



Exercise Blood Pressure & Cardiovascular Disease: Clinical & Methodological Considerations.

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To Wayne and Susan

To David, Fiona, Esther, Sarah and Melinda

STATEMENT AND DECLARATIONS.

Declaration of originality

This thesis contains no material that has previously been accepted for a degree or diploma by the University of Tasmania, or any other institution, except by way of background information and of which is duly acknowledged in the thesis. To the best of my knowledge and belief, this thesis contains no material that has previously been published or written by another person, except where due acknowledgement is made in the text of the thesis, nor does this thesis contain any material that infringes copyright. I have acknowledged, where appropriate, the specific contributions made by my co-authors of published and submitted manuscripts.

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The candidate was supported by an Australian Government Research Training Program (RTP) Scholarship and The Broadreach Elite PhD scholarship.

Statement of ethical conduct

All research associated with this thesis abides by the International and Australian codes of human and animal experimentation, and full ethical approval from relevant institutions was obtained for all studies outlined in this thesis. All individual participants provided written informed consent for involvement in the respective research studies.

Myles Nicholas Moore

1 November 2021

PUBLICATIONS BY THE AUTHOR AND STATEMENT OF CO AUTHOR CONTRIBUTION TO PAPERS CONTAINED WITHIN THIS THESIS.

The following papers are incorporated into the Chapters of this thesis and were either published or submitted for publication in peer-reviewed scientific journals during the course of candidature. The papers appear as they were published (or submitted) with minor modifications to fit in context with this thesis.

Chapter 2

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Author contributions:

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J.E. Sharman - Study conception, study design, critically revised the manuscript.

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Chapter 3

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**ABSTRACT PRESENTATIONS AT SCIENTIFIC
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Grace and Peace to you,

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THESIS ABSTRACT.

Cardiovascular disease (CVD) is the leading cause of morbidity and mortality worldwide, with the number one risk factor being high blood pressure (BP). The diagnosis and management of high BP has been traditionally made based on BP measured in a clinic setting under resting conditions. Based on this mode of assessment, it was estimated that in 2019 over 1.2 billion adults worldwide had high BP. However, many more people have high BP that is either not diagnosed or well-controlled. Indeed, 8-20% of individuals with normal clinic BP have high BP when measured outside of the clinic (based on gold-standard ambulatory BP monitoring) and thus remain at elevated CVD risk. Since out-of-clinic BP monitoring is not always available, alternative methods are needed to improve the identification and management of high BP and its related CVD risk.

Recent research indicates that an abnormally high BP response to dynamic exercise (termed a hypertensive response to exercise; HRE) is an independent signal for future cardiovascular morbidity, events and mortality, likely because of high BP missed by standard clinic (resting) BP. Whilst this work highlights the potential importance of measuring the BP response to exercise for the identification of high BP-related CVD risk, there are still several key gaps in the clinical understanding of exercise BP. Indeed, several CVD risk factors may influence the BP response to exercise, but the specific nature of these relationships is unknown, and whether CVD risk is different in those with an HRE remains unclear. Additionally, several factors that relate to how exercise BP is measured (i.e. methodological considerations) may influence clinical interpretation of the exercise BP response. Thus, the broad aims of this research were to determine: (1) the relationship between exercise BP and individual CVD risk factors and (2) if some methodological factors may influence clinical interpretation of exercise BP.

Manual measurement of BP during an exercise test is the recommended standard, but automated BP measurement is an alternative method routinely used in clinical settings. Study 1 (Chapter 2) was undertaken to determine the concordance between manual and automated BP during a standard treadmill exercise test in 41 individuals with type 2 diabetes mellitus (66 ± 5 years; 54% male). Concordance between manual and automated BP across all exercise stages was found to be excellent for systolic BP (intraclass correlation=0.964 [95% confidence intervals: 0.942-0.977]). Concordance between manual and automated diastolic BP across all exercise stages was found to be moderate-to-good (intraclass correlation=0.784 [95% confidence interval: 0.672-0.858]). These results highlight that automated measurement of BP may be a suitable alternative to manual measurement of BP during clinical exercise testing among individuals with type 2 diabetes mellitus.

Study 2 (Chapter 3) was a systematic review and meta-analysis to (1) assess the relationship between exercise BP and cardiac structure, and (2) determine if cardiac structure is different in those with an HRE, across various study populations (including those with or without high BP at rest). Exercise systolic BP (at any intensity) was associated with increased left ventricular (LV) mass, LV mass index, relative wall thickness, posterior wall thickness and interventricular septal thickness ($p < 0.05$ all). Those with an HRE (recorded at any intensity) had higher risk of LV hypertrophy, increased LV mass, LV mass index, relative wall thickness, posterior wall thickness, interventricular septal thickness and left atrial diameter vs. those without an HRE ($p < 0.05$ all). Results were broadly similar between studies with different population characteristics and highlight the potential hypertension-related CVD risk associated with an HRE.

A second systematic review and meta-analysis was performed as Study 3 (Chapter 4) to examine the relationship between exercise BP and general CVD risk factors. This study also aimed to determine if CVD risk was higher in those with an HRE compared to those without an HRE across different study populations (including those with or without high BP at rest). Exercise systolic BP (at any intensity) was associated with arterial, lipid and kidney function-related CVD risk markers ($p < 0.05$ all). Those with an HRE (during any intensity) had greater arterial stiffness, elevated metabolic and lipid profiles, a higher degree of inflammation, and lower kidney function than those without an HRE ($p < 0.05$ all). The poorer CVD risk profile among those with an HRE was also consistent amongst population groups with or without high BP at rest. These results suggest that an HRE should be considered an important indicator of heightened CVD risk.

To gain a deeper understanding of the relationships between CVD risk factors and exercise BP, Study 4 (Chapter 5) was conducted with the aim to quantify the various pathways of association between CVD risk factors and exercise BP, whilst also determining what CVD risk factor/s were most-strongly related to exercise BP. This study was a cross-sectional analysis of data from 660 participants (44.3 ± 2.6 years; 53% male) in the Childhood Determinants of Adult Health 3 study that had BP measured during a submaximal exercise test. Most CVD risk factors were found to be associated with exercise systolic BP via a relation with clinic (resting) BP ($p < 0.05$ all). Clinic BP, waist-to-hip ratio and cardiorespiratory fitness were the variables most-strongly associated with exercise systolic BP ($p < 0.05$ all), suggesting lifestyle modification of these risk factors could be a worthwhile strategy to decrease exercise BP-related CVD risk.

Pharmacotherapy can decrease clinic (resting) BP, and therefore, may also be expected to lower exercise BP. Some medications, such as spironolactone, can also improve cardiorespiratory fitness, which has the potential to mask any treatment effects on exercise BP. Therefore, Study 5 (Chapter 6) was conducted to examine the effect of spironolactone on exercise BP after considering (correcting for) cardiorespiratory fitness using data from a previously completed three month clinical trial of spironolactone intervention compared with placebo. This post-hoc analysis included 102 participants with an HRE (54 ± 9 years; 52% male) that had exercise BP measured during low intensity cycling (50, 60 or 70% age-predicted maximal heart rate). Spironolactone improved exercise systolic BP vs. placebo ($p=0.045$, Cohen's $d=0.42$). When treatment effects were expressed as the change in exercise systolic BP relative to the change in cardiorespiratory fitness, a larger effect size was observed ($p=0.01$, Cohen's $d=0.58$). Therefore, while spironolactone reduces submaximal exercise BP, the full treatment effects may be hidden by improved cardiorespiratory fitness. These findings support previous observations and altogether indicates that cardiorespiratory fitness should be considered when interpreting the clinical relevance of exercise BP.

This thesis has identified several clinically relevant results related to exercise BP. Exercise BP was found to share a relationship with several CVD risk factors and different structural cardiac parameters, which highlights the high BP-related CVD risk associated with exercise BP. There appears to be good concordance between manual and automated measurement of exercise BP, suggesting the type of method used for the measurement of exercise BP may not influence the clinical interpretation of the BP response. Moreover, the assessment of exercise BP without considering changes in cardiorespiratory fitness brought about by an intervention may mask the effects of treatment on exercise BP.

Taken all together, the work in this thesis further highlights the potential importance of measuring exercise BP in clinical settings to improve the identification of CVD risk related to high BP.

LIST OF ABBREVIATIONS.

Abbreviation	Full-text
BMI	Body mass index
BP	Blood pressure
CVD	Cardiovascular disease
CI	Confidence intervals
DBP	Diastolic blood pressure
ICC	Intra-class correlation
HbA1c	Haemoglobin A1c
HOMA-IR	Homeostatic model assessment of insulin resistance
HOMA1-IR	Homeostatic model assessment 1 - insulin resistance
HOMA2- β	Homeostatic model assessment 2 – beta-cell function
HOMA2-IR	Homeostatic model assessment 2 - insulin resistance
HRE	Hypertensive response to exercise
LV	Left ventricle (or left ventricular)
mmHg	Millimetres of mercury
N	Number of subjects (or studies)
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
r	Pearson's correlation coefficient
SBP	Systolic blood pressure
SD	Standard Deviation
SEM	Structural equation model
VO _{2peak}	Peak oxygen consumption

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PREFACE.

High blood pressure (BP) is the leading modifiable risk factor for cardiovascular morbidity and mortality [1,2]. Assessment of BP is traditionally completed with the measurement taken at rest in clinical settings. Based on this measurement of BP, over 1.2 billion adults around the world in 2019 were estimated to have high BP [3]. However, BP measured in the clinic may not always reflect out-of-clinic BP [4,5]. Indeed, BP is overestimated when measured in the clinic in approximately 40% of individuals compared to when assessed out of the clinic (based on gold-standard ambulatory BP monitoring) [4]. Another 8-20% of individuals with normal clinic BP have high BP when measured out of the clinic [5]. Thus, many people may have high BP that is either not diagnosed or well-controlled. Given this misidentification of BP with current standard measurements in the clinic, alternative methods are sought after to improve the identification of high BP and its related CVD risk.

Clinical exercise testing is regularly performed worldwide to screen for CVD risk or to evaluate the level of cardiorespiratory fitness [6–8]. The measurement of BP is standard practice with any exercise test [6–8], and may provide the opportunity for the identification of high BP-related CVD risk. Indeed, an abnormal BP response to exercise, such as a hypertensive response to exercise (HRE), is an independent risk factor of cardiovascular morbidity, events and mortality and reveals high BP missed under resting conditions [9–11]. Despite this evidence, there are still several gaps around the clinical understanding of exercise BP and its association with CVD risk, which will be addressed in Chapters 3, 4, and 5. Some methodological considerations may also influence the clinical interpretation of exercise BP. Whilst several methodological factors could have been investigated, those in Chapters 2 and 6 used available data.

THESIS AIMS.

The broad aims of this thesis were to determine:

1. The relationship between exercise BP and individual CVD risk factors.
 - a. The association between exercise BP and cardiac structure, and difference in cardiac structure between those with and without an HRE (Chapter 3).
 - b. The association between exercise BP and CVD risk factors, and difference in CVD risk factors between those with and without an HRE (Chapter 4).
 - c. The different pathways of associations between CVD risk factors and exercise BP, and which CVD risk factor/s most-strongly relate to exercise BP via structural equational modelling (Chapter 5).
2. If some methodological factors may influence the measurement of exercise BP.
 - a. The concordance between manual and automated BP during a standard clinical treadmill exercise test (Chapter 2).
 - b. If BP lowering medication can lower the BP response to submaximal exercise (Chapter 6).

Individual study manuscripts included in this thesis have been published, submitted, or finalised for submission to peer-reviewed scientific journals. The separate studies in Chapters 2, 3, 4 and 6 have been largely presented in the final published or submitted format. Select tables and figures published as peer-reviewed supplemental material have been added to the main results of this thesis.

1 REVIEW OF LITERATURE.

1.1 INTRODUCTION.

High blood pressure (BP) is the leading risk factor for cardiovascular disease (CVD) [1,2]. Diagnosis and management of high BP is traditionally assessed with BP measured in clinical settings under resting conditions. Utilising the measurement of clinic BP, over 1.2 billion adults globally were estimated in 2019 to have high BP [3]. However, many more people have high BP that is not diagnosed or well-controlled. Therefore, alternative methods are needed to improve the identification of high BP and its related CVD risk.

Millions of exercise tests are performed around the world in cardiology departments and exercise physiology clinics each year. In Australia alone, >500,000 exercise tests are performed in cardiology departments [12]. Another >300,000 individuals each year are referred to exercise physiology services [13], where exercise tests are regularly performed. Whilst exercise tests are performed to screen for CVD or evaluate the level of fitness [14,15], the measurement of BP is a standard part of any test and may be an opportunity for the identification of high BP. Indeed, the BP response during an exercise test may highlight high BP-related CVD risk been missed by traditional measurement of clinic (resting) BP [9–11], but the clinical understanding of exercise BP still remains largely unknown. Thus, the following review aims to summarise the literature (1) around exercise BP and its association with high BP-related CVD risk; (2) highlight some factors that may influence the clinical interpretation of exercise BP.

1.2 BLOOD PRESSURE.

1.2.1 What is blood pressure?

The amount of force that the blood exerts on the arterial walls is referred to as BP. Two BP indices are obtained with the measurement of BP: systolic and diastolic BP.

Systolic BP defines the maximum force placed onto the arterial walls and occurs as the left ventricle (LV) ejects blood into the circulatory system. Diastolic BP is the minimum force placed onto the arterial walls when the LV is in diastole.

1.2.2 Traditional methods for measuring blood pressure.

The measurement of BP is commonly completed under resting conditions in clinical settings. Clinic BP is measured with manual auscultation or an automated oscillometric device following recommended methods in international hypertension guidelines [16]. However, these recommended methods for measuring BP in clinical settings are often not followed and can misclassify BP and its associated CVD risk [17,18]. Several patient-, procedure-, equipment- and observer-related factors may also influence the assessment of clinic BP (Table 1.1) [19]. Thus, clinic BP can be subject to error and variation and mislead the identification of high BP and its related CVD risk.

Although following the recommended methods for measuring BP in the clinic can improve identification of high BP [17], careful measurement of clinic BP may not always reflect BP outside of the clinic [4,5]. Measurement of BP outside of the clinic can include 24-hour ambulatory or home BP monitoring, which are superior to clinic measured BP for predicting CVD risk [20]. Whilst home BP monitoring can also be helpful for long-term BP management, this review focuses on 24-hour ambulatory BP monitoring because it is the gold standard for the identification of high BP [16]. Ambulatory BP monitoring can assess how BP changes over time and may identify individuals with BP in the clinic that is different from measured outside of the clinic. Indeed, some individuals can have high clinic BP, but have normal ambulatory BP, termed white coat hypertension. On the other hand, individuals with normal clinic BP can have high ambulatory BP, termed masked hypertension [21]. The identification of individuals with masked hypertension is crucial because CVD risk in this population

is similar to those with high clinic and ambulatory BP [22,23]. Moreover, masked hypertension is estimated to be prevalent in approximately 8-20% of the general population [24], which means many individuals would remain at elevated CVD risk if the measurement of out-of-clinic BP is not performed. However, ambulatory BP monitoring may sometimes be unavailable or be poorly tolerated by some individuals [25]. Thus, the measurement of BP in clinical settings is regularly relied on for the identification of high BP.

1.3 EXERCISE BLOOD PRESSURE.

Clinical exercise tests are performed worldwide in cardiology departments and exercise physiology clinics. An exercise test can be performed using a treadmill, cycle, step or walk-based modality to screen for CVD risk or evaluate aerobic/functional capacity [14,15]. A mandatory part of every exercise test is the measurement of BP is taken before, during and after each dynamic exercise test.

1.3.1 Normal blood pressure response during exercise.

Upon the onset of dynamic exercise, cardiac output will increase (through an elevation in heart rate and stroke volume) to meet the oxygen and metabolic demands of the active muscles [26]. Simultaneously, the lumen of peripheral arteries will dilate to improve blood flow towards the exercising muscles. This peripheral vasodilation during exercise is however insufficient to counter the elevation in cardiac output, which will subsequently increase systolic BP. Moreover, systolic BP rises incrementally as exercise intensity increases before plateauing at maximal exercise workloads [27,28]. The BP response during exercise can be higher while cycling compared to treadmill exercise [29–31], possibly because of the isometric gripping of the cycle ergometer handlebars [29–31]. Non-modifiable and modifiable CVD risk factors (such as age, sex, body composition and cardiorespiratory fitness) may also influence the exercise BP response (and is further discussed in section 1.6). Taken

together, the influence of these various physiological and methodological factors on exercise BP could be why there is no consensus on what is a 'normal' or 'abnormal' systolic exercise BP response [32–34]. Unlike systolic BP, diastolic BP remains relatively stable and may slightly decrease during high exercise intensities in response to peripheral vasodilation

1.3.2 Abnormally low exercise blood pressure response.

An inadequate rise or drop in BP as dynamic exercise workloads increase is one possible abnormal BP response and is termed a hypotensive response to exercise. A hypotensive exercise BP response is absolute criteria for terminating a clinical test because it is associated with aortic outflow obstruction, severe LV dysfunction or the presence of myocardial ischemia [6,8,35,36]. Moreover, a hypotensive response to exercise is associated with increased risk of non-fatal and fatal cardiovascular events and all-cause mortality (over an average of 4.4 years) based on a meta-analysis including 19 prospective studies [37]. This risk associated with a hypotensive response to exercise was also irrespective of exercise modality, the intensity at the time BP was measured and the disease status of the study population [37]. More recent data from the Fitness Registry and the Importance of Exercise National Database and Henry Ford Exercise Testing Project has also suggested that low maximal exercise BP response is associated with cardiovascular events and mortality [38,39]. Whilst this work highlights the importance of a hypotensive response to exercise, this BP response only appears in 2-6% of individuals who complete an exercise test [40,41], and is considered a poor prognostic sign among individuals with already established CVD.

1.3.3 Abnormally high exercise blood pressure response.

Some individuals may experience an abnormally high BP response to exercise, termed an HRE (or exercise hypertension). According to exercise testing guidelines, a BP $\geq 250/115$ at any intensity of exercise is an indication to terminate exercise testing

[6,8,35,36]. An HRE during maximal intensities has also been commonly defined as $\geq 210/\geq 110$ mmHg for males and $\geq 190/\geq 105$ mmHg for females [42,43]. However, this threshold for an HRE during maximal intensities has ranged from a systolic BP ≥ 190 to ≥ 220 mmHg [44,45]. Small select studies also use different thresholds for an HRE during submaximal intensities that range from a systolic BP ≥ 150 to ≥ 180 mmHg [10,46], and are shown to indicate high BP-related CVD risk [10,46]. This inconsistency in the definition of an HRE may partly be because of the use of different criteria, e.g. the 90-95th percentile or the highest tertile of exercise BP [47,48]. Nevertheless, an HRE can appear irrespective of clinic (resting) BP or whether anti-hypertensive medication is prescribed or not.

Whilst this thesis focuses on the BP response to dynamic exercise, BP can also be measured following isometric exercise (e.g. handgrip test). This mode of exercise can induce a pressor reflex, which is a neural feedback system triggered by mechano- and chemical receptors in response to exercise to elicit an increase in sympathetic nervous system activity [49]. An HRE can occur following isometric exercise and several previous studies have shown that this abnormal BP response to exercise is associated with high BP missed under resting conditions [50,51].

Table 1.1. Potential patient-, procedure- and observer-related sources of inaccuracy in the measurement of resting blood pressure.

Potential source of inaccuracy	Range of reported significant mean effects (in mmHg) unless specified	
	Systolic BP	Diastolic BP
Patient-related		
Acute meal ingestion	↓ ^a	↓
Acute caffeine use	↑	↑
Acute nicotine use or exposure	↑	↑
Bladder distension	↑	↑
Cold exposure	↑	↑
White-coat effect	≠	≠
Procedure-related		
Insufficient rest	↑	↑
Legs crossed at knees	↑	↑
Unsupported arm	↑ ^a	↑
Arm lower than heart level	↑	↑
Incorrect choice of cuff size		
Smaller cuff	↑	↑
Larger cuff	↓	↓
Stethoscope under cuff	↑	↓
Talking during measurement	↑	↑
Fast cuff deflation rate	↓	↑
Reliance on a single measurement	↑	≠
Observer-related		
Observe hearing deficit	↓	↑
Korotkoff phase IV (vs V) for diastolic BP	NA	↑ ^a
Over-representation of terminal digit preference for zero	1-79%	3-79%

Table adapted from Kallioinen et al.[19] BP, blood pressure; NA, not available; ↑, higher BP than reference method; ↓ lower BP than reference method; ≠ significant effects reported in each direction or no significant effects reported; ^aonly one study found a significant effect.

