Supplementary Material

Supplementary Material 1. Full methods

Methods

This study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA)[1], Transparency and Openness Promotion (TOP)[2] and A Measurement Tool to Assess Systematic Reviews 2 (AMSTAR)[3] guidelines. The protocol was pre-registered on the Open Science Framework (OSF) (doi:10.17605/OSF.IO/H58BZ) and PROSPERO (CRD42020201888) prior to conducting searches. The data and code used for this review are available on OSF and the full description of the methods can be found in the review protocol[4]. Deviations from the protocol, with reasons, are stated as such.

Eligibility Criteria

Study Design

We included randomized controlled trials (RCTs), including cross-over trials, written in any language. There were no restrictions on publication status, as unpublished data may result in meaningful differences in outcomes of systematic reviews[5]. Publication bias or selective omission of data is of particular concern regarding adverse events, which have been shown to be significantly higher in unpublished studies[6].

Participants

We included trials examining adults with mean office BP classed as: high-normal (SBP 130-139mmHg or DBP 85-89mmHg), grade 1 hypertension (SBP 140-159mmHg or DBP 90-99mmHg) or grade 2 hypertension (SBP ≥160mmHg or DBP ≥100mmHg) according to the International Society of Hypertension guidelines[7].

Interventions

We included trials that examined IRT, defined as exercise involving muscular contraction against an immoveable resistance or load with negligible change in length of the muscles involved[8]. Trials were included if IRT was performed for at least three weeks, the minimum duration believed to produce an effect on BP[9], without restrictions on the frequency, volume or intensity of IRT prescribed.

Comparators

We included the following comparators: aerobic exercise, dynamic resistance exercise and non-exercise controls including lifestyle modification (e.g. advice to be physically active), non-exercise control or sham isometric exercise.

Outcomes

The primary outcome was the mean difference in BP change scores between the IRT and control groups. Blood pressure included systolic and diastolic pressures, measured as office (brachial), central or 24hr ambulatory BP, which we analysed as separate outcomes.

The secondary outcome was safety. Safety was expressed as the number of participants who experienced an adverse or serious adverse event, either during, or after the exercise. Adverse events were defined as 'any untoward medical occurrence associated with the use of an [intervention] in humans, whether or not considered treatment related'[10]. Serious adverse events were defined as an event that resulted in any of the following: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions[10].

Searches

We searched electronic databases of published and unpublished literature up to August 2020, including: MEDLINE, EMBASE, Cumulative Index to Nursing and Allied Health Literature (CINAHL), Physiotherapy Evidence Database (PEDro), SPORTDiscus, Cochrane Register of Controlled Trials (CENTRAL), ClinicalTrials.gov, Australian New Zealand Clinical Trials Registry (ANZCTR), European Union Clinical Trial Registry (EU-CTR). The full list of search strategies and databases searched are available in Supplementary Material 1. We also searched previous systematic reviews and conducted forward and backwards citation tracking of included studies to identify further relevant articles.

Two reviewers (HJH, MDJ) independently conducted two stages of eligibility screening in duplicate: i) title and abstract; ii) full text. Disagreements were resolved through discussion with a third reviewer (BJP) when required.

Data extraction

Descriptive data and results from included studies were extracted independently and in duplicate by authors (HJH, MDJ, KAM, MAW) into a standardized document, with disagreements resolved through discussion. When data was only presented in figures, we extracted it using WebPlotDigitizer[11]. If studies did not report outcomes of interest (e.g. adverse events), the authors were contacted up to three times requesting the relevant data. If no reply was received within six weeks, the data was considered unobtainable.

For each outcome, we prioritized extracting the mean change and SD of change (SD_{change}) for the intervention and control groups. We transformed standard error and 95% confidence intervals (CI) using methods outlined by the Cochrane Collaboration[12]. If the mean change and SD_{change} were not reported, we calculated them from the baseline and post-intervention values based on recommendations from the Cochrane Collaboration[12]. In order to calculate the SD_{change}, we used the median correlation of 0.7 (range 0.05 to 0.95) from the exercise and control arms of five studies which provided both change and endpoint values with corresponding SDs[12-17].

Risk of Bias in individual Studies

We used the Cochrane risk of bias tool to assess the risk of bias[18]. Each trial was appraised independently and in duplicate by two authors (HJH, MDJ, KAM, MAW) and disagreements were resolved through discussion. The domains assessed included: selection, performance, attrition, detection, reporting, and other sources of bias. Overall risk of bias for each trial was determined 'high,' 'some concerns' or 'low' (see Supplementary Material 2 for details on risk of bias classifications[18]).

Data Analysis

Random-effect meta-analyses were conducted by two authors (HJH, MAW) using the *metafor* package in R[19]. The effects of IRT on BP compared to a non-exercising control and aerobic exercise were summarized separately using mean difference and 95%CI. Safety was determined using risk ratio (RR) and risk difference (RD) with 95%CI. Heterogeneity was quantified using Cochran's Q, τ^2, the I^2 statistic and 95% prediction intervals (PI). A clinically important difference in SBP was determined to be 5mmHg based on expert consultation (AES), and 2mmHg for DBP based on previous research[20]. Funnel plots were produced with *metafor* to assess publication bias/data dredging[21]. Extended funnel plots were constructed using the *extfunnel* package in R to determine the impact of the results of a future study on the pooled effect observed in this review[22]. We conducted several prespecified sub-analyses, including medication status and type of exercise and blood pressure classification. A study was deemed to have 'medicated' participants if >80% of participants were medicated. This was an arbitrary cut off based on expert consultation (AES). An exploratory post hoc sub-analysis of age (< or ≥ 65 years old) was also conducted. Where IRT is compared to aerobic exercise, positive values indicate a reduction in BP favouring aerobic exercise.

Confidence in cumulative evidence

Two reviewers (MDJ, HJH) assessed the quality of evidence and strength of recommendations using GRADE[23]. Quality of evidence was downgraded for risk of bias, inconsistency, indirectness, imprecision and publication bias (see Supplementary Material 3 for details).

Supplementary Material 2. Search strategies for databases

<u>MEDLINE</u>

Search: (Isometric exercise) OR (Isometric training) AND (Resistance training) OR (Strength training) OR (exercise [MeSH Terms]) AND (High blood pressure) AND (hypertens*) NOT (review) AND (human)

Filters: N/A

<u>EMBASE, CINAHL, SPORTDiscus, Australian New Zealand Clinical Trials Registry (ANZCTR), European Union Clinical Trial Registry (EU-CTR)</u>

Search: (Isometric and (training or resistance or exercise or strength) AND (blood pressure or hypertens* or prehypertens*)

Filters: N/A

<u>PEDro</u>

Search: isometric* blood pressure trial

Filters: N/A

<u>Cochrane Register of Controlled Trials (CENTRAL)</u>

Search:

ID	Search	Hits
#1	Isometric	5558
#2	Strength OR Resistance	88012
#3	exercise OR Training	155496
#4	hypertens* OR prehypertens*	67294
#5	high blood pressure OR elevated blood pressure OR Blood pressure OR arterial pressure	109222
#6	#1 AND (#2 OR #3) AND (#4 OR #5)	693

Filters: N/A

<u>ClinicalTrials.gov</u>

Search: Blood pressure OR arterial pressure OR prehypertens* | Hypertension | isometric AND Resistance OR Strength OR Exercise | Adult, Older Adult

Filters: Adult (18–64), Older Adult (65+), Accepts Healthy Volunteers

Note: all searches run on 03/08/2020

Supplementary Material 3: Risk of Bias Classifications

A trial is said to have a ‘high’ risk of bias if it is judged to be at a high risk of bias in at least one domain or contains some concerns for multiple domains in a way which substantially lowers confidence in the result.

A trial is deemed to have ‘some concerns’ about its risk of bias if it is judged to raise ‘some concerns’ in at least one domain but not a high risk in any domains.

A trial is deemed to have a low risk of bias if it is judged to be at a low risk of bias for all domains

Supplementary Table 4. Characteristics of participants of included studies

Study (first author, year)	**Sample Size** (n)	**Mean Age,** year ± SD	**Female** (%)	**Mean baseline BP,** Sys/Dia (mmHg)	**BP Meds** (%)
Grade 1 Hypertension (SBP ≥ 140mmHg OR DBP ≥ 90mmHg OR 100% medicated)					
Ahmed, 2019	40	55±3.3	100	IRT: 156 / 95 Con: 155 / 95	100
Correia, 2020	102	66.5±11.5	54	IRT: 143 / 74 Con: 149 / 75	NR
Farah, 2018	72	59.3±15.9	70	IRT_{Home}: 130 / 73 IRT_{Lab}: 129 / 73 Con: 132 / 71	100
Forjaz, 2019*	24	54±8.3	0	IRT: 130 / 89 Con: 127 / 88	100
Okamoto, 2019	22	64.5±11	59	IRT: 156 / 94 Con: 158 / 93	0
Punia, 2020	40	30 to 45	50	IRT: 144 / 93 Con: 142 / 90	NR
Ritti-Dias, 2017*	63	53.5±3.2	70	IRT: 129 / 83 Con: 126 / 81	100
Stiller-Moldovan, 2012	25	61.3±7.3	40	IRT: 112 / 69 Con: 113 / 62	100
Taylor, 2003	17	66.9±5.8	41	IRT: 156 / 82 Con: 152 / 87	76
High-normal BP (SBP = 130-139mmHg OR DBP = 85-89mmHg)					
Badrov, 2013	23	64±8	46	IRT: 129 / 72 Con: 130 / 73	83
Baross, 2013	20	54±5	0	$IRT_{70\%HRpeak}$: 137 / 78 $IRT_{85\%HRpeak}$: 139 / 78 Con: 139 / 79	0
Baross, 2012	30	53.9±5.3	0	IRT: 139 / 85 Con: 139 / 85	0
Carlson, 2016	40	53±8	63	IRT: 136 / 77 Con: 128 / 74	65
Goessler, 2018	60	33.1±10.1	52	IRT: 125 / 85 Con: 131 / 84	0
Gordon, 2018	22	49.7±2.3	73	IRT_{LAB}: 138 / 88 IRT_{HOME}: 138 / 87 Con: 137 / 87	91
Gregory, 2012†	8	65.1±6	100	IRT: 138 / 72 Con: 142 / 82	63
Herrod, 2020	23	71±4	52	IRT: 139 / 81 Con: 130 / 80	22
Jae, 2019	60	69.1±5.7	72	IRT: 133 / 85 Con: 129 / 78	90
Morrin, 2016†	17	64.8±6	47	IRT: 139 / 86 Con: 143 / 78	NR
Ogbutor, 2019	400	40±6.2	47	IRT: 134 / 88 Con: 126/ 82	0
Pagonas, 2017	75	60±9	57	IRT: 135 / 78 Con: 139 / 79	76
Taylor, 2019	48	43.8±7.3	NR	IRT: 132 / 81 Con: 132 / 82	0
Wiley, 1992	20	20 to 35	NR	IRT: 134 / 87 Con: 134 / 83	NR
	42	49.1±6.4	100	IRT: 132 / 73	NR

Worachet, 2017	Con: 131 / 73

n = sample size, sys = systolic, dia = diastolic, BP = blood pressure, mmHg = millimetres of mercury, Meds = medications, IRT = Isometric resistance training, NR = data not reported, * = study unpublished, † = PhD thesis, LBP = Lower back pain

Supplementary Material 5 - Reasons for exclusion at the level of full text

1. Studies excluded as full text articles were not available

i. Anand MP, Dattani KK, Datey KK. Effect of isometric exercise and mental stress on blood pressure - Comparative effects of propranolol and labetalol. Indian Heart Journal 1984;36:4-7.
ii. Baldwa VS, Gupta BS, Chittora MD. Cardiovascular response to isometric stress (handgrip) in patients with essential hypertension before and after antihypertensive therapy with propranolol or alpha methyldopa. Indian Heart Journal 1983;35:333-6.
iii. Bindiya S, Damodara Gowda KM, Mirajkar AM. Influence of body fat percentage on blood pressure responses to isometric hand grip test among young individuals. Indian Journal of Physiology and Pharmacology 2017;61 (5 Supplement 1):185-6.
iv. Caldari R, Borghi C, Costa FC, Strocchi E, Ambrosioni E. Cardiovascular response to mental stress, dynamic and isometric exercise in a group of hypertensive patients treated with prizidilol (SK&F 92657). [Italian]. Cardiologia (Rome, Italy) 1982;27:635-42.
v. Camus G, Thys H, Pigeon G, Dreezen E. Modifications cardio-vasculaires induites par l'exercice isometrique chez les sujets ages. / Cardiovascular changes induced by isometric exercise in aged subjects. Comptes Rendus Des Seances de la Societe de la Biologie & de Ses Filliales 1982;176:740-3.
vi. Carrick F. Effects of Isometric Exercises on Balance, Heart Rate, Pulse Ox and Blood Pressure. https://clinicaltrialsgov/show/NCT02599727 2015.
vii. Deepika V. The efficacy of isometric hand grip training on arterial stiffness and blood pressure in prehypertensive individuals-an interventional study. Indian Journal of Physiology and Pharmacology 2017;61 (5 Supplement 1):68-9.
viii. Dempster KS, McGowan CL, Wade TJ, O'Leary DD. Effects of isometric handgrip exercise training on systemic arterial stiffness, cardiovagal baroreflex sensitivity, and cognition in treated adults with hypertension: A pilot study. Critical Reviews in Physical and Rehabilitation Medicine 2018;30:219-37.
ix. DiCarlo SE. Effects of isometric training on cardiovascular and metabolic responses to isometric stress. Eugene, Ore.;: Microform Publications, University of Oregon; 1983.
x. Escobar E, Chamorro G, Baeza H, Novoa O, Bull R. Effects of isometric exercise ("handgrip") on left ventricular pressure and volume in patients with aortic insufficiency (author's transl). [Spanish]. Revista medica de Chile 1978;106:671-6.
xi. Lansimies E, Rauhala E, Rauramaa R, Kukkonen K, Voutilainen E. Effect of training on isometric handgrip response in borderline hypertensive middle-aged men. Clin-physiol 1981;1:602-3.
xii. Liu XH, Peng RH, Xie XL, Liu GH. Effects of integrated isotomic exercise on blood pressure and plasma endothelims in hypertension patients. [Chinese]. Chinese Journal of Clinical Rehabilitation 2005;9:95-7

2. Studies excluded due to the wrong population

a. Ash GI, Taylor BA, Thompson PD, et al. The antihypertensive effects of aerobic versus isometric handgrip resistance exercise. Journal of Hypertension 2017;35:291-9.
b. Baddeley-White DS, McGowan CL, Howden R, Gordon BD, Kyberd P, Swaine IL. Blood pressure lowering effects of a novel isometric exercise device following a 4-week isometric handgrip intervention. Open Access J Sports Med 2019;10:89-98.
c. Badrov M, Bartol C, DiBartolomeo M, Millar P, McNevin N, McGowan C. Effects of isometric handgrip training dose on resting blood pressure and resistance vessel endothelial function in normotensive women. European Journal of Applied Physiology 2013;113:2091-100.
d. Badrov MB, Freeman SR, Millar PJ, McGowan CL. Sex-differences in the effects of isometric handgrip training on resting blood pressure and resistance vessel function. FASEB Journal Conference: Experimental Biology 2013;27.
e. Badrov MB, Freeman SR, Zokvic MA, Millar PJ, McGowan CL. Isometric exercise training lowers resting blood pressure and improves local brachial artery flow-mediated dilation equally in men and women. Eur J Appl Physiol 2016;116:1289-96.
f. Baross AW, Milne KJ, McGowan CL, Swaine IL. Effects of isometric leg training on ambulatory blood pressure and morning blood pressure surge in young normotensive men and women. Hypertension Conference: American Heart Association's Council on Hypertension 2017;70.
g. Bartol C, Kenno K, McGowan CL. Post-exercise hypotension: effects of acute and chronic isometric handgrip in well- controlled hypertensives. Critical reviews in physical and rehabilitation medicine 2012;24:137-45.
h. Carlson KE, Montero JC, Gerontinos EM, Kerrins RK. The use of gravity in isometric exercise. American corrective therapy journal 1971;25:19-22.
i. Devereux G, Wiles J, Howden R. Immediate post-isometric exercise cardiovascular responses are associated with training-induced resting systolic blood pressure reductions. European Journal of Applied Physiology 2015;115:327-33.
j. Devereux GR, Coleman D, Wiles JD, Swaine I. Lactate accumulation following isometric exercise training and its relationship with reduced resting blood pressure. Journal of Sports Sciences 2012;30:1141-8.
k. Devereux GR, Wiles JD, Swaine I. Markers of isometric training intensity and reductions in resting blood pressure. Journal of Sports Sciences 2011;29:715-24.
l. Devereux GR, Wiles JD, Swaine IL. Reductions in resting blood pressure after 4 weeks of isometric exercise training. European Journal of Applied Physiology 2010;109:601-6.
m. Gill KF, Arthur ST, Swaine I, et al. Intensity-dependent reductions in resting blood pressure following short-term isometric exercise training. Journal of sports sciences 2015;33:616-21.
n. Gordon BDH, Whitmire S, Zacherle EW, et al. "Get a Grip on Hypertension": Exploring the use of isometric handgrip training in cardiopulmonary rehabilitation patients. Journal of Cardiopulmonary Rehabilitation and Prevention 2019;39:E31-E4.
o. Herrod PJJ, Blackwell JEM, Moss BF, et al. The efficacy of 'static' training interventions for improving indices of cardiorespiratory fitness in premenopausal females. Eur J Appl Physiol 2019;119:645-52.
p. Howden R, Lightfoot JT, Brown SJ, Swaine IL. The effects of isometric exercise training on resting blood pressure and orthostatic tolerance in humans. Experimental physiology 2002;87:507-15.

