47, 80-83], low intensity exercise [29, 84] or yoga [85] 2-3 days·wk^{-1}, weekly health education lectures [86], or a once-daily supplement (i.e., sugar pill) [87].

[INSERT FIGURE 1]

Included interventions achieved “moderate” or “fair” quality on average (64.5% of items satisfied) [52, 53], although methodological study quality scores varied widely (41.4-86.2%). (Appendix 5 summarizes the overall methodological study quality for the AET sample and how well AET interventions satisfied individual quality items). Trials were most likely to satisfy the reporting

(77.5%±13.4%), internal validity-bias (70.0%±9.6%), and internal validity-confounding (62.6%±21.0%) quality subscales, but were least likely to satisfy external validity (49.6%±40.7) and power (1.7%±11.7%). None of the individual quality subscales emerged as significant moderators of the BP response to AET. Finally, only two trials satisfied ≥80% of the Downs and Black study quality checklist items (83.6%±2.8%) [38, 77]. (Appendix 6 in describes the overall and itemized methodological study quality for each of the included AET trials).

Sample Characteristics

Baseline sample characteristics were similar between the AET (*n*=2,200) and non-exercise control (*n*=1,434) groups ($p>0.05$). Overall, participants (*n*=3,634) were sedentary (97%), middle-aged (47.9±12.9 yr), overweight (27.6±3.3 kg·m^{-2}) adults with prehypertension (SBP/DBP: 130.8±12.7/ 81.6±9.0 mmHg). The included interventions had mostly White (80%, *k*=72) samples (*n*=2,995), with 20% comprising a "non-White" sample: 11% (*k*=10) Asian (*n*=391) [41, 50, 78, 88-94], 6% (*k*=5) African American (*n*=169) [45, 47, 49, 95, 96], and 3% (*k*=3) Hispanic/Latino (*n*=79) [80-82]. Approximately 13% (*n*=472) of the AET sample was on antihypertensive medication, but nearly half of AET trials failed to disclose BP medication use (58% did). Almost all of the AET interventions (88%, *k*=92) assessed physical fitness before and after AET, of which ~69% (*k*=73) did so via maximal or peak oxygen consumption expressed relative to body weight (58%, *k*=61) (ml·kg·min^{-1}) or in absolute units (11%, *k*=12). Table 1 provides additional details regarding the different assessment techniques used to quantity fitness (see Table 1 footnote). To accommodate various physical fitness measurements, we examined the percent change in fitness after versus before AET (% change=$[\text{Fitness}_{Post-Pre}/\text{Fitness}_{Pre}]\times 100\%$). Collectively, AET and control samples had poor physical fitness levels at baseline (29.0±8.1 ml·kg·min^{-1}) [97]; non-White (22.7±5.0 ml·kg·min^{-1}) were lower than White samples (29.7±7.7 ml·kg·min^{-1}) ($p<0.001$). Overall, AET significantly improved physical fitness compared to baseline values (~17%); fitness gains were larger

among non-White (19.5%±12.4%) than White samples (16.2%±14.8%) (*p*<0.001). In addition to improved physical fitness, the AET group reduced body weight, body mass index and body fat percent compared to baseline values (*ps*<0.001); the percent change from baseline was greater following AET versus control for body weight (-1.4%, *p*<0.01), body fat percent (-3.4%, *p*<0.01), and body mass index (-1.3%, *p*=0.05) (see Appendix 7 for a summary of select characteristics evaluated post- versus pre-intervention for AET and control groups).

[INSERT TABLE 1 HERE]

Aerobic Exercise Training Intervention Characteristics

AET was performed at moderate-to-vigorous intensity (5.9±1.7 metabolic equivalents [MET]) for 44.4±23.7 min·session^{-1}, 3.5±1.1 days·week^{-1} for 18.3±16.6 weeks. Most AET programs involved walking (26%), cycling (24%), or combinations of walking with cycling, jogging or running (23%). (See Appendix 8 for a general description of the AET and control intervention characteristics). Overall, AET programs were within the recommended AET volume range of ≥500–1,000 MET·min·week^{-1} (~850 MET·min·week^{-1}) [97], with no difference in the exercise volume performed among White (856.5±411.7 MET·min·week^{-1}) and non-White samples (827.8±300.5 MET·min·week^{-1}) (*p*=0.780). Direct supervision was reported in 52% of the AET interventions (*k*=55); 14% of interventions used a combination of supervised and unsupervised sessions (*k*=15), and 18% of interventions were not supervised (*k*=19). Finally, samples demonstrated high adherence to AET completing ~87% of all training sessions, but only 64% reported this detail (Appendix 8).

Resting Blood Pressure Assessment

Overall, included AET trials failed to disclose important details related to the resting BP assessment. The majority of AET interventions assessed BP manually (53%) or with an automated monitor (21%) while participants were in a seated (68%) or supine (32%) position, yet one-fourth of trials did not report these details (See Appendix 9 for the general description of the resting BP assessment details). A small subset of AET interventions (*k*=9) assessed ambulatory BP in addition

to causal/clinic BP [29, 30, 39, 78, 82, 89, 98, 99], but less than half monitored BP for 24 hours [29, 82, 89]. AET interventions were least likely to disclose the timing of pre-and post-BP assessments: Only half (52%) reported the duration (minutes) of quiet rest preceding baseline BP assessment, and even fewer reported (20%) the duration (hours) between the last exercise bout and the final post-intervention BP measurement (Appendix 9).

The Antihypertensive Effects of Aerobic Exercise Training

On average, small to moderate reductions in SBP (d_+=-0.37; 95% *CI*: -0.48, -0.27; -3.5 mmHg) and DBP (d_+=-0.35; 95% *CI*: -0.45, -0.24; -2.7 mmHg) were observed following AET relative to control, whereas moderate to large reductions in SBP (d_+=-0.45; 95% *CI*: -0.53, -0.37; -5.9 mmHg) and DBP (d_+=-0.41; 95% *CI*: -0.49, -0.33; -3.7 mmHg) were observed after versus before AET only (i.e., within-group weighted mean effect size estimates). Collectively, these effect size estimates lacked homogeneity. Appendix 10 provides the weighted mean effect sizes and tests for homogeneity (i.e., *Cochran Q* [100] and I^2 [70, 75] statistics) for SBP and DBP. (See Appendix 12, Figure S2, for the contour-enhanced funnel plots, i.e., confunnels, for the visual representation of the effect size distribution for SBP and DBP).

Moderator Analyses

Bivariate meta-regression analyses revealed significant moderators for SBP and DBP related to sample, AET, and methodological quality characteristics. When combined in a multiple moderator models, significant bivariate models explained between ~48% and 90% of the observed heterogeneity in the BP response to AET (see Tables 2 and 3).

Five moderators explained unique variance relating to the effectiveness of AET to reduce SBP when entered in a multiple regression model, accounting for ~92% of the between-study variance (see Table 2). Among the AET groups, SBP reductions were greater among samples with higher resting SBP (p=0.033), which occurred in a dose response fashion: -7.2 mmHg for

hypertension, -5.0 mmHg for prehypertension, and -3.3 mmHg for normal SBP (*ps*<0.05). SBP was also reduced to greater levels among non-White (-4.1 mmHg) than White samples (-2.2 mmHg) (*p*=0.044). Furthermore, SBP reductions occurred in a dose-response pattern as a direct function of physical fitness gains (*p*=0.026): -8.4 mmHg for large (>25%–~50%), -5.0 mmHg for moderate (~25%), and -2.4 mmHg for small (5%) gains (*ps*<0.05). The greatest SBP reductions occurred among samples with hypertension that achieved the largest fitness gains (-9.4 mmHg, 95% *CI:* -12.0, -6.8), an effect that was significantly greater among non-White (-12.0 mmHg) than White samples (-6.8 mmHg) (See Table 2, Additive Model).

[INSERT TABLE 2 HERE]

Three moderators explained unique variance relating to the effectiveness of AET to reduce DBP when entered in a multiple regression model, accounting for ~48% of the between-study variance (see Table 3). Among the AET groups, DBP reductions were greater among samples with higher resting DBP (*p*=0.019), which occurred in a dose response fashion: -6.1 mmHg for hypertension, -4.3 mmHg for prehypertension, and 1.1 mmHg for normal DBP (*ps*<0.05). DBP was also reduced to a greater levels among non-White (-3.0 mmHg) than White samples (-0.4 mmHg) (*p*=0.004). The greatest DBP reductions occurred among samples with hypertension that performed high volumes of AET (~1200 MET·min·week^{-1}) (-9.3 mmHg, 95% *CI:* -11.9, -6.7), an effect that was significantly greater among non-White (-12.2 mmHg) than White samples (-6.3 mmHg) (See Table 3, Additive Model).

[INSERT TABLE 3 HERE]

Discussion

The primary aim of our meta-analysis was to identify what patient and AET characteristics associated with the greatest antihypertensive therapeutic BP benefits. Consistent with prior meta-analyses [14, 15, 101-104], we found that AET on average reduced BP ~3-4 mmHg compared to

control (*ps*<0.001). We also found the BP reductions following AET occurred in dose response fashion such that greater BP reductions occurred among samples with hypertension (~7/6 mmHg) followed by prehypertension (~5/4 mmHg), and normal BP (~3/1 mmHg) ($ps \leq 0.033$), which is consistent with a small subset of previously published meta-analyses [15, 103, 105, 106]. However, our moderator analyses revealed important, new findings that merit further comment.

Our meta-analysis is the first to find greater BP reductions among samples with hypertension that achieved large fitness gains and performed high volumes of AET, an effect that was more pronounced among non-White (~12 mmHg) than White (~6-7 mmHg) samples. Our findings indicate that non-White samples, notably African American (i.e., non- Hispanic Blacks), Asian, and Hispanic/Latino populations, may benefit the most from the antihypertensive therapeutic benefit of AET. This finding is important because these patient populations tend to be at disproportionate risk of the sequela from CVD and other hypertension-related diseases and health conditions [1, 107-109]. Clearly, there is a need for RCTs that examine how different doses of AET influence the BP response to exercise among patient populations at disproportionate risk of CVD. Thus, more precise exercise prescriptions can be applied to maximize the effectiveness of AET as antihypertensive therapy for populations in most need of these benefits [8].

Surprisingly, there is little prior meta-analytic evidence to support that patient and exercise characteristics influence the BP response to AET [11]. Therefore, the present exercise recommendations for hypertension of 30-60 $\text{min}\cdot\text{day}^{-1}$ of moderate intensity aerobic exercise on most days of the week [2-5, 7] are based primarily upon findings from studies of White, middle aged men and women adults with normal BP to stage-1 hypertension [2, 11]. Yet, ~20-25% of individuals do not lower their BP by following these recommendations [110, 111], and for the majority that do, the resultant BP reductions following AET vary considerably (1-9 mmHg) [8]. Accordingly, our meta-analysis that adhered to high-quality methodological, contemporary standards provides insight into possible reasons for this variability, revealing that AET programs that produced large gains in

physical fitness and consisted of high exercise volume were the most effective antihypertensive lifestyle therapy, and the magnitude of the therapeutic BP benefit differed by race/ethnicity. How these new findings will translate into more precise exercise prescriptions among patient populations of differing race/ethnicity merits further investigation because the estimates produced with our additive models indicated that certain people can lower their BP following AET to similar or even greater magnitude than those reported with antihypertensive medications[112, 113].

To the best of our knowledge, only one other meta-analysis [51] has investigated the potential impact of race/ethnicity on the BP response to AET, while two meta-analyses found that AET duration (min·session^{-1}) [16, 17], intensity [15] and volume (min·week^{-1}) [15] moderated the magnitude of BP reductions following AET. Reasons for our ability to better capture moderator patterns than prior meta-analyses are not completely clear but may reside in the fact we: (1) adhered to high quality contemporary, methodological standards [18, 19]; (2) evaluated and *quantitatively* incorporated the methodological quality of included AET trial into our analyses [11, 13] under the assumption that clearer moderation patterns and dose-response functions *should* be more visible when methodological deficits across studies are controlled [56]; and (3) applied more sophisticated approaches, i.e., multiple moderator models [114, 115] and the moving constant technique [76] to conventional meta-analytic methods (i.e., meta-regression) versus limited subgroup analysis [116, 117]. These techniques, supplemented by our large number of included AET trials (one of the largest meta-analytic samples to date), enabled us to estimate the influence of individual moderators while statistically controlling for the presence of others in the model, and to identify novel race/ethnic-dependent moderation patterns by generating theoretically-driven interaction terms that provided greater clinical translation of our findings.

We, along with prior meta-analyses [8, 11, 17], have found this literature to be of "fair to moderate" methodological quality [52, 53]. In the absence of a higher quality literature, there is the potential risk of bias or other threats to the validity of our findings. Therefore, it is also noteworthy to

mention that in addition to study quality, we also examined other sources of potential bias related to the Downs and Black quality subscales, whether trials had BP-focused outcomes, and if our results differed based on the publication year, type of trial (i.e., RCT versus non-RCT), or number of funding sources. We then statistically examined whether these potential biases modulated the BP response to AET; even when these features were non-significant in bivariate meta-regression models, we incorporated them (when possible) to control for confounding or suppression effects that could arise from lower-quality trials [11, 56]. We found that higher study quality was associated with trials that were: published more recently (r=0.15, p=0.033), were RCTs (versus non-RCTs) (r=0.36, p<0.001), adequately powered to detect BP outcomes (Downs and Black Checklist Item 28) (r=0.26, p=0.087), and received greater amounts of funding support (r=0.12, p=0.096). Interestingly, trials that received greater funding support were also adequately powered (r=0.67, p<0.001) and tended to follow standard protocols/established guidelines when measuring BP (i.e., American Heart Association Council on High BP Research Part 1: Recommendations for BP measurement in Humans [118]) (r=0.12, p=0.099). Not surprisingly, trials that used standard protocols/established guidelines for BP assessment had BP-focused primary outcomes (r=0.22, p=0.002) and reported more reliable and accurate BP assessment methods (Downs and Black Checklist Item 21) (r=0.19, p=0.006). By examining the potential bias from several sources and incorporating them into our multiple moderator models (i.e., study quality, trial type, funding support) we can be more confident in our study results despite the number of methodological deficits and inconsistencies we have documented in this literature.

Our meta-analysis also identified patient profiles that may benefit the most from AET as antihypertensive therapy. In agreement with Whelton et al. [51] we found that greater BP reductions occurred among African American/Hispanic (~10/5 mmHg; k=9) and Asian (~9/6 mmHg; k=10) compared to White (~5/3 mmHg; k=86) samples (ps<0.034). We also found that the greatest BP reductions occurred among samples with hypertension that achieved the largest gains in physical

fitness, an effect that was more pronounced among non-White (~12 mmHg) than White (~7 mmHg) samples.

Although we are not the first to report that the magnitude of BP reductions were directly related to improvements in fitness [101, 103, 104, 119], we are the first to document its interaction with race/ethnicity. Differences in cardiorespiratory fitness levels have been documented across racial/ethnic groups, in particular that African American [120-122] and South Asian [123, 124] populations have lower fitness levels compared to Whites. In support of these reports, we found that cardiorespiratory fitness before AET was lower among non-White than White samples (22.8 versus 29.5 ml·kg·min^{-1}, p=0.006). The exact mechanisms accounting for racial/ethnic differences in fitness levels are not fully understood, but may be related to these populations simply being more physically inactive [120-122, 125-127], in addition to greater vascular dysfunction [109, 120, 128, 129] related to elevated levels of inflammatory [130], oxidative stress and vasoconstrictive factors [128, 131]. AET has been shown to improve endothelial function and reverse vascular damage through repeated, chronic bouts of increased shear stress and by modifying other CVD risk factors [132-134], but these improvements are largely dependent on the level of *dysfunction* prior to AET [129, 132, 133, 135]. Interestingly, we observed greater reductions in pulse pressure, an indicator of vascular health, after versus before AET among non-White (-7.9%) versus White (-3.4%) samples (p<0.001). Changes in pulse pressure were also moderately correlated with baseline fitness (r=0.27, p=0.006), such that greater reductions were observed among those with low physical fitness levels (i.e., non-White samples).

We also found that higher volumes of AET (~1200 MET·min·week^{-1}) elicited the greatest BP benefit among adults with hypertension, ranging from ~6-12 mmHg among White and non-White samples, respectively. Cornelissen and Smart [15] recently reported that AET lasting 30-45 min·session^{-1}, performed at moderate-to-vigorous than low intensity, and lower exercise volumes (<210 versus $\geq$210 min·week^{-1}) were most effective at reducing BP. Unfortunately, the authors were

unable to comment on how these FIT characteristics may interact with each, or with patient clinical characteristics, due to the limitations of subgroup analysis. Our meta-analysis did not bear the same limitations. When we examined the FIT components and their interaction term (i.e., exercise volume=*F*requency × *I*ntensity × *T*ime) simultaneously, their individual effects were no longer significant. Our findings support the current exercise volume recommendations for healthy adults (500-≥1000 MET·min·week^{-1}), except that higher volumes of exercise appear more efficacious among non-White samples as antihypertensive lifestyle therapy. It is important to note that in our meta-analysis high volumes of exercise were achieved with more rigorous intensity AET (~8 MET) performed on 3-5 days·week^{-1} for 30-40 min·session^{-1}, rather than combinations of AET consisting of lower intensity, high frequency (>5 days·week^{-1}) and longer duration (>40 min·session^{-1}).

Despite the significant volume of exercise and hypertension literature, to date meta-analyses have contributed little to our understanding of what patient characteristics and AET 'dose' confers the greatest therapeutic BP benefit. In agreement with the current exercise recommendations for hypertension, we found that 18 weeks of moderate-to-vigorous AET performed 3-4 days·week^{-1} for ~40 min·session^{-1} reduced resting BP ~6-7 mmHg among adults with hypertension (Table S6). Yet, we observed even greater reductions among samples that achieved large gains in physical fitness and performed higher volumes of AET, an effect that was greatest among non-White samples. Nonetheless, ~80% of our sample was considered White, AET interventions used various methods to assess physical fitness (only ~58% reported VO_{2peak}), and features of the AET intervention were inconsistently reported (i.e., AET intensity, level of supervision, adherence, etc.) so that the optimal FIT AET prescription for hypertension and for what populations it may work best as antihypertensive therapy has yet to be fully elucidated.

Even though we examined several sources for potential biases, of which some addressed the validity of the BP assessment methods used, it important to reinforce the poor reporting of these variables in the existing literature. Several reviews [2, 8, 11, 111] have commented on how the level

of reporting and quality of BP assessment procedures may contribute to the discrepancies observed across studies in the magnitude of the BP reductions following AET (i.e., unaccounted sources of heterogeneity). Yet, 38% of AET interventions failed to disclose *any* BP assessment procedures, while ~20-30% of AET trials failed to report specific details that included: the type of BP monitor or assessment tool (76% did), the body position during the BP measurement (72% did), and the timing of BP measurements at baseline (61% did) and post-intervention (17% did). At this time, it is unclear how the poor reporting and variability in these parameters influenced our results.

In summary, our meta-analysis that adhered to high-quality methodological, contemporary standards confirmed that AET is effective antihypertensive therapy for adults with hypertension. Furthermore, we revealed that AET programs that produced large fitness gains and consisted of high exercise volume maximized the effectiveness of AET as antihypertensive therapy, most notably for non-White samples. These results indicate that the present exercise recommendations for hypertension should be revisited to include more precise exercise prescriptions for patient populations of differing race/ethnicity who are at disproportionate CVD risk. Our findings indicate a compelling need for additional RCTs to investigate what combinations of patient and AET characteristics elicit optimal antihypertensive lifestyle benefit.

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Conflicts of Interest

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Table 1. Summary of the baseline sample characteristics for the aerobic exercise training (*k*=105) and control (*k*=90) groups.

	AET (*n*=2,200)			Control (*n*=1,434)		
Characteristics	***k***	***M*ean ± *sd***	**Range**	***k***	***M*ean ± *sd***	**Range**
Women (%)	101	41.7 ± 38.1	0.0, 100.0	84	40.5 ± 37.8	0.0, 100.0
Age (years)	105	47.9 ± 12.8	20.1, 72.0	85	47.8 ± 13.0	21.6, 72.0
BP Medication Use (%)	75	12.0 ± 24.7	0.0, 100.0	53	12.5 ± 22.6	0.0, 100.0
CVD risk factors/ presence of disease (%)	101	29.6 ± 45.6	0.0, 100.0	53	12.5 ± 22.6	0.0, 100.0
Race/Ethnicity (%) *						
White	86	81.9%	*n*=1,849	72	80.0%	*n*=1,146
Asian	10	9.5%	*n*=223	10	11.1%	*n*=168
African American/Black	6	5.7%	*n*=91	5	5.6%	*n*=78
Hispanic/Latino/Caribbean	3	2.9%	*n*=37	3	3.3%	*n*=42
Sedentary (%)	105	97.4 ± 15.2	0.0, 100.0	90	97.3 ± 15.0	0.0, 100.0
Body Composition						
Body Weight (kg)	79	78.8 ± 10.4	53.4, 102.4	65	78.2 ± 11.4	53.3, 107.3
Body Mass Index ($kg{\cdot}m^{-2}$)	79	27.4 ± 3.2	21.9, 35.4	63	27.6 ± 3.5	20.3, 37.2
Body Fat (%)	29	30.4 ± 7.4	22.0, 49.6	27	30.4 ± 7.4	22.0, 49.6
Resting Hemodynamics						
Systolic BP (mmHg)	105	130.7 ± 12.7	101.2, 167.6	89	130.8 ± 12.7	101.2, 160.0
Diastolic BP (mmHg)	101	81.7 ± 9.0	63.0, 102.0	85	81.5 ± 9.1	58.0, 102.0
MAP (mmHg)	101	98.1 ± 10.0	78.3, 123.5	85	98.1 ± 9.9	74.0, 120.0
Pulse Pressure (mmHg)	101	49.2 ± 6.9	35.0, 77.5	85	49.8 ± 7.3	35.0, 77.5
Heart Rate ($beats{\cdot}min^{-1}$)	12	71.1 ± 3.8	65.0, 75.0	12	71.3 ± 7.6	59.8, 84.0
Physical Fitness †	92	87.6%		65	72.2%	
VO_{2max}/VO_{2peak} ($ml{\cdot}kg{\cdot}min^{-1}$)	61	28.8 ± 7.4	14.5, 45.7	43	29.4 ± 8.2	14.3, 49.4
VO_{2max} ($L{\cdot}min^{-1}$)	12	1.7 ± 1.0	0.3, 3.1	8	1.6 ± 1.0	0.3, 3.0
6MWT/SWT (m)	4	583.3 ± 55.4	504.6, 631.0	3	521.5 ± 33.4	500.0, 560.0

Note. Descriptive statistics are presented as *M*ean ± standard deviation (*sd*) unless otherwise stated; Range= Minimum, Maximum. *k*=the number of observations. ***Abbr.*** AET=Aerobic exercise training. BP=Blood pressure. CVD= Cardiovascular disease. MAP=Mean arterial pressure. VO_{2max}=Maximal oxygen uptake. VO_{2peak}=Peak oxygen uptake. 6MWT=Six minute walk test. SWT=Shuttle walk test. *** Ethnicity/Race** was reported in 16 interventions: White (76-100%) [25, 34, 39, 40, 42-44, 46]; African American/Black (100%) [45, 49]; Asian (100%) [41, 50]; or mixed samples (White=50-98%, Black=17-43%, Hispanic=7% or 'Other'=3%) [38, 47, 48]. **† Other physical fitness assessments:** Exercise/ physical work capacity (Watts) [78, 135, 136]; Graded exercise test (min) [137]; Timed 1.5 mile run (min) [138]; Maximal exercise capacity (Metabolic equivalent unit) [89]; Maximal exercise capacity (Heart rate, $beats{\cdot}min^{-1}$) [92]; Walking activity ($km{\cdot}day^{-1}$ [139] or $steps{\cdot}day^{-1}$ [140, 141]); 400-m Endurance capacity test ($min{\cdot}km^{-1}$) [142]; Cardiorespiratory endurance index step test (no units) [94]; Maximal workload (work level) [35]; Physical activity ($kcal{\cdot}day^{-1}$) [98]; Rate pressure product [143].

Table 2. Multiple moderator model: The systolic blood pressure response to aerobic exercise training (k=154).

Moderator Dimension/ Level	d_+ (95% *CI*) * †	β	*p*	Difference (95%*CI*)	Model Summary
Resting Systolic BP (mmHg) of Intervention Groups		**0.025**	**0.806**		I^2 Residual=6.8%
Intervention Groups		**-0.283**	**0.012**		Multiple R=91.9%
Non-Exercise Control (k=65)	-0.27 (-0.40, -0.13)			-3.2 (-4.8, -1.6)	
¶ AET (k=89)	-0.40 (-0.49, -0.30)			-4.8 (-5.9, -3.6) ‖	
Race/Ethnicity of Intervention Groups		**-0.162**	**0.044**		
White Samples (k=136)	-0.18 (-0.29, -0.07)			-2.2 (-3.5, -0.8)	
§ Non-White Samples (k=18)	-0.34 (-0.51, -0.18)			-4.1 (-6.1, -2.2) ‖	
Change in Physical Fitness (% Increase) ‡		**-0.439**	**0.026**		
No Increase=0% (≤10th percentile, k=47)	-0.15 (-0.24, -0.05)			-1.8 (-2.9, -0.6)	
Small=5% (25th percentile, k=47)	-0.20 (-0.29, -0.11)			-2.4 (-3.5, -1.3)	
Moderate=25% (50–75th percentile, k=37)	-0.42 (-0.66, -0.19)			-5.0 (-7.9, -2.3) ‖	
¶ Large=>25%–~50% (>75th percentile, k=26)	-0.70 (-1.17, -0.24)			-8.4 (-14.0, -2.9) ‖ §	
Intervention Group × Resting Systolic BP (mmHg)		**-0.267**	**0.033**		
Non-Exercise Control Groups					
Normal BP=115±11 (k=15)	-0.28 (-0.46, -0.11)			-3.1 (-5.1, -1.2)	
Prehypertension BP=135±12 (k=37)	-0.26 (-0.39, -0.12)			-3.1 (-4.7, -1.4)	
Hypertension BP=155±13 (k=13)	-0.23 (-0.43, -0.03)			-3.0 (-5.6, -0.4)	
AET Groups					
Normal BP=115±11 (k=22)	-0.30 (-0.43, -0.18)			-3.3 (-4.7, -2.0)	
Prehypertension BP=135±12 (k=49)	-0.42 (-0.53, -0.32)			-5.0 (-6.4, -3.8) ‖	
¶ Hypertension BP=155±13 (k=21)	-0.55 (-0.72, -0.37)			-7.2 (-9.4, -4.8) ‖ §	
Intervention × Change in Fitness (% Increase)		**-0.126**	**0.571**		
¶ Race/Ethnicity × Intervention × Change in Fitness		**-0.507**	**0.001**		
¶ Additive Model: Greatest Systolic BP Benefit for	***White Samples***	**-0.52**	**(-0.72, -0.32)**	**-6.8 mmHg (-9.4, -4.2)**	
	Non-White Samples	**-0.92**	**(-1.16, -0.67)**	**-12.0 mmHg (-15.1, -8.7)**	

Note. k=number of observations. β=Standardized coefficients. Multiple R=Between-study variance explained by model, adjusted for number of moderators. I^2 Residual=Variance unexplained by model. ***Abbr.*** AET=Aerobic exercise training. BP=Blood pressure. CI=Confidence interval. *** Model** follows maximum likelihood assumptions with a random-effects constant; negative values imply BP was reduced at post- compared to pre-intervention. † **Weighted mean effect sizes (d_+)** controls for the presence of each moderator and for other values of interest within that range, including: study design, study quality, number of funding sources (now shown). ‡ **Physical Fitness Change (%)=**[(Fitness$_{Post-Pre}$)÷ Fitness$_{Pre}$] × 100%. **BP change is different from (p<0.05):** ‖ Control; White samples; 0% and 5% increase in physical fitness; Control × all BP levels and AET × normal BP; § 25% increase in physical fitness; AET × prehypertension. ¶ Indicates moderator dimension/level used in the **Additive Model;** represents the greatest *potential* antihypertensive benefit that can be achieved with AET.

Table 3. Multiple moderator model: The diastolic blood pressure to aerobic exercise training (k=171).