1.4 ASSOCIATION BETWEEN HIGH BLOOD PRESSURE RESPONSE TO EXERCISE AND CARDIOVASCULAR DISEASE RISK.

1.4.1 Association between exercise blood pressure and cardiovascular events and mortality.

Several prospective studies have investigated the association between an HRE and the risk of cardiovascular events and mortality. Filipovsky et al. [52] first reported that BP measured during a fixed cycling workload (164 watts) was associated with cardiovascular events and mortality in 4907 healthy men after adjustment for age, clinic BP and other traditional CVD risk factors. These results of Filipovsky et al. [52] were combined with 11 other prospective studies via a systematic review and meta-analysis performed by Schultz et al.[9] This meta-analysis included 46,314 normotensive individuals followed over 15 ± 4 years and showed every 10 mmHg increase in submaximal exercise systolic BP was independently associated with a 4% (95% CI: 1-7%) higher risk of cardiovascular events and mortality. Moreover, an HRE during submaximal intensities was independently associated with cardiovascular events and mortality (hazard ratio = 1.36 [95% CI: 1.02–1.83]). Schultz et al. [9] also found that exercise BP during maximal intensities was however not associated with cardiovascular events and mortality after adjusting for other CVD risk factors. More recently, results from 10,096 exercise tests linked to national Swedish registries also suggest that peak exercise BP is not associated with incident CVD and mortality after adjusting for other CVD risk factors [53].

Several previous studies have investigated the association between the BP response after exercise and elevated CVD risk. A delayed rate of decline and paradoxical increase in recovery-exercise systolic BP have been associated with the presence of myocardial ischemia and coronary artery disease and cardiovascular mortality [54–57]. However, recovery-exercise systolic BP was not associated with risk of cardiovascular mortality

in apparently health individuals [58]. Some individuals may have a post-exercise hypotensive response (where BP after exercise is below that of BP measured at rest). However, extensive discussion of post-exercise hypotension is beyond the scope of this thesis, and can be found elsewhere [59,60]. Because of the limited data on the association between post-exercise BP and CVD risk, the later sections of this review will focus on the BP response during dynamic exercise.

1.4.2 Association between exercise blood pressure and incident hypertension.

Several longitudinal studies have investigated the association between exercise BP and incident hypertension. Wilson and Meyer [61] first reported that individuals with normal resting BP and maximal exercise BP $\geq 225/90$ mmHg were, on average, at 2.28 higher risk of incident hypertension after an average of 32 months than those with maximal exercise BP $\leq 225/90$ mmHg. Several other longitudinal studies have since reported similar findings that an HRE is associated with an increased risk of incident hypertension [62,63]. In a second systematic review and meta-analysis by Schultz et al.[11], the risk of incident hypertension increased by 19% with each 10 mmHg increase in exercise BP among 23,207 individuals followed on average for 5.3 years after adjusting for age, resting BP, and other CVD risk factors. An HRE during submaximal intensities also independently correlated with incident hypertension after adjusting for age, sex, resting BP, and other CVD risk factors (risk estimate: 1.90 [95% CI: 1.11-3.28]), which was not as evident with maximal exercise BP (risk estimate: 1.52 [95% CI: 0.99-2.33]). Following the publication by Schultz et al.[11], Caselli et al.[64], has reported the risk of incident hypertension to be 3.6 times higher in normotensive athletes with an HRE (maximal exercise BP $\geq 220/85$ mmHg in males and $\geq 200/80$ mmHg in females) followed over 6.5 ± 2.8 years compared to those without an HRE after adjustment for resting BP. Methodological considerations (i.e. statistical power, dissimilar study populations and the threshold used to define an HRE)

could contribute to the difference in association between an HRE at maximal intensities and incident hypertension reported by Schultz et al.[11] and Caselli et al.[64] However, an HRE may also reveal high BP-related CVD risk missed under resting conditions.

1.4.3 Association between exercise blood pressure and ambulatory blood pressure.

Ambulatory BP monitoring is the gold standard method to assess BP [16]. Several previous studies have found that exercise BP shares an association with 24-hour and daytime ambulatory BP, but these relationships have not always been reported (Table 1.2). The findings of the three studies that report no association between exercise and ambulatory BP could be due to the small sample size of the study, or other unknown factors related to the study design [65–67]. Findings also vary on whether ambulatory BP is similar or different (higher) in individuals with an HRE compared to those without an HRE (Table 1.3). The variation in these previous findings could be due to studies including various populations, measuring BP during different exercise modalities or using thresholds to define an HRE. The exercise intensity when BP was measured could also contribute to the variation in results between exercise BP and ambulatory BP. Indeed, ambulatory BP monitoring is more akin to exercise BP during submaximal (low-to-moderate) intensities rather than during maximal intensities. However, of the previous studies that compared ambulatory BP between those with and without an HRE, only Tzemos et al. [68] measured BP during submaximal exercise intensities and reported no difference in daytime ambulatory BP between individuals that had established hypertension with or without an HRE. In contrast, in individuals with normal resting BP and no history of high BP, an HRE during submaximal intensity may indicate elevated 24-hour and daytime ambulatory BP [10,69]. An HRE during submaximal intensities has also been found to be more

prevalent (>40%) among individuals at elevated high BP-related CVD risk (such as those with type 2 diabetes mellitus, masked hypertension or established hypertension) [43,70,71]. The possible high-BP related CVD risk associated with an HRE may be why several international position statements recommend that follow up assessment of BP is performed on individuals with an HRE to rule out the possible presence of high BP [25,72]. Moreover, the various physiological factors and mechanisms that underlie an HRE during submaximal exercise intensity may also underpin the presence and development of high BP, which will be discussed in section 1.6.

1.4.4 Association between exercise blood pressure and cardiac structure.

Raised LV mass is an independent determinant of elevated CVD risk and a principle sign of organ damage related to high BP [73]. Several studies report that exercise BP is associated with different parameters of cardiac structure (such as LV mass, LV mass index and relative wall thickness) [74,75]. These same structural cardiac parameters have also appeared higher in those with an HRE compared to those without an HRE [45,76]. However, not all studies have found a relationship between exercise BP and cardiac structure as assessed by various parameters (e.g. left ventricle mass index and relative wall thickness) [43,77], or reported a difference in cardiac structure between those with and without an HRE [78–80]. These disparities in study findings may in part be because the measurement of BP is during different exercise intensities, where submaximal exercise BP has a stronger association with CVD events and mortality and high ambulatory BP compared to maximal exercise BP (as discussed in sections 1.6.1 and 1.6.3).

The different study populations may also influence the relationship between exercise BP and different parameters of cardiac structure and the difference in cardiac structure between those with and without an HRE. Whilst individuals at elevated CVD risk (e.g. those with masked hypertension or type 2 diabetes mellitus) can have an HRE during

any intensity [10,70,81], athletes can have an HRE during maximal intensities [82,83]. Athletes and individuals at elevated CVD risk may have also undergone cardiac structural adaptation [46,83–85]. The cardiac structural adaptation among athletes could be a typical “physiological” response to regular exercise [84]. For example, the high cardiac output and volume overload that endurance athletes have during sustained training may contribute to the increase wall thickness and internal diameter of the left ventricle [84]. In contrast, the potential pressure overload from the increase in cardiac afterload that strength athletes sustain during training may contribute to the increase wall thickness, but not internal diameter of the left ventricle [84]. The structural cardiac adaptation in strength-trained individuals can be similar to those at elevated CVD risk (and low cardiorespiratory fitness) [84]. However, the structural cardiac adaptation in those at elevated CVD risk would be considered “pathological” rather a “physiological.”[73]. Whether the relationship between exercise BP and cardiac structure between different populations may influence the clinical interpretation of exercise BP is unknown. *Chapter 3 of this thesis aims to determine the relationship between exercise BP and cardiac structure and whether cardiac structure parameters are different between those with and without an HRE via a systematic review meta-analysis.*

1.5 CONCORDANCE BETWEEN DIFFERENT METHODS FOR MEASURING EXERCISE BLOOD PRESSURE.

Manual auscultation is recommended for the measurement of exercise BP, but automated BP measurement is an alternative method used in clinical settings [6,7,36]. Automated BP devices may unreliably report BP during high exercise intensities due to the interference of noise and movement artifact [8], which may also affect the manual measurement of exercise BP [7,8]. How noise and movement artifact is handled by automated BP devices, exercise modality, exercise intensity at when BP is

measured or sample size may be why automated exercise BP is concordant with manual auscultation in several studies, but not all (Table 1.4). The variance in the concordance between manual and automated exercise systolic BP reported by Modesti et al.[86] was similar during the first four stages of a modified Bruce treadmill test. Two studies have also used the same automated BP device (Tango+) [87,88], which was concordant with manual auscultation during supine cycling, concordant with invasive BP during a Bruce treadmill protocol and had good test-retest reliability.

In addition to methodological considerations, previous studies that investigated the concordance between manual and automated exercise BP include exclusively healthy populations with no history of CVD or high clinic BP, except for Modesti et al.[86], with 16 individuals with established high BP (Table 1.4). Data is therefore scarce on the concordance between manual and automated BP in a population that typically undertake a clinical exercise test, such as individuals with type 2 diabetes mellitus that have an increase in arterial stiffness [89]. An increase in arterial stiffness may diminish the movement of the arterial wall, which could decrease the loudness of the Korotkoff sounds and make BP harder to measure with manual auscultation and with an automated BP device and potentially affect the concordance between the two measurement methods for exercise BP [90]. *Chapter 2 of this thesis aims to determine whether manual and automated exercise BP are concordant during a standard exercise test in a population with type 2 diabetes mellitus.*

1.6 ASSOCIATIONS BETWEEN EXERCISE BLOOD PRESSURE AND CARDIOVASCULAR DISEASE RISK FACTORS.

1.6.1 Associations between exercise blood pressure and non-modifiable cardiovascular risk factors.

Previous data including >1000 healthy individuals have shown an increase in age is associated with an increase in submaximal and maximal exercise BP [32,33,40,98,99].

An increase in age is also associated with an elevation in arterial stiffness [100], which may influence BP during exercise (discussed in section 1.6.4 of this review). Previous studies also report that exercise BP is generally higher in males than in females [32,33,40,98,99]. The elevated cardiac output and reduced total peripheral resistance during exercise in males compared to females may contribute to the difference in exercise BP between genders [101]. Whilst data is scarce, exercise BP appears higher in individuals from an African American ethnic background compared to individuals that are of Caucasian ethnicity [102,103]. Taken all together, this earlier work highlights that non-modifiable CVD risk factors are associated with exercise BP and may influence the clinical interpretation of the BP response.

Table 1.2. Continuous association between exercise blood pressure (BP) and ambulatory BP.

Study (first author)	Population		Exercise testing method when BP was measured	24-hour ambulatory BP	Daytime ambulatory BP only
	General characteristics	Inclusion based on clinic BP measured at rest			
Fossum [66]	27 health men on no medication randomly selected 3500 individuals who completed a military medical procedure in 1993.	NR	Submaximal intensity (~100 watts) during a cycling test	NR	No association
Herkenhoff [65]	20 sedentary men aged 35-50 years old	normal (threshold not reported)	Maximal intensity during a cycling test	No association	NR
Lima [67]	30 sedentary men (42 ± 4 years old)	high normal (systolic BP, ≥130 and <139 mm Hg; diastolic BP, ≥85 and <89 mm Hg)	Maximal intensity during a cycling test	No association	NR
Bratberg [71]	77 participants (60% female) with body mass index <27 kg/m ² and without known heart disease	NR	Maximal intensity during a treadmill test	Associated	NR
Kasiakogias [82]	57 men with and without untreated obstructive sleep apnoea.	newly diagnosed essential hypertension	Maximal intensity during a treadmill test	Associated.	NR
Schultz [10]	75 untreated subjects with a hypertensive response during peak exercise intensity (≥ 210 mmHg for males and ≥ 190 mmHg for females)	Normal (≤140/90 mmHg)	Submaximal intensity during a cycling test	Associated	NR

Schultz [69]	100 patients free from coronary artery disease (aged 56 ± 9 years, 72% male)	No exclusion	Submaximal intensity during treadmill test	Associated	Associated
Tsiachris [80]	99 never-treated hypertensive patients (61% male)	NR (ambulatory BP $>135/85$ mmHg)	Maximal intensity during a treadmill test	Associated.	NR
Vriend [91]	144 consecutive post-coarctectomy Patients (63% male)	NR	Maximal intensity during treadmill test	NR	Associated
Zanettini [92]	75 patients with normal clinic blood pressure	NR	Maximal intensity during treadmill test	Associated	Associated
NR, not reported.					

Table 1.3. 24-hour and daytime ambulatory blood pressure (BP) between individuals with a hypertensive response to exercise (HRE) compared to those without an HRE.

Study (First Author)	Population General characteristics	Inclusion based on clinic (resting) BP	Exercise testing method when BP was measured	HRE threshold (systolic BP; mmHg)	24-hour ambulatory BP	Daytime ambulatory BP
Herkenhoff [65]	20 men aged 35-50 years old	Normal	Maximal intensity during a cycling test	≥ 220	No difference	NR
Tzemos [68]	11 apparently healthy individuals with and without an HRE	Hypertensive	Submaximal intensity directly post-Dundee step test	≥ 200	NR	No difference
Kasiakogias [82]	57 men with and without untreated obstructive sleep apnoea.	Hypertensive	Maximal intensity during a treadmill test	≥200	No difference	NR
Bratberg [71]	77 subjects with body mass index <27 kg/m ² and without known heart disease	NR	Maximal intensity during a treadmill test	≥ 200	Higher	NR
Lima [67]	30 sedentary subjects (42 ± 4 years old)	High-normal	Maximal intensity during a cycling test	≥220	Higher	NR
Tsiachris [80]	63 never-treated hypertensive patients without an HRE and 36 never-treated hypertensive patients with an HRE	Hypertensive	Maximal intensity during a treadmill test	≥ 210 for men ≥ 190 for women	Higher.	NR
Tsioufis [93]	48 apparently healthy individuals with an HRE and 123 apparently healthy individuals without an HRE	Hypertensive	Maximal intensity during a treadmill test	≥210	Higher	NR
Vriend [91]	144 consecutive post-coarctectomy patients	Normal	Maximal intensity during treadmill test	≥ 200	NR	Higher
NR, not reported						

Table 1.4. Observational studies investigating the concordance between manual and automated measurement of blood pressure taken during an exercise test.

Study (first author)	Study population	Exercise testing methodology	Automated device used	Exercise stage / intensity when BP was measured	Korotkoff sound used to measure BP	Exercise BP measured with an automated device compared to manual auscultation
Cameron [87]	Five healthy adults	Supine cycling	Tango exercise BP monitor	NR	SBP - K1 DBP - K5	↑ SBP ↔ DBP
Garcia-Gregory [94]	277 healthy males	Bruce Treadmill	BP measuring system	Stages 1 - 4	SBP - K1 DBP - K5	↑ SBP ↓ DBP
MacRae [95]	19 healthy normotensive subjects	Bruce Treadmill	CardioDyne NBP 2000	Stages 1 - 4	NR	↔ SBP ↔ DBP
Bond [96]	18 healthy men	Incremental cycling	Colin STBP-680	40%, 70% and peak of VO ₂	SBP - K1 DBP - K5	↔ SBP ↑ DBP (at 70% and peak VO ₂) ↔ DBP (at 40% VO ₂)
Modesti [86]	34 normotensive and 16 hypertensive adults	Modified Bruce Treadmill	NR	Stages 1 - 4	SBP - K1 DBP - K5	↔ SBP ↓ DBP
Lightfoot [97]	11 healthy subjects	Incremental cycling	Small condenser microphone mounted to a Sony TCD5M cassette tape recorder	25%, 50%, 75% 100% age-predicted maximal heart rate	SBP - K1 DBP - K4	↑ SBP ↑ DBP
Diastolic blood pressure, DBP; NR, not reported; systolic blood pressure, SBP; VO ₂ , oxygen consumption. ↑, higher BP measured with an automated device compared to manual auscultation; ↓, lower BP measured with an automated device compared to manual auscultation; ↔, similar BP measured with an automated device compared to manual auscultation						

1.6.2 Associations between exercise blood pressure and modifiable neural-related cardiovascular risk factors.

Autonomic nervous system activity and feedback may influence the BP response during exercise. Indeed, Tanindi et al.[104] found that apparently healthy individuals with elevated low and high frequency power content ratio (an indirect indicator of low sympathetic withdrawal) had higher submaximal exercise systolic BP compared to those with a low power content ratio. Eryonucu et al.[105] also found that individuals with an HRE had a higher low and high frequency ratio at rest compared to those without an HRE. In contrast, Weston et al.[106] found that the low and high frequency power content ratio at rest was similar among those with type 2 diabetes mellitus with or without an HRE. However, Weston et al.[106] did find that post-exercise heart rate variability was higher among those with an HRE compared to those without an HRE and that post-exercise total spectral power (a parameter in the heart rate variability domain), cardiac autonomic neuropathy (determined from a battery of seven autonomic function tests) were associated with maximal systolic BP independent resting BP. Sharman et al.[107] has found that resting carotid baroreceptor sensitivity was higher among those with an HRE during submaximal intensities compared to those without an HRE. Moreover, Sharman et al.[107] found that low baroreceptor sensitivity was associated with an HRE among those with normal resting BP after adjustment for other CV risk factors (odds ratio [95% CI]: 1.16 [1.01, 1.33]). Therefore, elevated autonomic activity and inappropriate sensory feedback could underpin an HRE and contribute to the development of high BP.

1.6.3 Associations between exercise blood pressure and hormonal-related modifiable cardiovascular risk factors.

Several studies have investigated whether exercise BP was correlated with different hormones, and if there is a difference in hormonal profiles between those with and

without an HRE. resting cortisol and plasma-renin activity has been reported to be higher in those with an HRE at 150 Watts compared to those without an HRE [108]. Submaximal exercise BP has also been associated with the log of plasma aldosterone to renin activity ratio independent of age and sex among individuals with untreated hypertension ($r = 0.24$, $p < 0.001$) [109]. In contrast, no difference in plasma renin activities or aldosterone was found between those with and without an HRE at peak intensities [79]. However, Shim et al.[79] found the level of angiotensin II to be higher among those with an HRE compared to those without an HRE. Overall, the over excretion of different hormones related to the renin-angiotensin-aldosterone system may contribute to an HRE.

1.6.4 Associations between exercise blood pressure and vascular-related modifiable cardiovascular risk factors.

Vascular-related factors that may influence the BP response to exercise can be broadly grouped into biological categories, such as arterial structure and function, metabolic, lipid, inflammatory and kidney function. It may also be possible that an HRE can contribute to the change in different modifiable CVD risk factors.

Large artery (aortic) stiffness is an independent risk factor of CVD mortality [110]. An increase in aortic stiffness may also dampen the ability of the aorta to buffer the exercise-induced elevation in cardiac output and cause a higher than normal BP response to exercise [111]. Indeed, exercise BP (during any intensity) is cross-sectionally associated with aortic stiffness (that ranges in the strength of association from Pearson's $r = 0.25$ to 0.64) in individuals with normal and high clinic BP [70,80,93,112]. Healthy individuals with an HRE can also have higher aortic stiffness compared to those without an HRE, even when resting BP is normal or high [112,113]. However, no difference in aortic stiffness was found by Currie et al.[77] in athletes with and without an HRE during peak intensities.

While data is sparse, different characteristics of the peripheral arteries may also influence the BP response to exercise. Firstly, individuals with an HRE during submaximal intensities have higher carotid stiffness than those without an HRE [107]. Submaximal exercise BP has also been associated with brachial-ankle pulse wave velocity and flow-mediated vasodilation, independently of age, sex, and other traditional CVD risk factors [114,115]. Individuals with an HRE during maximal intensities are also at higher risk of carotid atherosclerosis independent of age, resting BP and other traditional CVD risk factors (odds ratio: 2.02 [1.33, 3.05]) [116]. Flow-mediated vasodilation is also lower among healthy individuals with an HRE during maximal intensities and normal clinic BP than those without an HRE [117,118].

Several metabolic-related CVD risk factors (including fasting glucose, insulin, HbA1c and homeostatic model assessment of insulin resistance [HOMA-IR]) may influence the BP response to exercise. Indeed, metabolic-related CVD risk factors have appeared higher in individuals with an HRE than those without an HRE [45,80,119–121], but not in all studies [71,122,123]. Three of these previous studies include >1500 individuals [45,116,119], while other studies have small and select population groups, which may partly account for the variance in results. The methods used during the exercise test (i.e. modality and intensity when BP is measured) also vary between studies. Taken all together, whether metabolic-related CVD risk factors do influence the clinical interpretation of exercise BP remains to be determined.

In several studies, exercise BP has been associated with elevated total cholesterol and triglycerides [43,112,124], but not necessarily in all studies [125]. Total and low-density lipoprotein cholesterol and triglycerides also appear higher, while high-density lipoprotein cholesterol is lower among individuals with an HRE (with either normal or high clinic BP) compared to those without an HRE in several studies

[78,119,126,127], but not all studies [45,71,128]. The variation in population sample and health status and exercise testing methods used in previous studies to measure BP may influence the clinical interpretation of exercise BP and its association with lipid-related CVD risk factors. Thus, it is uncertain whether exercise BP is associated with lipid-related CVD risk factors.