q. McGowan CL, Levy AS, McCartney N, MacDonald MJ. Isometric handgrip training does not improve flow-mediated dilation in subjects with normal blood pressure. Clinical science (london, england : 1979) 2007;112:403-9.
r. Millar PJ, Bray SR, MacDonald MJ, McCartney N. The hypotensive effects of isometric handgrip training using an inexpensive spring handgrip training device. J Cardiopulm Rehabil Prev 2008;28:203-7.
s. Millar PJ, Levy AS, McGowan CL, McCartney N, MacDonald MJ. Isometric handgrip training lowers blood pressure and increases heart rate complexity in medicated hypertensive patients. Scand J Med Sci Sports 2013;23:620-6.
t. Ray CA, Carrasco DI. Isometric handgrip training reduces arterial pressure at rest without changes in sympathetic nerve activity. American journal of physiology - heart and circulatory physiology 2000;279:H245-H9.
u. Ritti Dias RM. Sedentary Behavior Breaks With Isometric Exercise in Cardiovascular Health Indicators. https://clinicaltrialsgov/show/NCT03949205 2019.
v. Sagiv M, Fisher N, Yaniv A, Rudoy J. Effect of running versus isometric training programs on healthy elderly at rest. Gerontology 1989;35:72-7.
w. Somani Y, Hanik SA, Malandruccalo A, et al. Isometric handgrip (IHG) training-induced reductions in resting blood pressure: Reactivity to a 2-minute handgrip task identifies responders and non-responders in young normotensive individuals. FASEB Journal Conference: Experimental Biology 2014;28.
x. Somani YB, Baross AW, Brook RD, Milne KJ, McGowan CL, Swaine IL. Acute Response to a 2-Minute Isometric Exercise Test Predicts the Blood Pressure-Lowering Efficacy of Isometric Resistance Training in Young Adults. Am J Hypertens 2018;31:362-8.
y. Tong CQ, Zhao J, Bo H, Xiang XH. Influence of isometric exercise on vascular functions of recruits from the Chinese People's armed police forces during hypoxic training. [Chinese]. Journal of Clinical Rehabilitative Tissue Engineering Research 2007;11:6424-7.
z. Tsitoglou K, Martin U, Marshall J. Effects of isometric handgrip (IHG) training of one forearm on reactive and exercise hyperaemia in the ipsilateral and contralateral arm of White European young men. FASEB Journal Conference: Experimental Biology 2016;30.
aa. Tsitoglou K, Martin U, Marshall J. Effects of isometric handgrip training (IHG) training on endothelium-dependent vasodilatation in older (O) men: Contribution of cyclooxygenase (COX) products. Journal of Human Hypertension 2017;31 (10):676.
bb. Tsitoglou K, Martin U, Marshall J. Isometric handgrip (IHG) training of one forearm reduces resting arterial pressure and augments reactive and exercise hyperaemia in the non-trained arm of older, normotensive men. Journal of Human Hypertension 2017;31 (10):661-2.
cc. Wiles JD, Coleman DA, Swaine IL. The effects of performing isometric training at two exercise intensities in healthy young males. European journal of applied physiology 2010;108 (3):419-28.

3. Not a randomised control trial

a. Abe N, Bisognano JD. Non-pharmacological interventions for patients with resistant hypertension. Interventional Cardiology (London) 2012;7:93-6.
b. Abinader EG, Sharif DS. Age-associated changes in left ventricular diastolic performance during isometric stress [1]. American Journal of Cardiology 1993;71:629.

c. Buck C, Donner AP. Isometric occupational exercise and the incidence of hypertension. Journal of Occupational Medicine 1985;27:370-2.
d. Hanik SE, Badrov MB, Stiller-Moldovan C, et al. Isometric handgrip training induces equal blood pressure reductions in normotensive males and females without influencing heart rate variability. Canadian Journal of Cardiology 2012;28:S118-S9.
e. Kiveloff B, Huber O. Brief maximal isometric exercise in hypertension. Journal of the American Geriatrics Society 1971;19:1006-12.
f. Kiveloff B, Huber O. New approach to lowering blood pressure with brief isometric exercise. Journal of Physical Education 1975;72:92-.
g. McGowan CL, Levy AS, Millar PJ, et al. Acute vascular responses to isometric handgrip exercise and effects of training in persons medicated for hypertension. Am J Physiol Heart Circ Physiol 2006;291:H1797-802.
h. McGowan CL, Visocchi A, Faulkner M, et al. Isometric handgrip training improves local flow-mediated dilation in medicated hypertensives. Eur J Appl Physiol 2006;98:355-62.
i. Peters PG, Alessio HM, Hagerman AE, Ashton T, Nagy S, Wiley RL. Short-term isometric exercise reduces systolic blood pressure in hypertensive adults: possible role of reactive oxygen species. Int J Cardiol 2006;110:199-205.
j. Somani Y, Baross A, Levy P, et al. Reductions in ambulatory blood pressure in young normotensive men and women after isometric resistance training and its relationship with cardiovascular reactivity. Blood Press Monit 2017;22:1-7.
k. Zhang J. Effect of isometric handgrip exercise training on resting hemodynamics: a pilot study. Journal of Chiropractic Medicine 2003;2:153-6.

4. Wrong intervention
a. Akihiro I. The Effectiveness of Handgrip exercise in Hypertension. http://wwwwhoint/trialsearch/Trial2aspx?TrialID=JPRN-UMIN000035408 2019.
b. Bentley DC, Nguyen CHP, Thomas SG. High-intensity handgrip training lowers blood pressure and increases heart rate complexity among postmenopausal women: a pilot study. Blood Press Monit 2018;23:71-8.
c. Bertani RF, Campos GO, Perseguin DM, et al. Resistance Exercise Training Is More Effective than Interval Aerobic Training in Reducing Blood Pressure During Sleep in Hypertensive Elderly Patients. J Strength Cond Res 2018;32:2085-90.
d. Bouzas-Mosquera MC, Bouzas-Mosquera A, Peteiro J. Excessive blood pressure increase with exercise and risk of all-cause mortality and cardiac events. Eur J Clin Invest 2016;46:833-9.
e. Brito Ade F, de Oliveira CV, Santos Mdo S, Santos Ada C. High-intensity exercise promotes postexercise hypotension greater than moderate intensity in elderly hypertensive individuals. Clin Physiol Funct Imaging 2014;34:126-32.
f. Bunsawat K, Baynard T. Cardiac autonomic modulation and blood pressure responses to isometric handgrip and submaximal cycling exercise in individuals with down syndrome. Clinical Autonomic Research 2016;26:253-60.
g. Collier SR, Kanaley JA, Carhart R, Jr., et al. Cardiac autonomic function and baroreflex changes following 4 weeks of resistance versus aerobic training in individuals with pre-hypertension. Acta Physiol (Oxf) 2009;195:339-48.
h. de Barros Carvalho Canuto PM, Nogueira IDB, Cunha ESd, et al. Influence of Resistance Training Performed at Different Intensities and Same Work Volume over BP of Elderly

Hypertensive Female Patients. Revista Brasileira de Medicina do Esporte 2011;17:246-9.

i. de Carvalho CJ, Marins JCB, de Lade CG, et al. Aerobic and resistance exercise in patients with resistant hypertension. / Ejercicio aeróbico y resistido en pacientes con hipertensión arterial resistente. Revista Brasileira de Medicina do Esporte 2019;25:107-11.

j. Di Girolamo D, Mascia F, Coviello M, et al. Effects of isometric exercise on the blood pressure in the small circulation in healthy subjects. [Italian]. Bollettino della Societa italiana di biologia sperimentale 1978;53:2380-4.

k. Dobrosielski DA, Gibbs BB, Ouyang P, et al. Effect of exercise on blood pressure in type 2 diabetes: a randomized controlled trial. J Gen Intern Med 2012;27:1453-9.

l. Donato M, Gabay J, Pascua A, et al. Effect of isometric exercise on diastolic function in patients with severe aortic stenosis. [Spanish]. Medicina 2003;63:33-6.

m. Eckberg DL, Wallin BG. Isometric exercise modifies autonomic baroreflex responses in humans. Journal of Applied Physiology 1987;63:2325-30.

n. Fahs CA, Rossow LM, Loenneke JP, et al. Effect of different types of lower body resistance training on arterial compliance and calf blood flow. Clinical Physiology & Functional Imaging 2012;32:45-51.

o. Filipovský J, Simon J, Chrástek J, Rosolová H, Haman P, Petríková V. Changes of blood pressure and lipid pattern during a physical training course in hypertensive subjects. Cardiology 1991;78:31-8.

p. Garg R, Malhotra V, Kumar A, Dhar U, Tripathi Y. Effect of isometric handgrip exercise training on resting blood pressure in normal healthy adults. Journal of Clinical and Diagnostic Research 2014;8:BC08-BC10.

q. Hambrecht R, Wolf A, Gielen S, et al. Effect of exercise on coronary endothelial function in patients with coronary artery disease. N Engl J Med 2000;342:454-60.

r. Hansen AH, Nielsen JJ, Saltin B, Hellsten Y. Exercise training normalizes skeletal muscle vascular endothelial growth factor levels in patients with essential hypertension. J Hypertens 2010;28:1176-85.

s. Hansen AH, Nyberg M, Bangsbo J, Saltin B, Hellsten Y. Exercise training alters the balance between vasoactive compounds in skeletal muscle of individuals with essential hypertension. Hypertension 2011;58:943-9.

t. Hess NC, Carlson DJ, Inder JD, Jesulola E, McFarlane JR, Smart NA. Clinically meaningful blood pressure reductions with low intensity isometric handgrip exercise. A randomized trial. Physiol Res 2016;65:461-8.

u. Millar PJ, Bray SR, MacDonald MJ, McCartney N. Cardiovascular reactivity to psychophysiological stressors: association with hypotensive effects of isometric handgrip training. Blood Press Monit 2009;14:190-5.

v. Tsitoglou K, Martin U, Marshall J. Effects in young men of isometric handgrip training (IHG) on endothelium-dependent vasodilator responses in the contralateral arm: Changes in the contribution of cyclooxygenase (COX) products. FASEB Journal Conference: Experimental Biology 2016;30.

w. Wiles JD, Taylor K, Coleman D, Sharma R, O’Driscoll JM, O'Driscoll JM. The safety of isometric exercise: Rethinking the exercise prescription paradigm for those with stage 1 hypertension. Medicine 2018;97:1-8.

x. Nastaran HJ, Farhad D, Mohammad Ali BB, et al. The effect of four weeks of isometric handgrip training on peripheral vascular resistance and blood pressure in women with

hypertension. Journal of Shaheed Sadoughi University of Medical Sciences & Health Services 2017;25:123-31.

5. Secondary study without additional data or registered clinical trial without data available
    a. Bauer F, Vlatsas S, Seibert FS, Westhoff TH, Pagonas N. Effect of different exercise modalities on blood pressure variability. Journal of hypertension 2015;33:e287-.
    b. Cahu Rodrigues SL, Farah BQ, Silva G, et al. Vascular effects of isometric handgrip training in hypertensives. Clin Exp Hypertens 2020;42:24-30.
    c. Carlson DJ, Dieberg G, McFarlane JR, Smart NA. Isometric handgrip exercise reduces 24HR ambulatory blood pressure. Circulation Conference: Resuscitation Science Symposium, ReSS 2017;136.
    d. Carlson DJ, McFarlane JR, Dieberg G, Smart NA. Isometric Handgrip Exercise to Reduce Hypertension for Stroke Prevention and Recovery...American Congress of Rehabilitation Medicine Annual Conference 25-30 October, 2015, Dallas, TX, USA. Archives of Physical Medicine & Rehabilitation 2015;96:e25-e.
    e. Carlson DJ, McFarlane JR, Dieberg G, Smart NA. Isometric handgrip exercise to reduce hypertension for stroke prevention and recovery. Archives of physical medicine and rehabilitation 2016;96:e25.
    f. Farah BQ. Effect of Isometric Handgrip Training on Cardiovascular Risk in Hypertensives. Goessler KF, Vander Trappen D, Van Humbeek L, Cornelissen VA. Isometric handgrip training versus aerobic exercise training to control blood pressure. Preliminary results of the TRiHYP (TRaining in Hypertension) Study. European journal of preventive cardiology 2017;24:S154-. https://clinicaltrialsgov/show/NCT02348138 2015.
    g. Jae SY, Yoon ES, Kim HJ. Effects Of Isometric Handgrip Versus Aerobic Exercise On Blood Pressure In Elderly Hypertensive Patients: 998 Board #259 May 30 2:00 PM - 3:30 PM. Medicine & Science in Sports & Exercise 2018;50:236-.
    h. Jørgensen MG. Isometric handgrip home training to lower blood pressure in hypertensive older adults. https://clinicaltrialsgov/show/NCT03069443 2017.
    i. Millar PJ, Bray SR, McGowan CL, et al. Effects of isometric handgrip training among people medicated for hypertension: a multilevel analysis. Blood Pressure Monitoring 2007;12:307-14.
    j. Pagonas N, Vlatsas S, Bauer F, et al. The impact of aerobic and isometric exercise on different measures of dysfunctional high-density lipoprotein in patients with hypertension. European journal of preventive cardiology 2019.
    k. Farah BQ, Farias Menezes R, Jacinto Sobral RA, et al. Isometric handgrip training does not improve quality of life in hypertensives. / Treinamento isométrico com handgrip não melhora qualidade de vida em hipertensos. Revista Brasileira de Ciência e Movimento: RBCM 2019;27:117-24.
    l. Smart NA. Isometric Handgrip Exercise for Blood Pressure Management. https://ClinicalTrials.gov/show/NCT02458443; 2016.

Supplementary Table 6: Characteristics of interventions

Study (first author, year)	**Intervention**	**Duration** (weeks)	**Frequency** (days per week)	**Intensity**	**Session Duration** (mins)	**Reps x Holds** (mins) [rest (mins)]	**Description of control**	**Author Contacted**	**Adverse Events,** n, description of event [group])
Grade 1 Hypertension (SBP ≥ 140mmHg AND/OR DBP ≥ 90mmHg OR 100% using anti-hypertensive medication)									
Ahmed, 2019[24]	IHG + Anti-HT	6	4	30-40% MVC	32	4 x 3 [5]	Anti-hypertensive drug therapy	Uncontactable	NR
Correia, 2020[25]	IHG	8	3	30% MVC	12	4 x 2 [1]	Compression ball sham (3x10 3x/week)	Reported	n = 2 (instability of disease [IRT])
Farah, 2018[26]	IHG	12	3	30% MVC	12	4 x 2 [1]	Non-exercise control	Reported	n = 1 (dyspnea and tachycardia [IRT_{Home}]) + 'some reported hand pain' [both IRT groups]
Forjaz, 2019*	IHG	10	3	30% MVC	8	4 x 2 [NR]	30mins stretching	Responded	n = 3 (LBP [control], uncontrolled BP [IRT], acute MI [dynamic resistance training])
Okamoto, 2019[27]	IHG	8	5	30% MVC	12	4 x 2 [1]	Non-exercise control	Contacted	NR
Punia, 2020[15]	IHG	8	3	30% MVC	24	4 x 2 [4]	Non-exercise control	Reported	n = 0
Ritti-Dias, 2017*[28]	IHG	12	3	30% MVC	12	4 x 2 [1]	Encouraged to increase activity	Responded	n = 1 (hand pain [IRT])
Stiller-Moldovan, 2012[29]	IHG	8	3	30% MVC	12	4 x 2 [1]	Non-exercise, attention control	Responded	n = 0
Taylor, 2003[30]	IHG	10	3	30% MVC	12	4 x 2 [1]	Non-exercise control	Contacted	NR
High-normal BP (SBP = 130-139mmHg AND/OR DBP = 85-89mmHg)									
Badrov, 2013[31]	IHG	10	3	30% MVC	12	4 x 2 [1]	Non-exercise control	Contacted	NR

Baross, 2012[32]	Isometric Leg Exercise	8	3	85% HRpeak[‡]	16	4 x 2 [2]	Non-exercise control	Responded	n = 0
Baross, 2013[33]	Isometric Leg Exercise	8	3	85% HRpeak[‡]	16	4 x 2 [2]	Non-exercise control	Responded	n = 0
Carlson, 2016[34]	IHG	8	3	30% MVC	20	4 x 2 [3]	5% MVC IHG (Identical Rx)	Reported	n = 0
Goessler, 2018[35]	IHG	8	7	30% MVC	12	4 x 2 [1]	Non-exercise control	Responded	n = 0
Gordon, 2018[13]	IHG	12	3	30% MVC	12	4 x 2 [1]	Non-exercise control	Contacted	NR
Gregory, 2012[36]	IHG	8	3	30% MVC	12	4 x 2 [1]	3% MVC IHG (Identical Rx)	Responded	n = 0
Herrod, 2020[37]	IHG	6	3	30% MVC	16	4 x 2 [2]	Non-exercise control	Reported	n = 0
Morrin, 2016[16]	IHG	10	3	CR-10 level 6 (10-40% MVC)	8	4 x 2 [NR]	Non-exercise control	Reported	n = 0
Ogbutor, 2019[14]	IHG	3.4	7	30% MVC	14	2x2 [5]	Educated on lifestyle modification	Responded	n = 5 (forearm fatigue and pain [IRT])
Pagonas, 2017[38]	IHG	12	5	30% MVC	12	4 x 2 [1]	5% MVC IHG (Identical Rx)	Contacted	NR
Taylor, 2019†[39]	Isometric Leg Exercise	4	3	95% HRpeak[‡]	16	4 x 2 [2]	Non-exercise control, 3-week washout	Responded	n = 0
Wiley, 1992[40]	IHG	8	3	30% MVC	20	4 x 2 [3]	Non-exercise control	Uncontactable	NR
Worachet, 2017[41]	IHG	4	3	30% MVC	12	4 x 2 [1]	Non-exercise control	Contacted	NR
Yoon, 2019[17]	IHG	12	3	30% MVC	8	4 x 2 [NR]	Non-exercise control	Responded	n = 0
Trials not contributing to quantitative synthesis									
Alves, 2020*[42]	IHG	8	3	NR	NR	NR	Usual medical care	Responded	Trial on hold; no data to provide
Fujimoto, 2017*[43]	IHG	12	3	30% MVC	12	4 x 2 [1]	Non-exercise control	Contacted	NR