Moderator Dimension/ Level	d_+ (95% *CI*) * †	β	*p*	Difference (95% *CI*)	Model Summary
Resting DBP (mmHg) of Intervention Groups		**-0.083**	**0.388**		I^2 Residual=40.9%
Intervention Groups		**-0.268**	**0.073**		Multiple *R*=47.9%
Non-Exercise Control (*k*=65)	-0.15 (-0.33, 0.02)			-1.4 (-3.0, 0.2)	
§ AET (*k*=89)	-0.37 (-0.56, -0.18)			-3.3 (-5.0, -1.6) ‖	
Race/Ethnicity of Intervention Groups		**-0.259**	**0.004**		
White Samples (*k*=151)	-0.04 (-0.17, 0.10)			-0.4 (-1.5, 0.9)	
§ Non-White Samples (*k*=35)	-0.33 (-0.52, -0.15)			-3.0 (-4.7, -1.4) ‖	
Intervention Intensity (MET)		**-0.126**	**0.380**		
Intervention Frequency (days·week^{-1})		**-0.232**	**0.161**		
Intervention Group × Resting Diastolic BP (mmHg)		**-0.273**	**0.019**		
Non-Exercise Control Groups					
Normal BP=70±8 (*k*=36)	-0.14 (-0.35, 0.07)			-1.1 (-2.8, 0.6)	
Prehypertension BP=88±9 (*k*=33)	-0.19 (-0.37, -0.01)			-1.7 (-3.3, -0.1)	
Hypertension BP=95±10 (*k*=16)	-0.21 (-0.42, -0.01)			-2.1 (-4.2, -0.1)	
AET Groups					
Normal BP=70±8 (*k*=43)	-0.14 (-0.40, 0.11)			-1.1 (-3.2, 0.9)	
Prehypertension BP=88±9 (*k*=42)	-0.48 (-0.66, -0.31)			-4.3 (-5.9, -2.8) ‖	
§ Hypertension BP=95±10 (*k*=16)	-0.61 (-0.80, -0.42)			-6.1 (-8.0, -4.2) ‖	
Intervention Group × Frequency (days·week^{-1})		**0.040**	**0.789**		
Intervention Group × Race/Ethnicity		**-0.059**	**0.637**		
§ Race/Ethnicity × AET Volume ‡		**0.218**	**0.033**		
§ Additive Model: Greatest Diastolic BP Benefit for	***White Samples***	**-0.63**	**(-0.88, -0.37)**	**-6.3 mmHg (-8.8, -3.7)**	
	Non-White Samples	**-1.22**	**(-1.55, -0.89)**	**-12.2 mmHg (-15.5, -8.9)**	

Note. *k*=number of observations in the model. β=Standardized coefficients. Multiple *R*=Between-study variance explained by model, adjusted for number of moderators. I^2 Residual=Variance unexplained by model. ***Abbr.*** AET=Aerobic exercise training. BP=Blood pressure. CI=Confidence interval. MET= Metabolic equivalent unit. * **Model** follows maximum likelihood assumptions with a random-effects constant; negative values imply that BP was reduced at post- compared to pre-intervention. † **Weighted mean effect sizes (d_+)** controls for the presence of each moderator and for other values of interest within that range, including: study design, study quality, and number of funding sources (not shown). ‡ **Volume (MET·min·week^{-1})** was estimated using *I*ntensity × *T*ime × *F*requency. ‖ **BP change is different (p<0.05) from:** Control; White samples; Control × all BP levels and AET × normal BP. **§** Indicates moderator dimension/level used in the **Additive Model;** represents the greatest *potential* antihypertensive benefit that can be achieved with AET.

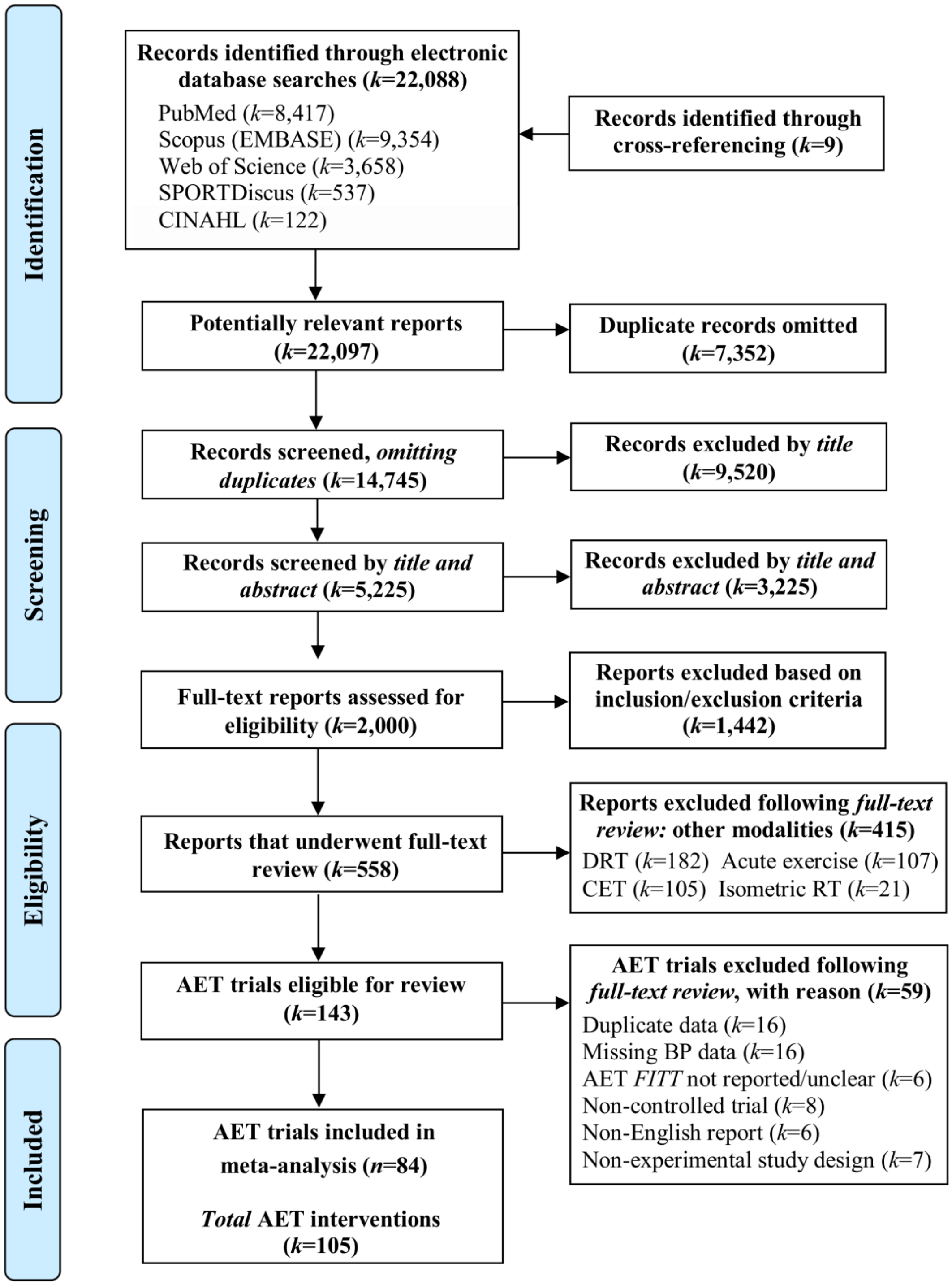

Figure 1. Flow chart detailing the systematic search of potential reports (*k*) and selection process of included aerobic exercise training trials. *Note.* AET=Aerobic exercise training. BP=Blood pressure. CINAHL=Cumulative index to nursing and allied health literature. CET=Concurrent exercise training. DRT=Dynamic resistance training. *FITT*=*F*requency, *I*ntensity, *T*ime, and *T*ype. RT=Resistance training.

Chapter 3

Dynamic Resistance Training as Stand-Alone Antihypertensive Lifestyle Therapy: A Meta-Analysis

DYNAMIC RESISTANCE TRAINING AS STAND-ALONE ANTIHYPERTENSIVE LIFESTYLE THERAPY: A META-ANALYSIS

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Abstract

Aerobic exercise is recommended as first-line antihypertensive lifestyle therapy due to a strong body of evidence showing it lowers blood pressure (BP) 5-7 mmHg among adults with hypertension. Due to weaker evidence showing dynamic resistance training (RT) reduces BP 2-3 mmHg among adults with hypertension, RT is recommended as adjuvant lifestyle therapy to aerobic exercise training. Yet, several lines of evidence exist that suggest RT can lower BP to equal to or greater levels than aerobic exercise. Therefore, we meta-analyzed 64 controlled trials (71 RT interventions) to determine the efficacy of dynamic RT as stand-alone antihypertensive therapy. Participants (n=2,374) were White (56%), middle-aged (47.2±19.0 yr), overweight (26.8±3.4 kg·m^{-2}) adults with prehypertension (systolic BP [SBP]/diastolic BP [DBP]: 126.7±10.3/76.8±8.7 mmHg); with 17% on antihypertensive medication. Overall, moderate-intensity dynamic RT was performed 2.8±0.6 days·week^{-1} for 14.4±7.9 weeks and elicited small-to-moderate reductions in SBP (d_+=-0.31, 95% *CIs*: -0.43, -0.19; -3.0 mmHg) and DBP (d_+=-0.30, 95% *CIs*: -0.38, -0.18; -2.1 mmHg) compared to controls (ps<0.001). Greater BP reductions occurred among samples with higher resting BP: ~6/5 mmHg for hypertension, ~3/3 mmHg for prehypertension, and ~0/1 mmHg for normal BP (p=0.001/0.023 for SBP/DBP, respectively). Furthermore, BP reductions approximately double the magnitude of those reported following aerobic exercise training occurred among non-White samples with hypertension (-14.3 mmHg, 95% *CIs*: -19.0, -9.4/-10.3 mmHg, 95% *CIs*: -14.5, -6.2). Our results indicate that for adults with hypertension, notably non-White samples, dynamic RT may be as or even more effective than aerobic exercise in lowering BP. RT should be further investigated as a viable stand-alone therapeutic exercise option for adults with hypertension.

Key words: Blood Pressure; Exercise; Hypertension; Strength Training; Systematic Review

Introduction

Hypertension is the most prevalent, modifiable and costly risk factor for cardiovascular disease (CVD) [1]. Hypertension leads to an estimated 9.4 million annual deaths worldwide, which is about as many deaths that result from all infectious diseases combined [2]. Nearly ~33% (80 million) of US adults currently have hypertension [1]; and by 2030, this number is projected to reach 41.1% [1, 3]. Lifestyle-related factors are the only modifiable determinants of hypertension [3]; therefore, more intensive efforts should be focused on promoting these strategies to reduce the significant public health burden of hypertension [1].

Many randomized control trials (RCTs) have investigated the antihypertensive effects of exercise, and in turn, over 33 meta-analyses have been published to date [4, 5]. Collectively, these meta-analyses concluded that aerobic training lowers blood pressure (BP) 5-7 mmHg [6-8], while dynamic resistance training (RT) lowers BP 2-3 mmHg [6, 8-11] among adults with hypertension. Accordingly, 30-60 $min \cdot day^{-1}$ of moderate-intensity aerobic exercise is recommended on most days of the week [6, 12-15] supplemented by moderate-intensity dynamic RT on ≥2 $days \cdot week^{-1}$ [6, 12, 14] to prevent, treat and control hypertension. Yet, a more critical review of this literature revealed considerable variability in the magnitude of the BP reductions following both aerobic exercise training (i.e., 1-9 mmHg) [5] and dynamic RT (i.e., 0-6 mmHg) [6, 10, 16, 17], for reasons that are not clear [5, 12].

In contrast to the high-level of evidence supporting the BP-lowering effects of aerobic training [5], there is much weaker evidence supporting the efficacy of RT as a viable therapeutic option to lower BP among adults with hypertension that is primarily based on the findings of six meta-analyses [5, 8-11, 16, 17]. Surprisingly, these meta-analyses included mostly healthy adults with normal BP and prehypertension. Furthermore, none of these meta-analysis completely satisfied contemporary methodological study quality standards [4, 18, 19], nor were they able to identify important patient or RT characteristics that modulated the BP response to dynamic RT. Collectively,

these observations suggest that the antihypertensive effects of RT may have been underestimated, and they call into question the generalizability of this weak and limited literature to adults with hypertension [4, 5].

Furthermore, several primary level RT studies have shown that the resultant BP reductions following dynamic RT may be comparable to that of aerobic training among adults with hypertension [20-29]. Mota and colleagues [29] found that 16 weeks of moderate-intensity dynamic RT reduced BP ~14/4 mmHg among 32 older women with controlled hypertension. In another study, Moraes et al. [30] found that 12 weeks of moderate-intensity RT reduced BP ~16/12 mmHg among 15 middle-aged men with hypertension. Moraes et al. concluded that dynamic RT performed three days per week was effective as stand-alone antihypertensive therapy. A limited number of controlled trials have directly compared the effectiveness of aerobic training versus RT as antihypertensive therapy [21-23, 26, 31-34]. Yet, most of these trials found that aerobic exercise training and dynamic RT lowered systolic BP (SBP)/diastolic BP (DBP) to similar levels among adults with untreated (~7/6 mmHg [22]; 14/8 mmHg [21]) and controlled (~10/3 mmHg) hypertension [23, 26]. BP reductions of this magnitude following RT have also been observed among young (~9-15/6-8 mmHg) [31, 32, 35] and middle-aged (~8-10/5-7 mmHg) [33, 34, 36] adults with prehypertension.

Therefore, the purposes of our meta-analysis are to determine the efficacy of dynamic RT as stand-alone antihypertensive therapy, and identify potential moderators of the BP response to provide insight into the optimal dose of RT to lower BP among adults with hypertension.

Methods

This study fully satisfies the criteria implied by the PRISMA Statement (*P*referred *R*eporting *I*tems for *S*ystematic *R*eview and *M*eta-*A*nalyses) [19, 37] and AMSTAR Methodological Quality Scale (*A*ssessment of *M*ultiple *S*ys*T*em*A*tic *R*eviews) [18, 38].

Inclusion Criteria

Included reports satisfied four *a priori* inclusion criteria: (1) involved adult participants (≥19 yrs) [39-41]; (2) followed a controlled study design comparing dynamic RT to a non-exercise, non-diet control or comparison group; (3) reported pre-and post-intervention BP for the RT and the control/comparison groups; and (4) reported the *F*requency, *I*ntensity, and *T*ime (or FIT) of the RT intervention. Trials were excluded if they involved populations with diseases unrelated to CVD (i.e., cancer survivors, substance abusers, human immunodeficiency virus or AIDS) or if they involved participants using weight loss drugs, diet therapy, or diet modifications.

Search Strategy

Aided by a medical librarian at the University of Connecticut (JL), we systematically searched several electronic interfaces from their inception until January 31, 2014 using a Boolean search strategy. Potential qualifying reports were retrieved from the following electronic databases: Cumulative Index to Nursing and Allied Health Literature, PubMed (including Medline), Scopus (including EMBASE), SportDiscus, and Web of Science (see Appendix 1 for the complete search strategy). The reference lists of included studies and relevant meta-analyses and reviews were also manually searched for additional reports. After retrieving all potentially qualifying reports, duplicate records were removed, and four investigators (HVM, TUG, KF, LML) screened the sample for inclusion with duplication of effort.

We identified 64 controlled trials that satisfied the inclusion criteria (See Appendix 13 for the reference list of included studies). Figure 1 shows the systematic search for potential reports and selection process of included dynamic RT trials. Seven trials involved ≥1 RT groups comparing: lower versus high intensity RT [42-45], strength versus power RT [46], elastic band versus aquatic RT [47], and eccentric versus concentric RT [48], yielding 71 *total* interventions.

Data Extraction and Coded Variables

All coded variables were extracted using a standardized coding form and coder manual that was previously developed by a team of experts (LSP, BTJ, TBHM) and pilot tested. Two trained coders (HVM, KF) independently extracted and entered the study information with high reliability across all dimensions (mean Cohen's κ=0.86 for categorical variables [49]; mean Pearson's r=0.94 for continuous variables); all disagreements were resolved by discussion. Coded variables included: (1) study characteristics (e.g., publication year, study location or region, primary study outcome); (2) experimental study design (e.g., single versus multiple RT interventions, between or within-group design, level of supervision); (3) sample clinical characteristics (e.g., baseline BP, age, race/ethnicity, sex/gender, BP medication use); and (4) features of the dynamic RT intervention including the FIT characteristics.

Included trials rarely disclosed the race/ethnicity of their study participants (only 14% did) [22, 23, 42, 50-55]. When unreported, we estimated race/ethnicity based on the study location [56]. Samples were considered "White" when the study was conducted in North America, Europe and Australia; "Asian" when conducted in Asian countries; "Hispanic and/or Latino" when conducted in South America; and "Black" when conducted in African countries.

Methodological Study Quality Assessment

Included trials were assessed for methodological study quality using a modified version of the Downs and Black Checklist [57, 58] (see Appendix 3 for the augmented checklist). This instrument [59] is well validated in the health promotion literature and has been shown to be valid and reliable in assessing RCTs and non-RCTs. The Downs and Black Checklist [59] addresses five subscales of methodological quality: (1) reporting, (2) external validity, (3) bias, (4) confounding, and (5) power, making it one of the most comprehensive extant instruments to evaluate study quality [60]. Methodological study quality score was gauged as percentage of items satisfied out of a possible 29-point total. A similar approach was used to evaluate each study quality subscale, which

provided a summary of the methodological strengths and weaknesses for each study. Consistent with other reviews [57, 58], ranges in overall methodological study quality scores were grouped into three quality levels: low (≤14 points, <50%), moderate (>14 to 23 points, 50-79%), and high (≥24 points, ≥80%). In addition to quantifying the overall quality of the dynamic RT literature, we examined how overall study quality (or individual quality items) influenced the BP response to dynamic RT independently or interactively [61] with other moderators.

Study Outcomes, Effect Size Calculation, and Moderator Analyses

The standardized mean difference effect size (*d*) was used to quantify the effectiveness of dynamic RT as stand-alone antihypertensive therapy, defined as the magnitude of change in resting SBP and DBP post- versus pre-intervention values, correcting for small sample size bias and baseline differences[62, 63] (see Appendix 4.1 for effect size estimations). Because our effect size estimate is in a comparable parameter, *d*, studies with different experimental designs (i.e., parallel study design versus within-in subject, cross-over design) were combined to maximize the number of studies in our sample, thus improving the power of our meta-analysis [64-66]. We disaggregated comparisons for trials with more than one RT intervention (e.g., high versus low intensity RT) [42-48]; effect sizes were calculated for each comparison and analyzed as separate studies [67]. To control for non-independent effect sizes (i.e., RT studies with multiple treatment groups compared to a single control [68]), we performed alternative analyses using the Metafor package [69] for R [70] that accounted for these issues and yielded the same pattern of results. For simplicity of interpretation, we report the maximum likelihood estimation analyses for SBP and DBP. Negative *d* values indicated that dynamic RT reduced BP more than the non-exercise control/comparison group; the magnitude of the mean difference can be interpreted as -0.20, -0.50, and -0.80 for small, medium and large reductions in resting BP [71]. Last, we provided the equivalent BP change in mmHg as a supplement to the observed *d* in order to enhance the clinical relevance of our findings (see Appendix 4.3 for the methods used to calculate the raw metric in mmHg).

We used Stata 13.1 (StataCorp, College Station, TX) [72] with macros for meta-analysis [67] to perform all statistical analyses, incorporating random-effects assumptions. We visually examined funnel plots for any asymmetries in the effect size distribution to identify potential publication or other reporting biases [73]. In addition, we tested our data for publication bias using Begg [74] (SBP: z=-0.46, p=0.64; DBP: z=-1.32, p=0.19) and Egger [75] (SBP: t=-1.30, p=0.20; DBP: t=-1.19, p=0.24) methods; no publication bias was detected by either test (See Appendix 19, Figure S3, for the Begg and Egger funnel plots). Inconsistencies in *d* values were estimated with the I^2 statistic and its confidence intervals (95% *CIs*) [76, 77]. I^2 values range from 0% (homogeneity) to 100% (greater heterogeneity). As I^2 increases, homogeneity is less likely and heterogeneity is more likely; a *CI* that does not include 0% indicates that the hypothesis of homogeneity is rejected, and an inference of heterogeneity is merited [77, 78].

Moderator analyses were used to explain variability in *d*s for SBP and DBP, using weighted regression models with maximum likelihood estimation of the random-effects weights, the inverse of the variance for each *d*. Continuous moderators were mean centered and categorical variables were contrast coded before generating interaction terms or examining multiple moderators simultaneously [61, 79]. Significant moderators identified with bivariate meta-regression analyses were combined in multiple moderator models for SBP and DBP and examined simultaneously to explain unique study variance. In each multiple moderator model, the moving constant technique [79] was used to estimate the magnitude of weighted mean effect sizes ($\hat{d}_+$) and their *CIs* at different levels of interest for individual moderators that represented a range of observations, including minimum and maximum values while statistically controlling for the presence of moderators. For both SBP and DBP, an additive model was generated from the final model that represented the greatest *potential* antihypertensive benefit that can be achieved with dynamic RT. Individual moderators and interaction terms were evaluated simultaneously at the level that conferred the greatest BP benefit

(i.e., greatest BP reductions), which in turn, demonstrated the combination of patient and RT characteristics that elicited optimal antihypertensive therapy. Finally, the proportion of between-study variance explained by the model (i.e., Multiple *R*) and the residual unexplained variance (i.e., I^2 Residual) are provided (see Model Summary for Tables 2 and 3). Summary statistics are presented as *M*ean ± standard deviation (*M* ± SD) unless otherwise stated. Two-sided statistical significance was $p<0.05$.

Results

Study Characteristics

RT interventions were published between 1987 and 2013 (2006.7±6.4), and were conducted in North American (32%, *k*=23), Asia (24%, *k*=17), Europe (20%, *k*=14), South America (17%, *k*=12), Australia (6%, *k*=4), and Africa (1%, *k*=1). Among the trials that reported sex/gender (two trials did not), 19 interventions involved all women (26.8%), 20 interventions involved all men (28.2%), and the remaining trials involved samples of mixed sex/gender (42.3%, *k*=30). The majority of RT interventions were RCTs (81.7%, *k*=58), but only half examined BP as a primary study outcome (47.9%, *k*=34). Of these, ~70% of RCTs used a parallel (i.e., between-subject) study design (*k*=50), two studies [50, 80] used a within-subject, cross-over design, and nine studies involved a "placebo" comparison group instead of a non-exercise or 'wait-listed' control. "Placebo" interventions included light/low intensity, full body stretching performed two [81, 82] or three days per week [26, 28, 83, 84], health education lectures that occurred weekly [27] or once every fourth week [52], or a supplement (i.e., sugar pill) was taken once daily [85].

[INSERT FIGURE 1]

Included trials achieved "moderate quality" (~63% of items satisfied) [57, 58] despite widely varying methodological quality scores (41%-85%). (Appendix 14 summarizes the overall methodological study quality for the RT sample and how well RT interventions satisfied individual quality items). Trials were most likely to satisfying the reporting (78.6%±10.2%), internal validity-

bias (70.2%±14.9%) and internal validity-confounding (51.5%±30.1%) quality subscales, but were least likely to satisfy external validity (46.5%±42.3) and power (9.2%±24.4%). None of the individual quality subscales emerged as significant moderators of the BP response to dynamic RT. Finally, only seven trials satisfied ≥80% of the Downs and Black study quality checklist items (83.3%±1.3%). (Appendix 15 describes the overall and itemized methodological study quality for each of the included dynamic RT trials).

Sample Characteristics

Dynamic RT (*n*=1,304) and control participants (*n*=1,070) were largely healthy (61%, *k*=43), sedentary, middle-aged (47.4±19.0 yr), overweight (26.7±3.5 kg·m^{-2}) adults with prehypertension (SBP/DBP: 126.4±9.4/76.6±8.4 mmHg). Nonetheless, a smaller subset consisted of samples with CVD risk factors or known disease (27%, *k*=19) including: type 2 diabetes mellitus (3%, *k*=2), the metabolic syndrome (2%, *k*=1), dyslipidemia (2%, *k*=1), obesity (5%, *k*=3), CVD (2%, *k*=1), or combinations of chronic diseases and health conditions (15%, *k*=9). Included RT trials yielded a diverse sample with 56% (*k*=40) White (*n*=1,402) and 44% (*k*=31) non-White that included: 18% Hispanic/Latino (*n*=1,505), 24% Asian (*n*=521), and 1% African American (*n*=28). Approximately 17% (*n*=222) of the RT sample was on antihypertensive medication, but approximately one-third of RT trials failed to disclose BP medication use (68% did). There were no differences in baseline sample characteristics between the dynamic RT and control groups (see Table 1).

[INSERT TABLE 1 HERE]

Dynamic Resistance Training Intervention Characteristics

Dynamic RT interventions ranged from six to 48 weeks (14.4±7.9 weeks) and consisted of two to five sessions·week^{-1} (2.8±0.6 days·week^{-1}). Dynamic RT was performed at moderate-intensity or levels of exertion that corresponded to 65-70% of one repetition maximum (% of 1-RM) (64.7±13.0% of 1-RM). Eleven trials (15.5%) failed to disclose RT intensity, and one used the OMNI-RT scale (see Appendix 16 for a general description of the RT programs). RT programs

generally targeted the whole body (91.0%, *k*=63); four interventions focused on the lower body, and one involved unilateral, upper body RT. Most RT programs reported using machine weights, free weights, or a combination of modalities (76.1%, *k*=54) to train muscles groups of the upper and lower body; however, RT interventions varied widely in their prescription of acute program variables (see Appendix 16). In general, RT interventions prescribed 2.8±0.9 sets·exercise^{-1} (range: 1-5) of 11.0±3.8 repetitions·set^{-1} (range: 5-30) for 7.9±2.9 RT exercises per session (range: 1-16). Direct supervision was reported in 63% of the RT interventions (*k*=45), including one-on-one supervision and small group processes; 10% (*k*=7) reported a combination of supervised and unsupervised sessions, and 27% (*k*=19) of trials failed to disclose the level of supervision. The overall adherence to the RT intervention was high (92.3%±8.9%), but only 65% reported this detail (Appendix 16).

Resting Blood Pressure Assessment

Overall, included RT trials failed to disclose important details related to the resting BP assessment. Most RT interventions reported the BP assessment tool (81.7%, *k*=58); of these, two trials assessed ambulatory BP in addition to causal/clinic BP [22, 86]. BP measurements were taken in the seated (42.3%) or supine (26.8%) position, yet ~69% of RT interventions did not report these details. RT interventions were least likely to disclose the timing of pre-and post-BP assessments: only half (52.1%) reported the duration (minutes) of quiet rest preceding baseline BP assessment, and even fewer reported (19.7%) the duration (hours) between the last exercise bout and the final post-intervention BP measurement. Appendix 17 provides a general description of the BP assessment details.

Dynamic Resistance Training as Stand-Alone Antihypertensive Therapy

Small to moderate reductions in SBP (d_+=-0.31, *CIs*: -0.43 to -0.19; -3.0 mmHg) and DBP (d_+=-0.30, *CIs*: -0.38 to -0.18; -2.1 mmHg) were observed following dynamic RT relative to control; and collectively, the effect sizes lacked homogeneity (SBP: I^2=51%; 95% *CIs*: 36%-63% and DBP: I^2=35%; 95% *CIs*: 13%-52%). Appendix 18 provides the weighted mean effect sizes and tests for

homogeneity (i.e., *Cochran Q* [87] and I^2 [77, 78] statistics) for SBP and DBP. (See Appendix 20, Figure S4, for the contour-enhanced funnel plots, i.e., confunnels, for a visual representation of the effect size distribution for SBP and DBP).

Moderator Analyses

Bivariate meta-regression analyses revealed significant moderators for SBP and DBP related to sample, dynamic RT, and methodological quality characteristics. When combined in multiple moderator models, significant bivariate models explained ≥50% of the observed heterogeneity in the BP response to dynamic RT (see Tables 2 and 3).

Five moderators explained unique variance relating to the effectiveness of dynamic RT to reduce SBP when entered in a multiple regression model, accounting for ~67% of the between-study variance. SBP reductions were greater among samples with higher resting SBP (p=0.011), which occurred in a dose response fashion: -5.7 mmHg for hypertension, -3.0 mmHg for prehypertension, and 0.0 mmHg for normal SBP. SBP was also reduced to a greater extent among Non-White (-4.7 mmHg) than White samples (0.0 mmHg) (p=0.002), and among samples who were not taking BP medication (-4.3 mmHg) compared to those that were (-0.4 mmHg) (p=0.034). Finally, greater SBP reductions occurred following RT programs that involved ≥8 versus <8 RT exercises per session (-4.4 versus -1.4 mmHg, respectively) (p=0.043) and among trials that had BP-focused primary outcomes versus those that did not (-3.9 versus -0.8 mmHg, respectively) (p=0.032) (see Table 2). The greatest SBP reductions occurred among samples with untreated hypertension who performed ≥8 RT exercises per session (-11.8 mmHg, 95% *CI:* -16.0, -7.4), an effect that was significantly greater among non-White (-14.3 mmHg) than White samples (-9.2 mmHg) (Table 2, Additive Model).

[INSERT TABLE 2 HERE]

Four moderators explained unique variance relating to the effectiveness of dynamic RT to reduce DBP when entered in a multiple regression model, accounting for ~50% of the between-study variance. DBP reductions were greater among samples with higher resting DBP (p=0.023): -5.2

mmHg for hypertension, -3.3 mmHg for prehypertension, and -1.0 mmHg for normal DBP. DBP was also reduced to a greater extent among samples who were not taking BP medication (-3.5 mmHg) compared to those that were (-1.2 mmHg) (p=0.028). Last, greater DBP reductions occurred when dynamic RT was performed ≥3 versus <3 days·wk^{-1} (-4.5 versus -0.9 mmHg, respectively) (p=0.02), and among trials that achieved lower than higher study quality (-3.7 versus -0.3 mmHg, respectively) (p=0.019) (See Table 3). The greatest DBP reductions occurred among samples with untreated hypertension who performed RT on 3 or more days·week^{-1} (-9.9 mmHg, 95% *CI:* -13.9, -5.9), an effect that was slightly more pronounced among non-White (-10.3 mmHg) than White samples (-9.2 mmHg) (Table 3, Additive Model).

