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# A Meta-Analysis of Candidate Gene Association Studies on the Blood Pressure Response to Aerobic Exercise

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A Meta-Analysis of Candidate Gene Association Studies on  
the Blood Pressure Response to Aerobic Exercise

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A Meta-Analysis of Candidate Gene Association Studies on  
the Blood Pressure Response to Aerobic Exercise

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## ABSTRACT

**Purpose:** Aerobic exercise (AE) lowers blood pressure (BP) 5-7 mmHg among those with hypertension, but there is considerable variability in the BP response to AE. Genetic predispositions account for 40-65% of this variability; however, identifying genetic variants that associate with the BP response to AE is a challenge. We performed a meta-analysis to integrate the small number of studies that examined the influence of candidate genes on the BP response to AE. **Methods:** Studies retrieved included an acute or chronic AE intervention; BP before and after AE by genotype; and candidate gene polymorphisms. Effect sizes were the standardized mean difference of BP post-vs. pre-exercise for AE training interventions, and post-vs. pre-exercise BP vs. control for acute AE interventions. Effect sizes were disaggregated for genotype and adjusted for baseline sample features. Analyses followed fixed-effects assumptions. **Results:** 11 AE training ( $N=2646$ ) and 4 acute AE ( $N=50$ ) studies qualified. AE training interventions were performed at  $62.3\pm 7.5\%$  (Mean $\pm$ SD) maximum oxygen consumption for  $43.8\pm 11.6$  min-session<sup>-1</sup>,  $3.6\pm 1.2$  d-wk<sup>-1</sup> for  $15.3\pm 7.6$  wk. Participants were mostly non-Hispanic white ( $N=1,736$ ) men ( $N=1,278$ ) and women ( $N=1,360$ ),  $44.2\pm 10.7$  yr with a BP of  $134.4\pm 11.9/78.6\pm 9.3$  mmHg and body mass index of  $26.9\pm 2.6$  kg.m<sup>-2</sup>. The effect of exercise on the BP response to AE training was small but statistically significant for systolic BP (SBP) ( $d_+ = -0.21$  [95% CI = -0.247, -0.168], -3.1 mmHg,  $I^2=77.8\%$ ) and diastolic BP (DBP) ( $d_+ = -0.20$  [95% CI = -0.235, -0.158], -1.9 mmHg,  $I^2=62.2\%$ ). Sample features explained 59.1-71.5% of the variability in the BP response to AE training ( $P < 0.001$ ), and reductions were greater among samples that had a higher resting BP (SBP:  $\beta = -0.68$ ,  $P < 0.001$ ; DBP:  $\beta = -0.56$ ,  $P = 0.01$ ), that were younger (SBP:  $\beta = 0.34$ ,  $P < 0.01$ ; DBP: NS,  $P > 0.05$ ), and that included more women than men (SBP:  $\beta = 0.41$ ,  $P < 0.001$ ; DBP:  $\beta = 0.52$ ,  $P < 0.001$ ). Only the angiotensinogen (*AGT*) M235T (rs699) polymorphism showed a significant association with the DBP response to AE training (Multiple  $R=0.058$ ,  $P=0.02$ ), explaining 0.3% of the variability in the DBP response. Pairwise comparisons of *AGT* M235T genotypes showed those with the *AGT* MM genotype reduced DBP 2.9 mmHg more in response to AE training compared to those with the *AGT* TT genotype (Multiple  $R=0.076$ ,  $P=0.02$ ). Acute interventions were performed at  $50.1\pm 10.1\%$  maximum oxygen consumption for 40 min-session<sup>-1</sup>. Participants were men,  $44.1\pm 1.0$  yr with a BP of  $145.7\pm 1.7 / 85.8\pm 0.9$  mmHg and body mass index of  $29.9\pm 0.3$  kg.m<sup>-2</sup>. BP responses to acute AE were large and heterogeneous for SBP ( $d_+ = -0.62$  [95% CI = -0.75, -0.50], -5.5

mmHg,  $I^2=48\%$ ), and small and homogeneous for DBP ( $d_+ = -0.28$  [95% CI = -0.40, -0.16], -1.7 mmHg,  $I^2 = 0\%$ ). Sample features explained 55.2-82.3% of the variability in the BP response to acute AE ( $P < 0.001$ ), while candidate gene polymorphisms explained a marginally significant 4.6-6.0% of the variability ( $P=0.08$ ). Analyses of individual polymorphisms were not feasible due to the low numbers of interventions and observations. **Conclusions:** Despite our attempt to increase the sample size to detect polymorphism associations with the BP response to AE, sample features explained most of the variability across trials, although the *AGT M235T* polymorphism is promising. These findings reinforce the notion that most genetic variants explain only a small amount of variability in the response of health/fitness phenotypes to exercise, if any. Future research efforts seeking to explain the variability of health/fitness phenotypes to exercise such as BP should explore sample features known to influence the phenotype of interest, as well as the multiple levels of gene regulation using high throughput screening in larger, more ethnically diverse samples of men and women with HTN.

## INTRODUCTION

Hypertension (HTN) is a major public health issue in the United States (US) affecting an estimated 77.9 million US adults (33.3%) 20 years of age and older (Go et al., 2013; JNC VII, 2003) [Table 1]. In addition, HTN is a major independent risk factor for cardiovascular disease (CVD) and is the most common primary diagnosis in the US (Go et al., 2013). The prevalence of HTN is higher in men (16.8%) than women (12.2%) until 45 years, similar from 45 to 64 years (44.0%), and higher in women (75.5%) than men (68.0%) after 64 years (Go et al., 2013). The prevalence among blacks (41.3%) is higher than whites (28.9%), especially among black (47.0%) versus white (30.7%) women (Go et al., 2013). Therefore, due to its significant impact on US public health, the prevention, treatment, and control of HTN has become a major public health priority (Pescatello, 2010).

**Table 1: Classification of blood pressure among adults (JNC VII, 2003)**

Blood Pressure Classification	SBP (mmHg)	DBP (mmHg)
Normal	< 120	and < 80
Prehypertension	120-139	or 80-89
Stage 1 Hypertension	140-159	or 90-99
Stage 2 Hypertension	A 160	or $\geq$ 100
Stage 3 Hypertension	$\geq$ 180	or $\geq$ 110

Abbreviations. SBP, systolic blood pressure; DBP, diastolic blood pressure; mmHg, millimeters of mercury.

Aerobic exercise (AE) is an effective lifestyle therapy to prevent, treat, and control HTN because it reduces BP 5-7 mmHg among those with HTN

(Pescatello et. al., 2004). Evidence shows BP reductions of this magnitude can lower the risk of developing CVD by 20-30% (JNC VII, 2003). Therefore, the American College of Sports Medicine (ACSM) recommends a *Frequency, Intensity, Time and Type (FITT)* exercise prescription (Ex R<sub>x</sub>) for HTN of AE performed at moderate intensity (40-60% of maximum oxygen reserve [VO<sub>2</sub>R]) for 30-60 minutes, on most preferably all days of the week that is supplemented by resistance exercise (Pescatello et. al., 2004; Thompson, Gordon, Pescatello, & American College of Sports Medicine, 2009).

### **Statement of the Problem**

Despite the ACSM *FITT* Ex R<sub>x</sub> to prevent, treat, and control HTN [Table 2], there is considerable variation in the BP response to exercise, with 25% of the people with HTN not lowering their BP with exercise (Hagberg, Park, & Brown, 2000). Bouchard and Rankinen (2001) examined the inter-individual variation in the BP response to a standardized 20 week AE training program among 481 sedentary, adult Caucasians from 98 two-generation families as part of the HEalth, RIsk factors, exercise Training And GENetics (HERITAGE) family study. They found although there was an average systolic BP (SBP) post training reduction of  $8.2 \pm 11.6$  mmHg, a considerable amount of heterogeneity remained with some subjects experiencing significant SBP decreases (> 40 mmHg) and other subjects experiencing significant SBP *increases* (> 20 mmHg) (Bouchard & Rankinen, 2001; Bouchard et al., 2012). In addition, the standard deviation of the mean BP response to AE training exceeded the mean value itself, further supporting the inference of heterogeneity in the BP response to exercise. These findings suggest that there are environmental and genetic components that contribute to the inter-individual variation observed in the BP response to AE, with heritability estimates

of approximately 40-65% across generations (Bouchard & Rankinen, 2001; Bouchard et al., 2012).

**Table 2: ACSM *FITT* Ex  $R_x$  for Hypertension (Thompson et al., 2009)**

<b>Frequency</b>	On most, preferably all days of the week 700 - > 2,000 kcal·wk <sup>-1</sup>
<b>Intensity</b>	40-60% VO <sub>2</sub> R or HRR 64-84% HRmax Borg RPE 11-14
<b>Time</b>	30-60 m·d <sup>-1</sup> continuous or accumulated
<b>Type</b>	Aerobic supplemented by resistance exercise

Abbreviations. HRmax, heart rate max; HRR, heart rate reserve; kcal·wk<sup>-1</sup>, kilocalories per week; m·d<sup>-1</sup>, minutes per day; RPE, rating of perceived exertion; VO<sub>2</sub>R, maximal oxygen consumption reserve.

Candidate gene studies aim to identify whether an association exists between a specific genetic variant and health/fitness phenotype such as the BP response to exercise. Presently, 26 different candidate gene polymorphisms have been reported to be associated with the BP response to AE (Alioglu et al., 2010; Augeri et al., 2009; Blanchard et al., 2006; Delmonico et al., 2005; de Luis et al., 2006; Fearheller et al., 2009; Flavell et al., 2006; Franks et al., 2004; Friedl, Krempler, Sandhofer, & Paulweber, 1996; Grove et al., 2007; Hagberg, Ferrell, Dengel, & Wilund, 1999; Hautala et al., 2006; Jones et al., 2006; Kilpelainen et al., 2008; Kimura et al., 2003; Macho-Azcarate, Marti, Calabuig, & Martinez, 2002; Ortlepp et al., 2003; Pescatello et al., 2007a; Pescatello et al., 2007b; Pescatello et al., 2009; Rankinen et al., 2000; Rankinen et al., 2002; Rankinen et al., 2007; Rauramaa, et al. 2002; Rivera et al., 2001; Takakura et al., 2006; Vargas et al., 2013; Zateyschikov, 2007 et al.; Zhang et al., 2002) [Appendix A]. These polymorphisms include those involved with: 1) Renin Angiotensin System (RAS) and/or

Renal Function [angiotensin converting enzyme (*ACE*) (rs4340), adducin 1 alpha (*ADD1*) (rs4961), angiotensinogen (*AGT*) (rs699), angiotensin 2 type 1 receptor (*AGTR1*) (rs5186), and aldosterone synthase (*CYP11B2*) (rs1799998); 2) Sympathetic Nervous System [adenosine monophosphate deaminase 1 (*AMPD1*) (rs17602729), adrenergic receptor, beta 1 (*ADRB1*) (rs1801253), adrenergic receptor, beta 2 (*ADRB2*) (rs1042714), cholinergic receptor (*CHRM2*) (rs324640, rs8191992), guanine nucleotide binding protein system alpha subunit (*GNAS*) (rs7121), and guanine nucleotide binding protein, beta polypeptide 3 (*GNB3*) (rs5443)]; and 3) Nitric Oxide Synthase Pathway and/or Vascular Function [endothelin 1 (*EDNI*) (rs5370, rs2070699, rs5369), endothelial nitric oxide synthase (*NOS3*) (rs2070744), and transforming growth factor, beta 1 (*TGFB1*) (rs1800470)]. Other polymorphisms identified as established and emerging cardiovascular disease risk factors implicated with the etiology of HTN include: 1) Dyslipidemia [apolipoprotein (*APOE*) (rs7412, rs429358), fatty acid binding protein 2 (*FABP2*) (rs1799883), and lipoprotein lipase (*LPL*) (rs328)]; 2) Obesity [leptin receptor (*LEPR*) (rs1137100)]; and 3) Inflammatory Biomarkers [cytochrome b-245 alpha polypeptide (*CYBA*) (rs4673, rs1049255), cytochrome P450 superfamily (*CYP2D6*) (rs1065852), and interleukin 6 receptor (*IL6R*) (rs2228145)].

Although these findings are promising, identifying specific genetic variants that associate with the BP response to AE remains a significant challenge. Specifically, BP candidate gene studies are limited by small sample sizes, a small number of common single nucleotide polymorphisms (SNPs) examined, and lack of statistical correction for multiple comparison testing. For these reasons, BP candidate gene association studies are

plagued by a lack of replication, and ultimately, a large proportion of the variability in the BP response to AE as related to genotype is left unexplained.

Meta-analysis systematically and quantitatively integrates the results of a body of literature addressing a related hypothesis, ultimately increasing the sample size and power to detect statistical differences (Bornstein, 2009). In addition, meta-analysis is able to identify sources of diversity across different study designs and detect biases and deficiencies in research (Ioannidis & Lau, 1999). Theoretically, meta-analysis should be able to address some of the limitations of candidate gene association studies by increasing the sample size to detect genotype/phenotype associations with the BP response to AE.

In summary, 26 different candidate gene polymorphisms have been reported to be associated with the BP response to AE. However, identifying specific genetic variants accounting for the BP response variability remains a significant challenge due to the limitations in candidate gene association studies examining the BP response to AE. Theoretically, the use of meta-analysis should be able to increase the sample size of current BP candidate gene studies to detect genotype/phenotype associations and provide clearer insights regarding the role of genetic predispositions on the BP response to AE. This study serves as the first meta-analysis to systematically and quantitatively integrate the results of candidate gene association studies and the BP response to AE. In addition, this study attempted to identify the specific genetic variants (if any) that associate with the BP response to AE that can be explored in future work.

## Specific Aims & Hypotheses

The primary aim of this study was to perform a meta-analysis of candidate gene association studies examining the BP response to AE. Through application of meta-analytic procedures, this study intended to identify the overall and individual genotype effect size values accounting for the variability in the BP response to AE.

*Specific Aim 1:* To determine the overall and individual genotype effect size values that account for the missing BP response variability in AE.

*Hypothesis 1:* The overall and individual genotype effect size values on the BP response to AE will be small to medium across studies.

*Specific Aim 2:* To disaggregate candidate gene polymorphisms based upon the number of minor alleles (i.e., 0, 1, or 2) and to determine both the overall and individual additive effect of candidate genes on the BP response to AE.

*Hypothesis 2:* As the number of minor alleles increase, the magnitude of the BP reduction resulting from AE will be greater.

*Specific Aim 3:* To investigate the pairwise interactive effects of genotype (i.e., 0 vs. 1, 0 vs. 2, and 1 vs. 2 minor alleles) within candidate gene polymorphisms and the BP response to AE.

*Hypothesis 3:* Genotype groups with the greater number of minor alleles will reduce BP in response to AE more than will genotype groups with the greater number of common alleles.

*Specific Aim 4:* To examine the moderating effects of study level sample features (i.e., age, gender, BMI, pre-exercise BP) on the BP response to AE.

*Hypothesis 4:* Candidate gene polymorphisms will better predict the unexplained variability in the BP response to AE than will study level sample features.