Gerage, 2019*[44]	IHG	24	3	30% MVC	12	4 x 2 [1]	Non-exercise control	Contacted	NR
Jørgenson, 2018§[45]	IHG	20	3	30% MVC	12	4 x 2 [1]	Non-exercise control	Contacted	Trial awaiting publication, declined to provide data
Pedrosa, 2018*[46]	IHG	12	3	30% MVC	16	4 x 2 [2]	Non-exercise control	Contacted	NR

Reps = repetitions, IHG = Isometric hand grip, Anti-HT = antihypertensive drug therapy, MVC = maximal voluntary contraction, * = study unpublished, NR = data not reported, LBP = low back pain, MI = myocardial infarction, † = Crossover RCT study type, HR = heart rate, HRpeak = peak HR, HRmax = maximum heart rate, CR-10 = Borg CR10 rating of exertion scale, level 6 indicating severe to very severe exertion, Rx = prescription. ‡ = Participants performed an MVC test then incremental leg dynamometer exercise test to determine HRpeak, intensity was then determined as the EMG values which corelated to the desired HR. § = Study protocol

Note: Session duration is inclusive of rest period

Supplementary Table 7. Risk of bias assessment of included studies

	1- selection bias: random sequence generation	2- selection bias: allocation concealment	3- reporting bias: selective reporting	4- Performance bias: blinding (participants and personnel)	5- Detection bias: blinding (outcome assessment)	6- attrition bias: incomplete outcome data (high if <85% completion)	7- other sources of bias	**Final Risk of Bias**
Ahmed, 2019	Unclear	Unclear	Unclear	High	Unclear	Low	Unclear	High
Badrov, 2013	Unclear	High	High	High	Unclear	Low	Unclear	High
Baross, 2012	Unclear	Unclear	High	High	Unclear	Low	Unclear	High
Baross, 2013	Unclear	Unclear	High	High	Unclear	Low	Unclear	High
Carlson, 2016	Low	High	High	Low	Unclear	Low	Low	High
Correia, 2020	Low	Low	Low	High	Unclear	Low	Low	High
Farah, 2018	Low	Low	Low	High	Low	High	Unclear	High
Forjaz, 2019	Unclear	Unclear	Unclear	High	Unclear	Low	Unclear	High
Goessler, 2018	Low	Unclear	High	High	Unclear	Low	Unclear	High
Gordon, 2018	Unclear	Unclear	High	High	Unclear	Low	Low	High
Gregory, 2012	High	Low	Unclear	High	Unclear	Low	Unclear	High
Herrod, 2020	Low	Unclear	High	High	Unclear	Low	Low	High
Morrin, 2018	Unclear	Unclear	Low	High	Unclear	Low	Unclear	High
Ogbutor, 2019	Low	Low	Unclear	High	Unclear	Low	Low	High
Okamoto, 2019	Unclear	Unclear	Unclear	High	Low	Low	Low	High
Pagonas, 2017	Unclear	Unclear	Low	Unclear	Unclear	Low	Low	High
Punia, 2020	Low	Unclear	Low	Unclear	Low	Low	Unclear	High
Ritti-Dias, 2017	Low	Low	Low	High	Low	High	Low	High
Stiller-Moldovan, 2012	Low	Low	Low	High	Unclear	High	Unclear	High
Taylor, 2003	Unclear	Unclear	Unclear	High	unclear	Low	Low	High
Taylor, 2019	Unclear	Unclear	Low	High	Unclear	Low	Unclear	High
Wiley, 1992	Low	Unclear	Unclear	Unclear	Unclear	High	Unclear	High
Worachet, 2017	Unclear	Unclear	Unclear	High	Unclear	Low	Unclear	High
Yoon, 2019	Unclear	Unclear	High	High	Low	Low	Low	High

Supplementary Material 8. Domains Assessed in Grading the Strength of Recommendations

Risk of bias: we will decrease the quality of evidence recommendations by one level if >25% but <50% of the participants in our analysis come from trials we have evaluated to be at a high risk of bias, and by two levels if >50% of participants come from trials we have evaluated to be at a high risk of bias.

Inconsistency of results: inconsistency of results refers to significant heterogeneity within the results, we will assess between-study variation using τ^2 and the proportion of study variance not due to sampling error using I^2 and if the included studies have excessive variance (>50%) we will downgrade the quality of evidence recommendations,

Indirectness of evidence: we will initially rate RCTs as 'high' quality and non-RCTs as 'low' quality unless there are important limitations or strengths respectively.

Imprecision: if the confidence intervals are unreasonably large, resulting in a decreased ability to produce a significant result then the quality of recommendations will be downgraded

Publication bias: a sensitivity analysis will be conducted assessing the impact on unpublished studies on the analysis, this will be used to assess publication bias and the quality of evidence recommendations will be downgraded if significant publication bias is present

Supplementary Table 9. GRADE assessment of quality of evidence

Outcome, *no. of studies*	**Risk of Bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication Bias**	**Overall Quality**
Office SBP, *n = 24*	Serious limitations due to high risk of bias	Serious Limitations (I^2 > 50%)	No limitations	No limitations	Undetected	Very Low-Quality Evidence
Office DBP, *n = 24*	Serious limitations due to high risk of bias	Serious Limitations (I^2 > 50%)	No limitations	No limitations	Undetected	Very Low-Quality Evidence
Central SBP, *n = 4*	Serious limitations due to high risk of bias	Serious Limitations (I^2 > 50%)	No limitations	No limitations	Undetected	Very Low-Quality Evidence
Central DBP, *n = 3*	Serious limitations due to high risk of bias	No Limitations	No limitations	No limitations	Undetected	Low-Quality Evidence
Ambulatory SBP, *n = 8*	Serious limitations due to high risk of bias	Serious Limitations (I^2 > 50%)	No limitations	No limitations	Undetected	Very Low-Quality Evidence
Ambulatory DBP, *n = 8*	Serious limitations due to high risk of bias	Serious Limitations (I^2 > 50%)	No limitations	No limitations	Serious Limitations	Very Low-Quality Evidence
Adverse Events *n = 17*	Serious limitations due to high risk of bias	No Limitations	No limitations	No limitations	N/A	Low-Quality Evidence

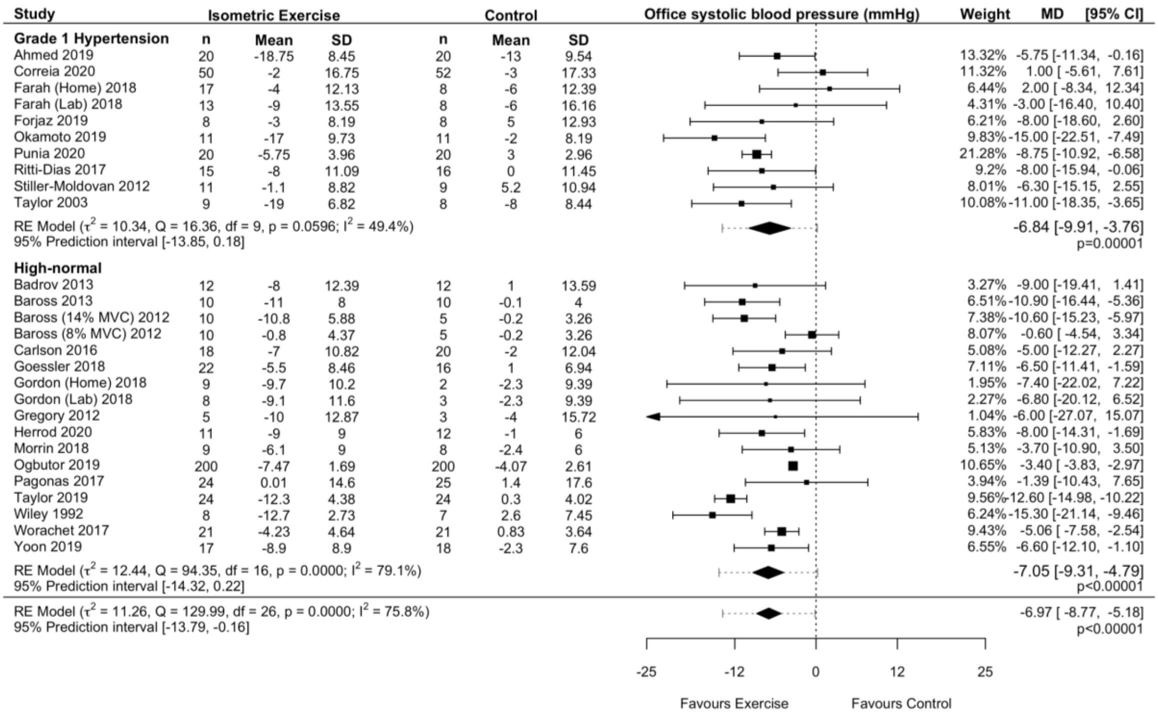
Supplementary Table 10 – Sources of funding in individual studies

Study (Author, year)	**Description of funding as reported by authors in manuscript**
Badrov, 2013	The IHG dynamometers used in this study were donated by Zona Health (Boise, ID). This work was supported by the University of Windsor (Grant # 808316; CLM), a Heart and Stroke Foundation of Canada Post- doctoral Fellowship (PJM), and an Ontario Graduate Scholarship (MBB)
Baross, 2012	NR
Baross, 2013	NR
Carlson, 2016	Australian Postgraduate Award (postgraduate student scholarship). University of New England, postgraduate research funds for equipment purchases. University of New England, Seed Grant to assist with paying research assistants.
Correia, 2020	This work was supported by grants from “Fundac"~ao de Amparo a Pesquisa do Estado de S~ao Paulo – FAPESP” (process#2016/ 16425-9), “Conselho Nacional de Desenvolvimento Cientıfico e Tecnologico–CNPQ” (process# 310508/2017-7), and “Coor- denac"~ao de Aperfeic"oamento de Pessoal de Nıvel Superior– CAPES” (process# 88881.133008/2016-01).
Farah, 2018	Supported by grants from “Conselho Nacional de Desenvolvimento Científico e Tecnológico – CNPQ”
Goessler, 2018	V.A.C was supported as a postdoctoral research fellow by Research Foundation Flanders (FWO). K.F.G was supported as a postdoctoral research fellow by CNPq (Brazil). V.A.C was supported by a research grant from Research Foundation Flanders (FWO). R.B. was supported by a research grant from Research Foundation Flanders (FWO).
Gordon, 2018	NR
Yoon, 2019	This work was supported by the Ministry of Education of the Republic of Korea and the National Research Foundation of Korea (NRF-2016 S1A 5A2A 03928101).
Jørgensen, 2018	Funding for the study has been obtained through internal funding from Aalborg University Hospital.
Ogbutor, 2019	Nil.
Okamoto, 2019	There are no funding sources for the present study.
Pagonas, 2017	NR

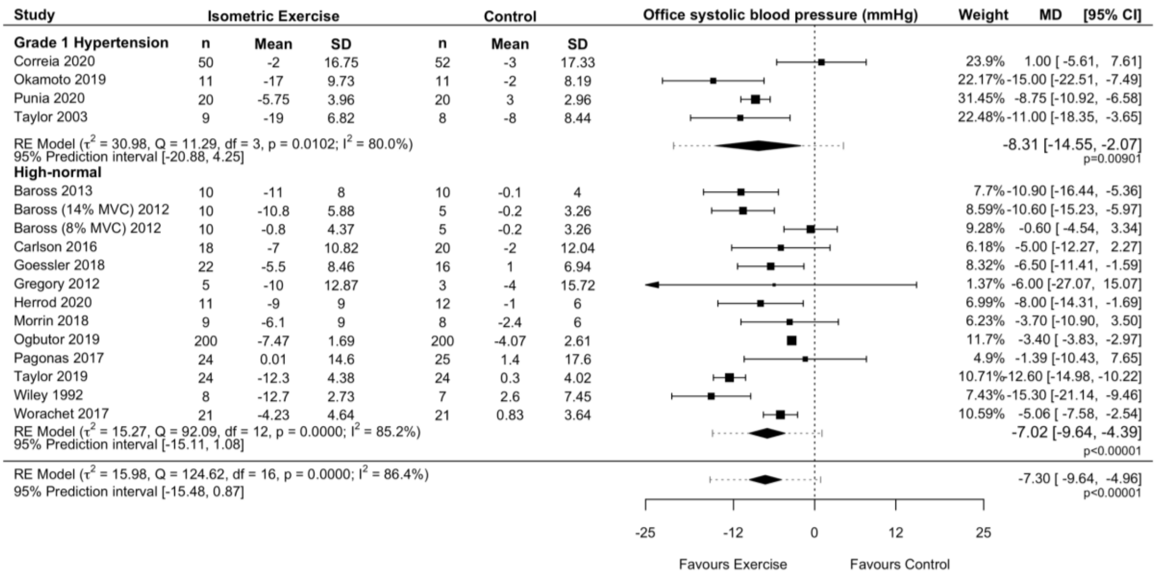
Pedrosa, 2018	NR
Punia, 2020	NR
Stiller-Moldovan, 2012	supported by the Canadian Institutes of Health Research (Frederick Banting and Charles Best Canada Graduate Master's Scholarship awarded to C. Stiller-Moldovan); University of Windsor (Start-Up Grant #808316 awarded to C. McGowan); Zona Health (Loan of programmed handgrip dynamometers).
Ritti-Dias, 2017	RMRD and MVGB hold a research productivity fellowship granted by CNPq and 'Fundação de Amparo à Ciência e Tecnologia do Estado de Pernambuco' – FACEPE (APQ-1177-4.09/14). This study is also supported by CAPES.
Taylor, 2003	NR
Wiley, 1992	NR
Ahmed, 2019	NR
Morrin, 2018	NR
Taylor, 2019	NR
Gregory, 2012	NR
Worachet, 2017	Research funding from Faculty of Medical Technology
Fujimoto, 2017	This work was supported by Grant-in-Aid for Scientific Research©
Forjaz, 2019	Fundação de Amparo à Pesquisa do Estado de São Paulo - Brazil, secondary - Laboratório de Hipertensão do Hospital das Clínicas da Faculdade de Medicina da USP - Brazil
Gerage, 2019	NR
Herrod, 2020	This research was funded by the Medical Research Council and Versus Arthritis via the MRC-ARUK Centre for Musculoskeletal Ageing Research (MR/P021220/1). P.J.J. Herrod is supported by a research training fellowship jointly awarded by the Royal College of Surgeons of England and the Dunhill Medical Trust.

NR = Not reported

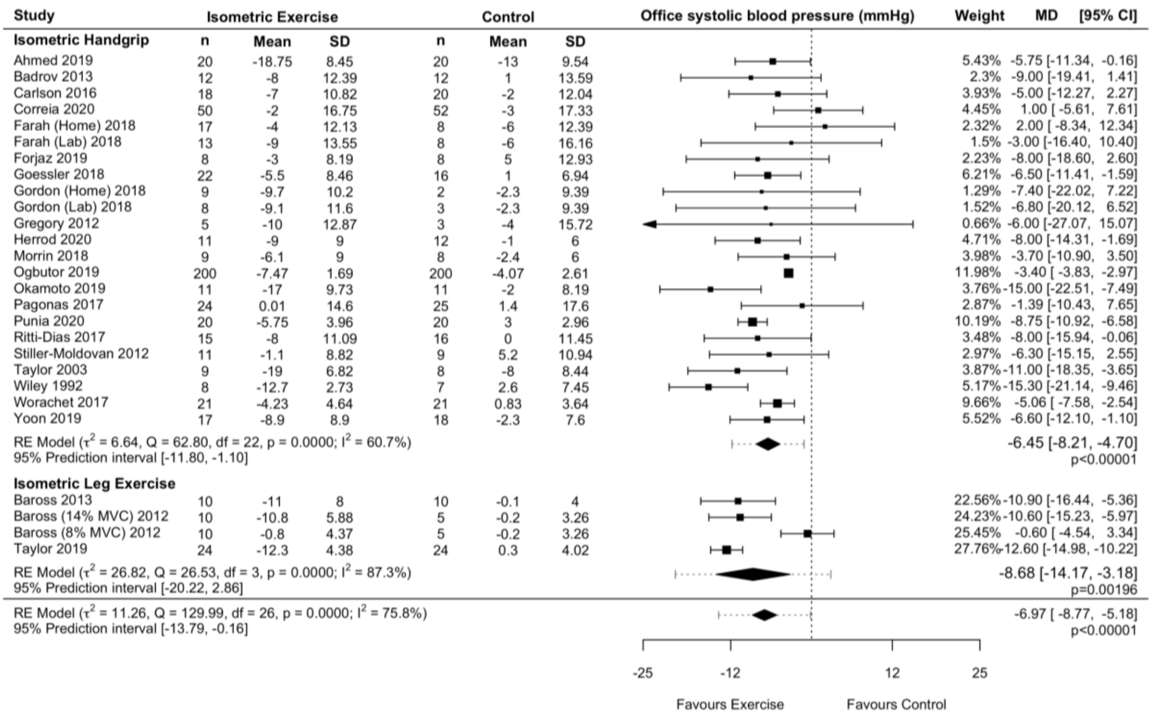
Supplementary Figure 11. Effect of isometric resistance training on office systolic blood pressure, with sub-analysis by baseline blood pressure classification.