[INSERT TABLE 3 HERE]

Discussion

The present meta-analysis aimed to determine the efficacy of dynamic RT as stand-alone antihypertensive therapy, and to identify potential moderators of the BP response to provide insight into the optimal dose of RT to lower BP among adults with hypertension. Consistent with prior meta-analyses [6, 8-11], overall, we found that moderate-intensity dynamic RT on average reduced BP ~2-3 mmHg compared to control (ps<0.001). Importantly, our moderator analyses revealed new findings that merit further comment. We found the BP reductions following RT occurred in dose response fashion such that greater BP reductions occurred among samples with hypertension (~6/5 mmHg) followed by prehypertension (~3/3 mmHg), and normal BP (~0/1 mmHg) (ps≤0.023). Dynamic RT elicited BP reductions that were comparable to those observed with aerobic exercise training among adults with hypertension. Furthermore, non-White samples with hypertension achieved even larger BP reductions, approximately double the magnitude reported following aerobic exercise (~10-14 mmHg). Our results indicate that for adults with hypertension, notably non-White (i.e., Hispanic/Latino and Asian) samples, dynamic RT may be as or even more effective than aerobic

exercise training in lowering BP. Due to the novel nature of our findings, RT should be further investigated as a viable stand-alone therapeutic exercise option for adults with hypertension.

Presently, 30-60 min·day^{-1} of moderate intensity aerobic exercise is recommended on most days of the week supplemented by dynamic RT on ≥2 days·wk^{-1} [6, 12-15] as first-line antihypertensive therapy to lower BP 5-7 mmHg among adults with hypertension. Dynamic RT is recommended as adjuvant antihypertensive lifestyle therapy to aerobic exercise training because there is a weaker body of evidence indicating it lowers BP to lesser levels among adults with hypertension [5, 8-11, 16, 17]. Yet, our meta-analysis, which that adhered to high-quality methodological standards, revealed that the magnitude of the BP reductions resulting from dynamic RT are comparable to or greater than those achieved with aerobic exercise training among adults with hypertension, particularly for non-White samples. Accordingly, our results indicate that the present exercise recommendations for hypertension should be revisited to include dynamic RT (in addition to aerobic exercise) as stand-alone antihypertensive lifestyle therapy.

Our meta-analysis adds other new information to the literature, namely we are the first to identify important moderators of the BP response to dynamic RT. Our most noteworthy and clinically relevant finding was that dynamic RT elicited BP reductions in dose-response fashion, findings that align with those reported for aerobic exercise training [4-6], but not with other meta-analyses examining the BP response to RT. Reasons for the differences observed in our meta-analysis compared others are not completely clear but may reside in the fact that we performed one of the largest and most comprehensive electronic searches to date, included RCT and non-RCTs, and identified twice the number of RT interventions involving adults with hypertension (k=8) [20-24, 52, 88, 89] than previously reported (k=4) [8]. Furthermore, the other meta-analyses examined potential moderators of the BP response to RT using subgroup analysis, which lacks the sensitivity and precision needed to detect small exercise-related changes in BP [90, 91]. We applied conventional meta-analytic techniques (i.e., meta-regression) and more sophisticated approaches, i.e., multiple

moderator models [92, 93] and the moving constant technique [79], which allowed us to estimate BP changes at different levels of individual moderators (i.e., sample and RT characteristics) and provided greater clinical translation. Second, we *quantitatively* incorporated and examined whether study quality independently [4, 18] or interactively [61] modulated the BP response to dynamic RT. We found that BP reductions were greater among trials that achieved lower than higher study quality, although, only seven RT trials [32, 50, 80-82, 94, 95] were considered to be of 'higher' quality satisfying ≥80% of the quality items. We also found that, despite overall quality, greater BP reductions occurred among trials that had BP-focused primary outcomes versus those that did not.

We, along with prior meta-analyses [8, 11, 17], have found this literature to be of 'fair to moderate' methodological quality [57, 58]. In the absence of a higher quality literature, there is the potential risk of bias or other threats to the validity of our findings. Therefore, it is also noteworthy to mention that in addition to study quality, we also examined other sources of potential bias related to the Downs and Black quality subscales, whether trials had BP-focused outcomes, and if our results differed based on the publication year, type of trial (i.e., RCT versus non-RCT), number of RT interventions (i.e., single versus multiple RT groups), or number of funding sources. We then statistically examined whether these potential biases modulated the BP response to AET; even when these features were non-significant in bivariate meta-regression models, we incorporated them (when possible) to control for confounding or suppression effects that could arise from lower-quality trials [4, 61]. We found that higher study quality was associated with trials that: were published more recently (r=0.45, p<0.001), were RCTs (versus non-RCTs) (r=0.23, p=0.052), were adequately powered to detect BP outcomes (Downs and Black Checklist Item 28) (r=0.41, p<0.001), compared a single-RT intervention to control (versus multiple RT groups) (r=0.22, p=0.069), and followed standard protocols or established guidelines when measuring BP (i.e., American Heart Association Council on High BP Research Part 1: Recommendations for BP measurement in Humans [96]) (r=0.24, p=0.045). Not surprisingly, trials that used standard protocols/established guidelines when

assessing BP also used more reliable and accurate BP assessment methods (Downs and Black Checklist Item 21) (r=0.76, p<0.001). Interestingly, trials that were adequately powered (Downs and Black Checklist Item 28) also received greater funding support (r=0.26, p=0.029). By examining the potential risk of bias from several sources and incorporating them into our multiple moderator models (i.e., study quality, BP-focused outcomes, number of RT interventions) we can be more confident in our study results despite the number of methodological deficits and inconsistencies we have documented in this literature.

Through our moderator analyses, we also addressed other noteworthy gaps in this literature. No meta-analysis conducted to date has identified features of the exercise intervention that influenced the BP response to dynamic RT, which in part, may be attributed to the poor disclosure of important RT intervention features. For example, most of the included trials reported the number of RT exercises (97% did), sets (94% did) and repetitions (92% did) performed at each session, yet only half reported the RT intensity as a percentage of 1-RM (~54%), and even fewer trials reported the duration of rest intervals prescribed between sets and/or exercises (~42%). Because BP increases proportionally to effort [97], muscle mass activation [98-101], intensity and duration of the set (especially those performed to failure [98, 101-103]), and decreases during rest intervals when blood flow is restored to working muscles [97, 101, 104, 105], the omission of specific RT features (i.e., acute program variables) adds to the lack of knowledge regarding what RT programs have the most favorable BP, and more generally, cardiovascular, benefit for adults with hypertension. Furthermore, one-third of RT programs did not incorporate fundamental strength and conditioning principles [97, 106], such as "progressive overload" (i.e., gradual increase in RT intensity/load; repetitions; RT volume; or introduction of more complex lifting techniques) (34% did) or "specificity" (28% did). Indeed, nearly 70% of all trials did not report RT progression (38%) or provided few details regarding *how* progression occurred (28%) that replication of the RT prescription is impossible. Given that training adaptations are specific to the stimulus applied (i.e., principle of specificity), it is

troubling that the majority of trials failed to report any rationale or theoretical basis for their RT program design. Nonetheless, in agreement with the current exercise recommendations for hypertension, we found that low to moderate-intensity RT programs (~60-65% of 1-RM; 8-15RM; 4-5 MET) consisting of ~3 sets of 10-12 repetitions for ~8 exercises (3-4 upper and 4-5 lower body exercises) performed ~3 days·wk^{-1} for 14 weeks significantly reduced resting BP ~5-6 mmHg among adults with hypertension. We observed even greater BP reductions following RT programs that involved ≥8 versus <8 RT exercises per session, and when dynamic RT was performed ≥3 versus <3 days·wk^{-1}. Even so, important features of the RT intervention (i.e., RT intensity/load, rest interval duration, etc.) were inconsistently reported so that the optimal FIT exercise prescription for dynamic RT among adults with hypertension is not clear (Appendix 16).

We also identified patient characteristics that may benefit the most from dynamic RT as stand-alone antihypertensive therapy. Namely, BP reductions were greater among samples who were not taking antihypertensive medications (~4 mmHg) compared to those that were (~1 mmHg). Although some studies have reported a synergistic effect between BP medication and the BP reductions following RT [29, 107, 108], others have found no difference in the resultant BP reductions between the two [21, 22, 30]. It is noteworthy to mention that only a small proportion of our RT sample was currently taking BP-lowering medications (~17%); this may be a reflection that approximately one-third of RT trials failed to disclose medication use, and the smaller number of samples with hypertension (~11%; k=8) than prehypertension (~71%; k=50) and normal BP (~18%; k=13) in our meta-analysis.

We found that dynamic RT elicited BP reductions that were comparable to or greater than those achieved with aerobic exercise training among adults with hypertension, particularly for non-White samples (i.e., Asian, Hispanic/Latino and African American), who achieved BP reductions approximately double the magnitude (~10-14 mmHg) associated with aerobic exercise training. To the best of our knowledge only one meta-analysis [56] has investigated the potential impact of

ethnicity/race on the BP response to exercise training. Whelton and colleagues [56] found that aerobic exercise training reduced resting BP to greater levels among Asian (6/7 mmHg) and Black (11/3 mmHg) compared to White samples (3/3 mmHg) (p<0.05). We observed a similar trend where greater BP reductions occurred among Hispanic/Latino (~13/10 mmHg; k=14) and Asian (~11/10 mmHg; k=12) compared to White samples (~9/10 mmHg; k=40), differences that achieved statistical significance only when examined collectively as non-White versus White samples. These findings are important because certain Hispanic/Latino and Asian populations experience a disproportionate burden of obesity and hypertension-related diseases [1, 109, 110], and these health disparities are further exacerbated by lower cardiorespiratory fitness levels and more sedentary lifestyles [1, 111-113] compared to Whites. Therefore, Hispanic/Latino, Asian and other racial/ethnic minority populations are less likely to engage in exercise as antihypertensive therapy despite the fact our findings showed they are the patients who may benefit the most. Our findings are promising in that they provide another viable therapeutic exercise option that can be performed in addition to aerobic exercise as stand-alone antihypertensive lifestyle therapy.

Even though we examined several sources for potential biases, of which some addressed the validity of the BP assessment methods used, it important to stress the poor reporting of these variables in this literature. Several reviews [4-6, 114] have commented on how the level of reporting and quality of BP assessment procedures may contribute to the discrepancies observed across studies in the magnitude of the BP reductions following exercise (i.e., unaccounted sources of heterogeneity). Yet, ~31% of RT interventions failed to disclose *any* BP assessment procedures, while ~20-30% of RT trials failed to report specific details that included: the type of BP monitor or assessment tool (82% did), the body position during the BP measurement (69% did), and the timing of BP measurements at baseline (52% did) and post-intervention (20% did). At this time, it is unclear how the poor reporting and variability in these parameters influenced our results.

In summary, our high quality methodological meta-analysis, which adhered to contemporary standards, revealed that dynamic RT is as effective if not more so than aerobic exercise as antihypertensive therapy among those with hypertension, notably non-White samples. These results indicate that the present exercise recommendations for hypertension should be revisited to include dynamic RT (in addition to aerobic exercise) as stand-alone antihypertensive lifestyle therapy. Despite these promising findings, this body of literature is of fair to moderate quality with other limitations noted within. Additional RCTs are needed to investigate RT as a viable stand-alone therapeutic exercise option among more ethnically/racially diverse samples with hypertension.

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Conflicts of Interest

None

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Table 1. Summary of the baseline characteristic for dynamic resistance training and non-exercise control groups.

Characteristic	*k*	Dynamic RT (*n*=1, 304)	*k*	Control (*n*=1, 070)
Women (%)	69	48.7 (39.1, 58.3)	68	49.3 (39.5, 59.0)
Age (years)	68	47.2 ± 19.0	67	47.2 ± 19.1
BP Medication (% using)	48	14.1 (5.6, 22.5)	48	12.3 (4.5, 20.0)
Race/Ethnicity, % (*n*)				
White	40	56.3 (774)	40	56.3 (628)
Asian	17	23.9 (263)	17	23.9 (258)
Hispanic/Latino/Caribbean	13	18.3 (254)	13	18.3 (251)
African American/Black	1	1.4 (13)	1	1.4 (15)
Sedentary (%)	54	92.6 (85.4, 99.8)	53	92.4 (85.1, 99.8)
Body Composition				
Body weight (kg)	61	75.0 ± 11.7	59	74.1 ± 12.0
Body Mass Index ($kg \cdot m^{-2}$)	60	26.8 ± 3.4	58	26.6 ± 3.7
Waist circumference (cm)	17	96.9 ± 9.3	17	96.1 ± 10.0
Body Fat (%)	36	29.7 ± 6.9	36	29.3 ± 7.9
Fat Mass (kg)	11	26.4 ± 6.8	11	26.7 ± 7.2
Lean Mass (kg)	20	50.9 ± 11.2	20	49.4 ± 11.1
Resting Hemodynamics				
Systolic BP (mmHg)	71	126.7 ± 10.3	70	126.3 ± 9.4
Diastolic BP (mmHg)	71	76.8 ± 8.7	70	76.5 ± 8.6
MAP (mmHg)	71	93.2 ± 8.0	70	93.2 ± 8.2
Pulse Pressure (mmHg)	71	49.4 ± 8.3	70	49.8 ± 6.8
Heart rate ($beats \cdot min^{-1}$)	41	70.1 ± 6.9	40	69.1 ± 7.3
Strength and Fitness Measures				
Upper body strength (kg) *	18	44.5 ± 31.3	10	43.4 ± 36.5
Lower body strength (kg) †	24	92.3 ± 58.8	16	97.3 ± 69.7
Cardiorespiratory Fitness ‡	37		36	
Oxygen Uptake ($ml \cdot kg \cdot min^{-1}$)	24	28.6 ± 9.9	23	29.7 ± 9.4

Note. Based on 71 observations (*k*). Summary statistics are presented as *M*ean ± Standard Deviation or as *M*ean (Lower, Upper 95% Confidence Interval). ***Abbr.*** BP=Blood pressure. MAP=Mean arterial pressure. RT=Resistance training. *** Upper body strength** was assessed in 25 RT and 14 Control groups; *k*=18 and *k*=10 quantified pre-intervention strength in kilograms. † **Lower body strength** was assessed in 33 RT and 24 Control groups; *k*=24 and *k*=16 quantified pre-intervention strength in kilograms. ‡ **Fitness** was assessed in 37 RT and 36 Control groups; *k*=24 and *k*=23 measured pre-intervention fitness as peak or maximal oxygen uptake.

Table 2. Multiple moderator analysis of the systolic blood pressure response to dynamic resistance training (*k*=69).

Moderator Dimension/ Level *	d_+ (95% *CI*) † ‡	β	*p*	Difference(95% *CI*) §	Model Summary
Resting SBP (mmHg) of RT Sample		**-0.311**	**0.011**		I^2Residual=27.3%
Normal=115±11 (*k*=18)	0.00 (-0.23, 0.23)			0.0 (-2.5, 2.5)	Multiple *R*=67.1%
Prehypertension=130±13 (*k*=45)	-0.23 (-0.39, -0.07)			-3.0 (-5.1, -1.0) ‖	
** Hypertension =142±14 (*k*=8)	-0.41 (-0.64, -0.19)			-5.7 (-9.0, -2.7) ¶	
Race/Ethnicity of RT Sample		**0.354**	**0.002**		
White Samples (*k*=40)	-0.00 (-0.20, 0.20)			0.0 (-2.6, 2.6)	
** Non-White Samples (*k*=31)	-0.36 (-0.56, -0.16)			-4.7 (-7.3, -2.1) ‖	
Antihypertensive Medication Use of RT Sample		**0.261**	**0.034**		
Currently Taking BP Medication (*k*=14)	-0.03 (-0.29, 0.23)			-0.4 (-3.8, 3.0)	
** Not Taking BP Medication (*k*=57)	-0.33 (-0.48, -0.17)			-4.3 (-6.2, -2.2) ‖	
RT Exercises Performed per Session		**-0.221**	**0.043**		
<8 RT exercises=6 RT exercises (*k*=37)	-0.11 (-0.29, 0.08)			-1.4 (-4.4, 1.0)	
** ≥8 RT exercises=12 RT exercises (*k*=32)	-0.34 (-0.55, -0.12)			-4.4 (-7.2, -1.6) ‖	
Primary Outcome of RT Intervention		**-0.238**	**0.032**		
** BP Focused Study Outcome (*k*=34)	-0.30 (-0.49, -0.10)			-3.9 (-6.4, -1.3) ‖	
Non-BP Focused Study Outcome (*k*=37)	-0.06 (-0.26, 0.14)			-0.8 (-3.4, 1.8)	
****Additive Model: Greatest SBP Benefit for**	***Non-White Samples***	**-1.02 (-1.36, -0.67)**		**-14.3 mmHg (-19.0, -9.4)**	
	White Samples	**-0.66 (-0.97, -0.35)**		**-9.2 mmHg (-13.6, -4.9)**	

Note. *k*=number of comparisons. β=Standardized coefficients. Multiple *R*=Between-study variance explained by model, adjusted for number of moderators. I^2 Residual=Variance unexplained by model. ***Abbr.*** BP=Blood pressure. CI=Confidence interval. RT=Resistance training. SBP=Systolic BP. * **Model** follows maximum likelihood assumptions with a random-effects constant; negative values imply BP was reduced to a greater extent in the RT intervention than control groups. † **Weighted mean effect size (d_+)** controls for the presence of each moderator and for other values of interest within that range, including: multiple *vs*. single-RT interventions, and the interaction between resting SBP × the number of RT exercises performed per session (not shown). ‡ **Predicted d_+ values** represent moderator dimensions and their levels of interest. § **Difference (mmHg)**=d_+ × standard deviation of the mean resting SBP for the sample (prehypertension SBP=110±11mmHg). ‖ **SBP change is different from (*p*<0.05):** Normal SBP; White samples; 6 RT exercises; Current BP Medication Use; Trials lacking BP-focused outcomes; ¶ Normal and Prehypertension SBP. ** Indicates moderator dimension/ level used in the **Additive Model;** represents the greatest *potential* antihypertensive benefit that can be achieved with dynamic RT.

Table 3. Multiple moderator analysis of the diastolic blood pressure response to dynamic resistance training (k=71).

Moderator Dimension/ Level *	d_+ (95% *CI*) † ‡	β	*p*	Difference(95% *CI*) §	Model Summary
Resting DBP (mmHg) of RT Sample		**-0.317**	**0.023**		I^2Residual=19.6%
Normal =69±8 (k=40)	-0.13 (-0.30, 0.31)			-1.0 (-2.4, 2.5)	Multiple R=49.9%
Prehypertension =83±9 (k=27)	-0.37 (-0.59, -0.15)			-3.3 (-5.3, -1.4) ‖	
** Hypertension =92±10 (k=4)	-0.52 (-0.84, -0.19)			-5.2 (-8.4, -1.9) ‖	
Antihypertensive Medication Use of RT Sample		**0.260**	**0.028**		
Currently Taking BP Medication (k=14)	-0.13 (-0.38, 0.11)			-1.2 (-3.4, 1.0)	
** Not Taking BP Medication (k=57)	-0.39 (-0.55, -0.23)			-3.5 (-5.0, -2.1) ‖	
Weekly Frequency of RT Sessions		**-0.262**	**0.020**		
<3 days=2 days weekly (k=22)	-0.10 (-0.31, 0.11)			-0.9 (-2.8, 1.0)	
** ≥3 days=4 days weekly (k=49)	-0.50 (-0.76, -0.23)			-4.5 (-6.8, -2.1) ‖	
Methodological Study Quality		**0.296**	**0.019**		
** Lower Quality=49% of Items Satisfied (k=25)	-0.41 (-0.62, -0.19)			-3.7 (-5.6, -1.7) ¶	
Moderate Quality=63% of Items Satisfied (k=35)	-0.20 (-0.38, -0.03)			-1.8 (-3.4, -0.3) ‖	
Higher Quality=82% of Items Satisfied (k=11)	-0.03 (-0.28, 0.22)			-0.3 (-2.5, 2.0)	
****Additive Model: Greatest DBP Benefit for**	***Non-White Samples***	**-1.03 (-1.45, -0.62)**		**-10.3 mmHg (-14.5, -6.2)**	
	White Samples	**-0.95 (-1.35, -0.54)**		**-9.5 mmHg (-13.5, -5.2)**	

Note. k=number of comparisons. β=Standardized coefficients. Multiple R=Between-study variance explained by model, adjusted for number of moderators. I^2 Residual=Variance unexplained by model. ***Abbr.*** BP=Blood pressure. CI=Confidence interval. RT=Resistance training. SBP=Systolic BP. * **Model** follows maximum likelihood assumptions with a random-effects constant; negative values imply BP was reduced to a greater extent in the RT intervention than control groups. † **Weighted mean effect size (d_+)** controls for the presence of each moderator and for other values of interest within that range, including: the race/ethnicity of the RT sample, multiple *vs*. single-RT interventions, and its interaction with resting DBP (not shown). ‡ **Predicted d_+ values** represent moderator dimensions and their levels of interest. § **Difference (mmHg)**=d_+ × standard deviation of the mean resting DBP for the sample (prehypertension DBP=86±9 mmHg). ‖ **DBP change is different from (p<0.05):** Normal DBP; Current BP Medication Use; RT performed 2 days weekly; Higher quality trials; ¶ Moderate and Higher quality trials. ** Indicates moderator dimension/ level used in the **Additive Model;** represents the greatest *potential* antihypertensive benefit that can be achieved with dynamic RT.

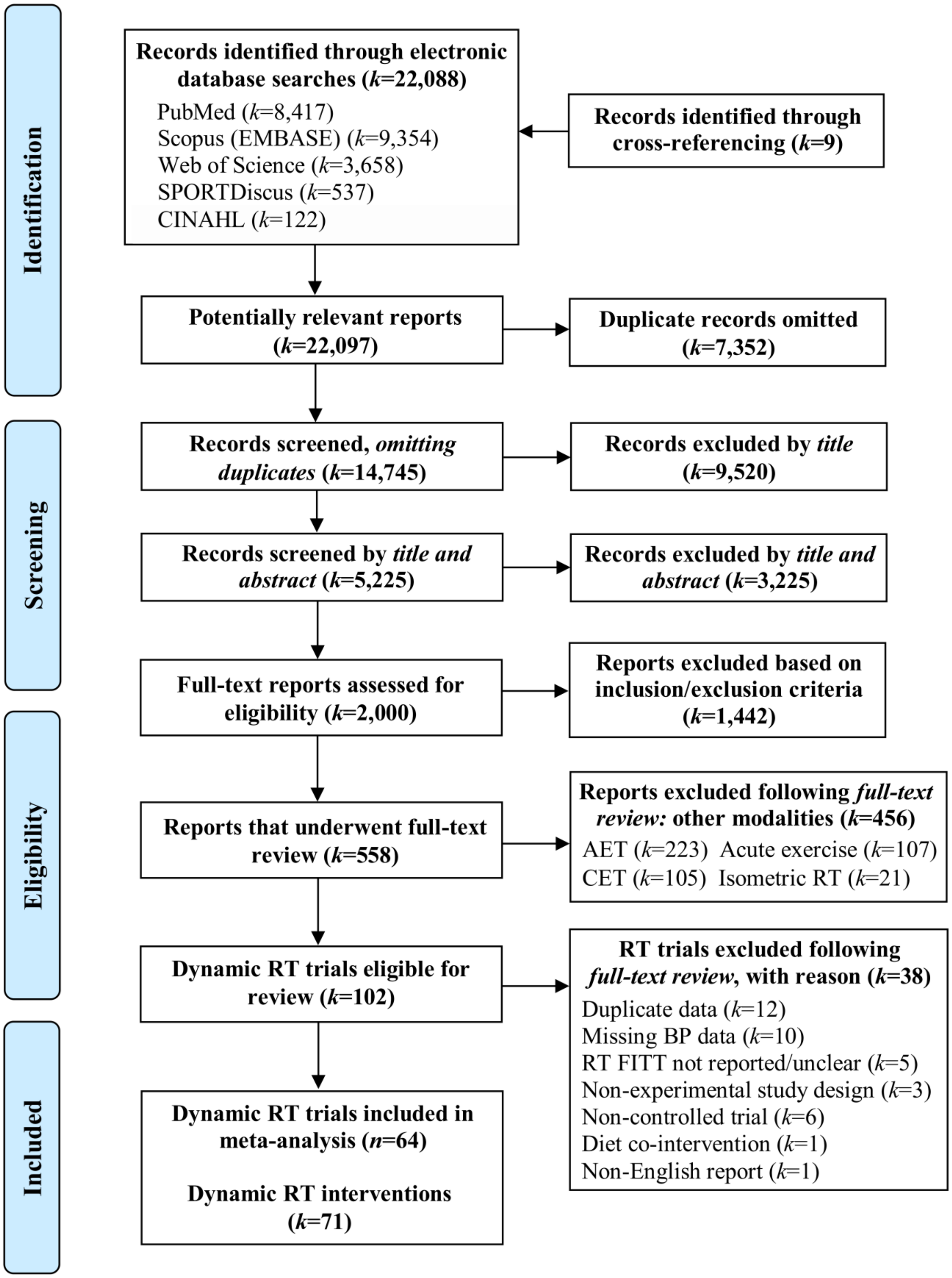

Figure 1. Flow chart detailing the systematic search of potential reports (*k*) and selection process of included dynamic resistance training trials. *Note.* AET=Aerobic exercise training. BP=Blood pressure. CINAHL=Cumulative index to nursing and allied health literature. CET=Concurrent exercise training. FITT=Frequency, Intensity, Time and Type. RT=Resistance training.

Chapter 4

Discussion

The present dissertation includes two meta-analyses that aimed to determine the influence of modality on the antihypertensive effects of exercise and to identify what combinations of patient clinical characteristics and exercise intervention features elicited optimal therapeutic BP benefit. This chapter provides a summary of our most relevant findings and serves as the concluding statement on the antihypertensive effects of AET and dynamic RT. First, we will overview our major findings as they relate to our specific aims and hypotheses. This will be followed by a discussion on the implications of our findings on the current exercise recommendations for adults with hypertension. Finally, we will discuss the remaining gaps in the existing literature and present potential directions for future research.

4.1 Specific Aims and Hypotheses

The results from these two meta-analyses support our initial specific aims and hypotheses for outlined in Chapter 1. Below find a reiteration of our major findings for AET and dynamic RT in the context of our specific aims and hypotheses.

Specific Aim 1: To meta-analyze the existing AET literature with high quality methods to determine the effectiveness of AET as an antihypertensive therapy and identify what patient clinical and AET FIT characteristics elicit optimal antihypertensive BP benefit.

Hypothesis 1: Patient clinical (i.e., age, body mass index, sex/gender, race/ethnicity, BP medication use, etc.) and AET FIT characteristics will moderate the antihypertensive effects of AET.

We observed that AET on average reduced BP by ~3-4 mmHg compared to control. Of note, we found that BP reductions occurred in dose response fashion such that greater BP reductions were observed among samples with hypertension (~7/6 mmHg) than prehypertension (~5/4 mmHg), and normal BP (~3/1 mmHg). Furthermore, even larger BP reductions were observed among samples with hypertension that achieved large gains in physical fitness and performed high volumes of AET,

an effect that was more pronounced among non-White (~12 mmHg) than White (~6-7 mmHg) samples. Our results confirm the effectiveness of AET as antihypertensive lifestyle therapy for adults with hypertension, notably among African American (i.e., non- Hispanic Blacks), Asian, and Hispanic/Latino samples, who achieved BP reductions that nearly doubled the magnitude previously reported for AET.

Specific Aim 2: To meta-analyze the existing dynamic RT literature with high quality methods to determine the effectiveness of RT as stand-alone antihypertensive therapy and identify important moderators (i.e., patient clinical and RT FIT characteristics) of the BP response to provide insight into the optimal dose of RT to lower BP among adults with hypertension.

Hypothesis 2: Patient clinical (i.e., age, body mass index, sex/gender, race/ethnicity, BP medication use, etc.) and RT FIT characteristics will moderate the antihypertensive effects of dynamic RT and provide insight into the optimal dose of RT as stand-alone antihypertensive therapy for adults with hypertension.

We observed that dynamic RT on average reduced BP by ~2-3 mmHg compared to control. However, we found that BP reductions occurred in dose response fashion such that greater BP reductions were observed among samples with hypertension (~6/5 mmHg) than prehypertension (~3/3 mmHg), and normal BP (~0/1 mmHg). Furthermore, even larger BP reductions were observed among samples with hypertension following RT that involved ≥8 RT exercises per session and was performed 3 or more days·week^{-1}, an effect that was more pronounced among non-White (~10-14 mmHg) than White (~9-10 mmHg) samples. Our results revealed that dynamic RT is as effective if not more so than AET as antihypertensive therapy among those with hypertension, notably Hispanic/Latino and Asian samples. These results indicate that the present exercise recommendations for hypertension should be revisited to include dynamic RT (in addition to aerobic exercise) as stand-alone antihypertensive lifestyle therapy. In addition, high quality RCTs should be designed to further substantiate our findings.