## **METHODS**

This chapter outlines the methods used to perform this meta-analysis. In particular, this chapter first discusses the literature search strategy that was used to gather relevant studies for this meta-analysis. Then, the predetermined inclusion/exclusion criteria, study outcome measure(s), and specific meta-analytic and statistical procedures used to perform this meta-analysis will be discussed.

### **Literature Search**

#### *Search methods for identifying relevant studies*

A systematic search was conducted using the following electronic databases: MEDLINE (to April 2013), Biosis (to April 2013), Scopus (to April 2013), and Web of Science (to April 2013). The keywords “blood pressure,” “exercise,” “randomized control trial,” and “genes” were used in combination with medical subject heading (MeSH) descriptors to search the databases for relevant studies [Table 3, Appendix B]. Article citation lists were also reviewed to identify additional studies. No language restrictions were applied when attempting to locate studies for inclusion in this meta-analysis.

The studies produced from the systematic search were screened via title and abstract by two coders (MLB, KAL) for inclusion/exclusion criteria. To confirm the accuracy of the screening process, the coders re-screened all studies that were initially excluded to check for subtle errors (e.g., identifying excluded studies meeting the predetermined inclusion criteria). Studies were included if they: 1) involved an acute

(response to a single bout of exercise) or chronic (response to training) AE intervention; 2) measured pre- and post-AE BP by genotype; 3) examined at least one candidate gene polymorphism for association with the BP response to AE; and 4) contained a case-control, cross-sectional, or family based study design. Studies were excluded if they: 1) involved animal or non-human models; 2) included literature lacking a peer review process; or 3) examined the BP response to AE without a candidate gene polymorphism such as in heritability or linkage studies [Appendix C].

**Table 3. Keywords used in the literature search.**

<b>Blood Pressure-Keywords</b>	<b>Genetic-Keywords</b>	<b>Exercise-Keywords</b>
Mean Arterial Blood Pressure(s) Arterial Pressure(s) Hypertension Hypotension Normotension Hypertensive Hypotensive Normotensive Systolic Pressure Diastolic Pressure Pulse Pressure Venous Pressure Pressure Monitor Pre-Hypertension Blood Pressure Response Blood Pressure Decrease Blood Pressure Reduction Blood Pressure Monitor(s) Blood Pressure Measurement	Gene(s) Genotype(s) Single Nucleotide Polymorphism(s) Polymorphism Deoxyribonucleic Acid Minor Allele(s) Genetic	Exercise(s) Running Cycle(s) Cycling Walking Treadmill Endurance Training Weight Training Speed Training Training Duration Training Frequency Training Intensity Aerobic Endurance
All words used in: title, original title, substance word, subject heading word, and abstract. Randomized control trial (RCT) filter applied in all search commands		

***Types of participants***

Study participants involved adults'  $\geq 19$  years. The participants were of any gender, ethnicity, body composition, BP classification, or physical activity status. In addition, the included participants may have had a family history of heart disease or

HTN, possessed a known disease or chronic condition(s) related to CVD (e.g., congestive heart failure, metabolic syndrome [MetS]), or consumed prescribed BP medication of any kind. Excluded participants possessed known disease or chronic health conditions unrelated to CVD (e.g., cancer, neoplasms, fibromyalgia, Alzheimer's, pregnancy, epilepsy, pneumonia, septicemia, HIV, AIDS, and meningitis). In addition, study participants consuming prescribed BP medications that did not undergo a sufficient washout period prior to exercise were excluded. All coded descriptive participant variables are listed within the comprehensive coding form [Appendix D].

### ***Types of interventions***

Only acute and chronic AE interventions were included in the meta-analysis. Acute studies must have compared an exercise intervention group to either a non-exercise control group or a control session. Chronic studies must have compared an exercise intervention group to either a non-exercise control group or control session (if possible), or compared an exercise intervention group cross-sectionally by genotype(s). The exercise interventions were permitted to occur in any setting—hospital, clinic, academic research laboratory, fitness center, or other venue. Exercise interventions were delivered via one-to-one (e.g., personal training) or in groups, and were supervised or unsupervised. All descriptive intervention variables that were coded are listed within the comprehensive coding form [Appendix D].

### ***Outcome measure***

The primary goal of this meta-analysis was to determine the overall and individual genotype effect size values accounting for the variability in the BP response to AE. The overall effect size estimate was measured using Becker's  $d$  to quantify the

magnitude of BP change (across all polymorphisms) in response to exercise. Becker's  $d$  was computed as the post- vs. pre-exercise BP response divided by the pre-exercise standard deviation. The effect size estimates were then disaggregated by genotype for each polymorphism examined, yielding either two (dominant or recessive models) or three (co-dominant or additive models)  $d$  values for each study (Becker, 1988). Negative values of  $d$  implied BP was lower at post- versus pre-exercise, thereby demonstrating a favorable response to exercise.

### ***Data extraction***

After screening potential articles for inclusion/exclusion criteria via title and abstract, the remaining studies underwent a full-text review. Studies that continued to fulfill the inclusion/exclusion criteria were subject to data extraction via a 246-item coding form [Appendix D]. Two coders (MLB, KAL) independently performed the data extraction procedures; the coders were trained from an expert in meta-analysis (TBH-M) with 10 pilot studies to ensure accurate and reliable interpretation of coded studies. The coders then reviewed the 10 pilot studies with the meta-analytic expert and resolved discrepancies in coding. If a consensus could not be reached, a third coder mediated unresolved discrepancies. Once an inter-rater reliability of 0.80 was reached on the sampled pilot studies, the coders then coded the remaining included studies. The coders continued to meet weekly to review the coded studies and compare coded data line-by-line, continuing to address any questions, concerns or issues encountered throughout the data extraction process. Extracted study and subject data included variables related to: age, body mass index (BMI), baseline or pre-exercise systolic (SBP) and diastolic (DBP) BP, gender, ethnicity, study quality, and geographical region or

population. Extensive and detailed study, subject, and intervention variables were coded on the comprehensive coding form [Appendix D].

### ***Study Quality***

Study quality was assessed with the Down and Black's (1998) methodological quality checklist, a 27-item questionnaire with items in the five general domains of: 1) the appropriateness of assessing randomized and non-randomized control trials; 2) the provision of computing both an overall score for study quality and a profile of scores not only for the quality of reporting; 3) internal validity (bias and confounding); 4) external validity; and 5) power [Appendix D].

### ***Data extraction agreement***

A Kappa statistic was computed to assess inter-coder reliability for categorical variables. The Kappa statistic is interpreted as follows:  $< 0.00$  = poor,  $0.00-0.20$  = slight,  $0.21-0.40$  = fair,  $0.41-0.60$  = moderate,  $0.61-0.80$  = substantial and  $0.81-1.00$  = almost perfect agreement between coders (Meyer, 1999). The Pearson's  $r$  correlation is a statistical measure that ranges in value from  $+1$  and  $-1$ , and accounts for the percent of between rater agreements for a given variable. The Pearson  $r$  correlation is interpreted as follows:  $\leq -0.70$  = very strong negative relationship,  $-0.40$  to  $-0.69$  = strong negative relationship,  $-0.30$  to  $-0.39$  = moderate negative relationship,  $-0.20$  to  $-0.29$  = weak negative relationship,  $-0.01$  to  $-0.19$  = no or negligible relationship,  $+0.01$  to  $+0.19$  = no or negligible relationship,  $+0.20$  to  $+0.29$  = weak positive relationship,  $+0.30$  to  $+0.39$  = moderate positive relationship,  $+0.40$  to  $+0.69$  = strong positive relationship,  $\geq +0.70$  = very strong positive agreement. Reliability was assessed regularly during the coding of studies (every 2 weeks) to ensure that inter-coder agreement remained at high levels.

### ***Effect Size Estimate***

The overall effect size estimate was computed using Becker's  $d$  to quantify the magnitude of BP change (across all polymorphisms) in response to exercise. Becker's  $d$  was computed as the post- vs. pre-exercise BP response divided by the pre-exercise standard deviation (Becker, 1998). The effect size estimates were then disaggregated by genotype for each polymorphism examined. The purpose of this procedure was to quantify the individual effect size estimate of each genotype for every polymorphism examined for every intervention arm of each study. Therefore, there were either two (dominant or recessive models) or three (co-dominant or additive models)  $d$  values for each study intervention (Becker, 1988). Acute studies were computed as the post- vs. pre-exercise BP response compared to control while chronic studies were computed with no control comparison. Negative values of  $d$  implied BP was lower at post- versus pre-exercise, implying a favorable response to exercise.

### **Average Effect Size Calculation (Fixed Effects vs. Random Effects)**

#### ***Fixed Effects Modeling***

Analyses followed fixed-effects assumptions because studies meeting our predetermined inclusion/exclusion criteria were of small quantity and therefore offered low precision in estimating population variation in effects. Fixed-effects models assume that all studies in a meta-analysis share a common effect size (Borenstein, 2009). Each effect size value was assigned a weight that corresponded to the inverse study variance.

#### ***Random Effects Modeling***

Random effects modeling, like fixed effects modeling, is weighted by the inverse study variance. However, random effects modeling also factors *between-study* variance

into the estimate of the constant, denoted as  $\tau^2$  (tau-squared). The random-effects model assumes that there are uncontrolled factors influencing the effect sizes of the studies' observed. Under heterogeneity, such models provide wider confidence intervals around mean effect sizes, reflecting a relatively conservative analytic approach (Bornstein, 2009). However, because the number of studies meeting our predetermined inclusion/exclusion criteria was small, the random effects model was not used in the meta-analysis (Bornstein, 2009).

### ***Publication Bias***

Potential for publication bias was assessed graphically via forest plots and funnel plots, and statistically via Begg's and Egger's methods (Begg & Mazumder, 1994; Borenstein, 2009; Egger, Davey Smith, Schneider, & Minder, 1997). Tests for publication bias assume that asymmetries in the distribution of effect size estimates imply publication biases. As a result, forest plots illustrate the variability of an effect size between sampled studies, while funnel plots depict an effect size across sampled studies by plotting an effect size against its variance (Borenstein, 2009). The graphical presence of publication bias was identified as an asymmetrical funnel shape in a funnel plot, while symmetrical funnel shapes indicated the absence of publication bias (Borenstein, 2009). If publication bias was present in the meta-analysis, the "Trim and Fill" method was used (Duval & Tweedie, 2000). The "Trim and Fill" method provides a statistically unbiased pooled estimate of study effects with varying results by imputing the presence of missing studies (Duval & Tweedie, 2000).

### ***Heterogeneity***

The  $Q$  (unstandardized) and  $I^2$  (standardized) statistics were used to determine if the between-study variance exceeded what would be expected on the basis of sampling error alone, justifying an inference of heterogeneity (Higgins & Thompson, 2002; Huedo-Medina, Sanchez-Meca, Marin-Martinez, & Botella, 2006). The  $Q$  statistic is an unstandardized inference of homogeneity, making it difficult to interpret in meta-analysis (Higgins & Thompson, 2002). Therefore, the  $I^2$  statistic was indexed on the basis of  $Q$  to assess homogeneity (Huedo-Medina et al., 2006).  $I^2$  values range from 0-100%, with values closer to 0% indicating homogeneity (studies exhibit a similar or homogenous pattern) and values closer to 100% indicating heterogeneity (studies exhibit a dissimilar or heterogeneous pattern) between study effect sizes (Huedo-Medina et al., 2006).

### ***Meta-Regression***

Moderator (i.e., covariate) analyses were examined using bivariate and multivariate meta-regression techniques to determine their influence on the BP response to AE. Analyses first controlled for clinical sample characteristics (i.e., age, BMI, gender, and pre-exercise BP) and then examined whether genotype BP associations explain the unique variation in  $ds$ . Candidate gene meta-regression analyses followed an additive model to determine the linear trends of genotype by the number of minor alleles in a given polymorphism. When there were at least nine effect size observations (cases) for a given candidate gene polymorphism, meta-regressions were also used to compare each pair of possible genotype combinations (i.e., 0 vs. 1, 0 vs. 2, and 1 vs. 2 minor alleles). If a significant genotype BP association appeared on a bivariate basis for a particular polymorphism, the polymorphism was then evaluated against the entire set of  $ds$  in the

multivariate model. Specifically, an interaction term was computed to determine whether the associated polymorphism differed significantly from all other polymorphisms in the model. The moving constant technique was used to estimate  $d$  for different genotypes that meta-regression models linked to the BP response to AE (Johnson & Huedo-Medina, 2011). The moving constant technique illuminates patterns in multivariate regression models by estimating both effect size values and confidence intervals at moderator levels of interest and the meta-regression line itself (Johnson & Huedo-Medina, 2011). To control for simultaneous statistical tests, a Bonferroni-corrected  $\alpha$ -level of  $p \leq .03$  ( $k=44$ ) was used for dominant/recessive models with two genotype groupings and  $p \leq .02$  ( $k=286$ ) was used for co-dominant/additive models with three genotype groupings (Abdi & Valentin, 2007).

### ***Statistical Computing***

Analyses were completed using Stata version 11.1 with macros (i.e., meanes, metareg, metafor, metan, metabias, and confunnel) for meta-analysis (StataCorp, 2009; Lipsey & Wilson, 2001; Wilson, 2001; Harris et al., 2008; Sterne, Harris, Harbord, Steichen, 2009). Data extraction agreement was completed using the Statistical Package for the Social Sciences and a Microsoft Excel Kappa statistic calculator (SPSS Inc., 2005; Huedo-Medina & Johnson, 2011). Individual effect size estimates were completed with a Microsoft Excel calculator (Huedo-Medina & Johnson, 2011).

### **Limitations**

Meta-analysis synthesizes prior empirical evidence and is therefore subject to the limitations of the literature it examines. Individual study quality of included trials can significantly impact the quality of the meta-analysis. To control for individual study

quality, a rigorous inclusion/exclusion criteria was used to screen relevant studies, and individual study quality was assessed with the Downs and Black methodological quality checklist (Downs & Black, 1998). In addition, study quality was examined as a moderating variable in meta-regression analyses to determine whether higher quality studies yield differing results from lower quality studies.

Secondly, because we examined published articles, our findings may have been subject to publication bias (Bornstein, 2009). We searched multiple databases and used broad search terminology when attempting to locate as many possible articles relating to the meta-analysis. However, there is the possibility that some studies were not located, perhaps skewing our effect size results. Therefore, publication bias was assessed graphically with funnel and forest plots, as well as with statistical procedures (i.e., Begg & Egger tests) to correct for publication bias when present (Borenstein, 2009).

Lastly, data extraction may also be a source of limitation. Despite training, a comprehensive coding form, and performing multiple pilot tests, subtle errors were still possible when coding large amounts of literature. To limit coding error, we used two coders. Coders were trained from an expert in meta-analysis (TBH-M) with 10 pilot studies. If discrepancies in coding could not be resolved, a third coder was used to mediate. Once an inter-rater reliability of 0.80 was reached on the 10 sampled pilot studies, coders began coding. Coders met weekly to review all coded studies, comparing answers line-by-line, and addressing any questions, concerns, or issues encountered throughout the data extraction process. In addition, data extraction agreement was assessed at weeks 2, 4, 6, and 8 to confirm inter-rater reliability across coded studies.