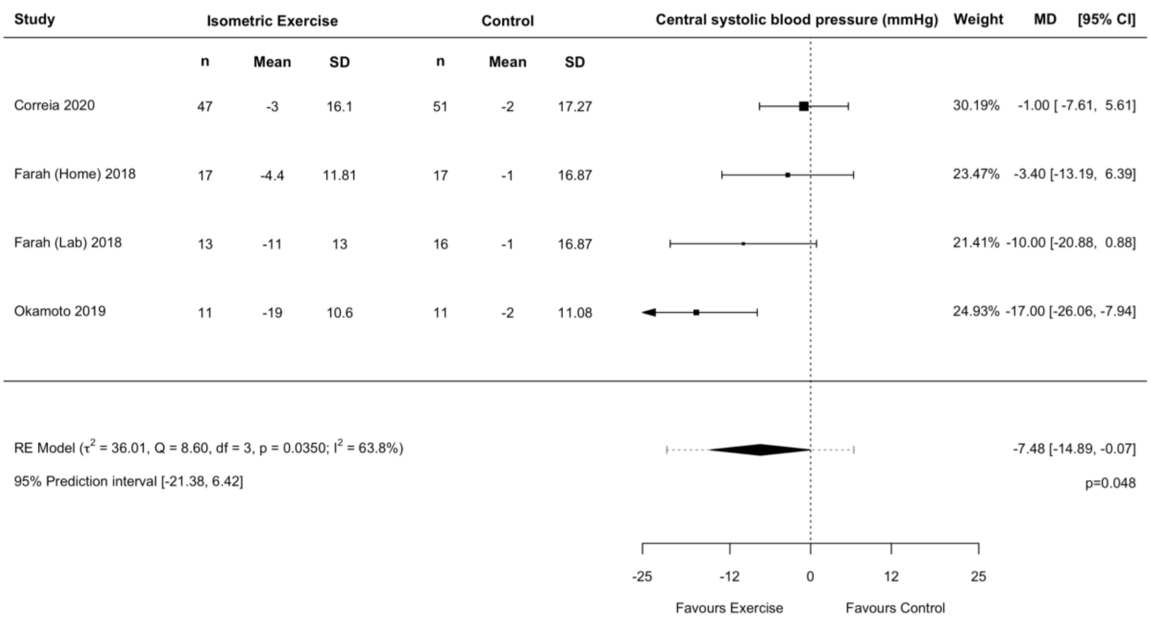
Supplementary Figure 12. Sensitivity analysis showing the effect of isometric resistance training on systolic blood pressure after removing studies where >80% of participants were medicated for hypertension



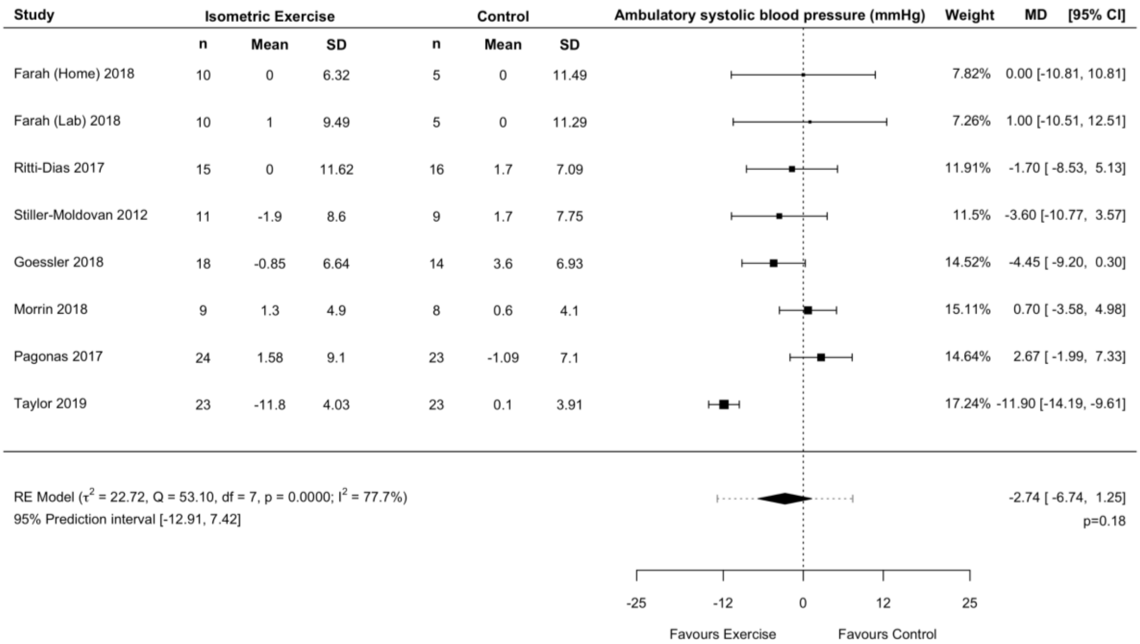
Supplementary Figure 13. Sub-analysis displaying the effect of different types of isometric resistance training, isometric handgrip (n = 23) or isometric leg exercise (n = 3) on systolic blood pressure



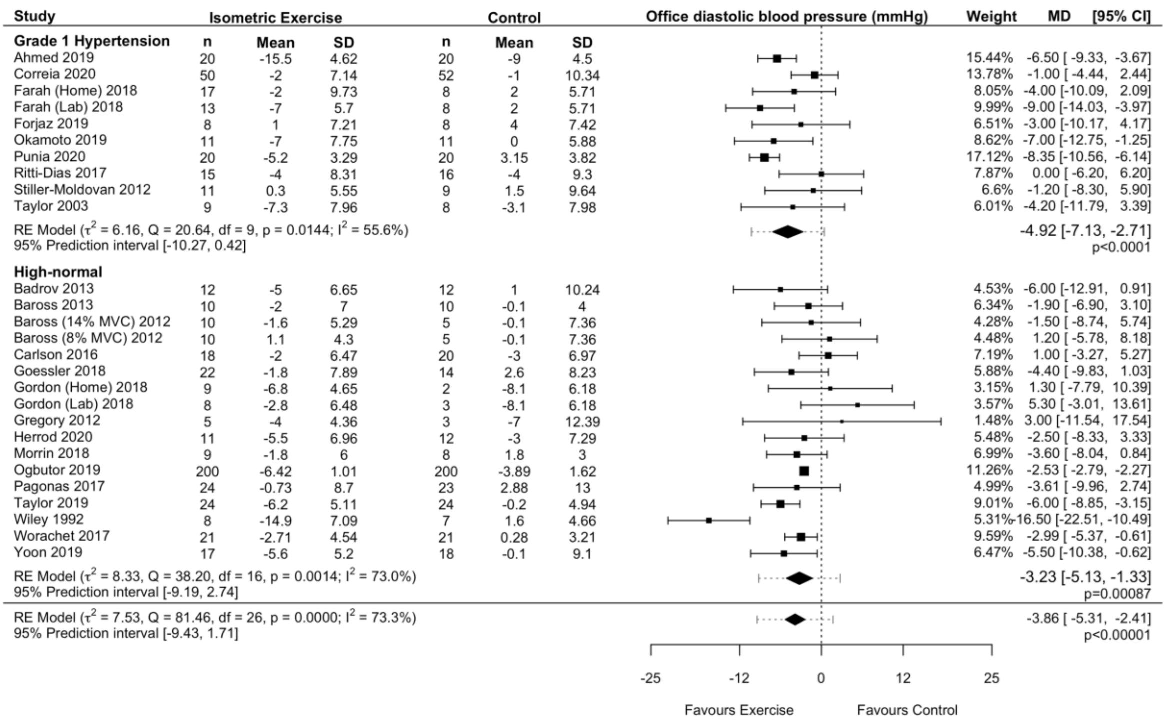
Supplementary Figure 14. Effect of isometric resistance training on central systolic blood pressure



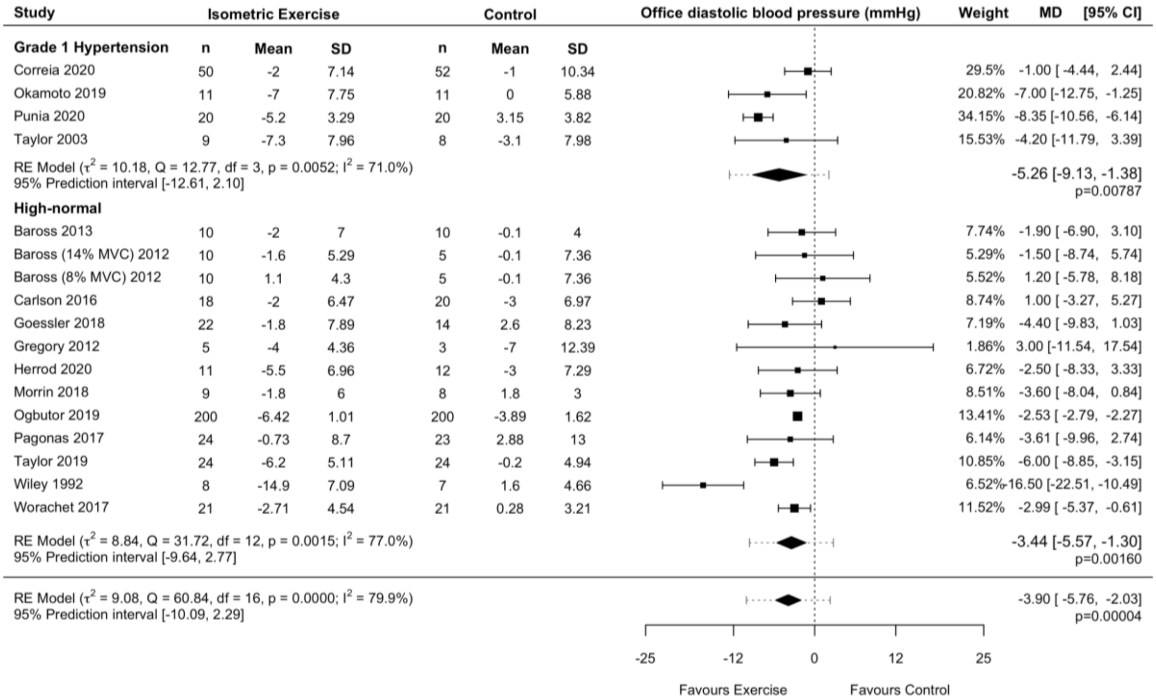
Supplementary Figure 15. Effect of isometric resistance training on 24-hour ambulatory systolic blood pressure



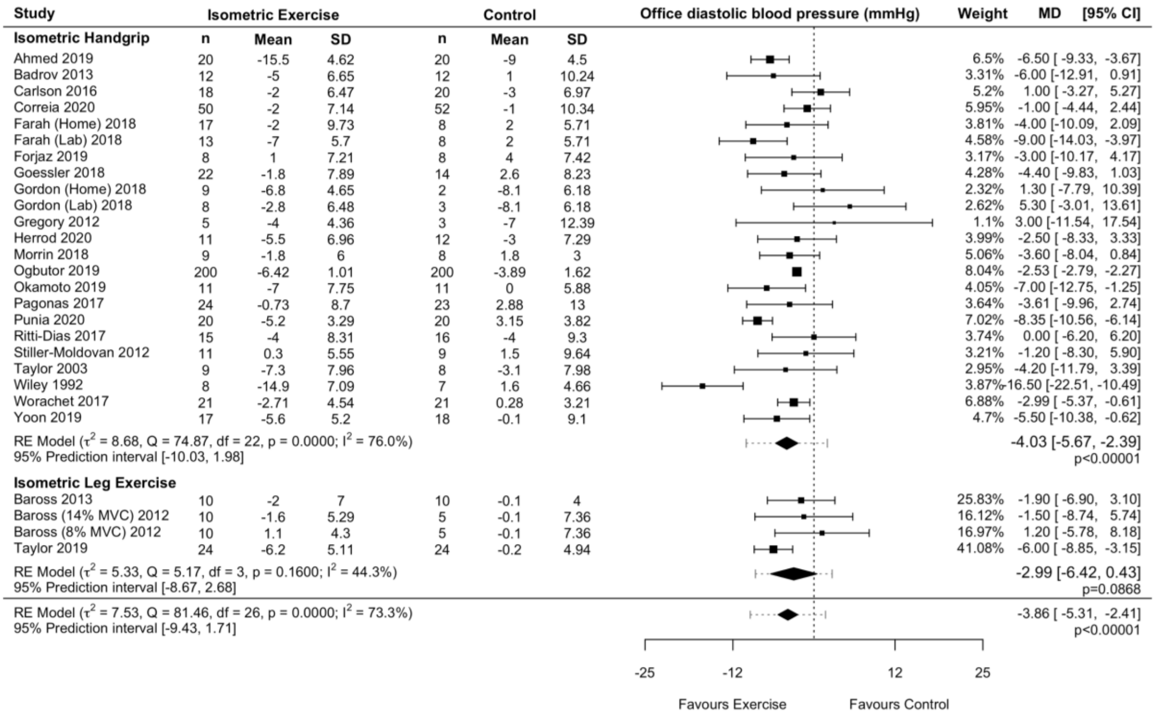
Supplementary Figure 16. Effect of isometric resistance training on office diastolic blood pressure, with sub-analysis by baseline blood pressure classification.



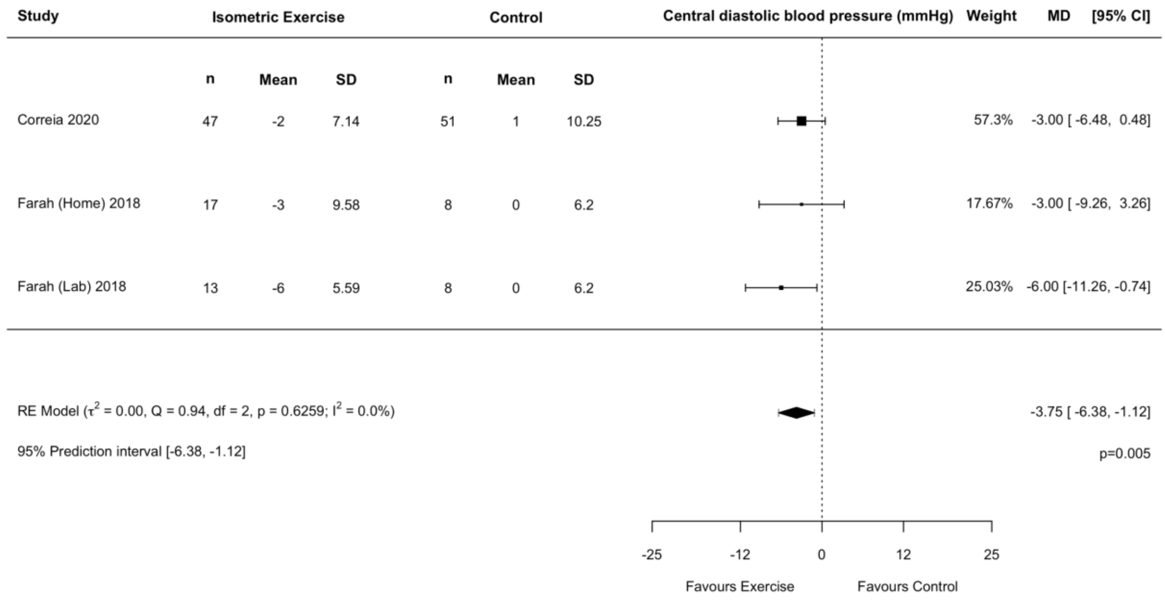
Supplementary Figure 17. Sensitivity analysis showing the effect of isometric resistance training on office diastolic blood pressure after removing studies where >80% of participants were medicated for hypertension



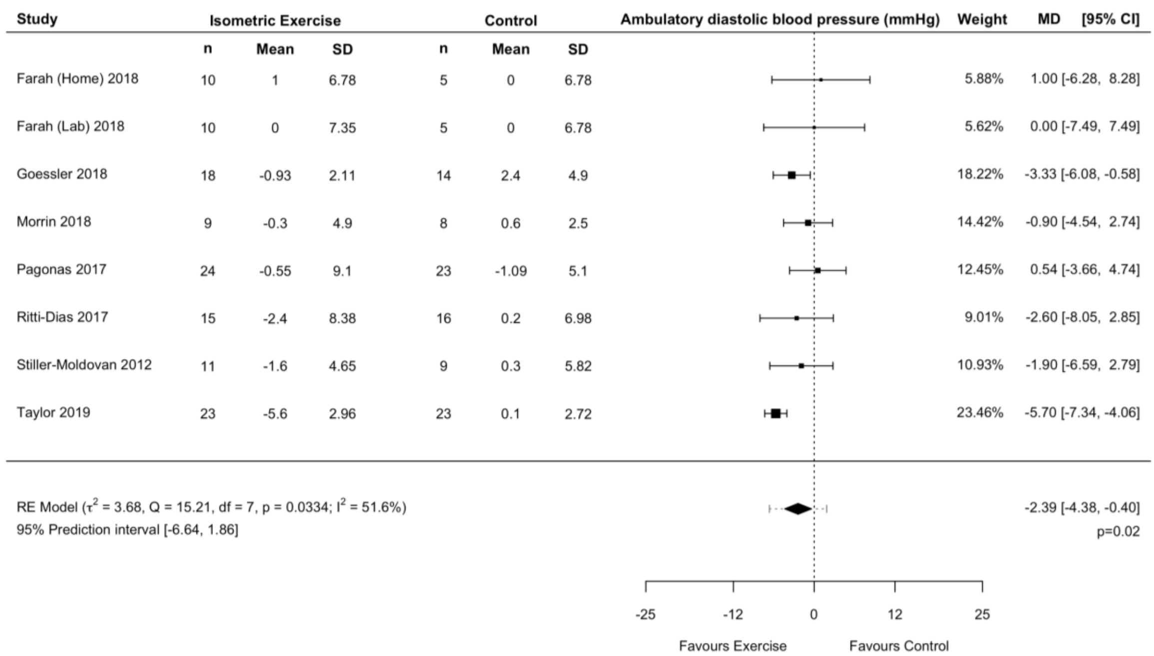
Supplementary Figure 18. Sub-analysis displaying the effect of different types of isometric resistance training, isometric handgrip (n = 23) or isometric leg exercise (n = 3) on office diastolic blood pressure