Several cross-sectional studies have investigated the association between exercise BP and several different inflammation-related CVD risk factors. White blood cell count and c-reactive protein appear higher in those with an HRE during peak intensities than those without an HRE [78,119,120], but the difference in c-reactive protein is not always apparent [123]. Whilst two cross-sectional studies have found no association between exercise BP and c-reactive protein [78,123]. Nikolic et al. [112] found that those with an HRE during submaximal intensities had higher levels of von Willebrand factor (a haemostatic marker of endothelial damage) than those without an HRE. Albumin-creatinine ratio (an indicator of lower kidney function) also appears lower among individuals with an HRE and normal clinic BP compared to those without an HRE in several studies [113,126]. Different studies have also reported that urine creatinine is higher [113], lower [126], and similar in those with an HRE compared to no HRE [45,74,80].

Overall, this previous work highlights that the exact nature of the relationship between exercise BP and several modifiable CVD risk factors remains unclear and should be fully elucidated. *Chapter 4 of this thesis aims to determine whether exercise BP is associated with different CVD risk factors and whether CVD risk factors are higher in individuals with an HRE than those without an HRE via a systematic review meta-analysis.*

1.6.5 Associations between exercise blood pressure and body composition.

The global prevalence of obesity among adults has tripled since 1975 [129]. There are several methods for the assessment of obesity, of which one standard measure is the calculation of body mass index. Body mass index is associated with high BP and other CVD risk factors [130]. Exercise BP (during any intensity) also shares an association with body mass index [131–133]. This relationship between exercise BP and body mass index could also be a ‘U-shaped’ [131].

Though body mass index is associated with total body fatness [134], it can also be a poor indicator of body fatness in some populations (particularly in athletes) [135,136]. This limitation of body mass index may be overcome with the additional measurement of various body circumferences or skinfolds, which can be used to estimate patterns and distributions of body fatness. Several studies report that exercise BP (at any intensity) is associated with waist circumference and body fat percentage [131,132,137]. Moreover, Hout et al. [138] found waist circumference was a stronger correlate of submaximal exercise BP than body mass index. In contrast, body fat percentage was not associated with submaximal exercise BP after adjusting for body mass index [132]. A decrease in exercise BP (during any intensity) has also been associated with a reduction in waist circumference and body fat percentage following lifestyle modification or surgical interventions [139,140]. The prevalence of an HRE during maximal intensities was shown to decrease by 23% six months following bariatric surgery among 60 severely obese individuals [141]. The factors and mechanisms that relate to obesity-related high BP, e.g. insulin resistance, and activity of the renin-angiotensin-aldosterone system and sympathetic nervous system may likely be involved in the decrease in exercise BP following surgery, but this still has not been fully described within the current literature. While data is limited, exercise BP is also associated with lean body mass [83,131]. Submaximal exercise BP is negatively

associated with lean body mass [131], which is also positively correlated with maximal exercise BP [83]. The difference in association between exercise BP and lean body mass could be because of the presence or absence of other CVD risk factors.

1.6.6 Associations between exercise blood pressure and cardiorespiratory fitness.

High cardiorespiratory fitness is an independent predictor of lower risk for CVD events and mortality [142,143]. Cardiorespiratory fitness may also influence the BP response to exercise. Indeed, several studies have reported that submaximal exercise BP is negatively associated with cardiorespiratory fitness [46,132,144,145]. Improved cardiorespiratory fitness following an aerobic exercise intervention is also associated with a decrease in submaximal exercise BP [139]. However, an improvement in cardiorespiratory fitness may also lead to superior workloads during maximal intensities by generating a greater cardiac output, which could lead to a higher exercise BP response [27,146]. This physiological response due to improved cardiorespiratory fitness may be why athletes can have an HRE during maximal intensities in the absence of other CVD risk factors and organ damage [27,77]. Despite these findings, the physiological and pathological mechanisms that underlie the high BP response during maximal exercise intensities among athletic populations continues to be debated within the literature [147].

1.6.7 Pathways of associations between exercise blood pressure and different cardiovascular risk factors.

In sections 1.6.1 to 1.6.4, several non-modifiable and modifiable CVD risk factors were highlighted to influence the exercise BP response and its clinical interpretation. Whilst this previous research has shown that exercise BP is associated with different CVD risk factors, it cannot account for how CVD risk factors can ‘cluster’ with one another [148,149]. Therefore, different CVD risk factors may influence exercise BP via various pathways of association. For example, one CVD risk factor may share a

relationship with exercise BP independently of other factors (termed a direct association) and have a correlation via another factor (termed an indirect association). These various pathways of association between exercise BP and different CVD risk factors have never been explored. *Chapter 5 of this thesis aims to quantify the direct and indirect associations between CVD risk factors and exercise BP, whilst also determining what CVD risk factor/s most-strongly relate to exercise BP.*

1.6.8 Potential mechanisms that underlie the association between the blood pressure response to exercise, different cardiovascular risk factors and high blood pressure.

Sections 1.6.1 to 1.6.7 highlighted that several non-modifiable and modifiable CVD risk factors may be associated with the BP response to dynamic exercise. From the perspective of the autonomic nervous system, sympathetic nervous activity is normally stimulated at the onset of exercise to increase cardiac output and vasoconstriction [26]. An overactive sympathetic nervous system may contribute to an HRE through the excretion of different hormones related to the renin-angiotensin-aldosterone system (as highlighted in section 1.6.4) or an increase in vascular (aortic) stiffness (as highlighted in section 1.6.5). This abnormal (overactive) neurohormonal activity could partly be due to inappropriate feedback from the baroreceptors, mechanoreceptors and chemoreceptors to regulate BP [49]. Baroreceptor sensitivity is depressed among obese individuals compared to those with less total and abdominal fat [150], and may underlie the association between exercise BP, body mass index and waist-to-hip ratio (as highlighted in section 1.6.5). An increase in metabolic- and lipid-related CVD risk factors can accompany characteristics of obesity [150], and also underlie the association between exercise BP and body composition. Metabolic- and lipid-related CVD risk factors may damage the arterial wall [151,152], which could further depress baroreceptor sensitivity and increase sympathetic nervous activity and level of

inflammation. The different neurohormonal- and vascular-related mechanisms that may underlie the association between exercise BP and different CVD risk factors could also contribute to the development of high BP-related CVD risk. The potential mechanisms that underlie an HRE among athletes may be different to those aforementioned and were discussed in Section 1.6.6.

1.7 INTERVENTIONS ON EXERCISE BLOOD PRESSURE

Clinic and ambulatory BP decrease following lifestyle modification, pharmacotherapy and surgery [153–157]. Therefore, these same interventions may also lower the BP response to exercise. The current evidence on the effect of surgical interventions on exercise BP has already been discussed in section 1.6.3.

1.7.1 The effect of lifestyle-based interventions on exercise blood pressure.

Lifestyle modification, such as diet and exercise, is the first level of treatment to improve BP-related CVD risk [16]. One study including 11 overweight and obese individuals has reported submaximal and maximal exercise BP decrease after diet counselling over a median of 20 weeks (95% confidence interval: 16–30 weeks) [158]. Similarly, submaximal exercise BP decreased by 5-19 mmHg following four months of aerobic exercise [159,160]. A combined aerobic and resistance exercise intervention performed over six months also led to a decrease in submaximal exercise BP by 1mmHg for every 1cm decrease in waist circumference or 1ml/kg/min increase in cardiorespiratory fitness [139].

The effect of lifestyle modification on maximal exercise BP has varied [159,161]. One study reported a decrease of 19 mmHg following a 16-week intervention [159], while no change was found following a one-year intervention in individuals with type 2 diabetes mellitus [161]. These two interventions vary by length (e.g. 12 weeks to 6 months) and type (e.g. aerobic exercise with or without resistance training), and are

therefore difficult to compare. However, exercise training can improve cardiorespiratory fitness and increase the maximal workload reached [162], which could lead to a higher exercise BP and influence the effect of lifestyle modification. Overall, exercise BP appears to decrease following lifestyle modification, but those with type 2 diabetes mellitus may need alternative interventions.

1.7.2 The effect of pharmacological interventions on exercise blood pressure.

Several studies have investigated if antihypertensive medication can decrease exercise BP. Two observational studies report submaximal and maximal exercise BP appears lower in individuals prescribed with a beta-blocker (as a mono- or combined therapy) than in those taking other antihypertensive medications [163,164]. Beta-blockers can decrease sympathetic nervous activity and reduce heart rate, which may contribute to resting and exercise BP being lower among those prescribed with beta-blockers compared to those taking other antihypertensive medications [163,164]. Peak workload reached (an indicator of cardiorespiratory fitness) being lower to those prescribed with other medications may also influence maximal exercise BP, potentially because a lower cardiac output is being generated during exercise. Exercise BP at submaximal intensities and fixed workload being lower among those prescribed with beta-blockers may indicate to an improvement in cardiac output or peripheral vascular resistance because of the decrease in sympathetic nervous activity [163]. Pharmacotherapy interventions can decrease submaximal and maximal exercise BP by 12-43mmHg and 5-44mmHg (respectively) in individuals with established disease (i.e., hypertension, metabolic syndrome or heart failure) [165–171]. The variable decrease in exercise BP following pharmacological intervention between studies may be due to the different effects of antihypertension medication to reduce cardiac output or inhibit vasoconstriction. The variation in dosage and duration of the medication may also contribute to the variable change in exercise BP. However, one study found no change

in submaximal exercise BP among individuals with hypertension following three-week treatment with lisinopril 40mg/d [172], which could be because of the low duration of the intervention. No change in maximal exercise BP was also found after six months of treatment with spironolactone 20mg/d in 101 individuals with preserved ejection heart failure [173]. The effect of spironolactone may unload pressure on the heart by improving aortic stiffness [165,174], left ventricular systolic strain and left ventricular diastolic volume [175–177], which are all factors that may improve cardiorespiratory fitness [165,176,177]. Whether the treatment effects of spironolactone on cardiorespiratory fitness may influence the effect on exercise BP is unknown. *Chapter 6 of this thesis aims to further investigate the effect of spironolactone on exercise BP.*

1.8 SUMMARY

An abnormal BP response to exercise, such as an HRE, is likely indicative of high BP-related CVD risk missed under resting conditions [9–11,69]. However, questions still remain around the clinical understanding of exercise BP, which include understanding (1) the relationship between exercise BP and different CVD risk factors and (2) methodological factors that relate to how BP is measured during an exercise test. Addressing these questions would improve the understanding of exercise BP and the factors that may influence the BP response and CVD risk.

2 COMPARISON OF MANUAL AND AUTOMATED AUSCULTATORY BLOOD PRESSURE DURING GRADED EXERCISE AMONG PEOPLE WITH TYPE 2 DIABETES.

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Link to online article: <https://pubmed.ncbi.nlm.nih.gov/31638321/>

Note: Use of the term ‘exercise hypertension’ in this chapter is synonymous with an HRE.

2.1 ABSTRACT

Manual measurement of blood pressure (BP) during exercise testing is the recommended standard. Automated measurement of BP is an alternative method used during clinical exercise testing, but there is little data comparing manual and automated BP in this setting. The aim of this study was to determine the concordance between manual and automated BP during a standard clinical treadmill exercise test. 41-participants (66 ± 5 years; 54% male) completed a Bruce treadmill exercise test at baseline or follow-up within a clinical trial of participants with type 2 diabetes mellitus. Manual and automated BP were measured simultaneously at each exercise test stage. Manual BP was measured by a technician blinded to automated BP values (Tango+, Suntech). Concordance between manual and automated BP was assessed using mean differences and intraclass-correlations (ICC). Concordance between manual and automated BP across all exercise stages was excellent for systolic BP (overall mean difference: 3 ± 11 mmHg, $p = 0.598$; ICC = 0.964 [95% CI 0.942-0.977] and pulse pressure (overall mean difference: 2 ± 14 mmHg, $p = 0.595$; ICC = 0.934 [95% CI 0.899-0.956]). Concordance between manual and automated diastolic BP across all exercise stages was moderate-to-good (overall mean difference: 1 ± 9 mmHg, $p = 0.905$; ICC = 0.784 [95% CI 0.672-0.858]). Automated BP using the Tango+ device is concordant with manual BP during early stages of a standard clinical exercise test. Thus, this automated method may be a suitable alternative to manual measurement of BP during clinical exercise testing.

2.2 INTRODUCTION

Clinical exercise testing is routinely indicated for the detection of coronary artery disease or to evaluate aerobic and functional exercise capacity [14,178]. International exercise testing guidelines recommend the monitoring of blood pressure (BP) during testing since abnormal exercise BP responses (e.g. exercise hypertension and hypotension) may indicate increased CVD risk and are used as clinical indications for terminating testing [6–8,35,36,179,180]. While manual measurement of BP is the recommended standard during exercise testing [8], automated BP measurement is an alternative method routinely undertaken in clinical settings [7,8,179]. Despite this, there is a scarcity of data to indicate the relative concordance between manual and automated exercise BP in populations who would typically undertake clinical exercise testing (e.g. those at increased CVD risk, such as individuals with type 2 diabetes mellitus). Assessing the concordance between manual and automated exercise BP is of importance since substantial differences between measurement methods could affect the ability to detect abnormal exercise BP responses. The aim of this study was to determine the concordance between manual and automated exercise BP during standard clinical exercise testing in a clinical population.

2.3 METHODS

Participants. Data for this study were drawn from an exercise-based clinical trial of participants with type 2 diabetes mellitus (<http://www.anzctr.org.au>; clinical trial ID: 12614000222640), the details of which have been previously reported [181]. Participants were included in the clinical trial if they had diagnosed type 2 diabetes mellitus as defined within the American Diabetes Association guidelines [182], were aged between 50-75 years, and willing to participate in a 6-month structured exercise program. Individuals with severe cardiovascular, orthopaedic or respiratory conditions

and contraindications to exercise (according to the American College of Sports Medicine guidelines)[179] were excluded. Individuals were further excluded if they had contraindications for magnetic resonance imaging, known dementia or central nervous system disorders (e.g. intracranial tumour, multiple sclerosis, Parkinson's disease) or if they were participating in ≥ 30 mins/week of structured exercise. A total of 68 exercise tests with simultaneously measured manual and automated BP were available for analysis at either baseline (n=37) or follow-up (n=31) from 45 participants. Participants who had an arm circumference outside the range of 27 to 40cm (which was required for the cuff of the automated BP device) were excluded (n=4), leaving a total of 41 participants included in this analysis that completed 60 exercise tests (n=33 at baseline and n=27 at follow-up). An exercise test with simultaneously measured manual and automated BP was completed on 14 participants at baseline, 8 participants at follow-up and 19 participants at both baseline and follow-up. The repeat measurement of manual and automated exercise BP at follow-up were excluded from this analysis for the 19 participants with measurement of BP taken baseline and follow-up. All participants provided written informed consent, and ethics approval was received from the Human Ethics Committee Tasmania Network (H0013664).

Protocol. Participants attended the Menzies Institute for Medical Research clinic in a fasted state, having been asked to avoid smoking and caffeine within three hours of attendance. Participants had fasting blood taken, completed a medical assessment and questionnaire (including medical history) and had standardised anthropometry measured. Clinic BP was measured, and a graded exercise test was completed. Manual and automated auscultatory BP was measured simultaneously pre-exercise and at each stage of the exercise test.

Exercise test. All participants completed a standard Bruce treadmill exercise testing protocol [178]. The initial exercise stage (exercise stage 1) involved walking on the treadmill at a speed of 2.7 km/hr with a 10% gradient. After three minutes, treadmill speed and gradient were increased with further increments every three minutes thereafter until the test was terminated. Criteria for termination were either upon volitional fatigue or when 85% of age-predicted maximal heart rate $((220 - \text{age})/0.85)$ was attained, or if any medical indications arose, or upon participant request. Oxygen consumption was measured using breath-by-breath gas-analysis (MasterScreen CPX, Vyaire Medical) during the exercise test. Peak oxygen capacity ($\text{VO}_{2\text{peak}}$) was defined as the oxygen consumption achieved when the exercise test was terminated.

Exercise BP. The reference manual BP device used in this study was a digital-display manual auscultatory sphygmomanometer (UM-101, A&D instruments, SA, Australia), which has been validated according to international standards [183,184]. The manual BP device was attached to the cuff of an automated device (Tango+, SunTech Medical Instruments, NC, USA) by a t-connection in order to record simultaneous manual and automated auscultatory BP. The automated cuff was positioned with the microphone within the cuff placed over the left brachial artery before beginning the exercise test. A trained technician read the BP values from the auscultatory sphygmomanometer while placing a stethoscope over the brachial artery next to the microphone within the automated device cuff. The technician was blinded from all BP values recorded by the automated device, which operated with an automated deflation rate of 3-8 mmHg/second. This process is illustrated in Appendix Figure 2.1. For all manual BP measurements, the 1st Korotkoff sound was taken as the systolic BP, while the 5th Korotkoff sound was taken as the diastolic BP. The automated method also measured BP by detection of Korotkoff sounds. A single simultaneous manual and automated BP measure was taken as participants stood on the treadmill before the exercise test

(pre-exercise) and at the second minute of each exercise stage (exercise stage 1 and 2).

All BP measurements were taken with the participant's arm supported on the shoulder of the technician and according to recommendations [7]. Pulse pressure was calculated as the difference between systolic and diastolic BP. Concordance between manual and automated BP was assessed at pre-exercise, at each exercise stage and as the delta BP (change from pre-exercise to each exercise stage).

Clinic BP. Clinic BP was measured using an automated device (Mobil-o-graph, IEM, GmbH) in a seated position according to guidelines [180]. Eight BP measures were taken over 15 minutes. The technician left the room after initiating the automated BP device and all eight BP measures were completed with the participant unobserved. The average of all eight BP measurements formed the clinic BP reported in Table 1.

Statistical analysis. Data were analysed using SPSS software version 24 for Windows (Chicago, Illinois). Variable distributions were assessed using Shapiro-Wilk tests for normality. Agreement and variability between manual and automated BP were assessed using a combination of methods. Independent and single sample t-tests were used to compare the mean difference between manual and automated BP for normally distributed data, and non-normally distributed variables were assessed using Mann-Whitney U-tests. Bland-Altman plots were constructed to visualise the level of variability and bias between measures [185]. Average measures intra-class correlations (ICC; two-way mixed with absolute agreement) were calculated to assess the level of concordance between manual and automated BP with level of agreement assessed from the 95% confidence intervals of the ICC according to Koo and Li [186], (<0.50 poor agreement, 0.50-0.75 moderate agreement, 0.75-0.90 good agreement, and >0.90 excellent agreement). Pearson correlations were also calculated to assess the relationship between measures and to determine any trends for systematic bias

within Bland-Altman and linear correlation plots. The percentage of readings in which the difference between manual and automated BP was ≤ 5 , ≤ 10 and ≤ 15 mmHg was also calculated as per international standards for the accuracy validation of automated BP monitors [187]. Logistic regression models were used to calculate the specificity and sensitivity of automated systolic BP to classify exercise hypertension defined by manual systolic BP according to two systolic BP cut points (≥ 150 mmHg and ≥ 175 mmHg) that have been associated with increased CVD risk [10,46,69,188].

2.4 RESULTS

Clinical characteristics. Table 2.1 includes a summary of participant characteristics. The study population were on average of middle-to-older age, predominately male with raised body mass index and waist-to-hip ratio, and low exercise capacity (based on $\dot{V}O_{2peak}$ achieved). Most participants self-reported a diagnosis of hypertension and were currently taking antihypertensive medication, but on average had controlled BP (clinic BP $< 140/90$ mmHg). Most participants also self-reported having high cholesterol, while few participants reported having a previous myocardial infarction or being treated with insulin therapy.

Table 2.1. Clinical characteristics of study participants (n = 41)

Variable	
Age (years)	66 ± 5
Sex (n, % male)	22 (53.7)
Height (cm)	167.1 ± 7.9
Weight (kg)	85 ± 13.3
Body mass index (kg/m ²)	30.4 ± 3.8
Waist circumference (cm)	105.0 ± 9.8
Hip circumference (cm)	106.5 ± 10.1
Waist-to-hip ratio	1.0 ± 0.08
Clinic systolic / diastolic blood pressure (mmHg)	122 ± 12 / 77 ± 9
Arm circumference (cm)	34.0 ± 3.2
Insulin (mg/L)	22.8 ± 27.1
Fasting blood glucose (mmol/L; n = 37)	8.0 ± 2.7
HbA1c (%; n = 39)	6.8 ± 1.1
Maximal oxygen capacity ($\dot{V}O_{2peak}$; ml/kg/min)	22.3 ± 4.9
Type 2 diabetes mellitus history (year, n = 39)	12.3 ± 6.8
Self-reported Hypertension (n, %; n = 40)	28 (70.0)
Self-reported High cholesterol (n, %; n = 40)	26 (65)
Past myocardial infarction (n, %; n = 40)	2 (5.0)
Insulin therapy (n, %; n = 39)	7 (18.0)
Anti-hypertensive medication use (n, %; n = 40)	33 (82.5)
Data presented as mean ± standard deviation for continuous variables or number (%) for categorical variables	

Comparison of manual and automated BP. A total of 90 manual and automated BP comparisons were available for analysis across all exercise stages, including 40 at pre-exercise, 33 at exercise stage 1, 17 at exercise stage 2. Manual and automated BP comparisons available above exercise stage 2 were excluded from analysis due to low sample sizes ($n = 1$ to 5). Appendix Figure 2.2 provides the reasons underlying the decreasing numbers of comparisons available with each exercise test stage.