## **Delimitations**

The primary goal of this meta-analysis was to identify the most relevant candidate genes associated with the BP response to AE. This study did not intend to affirm causation among candidate genes and the BP response to AE; rather, it aimed to elucidate which genetic variants may be associated to the BP response to AE. In addition, this meta-analysis attempted to circumvent the limitations of candidate gene association studies examining the response of health/fitness phenotypes to exercise by increasing the sample size needed to detect genotype and health/fitness phenotype associations. The information gained from this meta-analysis provides insight to exercise scientists examining the response variability of health/fitness phenotypes to exercise by determining the emergence of promising candidate gene polymorphisms that should be explored in future research.

## **Clinical Significance & Application**

The findings of our meta-analysis provide exercise scientists with new information on the role genetic predispositions might pose on the BP response to AE. New knowledge gained from this study may be useful in refining the Ex Rx for HTN by identifying candidate genes that may and may not influence the BP response to AE. This information can also be used to better tailor individualized Ex Rx for those who do and do not respond to AE as a therapeutic modality to prevent, treat, and control HTN. In addition, a better understanding of how genetic predispositions modulate the antihypertensive effects of AE may provide biological insight into the regulatory pathways of the BP response to AE, and perhaps the pathophysiology of HTN.

## RESULTS

### Aerobic Exercise Training

#### *Study Characteristics*

There were 523 potentially relevant studies retrieved. Of these, 11 ( $N=2,646$ ) studies met the predetermined inclusion/exclusion criteria and examined ten candidate gene polymorphisms (Fearheller et al., 2009; Flavell et al., 2006; Hautala et al., 2006; Jones et al., 2006; Rankinen et al., 2000; Rankinen et al., 2002; Rauramaa et al., 2002; Rivera et al., 2001; Takakura et al., 2002; Vargas et al., 2013; Zhang et al., 2002) [Figure 1]. The ten candidate gene polymorphisms examined were: angiotensin converting enzyme (*ACE*) (rs4340) ( $k=3$ ), angiotensinogen (*AGT*) (rs699) ( $k=4$ ), cholinergic receptor (*CHRM2*) (rs324640, rs8191992) ( $k=1$ ), cytochrome b-245 alpha polypeptide (*CYBA*) (rs4673, rs1049255) ( $k=1$ ), guanine nucleotide binding protein, beta polypeptide 3 (*GNB3*) (rs5443) ( $k=1$ ), interleukin 6 receptor (*IL6R*) (rs2228145) ( $k=1$ ), lipoprotein lipase (*LPL*) (rs328) ( $k=1$ ), and transforming growth factor, beta 1 (*TGFBI*) (rs1800470) ( $k=1$ ).

In total, 59 effect size estimates were computed for SBP and DBP, yielding 118 effect size estimates. Studies were completed in the US (45%), UK (27%), Japan (18%), and South America (9%) with the exercise interventions completed in academic research laboratories (82%) and/or university hospitals (18%). The average study quality score was  $15.2 \pm 2.1$  out of a possible 26 points on the Downs and Black (1998) scale, indicating poor to average study quality.

### *Study Characteristics*

Subjects were mostly middle aged ( $44.2 \pm 10.7$  yr), overweight ( $26.9 \pm 2.6$  kg·m<sup>-2</sup>) non-Hispanic white ( $N=1,764$ ) men ( $N=1,288$ ) and women ( $N=1,358$ ) with pre-HTN ( $134.4 \pm 11.9/78.6 \pm 9.3$  mmHg).

### *Aerobic Exercise Intervention Characteristics*

Aerobic exercise (AE) interventions were performed at an average vigorous intensity of  $62.3 \pm 7.5\%$   $\text{VO}_{2\text{max}}$  for  $43.8 \pm 11.6$  min·session<sup>-1</sup>,  $3.6 \pm 1.2$  d·wk<sup>-1</sup> for  $15.3 \pm 7.6$  wk. AE modalities included stationary cycling ( $k=6$ ), walking ( $k=3$ ), and two not specified. Participants were supervised by a trained exercise professional in seven AE interventions, unsupervised in two, and not reported in two. Exercise adherence was reported in only three of the AE interventions, with a mean adherence rate of  $87.6 \pm 1.1\%$ .

### *The BP Response to Aerobic Exercise Training*

The weighted mean effect size ( $d_+$ ) for the change in BP after versus before AE training was small but statistically significant (SBP  $d_+ = -0.21$  [95% CI= -0.247, -0.168], -3.1 mmHg,  $I^2=77.8\%$ ; and DBP  $d_+ = -0.20$  [95% CI= -0.235, -0.158], -1.9 mmHg,  $I^2=62.2\%$ ).

### ***Multi-Predictor Analyses***

#### *Sample Features Associated with the BP Response to Aerobic Exercise Training*

Sample features explained a large portion of the variance in the BP response to AE training, 71.5% for SBP (Multiple  $R=0.845$ ,  $P<0.001$ ) and 59.1% for DBP (Multiple  $R=0.769$ ,  $P<0.001$ ) [Tables 4 & 5]. Reductions in SBP after versus before AE training were greater in samples with higher resting SBP ( $\beta=-0.68$ ,  $P<0.001$ ); that were younger ( $\beta=0.34$ ,  $P<0.01$ ); and that included more women than men ( $\beta=0.41$ ,  $P<0.001$ ). For, SBP

decreased 8.8 mmHg among those with HTN,  $d_+ = -0.56$  [95% CI= -0.644, -0.469], and 3.0 mmHg among those with Pre-HTN,  $d_+ = -0.20$  [95% CI= -0.250, -0.158], while SBP increased 2.5 mmHg among those with normal BP,  $d_+ = 0.13$  [95% CI= 0.044, 0.211]. SBP decreased 8.8 mmHg among young adults,  $d_+ = -0.50$  [95% CI= -0.625, -0.374], and 3.1 mmHg among middle-aged adults,  $d_+ = -0.22$  [95% CI= -0.262, -0.169], while SBP increased 0.3 mmHg among older adults,  $d_+ = -0.04$  [95% CI= -0.156, 0.074]. Lastly, SBP decreased 8.4 mmHg among samples containing women only,  $d_+ = -0.55$  [95% CI= -0.669, -0.422], and 3.0 mmHg among samples containing approximately equal numbers of women and men,  $d_+ = -0.20$  [95% CI= -0.250, -0.156], while SBP increased 2.6 mmHg among samples containing men only,  $d_+ = 0.15$  [95% CI= 0.012, 0.282].

Reductions in DBP after versus before training were greater in samples with higher resting DBP ( $\beta = -0.56$ ,  $P = 0.01$ ); and that included more women than men ( $\beta = 0.52$ ,  $P < 0.001$ ). For, DBP decreased 5.3 mmHg among those with HTN,  $d_+ = -0.49$  [95% CI= -0.651, -0.332], and 2.3 mmHg among those with Pre-HTN,  $d_+ = -0.23$  [95% CI= -0.276, -0.183], while DBP increased 0.5 mmHg among those with normal BP,  $d_+ = 0.01$  [95% CI= -0.120, 0.131]. DBP decreased 5.4 mmHg among samples containing women only,  $d_+ = -0.55$  [95% CI= -0.660, -0.436], and 2.2 mmHg among samples containing approximately equal numbers of women and men,  $d_+ = -0.22$  [95% CI= -0.269, -0.175], while DBP increased 1.0 mmHg among samples containing men only,  $d_+ = 0.10$  [95% CI= -0.026, 0.220]. Age was not a significant correlate of the DBP response to AE training ( $P > 0.05$ ).

### *Candidate Gene Associations with the BP Response to Aerobic Exercise Training*

*AGT* M235T (rs699) significantly associated with the DBP response to AE training in the additive model of genotype association (Multiple  $R=0.058$ ,  $P=0.02$ ) [Table 4]. Specifically, the reduction in DBP was greater among individuals with the *AGT* MM genotype ( $N=174$ ) ( $d_+ = -0.53$  [95% CI= -0.684, -0.374], -5.6 mmHg) compared to those with the *AGT* TT genotype ( $N=179$ ) ( $d_+ = -0.23$  [95% CI= -0.389, -0.064], -2.7 mmHg) after versus before AE training [Table 5]. No parallel effects were found with the *AGT* M235T polymorphism and the SBP response to AE training ( $P=0.82$ ). In addition, none of the nine other candidate polymorphisms significantly associated with either the SBP or DBP response to AE training ( $P>0.05$ ).

### **Acute Aerobic Exercise**

#### *Study Characteristics*

There were 523 potentially relevant studies retrieved. Of these, four studies met the predetermined inclusion/exclusion criteria and examined six candidate gene polymorphisms (Augeri et al., 2009; Blanchard et al., 2006; Pescatello et al., 2007a, 2009) [Figure 2]. The six candidate gene polymorphisms that were examined were: angiotensin converting enzyme (*ACE*) (rs4340) ( $k=1$ ), adducin 1 (alpha) (*ADD1*) (rs4961) ( $k=1$ ), angiotensin 2 type I receptor (*AGTR1*) (rs5186) ( $k=1$ ), aldosterone synthase (*CYP11B2*) (rs1799998) ( $k=1$ ), guanine nucleotide binding protein system alpha subunit (*GNAS*) (rs7121) ( $k=1$ ), and endothelial nitric oxide synthase (*NOS3*) (rs2070744) ( $k=1$ ). In total, 128 effect size estimates were computed; 32 for SBP and DBP versus control to total 64 effect size estimates, plus 32 for the two experimental conditions to total 64 effect size estimates. All interventions were conducted in the US and in one laboratory.

The average study quality score was  $18.2 \pm 2.4$  out of a possible 26 points on the Downs and Black (1998) scale, indicating moderate to good study quality.

### *Study Participants*

Subjects were middle aged ( $44.1 \pm 1.0$  yr), overweight ( $29.9 \pm 0.3$  kg·m<sup>-2</sup>) non-Hispanic white ( $N=50$ ) men with HTN ( $145.7 \pm 1.7/85.8 \pm 0.9$  mmHg).

### *Aerobic Exercise Intervention Characteristics*

The aerobic exercise (AE) intervention involved acute cycle exercise performed at light (40% VO<sub>2peak</sub>) and moderate (60% VO<sub>2peak</sub>) intensity for 40 min·session<sup>-1</sup>. All participants were supervised by a trained exercise professional and were adherent to the AE intervention.

### *The BP Response to Acute Aerobic Exercise*

The weighted mean effect size ( $d_+$ ) for the change in BP after versus before acute AE compared to control was large for SBP ( $d_+ = -0.62$  [95% CI= -0.745, -0.504], -5.5 mmHg,  $I^2=48\%$ ), and small for DBP ( $d_+ = -0.28$  [95% CI= -0.398, -0.162], -1.7 mmHg,  $I^2=0\%$ ).

### ***Multi-Predictor Analyses***

#### *Sample Features Associated with the BP Response to Acute Aerobic Exercise*

Sample features explained a large portion of the variance in the BP response to acute AE for SBP (Multiple  $R=0.907$ ,  $P<0.001$ ), accounting for 82.3% of the variability in the SBP response. Sample features explained 55.2% of the DBP response to acute AE (Multiple  $R=0.743$ ,  $P=0.12$ ); however, this correlation did not achieve statistical significance [Table 6]. Univariate analyses were unable to determine which sample

feature(s) explained most of the variability in the SBP response to acute AE because all studies involved participants from the same sample.

*Candidate Gene Associations with the BP Response to Acute Aerobic Exercise*

Beyond the influence of sample features, candidate genes explained 4.6% of the variance in the SBP response to acute AE (Multiple  $R=0.214$ ,  $P=0.08$ ), a trend approaching significance. Similarly, candidate genes explained 6.0% of the variance in the DBP response to acute AE (Multiple  $R=0.245$ ,  $P=0.08$ ), a trend approaching significance. The analyses of individual polymorphisms were not feasible due to the low number of interventions and observations, and because all studies were derived from a single trial, making non-independence a potential threat.

**Table 4.** Blood pressure response to aerobic exercise training attributable to sample features and candidate genes, where the linear trends of candidate gene minor alleles comprised a test of the additive model of gene association.

Candidate gene(s)	Sample features' association with BP response to AE <sup>a</sup>			Candidate gene association with BP response to AE <sup>b</sup>		
	<i>k</i>	Multiple R	<i>p</i>	<i>k</i>	Multiple R $\Delta$	<i>p</i> <sup>c</sup>
SBP						
All	59	0.845	<0.001 <sup>†</sup>	59	0.120	0.22
<i>ACE</i>	15	0.790	0.08	15	0.396	0.64
<i>AGT</i>	15	0.926	<0.001 <sup>†</sup>	15	0.116	0.82
DBP						
All	59	0.769	<0.001 <sup>†</sup>	59	0.108	0.20
<i>ACE</i>	15	0.759	0.10	15	0.159	0.07
<i>AGT</i>	15	0.890	<0.001 <sup>†</sup>	15	0.058	0.02 <sup>†</sup>

Note 1. Models in each row are somewhat independent of the models in the other rows.

Note 2. Univariate sample feature analyses do not appear in this table since the focus of the analysis was on candidate gene polymorphisms.

Note 3. The term All under candidate gene(s) is the aggregate model of all nine candidate gene polymorphisms examined in this meta-analysis.

Abbreviations. AE=aerobic exercise. BP=blood pressure.  $\Delta$ =change. DBP=diastolic blood pressure. <sup>†</sup>=statistically significant association.

RAS=renin angiotensin system. SBP=systolic blood pressure. Gene abbreviations. *ACE*= angiotensin converting enzyme.

*AGT*=angiotensinogen.

<sup>a</sup>Competing variables are mean sample age, proportion male, mean BMI, and mean SBP prior to exercise.

<sup>b</sup>These models control for the competing variables, where possible.

<sup>c</sup>Bonferroni adjusted p-value set at  $p \leq .02$ .

**Table 5.** Blood pressure response to aerobic exercise training attributable to sample features and candidate genes, where pair-wise comparisons of genotype were made.

Candidate gene(s)	Sample features' association with BP response to AE <sup>a</sup>			Candidate gene association with BP response to AE <sup>b</sup>		
	<i>k</i>	Multiple <i>R</i>	<i>p</i>	<i>k</i>	Multiple <i>R</i> Δ	<i>p</i> <sup>d</sup>
SBP						
All trials						
CC vs. MM	37	0.835	<0.001 <sup>†</sup>	37	0.175	0.41
CM vs. MM	38	0.837	<0.001 <sup>†</sup>	38	0.159	0.28
CC vs. CM	37	0.848	<0.001 <sup>†</sup>	37	0.001	0.60
<i>Gene-specific comparisons for studies with independent replications<sup>c</sup></i>						
<i>AGT</i>						
MM vs. TT	10	0.863	<0.001 <sup>†</sup>	10	0.211	0.38
MT vs. TT	11	0.958	<0.001 <sup>†</sup>	11	0.232	0.76
MM vs. MT	9	0.976	<0.001 <sup>†</sup>	9	0.111	0.91
DBP						
All trials						
CC vs. MM	37	0.569	<0.001 <sup>†</sup>	37	0.153	0.81
CM vs. MM	38	0.572	<0.001 <sup>†</sup>	38	0.128	0.95
CC vs. CM	37	0.682	<0.001 <sup>†</sup>	37	0.001	0.46
<i>Gene-specific comparisons for studies with independent replications<sup>c</sup></i>						
<i>AGT</i>						
MM vs. TT	10	0.822	<0.01 <sup>†</sup>	10	0.076	0.02 <sup>†</sup>
MT vs. TT	11	0.929	<0.001 <sup>†</sup>	11	0.093	0.05
MM vs. MT	9	0.949	<0.001 <sup>†</sup>	9	0.221	0.32

*Note 1.* Models in each row are somewhat independent of the models in the other rows.