4.2 Additional Findings

In addition to our major findings detailed above, we also observed several interesting patterns related to the overall methodological study quality of the included trials, and sources of potential bias that may have contributed more substantially to the “fair to moderate” quality of the AET and dynamic RT literature. Overall, we found that primary-level AET and RT interventions included in our meta-analyses achieved similar methodological study quality (~65% and 63%), and for both modalities, there was considerable range in percentage of quality items that were fully satisfied, with overall methodological quality ranging from low (40%) to high (86%) [1, 2]. Surprisingly, only two AET interventions satisfied ≥80% of study quality items (83.6%±2.8%), which suggests ‘higher quality’, whereas seven RT trials achieved ≥80% (83.3%±1.3%).

Overall, AET and RT interventions yielded similar patterns regarding methodological deficits and potential risk of biases gauged as the percentage of items fully satisfied using an augmented version of the Downs and Black Checklist. This instrument [3] is well validated in the health promotion literature and has been shown to be valid and reliable in assessing RCTs and non-RCTs. The Downs and Black Checklist [3] addresses five subscales of methodological quality, making it one of the most comprehensive extant instruments to evaluate study quality [4]. The methodological subscales address potential risk for bias as it relates to: (1) reporting (i.e., how well were the intervention details and other important information reported so that readers could make an unbiased assessment of the study findings); (2) external validity (i.e., addresses the extent to which the study findings can be generalized to the population from which the study subjects were derived); (3) internal validity-bias (i.e., addresses the biases associated with the measurement of the intervention and the study outcomes); (4) internal validity-confounding (i.e., addresses the bias in the selection of study subjects); and (5) power (i.e., assesses whether the negative findings from a study could be due to chance, i.e., inadequately powered sample to detect study findings) [3]. AET and RT interventions were least likely to satisfy the methodological subscales that addressed external validity (AET:

49.6%±40.7; RT: 46.5%±42.3) and power (AET: 1.7%±11.7%; RT: 9.2%±24.4%). None of the individual methodology quality subscales emerged as significant moderators of the BP response to AET or dynamic RT. These findings highlight the significant limitations of the existing exercise and hypertension literature, namely that primary-level interventions lack the ability to generalize their findings to the population from which the study subjects were derived (i.e., poor external validity) and trials were not designed based on the sample size needed to detect exercise-related BP changes [5, 6]. As a result, research syntheses, i.e., meta-analyses, of these exercise interventions may be subject to the same limitations. Furthermore, exercise interventions that fail to fully satisfy these particular subscales add to the uncertainty and discrepancies observed across trials in the magnitude of BP reductions following exercise. It is unclear whether exercise interventions fail to observe significant BP reductions as a result of the Ex R_x employed the clinical population enrolled, or a small sample that was inadequately powered. Indeed, despite our meta-analyses constituting some of the largest samples to date [7], only 26% (k=27) of AET and 11% (k=8) of RT interventions involved adults with hypertension and sample sizes on average were small (n=18-20 participants).

Furthermore, we found that nearly 12% (k=10) of AET and 14% (k=9) of the RT trials incorporated a “placebo” or “active control” group instead of a, non-exercise or “wait-list” condition. Although this study design feature did not emerge as a significant moderator in either meta-analysis, it may have underestimated the antihypertensive effects of AET and dynamic RT. BP reductions were significantly smaller when compared to the placebo or active control groups (AET: -3.4/+0.8 mmHg; RT: +0.1/-0.3 mmHg) than all control groups (AET: -3.5/-2.7 mmHg; RT: -3.0/-2.1 mmHg).

4.3 Implications for the Exercise Prescription Recommendations for Hypertension

Based on the synthesis of the AET and dynamic RT literature presented in each meta-analysis, the following FITT-VP Ex R_x guidelines are suggested as a possible modification or expansion of the current exercise recommendations for hypertension:

*F*requency: **AET** reduced resting BP to the greatest extent among adults with hypertension (~6-7 mmHg). These reductions occurred with AET performed ~3-4 days·week^{-1}. Accordingly, AET should be performed on *at least* 3 days·week^{-1}, preferably most days of the week, to achieve optimal BP benefits. These recommendations are consistent with the current ACSM recommendations for hypertension [8] and other professional organizations/committees [6].

*F*requency: **Dynamic RT** reduced resting BP to the greatest extent among adults with hypertension (~5-6 mmHg). These reductions occurred with RT regimes that were performed ~3 days·week^{-1}. However, we observed greater BP reductions when RT was performed on 3 or more days·week^{-1}. Accordingly, dynamic RT should be performed 3-4 days·week^{-1} (in addition to aerobic exercise) as stand-alone antihypertensive lifestyle therapy. These recommendations are a departure from the current ACSM recommendations for hypertension [8] and other professional organizations/committees [8-12] that who endorse dynamic RT on ≥2 days·week^{-1} as adjuvant antihypertensive lifestyle therapy to AET.

*I*ntensity: **AET** performed at moderate-to-vigorous intensity (62.6%±10.6% VO_{2peak} [range: 40-83% VO_{2peak}]; 5.9±1.7 MET [range: 3-12 MET]) elicited BP reductions of ~6-7 mmHg among adults with hypertension. Nonetheless, high exercise volumes achieved with higher intensity (~8 MET) were more efficacious as antihypertensive among adults with hypertension (~9-12 mmHg). Our findings contribute to the growing body of literature that supports greater BP reductions can be achieved with greater levels of exertion, if the patient is willing and able to tolerate higher levels of exertion [13-15]. These recommendations align with ACSM [8] and others [6], and are consistent with the Lifestyle Work Group [10] and American Heart Association [9], who also endorse vigorous or high-intensity exercise.

*I*ntensity: **Dynamic RT** performed at low-to-moderate intensity (64.7%±13.0% of 1-RM [range: 40-80% of 1-RM]; range in 1-RM values: 8-15RM; 4.7±1.8 MET [range: 3-8 MET]) was sufficient to elicit BP reductions of ~5-6 mmHg among adults with hypertension. However, we observed RT

programs that involved ≥8 versus <8 RT exercises per session were more efficacious as stand-alone antihypertensive among adults with hypertension (~9-14 mmHg). These RT programs consisted of a greater number of upper (6 versus 3 exercises·session^{-1}) and lower body (5 versus 4 exercises·session^{-1}) (*ps*<0.001), a higher number of repetitions performed per set (13 versus 10 repetitions·set^{-1}, *p*=0.038), and shorter rest intervals between sets and exercises (30-60 versus 90-120 seconds, *p*=0.021) than RT programs involving <8 exercises per session. Nonetheless, many important features of the RT intervention were inconsistently reported, missing, or ranged considerably across trials so that the optimal FIT for dynamic RT as stand-alone antihypertensive therapy remains unclear [16, 17]. These recommendations are consistent with the current RT recommendations for healthy adults [18], and adults those with hypertension put forth by the ACSM [8] and other professional organizations/committees [8-12].

*T*ime: **AET** performed for ~40 min·session^{-1} was sufficient in lowering resting BP ~6-7 mmHg among adults with hypertension. Based on the recommended AET *F*requency, adults with hypertension should accumulate ~120-200 min·week^{-1}, which is consistent with the current exercise recommendations of ≥150 min·week^{-1} [6, 8].

*T*ime: **Dynamic RT** programs that consisted of ~3 sets of 10-12 repetitions for ~8 exercises (3-4 upper and 4-5 lower body exercises) significantly reduced resting BP ~5-6 mmHg among adults with hypertension. Overall, the average RT duration was not widely reported (~52% did; *k*=37), but of those that did, RT sessions lasted ~40-50 min·session^{-1}. Based on the recommended RT *F*requency, adults with hypertension should accumulate ~120-200 min·week^{-1}, which aligns with the exercise recommendations for hypertension [8] and for RT for healthy adults [18].

*T*ype: **AET** should emphasize dynamic, aerobic activities such as walking, jogging, swimming, running, and cycling [8]. **Dynamic RT** should target the major muscle groups of the upper and lower body and can be performed using machine or free weights using a conventional or circuit-style training approach [8, 18].

*V*olume: **AET** volume on average totaled ~850 MET·min·week^{-1} and elicited BP reductions of 6-7 mmHg among adults with hypertension. However, AET consisting of high volumes of exercise (~1200 MET·min·week^{-1}) were most efficacious in reducing BP among adults with hypertension (~9-12 mmHg), notably among non-White samples (~12 mmHg). It is noteworthy to mention that in our meta-analysis, high AET volume was achieved with more rigorous intensity AET (~8 MET) performed on 3-5 days·week^{-1} for 30-40 min·session^{-1}, and not through combinations of lower intensity, higher frequency (>5 days·week^{-1}) and longer duration (>40 min·session^{-1}) AET. This volume of exercise is within the range ACSM recommends for healthy adults (500-≥1000 MET·min·week^{-1}) [19]. Nonetheless, our results support that higher volumes of exercise appear to maximize the antihypertensive benefit of AET for adults with hypertension. **Dynamic RT** that consisted of ~3 sets of 10-12 repetitions for ~8 exercises (~45 min·session^{-1}), performed at low-to-moderate intensity on 3-4 days·week^{-1} totaled on average ~575 MET·min·week^{-1} (calculated as *F*requency × *I*ntensity [MET] × *T*ime). This volume of RT elicited BP reductions of 5-6 mmHg among adults with hypertension and is consistent with ACSM's recommendations for healthy adults (500-≥1000 MET·min·week^{-1}) [19] .

*P*rogression: Overall, the FITT-VP principle of the Ex R_x for healthy adults is applicable for those with hypertension. Modifications may need to be made to the Ex R_x under circumstances such as; a) improvement or worsening of BP control; b) development of co-morbid conditions; c) changes to BP or other medication use; and/or d) injury or physical disability. In general, the ACSM special considerations for AET and dynamic RT are still applicable and should be followed as necessary [14, 19]. The progression of AET and dynamic RT should be gradual, and tailored to individual patient's ability and tolerance [14, 19].

4.4 Additions to the Existing Literature

4.4.1 Aerobic Exercise Training

Our meta-analysis adds new and important contributions to the scarce body of literature that has identified patient characteristics (i.e., resting BP [20-23], race/ethnicity [24], age [25], and sex/gender [23]) and aspects of the FIT [25, 26] that modulate BP reductions following AET. We confirmed that AET is effective antihypertensive therapy for adults with hypertension, and that AET elicits BP reductions in a dose-response fashion such that the greatest BP reductions were observed among samples with hypertension (~7/6 mmHg) followed by prehypertension (~5/4 mmHg), and normal BP (~3/1 mmHg) [20-23]. In addition, we found AET programs that elicited large fitness gains (>25% to ~50%) and promoted high volumes of exercise (~1200 MET·min·week^{-1}) maximized the antihypertensive benefits of AET among adults with hypertension (~9 mmHg), an effect that was more pronounced among non-White (~12 mmHg) than White (~6-7 mmHg) samples.

Our most noteworthy and clinically relevant findings were that: (1) moderate-vigorous intensity AET reduced BP in a dose-response fashion, (2) large gains in physical fitness and high volumes of exercise elicited the greatest BP reductions among adults with hypertension, which are larger than previously reported, and (3) the antihypertensive benefits of AET were greatest among non-White samples, notably African American (i.e., non- Hispanic Blacks), Asian, and Hispanic/Latino populations, with hypertension that achieved BP reductions approximately double the magnitude (~12 mmHg) previously reported for AET.

4.4.2 Dynamic Resistance Training

Our meta-analysis adds novel information to the existing literature, namely that we are the first to document that RT reduces BP in dose-response fashion such that the greatest BP reductions occurred among samples with hypertension (~6/5 mmHg), followed by prehypertension (~3/3 mmHg), whereas those observed among samples with normal BP were negligible (~0/1 mmHg). Second, we are the first to identify features of the RT FIT that influenced the BP response to dynamic

RT. In agreement with the current exercise recommendations for hypertension, we found that low-to-moderate-intensity RT programs (~60% of 1-RM) consisting of ~3 sets of 10-12 repetitions for ~8 exercises (3-4 upper and 4-5 lower body exercises) performed on ~3 days·wk^{-1} significantly reduced resting BP ~5-6 mmHg among adults with hypertension. However, we observed the greatest BP reductions among adults with hypertension following RT programs that involved ≥8 versus <8 RT exercises per session, and when dynamic RT was performed ≥3 versus <3 days·wk^{-1}, (~9-14 mmHg), an effect that was more pronounced among non-White samples (i.e., Hispanic/Latino and Asian). Our most noteworthy and clinically relevant findings were that: (1) dynamic RT elicited BP reductions that were comparable to or greater than those achieved with AET among adults with hypertension, particularly among non-White samples, and (2) RT reduced BP in dose-response fashion, findings that align with those reported for AET [6-8], but not with other meta-analyses examining the BP response to RT. Our findings suggest that dynamic RT prescribed with the FIT recommendations above may be recommended as stand-alone antihypertensive therapy among adults with hypertension similar to the AET recommendations, however, new RCTs should be conducted to confirm this proposition.

4.4.3 Exercise Training Literature

Aerobic exercise training (AET) is universally recommended as first line antihypertensive lifestyle therapy due to the strong level of evidence supporting it lowers blood pressure (BP) 5-7 mmHg among most adults with hypertension [27]. Dynamic RT is recommended as adjuvant antihypertensive lifestyle therapy to aerobic exercise training because there is a weaker body of evidence indicating it lowers BP to lesser half that of AET among adults with hypertension (~2-3 mmHg) [6, 26, 28-32]. Therefore, the American College of Sports Medicine [8] and other professional organizations and committees [9-12, 33] recommend 30-60 min·day^{-1} of moderate intensity (i.e., 40% to <60% maximal oxygen consumption) AET on most days of the week *supplemented* by dynamic RT on ≥2 days·wk^{-1} [8-12] as first-line antihypertensive therapy for the

prevention, treatment, and control of hypertension. Yet, a more critical review of this literature revealed considerable variability in the magnitude of the BP reductions from these recommendations for both AET (i.e., 1-9 mmHg) [6] and dynamic RT (i.e., 0-6 mmHg) [8, 28, 30, 32]. Reasons for inter- and intra-individual variability are not clear not clear [6, 9] but may be attributable to differences in baseline sample clinical and exercise intervention characteristics (i.e., the FITT) of the Ex R_x. Nonetheless, few meta-analyses have documented significant moderation patterns pertaining to these characteristics [6, 7].

Our two meta-analyses addressed several of the research gaps noted above, notably, the fact we identified combinations of patient clinical and FIT characteristics that optimized the antihypertensive BP benefits following AET and dynamic RT among adults with hypertension. Some of our findings contradict earlier statements made by the ACSM in their evidence-based position on exercise and hypertension [8]. In particular, our findings related to race/ethnicity. In contrast to the *Category B* level of evidence rating (i.e., fewer RCTs trials with inconsistent findings) and their conclusion that “race/ethnicity does not modulate the BP response to exercise training”, we found that greater BP reductions occurred among non-White (i.e., African American, Hispanic/Latino, and Asian) than White samples following AET and RT. Collectively, these findings are important because racial/ethnic groups often experience a disproportionate burden of hypertension and CVD [34]. These health disparities are further exacerbated by lower cardiorespiratory fitness and more sedentary lifestyles [34-37] compared to Whites. Thus, racial/ethnic minority populations are less likely to engage in regular exercise as antihypertensive lifestyle therapy, despite the fact our findings showed they are the patients who may benefit the most. Our findings highlight the critical need for a more individualized, possibly, race/ethnicity-specific approach to the Ex R_x for hypertension in order to maximize the effectiveness of exercise as antihypertensive therapy.

Second, our meta-analyses gauged the individual study quality for each included trial using an augmented version of the Downs and Black Checklist [1, 2]. In addition, we *quantitatively*

incorporated methodological study quality and quality-related features of the exercise interventions (i.e., whether trials had BP-focused outcomes) to determine whether study quality independently [7, 38] or interactively [39] modulated the BP response to exercise training. We, along with prior meta-analyses [6, 7], have found the exercise and hypertension literature to be of 'fair to moderate' methodological quality [1, 2]. In the absence of a higher quality literature, there is the potential risk of bias or other threats to the validity of our findings. For this reason, we explored potential sources of bias related to the five quality subscales of the Downs and Black checklist, whether trials had BP-focused outcomes, and whether the publication year, type of trial (i.e., RCT versus non-RCT), or number of funding sources influenced our results. We then statistically examined whether these potential sources of biases modulated the BP response to AET and dynamic RT, and even when these features were non-significant in bivariate meta-regression models, we incorporated them to control for confounding or suppression effects that could arise from lower-quality trials [7, 39].

We found that higher study quality was associated with trials that: were published more recently (AET: r=0.15, p=0.03; RT: r=0.45, p<0.001), were RCTs (versus non-RCTs) (AET: r=0.36, p<0.001; RT: r=0.23, p=0.052), were adequately powered to detect BP outcomes (Downs and Black Checklist Item 28) (AET: r=0.26, p=0.09; RT: r=0.41, p<0.001), and followed standard protocols or established guidelines when measuring BP (i.e., American Heart Association Council on High BP Research Part 1: Recommendations for BP measurement in Humans [40]) (RT: r=0.24, p=0.045). Not surprisingly, trials that used standard protocols/established guidelines when assessing BP were more likely to have BP-focused outcomes (AET: r=0.22, p=0.002) and used more reliable and accurate BP assessment methods (Downs and Black Checklist Item 21) (r=0.19, p=0.006). Interestingly, trials that were adequately powered also had greater amounts of funding support (AET: r=0.68, p<0.001; RT: r=0.26, p=0.029). By examining the potential risk of bias from several sources and incorporating them into our multiple moderator models, we can be more confident in our study

results despite the number of methodological deficits and inconsistencies we have documented in this literature.

4.5 Limitations

Despite our novel and important contributions, we identified other noteworthy gaps in the extant literature. Other than Whelton and colleagues [24], no previous meta-analysis until ours has documented race/ethnicity-dependent BP reductions following exercise training. Furthermore, Whelton et al. [24] only identified race/ethnicity as a moderator of the BP response to AET, whereas we found this moderation pattern persisted across modalities for both AET and RT. Unfortunately, included trials rarely disclosed the race/ethnicity of their participants; only 18% of AET [27-41] and 14% of RT [22, 23, 42-48] trials reported this detail. Therefore, we employed the same strategy used by Whelton et al. [24] to estimate race/ethnicity when it was missing. It is well documented that certain racial/ethnic minority groups experience disproportionate health outcomes. Furthermore, there is a growing body of research that has documented the different physiological responses between 'White' and 'non-White' populations to the same exercise stimuli [41, 42], although the mechanisms to explain these differences have yet to be fully elucidated. In order to meaningfully contribute to this growing literature, a more comprehensive approach must be implemented for data collection at the primary-level to ensure that these important patient clinical characteristics are adequately reported.

Although we identified FIT characteristics that moderated the BP response to AET and dynamic RT, we found that many important FIT characteristics and features of the exercise intervention were assessed using a variety of methods (i.e., lack of standardization in cardiorespiratory fitness and 1-RM testing procedures), and in many cases it was inconsistently reported or missing completely. Given that training adaptations are specific to the stimulus applied (i.e., principle of specificity), it is troubling that the majority of AET and RT trials failed to adequately report important features of the Ex R_x or properly assess training-induced changes in

physical function, fitness, and strength. Inconsistent reporting of these intervention characteristics not only precludes exercise professionals from identifying the optimal AET and RT Ex R_x FIT for adults with hypertension, but limits our ability to gauge how well participants tolerated the Ex R_x (i.e., exercise adherence), and ultimately, its effectiveness as antihypertensive therapy.

Even though we examined several sources for potential biases, of which some addressed the validity of the BP assessment methods used, it important to reinforce the poor reporting of these variables in both the AET and RT literature. Several reviews [5-8] have commented on how the level of reporting and quality of BP assessment procedures may contribute to the discrepancies observed across studies in the magnitude of the BP reductions following exercise (i.e., unaccounted sources of heterogeneity). Yet, 38% of AET and 31% of RT interventions failed to disclose *any* BP assessment procedures, while ~20-30% of AET and RT trials failed to report specific details that included: the type of BP monitor or assessment tool (75-80% did), the body position during the BP measurement (69-72% did), and the timing of BP measurements at baseline (52-60% did) and post-intervention (17-20% did). At this time, it is unclear how the poor reporting and variability in these parameters influenced our results.

Finally, many of the limitations noted above are exacerbated by the use of *aggregated* data (i.e., *aggregate*-level meta-analysis). Individual-participant data (IPD) meta-analysis is the (emerging) gold standard in meta-analytic practice [43, 44], although it is rarely used in the exercise and health promotion literature. IPD meta-analyses are superior to those performed with aggregated-data because it avoids such issues as restriction in range of moderators (e.g. mean sample versus *individual* values that better capture the variability in training responses among samples) and ecological fallacy (e.g. assuming that all members of the exercise group benefit equally) [43, 45, 46]. On the other hand, IPD meta-analysis presents with a unique set of challenges, namely that it requires a greater time-commitment to obtain original, raw participant data from *all relevant trials* on specific topic [47, 48]. Furthermore, IPD approaches depend on collaborative efforts and the willingness of

researchers to share their data. If participant data is not available for all relevant trials, it is possible that the results will not be representative of the existing literature and lack generalizability to the population intended for treatment. Despite improved and likely greater precision in the analytic results from IPD meta-analyses, it is possible that aggregate-level meta-analyses are more appropriate to answer questions regarding the role of exercise training for the prevention, treatment and management of hypertension (i.e., Simpson's paradox [49, 50]). The decision to use aggregated-data versus IPD should be based on the most appropriate approach to answer the research question based on the available data with important consideration given to the strengths and weaknesses of their inherent assumptions [44, 45]. These steps, in addition to improved reporting transparency and adherence to contemporary methodological standards, should reduce the likelihood of Simpson's Paradox [49, 50], that different trends will result from the application of different statistical analyses and partitioning of data.

4.6 Strengths

Our meta-analyses had several strengths. The trial identification and selection process was comprehensive, and without restrictive inclusionary criteria that has been used in previously published meta-analyses. We strove to identify *all* potentially relevant reports from several electronic databases searched from their inception until our pre-specified end search date; we sought to locate reports in all languages regardless of publication status (i.e., our search permitted grey and unpublished literature), which yielded two of the largest meta-analyses conducted to date (86 AET trials,105 interventions; 64 RT trials, 71 interventions) [7]. We examined *a priori*, theoretically-driven moderator analyses using more sophisticated [51, 52] and complex meta-analytic techniques [53], that until now have not been used to examine the antihypertensive effects of exercise. Consequently, our meta-analysis adhered to high-quality, contemporary methodological standards [54, 55] and completely satisfied the criteria implied by the PRISMA Statement (*P*referred *R*eporting

*I*tems for *S*ystematic *R*eview and *M*eta-*A*nalyses) [54, 55] and the AMSTAR Scale (*A*ssessment of *M*ultiple *S*ys*T*em*A*tic *R*eviews) [38, 56].

4.7 Conclusions

In summary, our two high quality meta-analyses that adhered to contemporary methodological standards revealed several important findings. First, we confirmed that AET is effective antihypertensive therapy for adults with hypertension (~6-7 mmHg). We found for the first time that high volume AET programs and large gains in physical fitness were associated with the largest BP reductions (~9-10 mmHg), most notably for non-White samples (~12 mmHg). These results indicate that the present exercise recommendations for hypertension should be revisited to include individualized, race/ethnicity-specific exercise prescription recommendations for populations who experience disproportionate adverse CVD outcomes, with the goal of improving physician-patient interactions and adherence to exercise as lifestyle therapy.

Second, we demonstrated that BP reductions following RT occurred in dose response fashion such that greater BP reductions occurred among samples with hypertension (~5-6 mmHg), which is comparable to the magnitude reported with AET. Samples with hypertension that performed ≥8 RT exercises per session, on 3-4 days·wk^{-1} achieved the greatest BP reductions following RT (~9 mmHg), notably among non-White samples (~10-14 mmHg). Our results indicate that the present exercise recommendations for hypertension should be revisited to include dynamic RT (in addition to AET) as stand-alone antihypertensive lifestyle therapy.

Our findings suggest the following FITT-VP Ex R_x for the use of AET *and* dynamic RT as stand-alone antihypertensive therapy:

*F*requency: **AET:** 3-≥4 days·week^{-1}, preferably most days of the week *and* **dynamic RT:** 3-4 days·week^{-1}

*I*ntensity: **AET:** Moderate-to-vigorous intensity (40->60% VO_{2peak}; 3->6 MET). Progression to vigorous intensity AET may be warranted if the patient is willing and able to tolerate higher

levels of exertion. **Dynamic RT:** low-to-moderate intensity (~40-70% of 1-RM; 8-15RM; 3-<6 MET)

_T_ime: **AET:** ~40 min·session^{-1} *and* **dynamic RT:** ~3 sets of 10-12 repetitions for ~8-12 upper and lower body RT exercises lasting ~40 min·session^{-1} to achieve a *total amount of weekly exercise* ~120-200 min·week^{-1}

_T_ype: **AET:** dynamic, aerobic activities such as walking, jogging, swimming, running, and cycling *and* **dynamic RT:** should target the major and can be performed using machine or free weights using a conventional or circuit-style training approach that target the major muscle groups of the upper and lower body. Our meta-analysis examined the antihypertensive effects of *isolated* AET and RT, therefore it is unclear s *how* AET and dynamic RT should be *combined* as stand-alone antihypertensive therapeutic exercise options. Further investigations are warranted to determine the optimal AET and RT FIT, specifically focused on whether AET and RT should be performed on the *same (i.e., concurrently)* or *separate days (i.e., combined)*, and if *concurrent exercise* is most efficacious, further clarification is needed on whether AET should be performed *before* versus *after* or *simultaneously* (i.e., intermittent training) with RT.

_V_olume: Moderate to high volumes of **AET (**~850 MET·min·week^{-1}) *and* moderate volumes of **dynamic RT** (~575 MET·min·week^{-1}) *totaling* ≥1200 MET·min·week^{-1}

_P_rogression: In general, the special considerations already established in the ACSM's guidelines for **AET** *and* **dynamic RT** still apply. The progression of **AET** *and* **dynamic RT** should be gradual, and tailored to individual patient's ability and tolerance.

Despite the promising and positive findings from our two meta-analyses, the AET and dynamic RT body of literature is of fair to moderate quality with other limitations noted within. Additional high-quality RCTs that have BP-focused outcomes are needed to investigate the antihypertensive effects of AET and RT as stand-alone or combined therapeutic exercise options

among more racially/ethnically diverse samples with hypertension. Future researchers should also incorporate standard assessment methodology for key variables, such as cardiorespiratory fitness, strength (1-RM), and manipulate the AET and RT FIT characteristics to further clarify the optimal ‘dose’ of exercise to lower BP among adults with hypertension.

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The Influence of Modality on the Antihypertensive Effects of Exercise:

A Meta-Analysis

APPENDIX

Appendix 1. Full search strategy used for electronic databases.

Note. Full electronic search strategies for five databases, PubMed, Scopus (including EMBASE), Web of Science, SPORTDiscus, and CINAHL (Cumulative Index to Nursing and Allied Health Literature), are listed below. For each of the databases searched no start date was applied, and each database was searched from their inception or date of the earliest available publication.