Manual and automated systolic BP had a small mean difference and moderate-to-excellent agreement based on the 95% confidence intervals of the ICC during pre-exercise, exercise stage 1 and exercise stage 2. (Table 2.2). Manual and automated diastolic BP had a small mean difference during all exercise test stages. Based on the 95% confidence intervals of the ICC, there was good-to-excellent agreement during pre-exercise, poor-to-good agreement during exercise stage 1 and 2 (Table 2.2). Manual and automated pulse pressure had a small mean difference during all exercise test stages, with moderate-to-excellent agreement based on the 95% confidence intervals of the ICC during pre-exercise, exercise stage 1 and 2 (Table 2.2). Figure 2.1 presents the comparison between manual and automated systolic BP, diastolic BP and pulse pressure with each exercise stage using Bland-Altman and linear correlation plots. When combined across all exercise stages, manual and automated systolic BP and pulse pressure had small mean differences and excellent agreement based on the 95% confidence intervals of the ICC (Table 2.2, Figure 2.1A, 2.1B, 2.1E and 2.1F). Manual and automated diastolic BP had a small mean difference and moderate-to-good agreement (based on the 95% confidence intervals of the ICC) across all exercise stages combined (pre-exercise to exercise stage 2; Table 2.2, Figure 2.1C and 2.1D). Across all exercise stages combined there was some evidence of systematic bias with automated diastolic BP (Pearson $r = 0.451$, $p < 0.001$; Table 2.2, Figure 2.1C) measures underestimating manual measures at low BP values, and overestimating at high BP

values. There was no evidence of systematic bias with systolic BP (Pearson $r = 0.114$, $p = 0.286$; Figure 2.1A) and pulse pressure (Pearson $r = -0.035$, $p = 0.745$; Figure 2.1E) across all exercise stages combined. Results were consistent when pre-exercise comparisons were excluded (i.e. exercise stages 1 to 2 only; Table 2.2), except there was evidence of systematic bias between manual and automated systolic BP (Pearson $r = 0.309$, $p = 0.029$) for underestimating manual BP at low values and overestimating at high BP values.

The mean difference between manual and automated delta systolic BP was small with moderate-to-excellent agreement based on the 95% confidence intervals of the ICC from pre-exercise to exercise stage 1. (Appendix Table 2.1). The mean difference between manual and automated delta diastolic BP was small with poor-to-good agreement from pre-exercise to exercise stage 1, with poor-to-excellent agreement and from pre-exercise to exercise stage 2. The mean difference between manual and automated delta pulse pressure was small with poor-to-good agreement from pre-exercise to exercise stage 1 and poor-to-excellent agreement from pre-exercise to exercise stage 2.

The percentage of manual and automated systolic BP comparisons with mean differences ≤ 5 mmHg, ≤ 10 mmHg and ≤ 15 mmHg decreased with each exercise stage (Appendix Table 2.2). The percentage of manual and automated diastolic BP comparisons with mean differences ≤ 5 mmHg were similar across each exercise stage, while manual and automated diastolic BP comparisons with a mean difference ≤ 10 mmHg and ≤ 15 mmHg decreased with each exercise stage (Appendix Table 2.2). The percentage of manual and automated pulse pressure comparisons with mean differences ≤ 5 mmHg, ≤ 10 mmHg, and ≤ 15 mmHg decreased from pre-exercise to

Comparison of manual and automated auscultatory blood pressure during graded exercise among people with type 2 diabetes.

exercise stage 1 and persisted from exercise stage 1 to exercise stage 2 (Appendix Table 2.2).

Automated systolic BP had 97.7% sensitivity and 50.0% specificity for classifying exercise hypertension across exercise stages 1 and 2 defined by manual systolic BP as exercise systolic BP ≥ 150 mmHg, and 80.8% sensitivity and 75.0% specificity when defined as exercise systolic BP ≥ 175 mmHg.

Table 2.2. Comparison between manual and automated auscultatory blood pressure at pre-exercise and different stages of a Bruce treadmill exercise test.

	Pre-exercise	Exercise Stage 1	Exercise Stage 2	All Stages [†]	Exercise Stages only [‡]
Comparisons	n=40	n=33	n=17	n=90	n=50
Systolic blood pressure (mmHg)					
Automated	136 ± 15	175 ± 20	190 ± 30	160 ± 30	180 ± 25
Manual	133 ± 16	171 ± 18	187 ± 23	157 ± 29	177 ± 21
Mean difference	3 ± 8°	4 ± 12	2 ± 14	3 ± 11°	3 ± 12
ICC (95% confidence intervals)	0.920 (0.831-0.960)*	0.882 (0.760-0.942)*	0.933 (0.817-0.976)*	0.964 (0.941-0.977)*	0.915 (0.853-0.953)*
Diastolic blood pressure (mmHg)					
Automated	72 ± 10	73 ± 13	77 ± 15	74 ± 13	75 ± 14
Manual	73 ± 9	73 ± 8	72 ± 10	73 ± 9	72 ± 9
Mean difference	-1 ± 7	1 ± 10°	6 ± 11°	1 ± 9°	2 ± 10°
ICC (95% confidence intervals)	0.848 (0.714-0.919)*	0.743 (0.478-0.873)*	0.774 (0.329-0.919)*	0.784 (0.672-0.858)*	0.751 (0.563-0.858)*
Pulse pressure (mmHg)					
Automated	64 ± 16	101 ± 17	113 ± 26	87 ± 28	105 ± 21
Manual	59 ± 14	98 ± 18	115 ± 20	85 ± 29	104 ± 20
Mean difference	4 ± 11°	3 ± 15	-4 ± 17	2 ± 14	1 ± 16°
ICC (95% confidence intervals)	0.827 (0.650-0.911)*	0.768 (0.536-0.885)*	0.845 (0.580-0.943)*	0.934 (0.899-0.956)*	0.826 (0.692-0.901)*

Data represent mean ± standard deviation, unless specified. Mean difference corresponds to automated blood pressure minus manual blood pressure.

[†] pre-exercise to exercise stage 2. [‡] exercise stage 1 to stage 2 only (excluding pre-exercise). °comparison assessed using Mann-Whitney U test. ICC, intra-class correlation. *p < 0.001, **p < 0.05.

Comparison of manual and automated auscultatory blood pressure during graded exercise among people with type 2 diabetes.

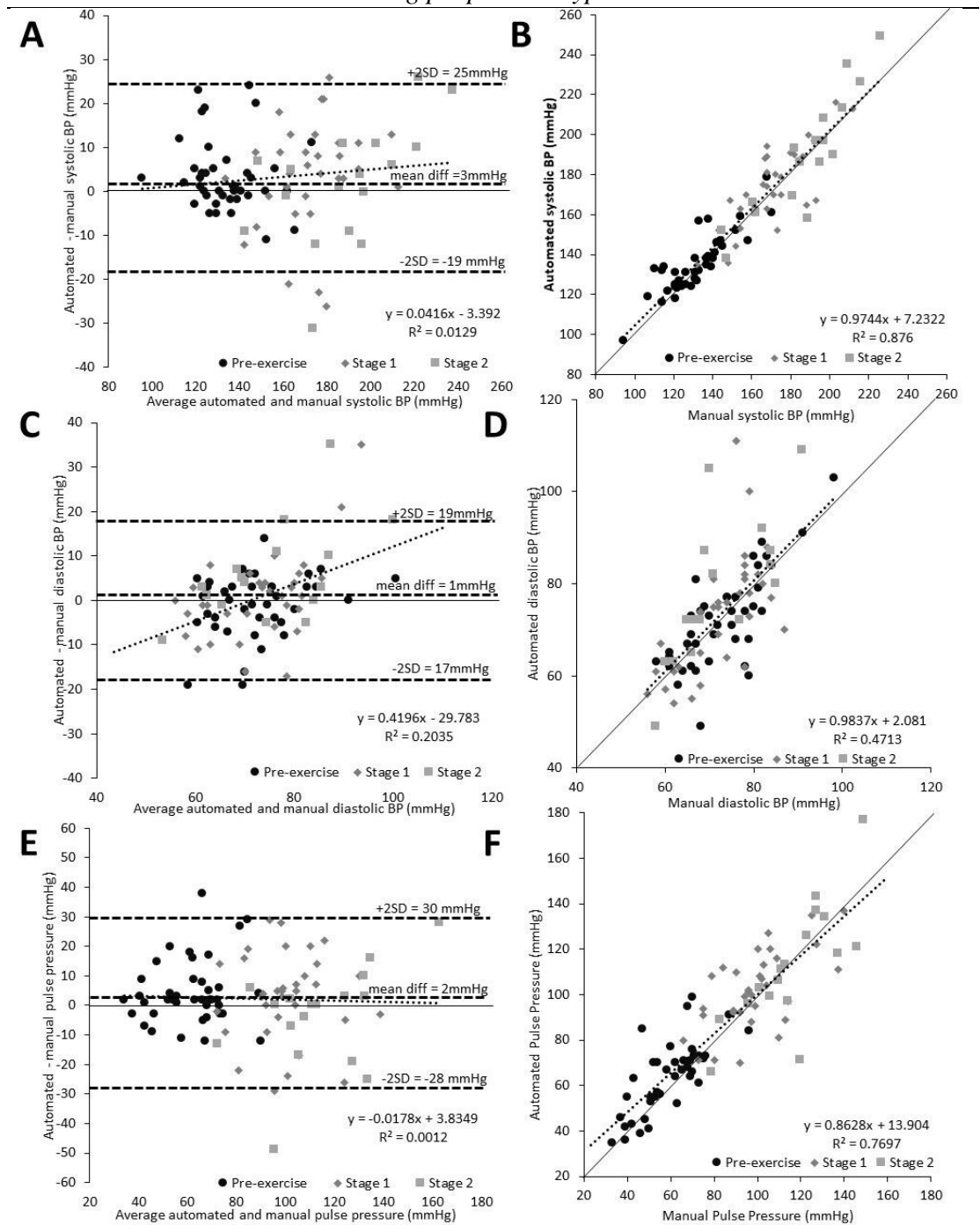


Figure 2.1. Comparison between manual and automated auscultatory blood pressure (BP) at different stages of a Bruce treadmill exercise test (n=90). Bland-Altman analyses comparing the agreement and variability between manual and automated systolic BP (A), diastolic BP (C), and pulse pressure (E), along with correlations between manual and automated systolic BP(B), diastolic BP(D), and pulse pressure(F). The solid line is the line of identity, and the broken line is the linear trend line across all exercise stages (pre-exercise to exercise stage 2).

2.5 DISCUSSION

The principle finding of this study was that automated BP measured with the Tango+ device was largely concordant with manual BP during early stages of a clinical treadmill exercise test involving a population of middle-to-older-aged people with type 2 diabetes mellitus. Results also indicated little difference in the ability of automated BP to appropriately classify exercise hypertension compared with manual auscultation. Overall, these results suggest that automated measurement of BP with the Tango+ BP device is appropriate to use during clinical exercise testing.

Six previous studies have explored the concordance between manual and automated measurement of BP during exercise [86,87,94,95,97,189]. Cameron et al. [87] found automated BP to be concordant with manual BP in five healthy adults during supine cycling, utilising the same automated BP device (Tango+) used in the current study. Our results are consistent with this, despite differences in the population and exercise protocol. Other studies have also indicated automated exercise BP (measured with a variety of devices) to be relatively concordant with manual BP during incremental treadmill exercise testing, especially at low-to-moderate exercise intensities [86,94,95,97,189]. Nonetheless, these studies have only included small sample sizes (n = 5 to 19 individuals) and ‘healthy’ populations that would not typically undergo exercise testing within clinical settings [95,97,189]. Other studies, including Gracia-Gregory et al.[94] also included a ‘healthy’ population but had a larger sample size (n= 277), while Modesti et al. included 16 participants with hypertension [86]. Our study extends on these studies in particular, and represents the first study to assess manual and automated exercise BP concordance in a population with type 2 diabetes mellitus during the early stages of a widely utilised clinical exercise testing protocol (Bruce treadmill).

In clinical practice, BP is often measured by an automated monitor during exercise testing. However, clinical exercise testing guidelines state a preference for manual BP measurement [8,179]. This is primarily due to the belief that automated BP devices may perform erratically during exercise, exacerbated during higher intensity exercise due to noise and movement artefacts [7,8,179]. Automated BP devices may also be unreliable during periods of elevated heart and respiratory rates [190]. On the other hand, accuracy of manual BP measurements may also be affected by noise and excessive patient movement, impairing technician ability to distinguish Korotkoff sounds, most notably the 4th and 5th Korotkoff sounds [86,94,97,189]. However, our results are consistent with observations from previous studies [86,94], indicating at least some level of variability that could be attributable to noise and movement artefact.

Assessment of BP during exercise testing is of clinical importance since abnormal readings are among the criteria for terminating testing on safety grounds [6–8,35,36,179,180]. Moreover, abnormal exercise BP responses (such as exercise hypertension) during low-to-moderate exercise intensity can indicate underlying raised BP missed by resting BP [10,69], and increase the risk for the future development of hypertension [11], cardiovascular morbidity and mortality [9]. Accurate measurement of exercise BP is likely to be of particular importance to individuals with type 2 diabetes mellitus since they carry a higher prevalence of exercise hypertension (reported as >50% in some studies) [43,161,191]. Our results indicate that automated BP has high sensitivity and low specificity for classifying exercise hypertension defined from manual exercise systolic BP ≥ 150 mmHg, with specificity increasing when exercise hypertension was classified using a threshold of exercise systolic BP ≥ 175 mmHg. This suggests clinicians can have confidence that the Tango+ device is suitable for identifying individuals with an abnormal BP response to light-to-moderate intensity exercise. These results also suggest confirmation of

abnormal exercise BP initially measured by the Tango+ device may not need to be subsequently confirmed by manual BP, as is the recommendation outlined in exercise testing guidelines [8,179].

Strengths and limitations. A strength of our study was the simultaneous measurement of manual and automated exercise BP on the same arm (rather than contralaterally), which eliminated any potential for inter-arm BP differences. However, our study population was exclusively those with type 2 diabetes mellitus. Consequently, our findings cannot be generalised to other clinical populations including those with cardiac arrhythmias where automated BP devices should be validated independently [192]. Our results are also limited by the small sample size and to the early stages of treadmill exercise testing only. However, people with type 2 diabetes mellitus are likely to only achieve exercise stage 1 or 2 due to early onset of fatigue and generally lower exercise/functional capacity [193,194]. It is possible that placement of the stethoscope in close proximity to the microphone within the automated device cuff may have impaired the quality of automated BP recordings, but the effects of this are unknown. It is also possible that the deflation rate of the automated BP device (which was set to operate automatically) could have affected the ability of the technician to accurately hear and record the Korotkoff sounds. However, the effect of deflation rate on measuring manual exercise BP is also likely minimal because manual and automated exercise BP was measured simultaneously on the same arm. Finally, it is worth noting that there is currently no standard procedure for the validation of BP devices during incremental exercise testing. The protocol followed for this study was also not in accordance with international standards for the accuracy validation of BP devices [187], because these standards are set exclusively for resting conditions. Indeed, the measurement of exercise BP during incremental exercise testing is more nuanced due to the rapidly changing conditions (i.e. increasing heart

rate and intensity). While it was therefore not possible to perform repeat measures of BP, we followed the clinical directive of a single measure in the final minute of each test stage [8,35]. It is however possible that only having one technician measure exercise BP could have introduced some degree of bias to the results.

2.6 CONTRIBUTION OF STUDY TO THESIS AIMS

Exercise BP can be measured with manual auscultation or an automated BP device. Data is scarce on whether the measurement of exercise BP with an automated BP device is in concordance with manual auscultation, with studies exclusively including small samples ($n < 20$) with healthy individuals. This study (Study 1) showed that there was good concordance between the manual and automated measurement of exercise BP in 41 individuals with type 2 diabetes mellitus during a standard treadmill exercise test. There was also little difference in the ability of automated BP to appropriately classify exercise hypertension compared with manual auscultation. Clinician and allied health professionals can, therefore, have confidence that automated measurement of exercise BP with the Tango+ BP device is appropriate for use during clinical exercise testing.

3 EXERCISE BLOOD PRESSURE AND CARDIAC STRUCTURE: A SYSTEMATIC REVIEW AND META-ANALYSIS OF CROSS-SECTIONAL STUDIES.

This thesis chapter has been published and formatted according to the guidelines of *Journal of Science and Medicine in Sport*.

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Link to online article: <https://pubmed.ncbi.nlm.nih.gov/33707155/>

3.1 ABSTRACT

Objectives. A hypertensive response to exercise (HRE) is associated with CVD and high blood pressure (BP). Sub-clinical changes to cardiac structure may underlie these associations, although this has not been systematically determined. Via systematic review and meta-analysis, we aimed to 1) assess the relationship between exercise BP and cardiac structure, and 2) determine if cardiac structure is altered in those with an HRE, across various study populations (including those with/without high BP at rest).

Design and Methods. Three online databases were searched for cross-sectional studies reporting exercise BP, HRE and cardiac structural variables. Random-effects meta-analyses and meta-regressions were used to calculate pooled correlations between exercise BP and cardiac structure, and pooled mean differences and relative risk between those with/without an HRE.

Results. Forty-nine studies, (n=23,707 total; aged 44±4 years; 63% male) were included. Exercise systolic BP was associated with increased left ventricular (LV) mass, LV mass index, relative wall thickness, posterior wall thickness and interventricular septal thickness (p<0.05 all). Those with an HRE had higher risk of LV hypertrophy (relative risk: 2.6 [1.85-3.70]), increased LV mass (47±7g), LV mass index (7±2g/m²), relative wall thickness (0.02±0.005), posterior wall thickness (0.78±0.20mm), interventricular septal thickness (0.78±0.17mm) and left atrial diameter (2±0.52mm) vs. those without an HRE (p<0.05 all). Results were broadly similar between studies with different population characteristics.

Conclusions. Exercise systolic BP is associated with cardiac structure, and those with an HRE show evidence towards adverse remodelling. Results were similar across different study populations, highlighting the hypertension-related CVD risk associated with an HRE.

3.2 INTRODUCTION

Systolic blood pressure (BP) normally rises with increasing exercise intensity [28]. Some individuals may experience an excessive rise in systolic BP during exercise (termed a hypertensive response to exercise; HRE) and this is associated with incident hypertension and an elevated risk of cardiovascular events and mortality [9,11]. Several studies also indicate that an HRE can reveal underlying high BP not detected during standard measurement conditions (at rest) in the clinic [10,69]. It follows that underlying the associations between exercise systolic BP and hypertension-related CVD risk is likely the presence of some cardiovascular abnormality such as structural cardiac disease. Indeed, some studies have shown elevated exercise systolic BP to be associated with markers of cardiac structure (including raised left ventricular [LV] mass index and relative wall thickness) [74,75], although others have not shown clear relationships [43,77]. The disparity in study findings may be due to differences between studies that have often included small, diverse populations (with or without diagnosed hypertension) with various exercise testing modalities and protocols. A pooled analysis of published study data has never been completed and may help to resolve equivocal findings. Therefore, the aims of this study were to 1) determine if there was a relationship between exercise systolic BP and cardiac structure, and 2) determine if cardiac structure is altered in those with an HRE compared to those without an HRE. A secondary aim was to determine whether these relationships differed across various study populations (including those with and without hypertension) via systematic review and meta-analysis.

3.3 METHODS

The literature search followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [195]. Three electronic databases

(MEDLINE, EMBASE and Scopus) were searched for articles reporting data on the relationship between exercise systolic BP and clinical markers of CVD for all years up to the August 18th 2020. (Appendix Table 3.1). Search strings included keywords such as “blood pressure”, “arterial pressure”, or “hypertension”; and “exercise”, “cardiopulmonary test”, or “stress test”; and “ventricular remodelling,” “cardiomyopathies”, or “cardiomegaly”. This search was conducted by two reviewers (MM and RC) independently. Reference lists of original and review articles were also searched for additional relevant literature. After full-text review of eligible articles, any discrepancies between the two reviewers were resolved via discussion with a third reviewer (MS).

Studies were eligible for inclusion if: 1) it was a full-length publication in an English language peer-reviewed journal; 2) the study population included human adults ≥ 18 years of age; 3) reported whether a relationship between exercise systolic BP (measured during dynamic exercise at submaximal and/or peak intensity) and any measure of cardiac structure and/or a difference in a structural cardiac variable between those with and without an HRE was found or not. Studies were excluded if exercise systolic BP was measured before or after dynamic exercise testing (e.g. pre-exercise test or during recovery) or an isometric test had been used (e.g. grip strength testing). All methods that measure cardiac structure (e.g. echocardiography and electrocardiography) were accepted for inclusion in this meta-analysis.