*Note 2.* Univariate sample feature analyses do not appear in this table since the focus of the analysis was on candidate gene polymorphisms.

*Note 3.* The term All trials under candidate gene(s) refers to the pair-wise aggregate models of all nine candidate gene polymorphisms examined in this meta-analysis.

Abbreviations. AE=aerobic exercise. BP=blood pressure. Δ=change. DBP=diastolic blood pressure. †=statistically significant association.

RAS=renin angiotensin system. SBP=systolic blood pressure. Gene abbreviations. ACE=angiotensin converting enzyme. AGT=angiotensinogen.

<sup>a</sup>Competing variables are mean sample age, proportion male, mean BMI, and mean SBP prior to exercise.

<sup>b</sup>These models control for the competing variables, where possible.

<sup>c</sup>Only one study was available for the genes *CYBA*, *CHRM2*, *GNB3*, *IL6R*, *LPL*, and *TGFBI*. <sup>d</sup>Bonferroni adjusted p-value set at  $p \leq 0.02$ .

**Table 6.** Ambulatory blood pressure response to acute aerobic exercise compared to control, attributable to sample features and candidate genes.

Blood Pressure	Sample characteristics association with BP response to AE <sup>a</sup>			Candidate gene association with BP response to AE <sup>b</sup>		
	<i>k</i>	Multiple <i>R</i>	<i>p</i>	<i>k</i>	Multiple <i>R</i> $\Delta$	<i>p</i> <sup>c</sup>
SBP	24	0.907	<0.001 <sup>†</sup>	24	0.214	0.08
DBP	24	0.743	0.27	24	0.245	0.08

Note 1. Models in each row are somewhat independent of the models in the other rows.

Note 2. Univariate sample feature analyses do not appear in this table since the focus of the analysis was on candidate gene polymorphisms.

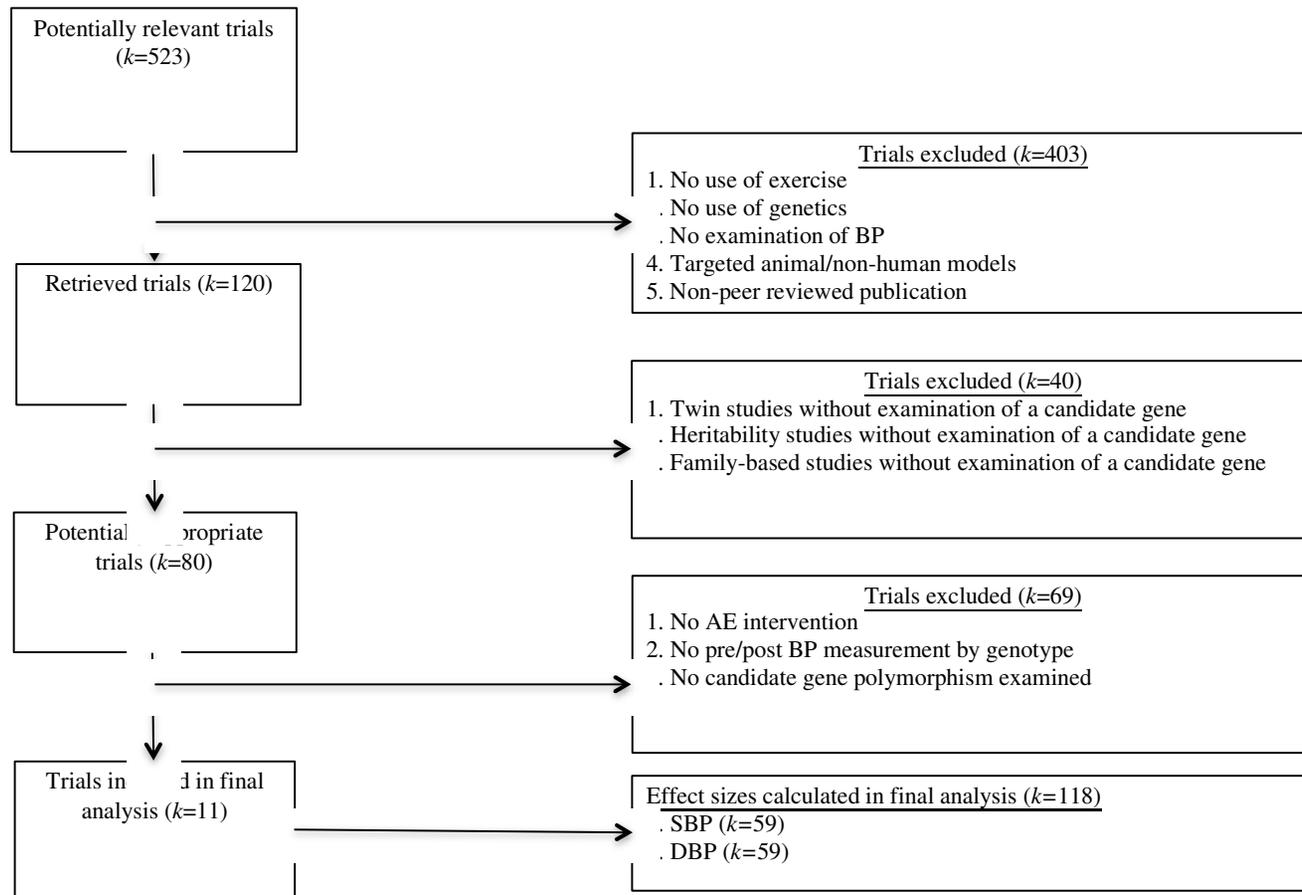
Note 3. All six-candidate gene polymorphisms are shown in aggregate form since there were not enough degrees of freedom to perform individual polymorphism analyses. Abbreviations. AE=aerobic exercise. BP=blood pressure.  $\Delta$ =change. DBP=diastolic blood pressure. <sup>†</sup>=statistically significant association. SBP=systolic blood pressure.

<sup>a</sup>Variables included: mean sample age, proportion male, BMI, and BP prior to exercise.

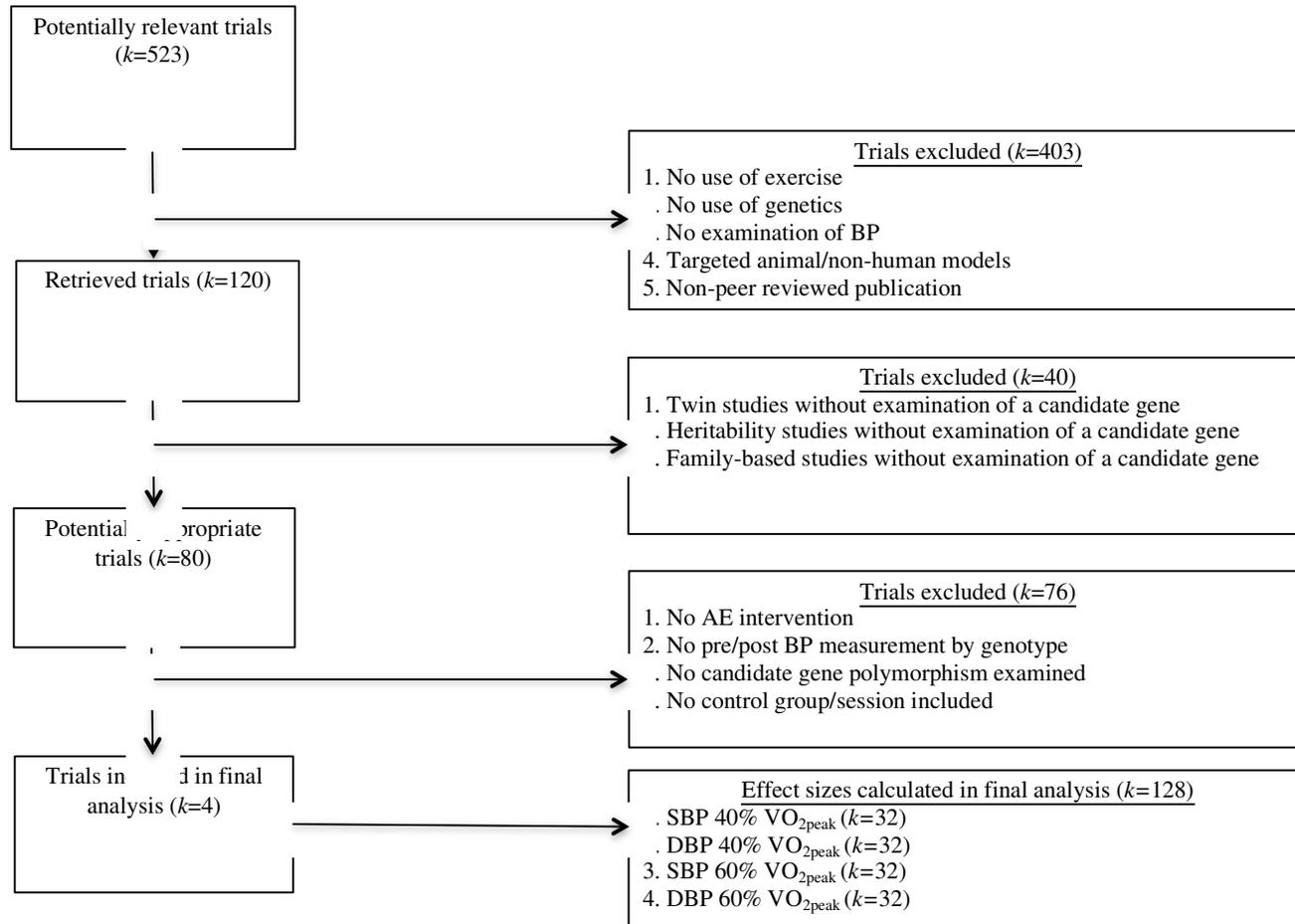
<sup>b</sup>These models control for the competing variables, where possible.

<sup>c</sup>Bonferroni adjusted p-value set at  $p \leq .03$ .

**Figure 1.** Flow Diagram of Trial Identification and Selection for Aerobic Exercise Training



**Figure 2.** Flow Diagram of Trial Identification and Selection for Acute Aerobic Exercise



## DISCUSSION

The purpose of this meta-analysis was to examine the effects of candidate gene polymorphisms on the BP response to aerobic exercise (AE). We also investigated patient characteristics that influenced the BP response to AE. The major findings of this meta-analysis were clinical sample features, rather than candidate gene polymorphisms, explained most of the variability in the BP response to AE. Collectively, age (SBP 0.6%; DBP 3.0%), gender (SBP 30.6%; DBP 23.1%) and resting BP (SBP 51.2%; DBP 8.1%) accounted for 82.4% of the SBP and 34.2% of the DBP response to AE training. Subgroup analyses of these sample features showed BP reductions were greater in samples that were younger, that included more women than men, and that had a higher pre-exercise resting BP. SBP was reduced 5.7 mmHg and 9.1 mmHg more among younger than middle-aged and older adults, respectively. SBP and DBP were reduced 5.4/3.2 mmHg and 11.0/6.4 mmHg more among women than gender mixed samples and samples with men only, respectively. Finally, SBP and DBP were reduced 5.8/3.0 mmHg and 11.3/5.8 mmHg more among persons with HTN than persons with prehypertension (pre-HTN) and normal BP, respectively.

In contrast to the significant proportion of variance in the BP response to AE explained by clinical sample features, the overall contribution of candidate gene polymorphisms on the BP response to AE training was small and non-significant. In fact, only the *AGT* M235T single nucleotide polymorphism showed a significant association with the DBP response to AE training, yet we found it to explain only 0.3% of the variability in the DBP response. Pairwise comparisons of *AGT* M235T genotypes

revealed those with the MM genotype reduced DBP 2.9 mmHg more in response to AE training compared to those with the *AGT* TT genotype.

Similar to AE training, the overall contribution of clinical sample features on the BP response to acute AE was large and significant, explaining 55.2% to 82.3% of the variability. In contrast, the contribution of candidate gene polymorphisms was marginally significant ( $P=0.08$ ), but did account for 21.4% to 24.5% of the BP response to acute AE. The contribution of individual polymorphisms on the BP response to acute AE could not be determined due to the small number of interventions and observations, and because all studies were derived from a single trial. In summary, our meta-analytic findings showed that clinical sample features explained a meaningful proportion of variance in the BP response to AE, ranging from 59.1% to 71.5% in response to AE training and 55.2% to 82.3% in response to acute AE, while the contribution of candidate gene polymorphisms modulating the BP response to AE was small and non-significant.

To date (to March 2013), 26 polymorphisms have been reported to be associated with the BP response to acute and chronic AE (Augeri et al, 2009; Blanchard et al., 2006; Delmonico et al., 2005; de Luis et al., 2006; Fairheller et al., 2009; Flavell et al., 2006; Franks et al., 2004; Grove et al., 2007; Hagberg et al., 1999; Hautala et al., 2006; Jones et al., 2006; Kilpelainen et al., 2008; Pescatello et al., 2007a; Pescatello et al., 2007b; Pescatello et al., 2009; Rankinen et al., 2000; Rankinen et al., 2002; Rankinen et al. 2007; Rauramaa et al., 2002; Rivera et al., 2001; Takakura et al., 2006; Vargas et al., 2013; Zateyschikov et al., 2007; Zhang et al., 2002). Of these, 16 polymorphisms include those involved with: 1) Renin Angiotensin System (RAS) and/or Renal Function [angiotensin converting enzyme (*ACE*) (rs4340), adducin 1 alpha (*ADD1*) (rs4961), angiotensinogen

(*AGT*) (rs699), angiotensin 2 type 1 receptor (*AGTR1*) (rs5186), and aldosterone synthase (*CYP11B2*) (rs1799998); 2) Sympathetic Nervous System [adenosine monophosphate deaminase 1 (*AMPD1*) (rs17602729), adrenergic receptor, beta 1 (*ADRB1*) (rs1801253), adrenergic receptor, beta 2 (*ADRB2*) (rs1042714), cholinergic receptor (*CHRM2*) (rs324640, rs8191992), guanine nucleotide binding protein system alpha subunit (*GNAS*) (rs7121), and guanine nucleotide binding protein, beta polypeptide 3 (*GNB3*) (rs5443)]; and 3) Nitric Oxide Synthase Pathway and/or Vascular Function [endothelin 1 (*EDN1*) (rs5370, rs2070699, rs5369), endothelial nitric oxide synthase (*NOS3*) (rs2070744), and transforming growth factor, beta 1 (*TGFB1*) (rs1800470)]. The remaining 10 polymorphisms are implicated in the etiology of HTN as established or emerging cardiovascular disease risk factors and include: 1) Dyslipidemia [apolipoprotein (*APOE*) (rs7412, rs429358), fatty acid binding protein 2 (*FABP2*) (rs1799883), and lipoprotein lipase (*LPL*) (rs328)]; 2) Obesity [leptin receptor (*LEPR*) (rs1137100)]; and 3) Inflammatory Biomarkers [cytochrome b-245 alpha polypeptide (*CYBA*) (rs4673, rs1049255), cytochrome P450 superfamily (*CYP2D6*) (rs1065852), and interleukin 6 receptor (*IL6R*) (rs2228145)].