Supplementary Figure 19. Effect of isometric resistance training on central diastolic blood pressure

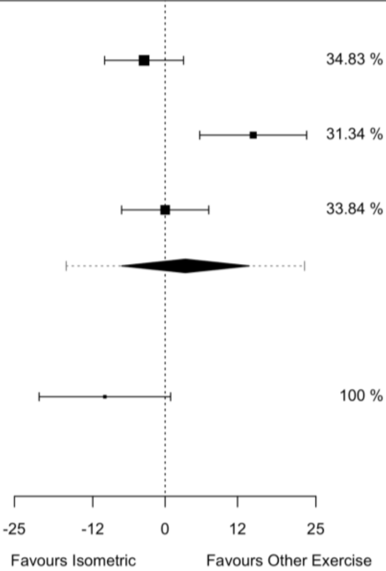


Supplementary Figure 20. Effect of isometric resistance training on 24-hour ambulatory diastolic blood pressure



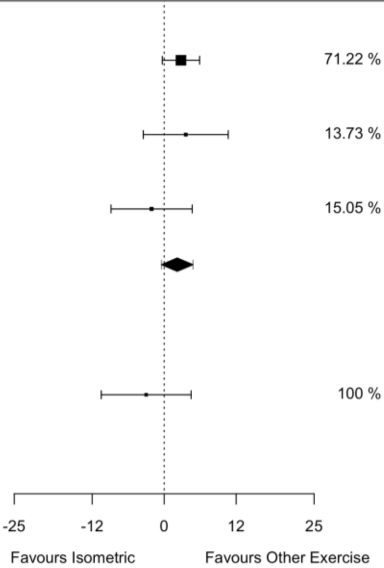
Supplementary Figure 21. Effectiveness of isometric resistance training compared to aerobic exercise and dynamic resistance exercise in reducing office systolic blood pressure

Study	Isometric Exercise			Other Exercise			Office systolic blood pressure (mmHg)	Weight	MD [95% CI]
Aerobic Exercise	**n**	**Mean**	**SD**	**n**	**Mean**	**SD**			
Yoon 2019	19	-9.1	11.1	17	-5.6	8.9		34.83 %	-3.50 [-10.04, 3.04]
Pagonas 2017	24	3.3	15.26	19	-11.3	14.29		31.34 %	14.60 [5.74, 23.46]
Herrod 2020	11	-9	9	13	-9	9		33.84 %	0.00 [-7.23, 7.23]
RE Model (τ^2 = 72.53, Q = 10.77, df = 2, p = 0.0046; I^2 = 83.3%) 95% Prediction interval [-16.41, 23.12]									3.36 [-7.22, 13.94] p=0.53
Dynamic Resistance Exercise									
Forjaz 2019	8	-5	8.96	8	5	12.93		100 %	-10.00 [-20.90, 0.90]

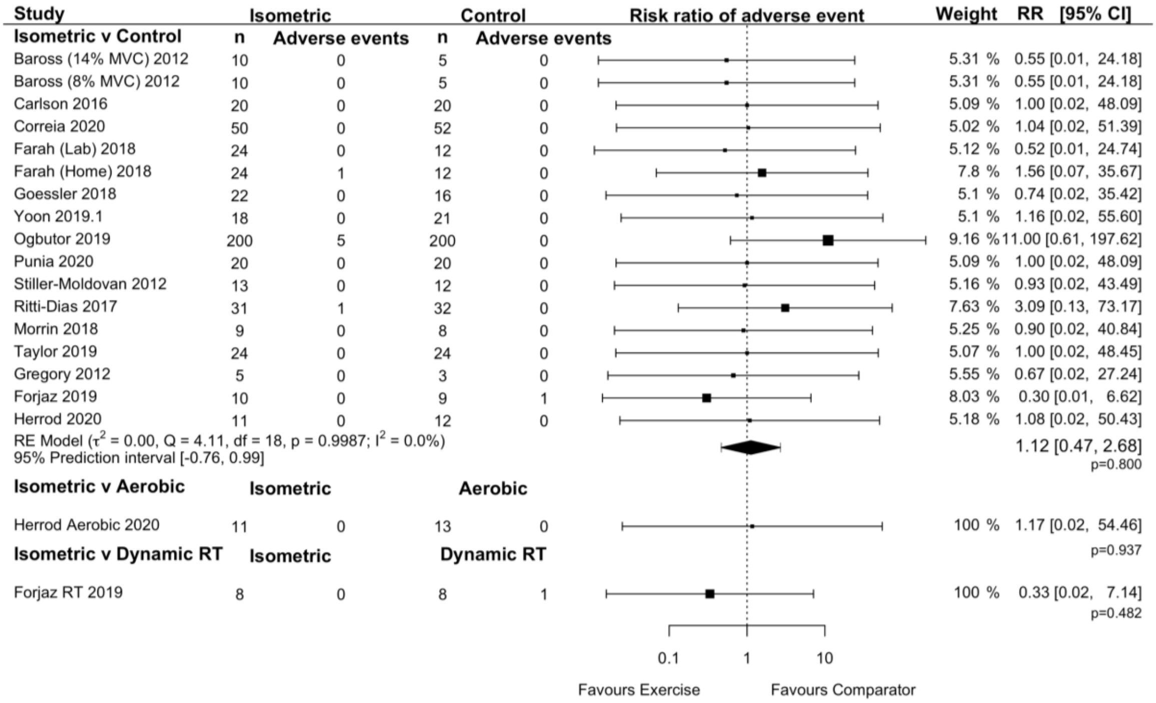


Supplementary Figure 22. Effectiveness of isometric resistance training compared to aerobic exercise and dynamic resistance exercise in reducing office diastolic blood pressure

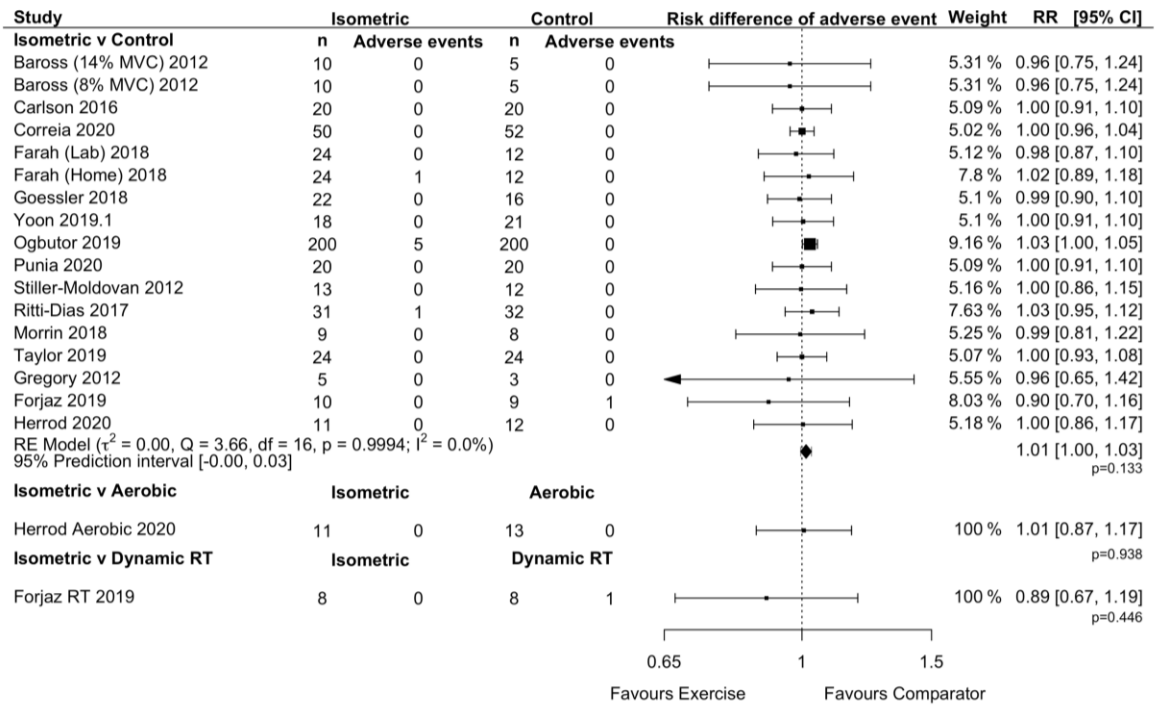
Study	Isometric Exercise			Other Exercise			Office diastolic blood pressure (mmHg)	Weight	MD [95% CI]
Aerobic Exercise	**n**	**Mean**	**SD**	**n**	**Mean**	**SD**			
Yoon 2019	19	-2.8	4.2	17	-5.6	5.2		71.22 %	2.80 [-0.31, 5.91]
Pagonas 2017	24	1.3	8.53	19	-2.3	13.81		13.73 %	3.60 [-3.48, 10.68]
Herrod 2020	11	-5.5	6.96	13	-3.4	9.88		15.05 %	-2.10 [-8.87, 4.67]
RE Model (τ^2 = 0.00, Q = 1.84, df = 2, p = 0.3977; I^2 = 0.0%) 95% Prediction interval [-0.45, 4.80]									2.17 [-0.45, 4.80] p=0.10
Dynamic Resistance Exercise									
Forjaz 2019	8	1	7.86	8	4	7.42		100 %	-3.00 [-10.49, 4.49]



Supplementary Figure 23. Relative risk of adverse events occurring during isometric exercise compared to a non-exercise control, aerobic exercise and dynamic resistance training (dynamic RT)



Supplementary Figure 24. Absolute risk of adverse events occurring during isometric exercise compared to a non-exercise control, aerobic exercise and dynamic resistance training (dynamic RT)

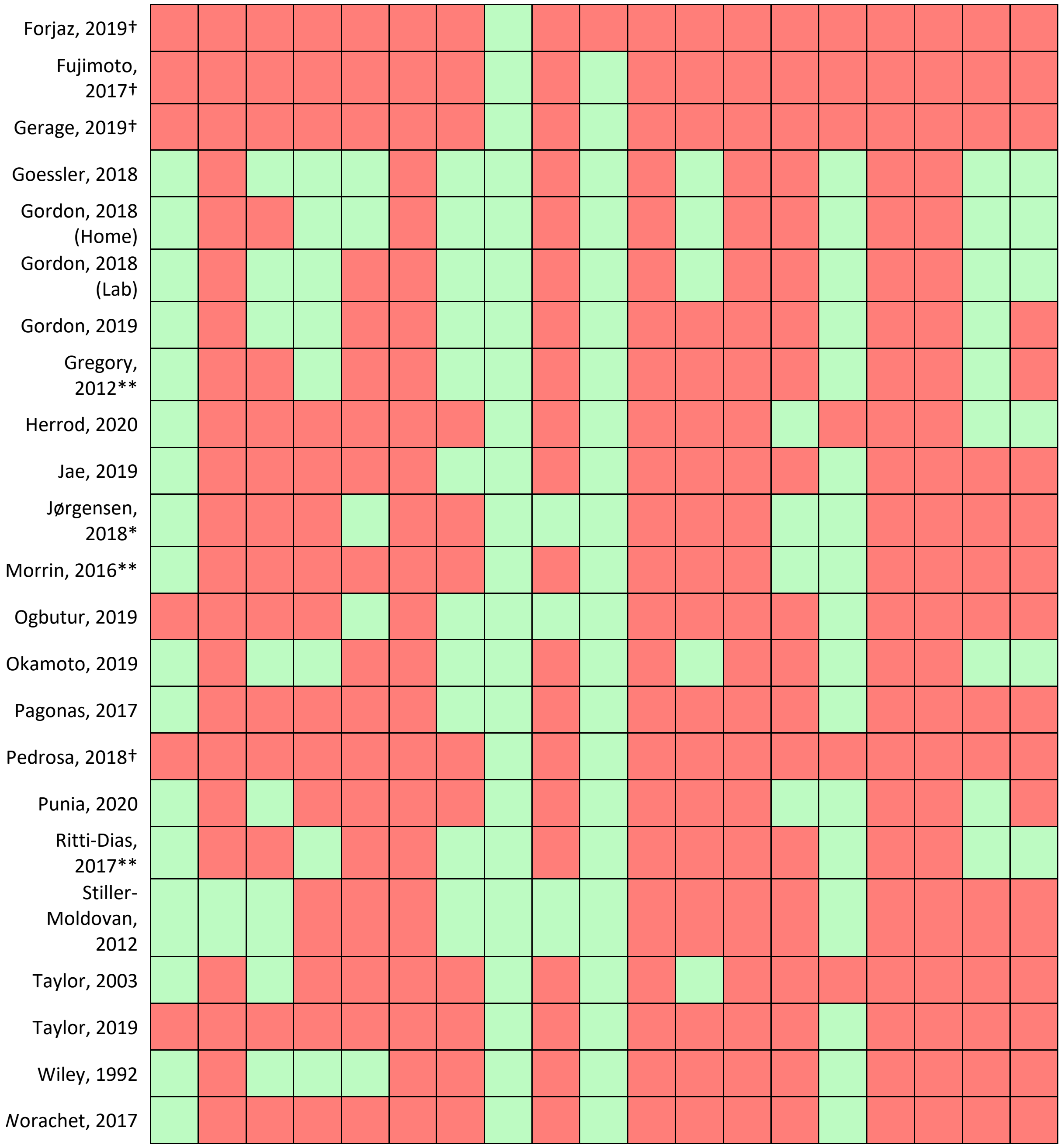


Supplementary Material 25: Quality of reporting

Quality of reporting was poor across the majority of studies (Supplementary Table 24). The mean number of CERT criteria[47] reported in the included studies was 6.4 out of a possible 19 (SD 2.9, range 4 to 12). There were five criteria of CERT which no study reported, including: 7a. rules for progression, 10. non-exercise components, 14a. tailoring of exercise, 14b. individual tailoring of exercise and 15. rule for determining starting level. All studies (n=24) reported criteria 8: description of exercise to enable replication.