The primary outcomes were 1) LV mass; 2) LV mass index; and 3) prevalence of LV hypertrophy. Secondary outcomes included LV relative, interventricular septal and posterior wall thickness, LV end-systolic and LV end-diastolic dimensions and left atrial diameter. All cardiac structural variables were recorded as continuous variables,

except for LV hypertrophy, which was defined based on individual study criteria and recorded as dichotomous variable.

The quality of individual studies was assessed by two reviewers (MM and RC) using the Newcastle-Ottawa scale [196], in which a higher score indicates the study is of higher quality with less potential for publication bias. Scores were based on selection and comparability of study participant selection, and outcome exposure.

Data were extracted by one reviewer (MM) and independently verified by another investigator (PO). Data extracted from each eligible study included: age, gender, population health and resting BP status, measurement method for measuring cardiac structure, exercise test modality and protocol, method of BP measurement, exercise intensity at which time BP was measured, HRE and LV hypertrophy threshold criteria, and categorical and/or continuous results related to exercise systolic BP and cardiac structure. Detailed information on the data that was extracted (and the rationale for this choice) is presented in the supplementary methods section of the manuscript (Appendix A).

All analyses in this study were conducted using R for Windows (Version 3.5.1). A single sample size, mean and standard deviation or association was calculated for each individual study (where necessary) and is described in Appendix A of the supplementary methods.

Random effects estimates were calculated for all meta-analyses performed because of the heterogeneity in the included population and design between individual studies. Meta-analyses of the pooled mean difference between groups above and below a defined HRE threshold (as reported in each individual study) were calculated for each cardiac structure, we have used the term “categorical” to describe this type of meta-analysis. Meta-analyses of pooled unadjusted Pearson correlation coefficients were

calculated to assess associations between exercise systolic BP and each cardiac structure, we have used the term “continuous” to describe this type of meta-analysis. The strength of pooled unadjusted associations was classified according to Cohen (0.1-0.29 weak strength of association, 0.3-0.49 moderate strength of association and ≥ 0.5 strong strength of association) [197].

Meta-regression was performed to assess the heterogeneity explained by different population characteristics and exercise test methodologies. Heterogeneity between studies included differences in resting hypertension status (e.g. those with and without hypertension) and health status irrespective of BP classification (e.g. athletic, apparently healthy or chronic disease other than hypertension). Populations were classified as “hypertensive” based on a resting BP $\geq 140/90$ mmHg or prescribed antihypertensive medication. Study populations were classified as having a “mixed” status when analyses comprised of individuals with and without resting BP or various health statuses, e.g. analyses including people with and without a chronic disease. Factors related to differences in exercise testing methodologies used within studies included exercise intensity at which time BP was measured and exercise modality. Studies were classified as measuring BP at a submaximal intensity when BP was measured at any intensity of exercise that was not considered to be ‘peak’ or ‘maximal’ intensity. Studies not included within specific meta-regression analyses are reported in Appendix A of the supplementary methods.

P-values and the heterogeneity explained (R^2) from the meta-regression analyses are reported within the text of this manuscript for selected subgroupings relating to the continuous and/or categorical relationship between exercise systolic BP and primary outcomes of cardiac structure. The heterogeneity explained (R^2), details on number of studies, pooled mean difference and Pearson’s correlation are reported in the

supplementary results (Appendix A). All results from the meta-regressions performed to assess the continuous and/or categorical relationship between exercise systolic BP and secondary outcomes of cardiac structure are described and reported in Appendix A.

Funnel plots and Egger's tests were performed to assess publication bias. Trim and fill analyses were used to predict the number of unpublished studies and estimate a summary effect after adjustment for publication bias [198].

3.4 RESULTS

A total of 29,851 original articles were found across the three online databases, of which 16,232 were duplicates. An additional 51 articles were identified from reference lists giving 13,670 articles for review by title and abstract. One hundred and thirty one articles were subsequently eligible for full-text review, of which 49 studies were suitable for the systematic review. A summary of the literature search and results is shown in Appendix Figure 3.1.

In the 49 eligible studies, there was a total of 23,707 participants who were of younger-to-older age (mean age = 44 years old, ranging from a mean age of 22 to 65 years) and 63% male. Studies included populations with varying health status (comprising of five studies with athletes, 37 with apparently healthy, two with chronic disease, and five with a "mixed" health status), as well as different resting BP classifications (including 28 studies without resting hypertension, 11 with resting hypertension, eight with a "mixed" resting BP status and two not reported). Thirty-four studies measured exercise systolic BP at peak intensity, while 15 studies measured systolic BP at a submaximal intensity. Treadmill walking/running was the modality for exercise testing in 34 studies, while 15 studies used cycle ergometry. The most common threshold for an HRE reported in 22 studies as systolic BP ≥ 210 mmHg for males and/or ≥ 190 mmHg

for females at peak intensity. Forty-five studies measured cardiac structure with echocardiography, two with magnetic resonance imaging, one with electrocardiography, and one with electrocardiography and echocardiography. See Appendix Table 3.2 for a summary of the 49 studies included in this systematic review. Of the 49 studies included in the systematic review, four studies were excluded from the meta-analysis because insufficient data were available or data were unable to be pooled with another study [70,199–201].

Exercise systolic BP had a moderate positive association with LV mass (n=12 studies, $r = 0.39$, 95% CI: 0.28, 0.49; $p < 0.001$; Appendix Figure 3.1). Those with an HRE had higher LV mass compared to those without an HRE (n=5 studies, mean difference = 47.25g, 95% CI: 32.70, 61.80; $p < 0.001$; Appendix Figure 3.2). The pooled unadjusted correlation between exercise systolic BP and LV mass was different across studies with varying resting hypertension, health status and study quality ($p < 0.05$ all; Appendix Table 3.2). The pooled mean difference in LV mass between those with and without an HRE was different across study populations with varying health status ($p = 0.002$; Appendix Table 3.3).

Exercise systolic BP had a moderate positive association with LV mass indexed by body surface area (n=14 studies, $r = 0.39$, 95% CI: 0.29, 0.45; $p < 0.001$; Figure 3.3) and indexed by height^{2.7} (n=3 studies, $r = 0.39$, 95% CI: 0.31, 0.48; $p < 0.001$; Appendix Figure 3.4). Those with an HRE had higher LV mass indexed by body surface area (n=20 studies, mean difference = 6.72g/m², 95% CI: 3.59, 9.86 $p < 0.001$; Figure 3.2) but not when indexed by height^{2.7} (n=3 studies, mean difference = 6.66 g/m^{2.7}, 95% CI: -1.36, 14.68; $p = 0.103$; Appendix Figure 3.5), compared to those without an HRE. The pooled unadjusted correlation between exercise systolic BP and LV mass indexed by body surface area was different between studies that measured BP at varying exercise

intensities, used different exercise modalities, and had discrepancies in quality scores ($p < 0.05$ all; Appendix Table 3.2). The pooled unadjusted correlation between exercise systolic BP and LV mass indexed by height^{2.7} was different between studies that measured BP at varying exercise intensities ($p < 0.001$, $R^2 = 100\%$; Appendix Table 3.3). The pooled mean difference in LV mass indexed by height^{2.7} was different between studies that measured BP at varying exercise intensities and had different quality scores ($p < 0.05$ both; Appendix Table 3.3).

Risk of LV hypertrophy was higher in those with an HRE compared to those without an HRE ($n = 10$ studies, risk ratio = 2.61, 95% CI: 1.85, 3.70; $p < 0.001$; Figure 3.3). Risk of LV hypertrophy was similar across studies with populations who had different resting hypertension and health status, and varying quality score ($p > 0.05$ all; Supplementary Table 3.4).

Exercise systolic BP had a weak positive association with LV relative wall thickness ($n = 3$ studies, $r = 0.18$, 95% CI: 0.13, 0.32; $p < 0.001$; Appendix Figure 3.6). Those with an HRE had higher LV relative wall thickness compared to those without an HRE ($n = 10$ studies, mean difference = 0.02, 95% CI: 0.01, 0.03; $p < 0.001$; Appendix Figure 3.7).

There was a weak positive association between exercise systolic BP and interventricular septal thickness ($n = 3$ studies, $r = 0.33$, 95% CI: 0.11, 0.56; $p = 0.004$; Appendix Figure 3.8). Those with an HRE had higher interventricular septal thickness compared to those without an HRE ($n = 10$ studies, mean difference = 0.78mm, 95% CI: 0.44, 1.13; $p < 0.001$; Appendix Figure 3.9).

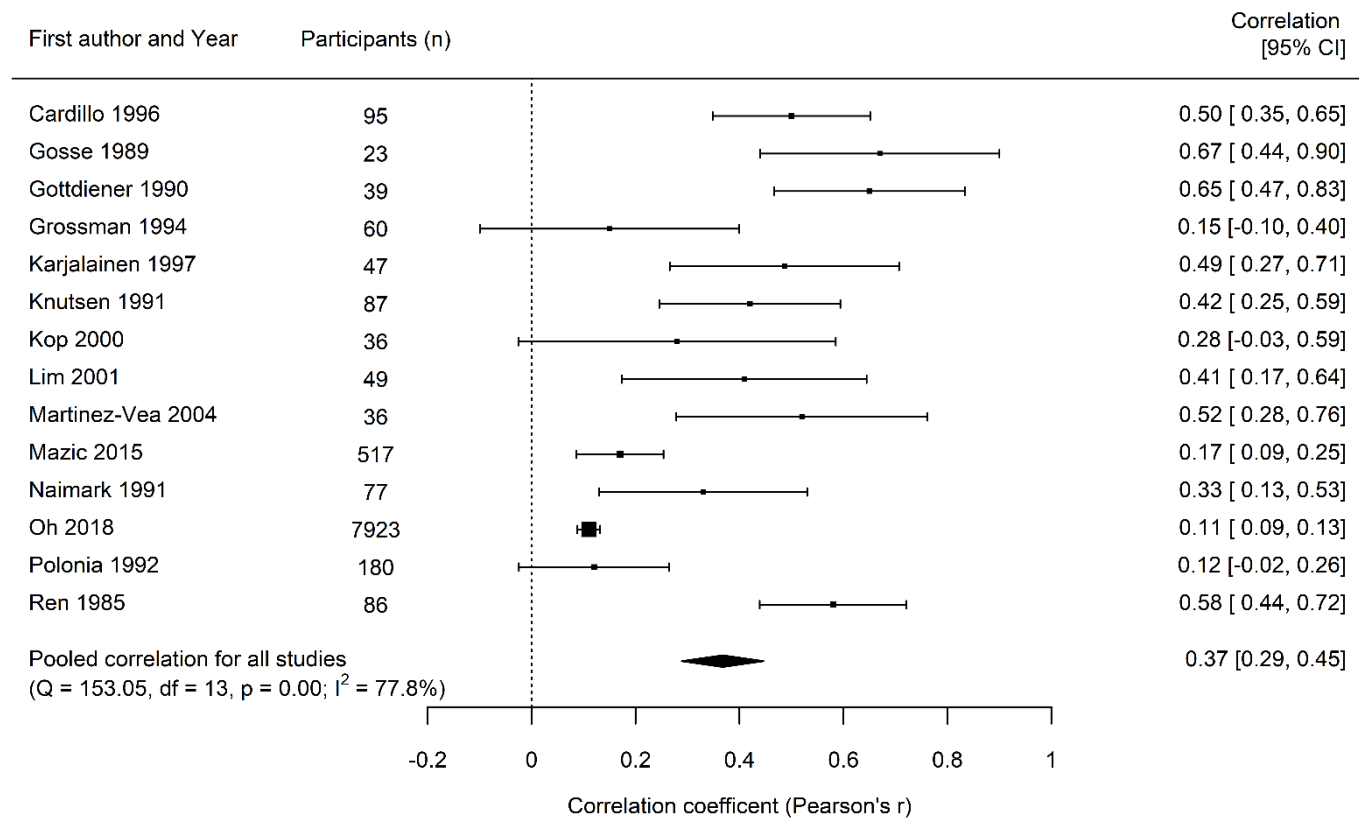


Figure 3.1. Random effect estimate for the unadjusted strength of association and 95% confidence intervals (CI) between exercise blood pressure and left ventricle mass indexed by body surface area.

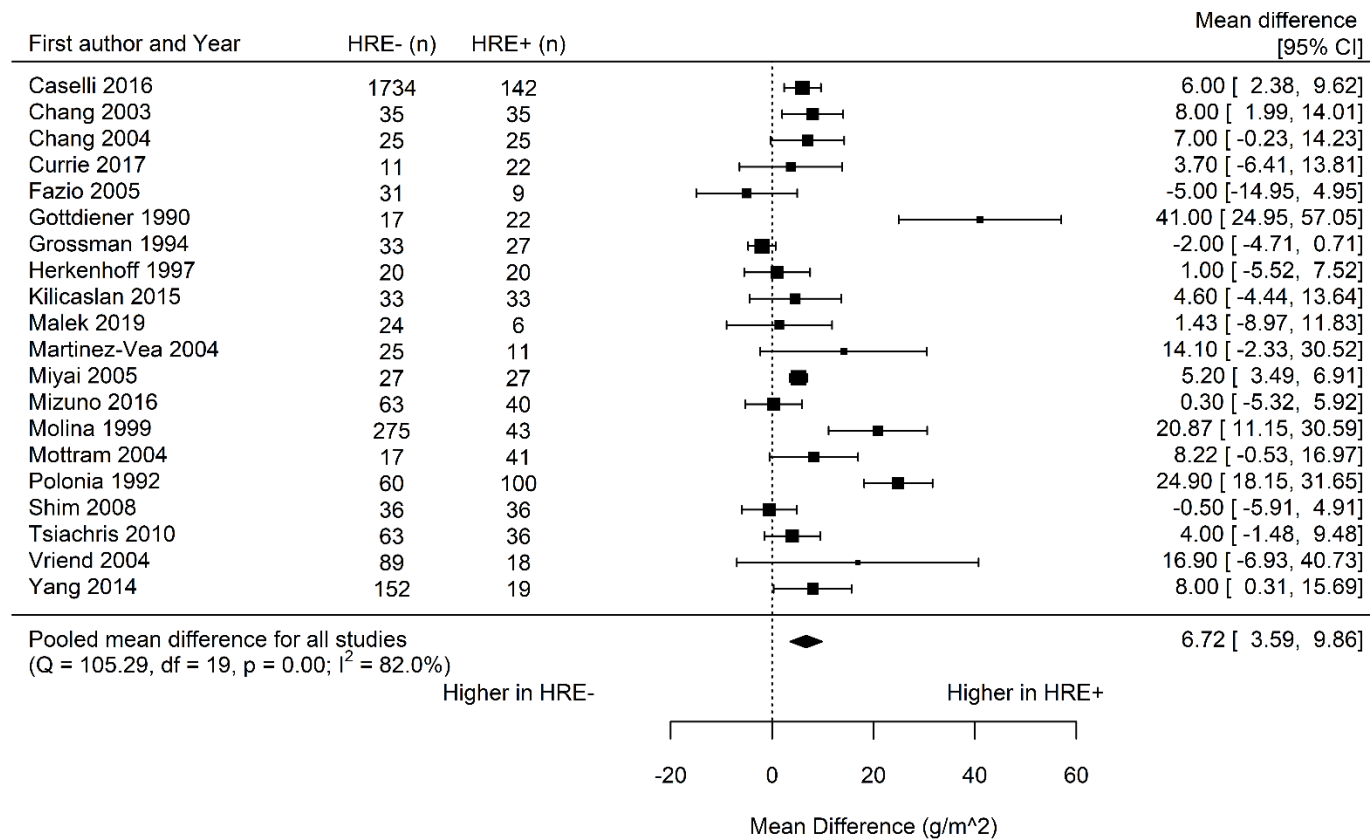


Figure 3.2. Random-effect pooled mean difference and 95% confidence intervals (CI) in left ventricular mass index (indexed by body surface area) between those where a hypertensive response to exercise was present (HRE+) or absent (HRE-).

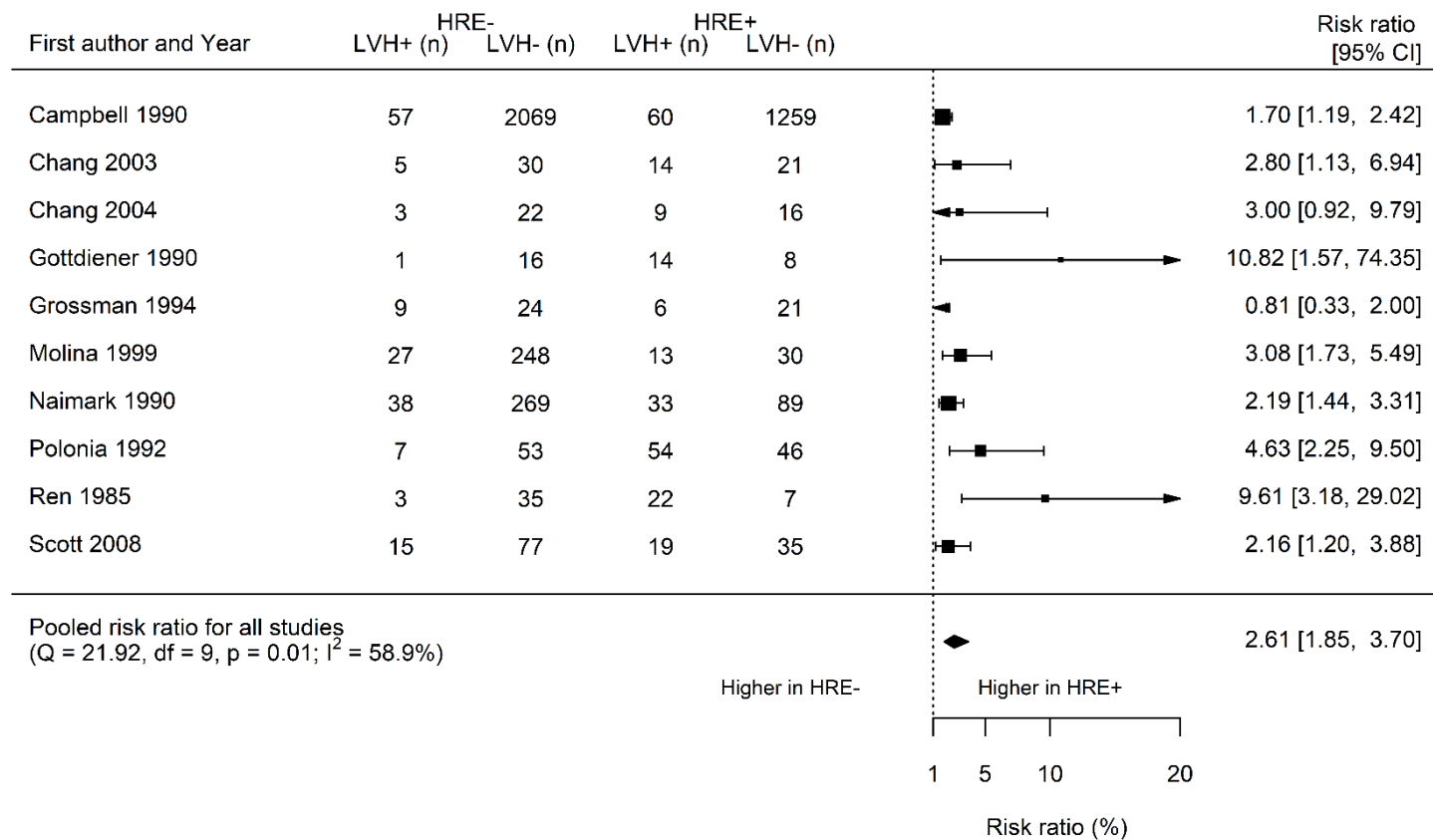


Figure 3.3. Random-effect pooled prevalence and 95% confidence intervals (CI) of left ventricular hypertrophy between those where a hypertensive response to exercise was present (HRE+) or absent (HRE-)

Exercise systolic BP had a weak positive association with LV posterior wall thickness (n=4 studies, $r = 0.36$, 95% CI: 0.19, 0.53; $p < 0.001$; Appendix Figure 3.10). Those with an HRE had higher LV posterior wall thickness compared to those without an HRE (n=8 studies, mean difference = 0.78mm, 95% CI: 0.29, 1.18; $p < 0.001$; Appendix Figure 3.11).

There was no difference between those with and without an HRE in LV end-systolic dimension (n=6 studies, mean difference = 0.45 mm, 95% CI: -1.75, 2.68; $p = 0.69$; Appendix Figure 3.12).

There was no difference between those with and without an HRE in LV end-diastolic dimension (n=14 studies, mean difference = 0.80 mm, 95% CI: -0.17, 1.76; $p = 0.11$; Appendix Figure 3.13).

Those with an HRE had higher left atrial diameter compared to those without an HRE (n=7 studies, mean difference = 2.25 mm, 95% CI: 1.23, 3.27; $p < 0.001$; Appendix Figure 3.14).

There was evidence for publication bias based on funnel plots and Egger's test for continuous associations between exercise systolic BP and cardiac structure, except for interventricular septal thickness (Appendix Figure 3.15). The trim and fill method added six theoretically missing studies to the pooled continuous analysis for LV mass indexed by body surface area, and reduced the pooled correlation estimate ($r = 0.20$, 95% CI: 0.14, 0.28, $p < 0.001$). There was no evidence for publication bias based on funnel plots and Egger's test for all pooled mean differences, except for LV mass indexed by body surface area ($p = 0.012$; Appendix Figure 3.16).