Of the 26 polymorphisms reported to be associated with the BP response to AE, 16 met our inclusion criteria and were included in our meta-analysis. Of these, only one polymorphism emerged as significantly associated with the DBP response to exercise in our meta-analysis, *AGT* M235T, and explained only 0.3% of the variability. Our finding confirmed those of Rankinen and Rauramaa et al. in that the *AGT* M235T polymorphism was associated with the DBP response to AE training, with greater DBP reductions observed with the *AGT* MM genotype than the *AGT* TT genotype. (Rankinen et al., 2000;

Rauramaa et al., 2002). Furthermore, this single *AGT* M235T finding demonstrates the difficulty in identifying genetic variants that account for the variability in the response of health/fitness phenotypes to exercise like the BP response to AE.

A proposed mechanism for the influence of the *AGT* M235T (rs699) polymorphism on the DBP response to AE training is the reported difference in plasma AGT levels by genotype (Rankinen et al., 2000; Rauramaa et al., 2002). Jeunemaitre et al. found resting plasma AGT levels were lower among M versus T allele carriers (Jeunemaitre et al., 1992). AGT, a substrate of renin that is released by the liver when blood volume is low, generates angiotensin I that is converted by ACE to angiotensin II, a potent vasoconstrictor. Angiotensin II increases sodium reabsorption and total peripheral resistance, thereby elevating BP under resting conditions. Consequently, Rauramaa et al. postulated higher plasma AGT concentrations among those with the *AGT* TT genotype at rest may translate to an over reactivity of the RAS during exercise, ultimately inducing an overproduction of angiotensin II, and a more potent constriction of the arterioles that counteract both the vasodilatory and antihypertensive effects of exercise on BP (Rankinen et al., 2000; Rauramaa et al., 2002).

The most noteworthy finding of this meta-analysis was the clinically meaningful amount of BP response variability explained by clinical characteristics that included age, gender and resting BP, accounting for 34.2% to 82.4% of the BP response to AE training. Bouchard and Rankinen examined individual differences in the BP response to a 20-week AE training program among 481 sedentary, adult Caucasians from 98 two-generation families as part of the HERITAGE family study (Bouchard & Rankinen, 2000; Bouchard, et al., 2012). They found gender and resting SBP explained 1.6% and 32.0% of the SBP

response to AE training, respectively (Bouchard & Rankinen, 2000; Bouchard, et al. 2012). Likewise, Pescatello and Kulikowich reviewed the ambulatory BP response to acute dynamic AE in 23 studies that primarily enrolled sedentary, overweight, non-Hispanic white men and women with Pre-HTN (Pescatello & Kulikowich, 2001). They found resting BP accounted for 27.0% to 30.0% of the ambulatory SBP and 33.0% to 37.0% of the ambulatory DBP response to acute AE (Pescatello & Kulikowich, 2001). Criqui et al. found age explained 15.0% to 44.0% of the peak SBP response to a GXT among 4,262 men and women in the Lipid Research Clinics Program Prevalence Study (Criqui et al., 1983). The findings from Bouchard and Rankinen, Pescatello and Kulikowich, and Criqui et al. are consistent with ours and show that the clinical sample features of age, gender, and resting BP explain a clinically meaningful proportion of variance in the BP response to AE.

The present meta-analysis is subject to several limitations. These include the use of previously reported literature that contained a small number of studies. Despite our effort to increase the sample size by aggregating the existing literature, our sample remained underpowered to detect significant associations with individual polymorphisms occupying  $\leq 9$  effect size estimates. This was especially true in acute studies, which were derived from a single trial, making non-independence of acute analyses a threat. Nonetheless, recent work by Lander et al. suggests that certain epistatic interactions could be causing underestimations in the amount of explained heritability of complex phenotypes like the BP response to AE (Zuk, Hechter, Sunyaey, & Lander, 2012). Future research efforts should therefore move beyond analyses of individual candidate gene polymorphisms and examine multiple levels of gene regulation via high throughput

screening involving genes, their regulatory factors, and the proteins they produce to better explain this phenomenon of missing heritability (Ash, Eicher, & Pescatello, 2012).

The strengths of this study lie in the meta-analytic study design. The use of meta-analysis allowed us to systematically integrate and quantify the results of fifteen candidate gene association studies, thereby enabling our ability to circumvent the limitations of the literature by increasing the sample size and power to detect statistical associations with the BP response to AE. The overall study quality of included trials was another strength of this meta-analysis, with mean methodological quality scores of  $18.2 \pm 2.4$  and  $15.2 \pm 2.1$  for acute and chronic trials, respectively. This meta-analysis satisfied 15 of the 18 items listed on a modified version of the Assessment of Multiple Systematic Reviews (AMSTAR), a content-validated measurement tool used to assess the methodological quality of systematic reviews by addressing deficiencies in poorer quality reviews (Johnson et al. 2013; Shea et al., 2007) [Appendix E]. In addition to satisfying the items of AMSTAR, this meta-analysis also provided detailed descriptions of each study's geographical location, study population (i.e., age, BMI, ethnicity, gender, and BP status), and exercise intervention (i.e., *FITT*, supervision, and adherence).

In summary, the purpose of this meta-analysis was to circumvent the limitations of the literature on candidate gene association exercise studies by increasing the sample size to detect genetic associations with the BP response to AE. Despite the emergence of the *AGT* M235T polymorphism as a promising variant to explore in future research, the clinical sample features of age, gender, and resting BP explained most of the variability in the BP response to AE. Our findings reinforce the notion that most genetic variants explain only a small amount of variability in the response of health/fitness phenotypes to

exercise, if any. Our findings also indicate that research efforts seeking to explain the variability of health/fitness phenotypes to exercise such as BP should explore clinical features known to influence the phenotype of interest, as well as the multiple levels of gene regulation using high throughput screening in larger, more ethnically diverse samples of men and women with HTN.

## APPENDIX A

A Descriptive Summary of Candidate Gene Association Studies and the Blood Pressure Response to Aerobic Exercise.

Gene	rs Number	Location	MAF	FITT	Age	Gender (M/W)	Ethnicity	BMI	SBP/DBP	Author
<b>Renin Angiotensin System</b>										
<i>ACE</i>	rs4340 (I/D)	17q23	D (0.50)	Cycle GXT	51.8	66/0		25.9	133.0/83.0	Friedl 1996
<i>ACE</i>	rs4340 (I/D)	17q23	D (0.50)	Cycle, 40% & 60% VO <sub>2peak</sub>	43.8	50/0	Caucasian	29.4	145.3/85.9	Pescatello 2007
<i>ACE</i>	rs4340 (I/D)	17q23	D (0.50)	Cycle, 40% & 60% VO <sub>2peak</sub>	44.2	47/0	Caucasian	29.6	145.1/85.1	Blanchard, 2006
<i>ACE</i>	rs4340 (I/D)	17q23	D (0.50)	Cycle, 50 W, 10wk	50.5	16/48	Asian	23.6	153.0/94.0	Zhang 2002
<i>ACE</i>	rs4340 (I/D)	17q23	D (0.50)	Max cycle GXT, pre/post 20 wk, AE	35.7	229/247	Caucasian	25.9	116.2/65.9	Rankinen 2000
<i>ACE</i>	rs4340 (I/D)	17q23	D (0.50)	AE, 65% HRR, 1 wk	54.9	23/0	African	31.6	139.0/84.3	Jones 2006
<i>ACE</i>	rs4340 (I/D)	17q23	D (0.50)	AE, 75%-85% VO <sub>2max</sub> , 3x/wk, 36wk	61.3	18/0			153.0/93.3	Hagberg 1999
<i>AGT</i>	rs699 (T>C)	1q42-q43	C (0.34)	Max cycle GXT, pre/post 20 wk, AE	35.7	224/247	Caucasian	25.9	116.2/65.9	Rankinen 2000
<i>AGT</i>	rs699 (T>C)	1q42-q43	C (0.34)	AE, 75%-85% VO <sub>2max</sub> , 3x/wk	57.0	140/0		27.0	137.4/91.7	Rauramaa 2002
									130.0/81.4	
<i>AGT</i>	rs699 (T>C)	1q42-q43	C (0.34)	AE, 65% HRR, 1 wk	56.0	23/0	African	31.0	139.0/84.0	Jones 2006
<i>AGT</i>	rs699 (T>C)	1q42-q43	C (0.34)	AE, 10.000 steps/day, 24 wk	58.8	0/120	Asian	32.2	152.0/89.0	Takakura 2006
<i>AGT</i>	rs699 (T>C)	1q42-q43	C (0.34)	Cycle GXT	33.0	1903/0	Caucasian	24.2	132.0/82.0	Ortlepp 2003
<i>AGT</i>	rs699 (T>C)	1q42-q43	C (0.34)	ST, 1-2 sets, 15 reps, 3x/wk, 23wk	69.0	34/36		27.0	128.0/75.0	Delmonico 2005
					66.0			27.4	123.0/77.0	
<i>AGTR1</i>	rs5186 (A>C)	3q24	C (0.15)	ST, 1-2 sets, 15 reps, 3x/wk, 23wk	69.0	34/36		27.0	128.0/75.0	Delmonico 2005
					66.0			27.4	123.0/77.0	
<i>AGTR1</i>	rs5186 (A>C)	3q24	C (0.15)	Cycle, 40% & 60% VO <sub>2peak</sub>	43.8	50/0	Caucasian	29.4	145.3/85.9	Pescatello, 2007
<i>AGTR1</i>	rs5186 (A>C)	3q24	C (0.15)	Cycle, 40% & 60% VO <sub>2peak</sub>	44.2	47/0	Caucasian	29.6	145.1/85.1	Blanchard, 2006
<i>CYP11B2</i>	rs1799998 (C>T)	8q24.3	C (0.36)	Cycle, 40% & 60% VO <sub>2peak</sub>	44.2	47/0	Caucasian	29.6	145.1/85.1	Blanchard, 2006
<i>CYP2D6</i>	rs1065852 (G>A)	22q13.1	A (0.26)	GXT	52.2	35/36		28.5	136.4/84.7	Zateyschchikov 2007
<b>Sympathetic Nervous System</b>										
<b>Adrenergic System</b>										
<i>ADRB2</i>	rs1042714 (C>G)	5q31-q32	G (0.24)	GXT to 85% HRM	40.0	0/12			127.2/81.6	Macho-Azcarate 2002
<i>CHRM2</i>	rs324640 (C>T)	7q31-q35	C (0.43)	AE, 75% HRRR, 5x/wk, 2 wk	41.0	36/44		25.0	123.0/78.0	Hautala 2006
<i>CHRM2</i>	rs8191992 (A>T)	7q31-q35	T (0.48)	AE, 75% HRRR, 5x/wk, 2 wk	41.0	36/44		25.0	123.0/78.0	Hautala 2006
<b>Guanine Binding Proteins</b>										
<i>GNAS</i>	rs7121 (T>C)	20q13.2	C (0.38)	Cycle, 40% & 60% VO <sub>2peak</sub>	43.7	48/0	Caucasian	29.6	145.1/85.5	Pescatello, 2009

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						African		116.4/66.0		
<i>GNB3</i>	rs5443 (C>T)	12p13	T (0.48)	Habitual PA measurement	54.4	5199/5789	Caucasian	27.0		Grove 2007
					53.6	1429/2299	African	29.6		
<b>Nitric Oxide Synthase Pathway</b>										
<i>EDN1</i>	rs5370 (G>T)	6p24.1	T (0.21)	AE, 55%-75% VO <sub>2max</sub> , 3x/wk, 20 wk	35.8	240/253	Caucasian	25.8	116.4/66.1	Rankinen 2007
<i>EDN1</i>	rs2070699 (G>T)	6p24.1	T (0.40)	AE, 55%-75% VO <sub>2max</sub> , 3x/wk, 20 wk	35.8	240/253	Caucasian	25.8	116.4/66.1	Rankinen 2007
<i>EDN1</i>	rs5369 (A>G)	6p24.1	A (0.10)	AE, 55%-75% VO <sub>2max</sub> , 3x/wk, 20 wk	35.8	240/253	Caucasian	25.8	116.4/66.1	Rankinen 2007
<i>NOS3</i>	Not available	7q36	N/A	Habitual PA measurement	54.4	372/460	Asian	23.2	130.1/NA	Kimura 2003
<i>NOS3</i>	rs2070744 (T>C)	7q36	C (0.26)	Cycle 40% & 60% VO <sub>2peak</sub>	43.7	49/0	Caucasian	29.5	145.6/85.9	Augeri, 2009
<i>TGFB1</i>	rs1800470 (C>T)	19q13.2	C (0.44)	Max cycle GXT, pre/post 20 wk, AE	35.3	737	Caucasian	26.6	119.6/70.0	Rivera 2001
<b>Energy Metabolism</b>										
<i>APOE</i>	rs7412 (C>T)	19q13.2	T (0.07)	AE, 75%-85% VO <sub>2max</sub> , 3x/wk, 36wk	60.5	18/0				Hagberg 1999
<i>APOE</i>	rs2223989 (C>T)	19q13.2	C (0.47)	AE, 75%-85% VO <sub>2max</sub> , 3x/wk, 36wk	60.5	18/0				Hagberg 1999
<i>LEPR</i>	rs1137100 (A>G)	1p31	G (0.39)	PA & supervised ST	55.4	162/325	Caucasian	31.3		Kilpelainen 2008
<i>LPL</i>	rs328 (C>G)	8p22	G (0.10)	AE, 75%-85% VO <sub>2max</sub> , 3x/wk, 36wk	60.5	18/0				Hagberg 1999
<i>LPL</i>	rs328 (C>G)	8p22	G (0.10)	ST and AE, 10 wk	19.6	146/0	Caucasian	23.1	117.5/66.1	Flavell 2006
<i>IL6R</i>	rs2228145 (A>C)	1q21.3	C (0.32)	AE, 60%-70% MHR, 3x/wk, 12wk	50.9	22/60	Caucasian		130.4/80.7	Vargas 2013
<b>Other</b>										
<i>ADD1</i>	rs4961 (G>T)	4p16.3	T (0.25)	Cycle, 40% & 60% VO <sub>2peak</sub>	43.7	48/0	Caucasian	29.6	145.1/85.5	Pescatello, 2007
<i>ADD1</i>	rs4961 (G>T)	4p16.3	T (0.25)	GXT, age-specific THR	53.2	20/29	Caucasian	29.2	124.4/81.4	Alioglu 2010
<i>FABP2</i>	rs1799883 (C>T)	4q28-q31	T (0.25)	AE, 3x/wk	43.5	69/0		34.1	129.8/76.1	de Luis 2006
<i>CYBA</i>	rs4673 (C>T)	16q24	T (0.31)	AE, 50% VO <sub>2max</sub> , 3x/wk, 24 wk	58.7	44/50		29.9	132.9/87.2	Fairheller 2009
<i>CYBA</i>	rs1049255 (A>G)	16q24	A (0.50)	AE, 50% VO <sub>2max</sub> , 3x/wk, 24 wk	58.6	44/50		29.0	132.9/87.1	Fairheller 2009

Abbreviations. BMI= body mass index. d-wk-1= days per week. DBP= diastolic blood pressure. k= number of cases. kg·m<sup>-2</sup>= kilograms per meter squared. M= mean. MAF= mean allele frequency. min-session-1= minutes per session. mmHg= millimeters of mercury. SBP= systolic blood pressure. SD= standard deviation. VO<sub>2max</sub>= maximal oxygen consumption. wk= week. yr= years. Gene abbreviations. ACE= angiotensin converting enzyme. AGT= angiotensinogen. ADD1= adducin 1 alpha. AGTR1= angiotensin 2 type 1 receptor. AMPD1= adenosine monophosphate deaminase 1. ADRB1= adrenergic receptor, beta 1. ADRB2= adrenergic receptor, beta 2. CHRM2= cholinergic receptor. CYBA= cytochrome b-245 alpha polypeptide. CYP11B2= aldosterone synthase. CYP2D6= cytochrome P450 superfamily. EDN1= endothelin 1. GNAS= guanine nucleotide binding protein system alpha subunit. GNB3= guanine nucleotide binding protein system alpha subunit. IL6R= interleukin 6 receptor. LPL= lipoprotein lipase. NOS3= endothelial nitric oxide synthase. TGFB1= transforming growth factor, beta 1.