PubMed (including MEDLINE). Hits = 8, 417 Vendor/Platform: National Library of Medicine. Coverage: Date of inception 1940's – January 31, 2014
PubMed was searched with appropriate Medical Subject Headings (MeSH) incorporated into hedges. Filters were set for Humans: ("mean arterial" OR "blood pressure"[mesh] OR "blood pressure" OR "blood pressures" OR "arterial pressure" OR "arterial pressures" OR hypertension OR hypotension OR normotension OR hypertensive OR antihypertensive OR hypotensive OR normotensive OR "systolic pressure" OR "diastolic pressure" OR "pulse pressure" OR "venous pressure" OR "pressure monitor" OR hypotension OR "pre hypertension" OR "bp response" OR "bp decrease" OR "bp reduction" OR "bp monitor" OR "bp monitors" OR "bp measurement") **AND** ("exercise"[majr] OR exercise[ti] OR exercises[ti] OR exercising[ti] OR postexercise[ti] OR running[mesh] OR running[ti] OR bicycling[mesh] OR bicycling OR bicycle* OR cycling[ti] OR treadmill* OR ergometer* OR "weight lifting" OR "weight training" OR "resistance training" OR "strength training" OR "endurance training" OR "speed training" OR "circuit training" OR "training duration" OR "training frequency" OR "training intensity" OR "aerobic endurance" OR "aerobic training" OR "interval training" OR "combination training" OR "combined training" OR plyometric* OR "HIIT" OR walking[mesh] OR walking[ti] OR swimming) **AND** ("randomized controlled trial"[pt] OR "controlled clinical trial"[pt] OR "random allocation" [mh] OR "clinical trial"[pt] OR "clinical trial"[tw] OR "latin square"[tw] OR random*[tw] OR "research design" [mh:noexp] OR "comparative study"[publication type] OR "evaluation studies"[publication type] OR "prospective studies" [mh] OR "cross-over studies" [mh] OR control[tw] OR controlled[tw]) **NOT** ("DASH"[tiab] OR cancer OR neoplasms OR review[pt] OR fibromyalgia OR alzheimers OR alzheimer OR pregnant OR pregnancy OR "obesity/drug therapy"[mesh] OR pharmacol*[ti] OR drug[ti] OR pharmacist*[ti] OR "diet therapy"[mesh] OR "diet therapy"[subheading] OR "nutritional intervention" OR "dietary intervention" OR "nutritional counseling" OR "dietary counseling" OR caffeine OR "eating change" OR "activities of daily living" OR "dehydration" OR "dehydrate" OR "dehydrated" OR "dietary salt" OR sodium OR epilepsy OR influenza OR flu OR pneumonia OR septicemia OR arthritis OR hiv OR "Acquired Immunodeficiency Syndrome" OR meningitis OR "substance abuse" OR alcoholism OR "drug abuse" OR "Cross-Sectional Studies"[MeSH Terms] OR "Case Reports"[pt] OR Comment[pt] OR Editorial[pt] OR Letter[pt] OR Review[pt] OR "case control"[ti] OR "case report"[ti] OR "case study"[ti] OR "case series"[ti] OR "Case-Control Studies"[Mesh] OR "Follow-Up Studies"[Mesh] OR "observational study"[ti] OR "prospective cohort"[ti] OR "cohort studies" [Mesh:NoExp] OR "cohort study"[ti] OR "Longitudinal Studies" [Mesh:NoExp] OR "Follow-Up Studies"[mesh] OR "Retrospective Studies"[mesh] OR "follow up study"[ti] OR rat[ti] OR rats[ti] OR mice[ti] OR mouse[ti] OR dog[ti] OR dogs[ti] OR cats[ti] OR "epidemiology"[Subheading])
Scopus (including EMBASE). Hits = 9, 354 Vendor/platform: Elsevier SciVerse. Coverage: Date of inception 1960 – January 31, 2014

Scopus was searched for the following terms in the "Article title, abstract, keywords." Filters were set for Document Type, excluding: Review, Letter, Note, Editorial. **Line 1 (in article, title, abstract, keywords):** ({mean arterial} OR {blood pressure} OR {blood pressures} OR {arterial pressure} OR {arterial pressures} OR hypertension OR hypotension OR normotension OR hypertensive OR hypotensive OR normotensive OR {systolic pressure} OR {diastolic pressure} OR {pulse pressure} OR {venous pressure} OR {pressure monitor} OR hypotension OR {pre hypertension} OR {bp response} OR {bp decrease} OR {bp reduction} OR {bp monitor} OR {bp monitors} OR {bp measurement}) **AND Line 2 (in article, title, abstract, keywords):** (bicycling OR bicycle* OR treadmill* OR ergometer* OR {weight lifting} OR {weight training} OR {resistance training} OR {strength training} OR {endurance training} OR {speed training} OR {circuit training} OR {training duration} OR {training frequency} OR {training intensity} OR {aerobic endurance} OR {aerobic training} OR {interval training} OR {combination training} OR {combined training} OR plyometric* OR HIIT OR swimming) **OR Line 3 (in article title):** (exercise OR exercises OR exercising OR postexercise OR running OR cycling OR walking) **AND Line 4 (in article, title, abstract, keywords):** ({clinical trial} OR {latin square} OR random* OR {comparative study} OR {evaluation study} OR {evaluative study} OR {prospective study} OR {cross-over study} OR control OR controlled) **NOT Line 5 (in article, title, abstract, keywords):** (DASH OR cancer OR neoplasms OR fibromyalgia OR alzheimer* OR pregnant OR pregnancy OR {nutritional intervention} OR {diet therapy} OR {dietary intervention} OR {nutritional counseling} OR {dietary counseling} OR caffeine OR {eating change} OR {activities of daily living} OR dehydration OR dehydrate OR dehydrated OR {dietary salt} OR sodium OR epilepsy OR influenza OR flu OR pneumonia OR septicemia OR arthritis OR hiv OR {Acquired Immunodeficiency Syndrome} OR meningitis OR {substance abuse} OR alcoholism OR {drug abuse}) **OR Line 6 (in article title):** (review OR pharmacol* OR drug OR pharmacist* OR {cross-sectional} OR {case report} OR comment OR commentary OR editorial OR letter OR {case control} OR {case study} OR {case series} OR {follow-up study} OR {observational study} OR {prospective cohort} OR {cohort study} OR {longitudinal study} OR {retrospective study} OR rat OR rats OR mice OR mouse OR dog OR dogs OR cats OR {epidemiology})
Web of Science (also known as Web of Knowledge). Hits = 3, 658 Vendor/platform: Thomson Reuters. Coverage: Earliest date available 1974 – January 31, 2014
Web of Science was searched using the following terms as "Topic" words. Filters were set for Document Type, including only: Articles, Proceedings Papers. Due to database limitations, excluded terms (i.e., "NOT" terms) were only searched in the article titles, and was performed using RefWorks. **Line 1 (in topic):** ("mean arterial" OR "blood pressure" OR "blood pressures" OR "arterial pressure" OR "arterial pressures" OR hypertension OR hypotension OR normotension OR hypertensive OR hypotensive OR normotensive OR "systolic pressure" OR "diastolic pressure" OR "pulse pressure" OR "venous pressure" OR "pressure monitor" OR hypotension OR "pre hypertension" OR "bp response" OR "bp decrease" OR "bp reduction" OR "bp monitor" OR "bp monitors" OR "bp measurement") **AND Line 2 (in topic):** (bicycling OR bicycle* OR treadmill* OR ergometer* OR "weight lifting" OR

"weight training" OR "resistance training" OR "strength training" OR "endurance training" OR "speed training" OR "circuit training" OR "training duration" OR "training frequency" OR "training intensity" OR "aerobic endurance" OR "aerobic training" OR "interval training" OR "combination training" OR "combined training" OR plyometric* OR HIIT OR swimming)

OR Line 3 (in article title): (exercise OR exercises OR exercising OR postexercise OR running OR cycling OR walking)

AND Line 4 (in topic): ("clinical trial" OR "latin square" OR random* OR "comparative study" OR "evaluation study" OR "evaluative study" OR "prospective study" OR "cross-over study" OR control OR controlled)

NOT Line 5 (in title): (DASH OR cancer OR neoplasms OR fibromyalgia OR alzheimer* OR pregnant OR pregnancy OR "nutritional intervention" OR "diet therapy" OR "dietary intervention" OR "nutritional counseling" OR "dietary counseling" OR caffeine OR "eating change" OR "activities of daily living" OR dehydration OR dehydrate OR dehydrated OR "dietary salt" OR sodium OR epilepsy OR influenza OR flu OR pneumonia OR septicemia OR arthritis OR hiv OR "Acquired Immunodeficiency Syndrome" OR meningitis OR "substance abuse" OR alcoholism OR "drug abuse" OR review OR pharmacol* OR drug OR pharmacist* OR "cross-sectional" OR "case report" OR comment OR commentary OR editorial OR letter OR "case control" OR "case study" OR "case series" OR "follow-up study" OR "observational study" OR "prospective cohort" OR "cohort study" OR "longitudinal study" OR "retrospective study" OR rat OR rats OR mice OR mouse OR dog OR dogs OR cats OR "epidemiology")

SPORTDiscus. Hits = 537

Vendor/platform: EbscoHost. Coverage: Date of inception 1975 – January 31, 2014

SportDiscus was searched for the following terms as "Topic" words. Filters were set for Publication Type, including only: Journal Articles; Peer Reviewed; Academic Journals:

Line 1: ("mean arterial" OR "blood pressure" OR "blood pressures" OR "arterial pressure" OR "arterial pressures" OR hypertension OR hypotension OR normotension OR hypertensive OR hypotensive OR normotensive OR "systolic pressure" OR "diastolic pressure" OR "pulse pressure" OR "venous pressure" OR "pressure monitor" OR hypotension OR "pre hypertension" OR "bp response" OR "bp decrease" OR "bp reduction" OR "bp monitor" OR "bp monitors" OR "bp measurement")

AND Line 2: (bicycling OR bicycle* OR treadmill* OR ergometer* OR "weight lifting" OR "weight training" OR "resistance training" OR "strength training" OR "endurance training" OR "speed training" OR "circuit training" OR "training duration" OR "training frequency" OR "training intensity" OR "aerobic endurance" OR "aerobic training" OR "interval training" OR "combination training" OR "combined training" OR plyometric* OR HIIT OR swimming)

OR Line 3 (in article title): (exercise OR exercises OR exercising OR postexercise OR running OR cycling OR walking)

AND Line 4: ("clinical trial" OR "latin square" OR random* OR "comparative study" OR "evaluation study" OR "evaluative study" OR "prospective study" OR "cross-over study" OR control OR controlled)

NOT Line 5 (in title): (DASH OR cancer OR neoplasms OR fibromyalgia OR alzheimer* OR pregnant OR pregnancy OR "nutritional intervention" OR "diet therapy" OR "dietary intervention" OR "nutritional counseling" OR "dietary counseling" OR caffeine OR "eating change" OR "activities of daily living" OR dehydration OR dehydrate OR dehydrated OR "dietary salt" OR sodium OR epilepsy OR influenza OR flu OR pneumonia OR septicemia OR arthritis OR hiv OR "Acquired Immunodeficiency Syndrome" OR meningitis OR "substance abuse" OR alcoholism OR

"drug abuse" OR review OR pharmacol* OR drug OR pharmacist* OR "cross-sectional" OR "case report" OR comment OR commentary OR editorial OR letter OR "case control" OR "case study" OR "case series" OR "follow-up study" OR "observational study" OR "prospective cohort" OR "cohort study" OR "longitudinal study" OR "retrospective study" OR rat OR rats OR mice OR mouse OR dog OR dogs OR cats OR "epidemiology")

CINAHL: Cumulative Index to Nursing and Allied Health Literature. Hits = 122
Vendor/Platform: EbscoHost. Coverage: Date of inception 1981 – January 31, 2014

CINAHL was searched with appropriate CINAHL subject headings incorporated into hedges, though not shown below, medical headings were included for “blood pressure”, “exercise”, “running”, and “weight lifting”. Filters were set for Research Article; Humans, All Adults. CINAHL hits excluded MEDLINE records.

Line 1: ("mean arterial" OR "blood pressure" OR "blood pressures" OR "arterial pressure" OR "arterial pressures" OR hypertension OR hypotension OR normotension OR hypertensive OR hypotensive OR normotensive OR "systolic pressure" OR "diastolic pressure" OR "pulse pressure" OR "venous pressure" OR "pressure monitor" OR hypotension OR "pre hypertension" OR "bp response" OR "bp decrease" OR "bp reduction" OR "bp monitor" OR "bp monitors" OR "bp measurement")

AND Line 2: (bicycling OR bicycle* OR treadmill* OR ergometer* OR "weight lifting" OR "weight training" OR "resistance training" OR "strength training" OR "endurance training" OR "speed training" OR "circuit training" OR "training duration" OR "training frequency" OR "training intensity" OR "aerobic endurance" OR "aerobic training" OR "interval training" OR "combination training" OR "combined training" OR plyometric* OR HIIT OR swimming)

OR Line 3 (in article title): (exercise OR exercises OR exercising OR postexercise OR running OR cycling OR walking)

AND Line 4: ("clinical trial" OR "latin square" OR random* OR "comparative study" OR "evaluation study" OR "evaluative study" OR "prospective study" OR "cross-over study" OR control OR controlled)

NOT Line 5 (in title): (DASH OR cancer OR neoplasms OR fibromyalgia OR alzheimer* OR pregnant OR pregnancy OR "nutritional intervention" OR "diet therapy" OR "dietary intervention" OR "nutritional counseling" OR "dietary counseling" OR caffeine OR "eating change" OR "activities of daily living" OR dehydration OR dehydrate OR dehydrated OR "dietary salt" OR sodium OR epilepsy OR influenza OR flu OR pneumonia OR septicemia OR arthritis OR hiv OR "Acquired Immunodeficiency Syndrome" OR meningitis OR "substance abuse" OR alcoholism OR "drug abuse" OR review OR pharmacol* OR drug OR pharmacist* OR "cross-sectional" OR "case report" OR comment OR commentary OR editorial OR letter OR "case control" OR "case study" OR "case series" OR "follow-up study" OR "observational study" OR "prospective cohort" OR "cohort study" OR "longitudinal study" OR "retrospective study" OR rat OR rats OR mice OR mouse OR dog OR dogs OR cats OR "epidemiology")

Appendix 2. Reference list for the included aerobic exercise training trials (*n*=84). Aerobic exercise training studies with >1 *independent* interventions (*n*=6) are bolded below (*k*=90 interventions).

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Appendix 3. Augmented version of the Downs and Black Checklist.

Individual Study Quality Items, Listed by Quality Subscale	Y	N	U/D	P
1. Is the hypothesis/aim/objective of the study clearly described? †	1	0	0	—
2. Are the main outcomes to be measured clearly described in the Introduction or Methods section? †	1	0	0	—
3. Is BP a primary outcome? *	1	0	0	½
4. Are the characteristics of the study population included in the study clearly described? ‡	1	0	0	½
5. Are the interventions under study clearly described? ‡	1	0	0	½
6. Are the distributions of principal confounders in each intervention clearly described? †	1	0	0	½
7. Are the BP findings of the study clearly described? §	1	0	0	—
8. Are estimates of the random variability (e.g., SE, SD, CIs, etc.) for BP outcomes reported? §	1	0	0	—
9. Have all important adverse events/negative outcomes that may be a consequence of the intervention been reported? If eligibility screening was reported, award partial score. ‡	1	0	0	½
10. Have the characteristics of study participants lost to follow up been described? †	1	0	0	—
11. Are actual values reported (e.g., 0.035 *vs*. <0.05) for BP outcomes except for values <0.001? §	1	0	0	—
Reporting ***Items satisfied*=___** *(11 possible points)*				
12. Were study subjects asked to participate representative of the population they were recruited? †	1	0	0	—
13. Were study subjects who agreed to participate representative of the population they were recruited? †	1	0	0	—
14. Were the staff, places, and facilities where the study subjects received the intervention representative of the intervention the majority of subjects receive? †	1	0	0	—
External Validity ***Items satisfied*=___** *(3 possible points)*				
15. Were subjects "blinded" to their assigned intervention until recruitment and baseline/pre-training measurements were completed and final? (i.e., subjects were unaware of the intervention they had received until these processes were complete). §	1	0	0	—
16. Was an attempt made to blind those measuring BP outcomes of the intervention? §	1	0	0	—
17. If any of the results of the study were based on "data dredging", was this made clear? †	1	0	0	—
18. In trials and cohort studies, do analyses adjust for different follow-up lengths for participants, or is the time period between the intervention and outcome the same for cases and controls? †	1	0	0	—
19. Were the statistical tests used to assess the main outcomes appropriate? †	1	0	0	—
20. Was compliance with the intervention reliable based on reported exercise adherence, level of supervision, or use of monitoring devices? §	1	0	0	—
21. Were the BP measures accurate? (i.e., were measures of resting BP and/ or ambulatory BP valid and reliable based on the tool(s) and procedures?) §	1	0	0	½
Internal Validity – Bias ***Items satisfied*=___** *(7 possible points)*				
22. Were study participants in the different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited from the same population? †	1	0	0	—
23. Were study participants in the different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited over the same period of time? †	1	0	0	—
24. Were study participants randomized to intervention groups? †	1	0	0	½
25. Was the randomized intervention assignment concealed from both study participants and intervention staff until recruitment was complete and irrecoverable? †	1	0	0	—
26. Was there adequate adjustment in analyses for confounding from which the main findings were drawn? †	1	0	0	—
27. Were losses of study participants to follow-up taken into account? †	1	0	0	—
Internal Validity – Confounding ***Items satisfied*=___** *(6 possible points)*				
28. Was a power analysis conducted to determine the sample size needed to detect a significant difference(s) in effect size for the BP or other outcome measure(s)? §	1/2	0	0	—
Power ***Items satisfied*=___** *(2 possible points)*				
***Total Study Quality Score* =______ of 29 possible points** *(sum of all subscale scores)*				

Note. BP=Blood pressure. N=No, not satisfied. P=Partially satisfied. U/D=Unable to determine. Y=Yes, fully satisfied. ***New item (not part of original checklist). † Original item. ‡ Clarified from original checklist. **§** Modified from original checklist.

Appendix 4. Methods used to calculate the standardized mean difference effect size (ES) estimations (and their components), and the unstandardized *or* raw metric (i.e., mmHg) for different study designs.

1. The standardized mean difference ES estimate for two independent groups (i.e., parallel study design; *between*-group ES) with a repeated-measures design (i.e., *post*- versus *pre*-intervention): Becker's *d* [1-3]:

$$d_b = c(N-2)\left[\frac{\overline{Y}^E_{Post} - \overline{Y}^E_{Pre}}{S^E_{Pre}} - \frac{\overline{Y}^C_{Post} - \overline{Y}^C_{Pre}}{S^C_{Pre}}\right], \qquad c(N-2) = 1 - \frac{3}{4(N-2)-1}$$

Note. $c(N-2)$=Correction factor for small sample size bias and baseline differences, where $N=n^E_{post} + n^C_{post}$ (i.e., the *total* number of participants in the exercise and control groups *post*-intervention). $\bar{Y}_{Post;\ Pre}$=Mean blood pressure for the sample taken at *post*- and *pre*-intervention. *E*=Exercise group. *C*=Non-exercise control group. S_{pre}=Standard deviation of the *pre*-intervention blood pressure for the exercise and control group.

2. The standardized mean difference ES estimate for a one-group (i.e., cross-over study design; *within*-group ES) repeated-measures design (i.e., *post*- versus *pre*-intervention): Becker's *d* [1-3]

$$d_b = c(n-1)\frac{\overline{Y}_{Post} - \overline{Y}_{Pre}}{S_{Pre}}, \qquad c(n-1) = 1 - \frac{3}{4(n-1)-1}$$

Note. $c(n-1)$=Correction factor for small sample size bias and baseline differences, where *n*=the number of participants *post*-intervention for the exercise or control group. $\bar{Y}_{Post;\ Pre}$=Mean blood pressure for the sample taken at *post*- and *pre*-intervention. S_{pre}=Standard deviation of the *pre*-intervention blood pressure for the exercise or control group.

3. The *unstandardized* mean difference ES estimate for two independent groups (i.e., parallel study design; *between*-group ES) with a repeated-measures design (i.e., *post*- versus *pre*-intervention) provided in the *raw metric* (mmHg) [2-4]:

$Raw\ ES\ (mmHg)\ UMD = \left[\left(\bar{Y}^E_{Post} - \bar{Y}^E_{Pre}\right) - \left(\bar{Y}^C_{Post} - \bar{Y}^C_{Pre}\right)\right]$, weighted by the inverse variance of the

$Raw\ ES\ (mmHg)\ UMD$: $\frac{1}{Var_{UMD}} = \frac{n_E n_C}{S_{Pooled}(n_E + n_C)}$, where $S_{Pooled} = \sqrt{\frac{(n_E-1)S_E^2 + (n_C-1)S_C^2}{n_E + n_C - 2}}$

Note. UMD=Unstandardized mean difference. $\bar{Y}_{Post} - \bar{Y}_{Pre}$=Difference in blood pressure (mmHg) taken at *post*- and *pre*-intervention for the Exercise (*E*) and Control (*C*) groups. $\frac{1}{Var_{UMD}}$ =Inverse variance of the

UMD. n_E=number of participants in the exercise group *post*-intervention. n_C=number of participants in the control group *post*-intervention. S_{pooled}=Pooled standard deviation. S_E=Standard deviation of the *post*-intervention blood pressure for the exercise group. S_C=Standard deviation of the *post*-intervention blood pressure for the control group.

4. The *unstandardized* mean difference ES estimate for a one-group (i.e., cross-over study design; *within*-group ES) repeated-measures design (i.e., *post*- versus *pre*-intervention) provided in the *raw metric* (mmHg) [2-4]:

   $Raw\ ES\ (mmHg)\ UMD = [(\bar{Y}_{Post} - \bar{Y}_{Pre})]$, weighted by the inverse variance of the

   $Raw\ ES\ (mmHg)\ UMD: \frac{1}{Var_{UMD}} = \frac{n}{S_{post}\,(n)}$

Note. UMD=Unstandardized mean difference. $\bar{Y}_{Post} - \bar{Y}_{Pre}$=Difference in the sample's blood pressure (mmHg) taken at *post*- and *pre*-intervention. *n*=number of participants *post*-intervention. $\frac{1}{Var_{UMD}}$ =Inverse variance of the UMD. S_{post}=Standard deviation of the sample's *post*-intervention blood pressure.

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Appendix 5. Summary of the overall methodological study quality, individual quality items, and quality subscales for the included aerobic exercise training interventions (*k*=90) gauged using the augmented Downs and Black Checklist.

MSQ Items	Fully Satisfied (*k*, %)		Partially Satisfied (*k*, %)		Not Fully Satisfied: Unsatisfied	U/D	(*k*, %)		MSQ Subscale: Mean ± *sd*	Median (Range)
Reporting	**(11 possible points)**								8.5 ± 1.5 77.5% ± 13.4%	9.0 (2.0, 10.5) 81.8% (18.2%, 95.5%)
Item 1	89	98.9%	—		1	—	1	1.1%		
Item 2	87	96.7%	—		3	—	3	3.3%		
Item 3 *	32	37.2%	10	11.6%	44	4	48	55.6%		
Item 4 *	61	67.8%	9	10.0%	20	—	20	22.2%		
Item 5 *	68	75.6%	10	11.1%	12	—	12	13.3%		
Item 6 *	28	31.1%	47	52.2%	15	—	15	16.7%		
Item 7	87	96.7%	—		3	—	3	3.3%		
Item 8	90	100.0%	—		0	—		0.0%		
Item 9	72	80.0%	—		18	—	18	20.0%		
Item 10	83	92.2%	—		7	—	7	7.8%		
Item 11	32	36.4%	—		56	2	58	64.4%		
External Validity (3 possible points)									1.5 ± 1.2 49.6% ± 40.7%	2.0 (0.0, 3.0) 66.7% (0.0%, 100.0%)
Item 12	47	56.6%	—		36	7		47.8%		
Item 13	47	56.6%	—		36	7		51.2%		
Item 14	40	48.2%	—		43	7		55.6%		
Internal Validity – Bias (7 possible points)									4.9 ± 0.7 70.0% ± 9.6%	5.0 (3.0, 7.0) 71.4% (42.9%, 100.0%)
Item 15	9	10.1%	—		80	1	81	90.0%		
Item 16	12	14.5%	—		71	7	78	86.7%		
Item 17	90	100.0%	—		0	—		0.0%		
Item 18	84	93.3%	—		6	—		6.7%		
Item 19	90	100.0%	—		0	—		0.0%		
Item 20	78	92.9%	—		6	6	12	13.3%		
Item 21 *	76	84.4%	4	4.4%	10	—	10	11.1%		
Internal Validity – Confounding (6 possible points)									3.8 ± 1.3 62.6% ± 21.0%	4.0 (0.5, 6.0) 66.7% (8.3%, 100%)
Item 22	58	69.9%	—		25	7	32	35.6%		

MSQ Items	Fully Satisfied (*k*, %)		Partially Satisfied (*k*, %)		Not Fully Satisfied				MSQ Subscale	
					Unsatisfied	**U/D**	**(*k*, %)**		**Mean ± *sd***	**Median (Range)**
Item 23	44	52.4%	—		40	6	46	51.1%		
Item 24 *	62	68.9%	12	13.3%	16	—	16	17.8%		
Item 25	9	10.5%	—		77	4	81	90.0%		
Item 26	81	98.8%	—		1	8	9	10.0%		
Item 27	78	86.7%	—		12	—	12	13.3%		
Power † (2 possible points)									0.03 ± 0.2 1.7% ± 11.7%	0.0 (0.0, 2.0) 0.0% (0.0%, 100.0%)
Item 28	1	4.6%	1	4.6%	20	68	88	97.8%		
Total MSQ Score (29 possible points)									**18.7 ± 2.9** **64.5% ± 10.2%**	**19.0 (12.0, 25.0)** **65.5% (41.4%, 86.2%)**

Note. — indicates the characteristic/scoring is not applicable. Summary statistics are presented as *M*ean ± *sd* unless stated otherwise; Range= Minimum, Maximum values. ***Abbr.*** MSQ=Methodological study quality. U/D=Unable to determine. SD=Standard deviation. * These items could have been *fully or partially* satisfied; 1 point was awarded to trials that *fully* satisfied these items; *partially* satisfied=0.5 points. † Power=2 points were awarded to trials that fully satisfied Item 28; partially satisfied=1 point.

Appendix 6. Item-by-item summary of methodological study quality for the included aerobic exercise training interventions (k=90) gauged using the augmented version of the Downs and Black Checklist.