3.5 DISCUSSION

The primary finding of this meta-analysis was that exercise systolic BP was associated with cardiac structure, such that those with an HRE were at more than two times

greater risk of LV hypertrophy and had a higher pooled mean LV mass, LV mass index and LV relative wall thickness compared to those without an HRE. Pooled mean differences in cardiac structural variables between those with and without an HRE were also broadly similar irrespective of hypertension status, health status and the exercise intensity at the time BP was measured. Taken together, these results highlight a relatively consistent relationship between exercise systolic BP and cardiac structure, which could explain some of the CVD risk associated with an HRE.

Cardiac structural adaptation (such as left ventricular hypertrophy) is one of the primary signs of hypertension-related organ damage [202]. In this context, the myocardium is remodelled due to chronic exposure to increased afterload [73], with elevated BP typically identified before progression to cardiac remodelling of clinical significance [203]. There is however evidence to suggest that an HRE likely indicates the presence of high BP undetected at rest [10,69], and thus may be used to reveal elevated CVD risk before overt clinical presentation. Whilst this meta-analysis does not explicitly confirm that an HRE is a signal for underlying high BP (which would require home or ambulatory BP monitoring for definitive diagnosis), we found exercise systolic BP to be consistently (and positively) associated with LV mass, LV mass index and LV relative wall thickness across most included studies. Most cardiac structural variables were also higher among those with an HRE compared to those with no HRE, and broadly similar between studies that included populations with a different status for resting BP. These consistent associations between exercise systolic BP and LV structure provide further important evidence to suggest that an HRE is indeed a signal for undetected high BP, and the differential cardiac structure is a manifestation of heightened CVD risk.

In this meta-analysis, we were unable to assess the many potential contributory factors that may underpin the relationship between exercise systolic BP and cardiac structure. However, several studies suggest that raised arterial stiffness may play a central role. Indeed, elevated arterial stiffness sustained over time may increase cardiac afterload, giving way to a pathological remodelling of the left ventricle [73]. A stiffened vasculature coupled to an exercise-induced elevation in stroke volume would also precipitate an acute elevation in exercise systolic BP [112]. Altered cardiac structure and an HRE has been reported as more prevalent in those with chronic health conditions, such as type 2 diabetes mellitus and hypertension [43,70], both synonymous with raised arterial stiffness [89]. As such, the relationship between cardiac structure and exercise systolic BP likely represents a more advanced stage of CVD in these individuals.

As expected, cardiac structural parameters were also higher in study populations with an HRE who were healthy and/or athletic. In these individuals, the cardiac structure and exercise systolic BP relationship is more likely to be a normal physiological response to regular physical activity. Indeed, while follow-up ambulatory monitoring in athletes who record an HRE is recommended to rule-out underlying hypertension [72], an HRE often occurs at maximal or peak workloads in highly fit and athletic populations in the absence of other (resting) cardiovascular abnormalities [45,77]. Whilst we were unable to account for training status or the level of cardiorespiratory fitness in this meta-analysis, both are known correlates of cardiac structural adaptation [84]. Individuals in the included studies described as ‘athletic’ may have therefore undergone some form of physiological LV remodelling, which via a Frank-Starling mechanism would facilitate greater cardiac output and thus higher systolic BP during longer duration or more intense exercise. This type of LV structural adaptation typically occurs with a sustained endurance training load (i.e. a volume overload

leading to eccentric LV hypertrophy) or strength training (i.e. potential pressure overload leading to concentric LV hypertrophy) [84]. However, the level of physical activity undertaken by the different study populations in this meta-analysis is unknown. Thus, further research is required to fully understand both the nature of and contributory factors of the exercise systolic BP and cardiac structure relationship.

To account for some of the heterogeneity and potential study bias associated with exercise systolic BP measurement, we combined eligible studies with similar exercise testing design and assessed differences using meta-regression. The difference in cardiac structure (namely LV mass index) between those with and without an HRE did vary slightly between studies that used a dissimilar exercise modality. It is possible that an HRE manifests differently with exercise modality and protocols, with data to suggest that systolic BP does not increase to the same extent in response to cycle exercise compared with treadmill exercise [31]. Nonetheless, to our knowledge there is no physiological rationale to suggest that exercise modality should affect the relationship between exercise systolic BP and cardiac structure. Differences and heterogeneity explained by studies using various modalities are perhaps more likely due to individual study population characteristics, exercise testing design, HRE and LV hypertrophy threshold or low statistical power, which we cannot account for in this meta-analysis. Exercise systolic BP is generally higher in males compared to females and increases with age in both sexes [40,204]. However, we were unable to pool associations adjusted for age and sex (as well as other potential confounding factors) due to the paucity of adjusted model data available and in the absence of individual participant data. Moreover, all studies included in this meta-analysis were cross-sectional in design. Therefore, an analysis of longitudinal data is required to more accurately understand future CVD risk, and whether the exercise systolic BP-cardiac

relationship is truly pathological in nature. Analyses of longitudinal data may also allow causal pathways between an HRE and LV hypertrophy to be identified.

Conclusion. This study systematically determined that an HRE is adversely associated with several markers of cardiac structure. Associations were relatively consistent across different study populations and exercise testing methodologies. These results highlight the hypertension-related CVD risk associated with an HRE. Further physiological and mechanistic studies are required to more fully understand factors that contribute to the association between exercise systolic BP and cardiac structure, in both sub-clinical and clinical populations.

Practical implications.

- The BP response to clinical exercise testing carries significant prognostic and clinical implications, being linked to hypertension-related cardiovascular morbidity and mortality.
- This meta-analysis represents the first systematic assessment of the relationship between exercise BP and cardiac structure, with the results revealing that a rather consistent relationship exists between an HRE and ‘adverse’ cardiac structure.
- This highlights the potential hypertension-related CVD risk associated with abnormal exercise BP.

3.6 CONTRIBUTION OF STUDY TO THESIS AIMS

Prior to Study 2, there was conflict between studies on the relationship between exercise BP and cardiac structure. It was also uncertain whether those with an HRE had structural cardiac adaptation that was different to those without an HRE because not all studies had reported this difference. This study (Study 2) has fully elucidated that exercise BP is associated with cardiac structure irrespective of clinic BP.

Additionally, those with an HRE had raised cardiac structure and risk of LV hypertrophy compared to those without an HRE irrespective of clinic BP. These findings suggest the potential hypertension-related CVD risk associated with abnormal exercise BP. This potential relationship may suggest there is an association between exercise BP and other CVD risk factors, which cluster with the presence of high BP. Therefore, Study 3 aimed to assess the relationship between exercise BP and CVD risk factors, and determine if CVD risk is higher in those with an HRE vs. no-HRE, via a second systematic review and meta-analysis.

4 EXERCISE BLOOD PRESSURE AND CARDIOVASCULAR DISEASE RISK: A SYSTEMATIC REVIEW AND META-ANALYSIS OF CROSS-SECTIONAL STUDIES.

This thesis chapter has been published and formatted according to the guidelines of *Journal of Hypertension*.

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Link to online article:

https://journals.lww.com/jhypertension/Abstract/9000/Exercise_blood_pressure_and_cardiovascular_disease.96596.aspx

4.1 ABSTRACT

Background. A hypertensive response to exercise (HRE) is associated with CVD and high blood pressure (BP). A poor CVD risk factor profile may underlie these associations, although this has not been systematically elucidated. Via systematic review and meta-analysis, we aimed to assess the relationship between exercise BP and CVD risk factors, and determine if CVD risk is higher in those with an HRE vs. no-HRE across different study populations (including those with/without high BP at rest).

Methods. Three online databases were searched for cross-sectional studies reporting data on exercise BP, an HRE and CVD risk factors (including arterial structure, lipid, metabolic, inflammatory and kidney function markers). Random-effects meta-analyses and meta-regression were used to calculate pooled correlations between exercise BP and each risk factor and pooled mean differences between those with/without an HRE.

Results. Thirty-eight studies (38,295 participants, aged 50 ± 3 years; 78% male) were included. Exercise systolic BP was associated with arterial, lipid, and kidney function risk markers ($p<0.05$). Those with an HRE had greater aortic stiffness ($+0.80\pm 0.35$ m/s), total ($+0.14\pm 0.03$ mmol/L) and low-density lipoprotein ($+0.12\pm 0.03$ mmol/L) cholesterol, triglycerides ($+0.24\pm 0.04$ mmol/L), glucose ($+0.15\pm 0.05$ mmol/L), white blood cell count ($+0.49\pm 0.16$ mmol/L) and albumin-to-creatinine ratio (standardised mean difference: $+0.97\pm 0.34$), and lower flow-mediated dilation ($-4.13\pm 1.02\%$) and high-density lipoprotein cholesterol (-0.04 ± 0.01 mmol/L) vs. those with no-HRE ($p<0.05$ all). Results were broadly similar across study populations.

Conclusions. Exercise systolic BP is associated with multiple CVD risk factors, which appear worse in those with an HRE vs. no-HRE. Since results were similar across population groups, an HRE should be considered an important indicator of CVD risk.

4.2 INTRODUCTION

Systolic blood pressure (BP) normally rises as the intensity of dynamic exercise testing increases [28]. However, irrespective of apparently normal BP at rest, some individuals may experience abnormally high systolic BP during exercise (termed a hypertensive response to exercise, HRE), which is associated with increased risk of incident hypertension, cardiovascular morbidity and mortality [9,11]. An HRE has also been shown to reveal high BP undetected by standard in-clinic measurement of BP at rest [10,43,69,70,205]. These data suggest there may be underlying relationships between exercise BP and other CVD risk factors. A pooled analysis of studies assessing the relationship between exercise BP and CVD risk factors has never been completed. Therefore, via systematic review and meta-analysis, we aimed to determine the association between exercise BP and individual CVD risk factors, as well as understand if those with an HRE display a worse CVD risk factor profile compared to those without an HRE. A further exploratory aim was to assess whether these relationships persisted amongst various study populations (including those with and without high BP at rest) and irrespective of the exercise testing methodology.

4.3 METHODS

Study identification. The literature search followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [206]. Two independent reviewers (MM and RC) searched three electronic databases (MEDLINE, EMBASE and Scopus) from inception to August 18th 2020 for studies reporting data on the relationship between exercise BP, and/or an HRE, and CVD risk factors (Appendix Table 3.1). Search terms included keywords such as “blood pressure” or “arterial pressure” and “exercise” or “cardiopulmonary test” or “stress test” and “atherosclerosis” or “vascular stiffness” or “carotid intima-media thickness” or

“glucose” or “cholesterol” or “creatinine” or “albuminuria.” Reference lists of original and review articles were also searched for additional studies. After full-text review of eligible articles, any discrepancies between the two reviewers were resolved via discussion with a third reviewer (MS).

Criteria for study inclusion. Studies were eligible for inclusion if the following criteria were satisfied: 1) full-length publication in an English language peer-reviewed journal; 2) human, adult study population ≥ 18 years of age and 3) data on an association between exercise BP and a CVD risk factor and/or difference in CVD risk factor between those with and without an HRE was reported. Studies were excluded if exercise BP was measured invasively, before or not immediately after a dynamic exercise test (i.e. pre-exercise or during recovery) or if an isometric exercise test had been used (e.g. grip strength testing).

Outcome measures. The following groupings of CVD risk factors were included as outcomes: arterial structure and function (aortic pulse wave velocity and flow-mediated dilation); lipids (total cholesterol, high and low-density cholesterol and triglycerides); metabolic (blood glucose, HbA1c, insulin and Homeostatic Model Assessment of Insulin Resistance [HOMA-IR]); inflammatory (c-reactive protein and white blood cell count) and kidney function (creatinine and albumin-creatinine ratio).

Data Extraction. Two reviewers (MM and RC) independently extracted data from eligible studies. Data reported in each study that was extracted included: age, sex, body mass index, health status or demographic of the study population (e.g. chronic disease or healthy), resting BP status (e.g. with or without resting high BP), diabetes status, smoking status, antihypertension medication status, exercise test modality, protocol and clinical indication, positive exercise-induced myocardial ischemia tests, exercise BP measurement method and intensity, HRE threshold, each CVD risk factor reported,

the time each CVD risk factor was measured respective to the exercise test, the analysis method used for each CVD risk factor and mean and standard deviation for each CVD risk factor for those with and without an HRE and/or Pearson correlation coefficient between exercise BP and CVD risk factors. More detailed information on data extraction is described in Appendix B of the supplementary material.

Publication quality. Two reviewers (MM and RC) independently assessed the quality of each study using the Newcastle-Ottawa scale [196]. Studies with a smaller score from the Newcastle-Ottawa scale indicated a lower quality. Scores were based on selection and comparability of study participants, and outcome ascertainment.

Statistical analysis. Random effects methods were used for all meta-analyses because of the heterogeneity between individual studies, including differences in participant characteristics, thresholds used to define an HRE, outcomes, exercise test modality and protocols. Individual studies were included in more than one meta-analysis if multiple CVD risk factors were able to be extracted or calculated. Some studies reported estimates for individual CVD risk factors in sub-groups[207–209], which were combined prior to inclusion in meta-analyses and are described in Appendix B of the supplementary material.

The pooled mean difference in each CVD risk factor between groups above and below a study-specific threshold of an HRE was calculated. CVD risk factors were converted to standardised units, e.g. mg/dl to mmol/L (where possible), for direct comparison with other studies. Alternatively, where it was not possible to homogenise units of measure, we calculated standardised mean differences for pooling.

Additionally, the pooled unadjusted Pearson correlation coefficient between exercise systolic BP and a CVD risk factor was calculated. The strength of the pooled correlation coefficients was interpreted according to Cohen [197] (0.1-0.29 weak

strength of association, 0.3-0.49 moderate strength of association and ≥ 0.5 strong strength of association).

Meta-regression was performed to assess the heterogeneity between studies. Characteristics assessed included populations with variable resting BP status, health status, exercise test methodology (exercise intensity at which time BP was measured and exercise modality) and Newcastle-Ottawa Scores. Study populations were classified as hypertensive if resting BP was $\geq 140/90$ mmHg or if reported current treatment with antihypertensive medication/s. Those with no history of any chronic disease were classified as apparently healthy. A study that comprised of a population with no defined resting BP status (i.e. included individuals with and without hypertension) or health status were classified as mixed. Exercise BP not measured at peak or maximal intensity was defined as submaximal. Meta-regressions were performed if there were at least three available studies that included different population characteristics and/or exercise testing methodologies. The P-value and the heterogeneity explained (R^2) for each selected subgrouping has been reported within the text of this manuscript, while Appendix B of the supplementary material include additional details on the number of included studies, pooled mean differences and Pearson correlations in each subgroup.

Funnel plots and Egger's test were utilised to assess publication bias when there were three or more available studies. Trim and fill analyses were used to predict the number of unpublished studies and estimate a summary effect after accounting for publication bias [198].

All analyses in this study were conducted using R for Windows (Version 3.5.1).

4.4 RESULTS

Literature search. A total of 29,851 original articles were found across the three online databases searched, of which 16,232 were duplicates. After adding 51 potential original articles found from reference lists, 13,670 articles were available for closer review by title and abstract. One hundred and thirty-one articles were subsequently found to be eligible for full-text review, of which 38 studies met the inclusion criteria for the systematic review. A summary of the literature search and results is shown in Appendix Figure 4.1.

Summary of studies included in systematic review and meta-analysis. Appendix Table 4.1 summarises the 38 eligible studies included in the systematic review. From the 38 studies, there was a total of 38,295 participants. Participants had a mean age of 50 years (range 24-60 years), were 78% male and had a mean body mass index of 25kg/m² (range 23-30.5 kg/m²). Twenty-eight studies included apparently healthy individuals, two exclusively included individuals with a chronic disease, two only included an athletic population and six included populations with a mixed health status. Twenty-one studies included individuals without resting hypertension, four with resting hypertension and 13 with a mixed BP status. A total of 7,396 individuals across all included studies were classified as hypertensive, of which 1,692 were on antihypertension medication. Exercise tests were principally performed for research purposes (n=22 studies), while clinical studies had indications for testing that varied between studies (n=16 studies; Appendix Table 4.1). One study reported test results indicating n=4 as positive for exercise-induced myocardial ischemia. Exercise systolic BP was measured at submaximal intensities in 13 studies, at peak intensities in 24 studies, and both submaximal and peak intensity in one study. The modalities of exercise testing included treadmill walking/running (n=25 studies), cycle ergometry (n=11 studies) and step testing (n=2 studies). An HRE was most commonly defined as

systolic BP ≥ 210 mmHg for males and ≥ 190 mmHg for females at peak intensity within the included studies (n=17 studies). Outcomes that required serum samples (e.g. cholesterol or glucose) were taken in a fasting state in all studies except two [128,207]. The timing of each outcome measurement in relation to the exercise test and the analysis methods used for each CVD risk factor varied between studies (Appendix Table 4.1). All studies that measured aortic pulse wave velocity used tonometry, while flow-mediated dilation was measured using ultrasound. Six studies were subsequently excluded from the meta-analysis because the required quantitative data was unable to be appropriately extracted or pooled with data from other studies [79,114,138,210–212], leaving 32 studies eligible for meta-analyses.

Arterial structure and function.

Meta-analyses. Exercise systolic BP had a moderate positive association with aortic pulse wave velocity (n=5 studies, $r = 0.35$, 95%CI: 0.25, 0.46; $p < 0.001$; Appendix Figure 4.1). Those with an HRE had higher aortic pulse wave velocity compared to those without an HRE (n=3 studies, mean difference = 0.80m/s, 95% CI: 0.12, 1.48, $p = 0.02$; Appendix Figure 4.2). Those with an HRE had lower flow-mediated dilation compared to those without an HRE (n=2 studies, mean difference = -4.13%, 95% CI: -6.12, -2.13, $p < 0.001$; Appendix Figure 4.3).

Meta-regressions. The pooled association between exercise systolic BP and aortic pulse wave velocity was similar across studies that had populations with varying resting BP status ($p = 0.80$, $R^2 = 0\%$; Appendix Table 4.2). The pooled mean difference in aortic pulse wave velocity was different across studies that had populations with varying health status ($p = 0.02$, $R^2 = 100\%$; Appendix Table 4.2).

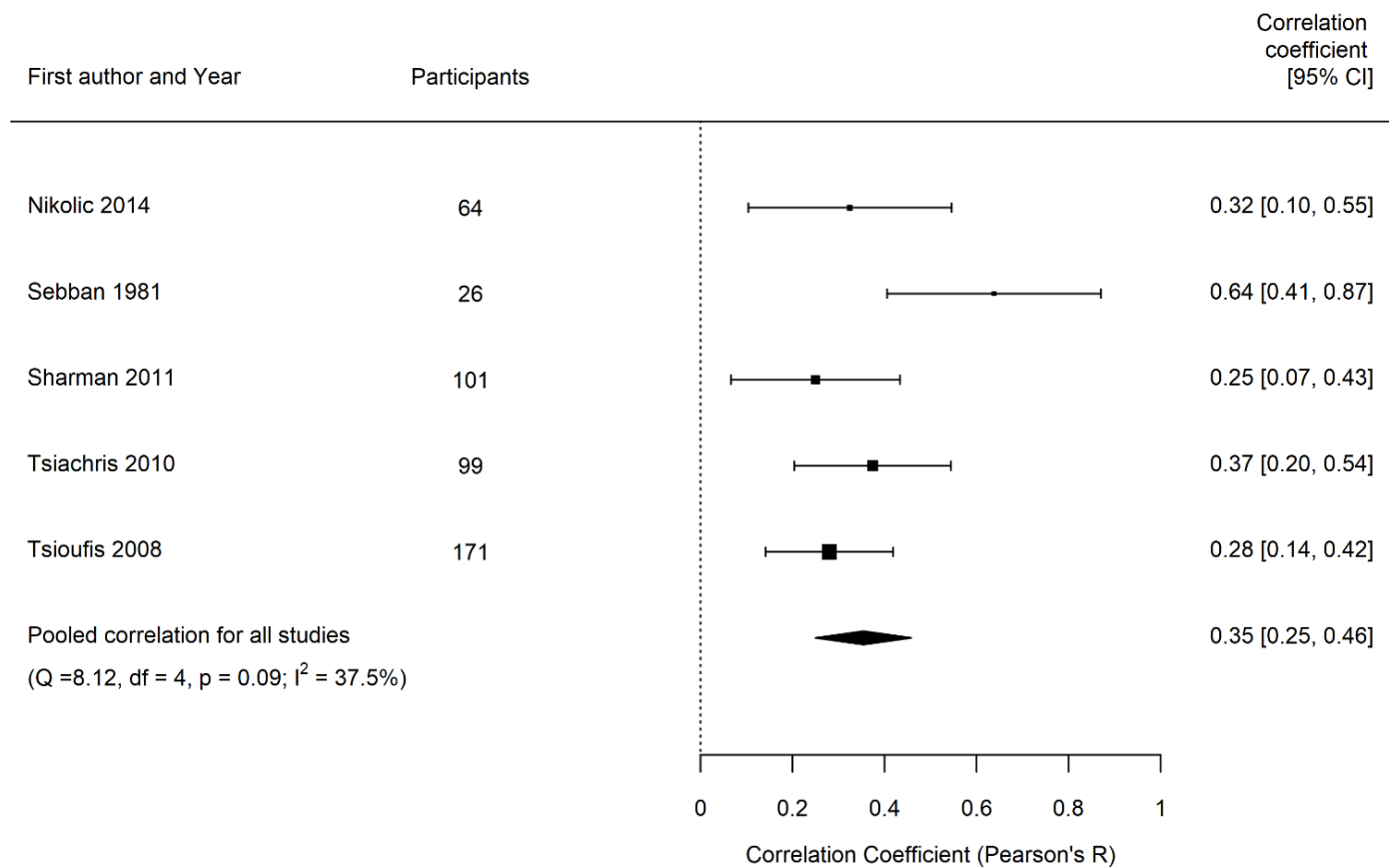


Figure 4.1. Pooled unadjusted correlation between exercise blood pressure and aortic pulse wave velocity.