## APPENDIX B

### PubMed Search Strategy

**Blood Pressure:** ("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 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")

**Exercise:** ("exercise"[mesh] OR exercise OR exercises OR running[mesh] OR "bicycle" OR "bicycles" OR "bicycling" OR walking[mesh] OR treadmill\* OR "weight lifting" OR "weight training" OR "weight bearing" OR "resistance training" OR "strength training" OR "endurance training" OR "speed training" OR "training duration" OR "training frequency" OR "training intensity" OR "aerobic endurance")

**Randomized Control Trial:** ("randomized controlled trial"[pt] OR "nonrandomized controlled" OR "nonrandomized control" OR controlled clinical trial[pt] OR "randomized controlled trial"[publication type] OR random allocation[mh] OR clinical trial[pt] OR "comparative study" OR "comparative studies" OR clinical trials[mh] 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])

**Gene:** ("gene" OR "genes" OR "genotype" OR "genotypes" OR "snp" OR polymorphism\* OR "DNA" OR "minor allele" OR "minor alleles" OR "single nucleotide polymorphism" OR "single nucleotides polymorphisms" OR genetic\*)

**Exclusion Search Terms:** ("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 "diet therapy"[mesh] OR "diet therapy"[subheading] OR "caffeine" OR "eating change" OR "activities of daily living" OR "dehydration" OR "dehydrate")

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OR "dehydrated" OR "dietary salt" OR "epilepsy" OR "influenza" OR "flu" OR "pneumonia"  
OR "septicemia" OR "hiv" OR "Acquired Immunodeficiency Syndrome" OR "meningitis" OR  
"substance abuse" OR "alcoholism" OR "drug abuse" OR "Cross-Sectional Studies"[MeSH  
Terms] OR "Prospective Studies"[MeSH Terms] OR "epidemiology"[Subheading])

**Abbreviations:** Medical Subject Heading=Mesh; MeSH Terms=mh; Text Word=tw;  
Title/Abstract Words=tiab; Publication Type=pt.

APPENDIX C

**Candidate Gene Meta-Analysis Selection Criteria Checklist**

Study ID: \_\_\_\_\_

Coder: \_\_\_\_\_

**Candidate Gene Meta-Analysis Selection Criteria**

Inclusion Criteria Trials <b>MUST</b> include all of the following:	Exclusion Criteria Trials <b>CANNOT</b> include any of the following:
An acute and/or chronic aerobic exercise intervention <input type="checkbox"/>	Cancer survivors <input type="checkbox"/>
A case-control, cross-sectional, or family based study design (Note: A non-exercise control or comparison group is required for all trials; and, a non-exercise control group or session is <b>required for all acute trials</b> ) <input type="checkbox"/>	Fibromyalgia <input type="checkbox"/>
Exercise intervention(s) involve all parameters of the <b>FITT (Note: all FITT parameters must be satisfied for inclusion):</b> <input type="checkbox"/>	Alzheimer’s disease <input type="checkbox"/>
Frequency <input type="checkbox"/>	Pregnant women <input type="checkbox"/>
Intensity <input type="checkbox"/>	Persons on weight-loss drugs, or undergoing dietary modifications and/or therapy <input type="checkbox"/>
Time <input type="checkbox"/>	Dehydration studies <input type="checkbox"/>
Type <input type="checkbox"/>	Epileptics <input type="checkbox"/>
A pre- <b>and</b> post-exercise blood pressure measurement by genotype <input type="checkbox"/>	Influenza, flu, or pneumonia <input type="checkbox"/>
A candidate gene polymorphism(s) <input type="checkbox"/>	Septicemia <input type="checkbox"/>
Adults (age 19+) <input type="checkbox"/>	HIV/AIDs <input type="checkbox"/>
	Meningitis <input type="checkbox"/>
	Substance abusers <input type="checkbox"/>
	Alcoholics <input type="checkbox"/>
	Prospective studies <input type="checkbox"/>
	Epidemiologic studies <input type="checkbox"/>

Note

## APPENDIX D

### CANDIDATE GENE ASSOCIATION STUDIES ON THE BLOOD PRESSURE RESPONSE TO ACUTE AND CHRONIC AEROBIC EXERCISE META-ANALYSIS CODING FORM

*Revised 8 April 2011*

*For any missing or unreported data, indicate with “.”*

(V1) CODER \_\_\_\_\_ Coder (Mike = 1, Kara = 2)

#### **Study Information**

(V2) ID \_\_\_\_\_ Study **ID #** Study Citation (AuthorYearJournal):

\_\_\_\_\_  
*(Use journal format from PubMed)*

(V3) PUB\_YR \_\_\_\_\_ Publication **year** (*consider this missing if unpublished*)

(V4) DATA \_\_\_\_\_ Estimated **year of data collection** (*earliest date for data collection or manuscript submission/publication; if unpublished and date unknown, use year manuscript was acquired; for dissertation or thesis, use year*)

(V5) LANG. \_\_\_\_\_ Language of **publication**

1=English

2=Spanish

3=Japanese

4=Other, specify: \_\_\_\_\_

(V6) SOURCE \_\_\_\_\_ **Source:**

1=Journal

2=Book

3=Thesis/Dissertation

4=Conference Paper

5=Unpublished Document

(V7) SCORE \_\_\_\_\_ **Impact Score of the Journal** (*use ISI Web of Knowledge journal citation reports*)

(V8) \_\_\_\_\_ **Notes on intervention within study relevant to coding (if more than one intervention in study)**

---

#### **Sample Characteristics** (*proportion: 0.0- 1.0*)

(V9) ETH \_\_\_\_\_ Ethnicity **reported?** 1 = Yes; 0 = No

(V10) PROP\_WH \_\_\_\_\_ Proportion White; if whole number available: \_\_\_\_\_

(V11) PROP\_BLK \_\_\_\_\_ Proportion Black; if whole number available: \_\_\_\_\_

(V12) PROP\_HISP \_\_\_\_\_ Proportion Latino/Hispanic; if whole number available: \_\_\_\_\_

(V13) PROP\_CARIB \_\_\_\_\_ Proportion Caribbean; if whole number available: \_\_\_\_\_

(V14) PROP\_ASIAN \_\_\_\_\_ Proportion Asian; if whole number available: \_\_\_\_\_

(V15) PROP\_MIX \_\_\_\_\_ Proportion Mixed/other; if whole number available: \_\_\_\_\_

(V16) EDU \_\_\_\_\_ Education **reported?** 1 = Yes; 0 = No

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- (V17) PROP\_HS \_\_\_\_\_ Proportion high school; if whole number available: \_\_\_\_\_
- (V18) PROP\_COL \_\_\_\_\_ Proportion college; if whole number available: \_\_\_\_\_
- (V19) PROP\_GRAD \_\_\_\_\_ Proportion graduate school; if whole number available: \_\_\_\_\_
- (V20) SES \_\_\_\_\_ **SES reported?** 1 = Yes; 0 = No
- (V21) PROP\_LOW \_\_\_\_\_ Proportion of low SES Low (< 25k)
- (V22) PROP\_MID \_\_\_\_\_ Proportion of middle SES (25k-100k)
- (V23) PROP\_HIGH \_\_\_\_\_ Proportion of high SES (>100k)
- (V24) #FEMALE \_\_\_\_\_ **# of females in sample**
- (V25) REGION \_\_\_\_\_ **Region of sample**  
 1=American city: \_\_\_\_\_  
 2=Other U.S. general region (*city not specified*): \_\_\_\_\_  
 3=Canada (city: \_\_\_\_\_)  
 4=Europe (city: \_\_\_\_\_)  
 5=South or Central America, Mexico, Caribbean (city: \_\_\_\_\_)  
 6=Africa (city: \_\_\_\_\_)  
 7=Asia (city: \_\_\_\_\_)  
 8=Australia (city: \_\_\_\_\_)
- (V26) US\_ZIP \_\_\_\_\_ **Zip Code (US Only)** \_\_\_\_\_
- (V27) POP \_\_\_\_\_ **Population**  
 0=Not reported  
 1=School or college  
 2=Community, not currently institutionalized; specify source (e.g., cancer clinic including University cancer treatment facilities):  
 \_\_\_\_\_  
 3=Community, institutionalized; specify source (e.g., inpatient cancer treatment center; currently hospitalized):  
 \_\_\_\_\_
- (V28) \_\_\_\_\_ **Notes on sample characteristics relevant to coding**
- 

**Risk Characteristics** (if SEM, change to SD;  $SD = SEM * \sqrt{n}$ ; use DSTAT to pool variances if applicable)

- (V29) AGE \_\_\_\_\_ **Mean age of total sample (years)**
- (V30) AGE\_SD \_\_\_\_\_ **SD for age (years)**
- (V31) HT \_\_\_\_\_ **Mean height of total sample (cm)**
- (V32) HT\_SD \_\_\_\_\_ **SD of height (cm)**
- (V33) WT \_\_\_\_\_ **Mean weight of total sample (kg)**
- (V34) WT\_SD \_\_\_\_\_ **SD of weight (kg)**
- (V35) WAIST \_\_\_\_\_ **Mean waist circumference of total sample (cm)**
- (V36) WAIST\_SD \_\_\_\_\_ **SD of waist circumference (cm)**
- (V37) W-H \_\_\_\_\_ **Mean waist-to-hip ratio of total sample**
- (V38) W-H\_SD \_\_\_\_\_ **SD of waist-to-Hip Ratio**
- (V39) BMI \_\_\_\_\_ **Body mass index of total sample (BMI,  $\text{kg}\cdot\text{m}^{-2}$ )**  
 (if calculating, use NHLBI equation)
- (V40) BMI\_SD \_\_\_\_\_ **SD of BMI**
- (V41) BMI\_NORM \_\_\_\_\_ **Proportion normal weight (18.5-24.9)**
- (V42) BMI\_OVER \_\_\_\_\_ **Proportion overweight (25.0-29.9)**
- (V43) BMI\_OBESE1 \_\_\_\_\_ **Proportion obese, Class I (30.0-34.9)**

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- (V44) BMI\_OBESE2 \_\_\_\_\_ Proportion **obese, Class II (35.0-39.9)**
- (V45) BMI\_OBESE3 \_\_\_\_\_ Proportion **obese, Class III ( $\geq 40.0$ )**
- (V46) BF% \_\_\_\_\_ Mean **value of body composition of total sample (Body Fat %)**
- (V47) BF%\_SD \_\_\_\_\_ **SD of body fat %**
- (V48) BF%\_ASS. \_\_\_\_\_ **Method of body fat % assessment**  
1=Skinfold thickness  
2=Hydrostatic weighing  
3=Bioelectrical impedance, specify: \_\_\_\_\_  
4=Air displacement plethysmography, specify: \_\_\_\_\_  
5=Dual energy x-ray absorptiometry (DEXA), specify: \_\_\_\_\_  
6=Other, specify: \_\_\_\_\_
- (V49) PROP\_HD \_\_\_\_\_ Proportion **of total sample with history of heart disease in immediate family members before age 55; if whole number available** \_\_\_\_\_
- (V50) PROP\_HTN \_\_\_\_\_ Proportion **of total sample with hypertension in immediate family members; if whole number available** \_\_\_\_\_
- (V51) DISEASE \_\_\_\_\_ **Known disease(s) or chronic condition(s) of total sample**  
0= Subjects were free of disease(s)/chronic condition(s)  
1= Pre-Hypertension  
2= Hypertension, specify stage: \_\_\_\_\_  
3= Cardiovascular disease(s) (coronary artery disease, peripheral artery disease, congestive heart failure, myocardial infarction)  
4= Stroke  
5= Diabetes  
6= Metabolic Syndrome (MetS)  
7= Arthritis  
8= Other, specify: \_\_\_\_\_  
9= Multiple, specify #s: \_\_\_\_\_
- (V52) CHF \_\_\_\_\_ **If congestive heart failure, indicate functional classification (according to NYHA criteria)**  
0= Not applicable  
1= Class I  
2= Class II  
3= Class III  
4= Class IV  
5= Multiple, specify #'s \_\_\_\_\_
- (V53) MetS \_\_\_\_\_ **If Metabolic Syndrome (MetS), what grouping system was used to define**  
0= Not applicable  
1= Specify: \_\_\_\_\_
- (V54) PROP\_SED \_\_\_\_\_ Proportion **of sample that was sedentary ( $\leq 2d \cdot wk^{-1}$  of regular physical activity); if whole number available** \_\_\_\_\_
- (V55) MED \_\_\_\_\_ Medication **use (0=No, 1= Yes)**

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- (V56) MED\_TYPE \_\_\_\_\_ Medication **Type**  
1=  $\beta$  Blockers  
2= Nitrates  
3= Calcium Channel Blockers  
4= Angiotensin Converting Enzyme (ACE) Inhibitors  
5= Diuretics  
6= Vasodilators, non-adrenergic  
7= NSAIDs  
8= Aspirin  
9= Other, specify: \_\_\_\_\_  
10= Multiple, specify numbers: \_\_\_\_\_
- (V57) O/C\_USE \_\_\_\_\_ Oral **Contraceptive use** (0=No, 1= Yes)
- (V58) CAFFEINE\_USE \_\_\_\_\_ Number of days per week of caffeine consumption  
(V59) CAFFEINE\_DR \_\_\_\_\_ Number of caffeinated beverages per day  
(V60) CAFFEINE\_WK \_\_\_\_\_ Number of caffeinated beverages per week  
(V61) PROP\_CAF \_\_\_\_\_ Proportion **of sample with regular caffeine consumption; if whole number available** \_\_\_\_\_
- (V62) ETOH\_USE \_\_\_\_\_ Number of days per week of alcohol consumption  
(V63) ETOH\_DR \_\_\_\_\_ Number of alcoholic drinks per day  
(V64) ETOH\_WK \_\_\_\_\_ Number of alcoholic drinks per week  
(V65) PROP\_ETOH \_\_\_\_\_ Proportion **of sample reporting regular alcohol consumption; if whole number available** \_\_\_\_\_
- (V66) SMOKING \_\_\_\_\_ **Currently smoking, or smoked within last 6 months** (0= No, 1= Yes)  
(V67) SMOKING\_YRS \_\_\_\_\_ Number of years smoking  
(V68) SMOKE\_PACK \_\_\_\_\_ Number of packs per week (*calculate in data base pack/ year*)  
(V69) PROP\_SMOKE \_\_\_\_\_ Proportion **of sample currently smoking or smoked within the last 6 months? ; if whole number available** \_\_\_\_\_
- (V70) \_\_\_\_\_ **Notes on risk characteristics relevant to coding**
- 