Author, Year	Reporting											External Validity			Internal Validity - Bias							Internal Validity - Confounding						Power	Total MSQ Score	
(AET Subgroup)	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28 *	(29-points)	
Albright, 1992 (M) [1]	1	1	0	1	1	1	1	1	1	1	0	0	0	0	0	0	1	1	1	1	1	1	1	1	0	1	1	—	20.0	69.0%
Albright, 1992 (W) [1]	1	1	0	1	1	1	1	1	1	1	0	0	0	0	0	0	1	1	1	1	1	1	1	1	0	1	1	—	20.0	69.0%
Arora, 2009 (T2DM) [2]	1	1	0	½	½	½	1	1	1	1	—	1	1	1	—	—	1	1	1	1	0	1	1	½	1	—	1	0	19.0	65.5%
Bateman, 2011 (MetS) [3]	1	1	½	1	1	½	1	1	1	1	—	1	1	1	1	1	1	1	1	1	0	1	1	½	1	1	1	0	23.5	81.0%
Beck, 2013 (PreHTN) [4]	1	1	0	½	½	½	1	1	1	1	1	1	1	1	1	—	1	1	1	1	1	1	1	1	1	1	1	0	22.5	77.6%
Bell, 2010 (Walk *vs.* Fitness) [5]	1	1	0	1	1	1	1	1	1	1	1	1	1	0	0	0	1	1	1	1	1	1	0	1	0	1	1	—	21.0	72.4%
Bernardi, 2007 [6]	1	1	0	0	1	0	1	1	0	1	0	1	1	1	0	0	1	0	1	1	1	1	0	1	0	1	1	—	17.0	58.6%
Blumenthal, 1991 (HTN) [7]	1	1	1	½	0	½	1	1	1	1	1	1	1	—	0	1	1	1	1	1	1	1	1	½	0	1	0	0	20.5	70.7%
Bowman, 1997 (Older adults) [8]	1	1	0	1	0	1	1	1	1	0	1	1	1	0	0	0	1	1	1	1	1	1	1	1	0	1	1	—	20.0	69.0%
Braith, 1994 (Older adults; Mod *vs.* Vig-AET) [9]	1	1	1	1	1	1	1	1	1	1	0	0	0	0	0	0	1	1	1	1	1	0	0	1	0	1	1	—	18.0	62.1%
Chaudhary, 2010 (Obese W) [10]	1	0	1	0	½	0	1	1	1	1	0	—	—	—	0	0	1	1	1	—	½	—	1	0	—	—	1	0	13.0	44.8%
Cononie, 1991 (HTN; Older adults) [11]	1	1	1	1	½	½	1	1	1	1	1	—	—	1	0	0	1	1	1	1	1	—	—	0	0	1	0	0	16.0	55.2%
Cononie, 1991 (NBP; Older adults) [11]	1	1	1	1	½	½	1	1	1	1	0	—	—	1	0	0	1	1	1	1	1	—	—	0	0	1	0	0	16.0	55.2%
Cooper, 2000 (HTN) [12]	1	1	1	1	1	1	1	1	1	1	0	0	0	0	0	0	1	1	1	1	1	0	0	1	0	1	1	—	18.0	62.1%
Dalleck, 2009 (PostMen; AET × 30 *vs.* 45 min) [13]	1	1	½	1	0	½	1	1	1	1	0	0	0	1	0	0	1	1	1	1	1	1	0	1	0	1	1	—	18.0	62.1%
Davies, 1977 (W) [14]	1	1	—	1	1	½	1	1	1	1	1	0	0	0	0	0	1	1	1	1	1	0	1	1	0	1	1	—	17.5	60.3%
Edwards, 2004 (CAD) [15]	1	1	0	1	1	1	1	1	0	1	1	1	1	1	0	0	1	1	1	1	1	1	1	1	0	1	1	—	21.0	72.4%
Ferrier, 2001 (ISH) [16]	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	—	25.0	86.2%
Fritz, 2006 (T2DM; Walk) [17]	1	1	½	0	1	½	1	1	1	1	1	1	1	1	0	0	1	1	1	1	1	1	1	0	0	1	1	—	20.0	69.0%
Gilders, 1989 (HTN) [18]	1	1	1	1	1	0	1	1	0	0	1	0	0	0	0	0	1	1	1	1	1	0	0	1	0	1	1	—	16.0	55.2%
Gilders, 1989 (NBP) [18]	1	1	1	0	1	1	1	1	1	1	0	0	0	0	0	0	1	1	1	1	1	1	1	1	0	1	1	—	19.0	65.5%
Gormley, 2008 (Mod *vs.* Vig *vs.* Max-AET) [19]	1	1	0	0	1	1	1	1	1	1	1	0	0	0	0	0	1	1	1	1	1	1	1	1	0	1	1	—	18.0	62.1%
Grant, 1992 (M) [20]	1	1	0	1	1	1	1	1	1	1	0	1	1	0	0	0	1	0	1	1	1	1	1	1	0	1	1	—	20.0	69.0%
Hass, 2001 (TBRS) [21]	1	1	0	0	0	0	1	1	0	1	1	0	0	0	0	0	1	1	1	1	1	1	1	0	0	1	1	—	14.0	48.3%
Higashi, 1999 (HTN) [22]	1	1	0	0	1	½	1	1	0	1	0	1	1	0	0	0	1	1	1	1	1	1	1	1	0	1	1	—	18.5	63.8%
Hill, 1993 (Older adults) [23]	1	1	0	1	1	1	1	1	1	1	0	1	1	1	0	0	1	1	1	1	1	1	1	1	0	1	1	—	22.0	75.9%
Ho, 2012 (Obese M & W) [24]	1	1	1	0	½	½	1	1	1	1	0	1	1	1	1	—	1	1	1	—	1	1	1	½	—	—	1	1	21.5	74.1%

Author, Year (AET Subgroup)	Reporting 1	2	3	4	5	6	7	8	9	10	11	External Validity 12	13	14	Internal Validity - Bias 15	16	17	18	19	20	21	Internal Validity - Confounding 22	23	24	25	26	27	Power 28 *	Total MSQ Score (29-points)	
Hua, 2009 (HTN; Low-AET) [25]	1	1	1	1	0	½	1	1	0	1	1	1	1	1	0	0	1	1	1	1	1	1	1	0	0	0	1	—	18.5	63.8%
Jones, 1989 (Postpolio) [26]	1	1	0	0	1	½	1	1	1	1	0	1	1	0	0	0	1	1	1	1	1	1	1	1	0	1	1	—	20.5	70.7%
Jorge, 2011 (T2DM) [27]	1	1	0	½	0	½	1	1	1	1	1	1	1	1	1	—	1	1	1	1	0	1	1	½	1	1	1	0	20.5	70.7%
Ketelhut, 2004 [28]	1	1	1	1	1	½	1	1	1	1	1	0	0	0	0	0	1	1	1	1	1	0	0	1	0	1	1	—	17.5	60.3%
King, 1991 (M) [29]	1	1	—	0	1	1	1	1	1	1	0	0	0	0	0	0	1	0	1	1	1	0	0	0	0	1	1	—	14.0	48.3%
King, 1991 (W) [29]	1	1	—	1	1	½	1	1	1	1	0	1	1	1	0	0	1	0	1	1	1	1	0	1	0	1	0	—	19.5	67.2%
Knoepfil-Lenzin, 2010 (M) [30]	1	1	½	1	1	½	1	1	1	1	1	1	1	1	0	0	1	0	1	1	1	1	0	1	0	1	0	—	20.0	69.0%
Kriz, 1992 (Postpolio) [31]	1	1	1	0	1	½	1	1	1	1	0	1	1	1	0	1	1	1	1	1	1	1	1	1	0	1	1	—	22.5	77.6%
Krustrup, 2010 (W) [32]	1	1	1	1	1	0	1	1	1	1	0	0	0	0	0	0	1	1	1	1	1	0	0	1	0	1	1	—	17.0	58.6%
Krustrup, 2009 (M) [33]	1	1	1	1	1	0	1	1	1	1	0	0	0	0	0	0	1	1	1	1	1	0	0	1	0	1	1	—	18.0	62.1%
Kukkonen, 1982 (PreHTN) [34]	1	1	1	1	0	½	1	1	1	1	0	0	0	1	0	0	1	1	1	1	1	1	0	1	0	1	1	—	18.5	63.8%
Kukkonen, 1982 (NBP) [34]	1	1	1	1	1	0	1	1	1	1	0	0	0	1	0	0	1	1	1	1	1	1	0	1	0	1	1	—	19.0	65.5%
Lamina, 2008 [35]	1	1	0	1	1	1	1	1	1	1	1	1	1	0	0	0	1	1	1	1	1	1	1	0	0	1	1	—	21.0	72.4%
Lavrencic, 2000 (MetS) [36]	1	1	0	1	0	1	1	1	0	1	0	0	0	0	0	0	1	1	1	0	1	0	0	1	0	1	1	—	14.0	48.3%
Lightfoot, 1989 [37]	1	1	0	0	1	0	1	1	1	1	1	1	1	0	0	0	1	1	1	0	1	1	1	1	0	1	1	—	18.0	62.1%
Lindheim, 1994 (W) [38]	1	1	0	0	1	½	0	1	0	1	0	1	1	1	0	0	1	1	1	0	0	1	0	1	0	1	0	—	14.5	50.0%
Madden, 2010 (HTN, T2DM) [39]	1	1	0	0	1	1	1	1	1	1	0	0	0	0	0	0	1	1	1	1	1	0	0	0	0	1	1	—	16.0	55.2%
Marceau, 1993 (HTN; Mod *vs.* Vig-AET) [40]	1	1	1	1	1	1	1	1	1	1	1	1	1	0	0	0	1	1	1	1	1	1	1	1	0	1	1	—	22.0	75.9%
Marioana, 2011 (CHF) [41]	1	1	0	1	0	½	1	1	1	1	1	—	—	1	0	1	1	1	1	1	0	—	—	½	0	—	0	0	14.0	48.3%
McDonald, 1993 (M) [42]	1	1	0	1	1	1	1	1	1	1	0	0	0	0	0	0	1	1	1	1	1	0	1	1	0	1	1	—	19.0	65.5%
Miyai, 2002 (M) [43]	1	1	1	1	1	1	1	1	0	1	0	0	0	1	0	1	1	1	1	0	1	0	0	1	0	1	1	—	18.0	62.1%
Moreau, 2001 (W) [44]	1	1	1	1	1	1	1	1	1	1	0	1	1	1	0	0	1	1	1	1	1	1	1	1	0	1	1	—	23.0	79.3%
Myslivecek, 2002 (PostMen) [45]	1	1	0	1	1	½	1	1	1	1	1	0	0	1	0	0	1	1	1	1	1	0	0	1	0	1	1	—	17.5	60.3%
Myslivecek, 2002 (PreMen) [45]	0	0	0	0	1	0	0	1	0	0	1	1	1	0	0	0	1	1	1	1	1	1	0	1	0	1	1	—	13.0	44.8%
Norris, 1990 [46]	1	0	1	0	0	0	1	1	0	0	1	1	1	1	0	0	1	1	1	—	0	1	1	0	0	—	0	0	12.0	41.4%
Nybo, 2010 (Cont *vs.* AIT) [47]	1	1	1	1	1	½	1	1	1	1	0	—	—	—	0	0	1	1	1	—	1	—	—	0	—	—	1	0	14.5	50.0%
Oliviera, 2012 (T2DM) [48]	1	1	0	½	1	½	1	1	1	1	0	1	1	1	1	—	1	1	1	1	0	1	1	1	1	1	1	0	23.0	79.3%
Oluseye, 1990 (Cont *vs.* AIT) [49]	1	1	1	1	1	½	1	1	1	1	0	0	0	1	0	0	1	1	1	1	1	0	0	0	0	1	1	—	18.5	63.8%
Parkkari, 2000 (Golf) [50]	1	1	0	0	1	0	1	1	0	1	1	0	0	0	0	0	1	1	1	0	1	0	0	0	0	1	1	—	12.0	41.4%
Pechter, 2003 (CKD; Aquatic AET) [51]	1	1	—	1	1	0	1	1	0	0	0	0	0	1	0	0	1	1	1	1	1	0	0	0	0	1	1	—	14.0	48.3%

Author, Year	Reporting											External Validity			Internal Validity - Bias							Internal Validity - Confounding						Power	Total MSQ Score	
(AET Subgroup)	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28 *	(29-points)	
Pollock, 1976 (M) [52]	1	1	0	1	1	1	1	1	1	1	0	1	1	0	0	0	1	1	1	1	1	1	0	1	0	1	1	—	20.0	69.0%
Posner, 1992 [53]	1	1	0	1	1	1	1	1	1	1	1	0	0	0	0	1	1	1	1	1	1	1	0	1	0	1	1	—	20.0	69.0%
Potempa, 1995 [54]	1	1	0	1	1	1	1	1	0	1	0	0	0	0	0	0	1	1	1	1	1	0	0	1	0	1	1	—	16.0	55.2%
Reboredo, 2010 (CKD) [55]	1	1	1	1	1	½	1	1	1	1	1	0	0	1	0	0	1	1	1	1	1	0	0	1	0	1	1	—	18.5	63.8%
Reid, 1994 [56]	1	1	½	1	1	½	1	1	1	1	0	0	0	0	0	0	1	1	1	1	1	0	0	1	0	1	1	—	17.0	58.6%
Sarsan, 2006 (Obese W) [57]	1	1	0	1	1	½	1	1	1	1	0	1	1	1	0	0	1	1	1	1	½	1	1	½	0	1	0	0	20.5	70.7%
Shaw, 2010 (AA M) [58]	1	1	0	0	1	½	1	1	0	0	0	1	1	0	0	0	1	1	1	1	1	1	0	1	0	1	1	—	17.5	60.3%
Sigal, 2007 (T2DM) [59]	1	1	0	½	½	½	1	1	1	1	1	1	1	1	0	—	1	1	1	1	½	1	1	½	0	1	1	2	22.5	77.6%
Sillanpaa, 2009 (M) [60]	1	1	0	1	1	½	1	1	1	1	0	1	1	1	0	1	1	0	1	1	1	1	1	½	0	1	0	0	21.0	72.4%
Sillanpaa, 2009 (W) [61]	1	1	0	1	1	½	1	1	1	1	0	1	1	1	0	1	1	1	1	1	1	1	1	½	0	1	0	0	22.0	75.9%
Smutock, 1993 (M) [62]	1	1	½	½	½	½	1	1	1	1	0	—	—	—	0	0	1	1	1	1	0	—	—	0	—	1	1	0	14.0	48.3%
Sohn, 2007 (AA W) [63]	1	1	1	1	1	1	1	1	0	1	0	1	1	0	0	0	1	1	1	1	1	1	1	1	0	1	1	—	21.0	72.4%
Spalding, 2004 (NBP) [64]	1	1	1	0	½	0	1	1	1	1	0	1	1	—	1	1	1	1	1	1	1	1	1	1	1	—	1	0	21.5	74.1%
Sridhar, 2010 (T2DM) [65]	1	1	0	1	0	1	1	1	1	1	0	1	1	0	0	0	1	1	1	1	1	1	0	1	0	1	1	—	19.0	65.5%
Steinhaus, 1990 (Older adults) [66]	1	1	0	1	1	½	0	1	1	1	0	1	1	1	0	0	1	1	1	0	1	1	1	1	0	1	1	—	19.5	67.2%
Stensvold, 2010 (MetS) [67]	1	1	½	½	1	0	1	1	1	1	1	1	1	—	1	1	1	1	1	1	½	1	1	½	1	—	1	0	22.0	75.9%
Suter, 1990 (M) [68]	1	1	1	1	1	½	1	1	1	1	0	0	0	1	0	0	1	1	1	1	1	1	1	1	0	1	1	—	20.5	70.7%
Swartz, 2003 (W; Walk) [69]	1	1	0	1	1	½	1	1	1	1	0	0	0	1	0	0	1	1	1	1	1	0	0	0	0	1	1	—	16.5	56.9%
Taylor, 1998 (E_x R_x from physician) [70]	1	1	½	1	0	½	1	1	0	1	1	0	0	1	0	0	1	1	1	1	1	0	0	1	0	1	1	—	17.0	58.6%
Thompson, 1981 (M; Arm *vs.* Leg Ergometer) [71]	1	1	0	1	1	½	1	1	1	1	0	1	1	0	0	0	1	1	1	1	1	1	1	1	0	1	1	—	20.5	70.7%
Tjonna, 2008 (MetS; Cont *vs.* AIT) [72]	1	1	½	1	1	½	1	1	1	1	1	0	0	0	0	0	1	1	1	1	1	0	0	1	0	1	1	—	18.0	62.1%
Tsai, 2004 (HTN) [73]	1	1	1	1	1	½	1	1	1	1	0	1	1	0	0	1	1	1	1	1	1	1	1	1	0	1	1	—	22.5	77.6%
Tseng, 2013 [74]	1	1	0	½	1	½	1	1	1	1	1	1	1	1	1	1	1	1	1	—	0	1	1	1	1	1	1	0	23.0	79.3%
Tsuda, 2003 [75]	1	1	0	1	1	½	1	1	1	1	0	0	0	0	0	0	1	1	1	1	1	0	0	1	0	1	1	—	16.5	56.9%
Tudor-Locke, 2004 (T2DM; Walk) [76]	1	1	0	1	1	½	1	1	1	1	1	1	1	1	0	0	1	1	1	1	1	1	1	1	0	1	1	—	22.5	77.6%
Tully, 2007 (AET × 3 *vs.* 5 d·weeks^{-1} [77]	1	1	½	1	1	½	1	1	1	1	1	1	1	1	0	0	1	1	1	1	1	1	1	1	0	1	1	—	23.0	79.3%
Tully, 2005 (Walk) [78]	1	1	1	1	1	½	1	1	1	1	1	1	1	0	0	0	1	1	1	1	1	1	0	1	0	1	1	—	21.5	74.1%
Van Hoof, 1989 (M) [79]	1	1	1	1	1	1	1	1	1	1	0	0	0	0	0	0	1	1	1	1	1	0	0	1	0	1	1	—	18.0	62.1%
Wang, 2005 (M) [80]	1	1	0	0	1	1	1	1	1	1	0	1	1	0	0	0	1	1	1	1	1	1	0	1	0	1	1	—	19.0	65.5%

Author, Year (AET Subgroup)	Reporting											External Validity			Internal Validity - Bias							Internal Validity - Confounding						Power	Total MSQ Score (29-points)	
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28 *		
Wang, 1997 (W) [81]	1	1	0	1	1	1	1	1	1	1	0	0	0	0	0	0	1	1	1	1	1	0	0	1	0	1	1	—	17.0	58.6%
Westhoff, 2008 (HTN; Arm Ergometer) [82]	1	1	1	1	1	½	1	1	1	1	1	1	1	0	0	0	1	1	1	1	1	1	0	1	0	1	1	—	21.5	74.1%
Williams, 1986 (W, Dance) [83]	1	1	0	1	1	0	1	1	1	0	0	0	0	0	0	0	1	1	1	1	1	1	0	1	0	1	1	—	16.0	55.2%
Wood, 2001 (Older adults) [84]	1	1	1	1	½	½	1	1	1	1	0	—	—	—	0	—	1	1	1	—	0	—	—	½	0	1	0	0	13.5	46.6%

Note. References for the included AET trials correspond to the citations listed in Appendix 2. MSQ scoring: 1=Fully satisfied. 0=Not satisfied. ½=Partially satisfied quality item. — =Unable to determine. * Item 28 (Power): 1=Partially satisfied; 2= Fully satisfied. ***Abbr.*** AET=Aerobic exercise training. AA=African American (i.e., 'Black'). AIT=Aerobic interval training. CAD=Coronary artery disease. CHF=Chronic heart failure. CKD= Chronic kidney disease. Cont= Continuous AET. $E_x R_x$=Exercise prescription. HTN=Hypertension. ISH=Isolated systolic HTN. Low=Low intensity AET. Max=Maximal intensity AET. M=Men. MetS=Metabolic syndrome. MSQ=Methodological study quality. Mod= Moderate intensity AET. NBP=Normal blood pressure. PreHTN=Prehypertension. Pre- or PostMen=Pre- or Post-menopausal women. TBRS=Total body recumbent stepper. T2DM=Type 2 diabetes mellitus. Vig=Vigorous intensity AET. W=Women.

Appendix 7. A summary of selected patient clinical characteristics *pre-* versus *post*-intervention for the aerobic exercise training (*k*=105) and control (*k*=90) groups.

	AET (*n*=2,200)				Control (*n*=1,434)				Diff
Characteristics	***k***	**Baseline**	**Change**	**Δ (%)**	***k***	**Baseline**	**Change**	**Δ (%)**	***P***
Body Composition									
Body weight (kg)	64	78.8 ± 10.4	-1.1 ± 1.5 ‡	-1.3 ± 1.7	53	78.2 ± 11.4	0.06 ± 0.7	0.1 ± 0.9	**-1.4%** <0.001
BMI ($kg \cdot m^{-2}$)	60	27.4 ± 3.2	-0.4 ± 0.5 ‡	-1.6 ± 1.7	47	27.6 ± 3.5	-0.1 ± 1.4	-0.3 ± 4.6	**-1.3%** 0.054
Body fat (%)	19	30.4 ± 7.4	-1.3 ± 1.0 ‡	-4.4 ± 3.6	15	30.4 ± 7.4	-0.3 ± 0.9	-1.0 ± 3.3	**-3.4%** <0.001
Hemodynamics									
SBP (mmHg)	105	130.7 ± 12.7	-5.7 ± 4.1 ‡	-4.3 ± 3.1	89	130.8 ± 12.7	-1.8 ± 3.8 ‡	-1.3 ± 2.8	**-2.9%** <0.001
DBP (mmHg)	101	81.7 ± 9.0	-3.6 ± 2.9 ‡	-4.3 ± 3.4	85	81.5 ± 9.1	-0.8 ± 3.0 *	-0.6 ± 3.8	**-3.7%** <0.001
MAP (mmHg)	94	98.1 ± 10.0	-4.4 ± 3.2 ‡	-4.4 ± 3.2	81	98.1 ± 9.9	-1.5 ± 3.0 ‡	-1.4 ± 3.1	**-3.0%** <0.001
PP (mmHg)	96	49.2 ± 6.9	-2.2 ± 2.7 ‡	-4.3 ± 5.3	71	49.8 ± 7.3	-1.2 ± 3.6 †	-2.2 ± 7.5	**-2.0%** 0.043
Physical Fitness									
VO_2 ($ml \cdot kg \cdot min^{-1}$)	61	28.8 ± 7.4	2.5 ± 1.5 ‡	14.7 ± 7.6	43	29.4 ± 8.2	2.5 ± 1.4 ‡	1.2 ± 4.1	**-13.4%** <0.001
VO_2 ($L \cdot min^{-1}$)	12	1.7 ± 1.0	0.1 ± 0.1	5.4 ± 6.0	8	1.6 ± 1.0	0.09 ± 0.1	0.3 ± 3.1	**-5.1%** 0.041

Note. Descriptive statistics for baseline and change are presented as *M*ean ± standard deviation; *k*=the number of observations available to calculate the change variable. *$p<0.05$ † $p<0.01$ ‡ $p<0.001$. Diff, *P*=Between-group difference in the percent change (Δ, %) for AET and control groups. ***Abbr.*** AET= Aerobic exercise training. BMI=Body mass index. DBP=Diastolic blood pressure. MAP=Mean arterial pressure. PP=Pulse pressure. VO_2 ($L \cdot min^{-1}$)=Maximal oxygen uptake. VO_2 ($ml \cdot kg \cdot min^{-1}$)=Peak oxygen uptake. SBP=Systolic blood pressure. Change=Within-group change from baseline. Δ (%)=Change expressed relative to baseline= $\left[\left(\overline{M}_{Post} - \overline{M}_{Pre}\right) \div \overline{M}_{Pre} \times 100\%\right]$

Appendix 8. A summary of the intervention characteristics for the aerobic exercise training and control groups.

Intervention Characteristics	Aerobic Exercise Training (*k*=105)				Control (*k*=90)			
	k	***Mean* ± *sd***	**Median**	**Range**	***k***	***Mean* ± *sd***	**Median**	**Range**
Participants (*n*) at baseline	105	25.5 ± 27.2	16.0	4.0, 181.0	80	20.2 ± 16.3	14.0	4.0, 87.0
Participants (*n*) at completion	105	21.0 ± 19.8	15.0	4.0, 166.0	80	17.9 ± 13.7	13.0	4.0, 81.0
Attrition (%)	105	11.7 ± 14.7	6.3	0.0, 58.9	89	7.4 ± 11.2	0.0	0.0, 50.0
Adherence (%)	67	87.1 ± 14.0	90.0	31.0, 100.0	71	98.4 ± 5.1	100.0	67.0, 100.0
Length (weeks)	105	18.3 ± 16.6	12.0	6.0, 144.0	90	17.6 ± 16.6	12.0	4.0, 144.0
Frequency (days·week^{-1})	103	3.5 ± 1.1	3.0	1.9, 7.0	90	0.5 ± 1.3	0.0	0.0, 7.0
* Intensity (% of VO_{2peak})	23	62.6 ± 10.6	65.0	40.0, 82.5	—	—	—	—
† *Estimated* Intensity (MET)	105	5.9 ± 1.7	5.3	2.8, 12.5	90	2.1 ± 0.3	2.0	2.0, 3.5
Time (min·session^{-1})	101	44.4 ± 23.7	40.0	15.0, 240.0	11	48.2 ± 24.2	60.0	10.0, 90.0
Weekly amount (min·week^{-1})	101	133.4 ± 64.7	122.5	20.0, 600.0	11	108.2 ± 70.7	90.0	30.0, 180.0
Volume (MET·min·week^{-1})	101	851.3 ± 392.8	768.0	198.0, 2437.5	11	328.6 ± 226.5	270.0	75.0, 630.0
Type (%)	105							
Walking	27	25.6%				—		
Cycle ergometer	26	24.4%				—		
AIT/ HIIT	14	13.3%				—		
Walking + Cycle, Jog or Run	24	23.3%				—		
Multiple modalities (≥3)	8	7.8%				—		
Other modalities	6	5.6%				—		
Type for Control Groups (%)					90			
Non-Exercise or “Wait List”		—			77	86.0%		
‡ “Placebo” or Active control		—			13	14.0%		
Stretching/Flexibility		—			5	5.6%		
Low intensity exercise/Yoga		—			3	3.2%		
Other		—			5	5.6%		

Notes. *k*=number of *total* comparisons. — Not applicable. ***Abbr.*** AIT=Aerobic interval training. HIIT=High-intensity interval training. MET= Metabolic equivalents unit. SD=Standard deviation. % of VO_{2peak}=Percentage of peak oxygen consumption. * Only interventions that prescribed intensity as % of VO_{2peak} (~86% reported Intensity). † Intensity was estimated using METs when unreported (*k*=26 did not)/or in other units. ‡ Light-intensity stretching/ flexibility: Full [27, 48] or lower body (during hemodialysis) [55]; ‘passive’ exercise [54] or stretching and flexibility (heart rate <100 beats·min^{-1}) [66]. Low intensity exercise/Yoga=Aerobic [18], non-aerobic, non-strenuous core and light strength training [39]; Hatha Yoga [8]. Other=Controls wore pedometers, tracked daily activity [5, 69]; took supplement (i.e., sugar pill) once-daily [24]; attended laboratory bi-weekly for blood pressure assessments [56], or attended lifestyle enrichment discussion(s) involving small groups and the group leader [53].

Appendix 9. Summary of resting and ambulatory blood pressure assessment techniques pre- and post-intervention (*k*=90).

Assessment Technique	*k*	*Mean* ± *sd*	Range
BP Assessment Procedures	**56**	**62.2%**	
Gold Standard Followed	10	11.1%	—
Some Procedures Disclosed	46	51.1%	—
No Procedures Disclosed	34	37.8%	—
Timing of BP Measurements	**59**	**65.6%**	
Pre-intervention: Seated or supine rest preceding baseline reading (minutes)	55	13.3 ± 10.5	3.0, 60.0
Post-intervention: duration (hours) between last exercise bout and post-BP reading	15	67.2 ± 44.4	24.0, 168.0
Less than 48 hours	2	30.0 ± 8.5	24.0, 36.0
≥48 to 96 hours	10	51.6 ± 11.4	48.0, 84.0
≥96 hours	3	144.0 ± 41.6	96.0, 168.0
Body Position	**65**	**72.2%**	—
Seated	44	67.7%	—
Supine	21	32.3%	—
BP Monitor/Assessment Tool	**68**	**75.6%**	—
Manual sphygmomanometer	36	52.9%	—
Random-zero	10	14.7%	—
Mercury	17	25.0%	—
"Standard aneroid"	9	13.2%	—
Automated	21	30.9%	—
Semi-automated/oscillometric device	11	16.2%	—
Ambulatory BP Monitoring	**9**	**13.2%**	—
Ambulatory BP Monitoring Period (hours)	9	19.3 ± 5.9	8.0, 24.0
24-Hour *	4	44.4%	—
Awake/Daytime †	8	9.9 ± 3.9	6.0, 16.0
Sleep/Nighttime ‡	6	11.8 ± 3.8	7.0, 16.0

Note. *k*=number of interventions. Statistics are presented as Mean ± Standard deviation (*sd*) unless otherwise stated; Range=Minimum, Maximum. BP=Blood pressure. * 24-Hour [18, 55, 73]; 3 trials reported 24-hour ambulatory BP monitoring; yet BP data was collected over 22 [40] and 18 hours [43, 79]. † Daytime ("awake") hours [7, 12, 18, 40, 43, 55, 79]. ‡ Nighttime ("sleep") hours [40, 43, 55, 79]; Gilders et al. [18] reported ABP data in three 8 hour segments (daytime, evening, nighttime); evening and nighttime were combined.

Appendix 10. The antihypertensive effects of aerobic exercise training versus non-exercise control: Summary of the weighted mean effect sizes and test for homogeneity for systolic and diastolic blood pressure.

			Systolic Blood Pressure				
			Homogeneity of *d*'s †			**Difference (mmHg) ‡**	
Intervention Group	***k***	**d_+ (95% *CI*) ***	**Q**	***p***	**I^2 (95% *CI*)**	***Mean* (95% *CI*)**	**Range**
Within-group							
Control	89	-0.09 (-0.15, -0.04)	95.9	0.265	8.2% (0.0, 30.0)	-1.8 (-2.6, -1.0)	-12.0, +4.3
AE training	105	-0.45 (-0.53, -0.37)	242.7	<0.001	57.2% (46.8, 65.5)	-5.9 (-6.5, -4.9)	-21.9, +1.7
Between-group							
AE training *vs.* Control	105	-0.38 (-0.48, -0.27)	261.8	<0.001	60.3% (50.8, 67.9)	-3.5 (-4.7, -2.3)	-17.6, +8.0

			Diastolic Blood Pressure				
			Homogeneity of *d*'s †			**Difference (mmHg) ‡**	
Intervention Group	***k***	**d_+ (95% *CI*) ***	**Q**	***p***	**I^2 (95% *CI*)**	***Mean* (95% *CI*)**	**Range**
Within-group							
Control	85	-0.06 (-0.13, +0.02)	139.8	<0.001	39.9% (21.8, 53.8)	-0.5 (-1.2, +0.1)	-11.0, +7.0
AE training	89	-0.41 (-0.49, -0.33)	185.3	<0.001	52.5% (39.5, 62.7)	-3.6 (-4.1, -3.0)	-11.0, +4.0
Between-group							
AE training *vs.* Control	101	-0.35 (-0.45, -0.24)	243.6	<0.001	58.9% (48.9, 67.0)	-2.7 (-3.7, -1.6)	-12.0, +7.5

Note. *k*=Number of observations. This model follows mixed-effects assumptions. ***Abbr.*** AE=Aerobic exercise. CI=Confidence interval. Range= Minimum, Maximum. * **Weighted mean effect size values** ($\hat{d}_+$) are negative when AE training *or* control groups reduced blood pressure at post- compared to pre-intervention (i.e., *within-group estimate*) or when the AE training intervention group reduced blood pressure to a greater extent than control (i.e., *between-group estimate*). † **Tests for homogeneity:** *Cochran Q*[1] indicates whether significant heterogeneity is *present* across study results (or not); this test has been shown to be poor at detecting true heterogeneity. *I^2 statistic*[2] quantifies the effect of heterogeneity by providing a measure of the *degree* or *level* of inconsistency across results; values range from 0% to 100%. Tentative cut-points for low, moderate, and high levels of heterogeneity correspond to 25%, 50%, and 75%. ‡ **Difference:** *within-group* estimates=change in blood pressure at post- versus pre-intervention; *between-group* estimate (i.e., AE *vs.* control)= change in blood pressure at post- versus pre-intervention for AE training relative to control.