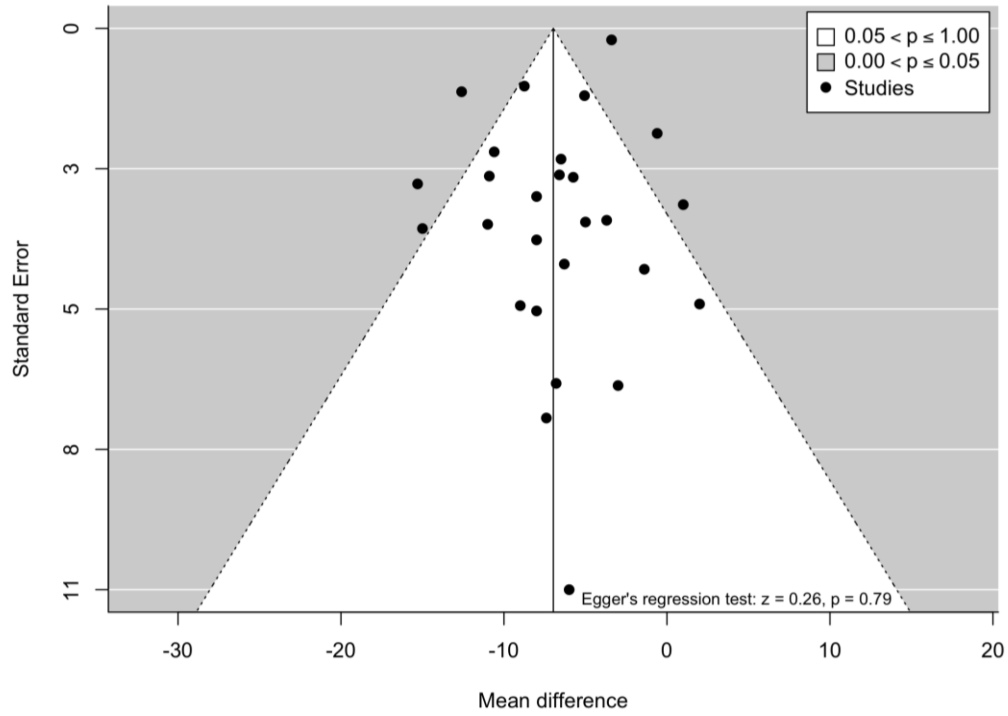
Supplementary Table 26. Table indicating the criteria of the consensus on exercise reporting template (CERT) met by the included studies. Green = Criteria satisfied, red = criteria not satisfied

CERT Criteria	Detailed description of:											Described:							
Study	1. Exercise Equipment	2. Qualification of supervisor	4. Supervision	5. How adherence was measured	6. Motivation strategies	7a. Rules for progression	7b. Progression	8. Exercise, to enable replication	9. Home component	13. Exercise intervention	14b. Individual tailoring of exercise	3. Individual or group	10. Non-exercise components	11. Type and n of adverse events	12. Setting of exercise	14a. Tailoring of exercise	15. Rule for determining starting level	16a. Adherence assessment	16b. Intervention delivered as planned
Ahmed , 2019	Green	Green	Red	Red	Red	Red	Green	Green	Green	Green	Red	Red	Red	Red	Green	Red	Red	Red	Green
Alves, 2020†	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red
Badrov, 2013	Green	Red	Green	Green	Red	Red	Green	Green	Red	Green	Red	Green	Red	Red	Green	Red	Red	Green	Green
Baross, 2012 (85% HRpeak)	Green	Red	Red	Red	Red	Red	Green	Green	Red	Green	Red	Red	Red	Red	Green	Red	Red	Red	Red
Baross, 2012 (70% HRpeak)	Green	Red	Red	Red	Red	Red	Green	Green	Red	Green	Red	Red	Red	Red	Green	Red	Red	Red	Red
Baross, 2013	Green	Red	Red	Red	Green	Red	Green	Green	Red	Green	Red	Red	Red	Red	Green	Red	Red	Red	Red
Carlson, 2016	Green	Red	Green	Red	Red	Red	Green	Green	Red	Green	Red	Red	Red	Green	Green	Red	Red	Green	Green
Correia, 2020	Green	Green	Green	Green	Green	Red	Red	Green	Green	Green	Red	Green	Red	Red	Green	Red	Red	Green	Green
Farah, 2018 (Home)	Green	Red	Green	Green	Red	Red	Green	Green	Red	Green	Red	Green	Red	Green	Green	Red	Red	Red	Red
Farah, 2018 (Lab)	Green	Red	Green	Green	Red	Red	Green	Green	Red	Green	Red	Red	Red	Green	Green	Red	Red	Red	Red

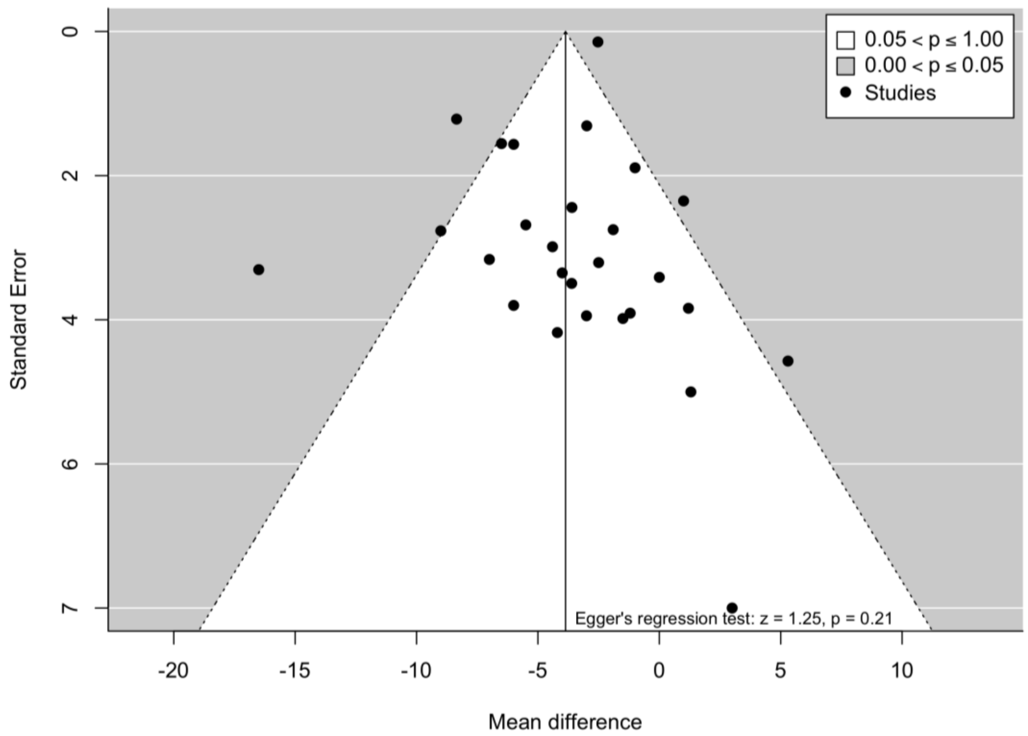


Forjaz, 2019†
Fujimoto, 2017†
Gerage, 2019†
Goessler, 2018
Gordon, 2018 (Home)
Gordon, 2018 (Lab)
Gordon, 2019
Gregory, 2012**
Herrod, 2020
Jae, 2019
Jørgensen, 2018*
Morrin, 2016**
Ogbutur, 2019
Okamoto, 2019
Pagonas, 2017
Pedrosa, 2018†
Punia, 2020
Ritti-Dias, 2017**
Stiller-Moldovan, 2012
Taylor, 2003
Taylor, 2019
Wiley, 1992
Norachet, 2017

Supplementary Figure 27. Conventional funnel plots for studies providing data for systolic (A) and diastolic (B) blood pressure, displaying no significant publication bias.

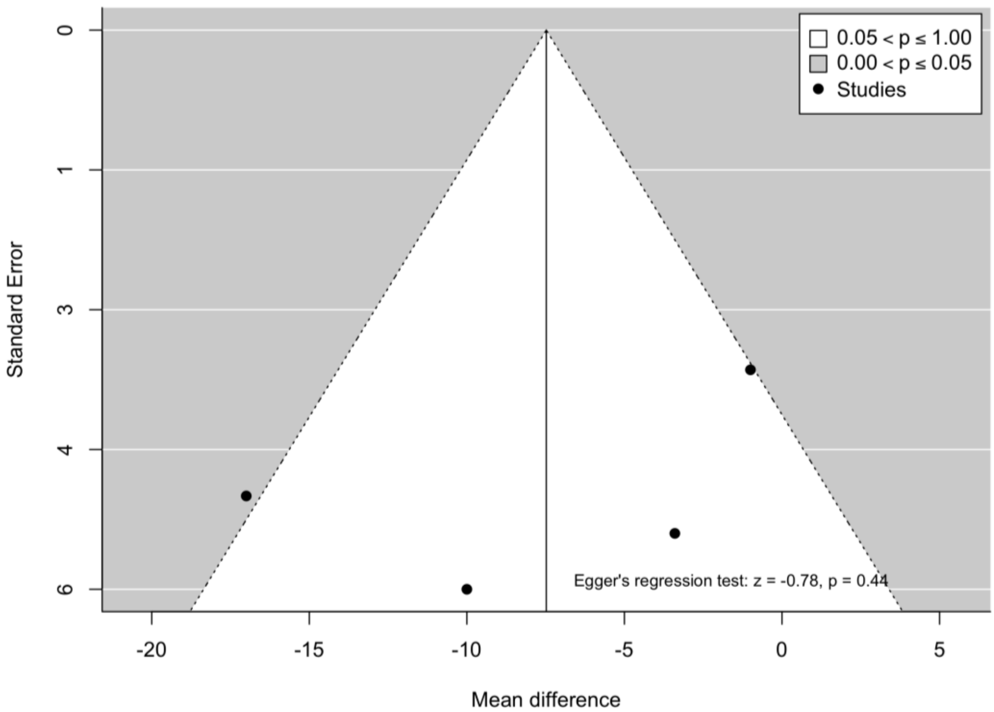


A

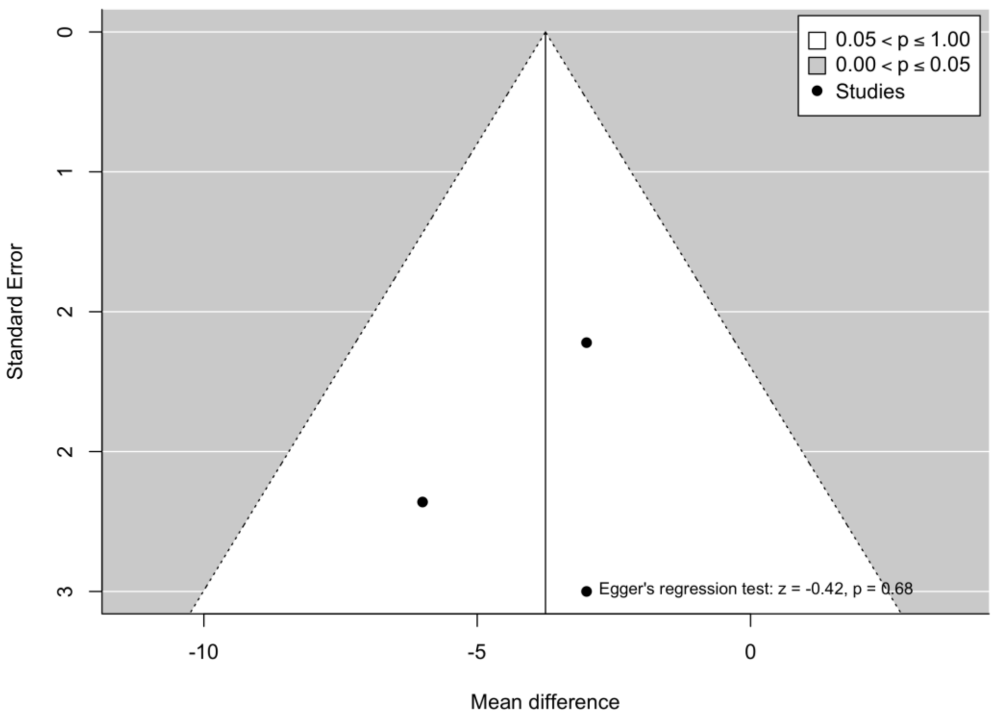


B

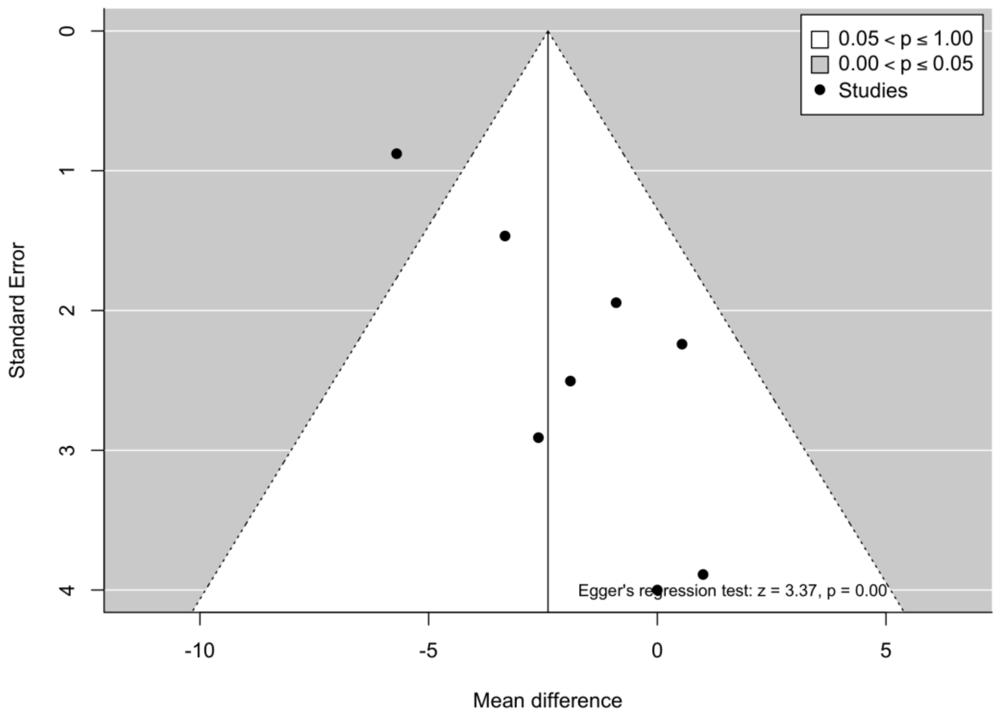
Supplementary Figure 28. Conventional funnel plots of central (A, B) and 24-hour ambulatory (C, D) systolic and diastolic blood pressure respectively



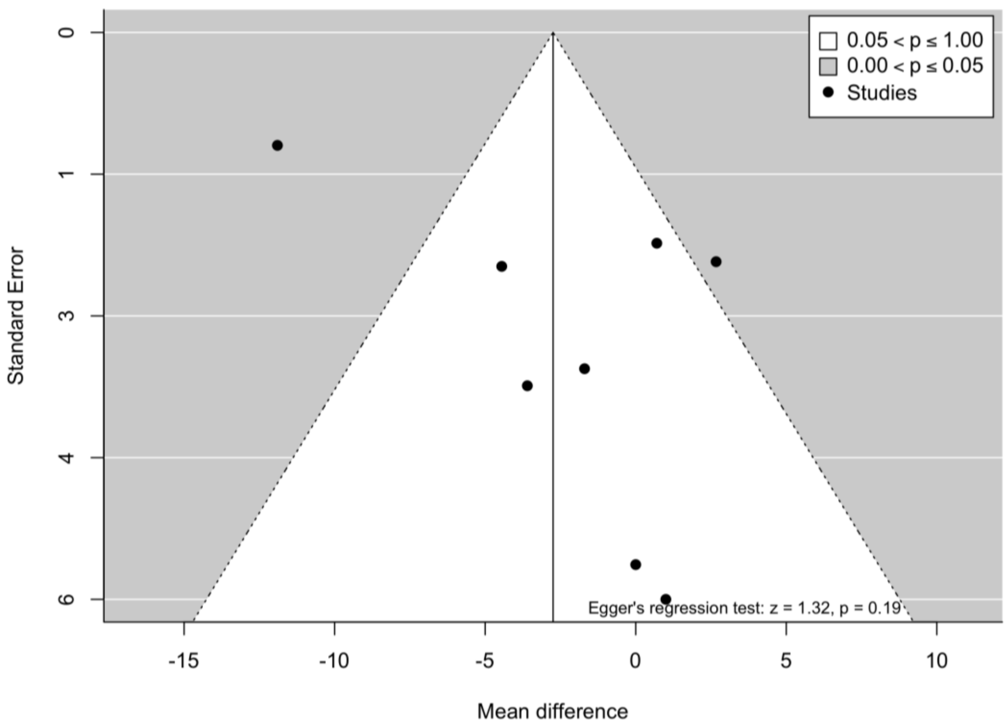
A



B

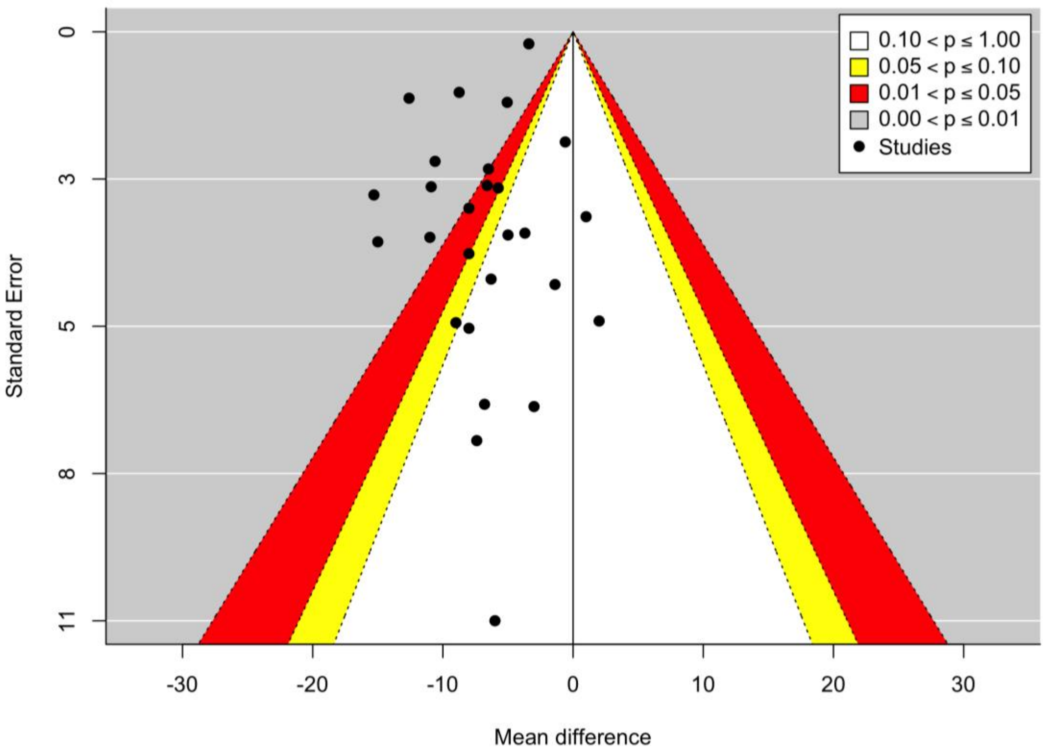

0.05 < p ≤ 1.00
0.00 < p ≤ 0.05
Studies
Standard Error
0
1
2
3
4
-10
-5
0
5
Mean difference
Egger's regression test: z = 3.37, p = 0.00