### *Methods & Design*

- (V71) RECRUIT \_\_\_\_\_ **Recruitment method**  
1=Self-selected from community (via flyers, community centers, etc.)  
2=Recruited through clinical contact  
3=Recruited through hospital  
4=Other, specify: \_\_\_\_\_
- (V72) CON\_GRP \_\_\_\_\_ **Type of control group used**  
1= Random assignment of individuals to conditions including a non-exercise control group  
2= Random assignment of individuals to conditions including a non-exercise control session  
3= Random assignment of individuals to conditions including a control group of stretching or yoga  
4= Other, specify: \_\_\_\_\_
- 
- (V73) #F/U \_\_\_\_\_ **Number of follow-ups:** \_\_\_\_\_  
(0=acute, 1= pre/post design)

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(V74) F/U\_INT. \_\_\_\_\_ Interval of follow-ups: \_\_\_\_\_  
(0=acute,1= pre/post design)  
(# of follow-ups refer to the assessments completed post intervention, i.e. 3, 6, 12 months post study)

(V75) \_\_\_\_\_ Notes on methods & study design relevant to coding

---

### ***Mechanism***

(V76) MECH \_\_\_\_\_ Mechanism  
0= None reported  
1= Genetic  
2= Neural  
3= Vascular  
4= Renal  
5= Other, specify: \_\_\_\_\_  
6= Multiple, specify #s: \_\_\_\_\_

(V77) \_\_\_\_\_ Notes on mechanisms relevant to coding

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(V78) BIO PATH \_\_\_\_\_ Major Biological Pathway  
0= None  
1= Renal/Renin Angiotensin System  
2= Sympathetic Nervous System  
3= Nitric Oxide Synthase Pathway  
4= Energy Metabolism  
5= Inflammation/Thrombosis/ Hemostasis  
6= Other

(V79) \_\_\_\_\_ Notes on mechanisms relevant to coding

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### Study Quality

#### Downs and Black tool (Downs and Black 1998)

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1. Is the hypothesis/aim/objective of the study clearly described?

Yes	1
No	0

2. Are the main outcomes to be measured clearly described in the Introduction or Methods section?

Yes	1
No	0

3. Are the characteristics of the patients included in the study clearly described?

Yes	1
No	0

4. Are the interventions of interest clearly described?

Yes	1
No	0

5. Are the distributions of principal confounders in each group of subjects to be compared clearly described?

Yes	2
Partially	1
No	0

6. Are the main findings of the study clearly described?

Yes	1
No	0

7. Does the study provide estimates of the random variability in the data for the main outcomes?

Yes	1
No	0

8. Have all important adverse events that may be a consequence of the intervention been reported?

Yes	1
No	0

9. Have the characteristics of patients lost to follow-up been described?

Yes	1
No	0

10. Have actual probability values been reported (e.g. 0.035 rather than  $<0.05$ ) for the main outcomes except where the probability value is less than 0.001?

Yes	1
No	0

#### External validity

All the following criteria attempt to address the representativeness of the findings of the study and whether they may be generalised to the population from which the study subjects were derived.

11. Were the subjects asked to participate in the study representative of the entire population from which they were recruited?

Yes	1
No	0
Unable to determine	0

12. Were those subjects who were prepared to participate representative of the entire population from which they were recruited?

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Yes	1
No	0
Unable to determine	0

13. Were the staff, places, and facilities where the patients were treated, representative of the treatment the majority of patients receive?

Yes	1
No	0
Unable to determine	0

### **Internal validity - bias**

14. Was an attempt made to blind study subjects to the intervention they have received?

For studies where the patients would have no way of knowing which intervention they received, this should be answered yes.

Yes	1
No	0
Unable to determine	0

15. Was an attempt made to blind those measuring the main outcomes of the intervention?

Yes	1
No	0
Unable to determine	0

16. If any of the results of the study were based on “data dredging”, was this made clear?

Yes	1
No	0
Unable to determine	0

17. In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients, or in case-control studies, is the time period between the intervention and outcome the same for cases and controls?

Yes	1
No	0
Unable to determine	0

18. Were the statistical tests used to assess the main outcomes appropriate?

Yes	1
No	0
Unable to determine	0

19. Was compliance with the intervention/s reliable?

Yes	1
No	0
Unable to determine	0

21. Were the patients in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited from the same population?

Yes	1
No	0
Unable to determine	0

22. Were study subjects in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited over the same period of time?

Yes	1
No	0
Unable to determine	0

23. Were study subjects randomised to intervention groups?

Yes	1
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No	0
Unable to determine	0

24. Was the randomised intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable?

Yes	1
No	0
Unable to determine	0

25. Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?

Yes	1
No	0
Unable to determine	0

26. Were losses of patients to follow-up taken into account?

Yes	1
No	0
Unable to determine	0

### Power

27. Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%? Sample sizes have been calculated to detect a difference of x% and y%.

	Size of smallest intervention group	
A	$<n_1$	0
B	$n_1 - n_2$	1
C	$n_3 - n_4$	2
D	$n_5 - n_6$	3
E	$n_7 - n_8$	4
F	$n_{8+}$	5

**Total Score:** 26

(V80) STUDY\_QUAL \_\_\_\_\_ **Total study quality score** (out of a possible 31 points)

### Experiment/Intervention Conditions

(V81) EXPERIMENT \_\_\_\_\_ **Experimental condition(s)**  
Independent groups (between-subjects design; participant only experiences one condition)

- 1= Non-exercise control/comparison + one experimental group
- 2= Non-exercise control/comparison + two experimental groups
- 3= Non-exercise control/comparison + three experimental groups

Non-Independent groups (within-subjects design; participant experiences more than one condition)

- 4= Non-exercise control/comparison + one experimental condition
- 5= Non-exercise control/comparison + two experimental conditions
- 6= Non-exercise control/comparison + three experimental conditions

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(V82) EXP\_SETTING \_\_\_\_\_ **Setting of Experiment/ Intervention**  
1= Hospital  
2= Clinic  
3= Academic Research Laboratory  
4= Fitness Center, Gym  
5= Other, specify: \_\_\_\_\_  
6= Multiple, specify: \_\_\_\_\_

(V83) PERSP \_\_\_\_\_ **Theoretical perspective:**  
0= None specified  
1= Psychological  
2= Other, specify \_\_\_\_\_

(V84) BEHAV\_TECH \_\_\_\_\_ **Behavioral technique used in study?**  
0= None  
1= Yes, specify (*positive reinforcement, modeling, contingency management, exercise and lifestyle information provided, etc.*)

(V85) INTER\_LVL \_\_\_\_\_ **Level of intervention used in the study**  
1=Primarily one-on-one (e.g., individual counseling sessions)  
2=Small group processes (interaction between leader and group, and group members)  
3=Supervised session(s)  
4=Unsupervised session(s)  
5=Multiply, specify #'s: \_\_\_\_\_

(V86) \_\_\_\_\_ **Notes on experiment/intervention conditions relevant to coding**

---

### *Candidate Gene Polymorphisms*

(V87) QUANT\_GENES \_\_\_\_\_ **Number of candidate genes examined**

(V88) GENE\_NAME \_\_\_\_\_ **Name of candidate gene (s) examined**

\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

(V89) QUANT\_SNP \_\_\_\_\_ **Number of SNPs examined**

(V90) SNP\_TEST \_\_\_\_\_ **Specific SNP(s) examined (include RS #'s if available)**

\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

(V91) CHROM\_NUMB \_\_\_\_\_ **Chromosome number(s)**

\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

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- (V92) CHROM\_BAND \_\_\_\_\_ **Chromosome band(s)**  
\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_
- (V93) CHROM\_SUB \_\_\_\_\_ **Chromosome sub-band(s)**  
\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_
- (V94) DESIGN \_\_\_\_\_ **Study design**  
1=Case-control  
2=Cross-sectional  
3=Family-based
- (V95) SNP\_RATION \_\_\_\_\_ **Rationale for SNP selection**  
1=Allele frequency  
2=Literature search  
3=Follow-up to GWAS
- (V96) SOURCE \_\_\_\_\_ **Source of samples**  
1=Clinic  
2=Population  
3=Athletes
- (V97) TECH \_\_\_\_\_ **Sampling technique(s)**  
1=Buccal swab  
2=Blood
- (V98) COMB\_MODEL \_\_\_\_\_ **Combination model**  
1=Dominant  
2=Recessive  
3=Co-dominant  
4=Incomplete/Semi-dominant
- (V99) OUTCOME \_\_\_\_\_ **Outcome**  
1=Positive  
2=Negative  
3=Trend
- (V100) MAJ\_FREQ \_\_\_\_\_ **Major Allele Frequency**  
(V112a)  
1=Stated in paper  
2=Calculated from paper  
3=Obtained from authors  
4=Unknown  
(V112b) \_\_\_\_\_ Case frequency  
(V112c) \_\_\_\_\_ Control frequency
- (V101) MIN\_FREQ \_\_\_\_\_ **Minor Allele Frequency**  
(V112a)  
1=Stated in paper  
2=Calculated from paper  
3=Obtained from authors  
4= Unknown  
(V112b) \_\_\_\_\_ Case frequency

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- (V112c) \_\_\_\_\_ Control frequency
- (V102) HWE \_\_\_\_\_ **Hardy Weinberg Equilibrium**  
1=Yes  
2=No  
3=Not stated
- (V103) LD \_\_\_\_\_ **Linkage Disequilibrium**  
1=Low (<. 5)  
2=Marginal (.6-.8)  
3=High (>.8)

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### CANDIDATE GENE CODING INFORMATION

*For Polymorphisms Studied by at Least One Paper*

VARIABLE	<i>List interventions from LOWEST intensity to HIGHEST intensity</i>			
	CONTROL	AEROBIC #1	AEROBIC #2	AEROBIC #3
(V104) <b>Subgroup</b> ( <i>i.e. men, women, hypertensive, normotensive, white, black, etc.</i> ), specify: _____ (0=Not applicable)				
(V105) GENE_NAME Name of candidate genes examined: _____				
(V106) SNP_TEST Specific SNP examined (include RS #'s if available): _____				
(V107) CHROM_NUMB Chromosome number _____				
(V108) CHROM_BAND Chromosome band _____				
(V109) CHROM_SUB Chromosome sub-band _____				
(V110) FUNCT Function (1=missense, 2=nonsense, 3=coding synonymous, 4=neargene-3, 5=neargene-5, 6=3'-UTR, 7=5'-UTR, 8=intron) _____				
(V111) # PART_BEG # of participants at beginning of intervention				
(V112) # PART_END # of participants at end of intervention				
(V113) # PART_LOST # of participants lost during intervention				
(V114) ADHERENCE Mean participant adherence ( $\frac{\text{completed sessions}}{\text{total sessions}}$ ) x100				
(V115) EX_INTENSITY Exercise intensity ( <i>specify method used to calculate intensity</i> ) 0=Control/Non-exercise comparison group/session (Note. If ranges are reported, compute the mean or average value)				
(V116) EX_TYPE Exercise modality 0=Control (non-exercise comparison) 1= Aerobic, treadmill 2= Aerobic, cycle ergometer 3= Other, specify: _____ 4= Multiple, specify numbers: _____				
(V117) EX_LENGTH Length of intervention (weeks) 0=Acute				
(V118) FREQ_SESSION Exercise Frequency (sessions per week) 0=Acute				
(V119) FREQ_WK Exercise Frequency (min per week) 0=Acute				
(V120) EX_TOTAL Total Exercise Duration (min per week)				

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(V121) EX_W/UP Warm-up (min per session)				
(V122) EX_TIME Exercise (min per session)				
(V123) EX_C/D Cool down (min per session)				
(V124) VAR_ALTER Study Variable manipulated 0= Control/ Non-exercise comparison 1=Exercise duration 2=Exercise intensity 3=Exercise frequency 4=Exercise modality 5=Exercise volume 6=Exercise vs. Control 7=Multiple, specify #s: _____				
(V125) ΔVO <sub>2</sub> VO <sub>2max</sub> change ( <i>specify method used to calculate intensity</i> ) 0= Acute				
(V126) BP_ASSESS BP Measurement 1=Manual 2=Ambulatory (ABP), hrs monitored: _____ 3=Automated 4=Multiple, specify #s_____				
(V127) BP_POSITION BP Measurement Position 1=Seated 2=Standing 3=Supine 4=Multiple, specify #s_____				
(V128) BP_BASE Duration prior to baseline BP assessment (min) ( <i>insert continuous variable, or "." if none or missing</i> )				
(V129) SBP_INITIAL Initial SBP (mmHg)				
(V130) INITIAL_SD SD of Initial SBP (mmHg)				
(V131) SBP_POST Post SBP (mm Hg)				
(V132) POST_SD SD of Post SBP (mmHg)				
(V133) SBP_ABΔ Absolute change SBP (mmHg) ( <i>if not calculated, insert "." and calculate in spreadsheet</i> )				
(V134) ABΔ_SD SD of Absolute change SBP (mmHg)				
(V135) DBP_INITIAL Initial DBP (mmHg)				
(V136) INITIAL_SD SD of Initial DBP (mmHg)				
(V137) DBP_POST				

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Post DBP (mmHg)				
(V138) POST_SD SD of Post DBP (mmHg)				
(V139) DBP_ABΔ Absolute change DBP (mmHg) <i>(if not calculated, insert “.” and calculate in spreadsheet)</i>				
(V140) ABA_SD SD of Absolute change DBP (mmHg)				
(V141) BP_POST Time of Post BP assessment (min) <i>(insert continuous variable, or “.” if none or missing)</i>				
(V142) MAP MAP (mm Hg) <i>(if not calculated, insert “.” and calculate in spreadsheet)</i>				

VARIABLE	<i>List interventions from LOWEST intensity to HIGHEST intensity</i>			
	CONTROL	STRENGTH #1	STRENGTH #2	STRENGTH #3
(V143) <b>Subgroup</b> <i>(i.e. men, women, hypertensive, normotensive, white, black, etc.)</i> , specify: _____ (0=Not Applicable)				
(V144) GENE_NAME Name of candidate genes tested: _____				
(V145) SNP_TEST Specific SNP examined (include RS #'s if available): _____				
(V146) CHROM_NUMB Chromosome number _____				
(V147) CHROM_BAND Chromosome band _____				
(V148) CHROM_SUB Chromosome sub-band _____				
(V149) FUNCT Function (1=missense, 2=nonsense, 3=coding synonymous, 4=neargene-3, 5=neargene-5, 6=3'-UTR, 7=5'-UTR, 8=intron) _____				
(V150) #PART_BEG # of participants at beginning of intervention				
(V151) #PART_END # of participants at end of intervention				
(V152) #PART_LOST # of participants lost during intervention				
(V153) ADHERENCE Mean participant adherence $\left(\frac{\text{completed sessions}}{\text{total sessions}}\right) * 100$				
(V154) EX_INTENSITY Exercise intensity <i>(specify method used to calculate intensity)</i> 0=Control/Non-exercise comparison group/session (Note. If ranges are reported, compute the mean or average value)				
(V155) EX_TYPE Exercise modality 0=Control (non-exercise comparison) 1=Dynamic resistance training (free weights) 2=Dynamic resistance training (machine)				