Lipids.

Meta-analyses. Exercise systolic BP had a weak positive correlation with total cholesterol (n=2 studies, $r = 0.19$, 95% CI: 0.09, 0.29; $p < 0.001$; Appendix Figure 4.4) and triglycerides (n=4 studies, $r = 0.20$, 95% CI: 0.13, 0.28; $p < 0.001$; Appendix Figure 4.5). Total cholesterol (n=24 studies, mean difference = 0.14mmol/L, 95% CI: 0.07, 0.21, $p < 0.001$; Appendix Figure 4.2), low-density lipoprotein cholesterol (n=17 studies, mean difference = 0.12mmol/L, 95% CI: 0.06, 0.18, $p < 0.001$; Appendix Figure 4.6) and triglycerides (n=18 studies, mean difference = 0.24mmol/L, 95% CI: 0.15, 0.33, $p < 0.001$; Appendix Figure 4.7) were higher among those with an HRE compared to those without an HRE. Those with an HRE had a lower high-density lipoprotein cholesterol compared to those without an HRE (n=19 studies, mean difference = -0.04mmol/L, 95% CI: -0.06, -0.01, $p = 0.003$; Appendix Figure 4.8).

Meta-regressions. The pooled association between exercise systolic BP and triglycerides was similar across studies that had populations with varying resting BP status and health status, studies with varying exercise testing methods and quality scores ($p > 0.05$ all; Appendix Table 4.3 and 4.4). The pooled mean difference in lipid risk factors were similar across studies that had populations with varying resting BP status and health status, studies with varying exercise testing methods and quality scores ($p > 0.05$ all; Appendix Table 4.3 and 4.4), except for low-density lipoprotein cholesterol across studies with varying exercise testing modalities ($p = 0.04$; $R^2 = 61\%$).

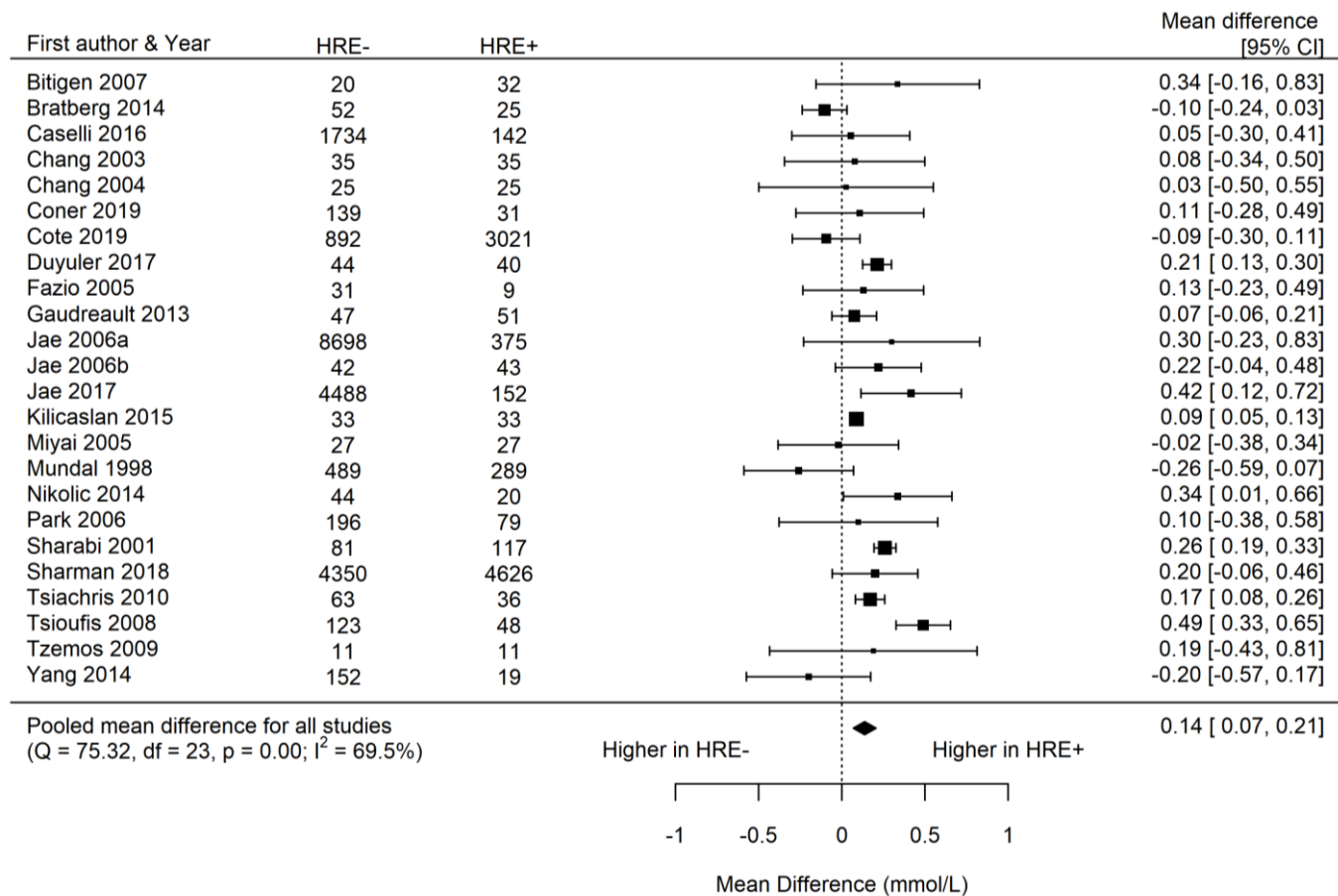


Figure 4.2. Pooled mean difference in total cholesterol between individuals where a hypertensive response to exercise was present (HRE+) or absent (HRE-).

Metabolic.

Meta-analyses. Those with an HRE had a higher level of glucose (n=18 studies, mean difference = 0.15mmol/L, 95% CI: 0.06, 0.24, p=0.002; Figure 4.3), insulin (n=4 studies, standardised mean difference = 0.34, 95% CI: 0.11, 0.57, p=0.003; Appendix Figure 4.9), HbA1c (n=4 studies, mean difference = 0.14%, 95% CI: 0.01, 0.26, p=0.038; Appendix Figure 4.10) and HOMA-IR (n=3 studies, mean difference = 0.56 IU, 95% CI: 0.21, 0.91, p=0.002; Appendix Figure 4.11) compared to those without an HRE.

Meta-regressions. The pooled mean difference in each metabolic risk factor was similar across studies that had populations with varying resting BP status and health status, studies with varying exercise testing methods and quality scores (p>0.05 all; Appendix Table 4.3 and 4.4), except for insulin across studies that had populations with varying health status (p=0.04; R²=80%), HbA1c across studies with varying quality scores (p=0.02; R²=73%) and HOMA-IR across studies that had populations with varying resting BP status (p=0.03; R²=100%) and studies with varying quality scores (p=0.04; R²=100%).

Inflammation.

Meta-analyses. There was negligible correlation between exercise systolic BP and c-reactive protein (n=2 studies, r = 0.08, 95%CI: -0.08, 0.23; p=0.35; Appendix Figure 4.12). White blood cell count (n=4 studies, mean difference = 0.49mmol/L, 95% CI: 0.17, 0.81, p=0.003; Appendix Figure 4.13) and C-reactive protein (n=2 studies, standardised mean difference = 0.34, 95% CI: 0.02, 0.66, p=0.039; Appendix Figure 4.14) was higher among those with an HRE compared to those without an HRE.

Meta-regressions. The pooled mean difference in white blood cell count was similar across studies with varying quality scores (Appendix Table 4.4).

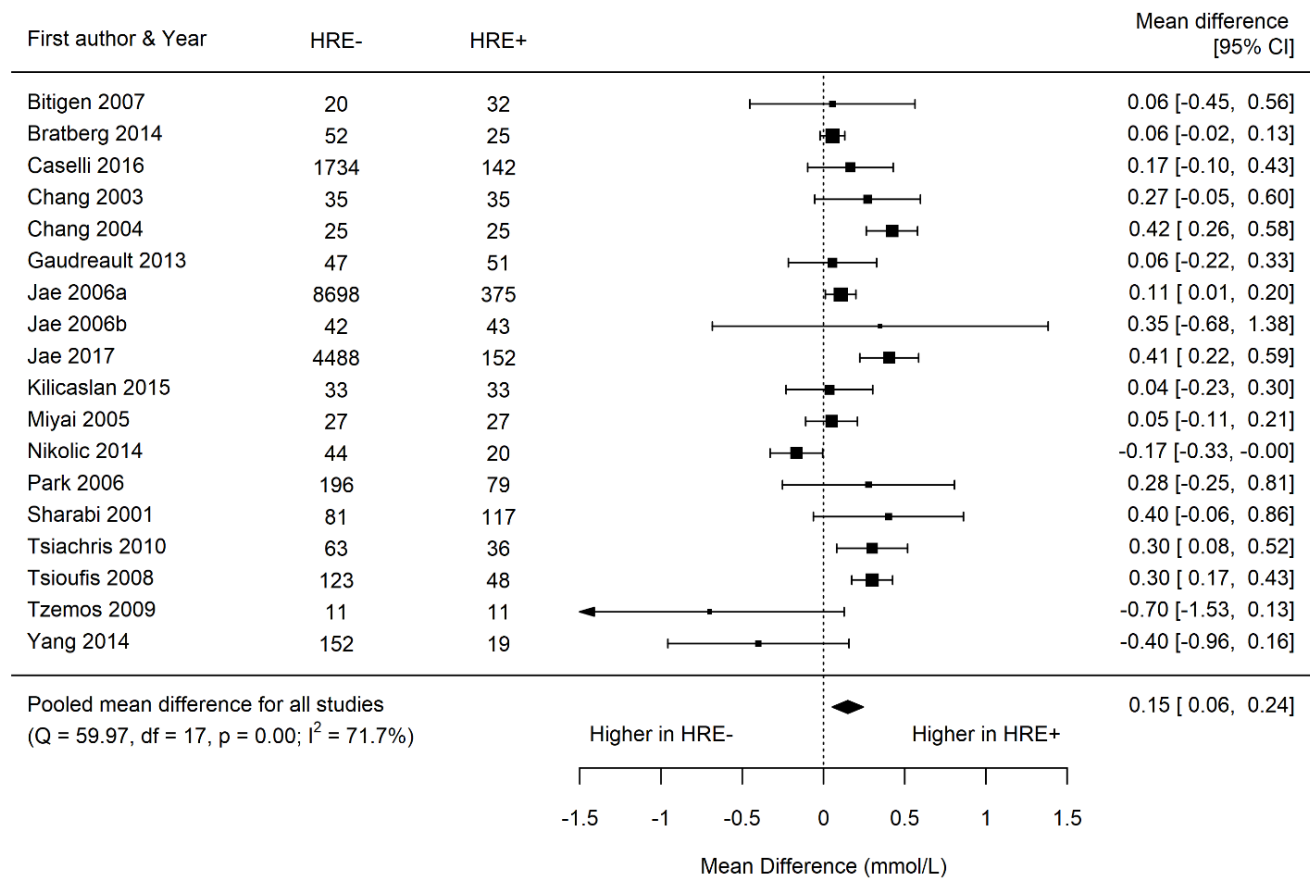


Figure 4.3. Pooled mean difference in glucose between individuals where a hypertensive response to exercise was present (HRE+) or absent (HRE-).

Kidney function.

Meta-analyses. Exercise systolic BP had a weak positive correlation with albumin-creatinine ratio (n=2 studies, $r = 0.19$, 95%CI: 0.09, 0.29; $p < 0.001$; Appendix Figure 4.15). Those with an HRE had higher albumin-to-creatinine ratio compared to those without an HRE (n=2 studies, standardised mean difference = 0.97, 95% CI: 0.30, 1.64, $p = 0.004$; Appendix Figure 4.16). There was negligible difference in creatinine between those with and without an HRE (n=6 studies, mean difference = 1.17mmol/L, 95% CI: -2.65, 4.99, $p = 0.55$; Appendix Figure 4.17).

Meta-regressions. The pooled mean difference in creatinine was similar across studies that had populations with varying resting BP status and health status, studies with varying exercise testing methods and quality scores (Appendix Table 4.3 and 4.4).

Publication bias.

There was no evidence of publication bias for all meta-analyses, except for the mean difference in insulin and white blood cell count (Appendix Figure 4.18 and 4.19). The mean difference in white blood cell count in those with an HRE compared to those without an HRE decreased to 0.31mmol/L (95% CI: -0.04, 0.63; $p = 0.053$) after two theoretically missed studies were added with the trim and fill method. The pooled mean difference in HbA1c between those with and without an HRE increased to 0.17% (95% CI: 0.05, 0.29; $p = 0.006$) after one theoretically missed study was added with the trim and fill method.

4.5 DISCUSSION

The results of this meta-analysis indicate exercise systolic BP to be associated with CVD risk factors, such that those with an HRE have a worse CVD risk factor profile compared to those without an HRE. This includes poorer arterial structure and function, a worse lipid and metabolic profile, a greater level of inflammation and poorer kidney

function. Moreover, observed associations and differences were broadly similar across study populations (including those with and without high BP at rest) and irrespective of the exercise testing methodology used. Altogether, this suggests that an HRE is an important indicator of CVD risk.

Clinical exercise testing is commonplace amongst cardiology and allied-health professions, typically performed to screen for coronary artery disease, arrhythmias or determine fitness and functional capacity. While exercise testing in this setting is not typically conducted for the evaluation of hypertension [25], the measurement of BP is a mandatory requirement of each exercise test [7,35]. Utilising these BP measures may therefore provide an opportunity to additionally screen for BP-related CVD. Indeed, previous data suggest that when the BP response is considered abnormal, such is the case with an HRE, it provides a signal of BP-related CVD risk that most likely went undetected by traditional methods of assessment at rest [9–11,69,70]. The current meta-analysis confirms this idea by demonstrating a multitude of CVD risk factors are associated with exercise systolic BP. Moreover, arterial structure and function, lipid and metabolic markers all appeared worse in those with an HRE. This is perhaps not unexpected, given it is known that such risk factors can ‘cluster’ together in the presence of hypertension [148,149,213]. However, an HRE may occur even with normal resting BP [10,74,93], and our results appeared consistent amongst those both with and without high BP at rest. Thus, exercise BP likely offers a unique opportunity to screen for BP-related CVD risk among individuals referred for a clinical exercise stress test. Moreover, the association between exercise BP and arterial stiffness suggests that opportunistic assessment of exercise BP in those completing exercise testing may add to clinical yield, since arterial stiffness is not routinely assessed in practice.

There are several physiological factors that likely underpin the BP response to exercise [124]. From a vascular standpoint, an increase in large artery stiffness may decrease the buffering capacity of the aorta and when coupled to an exercise-induced elevation in cardiac output, may precipitate an HRE [111]. Thus, our finding that aortic stiffness (assessed by pulse wave velocity) was positively associated with exercise systolic BP and higher in those with an HRE may not be surprising. Moreover, aortic stiffness is an independent risk factor for cardiovascular mortality [110], and often raised in those with type 2 diabetes mellitus [89], which provide an explanation as to why an HRE has been found to be more prevalent in these populations [43]. Similarly, raised aortic stiffness is associated with a poorer metabolic and lipid profile [214,215], which was also observed among those with an HRE in the current study. A poorer metabolic and lipid profile may contribute towards functional and structural decline of the microvasculature [151,152]. Microvascular damage may in-turn increase the pulsatility of blood flow to end-organs (such as the kidneys) [216], promoting damage, whilst stimulating an inflammatory response [217]. It is possible that this may underlie the observed differences (elevations) in c-reactive protein, albumin-creatinine ratio and white blood cell count in those with an HRE. Flow-mediated dilation was also found to be lower in those with an HRE. Such vascular damage is known to be associated with impaired nitric oxide production [218], which could in-part weaken the vasoactive function of peripheral vessels when faced with exercise-induced elevations in blood flow, ultimately promoting higher exercise BP [118]. Despite these observations, further work is required to fully understand the mechanisms underlying the BP response to exercise. This includes understanding the mechanisms that contribute to exercise BP among populations with established cardiac disease (e.g. heart failure), since a low BP response to exercise is potentially a poorer prognostic sign with differing aetiology in these individuals [37,219].

Limitations. Study populations included in this analysis were, on average, middle-to-older age and male, and thus results should not be generalised to other populations. Sufficient data was only available for unadjusted estimates were pooled for analysis. Subsequently, we were unable to consider potential factors, such as age, gender and smoking or disease status, that might influence the relationship between exercise BP and individual CVD risk factors. The timing of each CVD risk factor measurement in relation to the exercise test varied between studies, and it is possible that this may have influenced associations between exercise systolic BP and the individual risk factors. Thresholds to define an HRE were not uniform across the included studies, and in the absence of individual participant data, one could not be applied for analyses. Whilst this could potentially limit external applicability of the results, we were able to examine whether the heterogeneity in the mean difference between those with and without an HRE was associated with the different exercise intensities at which time BP was measured in meta-regression analyses. These meta-regression analyses show little difference across exercise intensities. Moreover, all included studies were cross-sectional in design. Thus, causal pathways between exercise BP and CVD risk factors, as well as potential future CVD risk cannot be fully described without longitudinal data.

Conclusion. Exercise systolic BP is associated with many CVD risk factors, which present worse in those with an HRE compared to those without an HRE. This result was relatively consistent amongst the population groups studied, including those with or without high BP at rest. An HRE should therefore be considered an important indicator of heightened CVD risk.

4.6 CONTRIBUTION OF STUDY TO THESIS AIMS

Prior to Study 3, the nature of the relationship between exercise BP and CVD risk factors were unclear as previous studies had reported conflicting results. Results of previous studies had also reported conflicting results on whether CVD risk factors among those with an HRE were different or similar to those without an HRE. Study 3 resolves this ambiguity by showing there is a relationship between exercise BP and different CVD risk factors irrespective of clinic BP. Many CVD risk factors were also worse in those with an HRE compared to those without an HRE irrespective of clinic BP, suggesting that an HRE should be considered as an important indicator of heightened CVD risk. The results of Study 3 suggest several CVD risk factors may influence the BP response to exercise. It is however unclear how individual CVD risk factors interact with one another to influence exercise BP, which was further explored in Study 4.

5 AN INVESTIGATION OF THE DIRECT AND INDIRECT EFFECTS OF CARDIOVASCULAR DISEASE RISK FACTORS ON EXERCISE BLOOD PRESSURE.

This thesis chapter has been formatted *for future submission* according to the guidelines of *Journal of Hypertension*.

Moore MN, Blizzard CL, Dwyer T, Magnussen CG, Venn AJ, Sharman JE, Schultz MG. An investigation of the direct and indirect effects of cardiovascular disease risk factors on exercise blood pressure.

5.1 ABSTRACT

Objective. Abnormal exercise blood pressure (BP) is independently associated with CVD outcomes. However, it is unknown how individual CVD risk factors may interact with one another to influence exercise BP. The aim of this study was to quantify direct and indirect associations between CVD risk factors and exercise BP, to determine what CVD risk factor/s most-strongly relate to exercise BP.

Methods. In a cross-sectional design, 660 participants (44 ± 2.6 years, 54% male) from the Childhood Determinants of Adult Health Study completed an exercise test with BP measurement during low-intensity exercise. CVD risk factors were measured, including body composition, clinic (rest) BP, blood biomarkers and cardiorespiratory fitness. Associations between CVD risk factors and exercise BP were assessed using linear regression, with direct and indirect associations assessed via structural equation model (SEM).

Results. Sex, waist-to-hip ratio, fitness, and clinic BP were independently associated with exercise systolic BP (SBP), and along with age, had direct associations with exercise SBP in the SEM ($p < 0.05$ all). Most CVD risk factors were indirectly associated with exercise SBP via a relation with clinic BP ($p < 0.05$ all). Clinic BP, waist-to-hip ratio and fitness had the highest total effect (direct and indirect association) on exercise SBP (β [95%CI]: 9.35 [8.04,10.67], 4.91 [2.56,7.26], and -2.88 [-4.25,-1.51] mmHg/SD, respectively).