C

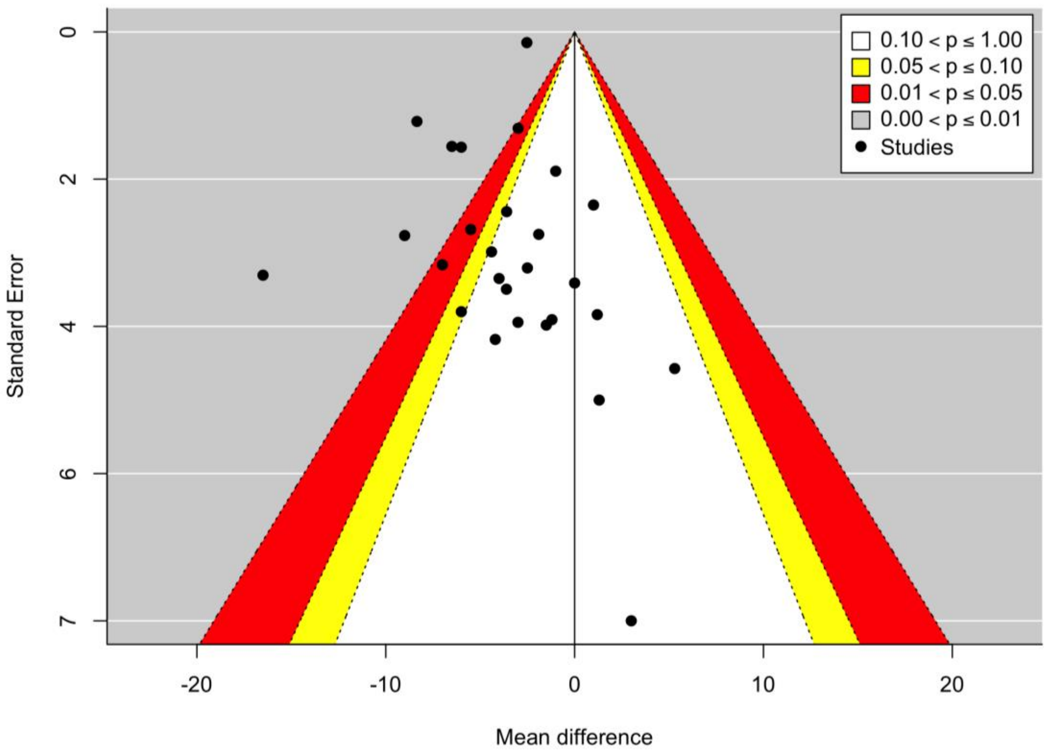

0.05 < p ≤ 1.00
0.00 < p ≤ 0.05
Studies
Standard Error
0
1
3
4
6
-15
-10
-5
0
5
10
Mean difference
Egger's regression test: z = 1.32, p = 0.19

D

Supplementary Figure 29. Contour-enhanced funnel plots for studies providing data for systolic (A) and diastolic (B) blood pressure, displaying no evidence of data dredging

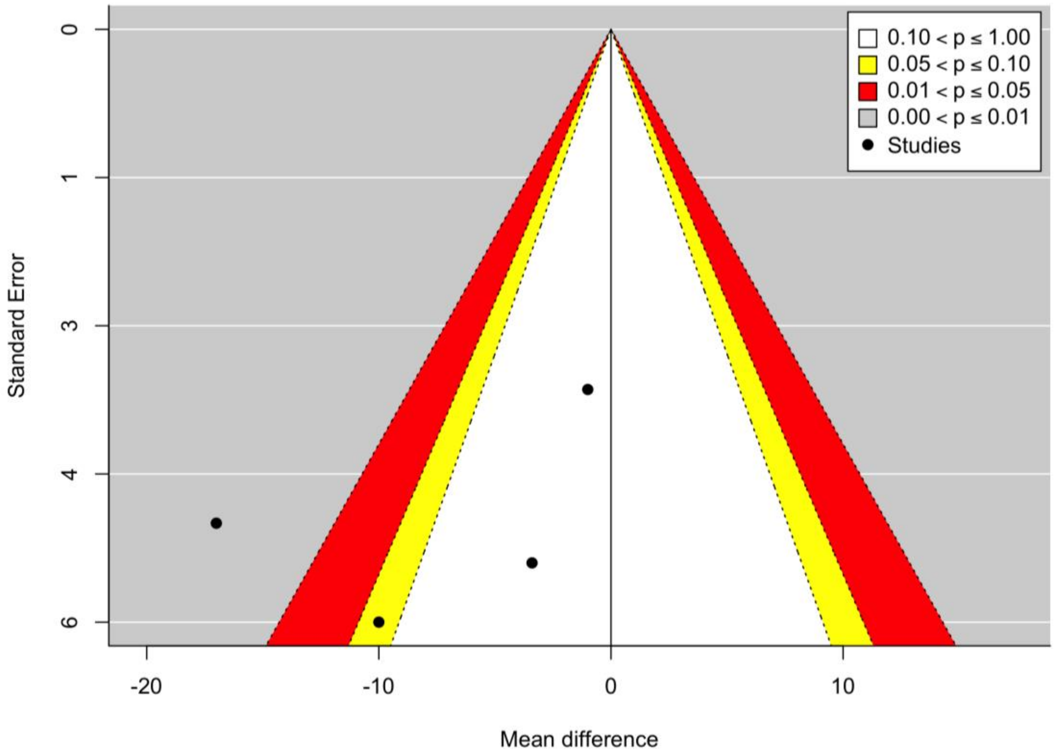


A

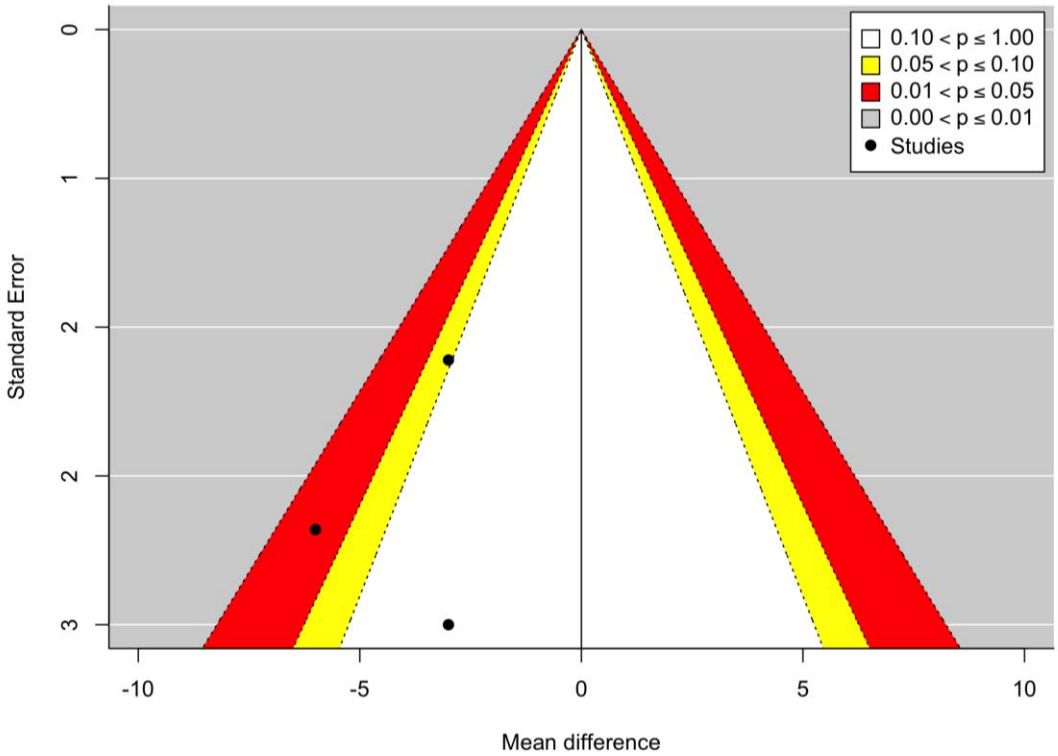


B

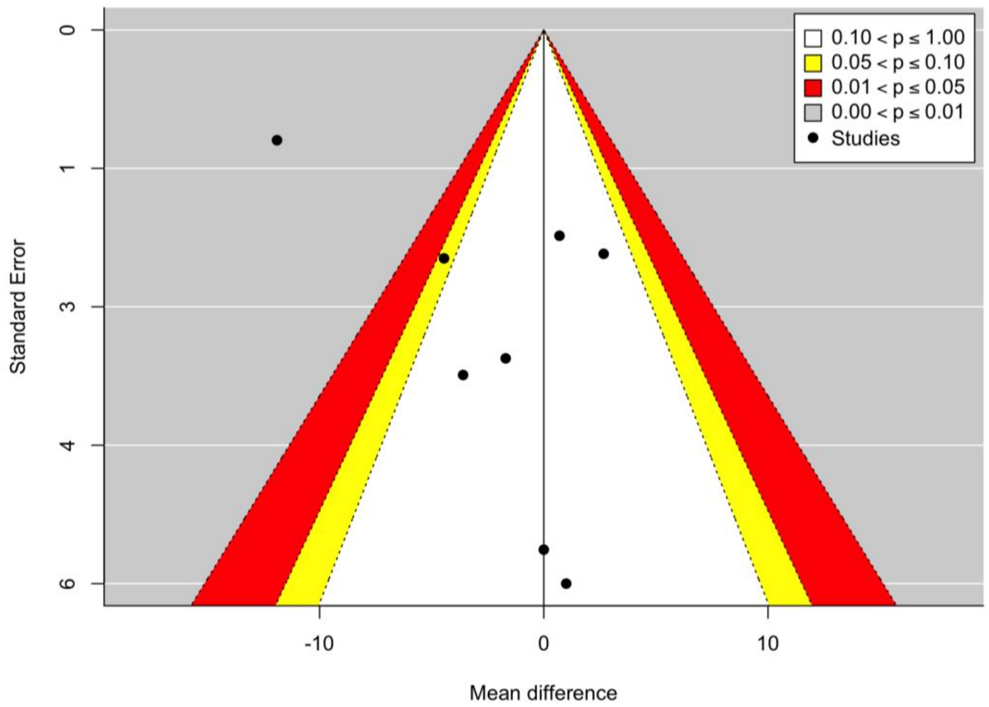
Supplementary Figure 30. Contour-enhanced funnel plots of central (A, B) and ambulatory (C, D) systolic and diastolic blood pressure respectively



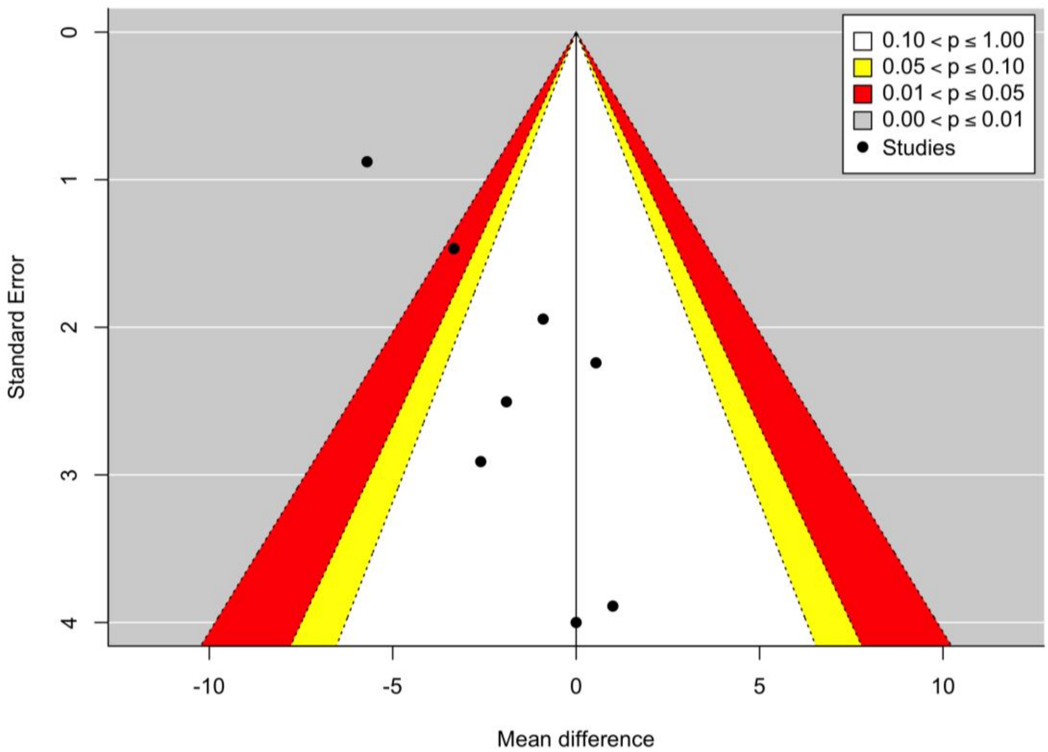
A



B

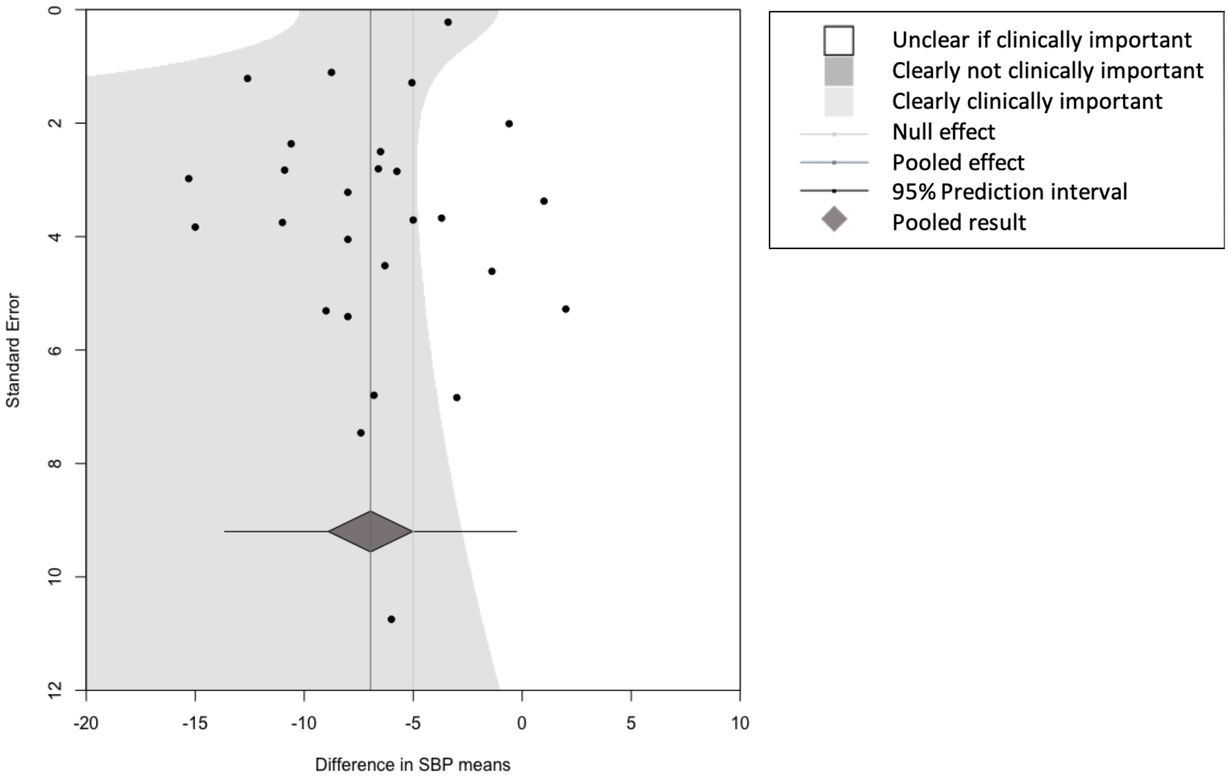

0.10 < p ≤ 1.00
0.05 < p ≤ 0.10
0.01 < p ≤ 0.05
0.00 < p ≤ 0.01
Studies
Standard Error
0
1
3
4
6
-10
0
10
Mean difference

C

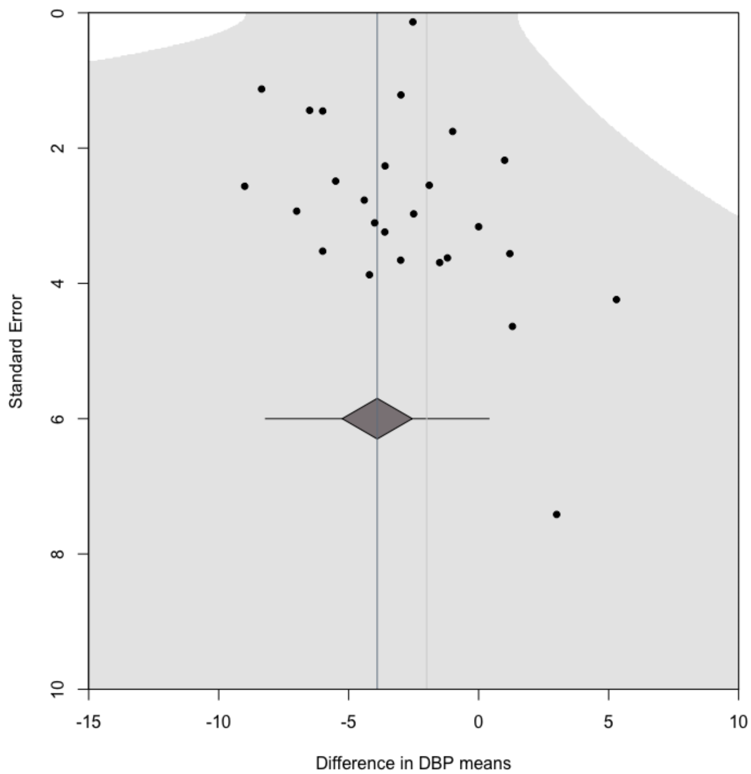

0.10 < p ≤ 1.00
0.05 < p ≤ 0.10
0.01 < p ≤ 0.05
0.00 < p ≤ 0.01
Studies
Standard Error
0
1
2
3
4
-10
-5
0
5
10
Mean difference