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weights) 3=Isometric resistance training 4=Other, specify: _____ 5=Multiple, specify numbers: _____				
(V156) EX_LENGTH Length of intervention (weeks) 0=Acute				
(V157) FREQ_SESSION Exercise Frequency (sessions per week) 0=Acute				
(V158) FREQ_WK Exercise Frequency (min per week) 0=Acute				
(V159) EX_TOTAL Total Exercise Duration (min per week)				
(V160) EX_W/UP Warm-up (min per session)				
(V161) EX_TIME Exercise (min per session)				
(V162) EX_C/D Cool down (min per session)				
(V163) EX_SETS Total # of sets performed in session				
(V164) EX_REPS Total # of reps performed in one set				
(V165) VAR_ALTER Study Variable manipulated 0=Control/Non-exercise comparison 1=Exercise duration 2=Exercise intensity 3=Exercise frequency 4=Exercise modality 5=Exercise volume 6=Exercise vs. Control 7=Multiple, specify #s: _____				
(V166) ΔVO <sub>2</sub> VO <sub>2max</sub> change ( <i>specify method used to calculate intensity</i> ) 0=Acute				
(V167) BP_ASSESS BP Measurement 1=Manual 2=Ambulatory (ABP), hrs monitored: _____ 3=Automated 4=Multiple, specify #s _____				
(V168) BP_POSITION BP Measurement Position 1=Seated 2=Standing 3=Supine 4=Multiple, specify #s _____				
(V169) BP_BASE Duration prior to baseline BP assessment (min) ( <i>insert continuous variable, or “.” if none or missing</i> )				
(V170) SBP_INITIAL				

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Initial SBP (mmHg)				
(V171) INITIAL_SD SD of Initial SBP (mmHg)				
(V172) SBP_POST Post SBP (mmHg)				
(V173) POST_SD SD of Post SBP (mmHg)				
(V174) SBP_ABΔ Absolute change SBP (mmHg) <i>(if not calculated, insert "." and calculate in spreadsheet)</i>				
(V175) ABΔ_SD SD of Absolute change SBP (mmHg)				
(V176) DBP_INITIAL Initial DBP (mmHg)				
(V177) INITIAL_SD SD of Initial DBP (mmHg)				
(V178) DBP_POST Post DBP (mmHg)				
(V179) POST_SD SD of Post DBP (mmHg)				
(V180) DBP_ABΔ Absolute change DBP (mmHg) <i>(if not calculated, insert "." and calculate in spreadsheet)</i>				
(V181) ABΔ_SD SD of Absolute change DBP (mmHg)				
(V182) BP_POST Time of Post BP assessment (min) <i>(insert continuous variable, or "." if none or missing)</i>				
(V183) MAP MAP (mmHg) <i>(if not calculated, insert "." and calculate in spreadsheet)</i>				

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### Statistical Analyses

<i>Statistical Variable: Homozygous Common Genotype (AA)</i>	<i>Control</i>	<i>Exercise group 1 (specify: _____)</i>	<i>Exercise group 2 (specify: _____)</i>
(V184) ____ Method of analysis (1=Dominant model, 2=Recessive model, 3=Risk allele)			
(V185) ____ Multiple testing correction (1=Yes, 2=Yes but questionable, 3=No)			
(V186) <b>SBP Mean &amp; SD</b> <i>(0=if not calculated)</i>			
(V187) <b>DBP Mean &amp; SD</b> <i>(0=if not calculated)</i>			
(V188) <b>SBP Correlation Coefficient</b> <i>(0=if not calculated)</i>			
(V189) <b>DBP Correlation Coefficient</b> <i>(0=if not calculated)</i>			
(V190) <b>SBP Odds ratio</b> <i>(0=if not calculated)</i>			
(V191) <b>DBP Odds ratio</b> <i>(0=if not calculated)</i>			
(V192) <b>SBP R-squared value</b> <i>(0=if not calculated)</i>			
(V193) <b>DBP R-squared value</b> <i>(0=if not calculated)</i>			
(V194) <b>SBP Chi-Squared Result</b> <i>(0=if not calculated)</i>			
(V195) <b>DBP Chi-Squared Result</b> <i>(0=if not calculated)</i>			
(V196) <b>SBP P-Value</b> <i>(0=if not calculated)</i>			
(V197) <b>DBP P-Value</b> <i>(0=if not calculated)</i>			
(V198) <b>SBP F Statistic</b> <i>(0=if not calculated)</i>			
(V199) <b>DBP F Statistic</b> <i>(0=if not calculated)</i>			
(V200) <b>SBP Confidence Interval</b> <i>(0=if not calculated)</i>			
(V201) <b>DBP Confidence Interval</b> <i>(0=if not calculated)</i>			
(V202) <b>SBP Other statistical outcome, specify: _____</b>			
(V203) <b>DBP Other statistical outcome, specify: _____</b>			

(V204) \_\_\_\_\_ **Notes on statistical analyses relevant to coding**

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<i>Statistical Variable: Heterozygous Genotype (AB)</i>	<i>Control</i>	<i>Exercise group 1 (specify:_____)</i>	<i>Exercise group 2 (specify:_____)</i>
(V205) ____Method of analysis (1=Dominant model, 2=Recessive model, 3=Risk allele)			
(V206) ____Multiple testing correction (1=Yes, 2=Yes but questionable, 3=No)			
(V207) <b>SBP Mean &amp; SD</b> <i>(0=if not calculated)</i>			
(V208) <b>DBP Mean &amp; SD</b> <i>(0=if not calculated)</i>			
(V209) <b>SBP Correlation Coefficient</b> <i>(0=if not calculated)</i>			
(V210) <b>DBP Correlation Coefficient</b> <i>(0=if not calculated)</i>			
(V211) <b>SBP Odds ratio</b> <i>(0=if not calculated)</i>			
(V212) <b>DBP Odds ratio</b> <i>(0=if not calculated)</i>			
(V213) <b>SBP R-squared value</b> <i>(0=if not calculated)</i>			
(V214) <b>DBP R-squared value</b> <i>(0=if not calculated)</i>			
(V215) <b>SBP Chi-Squared Result</b> <i>(0=if not calculated)</i>			
(V216) <b>DBP Chi-Squared Result</b> <i>(0=if not calculated)</i>			
(V217) <b>SBP P-Value</b> <i>(0=if not calculated)</i>			
(V218) <b>DBP P-Value</b> <i>(0=if not calculated)</i>			
(V219) <b>SBP F Statistic</b> <i>(0=if not calculated)</i>			
(V220) <b>DBP F Statistic</b> <i>(0=if not calculated)</i>			
(V221) <b>SBP Confidence Interval</b> <i>(0=if not calculated)</i>			
(V222) <b>DBP Confidence Interval</b> <i>(0=if not calculated)</i>			
(V223) <b>SBP Other statistical outcome, specify: ____</b>			
(V224) <b>DBP Other statistical outcome, specify: ____</b>			

(V225) \_\_\_\_\_ **Notes on statistical analyses relevant to coding**

**APPENDIX D**

<i>Statistical Variable: Homozygous Minor Genotype (BB)</i>	<i>Control</i>	<i>Exercise group 1 (specify:_____)</i>	<i>Exercise group 2 (specify:_____)</i>
(V226) ____ Method of analysis (1=Dominant model, 2=Recessive model, 3=Risk allele)			
(V227) ____ Multiple testing correction (1=Yes, 2=Yes but questionable, 3=No)			
(V228) <b>SBP Mean &amp; SD</b> <i>(0=if not calculated)</i>			
(V229) <b>DBP Mean &amp; SD</b> <i>(0=if not calculated)</i>			
(V230) <b>SBP Correlation Coefficient</b> <i>(0=if not calculated)</i>			
(V231) <b>DBP Correlation Coefficient</b> <i>(0=if not calculated)</i>			
(V232) <b>SBP Odds ratio</b> <i>(0=if not calculated)</i>			
(V233) <b>DBP Odds ratio</b> <i>(0=if not calculated)</i>			
(V234) <b>SBP R-squared value</b> <i>(0=if not calculated)</i>			
(V235) <b>DBP R-squared value</b> <i>(0=if not calculated)</i>			
(V236) <b>SBP Chi-Squared Result</b> <i>(0=if not calculated)</i>			
(V237) <b>DBP Chi-Squared Result</b> <i>(0=if not calculated)</i>			
(V238) <b>SBP P-Value</b> <i>(0=if not calculated)</i>			
(V239) <b>DBP P-Value</b> <i>(0=if not calculated)</i>			
(V240) <b>SBP F Statistic</b> <i>(0=if not calculated)</i>			
(V241) <b>DBP F Statistic</b> <i>(0=if not calculated)</i>			
(V242) <b>SBP Confidence Interval</b> <i>(0=if not calculated)</i>			
(V243) <b>DBP Confidence Interval</b> <i>(0=if not calculated)</i>			
(V244) <b>SBP Other statistical outcome, specify: ____</b>			
(V245) <b>DBP Other statistical outcome, specify: ____</b>			

(V246) \_\_\_\_\_ **Notes on statistical analyses relevant to coding**

## APPENDIX E

### ExBP Meta-Analysis Quality

**M-a (Author(s), Year, Journal):**

**Coder:**

Question	Rationale for Question	Score	Notes (If Any)
<b>1. Was an 'a priori' design provided?</b>	The research question and inclusion criteria should be established before the conduct of the review. Is it stated that these were finalized before commencing the review?		AMSTAR#1-modified
<b>2. Were population variables defined and considered in the methods?</b>	Blood pressure is related to patient (age, biological sex, ethnicity, BMI) and clinical (chronic disease, medication use) variables.		
<b>3. Was there duplicate study selection and data extraction?</b>	There should be at least two independent data extractors and a consensus procedure for disagreements should be in place; minimum moderate reliability (e.g., $r=.70$ ) should be reported.		AMSTAR#2
<b>4. Was a comprehensive literature search performed?</b>	At least two electronic sources should be searched. The report must include years and databases used (e.g. Central, EMBASE, and MEDLINE). All searches should be supplemented by consulting current contents, reviews, textbooks, specialized registers, or experts in the particular field of study, and by reviewing the references in the studies found.		AMSTAR#3-modified
<b>5. Is it possible to replicate the search?</b>	The Method or Supplementary Materials should make it possible for a second party to replicate the search, including all databases, search terms, and operators. Key words and/or MESH terms must be stated or available from the authors and where feasible the search strategy should be provided. <i>If authors report MeSH terms were used for searching, they must be stated in methods OR provided in supplementary material to be considered a "2."</i> <i>A note to contact the author for complete search strategy is also acceptable.</i>		AMSTAR#3-modified
<b>6. Did the inclusion criteria permit grey literature?</b>	The authors should state that they searched for reports regardless of their publication type. The authors should state whether or not they excluded any reports (from the systematic review), based on their publication status, language etc.		AMSTAR#4-modified
<b>7. Was a list of studies (included and excluded) provided?</b>	A list of included and excluded studies should be provided. A descriptive summary of reasons for excluding studies should be provided such as in a QUORUM or PRISMA figure.		AMSTAR#5-modified
<b>8. Were the characteristics of the included studies provided?</b>	In an aggregated form such as a table, data from the original studies should be provided on the participants, interventions and outcomes. The ranges of characteristics in all the studies analyzed e.g. age, race, sex, relevant socioeconomic data, disease status, duration, severity, or diseases. <i>Data must be presented for each study individually in a table to receive a score of "2" simply providing population or study description in the text is not sufficient.</i>		AMSTAR#6
<b>9. Was FITT defined for each study and examined in relation to BP effect sizes?</b>	Frequency, Intensity, Time and Type (FITT) of exercise define major components of exercise and logically relate to BP changes. Results need not show significant moderation patterns.		
<b>10. Was the scientific quality of the included studies assessed and documented?</b>	'A priori' methods of assessment should be provided (e.g., for effectiveness studies if the author(s) chose to include only randomized, double-blind, placebo controlled studies, or allocation concealment as inclusion criteria); for other types of studies alternative items will be relevant. <i>If study quality was assessed and documented with a tool and/ or scale, choose 2; if it was discussed in text only, choose 1; if it was not documented at all, choose 0</i>		AMSTAR#7
<b>11. Was the scientific quality of the included studies used appropriately in formulating conclusions?</b>	The results of the methodological rigor and scientific quality of the included studies must be considered in the analysis and the conclusions of the review, and explicitly stated in formulating recommendations to receive a "2" (i.e., study quality scores related to outcomes, discussion of individual study quality and its relation to outcome). Simply stating inclusion of specific study design (e.g., RCTs) because they are typically of higher quality is not sufficient.		AMSTAR#8
<b>12. Did results depend on study quality, either overall, or in interaction with moderators?</b>	Studies with higher methodological rigor (e.g., with a scale such as PEDro) should yield clearer findings, other factors equal.		
<b>13. Were the methods used to combine the findings of studies appropriate?</b>	For the pooled results, a test should be done to ensure the studies were combinable, to assess their homogeneity (i.e., $\chi^2$ for homogeneity or $I^2$ ). If heterogeneity exists, random-effects assumptions should be incorporated and/or the clinical appropriateness of combining should be taken into consideration (i.e. is it sensible to combine?). <i>If a test of homogeneity was conducted, the <math>\chi^2</math> or <math>I^2</math> value is reported, and they report the statistical assumptions (i.e., fixed vs. random-effects) choose 2; if they report some of the information but not all, choose 1; if they do not discuss homogeneity at all, choose 0.</i>		AMSTAR#9-modified
<b>14. Was the effect size index chosen justified, statistically?</b>	Comparisons of studies' results may be biased in the face of uncontrolled variables (e.g., standard deviations related to mm/Hg for SBP or DBP that vary widely across studies). If		

## APPENDIX

	<i>authors provide ES equation/ explain their ES calculation and relate it to the various study designs and methods of reporting results, choose 2; if authors provide ES information but do not relate it to various study designs, choose 1; if ES is not discussed at all, choose 0.</i>		
<b>15. Was individual-level meta-analysis used for moderator analyses?</b>	The authors should state whether or not they obtained original data from the study authors when performing moderator analyses.		
<b>16. Were clinical ramifications clearly addressed?</b>	The results and discussion should clearly lend themselves to informing clinical practice in relation to particular populations and health problems. <i>Reports must provide clear clinical ramification or recommendation (i.e., what does this study add?) Simply re-stating what is known in the literature, or introduction material is not adequate.</i>		
<b>17. Was the likelihood of publication bias assessed?</b>	Asymmetries in effect sizes are examined as evidence of potential publication bias and includes a combination of graphical aids (e.g., funnel plot, other available tests) and/or statistical tests (e.g., Egger regression test).		AMSTAR#10
<b>18. Was the conflict of interest stated?</b>	Potential sources of support or conflict should be clearly acknowledged in both the systematic review and the included studies.		AMSTAR#11

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