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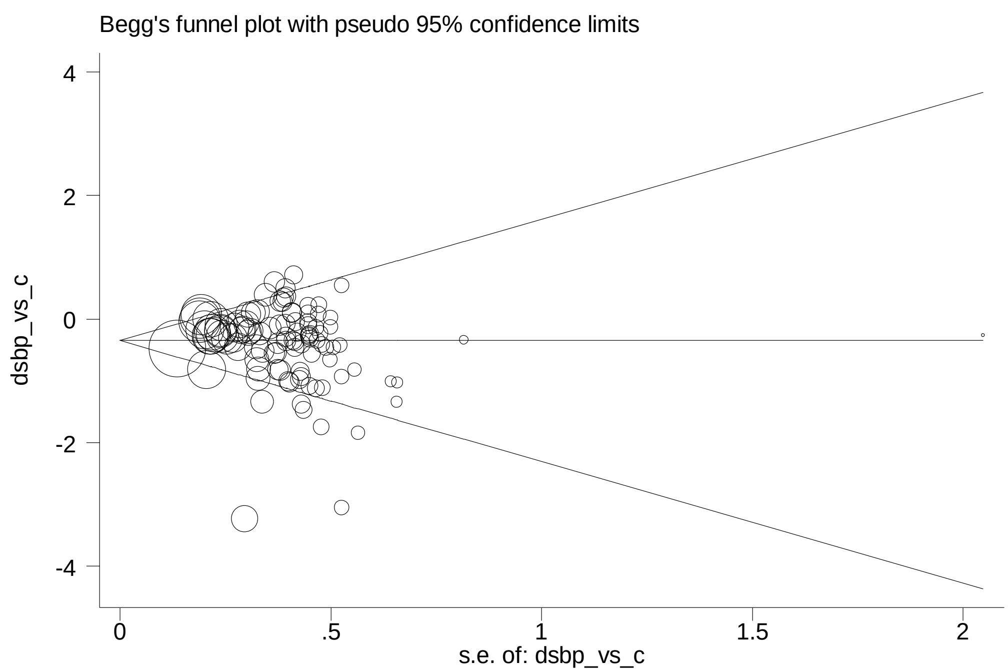
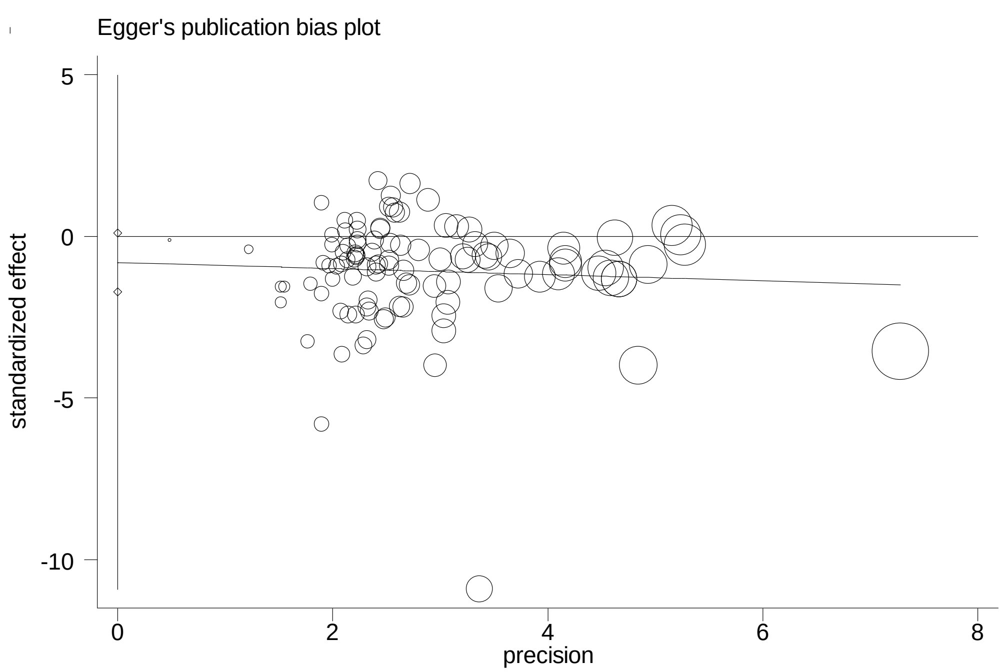
Appendix 11. Figure S1. Tests for publication bias: Unadjusted Begg and Egger funnel plots and adjusted funnel plot (via trim and fill procedures).

Note. Data points in the unadjusted plots are weighted and sized proportional to the inverse variance.

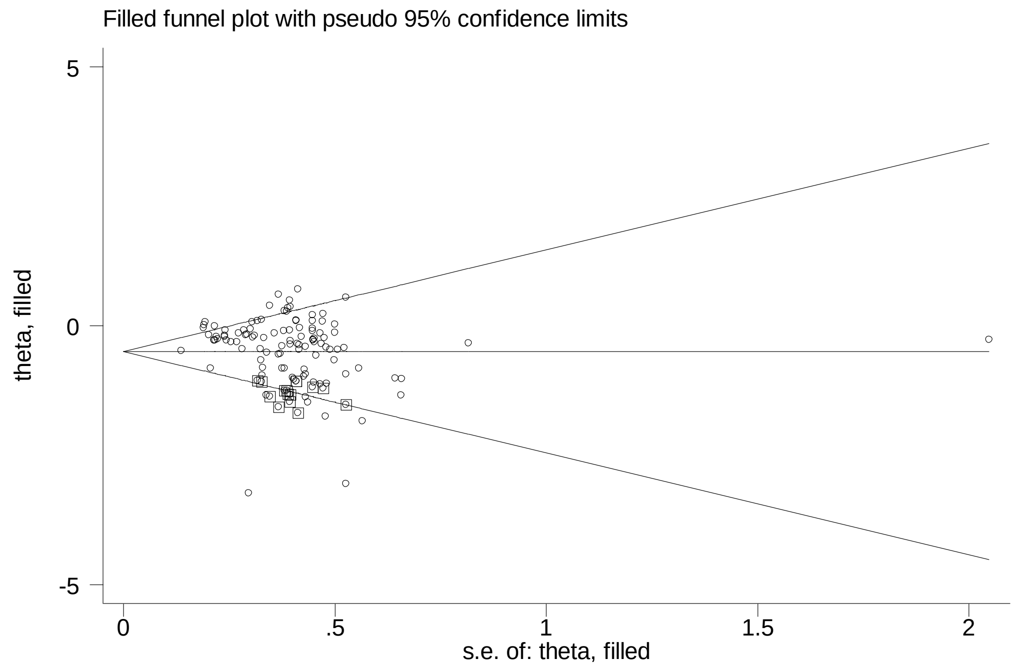
Systolic blood pressure: Aerobic exercise training versus non-exercise control:

Unadjusted Begg and Egger Plots:



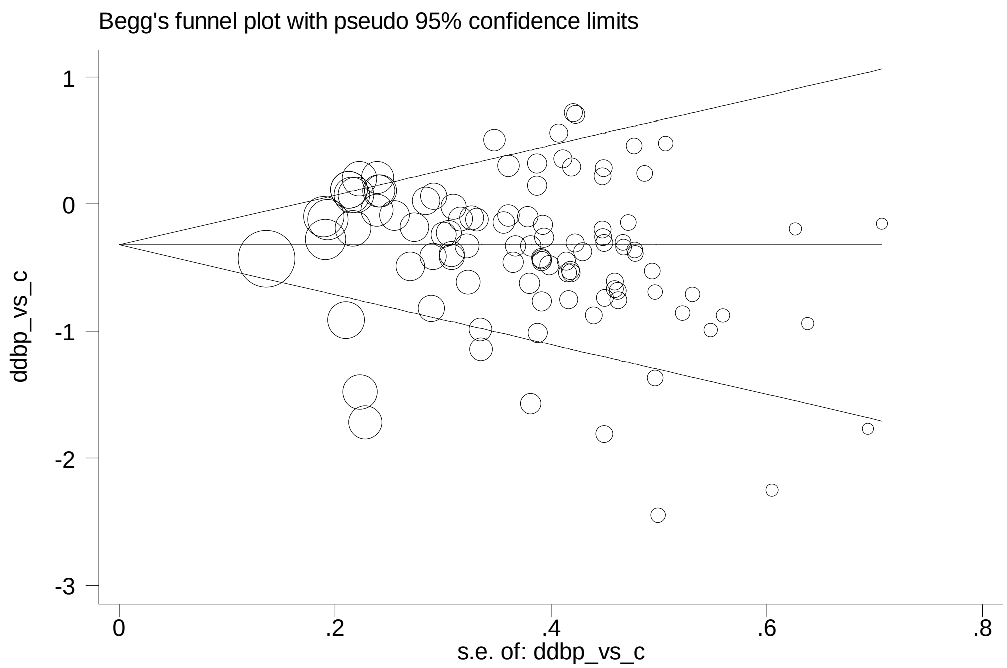


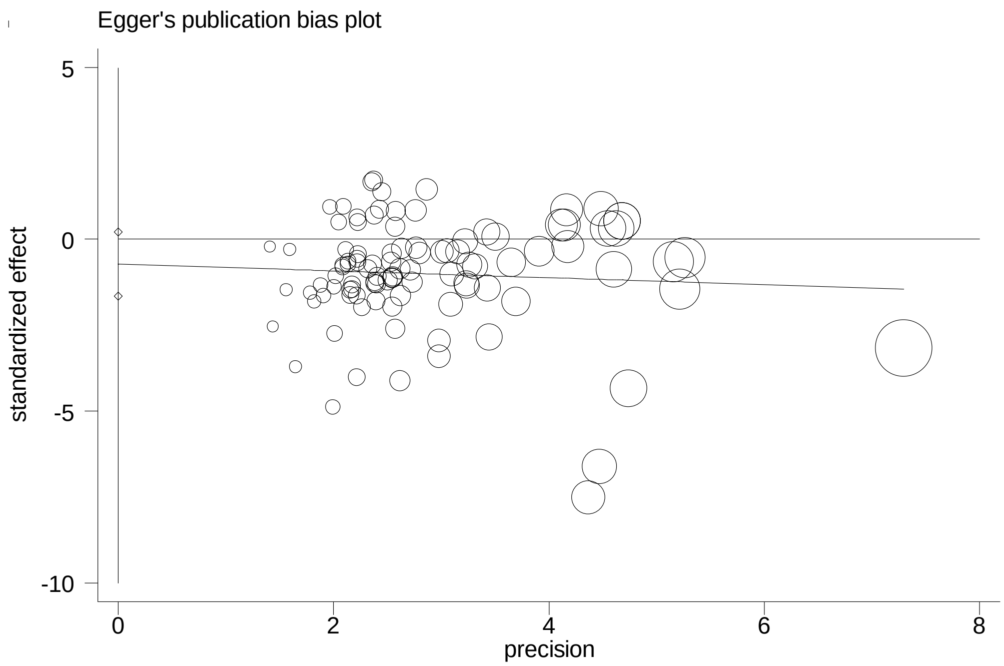
Adjusted Funnel Plot (Trim and Fill): 7 iterations “trimmed” and the “filled” analysis was based on *k*=120 versus *k*=105 comparisons



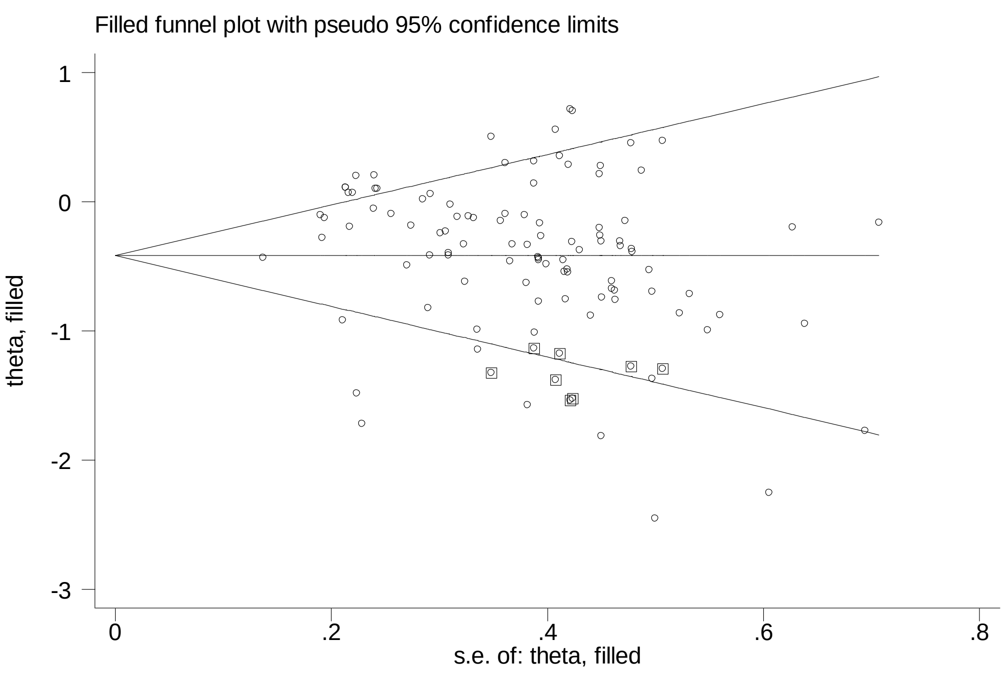
Diastolic blood pressure: Aerobic exercise training versus non-exercise control

Unadjusted Begg and Egger Plots:



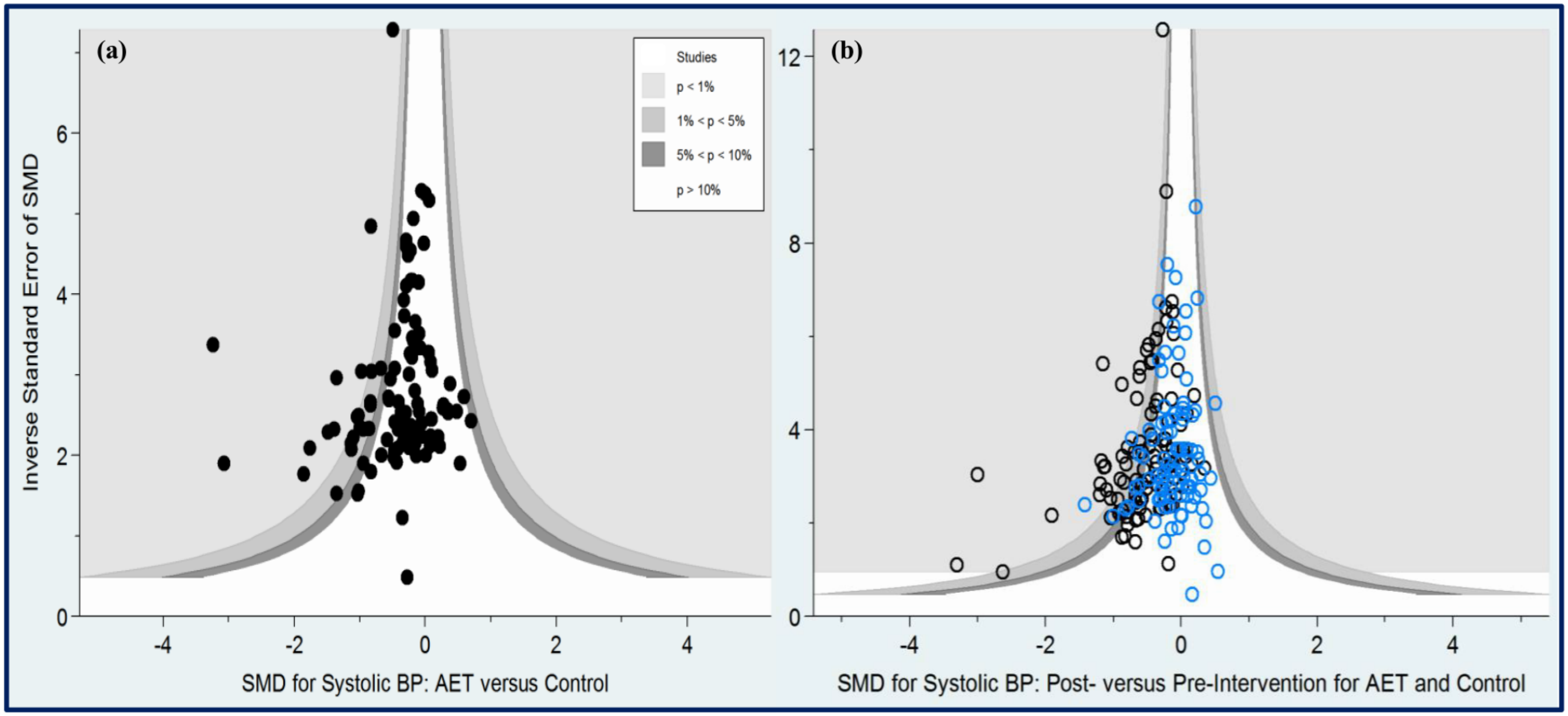


Adjusted Funnel Plot (Trim and Fill): 8 iterations "trimmed" and the "filled" analysis was based on *k*=109 versus *k*=101 comparisons



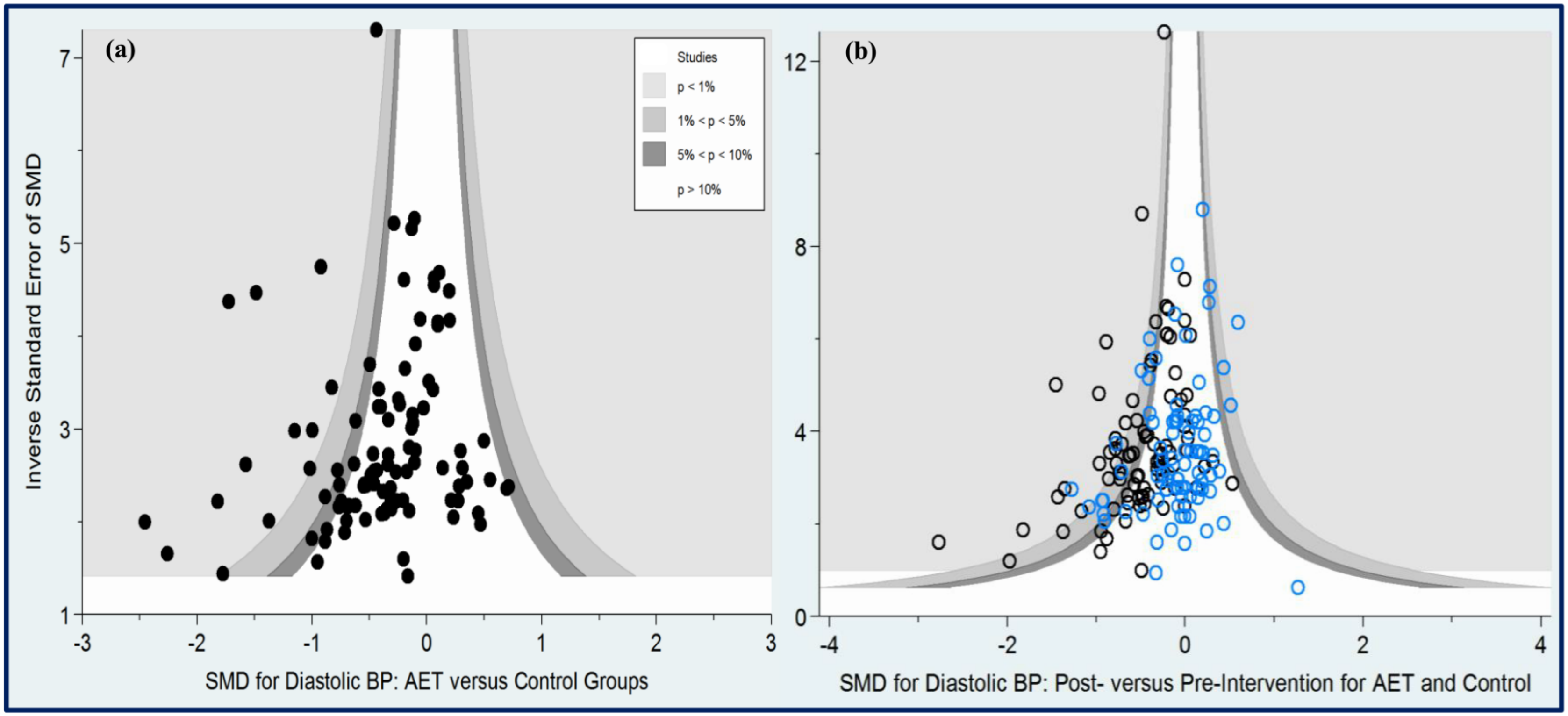
Appendix 12. Figure S2. Contour-enhanced funnel plots (i.e., confunnels): A visual representation of the effect size distribution for the antihypertensive effects of aerobic exercise training versus non-exercise control.

Systolic blood pressure:



Note. AET=Aerobic exercise training. BP=Blood pressure. SMD=Standardized mean difference. Confunnels of the blood pressure response to (a) aerobic exercise training relative to control (●), and (b) post- versus pre-intervention for aerobic exercise training (**O**) and control (**O**) groups. Weighted mean effect size values ($\hat{d}_{+}$) are negative when (a) AET reduced BP to a greater extent than control, and (b) when AET or control groups reduced BP at post- compared to pre-intervention.

Diastolic blood pressure:



Note. AET=Aerobic exercise training. BP=Blood pressure. SMD=Standardized mean difference. Confunnels of the blood pressure response to (a) aerobic exercise training relative to control (●), and (b) post- versus pre-intervention for aerobic exercise training (○) and control (○) groups. Weighted mean effect size values (d_+) are negative when (a) AET reduced BP to a greater extent than control, and (b) when AET or control groups reduced BP at post- compared to pre-intervention.

Appendix 13. Reference list for the included dynamic resistance training trial (*n*=64).

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Appendix 14. Summary of the overall methodological study quality, individual quality items, and quality subscales for the included dynamic resistance training interventions (k=71) gauged using the augmented Downs and Black Checklist.

MSQ	Fully		Partially		Not Fully Satisfied				MSQ Subscale	
Items	Satisfied (k, %)		Satisfied (k, %)		Unsatisfied	U/D	(k, %)		Mean ± *sd*	Median (Range)
Reporting (11 possible points)									8.6 ± 1.1 78.6% ± 10.2%	8.5 (4.0, 10.5) 77.3% (36.4%, 95.5%)
Item 1	71	100.0%	—		0	—	0	0.0%		
Item 2	71	100.0%	—		0	—	0	0.0%		
Item 3	69	97.2%	—		0	2	2	2.8%		
Item 4 †	30	42.3%	33	46.5%	8	—	8	11.3%		
Item 5 †	36	50.7%	30	42.3%	5	—	5	7.0%		
Item 6 †	29	40.8%	25	35.2%	7	10	17	23.9%		
Item 7	67	94.4%	—		4	—	4	5.6%		
Item 8	69	97.2%	—		2	—	2	2.8%		
Item 9	70	98.6%	—		1	—	1	1.4%		
Item 10	65	91.5%	—		5	1	6	8.5%		
Item 11	27	38.0%	—		42	2	44	62.0%		
External Validity (3 possible points)									1.4 ± 1.3 46.5% ± 42.3%	2.0 (0.0, 3.0) 66.7% (0.0%, 100.0%)
Item 12	36	50.7%	—		0	35	0	49.3%		
Item 13	36	50.7%	—		0	35	0	49.3%		
Item 14	27	38.0%	—		0	44	0	62.0%		
Internal Validity – Bias (7 possible points)									4.9 ± 1.0 70.2% ± 14.9%	5.0 (3.0, 7.0) 71.4% (42.9%, 100.0%)
Item 15	26	36.6%	—		39	6	45	63.4%		
Item 16	25	35.2%	—		8	38	46	64.8%		
Item 17	71	100.0%	—		0	—	0	0.0%		
Item 18	69	97.2%	—		2	—	0	2.8%		
Item 19	70	98.6%	—		0	1	1	1.4%		
Item 20	49	69.0%	—		0	22	22	31.0%		
Item 21 †	31	43.7%	16	22.5%	21	3	24	33.8%		
Internal Validity – Confounding (6 Possible Points)									3.1 ± 1.8 51.5% ± 30.1%	3.0 (0.0, 6.0) 50.0% (0.0%, 100%)
Item 22	36	50.7%	—		0	35	35	49.3%		

MSQ Items	Fully Satisfied (*k*, %)		Partially Satisfied (*k*, %)		Not Fully Satisfied				MSQ Subscale	
					Unsatisfied	U/D	(*k*, %)		Mean ± *sd*	Median (Range)
Item 23	38	53.5%	—		0	33	33	46.5%		
Item 24 †	14	19.7%	45	63.4%	12	—	12	16.9%		
Item 25	26	36.6%	—		39	6	45	63.4%		
Item 26	51	71.8%	—		0	20	20	28.2%		
Item 27	32	45.1%	—		38	1	39	54.9%		
Power * (2 possible points)									0.2 ± 0.5	0.0 (0.0, 2.0)
									9.2% ± 24.4%	0.0% (0.0%, 100.0%)
Item 28	3	4.2%	7	9.9%	61	—	61	85.9%		
Total MSQ Score (29 Possible Points)									**18.2 ± 3.7**	**18.0 (12.0, 24.5)**
									62.9% ± 12.9%	**62.1% (41.4%, 84.5%)**

Note. — indicates the characteristic/scoring is not applicable. Summary statistics are presented as *M*ean ± *sd* unless stated otherwise; Range=Minimum, Maximum values. ***Abbr.*** MSQ=Methodological study quality. U/D=Unable to determine. SD=Standard deviation.
* Power=2 points were awarded to trials that fully satisfied Item 28; partially satisfied=1 point. † These items could have been fully *or partially* satisfied; 1 point was awarded to trials that fully satisfied these items; partially satisfied=0.5 points.

Appendix 15. Item-by-item summary of methodological study quality for the included dynamic resistance training intervention (*k*=71) gauged using the augmented version of the Downs and Black Checklist.