D

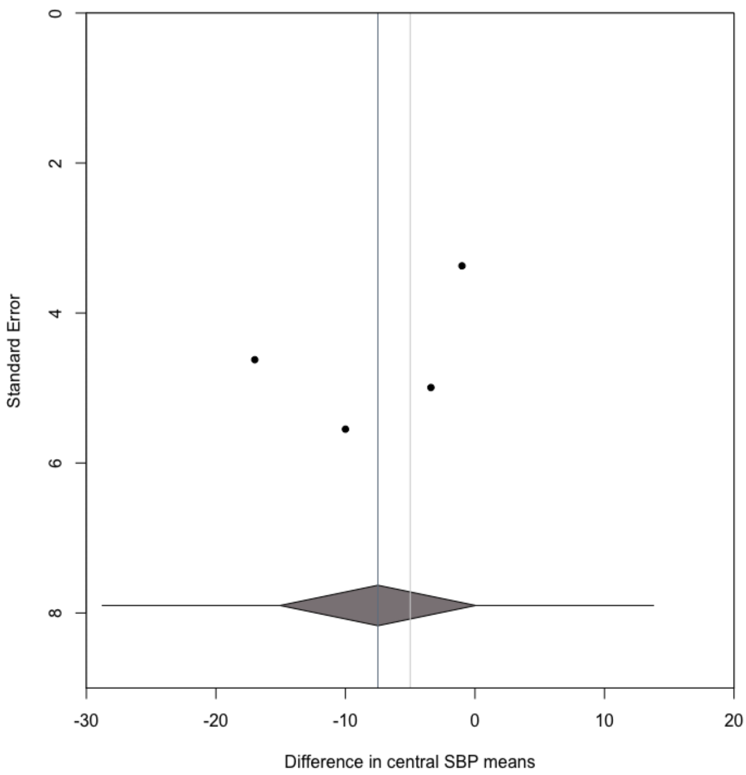
Supplementary Figure 31. Extended funnel plots displaying the implications of a future trial on the pooled effect. Plots are: A. Office systolic blood pressure, B. Office diastolic blood pressure, C. Central systolic blood pressure, D. Central diastolic blood pressure, E. 24-hour ambulatory systolic blood pressure, F. 24-hour ambulatory diastolic blood pressure



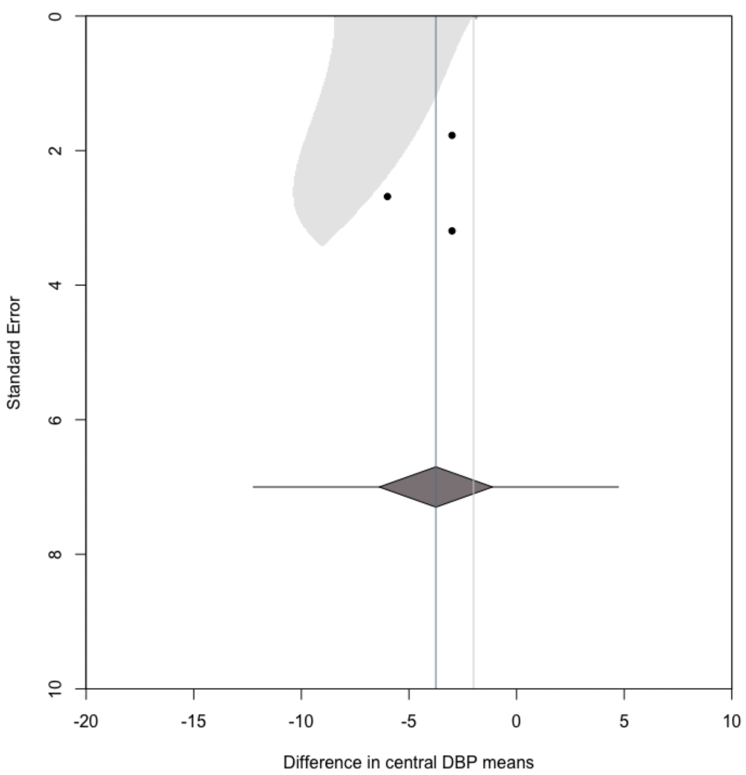
A. Office systolic blood pressure



B. Office diastolic blood pressure

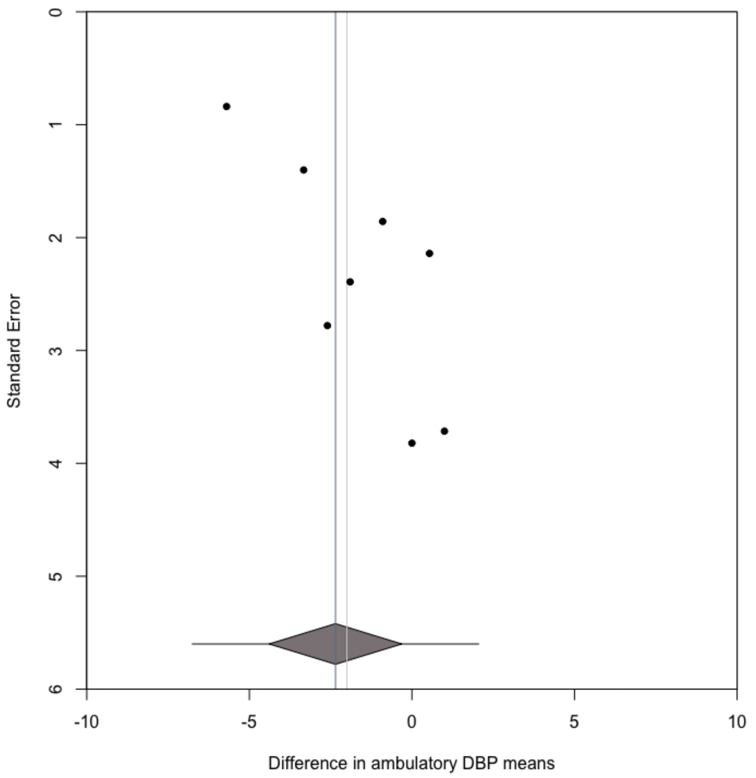


C. Central systolic blood pressure

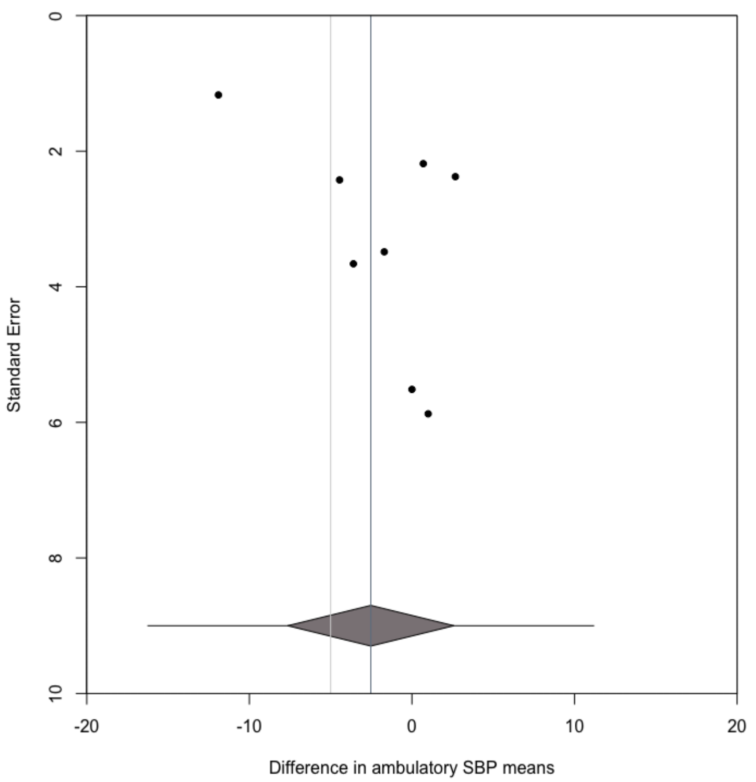


D. Central diastolic blood pressure

E. 24-hour ambulatory systolic blood pressure



F. 24-hour ambulatory diastolic blood pressure



References

1. Zorzela, L.*, et al.* PRISMA harms checklist: improving harms reporting in systematic reviews. *BMJ* **352**, i157 (2016).
2. Nosek, B.A.*, et al.* Transparency and openness promotion (TOP) guidelines. (2016).
3. Shea, B.J.*, et al.* AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *BMJ* **358**, j4008 (2017).
4. Hansford, H., Jones, M. D., Wewege, M., Parmenter, B., Smart, N., McLeod, K., & Schutte, A. . The Efficacy and Safety of Isometric Exercise for Blood Pressure Reduction in Adults with Raised Blood Pressure and Hypertension: A Systematic Review and Meta-Analysis Protocol. . Vol. osf.io/7fnga (Open Science Framework, 2020).
5. Halfpenny, N.J.A., Quigley, J.M., Thompson, J.C. & Scott, D.A. Value and usability of unpublished data sources for systematic reviews and network meta-analyses. *Evidence Based Medicine* **21**, 208 (2016).
6. Golder, S., Loke, Y.K., Wright, K. & Norman, G. Reporting of Adverse Events in Published and Unpublished Studies of Health Care Interventions: A Systematic Review. *PLoS medicine* **13**, e1002127-e1002127 (2016).
7. Unger, T.*, et al.* 2020 International Society of Hypertension Global Hypertension Practice Guidelines. *Hypertension* **75**, 1334-1357 (2020).
8. American College of Sports Medicine, Riebe, D., Ehrman, J.K., Liguori, G. & Magal, M. *ACSM's guidelines for exercise testing and prescription*, (Wolters Kluwer, 2018).
9. Inder, J.D.*, et al.* Isometric exercise training for blood pressure management: a systematic review and meta-analysis to optimize benefit. *Hypertens Res* **39**, 88-94 (2016).
10. Administration, U.S.F.a.D. Investigational new drug safety reporting. Vol. 21 (2019).
11. Rohatgi, A. WebPlotDigitizer. (2020).
12. Higgins JPT, T.J., Chandler J, Cumpston M, Li T, Page MJ, Welch VA (ed.) *Cochrane Handbook for Systematic Reviews of Interventions* (Cochrane, 2019).
13. Gordon, B.D.H.*, et al.* A comparison of blood pressure reductions following 12-weeks of isometric exercise training either in the laboratory or at home. *Journal of the american society of hypertension* **12**, 798-808 (2018).
14. Ogbutor, G.U., Nwangwa, E.K. & Uyagu, D.D. Isometric handgrip exercise training attenuates blood pressure in prehypertensive subjects at 30% maximum voluntary contraction. *Niger J Clin Pract* **22**, 1765-1771 (2019).
15. Punia, S. & Kulandaivelan, S. Home-based isometric handgrip training on RBP in hypertensive adults-Partial preliminary findings from RCT. *Physiother Res Int* **25**, e1806 (2020).
16. Morrin, N.M. Buckinghamshire New University (validated by Coventry University) (2018).
17. Yoon, E.S., Choo, J., Kim, J.-Y. & Jae, S.Y. Effects of Isometric Handgrip Exercise versus Aerobic Exercise on Arterial Stiffness and Brachial Artery Flow-Mediated Dilation in Older Hypertensive Patients. *The Korean Journal of Sports Medicine* **37**, 162-170 (2019).
18. Higgins, J.P.*, et al.* The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* **343**, d5928 (2011).

19. Viechtbauer, W. Conducting meta-analyses in R with the metafor package. *Journal of statistical software* **36**, 1-48 (2010).
20. Cook, N.R., Cohen, J., Hebert, P.R., Taylor, J.O. & Hennekens, C.H. Implications of small reductions in diastolic blood pressure for primary prevention. *Arch Intern Med* **155**, 701-709 (1995).
21. Sterne, J.A.C.*, et al.* Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. *BMJ* **343**, d4002 (2011).
22. Langan, D.S., Alexander; Higgins, Julian PT; Gregory, Walter. extfunnel: Additional Funnel Plot Augmentations. in *R Package* (2013).
23. Guyatt, G.H.*, et al.* GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* **336**, 924-926 (2008).
24. Ahmed, R.Y., Hanfy, H.M., Mahmoud, M.F. & Wafaa, M.K. The Effect of Isometric Hand Grip on Blood Pressure in Post Menopausal Hypertension. *The Medical Journal of Cairo University* **87**, 2685-2691 (2019).
25. Correia, M.A.*, et al.* Effects of isometric handgrip training in patients with peripheral artery disease: a randomized controlled trial [with consumer summary]. *Journal of the American Heart Association 2020 Feb 18;9(4):e013596* (2020).
26. Farah, B.Q.*, et al.* Supervised, but not home-based, isometric training improves brachial and central blood pressure in medicated hypertensive patients: A randomized controlled trial. *Frontiers in Physiology* **9**(2018).
27. Okamoto, T., Hashimoto, Y. & Kobayashi, R. Isometric handgrip training reduces blood pressure and wave reflections in East Asian, non-medicated, middle-aged and older adults: a randomized control trial. *Aging clinical and experimental research* (2019).
28. Ritti Dias, R.M. Isometric training on blood pressure and on the autonomic modulation of hypertensive patients. *https://clinicaltrials.gov/show/NCT03216317* (2017).
29. Stiller-Moldovan, C., Kenno, K. & McGowan, C.L. Effects of isometric handgrip training on blood pressure (resting and 24 h ambulatory) and heart rate variability in medicated hypertensive patients. *Blood Press Monit* **17**, 55-61 (2012).
30. Taylor, A.C., McCartney, N., Kamath, M.V. & Wiley, R.L. Isometric training lowers resting blood pressure and modulates autonomic control. *Med Sci Sports Exerc* **35**, 251-256 (2003).
31. Badrov, M.B., Horton, S., Millar, P.J. & McGowan, C.L. Cardiovascular stress reactivity tasks successfully predict the hypotensive response of isometric handgrip training in hypertensives. *Psychophysiology* **50**, 407-414 (2013).
32. Baross, A.W., Wiles, J.D. & Swaine, I.L. Effects of the intensity of leg isometric training on the vasculature of trained and untrained limbs and resting blood pressure in middle-aged men. *International Journal of Vascular Medicine* **2012 (no pagination)**(2012).
33. Baross, A.W., Wiles, J.D. & Swaine, I.L. Double-leg isometric exercise training in older men. *Open Access Journal of Sports Medicine 2013 Jan 30;4:33-40* (2013).
34. Carlson, D.J.*, et al.* The efficacy of isometric resistance training utilizing handgrip exercise for blood pressure management: A randomized trial. *Medicine (Baltimore)* **95**, e5791 (2016).
35. Goessler, K.F., Buys, R., vander Trappen, D., Vanhumbeeck, L. & Cornelissen, V.A. A randomized controlled trial comparing home-based isometric handgrip exercise

versus endurance training for blood pressure management. *Journal of the American Society of Hypertension 2018 Apr;12(4):285-293* (2018).
36. Gregory, M. The effects of isometric handgrip training on carotid arterial compliance and resting blood pressure in postmenopausal women. (2012).
37. Herrod, P.J.J., Lund, J.N. & Phillips, B.E. Time-efficient physical activity interventions to reduce blood pressure in older adults: a randomised controlled trial. *Age Ageing* (2020).
38. Pagonas, N.*, et al.* Aerobic versus isometric handgrip exercise in hypertension: a randomized controlled trial. *J Hypertens* **35**, 2199-2206 (2017).
39. Taylor, K.A.*, et al.* Neurohumoral and ambulatory haemodynamic adaptations following isometric exercise training in unmedicated hypertensive patients. *Journal of hypertension* **37**, 827-836 (2019).
40. Google Translate. (Google, 2020).
41. Worachet, S. & Nakmareong, S. Effect of isometric handgrip exercise on blood pressure in pre-hypertensive women. *Journal of Associated Medical Sciences* **50**, 197-197 (2017).
42. Alves, A. The Hypotensive Effects of Home-Based Isometric Handgrip Training in Older Adults With Pre-Hypertension and Hypertension - The HoldAge Trial. *https://clinicaltrials.gov/show/NCT04275037* (2020).
43. Fujimoto, N. Effects of Isometric Handgrip Training on Blood Pressure in Patients with Heart Failure. *http://www.who.int/trialsearch/Trial2.aspx?TrialID=JPRN-UMIN000027265* (2017).
44. Gerage, A.M. Effect of Isometric Handgrip Training on Ambulatory Blood Pressure in Patients With Hypertension. *https://clinicaltrials.gov/show/NCT03896334* (2019).
45. Jørgensen, M.G., Ryg, J., Danielsen, M.B., Madeleine, P. & Andersen, S. Twenty weeks of isometric handgrip home training to lower blood pressure in hypertensive older adults: a study protocol for a randomized controlled trial. *Trials* **19**(2018).
46. Pedrosa, R.P. Isometric Hand Grip Training in Obstructive Sleep Apnea (OSA). *https://clinicaltrials.gov/show/NCT03757169* (2018).
47. Slade, S.C., Dionne, C.E., Underwood, M. & Buchbinder, R. Consensus on Exercise Reporting Template (CERT): Explanation and Elaboration Statement. *Br J Sports Med* **50**, 1428-1437 (2016).