Author, Year (RT Subgroup)	Reporting											External Validity			Internal Validity - Bias							Internal Validity - Confounding						Power	Total MSQ Score (29-points)	
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28*		
Anton, 2006 [1]	1	1	0	½	½	1	1	1	1	1	0	—	—	—	0	1	1	1	1	1	—	—	—	½	0	1	0	0	14.5	50.0%
Arora, 2009 [2]	1	1	0	½	½	½	1	1	1	1	0	1	1	1	—	—	1	1	1	1	0	1	1	½	1	—	1	0	19.0	65.5%
Bateman, 2011 [3]	1	1	1	1	1	½	1	1	1	1	—	1	1	1	1	1	1	1	1	1	0	1	1	½	1	1	1	0	24.0	82.8%
Beck, 2013 [4]	1	1	0	½	½	½	1	1	1	1	—	1	1	1	1	—	1	1	1	1	1	1	1	1	1	1	1	0	22.5	77.6%
Blumenthal, 1991 [5]	1	1	1	½	0	1	1	1	1	1	1	1	1	—	0	1	1	1	1	1	1	1	1	½	0	1	0	0	21.0	72.4%
Carter, 2003 [6]	1	1	1	1	½	½	1	1	1	1	1	—	—	—	0	—	1	0	1	1	1	—	—	0	0	1	0	0	15.0	51.7%
Casey, 2007 [7]	1	1	0	1	½	½	1	1	1	1	0	—	—	1	0	1	1	1	1	1	1	—	—	0	0	1	0	0	16.0	55.2%
Castaneda, 2002 [8]	1	1	0	½	1	½	1	1	1	1	1	1	1	1	1	—	1	1	1	1	0	1	1	1	1	1	1	0	23.0	79.3%
Chaudhary, 2010 [9]	1	0	—	0	½	—	1	1	1	1	1	—	—	—	—	—	1	1	1	—	½	—	1	0	—	—	1	0	12.0	41.4%
Colado, 2009 (Aquatic RT) [10]	1	1	1	1	1	1	1	1	1	1	0	1	1	—	0	—	1	1	1	1	0	1	1	½	0	—	0	0	18.5	63.8%
Colado, 2009 (Therabands) [10]	1	1	1	1	1	1	1	1	1	1	0	1	1	—	0	—	1	1	1	1	0	1	1	½	0	—	0	0	18.5	63.8%
Conciecao, 2013 [11]	1	1	1	1	½	—	1	1	1	—	1	1	1	—	1	—	1	1	1	—	½	1	1	1	1	—	—	2	21.0	72.4%
Cononie, 1991 [12]	1	1	1	1	½	½	1	1	1	1	0	—	—	1	0	1	1	1	1	1	1	—	—	0	0	1	0	0	17.0	58.6%
Cortez-Cooper, 2005 [13]	1	1	0	1	½	½	1	1	1	1	0	—	—	—	0	—	1	1	1	1	½	—	—	0	0	—	0	0	12.5	43.1%
Cortez-Cooper, 2008 [14]	1	1	0	1	½	½	1	1	1	1	0	1	1	—	0	1	1	1	1	1	1	1	1	½	0	1	0	0	19.5	67.2%
Croymans, 2014 [15]	1	1	1	1	1	½	1	1	1	1	1	—	—	1	1	1	1	1	1	1	1	—	1	1	1	1	1	1	24.5	84.5%
Elliot, 2002 [16]	1	1	0	1	½	1	1	1	1	1	1	—	—	1	0	1	1	1	1	—	1	—	—	½	0	—	0	0	16.0	55.2%
Gelecek, 2012 [17]	1	1	1	½	1	0	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1	½	1	1	1	0	24.0	82.8%
Gerage, 2013 [18]	1	1	1	1	½	½	1	1	1	1	1	1	1	—	1	—	1	1	1	1	½	1	1	1	1	1	1	1	24.5	84.5%
Gurjao, 2013 [19]	1	1	1	½	1	½	1	1	1	1	1	1	1	—	1	—	1	1	1	1	½	1	1	1	1	1	1	0	23.5	81.0%
Harris, 1987 [20]	1	1	1	1	1	½	1	1	1	1	0	—	—	—	0	0	1	1	1	—	1	—	—	½	0	1	0	0	15.0	51.7%
Ho, 2012 [21]	1	1	1	0	½	1	1	1	1	1	1	1	1	1	1	—	1	1	1	—	1	1	1	½	—	—	1	1	22.0	75.9%
Hu, 2009 [22]	1	1	0	1	0	—	1	1	1	1	0	1	1	—	1	—	1	1	1	1	0	1	1	1	1	—	1	0	19.0	65.5%
Jakovljevic, 2013 [23]	1	1	1	½	½	—	1	1	1	1	1	1	1	—	1	—	1	1	1	—	½	1	1	1	1	1	1	0	21.5	74.1%
Jorge, 2011 [24]	1	1	0	½	0	1	1	1	1	1	0	1	1	1	1	—	1	1	1	1	0	1	1	½	1	1	1	0	21.0	72.4%
Kanegusuku, 2011 (Power RT) [25]	1	1	1	1	1	1	1	1	1	1	0	—	—	—	0	0	1	1	1	1	1	—	—	½	0	1	0	0	16.5	56.9%
Kanegusuku, 2011 (Strength RT) [25]	1	1	1	1	1	1	1	1	1	1	0	—	—	—	0	0	1	1	1	1	1	—	—	½	0	1	0	0	16.5	56.9%
Katz, 1992 [26]	1	1	1	0	1	—	1	1	1	0	1	—	—	—	1	—	1	1	—	—	½	—	—	1	1	—	1	0	14.5	50.0%

Author, Year (RT Subgroup)	Reporting											External Validity			Internal Validity - Bias							Internal Validity - Confounding						Power	Total MSQ Score (29-points)	
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28*		
Kawano, 2006 [27]	1	1	0	½	1	1	1	1	1	1	0	—	—	—	0	—	1	1	1	1	1	—	—	½	0	1	0	0	15.0	51.7%
Locks, 2012 [28]	1	1	0	0	1	0	1	1	1	1	1	1	1	1	1	—	1	1	1	1	1	1	1	½	1	—	1	1	22.5	77.6%
Lovell, 2009 [29]	1	1	1	1	1	½	1	1	1	1	1	—	—	—	1	1	1	1	1	1	1	1	1	1	1	1	1	1	24.5	84.5%
Marioana, 2011 [30]	1	1	0	1	0	1	1	1	1	1	0	—	—	1	0	1	1	1	1	1	0	—	—	½	0	—	0	0	14.5	50.0%
Miyachi, 2004 [31]	1	1	0	½	1	1	1	1	1	1	0	—	—	—	0	—	1	1	1	1	1	—	—	½	0	1	0	0	15.0	51.7%
Mota, 2013 [32]	1	1	1	½	1	—	1	1	1	1	1	—	—	—	—	—	1	1	1	—	1	—	—	0	—	1	1	0	15.5	53.4%
Norris, 1990 [33]	1	0	1	0	0	0	1	1	0	0	0	1	1	1	0	—	1	1	1	—	0	1	1	0	0	—	0	0	12.0	41.4%
Nybo, 2010 (Lower body-RT) [34]	1	1	1	1	1	½	1	1	1	1	0	—	—	—	—	—	1	1	1	—	1	—	—	0	—	—	1	0	14.5	50.0%
Okamoto, 2006 (Con-RT) [35]	1	1	0	½	½	1	1	1	1	1	0	—	—	—	0	—	1	1	1	1	0	—	—	½	0	1	0	0	13.5	46.6%
Okamoto, 2006 (Ecc-RT) [35]	1	1	0	½	½	1	1	1	1	1	0	—	—	—	0	—	1	1	1	1	0	—	—	½	0	1	0	0	13.5	46.6%
Okamoto, 2011 [36]	1	1	0	1	1	½	1	1	1	1	0	—	—	—	1	1	1	1	1	—	½	—	—	1	1	1	1	0	18.0	62.1%
Oliviera, 2012 [37]	1	1	0	½	1	½	1	1	1	1	1	1	1	1	1	—	1	1	1	1	0	1	1	1	1	1	1	0	23.0	79.3%
Olson, 2007 [38]	1	1	0	1	½	½	1	1	1	1	0	—	—	—	0	1	1	1	1	—	1	—	—	½	0	1	0	1	15.5	53.4%
Park, 2011 [39]	1	1	1	½	½	0	1	1	1	0	1	1	1	1	0	—	1	1	1	1	0	1	1	½	0	1	0	1	19.5	67.2%
Reis, 2012 [40]	1	1	0	1	1	½	1	1	1	1	0	1	1	—	1	1	1	1	1	—	0	1	1	½	1	1	1	0	21.0	72.4%
Sallinen, 2007 [41]	1	1	1	1	1	1	0	1	1	1	0	—	—	—	0	1	1	1	1	1	1	—	—	½	0	—	0	0	15.5	53.4%
Sarsan, 2006 [42]	1	1	0	1	1	1	1	1	1	1	1	1	1	1	0	0	1	1	1	1	½	1	1	½	0	1	0	0	21.0	72.4%
Shaw, 2010 [43]	1	1	1	½	1	—	1	1	1	1	1	—	—	—	—	—	1	1	1	1	½	—	—	0	—	1	1	0	16.0	55.2%
Sheikholeslami, 2011 (Heavy-RT) [44]	1	1	1	½	1	0	1	1	1	1	0	1	1	—	1	—	1	1	1	—	0	1	1	½	1	—	1	0	16.5	56.9%
Sheikholeslami, 2011 (Moderate-RT) [44]	1	1	1	½	1	0	1	1	1	1	0	1	1	—	1	—	1	1	1	—	0	1	1	½	1	—	1	0	19.0	65.5%
Sheikholeslami, 2012 [45]	1	1	1	½	1	0	1	1	1	1	0	—	—	—	1	—	1	1	1	—	½	—	—	½	1	1	1	0	19.0	65.5%
Sigal, 2007 [46]	1	1	0	½	½	1	1	1	1	1	1	1	1	1	0	—	1	1	1	1	½	1	1	½	0	1	1	2	23.0	79.3%
Sillanpaa, 2009 [47]	1	1	0	1	1	1	1	1	1	1	1	1	1	1	0	1	1	0	1	1	1	1	1	½	0	1	0	0	21.5	74.1%
Sillanpaa, 2009 [48]	1	1	0	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	½	0	1	0	0	22.5	77.6%
Simons, 2006 [49]	1	1	0	0	½	1	1	1	1	1	0	1	1	1	0	—	1	1	1	1	0	1	1	½	0	1	0	0	18.0	62.1%
Smutok, 1993 [50]	1	1	1	½	½	½	1	1	1	1	0	—	—	—	—	—	1	1	1	1	0	—	—	0	—	1	1	0	14.5	50.0%
Spalding, 2004 [51]	1	1	1	0	½	—	1	1	1	1	0	1	1	—	1	1	1	1	1	1	1	1	1	1	1	—	1	0	21.5	74.1%
Stensvold, 2010 [52]	1	1	1	½	1	—	1	1	1	1	1	1	1	—	1	1	1	1	1	1	½	1	1	½	1	—	1	0	22.5	77.6%
Tanimoto, 2009 (Heavy-RT) [53]	1	1	1	½	½	1	1	1	1	1	0	—	—	—	0	—	1	1	1	—	½	—	—	½	0	1	0	0	14.0	48.3%
Tanimoto, 2009 (Light-RT)	1	1	1	½	½	1	1	1	1	1	0	—	—	—	0	—	1	1	1	—	½	—	—	½	0	1	0	0	14.0	48.3%

Author, Year	Reporting											External Validity			Internal Validity - Bias							Internal Validity - Confounding						Power	Total MSQ Score	
(RT Subgroup)	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28*	(29-points)	
[53]																														
Terra, 2008 [54]	1	1	1	½	1	½	1	1	1	1	1	1	1	—	0	1	1	1	1	—	1	—	—	0	0	1	0	0	18.0	62.1%
Thomas, 2005 [55]	1	1	0	½	½	1	1	1	1	1	0	1	1	1	0	1	1	1	1	1	1	1	1	½	0	1	0	0	20.5	70.7%
Tseng, 2013 [56]	1	1	0	½	1	½	1	1	1	1	1	1	1	1	1	1	1	1	1	—	0	1	1	1	1	1	1	0	23.0	79.3%
Tsutsumi, 1997 (Heavy-RT) [57]	1	1	1	1	1	1	0	0	1	1	0	—	—	—	0	0	1	1	1	1	—	—	—	½	0	1	0	0	13.5	46.6%
Tsutsumi, 1997 (Light-RT) [57]	1	1	1	1	1	1	0	0	1	1	0	—	—	—	0	0	1	1	1	1	—	—	—	½	0	1	0	0	13.5	46.6%
Tsuzuku, 2007 [58]	1	1	1	½	½	½	1	1	1	1	0	1	1	—	0	—	1	1	1	1	½	1	1	0	0	1	0	0	18.0	62.1%
Van Hoof, 1996 [59]	1	1	0	½	1	1	1	1	1	1	1	—	—	—	0	1	1	1	1	1	1	—	—	½	0	1	0	0	17.0	58.6%
Vincent, 2003 (Heavy-RT) [60]	1	1	0	½	½	1	1	1	1	1	0	—	—	1	0	0	1	1	1	1	1	—	—	½	0	1	0	0	15.5	53.4%
Vincent, 2003 (Light-RT) [60]	1	1	0	½	½	1	1	1	1	1	0	—	—	1	0	0	1	1	1	1	1	—	—	½	0	1	0	0	15.5	53.4%
Williams, 2013 [61]	1	1	0	½	½	½	0	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	½	1	1	1	2	24.0	82.8%
Wood, 2001 [62]	1	1	1	1	½	1	1	1	1	1	0	—	—	—	0	—	1	1	1	—	0	—	—	½	0	1	0	0	14.0	48.3%
Yoshiwaza, 2009 [63]	1	1	0	1	1	½	1	1	1	0	0	—	—	—	0	—	1	1	1	—	0	—	—	½	0	1	0	0	12.0	41.4%
Zavanela, 2012 [64]	1	1	—	0	1	—	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	½	1	—	1	0	21.5	74.1%

Note. References for the included RT trials correspond to the citations listed in Appendix 11. MSQ scoring: 1=Fully satisfied. 0=Not fully satisfied. ½ =Partially satisfied quality item. — =Unable to determine. *Item 28: 1=Power analysis reported for one study outcome; 2= Power analysis reported for two or more study outcomes. ***Abbr.*** Con-RT=Concentric contraction RT. Ecc-RT=Eccentric contraction RT. Heavy-RT=Heavy load/high intensity RT. Light-RT=Light load/low intensity RT. Moderate-RT=Moderate load/moderate intensity RT. MSQ=Methodological study quality. RT=Resistance training

Appendix 16. A summary of the dynamic resistance training intervention characteristics (*k*=71).

Program Characteristics	*k*	*Mean* ± *sd*	Range	Median
Participants (*n*) at baseline	71	21.1 ± 14.9	8.0, 72.0	15.0
Participants (*n*) post-RT	71	18.4 ± 11.4	8.0, 60.0	14.0
Attrition in RT group (%)	71	8.5 ± 13.1	0.0, 53.0	0.0
Exercise Adherence (%)	46	92.3 ± 8.9	60.0, 100.0	95.0
Dynamic RT Program				
Length (weeks)	71	14.4 ± 7.9	6.0, 48.0	12.0
Frequency (days·week^{-1})	71	2.8 ± 0.6	2.0, 5.0	3.0
* Intensity or Load (% 1-RM)	63	67.2 ± 12.4	30.0, 100.0	70.0
† *Estimated* MET	71	4.7 ± 1.8	2.8, 8.5	3.8
Percentage of 1-RM (%)	38	64.7 ± 13.0	30.0, 87.5	65.0
MVC (%)	2	90.0 ± 14.4	80.0, 100.0	
10-15 RM	8	12.6%		
8-12 RM	8	12.5%		
6-16 RM	2	3.1%		
OMNI-RT Scale	2	3.1%		
Theraband (*not specified*)	3	4.7%		
Time (total work·session^{-1})				
Number of exercises·session^{-1}	69	7.9 ± 2.9	1.0, 16.0	7.0
Number sets·exercise^{-1}	67	2.8 ± 0.9	1.0, 5.0	3.0
Number reps·set^{-1}	65	11.0 ± 3.8	5.0, 30.0	10.0
Rest interval between sets (s)	30	96.3 ± 43.3	15.0, 180.0	90.0
Type of RT				
Conventional RT	54	76.0%		
Circuit-style RT	10	14.3%		
Therabands (i.e., elastic bands)	4	5.7%		
Ankle or shin weights	2	2.9%		
Muscle Groups Targeted				
Upper and Lower Body	63	91.3%		
Lower Body	4	5.8%		
Unilateral, Upper Body	2	2.9%		

Note. *k*=number of observations. ***Abbr.*** MVC=Maximum voluntary contraction. MET= Metabolic equivalent unit. Range=Minimum, Maximum values. Reps=Repetitions. RM= Repetition maximum. RT=Resistance training. s=seconds. %=Percentage. * When RT load was reported as MVC or 1-RM range, % of 1-RM was estimated and combined with trials that reported 1-RM (%). † When RT was unreported (*k*=12) or quantified in other units (*k*=39), % of 1-RM was estimated using a standardized unit (i.e., MET).

Appendix 17. Summary of the resting blood pressure assessment techniques pre-and post-intervention (*k*=71).

Assessment Technique	*k*	*Mean* ± *sd*	Range
BP Assessment Procedures	**49**	**69.0%**	—
Gold Standard Followed	12	16.9%	—
Some Procedures Disclosed	37	52.1%	—
No Procedures Disclosed	22	31.0%	—
Timing of BP Measurements			
Pre-intervention: Seated or supine rest preceding baseline reading (min)	37	10.3 ± 5.5	5.0, 25.0
Post-intervention: duration (hr) between last exercise bout and post-BP reading	14	79.9 ± 59.1	20.0, 192.0
Less than 24 hr	4	21.5 ±1.0	20.0, 22.0
24 to 48 hr	3	48.0 ± 0.0	—
>48 to 96 hr	2	84.0 ± 17.0	72.0, 96.0
>96 hr	5	144.0 ± 44.1	108.0, 192.0
Body Position	**49**	**69.0%**	—
Seated	30	61.2%	—
Supine	19	38.8%	—
Number of BP Readings	**43**	**3.1 ± 1.1**	**2.0, 6.0**
BP Monitor/ Assessment Tool	**58**	**81.7%**	—
Manual sphygmomanometer	29	40.8%	—
Random-zero	3	5.2%	—
Mercury	11	19.0%	—
"Standard aneroid"	15	25.9%	—
Automated	16	27.6%	—
Semi-automated/oscillometric device	13	22.4%	—
Ambulatory BP Monitor	2	4.1%	—

Note. *k*=number of observations. Statistics are presented as Mean ± Standard deviation (*sd*) unless otherwise stated; Range=Minimum, Maximum. BP=Blood pressure.

Appendix 18. The antihypertensive effects of dynamic resistance training versus non-exercise control: Summary of the weighted mean effect sizes and test for homogeneity for systolic and diastolic blood pressure.

			Systolic Blood Pressure				
			Homogeneity of *d*'s †			Difference (mmHg) ‡	
Intervention Group	***k***	**d_+ (95% *CI*) ***	***Q***	***p***	**I^2 (95% *CI*)**	***Mean* (95% *CI*)**	**Range**
Within-group							
Control	70	-0.04 (-0.19, +0.03)	66.3	0.571	0.0% (0.0, 31.0)	-1.0 (-2.0, -0.1)	-11.7, +8.0
Dynamic RT	71	-0.34 (-0.43, -0.25)	132.6	<0.001	47.2% (30.2, 60.0)	-4.9 (-6.1, -3.8)	-15.0, +4.0
Between-group							
Dynamic RT *vs.* Control	71	-0.31 (-0.43, -0.19)	143.4	<0.001	51.2% (35.9, 62.9)	-3.0 (-4.7, -2.1)	-18.6, +9.0
			Diastolic Blood Pressure				
			Homogeneity of *d*'s †			Difference (mmHg) ‡	
Intervention Group	***k***	**d_+ (95% *CI*) ***	***Q***	***p***	**I^2 (95% *CI*)**	***Mean* (95% *CI*)**	**Range**
Within-group							
Control	70	-0.03 (-0.10, +0.05)	88.9	0.054	22.3% (0.0, 42.8)	-0.5 (-1.2, +0.2)	-10.5, +5.0
Dynamic RT	71	-0.30 (-0.38, -0.22)	106.5	0.003	34.4% (11.9, 51.0)	-2.9 (-3.5, -2.2)	-11.0, +4.0
Between-group							
Dynamic RT *vs.* Control	71	-0.30 (-0.38, -0.18)	107.6	0.003	35.0% (12.9, 51.5)	-2.1 (-3.2, -1.5)	-10.0, +5.0

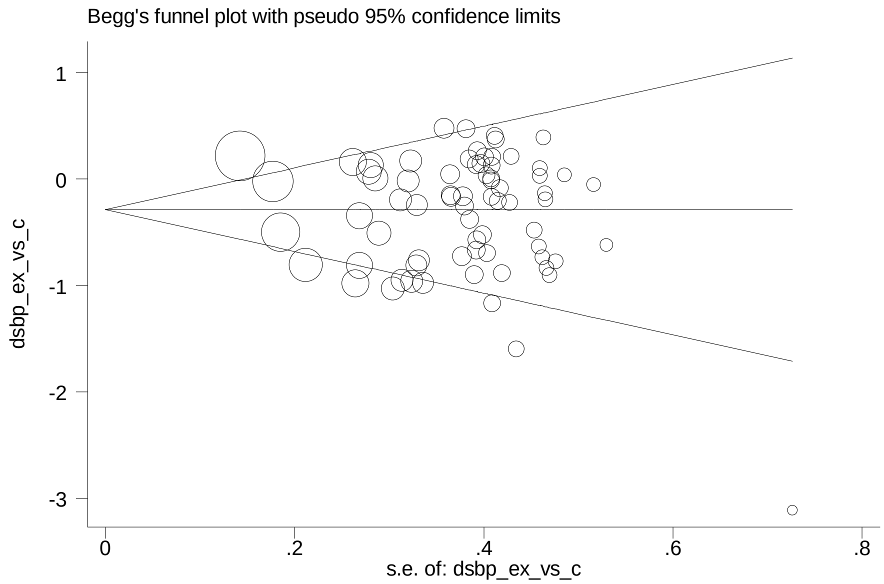
Note. *k*=Number of observations. This model follows mixed-effects assumptions. ***Abbr.*** CI=Confidence interval. Range=Minimum, Maximum. RT=Resistance training. ***Weighted mean effect size values** ($\hat{d}_+$) are negative when RT *or* control groups reduced blood pressure at post- compared to pre-intervention (i.e., *within-group estimate*) or when the RT intervention group reduced blood pressure to a greater extent than control (i.e., *between-group estimate*). † **Tests for homogeneity:** *Cochran Q* [1] indicates whether significant heterogeneity is *present* across study results (or not); this test has been shown to be poor at detecting true heterogeneity. *I^2 statistic* [2] quantifies the effect of heterogeneity by providing a measure of the *degree* or *level* of inconsistency across results; values range from 0% to 100%. Tentative cut-points for low, moderate, and high levels of heterogeneity correspond to 25%, 50%, and 75%. ‡ **Difference:** *within-group* estimates=change in blood pressure at post- versus pre-intervention; *between-group* estimate (i.e., RT *vs.* control)= change in blood pressure at post- versus pre-intervention for dynamic RT relative to control.

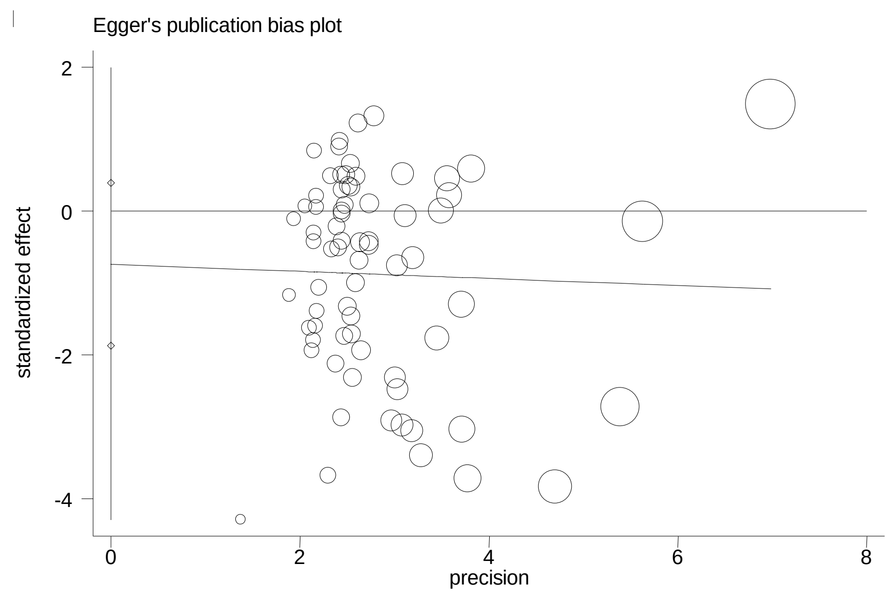
[1] Cochran W (1954) The combination of estimates from different experiments. *Biometrics* 10:101-129.

[2] Higgins JPT, et al. (2003) Measuring inconsistency in meta-analyses. *BMJ* 327:557-560; Huedo-Medina TB, et al. (2006) Assessing heterogeneity in meta-analysis: *Q* statistic or I^2 index? *Psychol Methods* 11:193-206.

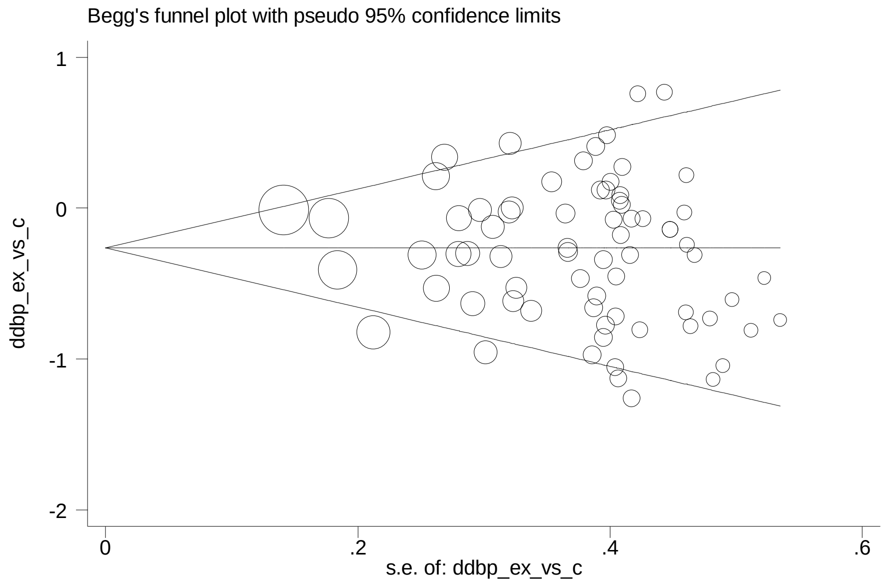
Appendix 19. Figure S3. Tests for publication bias: Funnel plots using Begg and Egger methods. ***Note.*** Data points are weighted and sized proportional to the inverse variance.

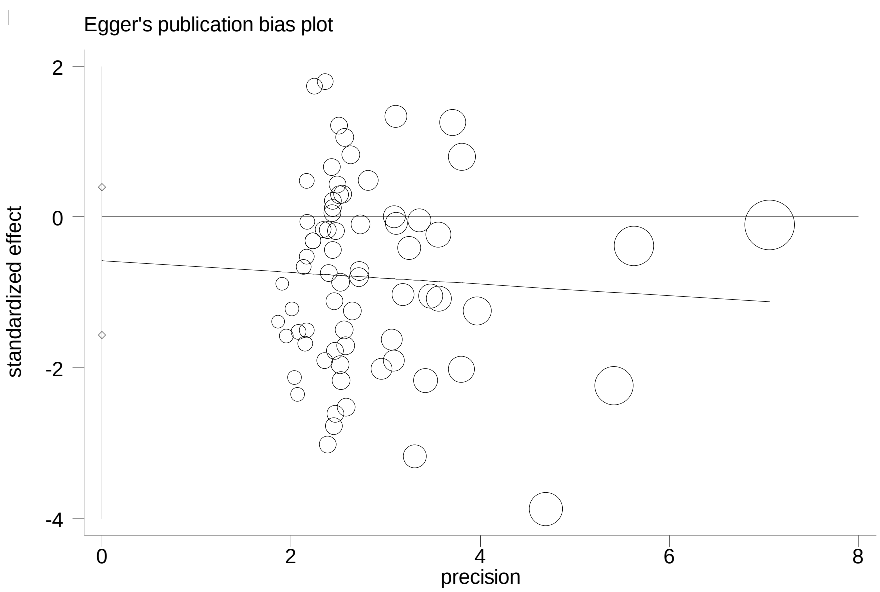
Systolic blood pressure: Dynamic resistance training versus non-exercise control





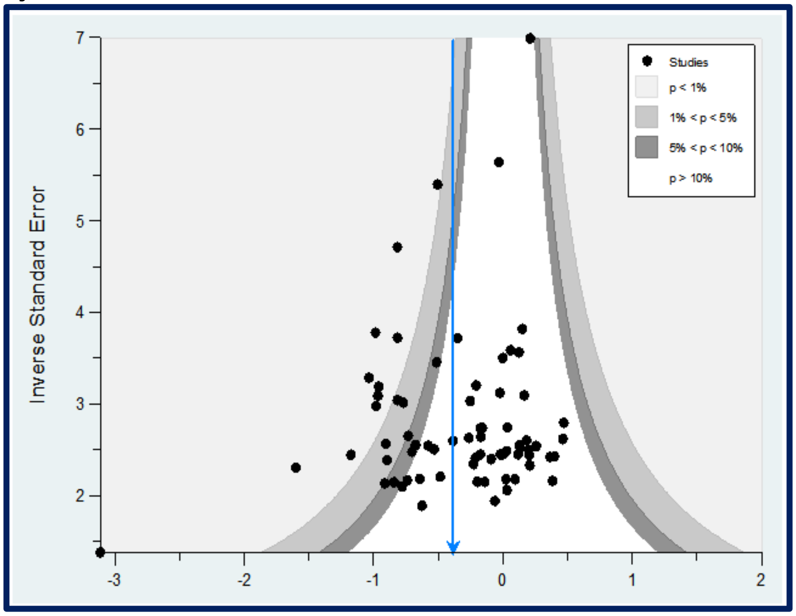
Diastolic blood pressure: Dynamic resistance training versus non-exercise control



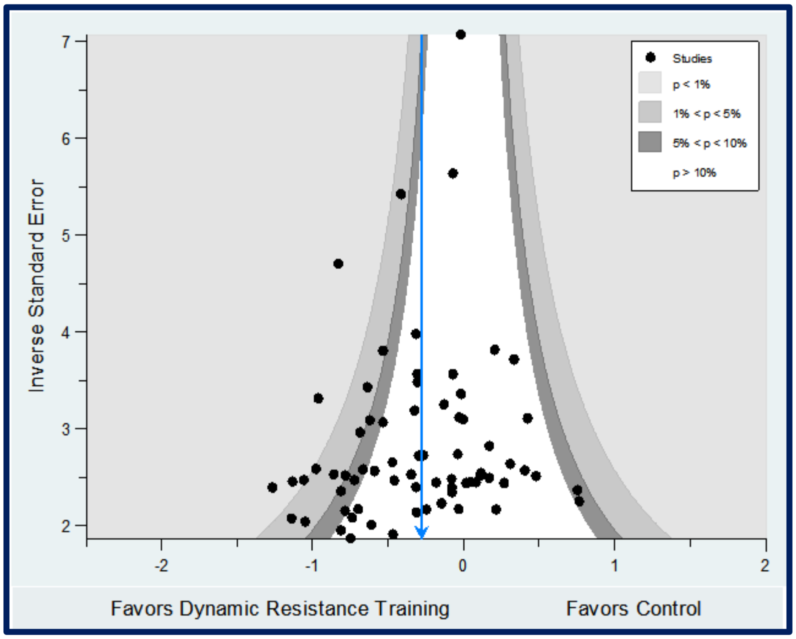


Appendix 20. Figure S4. Contour-enhanced funnel plots (i.e., confunnels): A visual representation of the effect size distribution (the standardized mean difference, d_+) for the antihypertensive effects of dynamic resistance training versus non-exercise control.

Systolic Blood Pressure



Diastolic Blood Pressure



Note. Weighted mean effect size values (d_+) are **negative** when dynamic resistance training reduced blood pressure to a greater extent than control. The blue line and arrowhead indicates the overall mean effect size.