Conclusion. Many CVD risk factors are associated with exercise BP, mostly with indirect effects via clinic BP. Clinic BP, body composition and fitness showed the highest total effects on exercise BP, suggesting lifestyle modification of these risk factors as a primary strategy to decrease exercise BP-related CVD risk.

5.2 INTRODUCTION

Systolic blood pressure (BP) will normally rise with dynamic exercise of incremental intensity [27]. This systolic BP response can, however, be abnormally high (termed a hypertensive response to exercise; HRE) and is independently associated with incident hypertension, cardiovascular morbidity and mortality [9,11,64]. Associations with hypertension-related CVD risk factors (e.g. raised left ventricular mass and aortic stiffness) [220,221] likely underpin the increased risk related to an HRE. Indeed, previous research suggests that an HRE reveals a hypertensive state gone undetected with standard measurement of BP at rest [10,69] and thus may be a useful clinical tool to identify CVD risk.

Several CVD risk factors are known to influence the BP response to exercise [124,144]. CVD risk factors rarely occur in isolation [148,149,213], and likely interact with one another via several pathways to influence exercise BP. Indeed, individuals with raised total and abdominal fat likely have raised metabolic- and lipid-related CVD risk factors [150]. These metabolic- and lipid-related CVD risk factors may damage the peripheral vasculature and inhibit vasodilation during exercise [151,152], which when accompanied with the exercise-induced elevation in cardiac output may elevate the BP response to exercise. These various pathways of association (i.e. direct and indirect effects) to exercise BP have never been explored, and cannot be assessed with traditional statistical methods (i.e. linear regression/correlation). This limitation of traditional statistics could be solved with a structural equation model (SEM), which can be used to identify, test and quantify possible pathways of association between different CVD risk factors simultaneously [222,223]. The various pathways of association between exercise BP and CVD risk factors are important to understand in order to improve the identification and treatment of CVD risk related to high BP. Thus, the aim of this study was to quantify the direct and indirect associations between CVD

risk factors and exercise BP, whilst also determining what CVD risk factor/s most strongly relate to exercise BP.

5.3 METHODS

Participants. Participants were initially recruited for the 1985 Australian Schools Health and Fitness Survey, which involved collection of lifestyle and physical data on 8948 school children aged 7-15 years across Australia [224]. Of these participants, 1363 attended a follow-up clinic from 2017 to 2019. Participants who attended a follow-up clinic completed a lifestyle questionnaire, including questions on hypertension and diabetes mellitus history, smoking status. Participants were excluded from the current analysis if: (1) a submaximal exercise (fitness) test was not completed, and (2) a BP was not measured during the warm-up stage of the exercise test at a fixed workload of 75 watts. Therefore, a total of 660 participants were available for this study. Appendix Figure 5.1 illustrates this flow of participants. All participants provided informed consent and ethics approval was received from the Southern Tasmania Health and Medical Human Research Ethics Committee.

Exercise test. The submaximal exercise test was performed on a cycle ergometer (Monark 928G3r; Monark exercise ab, vansbro, Sweden) to determine physical work capacity at a heart rate of 170 bpm (PWC_{170}) as an estimate of cardiorespiratory fitness [225]. The exercise test first involved participants cycling for two minutes at a fixed workload of 75 watts and cadence of 60 rpm. This stage of the exercise test was defined as the warm-up. Thereafter, the exercise test involved three 4-minute stages. The workload increased incrementally with each exercise test stage until participants reached the pre-specified target heart rate zone (first stage: 115-129 bpm; second stage: 130-144 bpm; and third stage: 145-160 bpm). The workload was adjusted during the first two minutes of each stage, so a steady-state heart rate was achieved by the fourth

minute of the exercise test stage. A fourth exercise test stage involving another increase in workload was performed when participants had not reached a steady-state heart rate of 145-160 bpm by the fourth minute of the third exercise test stage. Heart rate and workload were recorded during the last 15 seconds of each stage. Criteria for terminating the exercise test included a medical or technical indication arose or upon participant request. All participants completed a modified physical activity readiness questionnaire before starting the exercise test to rule-out any contraindications to exercise, which are reported in the supplementary material (Appendix D).

Exercise BP. A cuff attached to a manual auscultatory sphygmomanometer (UM-101, A&D instruments, SA, Australia) was placed onto the left arm of the participant before the exercise test. A single BP measurement was taken during the last minute of the 2-minute warm-up stage while participants continued to cycle. The technician read the BP values off the manual sphygmomanometer while listening for the 1st and 5th Korotkoff sounds (representing systolic and diastolic BP, respectively) in accordance with recommendations [7].

Cardiorespiratory fitness. Cardiorespiratory fitness was estimated using the heart rate and workload recorded during the three (or four) incremental exercise test stages. Workload was plotted against heart rate, then extrapolated using line-of-best-fit to estimate the workload at a heart rate of 170 bpm. This estimated workload represented PWC_{170} , which was regressed on lean body mass and the resultant residuals were used to account for the potential that individuals with greater lean body mass may achieve a higher workload for a given heart rate. [226].

Clinic (resting) BP and heart rate. At a separate time (but on the same day), clinic BP and resting heart rate was measured using an automated BP device (Omron HEM-907, Omron Healthcare, Kyoto, Japan) attached to a cuff on right arm of the participant

in a seated position [227]. Three measures for BP and heart rate were taken in one-minute intervals after five minutes of seated rest. The average of the three measurements was used to calculate clinic BP and resting heart rate.

Body composition. Weight was measured using a portable scale (Heine, Dover, NH, USA). Height was determined using a Leicester height measure (Invicta, Leicester, UK). Body mass index was calculated as weight (kg) divided by height (m²). Waist and hip circumference were measured in duplicate using a constant tension tape. SlimGlide calipers (Slim Guide, USA) were used to measure triceps, biceps, subscapular, and suprailiac skinfolds on the righthand side in duplicate. A third circumference or skinfold was taken if there is a >10% difference between the first two measurements. Circumferences and skinfolds were averaged for analysis. Fat and fat-free (lean) mass and fat mass percentage were calculated using sex-stratified equations based on the sum of skinfolds and weight [228].

Blood and urine biochemistry. Fasting blood samples were taken from the **antecubital** fossa and glucose, insulin, HbA1c, total cholesterol, high- and low-density lipoprotein cholesterol, triglycerides, high-sensitivity c-reactive protein and creatinine were measured. Homeostatic model assessment of insulin resistance (HOMA-IR) was also calculated with glucose and insulin, and these details are described in the supplementary material (Appendix D). Urine samples were collected for measurements of creatinine and albumin. Urine albumin-to-creatinine ratio was calculated as urine albumin divided by urine creatinine.

Muscular strength. Muscular strength was estimated from maximal voluntary isometric contraction of left and right handgrip, shoulder extension and flexion and leg extension. Because the association between exercise BP and muscular strength was

exploratory, further information on the protocols used for these strength variables are in the supplementary methods.

Statistical analysis. All statistical analyses were performed using Stata (Version 16.0, StataCorp, College Station, Texas). Statistical significance was defined as a p-value <0.05. Histograms and Q-Q plots were examined to assess the distribution of scaled variables. Participant characteristics were stratified by sex and presented either as mean and standard deviation or as median and interquartile range for scaled variables, and as percentage and relative frequency for categorical variables.

Exercise systolic and diastolic BP were transformed to remove skewness, and back-transformed for data presentation. The covariates for scaled study factors were centred at the mean prior to estimating their relationship with exercise BP using linear regression methods [229,230]. Non-linearity in the relationship was modelled by including the square and cube of the covariate in polynomial fits. All associations were adjusted for age and sex. Additional analyses were performed to assess age- and sex-interactions in the associations of exercise BP with a study factor and are reported in the supplementary material (Appendix D). The estimated cross-sectional responses of exercise BP to a one-unit change in each study factor are reported, together with 95% confidence intervals.

Multivariable linear regression analyses were performed to assess the associations between exercise BP and multiple study factors. To select what study factors to include in the multivariable models, each study factor was grouped according to potential mechanism of action on exercise BP. The broad categories included body composition, metabolic profile, lipid profile, inflammation, haemodynamic, cardiorespiratory fitness and kidney function. Further details are described in the supplementary material (Appendix D). The final multivariable linear regression models chosen for each broad category included only the CVD risk factors that were independently associated with

exercise BP, explaining the highest variance in the model (i.e., R^2). In general, only one study factor in each category was included in the final multivariable model.

An SEM was used to assess if a study factor included in the mutually adjusted multivariable linear regression analyses mediated the associations of another factor on exercise BP. Appendix Figure 5.2 includes the specification of the SEM where relationships were hypothesised to exist between exercise BP and the different CVD risk factors in the mutually-adjusted multivariable linear regression [231]. The SEM for which results are reported all satisfied conventional standards for model fit: the chi-square divided by degrees of freedom (χ^2/df) was <2.0 , root mean square error of approximation was <0.6 , and comparative fit index and Tucker-Lewis index were >0.95 [232,233]. A direct effect reported from the SEM was defined as a directional association from a study factor to exercise BP. An indirect effect was defined as a directional association from a study factor to exercise BP that was mediated through the relationship of another study factor/s. The joint direct and indirect effects of a study factor on exercise BP defined the total effect. The estimates reported are the cross-sectional response of exercise BP firstly to a one-unit change in the study factor, and secondly to a one-standard deviation change in the study factor.

5.4 RESULTS

Participant characteristics. Table 5.1 presents the sex-stratified participant characteristics. The study population were on average middle-aged with raised body mass index, waist-to-hip ratio and fat mass percentage with controlled clinic BP, fasting blood and urine biochemistry. Few participants self-reported having a history of smoking or diagnosis of hypertension or diabetes mellitus.

An investigation of the direct and indirect effects of cardiovascular disease risk factors on exercise blood pressure.

Table 5.1. Participant characteristics.

Characteristic	Male	Female
N	354	306
Age, years	44.3 (2.6)	44.4 (2.7)
Height, cm	179.9 (6.2)	165.5 (6.1)
Weight, kg	87.3 (14.0)	72.4 (15.1)
Body mass index, kg/m ²	27.0 (4.1)	26.4 (5.3)
Waist circumference, cm	91.7 (10.3)	81.5 (11.8)
Hip circumference, cm	101.4 (8.6)	101.4 (12.9)
Waist-to-hip ratio	0.9 (0.1)	0.8 (0.1)
Fat mass percentage, %	25.3 (5.4)	35.0 (5.7)
Smoking, n (%)	23 (6.6%)	19 (6.3%)
Hypertension, n (%)	42 (12.2%)	41 (13.5%)
Diabetes Mellitus, n (%)	3 (0.9%)	16 (5.3%)
Resting heart rate, bpm	60.2 (9.5)	64.8 (9.1)
Resting SBP, mmHg	124.7 (13.0)	112.6 (12.9)
Resting DBP, mmHg	75.7 (10.6)	71.2 (10.9)
Exercise SBP, mmHg	138.4 (16.9)	132.6 (18.0)
Exercise DBP, mmHg	77.2 (10.0)	74.3 (11.4)
Cardiorespiratory fitness unadjusted for lean body mass, Watts	176.0 (135.9-232.3)	103.7 (87.3-127.0)
Cardiorespiratory fitness adjusted for lean body mass, Watts	179.0 (144.3-226.8)	104.5 (88.1-127.5)
Dominant handgrip strength*, kg	48.3 (44.0-52.5)	29.9 (26.5-33.5)
Shoulder extension strength, kg	32.1 (24.6-38.9)	17.9 (14.3-22.2)
Shoulder flexion strength, kg	47.2 (38.4-55.8)	26.1 (21.3-31.3)
Leg strength, kg	173.9 (151.8-195.2)	101.2 (84.3-117.5)
Glucose, mmol/L	4.8 (0.7)	4.6 (0.6)
Insulin, pmol/L	34.7 (20.8-48.6)	34.7 (27.8-55.6)
HOMA1-IR	1.0 (0.7-1.6)	1.1 (0.7-1.6)
HOMA2-IR	0.6 (0.5-1.0)	0.7 (0.5-1.0)
HOMA2-β	79.4 (63.8-104.0)	91.1 (74.3-110.5)
HbA1c, %	5.2 (0.4)	5.2 (0.3)
Total cholesterol, mmol/L	5.2 (1.0)	5.1 (0.8)
HDLc, mmol/L	1.3 (0.3)	1.7 (0.4)
LDLC, mmol/L	3.3 (0.9)	3.0 (0.7)
Triglycerides, mmol/L	1.1 (0.8-1.5)	0.9 (0.7-1.2)
High-sensitivity c-reactive protein, mg/L	0.7 (0.3-1.4)	1.0 (0.4-2.1)
Serum creatinine, umol/L	82.4 (10.4)	65.6 (9.1)
Urine albumin, g/L	3.0 (1.0-8.0)	4.0 (1.0-7.0)
Urine creatinine, mmol/L	10.3 (5.8-14.6)	8.2 (4.1-12.7)
Albumin-creatinine ratio	0.5 (0.3-0.8)	0.6 (0.4-0.9)

Mean (Standard deviation) for normally distributed continuous variables, median (25th – 75 percentile) for non-normally distributed continuous variables, and n (%) for categorical variables. * n = 65 with dominant left hand and n = 564 with dominant right hand. DBP, diastolic blood pressure; HDLC, high-density lipoprotein cholesterol; HOMA1-IR, Homeostatic model assessment of insulin resistance (model 1); HOMA2-IR, Homeostatic model assessment of insulin resistance (model 2); HOMA2-β, Homeostatic model assessment of beta-cell function; LDLC, low-density lipoprotein cholesterol; SBP, systolic blood pressure

Univariable associations with exercise BP. Table 5.2 shows the association between exercise systolic and diastolic BP and each study factor after adjusting for age and sex. Age, male sex, body size and fatness (e.g., raised body mass index, waist-to-hip ratio and fat mass percentage), clinic BP, history of hypertension diagnosis, resting heart rate, and metabolic-, lipid-, and kidney-related CVD risk factors were positively associated with exercise systolic BP. Cardiorespiratory fitness was negatively associated with exercise systolic BP. Ever smoking status, history of diabetes mellitus, HbA1c, high-density lipoprotein cholesterol, creatinine and all measures of muscular strength had no association with exercise systolic BP. There was no sex- or age-interaction on any association between exercise systolic and diastolic BP and each study factor. The univariable associations between individual study factors and exercise diastolic BP were broadly similar to the results reported for exercise systolic BP.

Multivariable associations with exercise BP. Body mass index, waist-to-hip ratio (body composition), HOMA-IR (metabolic), low-density lipoprotein cholesterol, triglycerides (lipids), clinic BP, resting heart rate (haemodynamic), c-reactive protein (inflammation), and urine albumin-creatinine ratio (kidney function) and PWC₁₇₀ (cardiorespiratory fitness) were the study factors from grouped collections with the strongest association with exercise systolic BP (Appendix Table 5.1). Sex, waist-to-hip ratio, cardiorespiratory fitness and clinic BP were independently associated with exercise systolic BP after mutual adjustment of all the CVD risk factors found from grouped collections (Table 5.3).

Table 5.2. Univariable associations with exercise blood pressure (BP)

Study factor	Exercise systolic BP	Exercise diastolic BP
Age (years)	1.31 (0.18, 2.44) *	0.49 (0.18, 0.80) *
Female sex	-5.95 (-8.50, -3.41) *	-3.21 (-4.78, -1.63) *
Weight (kg)	0.25 (0.17, 0.34) *	0.25 (0.20, 0.30) *
Body mass index (kg/m ²)	0.87 (0.60, 1.15) *	0.86 (0.70, 1.03) *
Waist circumference (cm)	0.38 (0.27, 0.50) *	0.40 (0.34, 0.47) *
Hip circumference (cm)	0.17 (0.05, 0.29) *	0.34 (0.27, 0.41) *
Waist-to-hip ratio	95.79 (56.53, 135.04) *	43.77 (24.59, 62.95) *
Fat mass percentage (%)	0.64 (0.25, 1.03) *	0.53 (0.29, 0.76) *
Fat body mass (kg)	0.48 (0.32, 0.63) *	0.46 (0.37, 0.56) *
Lean (fat-free) body mass (kg)	0.37 (0.20, 0.53) *	0.38 (0.28, 0.48) *
Ever smoking status	2.07 (-3.35, 7.49)	3.54 (0.11, 6.97) *
Previous hypertension diagnosis	12.40 (8.13, 16.68) *	7.94 (5.33, 10.55) *
Previous diabetes diagnosis	6.89 (-1.64, 15.43)	2.57 (-2.52, 7.66)
Resting heart rate (bpm)	0.46 (0.32, 0.61) *	0.37 (0.28, 0.46) *
Clinic BP (mmHg)	0.69 (0.60, 0.78) *	0.67 (0.62, 0.73) *
Cardiorespiratory fitness unadjusted for lean body mass, Watts	-0.03 (-0.05, -0.01) *	-0.02 (-0.03, -0.01) *
Cardiorespiratory fitness adjusted for lean body mass, Watts	-0.05 (-0.08, -0.03) *	-0.04 (-0.06, -0.03) *
Dominant handgrip strength [#] , kg	0.05 (-0.18, 0.28)	-0.04 (-0.18, 0.10)
Shoulder extension strength, kg	0.14 (-0.02, 0.29)	0.01 (-0.09, 0.10)
Shoulder flexion strength, kg	-0.02 (-0.14, 0.10)	-0.04 (-0.12, 0.03)
Leg strength, kg	0.03 (-0.01, 0.08)	-0.02 (-0.05, 0.01)
Glucose (mmol/L)	3.42 (1.34, 5.50) *	3.93 (2.03, 5.84) *
Insulin (mIU/L)	1.15 (0.76, 1.54) *	1.23 (0.96, 1.51) *
HOMA1-IR	5.00 (3.18, 6.82) *	4.99 (3.98, 6.00) *
HOMA2-IR	9.67 (6.26, 13.07) *	9.83 (7.76, 11.90) *
HOMA2-β	0.08 (0.04, 0.13) *	0.10 (0.07, 0.13) *
HbA1c (%)	2.80 (-1.04, 6.64)	1.76 (-0.60, 4.11)
Total Cholesterol (mmol/L)	2.17 (0.68, 3.66) *	1.80 (0.89, 2.71) *
HDLC (mmol/L)	-2.40 (-6.02, 1.21)	-3.30 (-5.44, -1.17) *
LDLC (mmol/L)	2.41 (0.73, 4.08) *	2.07 (1.04, 3.09) *
Triglycerides (mmol/L)	3.68 (1.27, 6.09) *	4.10 (2.62, 5.59) *
Serum Creatinine (umol/L)	-0.07 (-0.15, 0.28)	0.01 (-0.07, 0.1)
High-sensitivity c-reactive protein (mg/L)	0.74 (0.19, 1.30) *	0.95 (0.61, 1.29) *
Urine albumin (g/L)	0.06 (0.01, 0.10) *	0.03 (0.00, 0.05)
Urine creatinine (mmol/L)	0.16 (-0.05, 0.36)	0.20 (0.08, 0.33) *
Urine albumin-creatinine ratio	1.10 (0.29, 1.91) *	-0.03 (-0.37, 0.31)

HDLC, high-density lipoprotein cholesterol; HOMA1-IR, Homeostatic model assessment 1-insulin resistance; HOMA2-IR, Homeostasis model assessment 2-insulin resistance; HOMA2-β, Homeostasis model assessment 2-beta cell function; LDLC, low-density lipoprotein cholesterol; All results are reported as an effect of a one-unit change in the study factor on exercise BP with 95% confidence intervals. [#] n = 65 with dominant left hand and n = 564 with dominant right hand. * denotes statistical significance (p<0.05) after adjusting for sex and age. Age was only adjusted for sex. Sex was only adjusted for age.

The SEM showed age, sex, waist-to-hip ratio, cardiorespiratory fitness, and clinic BP to be directly associated with exercise systolic BP ($p < 0.05$ all). All CVD risk factors in the SEM, except age, were associated with exercise systolic BP indirectly via a relationship with clinic BP ($p < 0.05$ all). The quantified direct and indirect effects on exercise systolic BP from each study factor included in the SEM are reported in Appendix Table 5.2 and Appendix Figure 5.3 illustrates the direct and indirect association of each study factor with exercise systolic BP in the SEM. Age, body mass index, waist-to-hip ratio, HOMA-IR, high-sensitivity c-reactive protein, low-density lipoprotein cholesterol, triglycerides, clinic BP and resting heart rate had a positive total effect (association) on exercise systolic BP, while female sex and cardiorespiratory fitness had a negative total effect association on exercise systolic BP (Table 5.3). Details for why albumin-creatinine ratio was excluded from the mutually adjusted multivariable analysis and SEM are reported in the supplementary material (Appendix D). Based on comparisons of the estimated response of exercise systolic BP to a one standard deviation change in each study factor, the study factor that had largest effect on exercise systolic BP was clinic BP, followed by waist-to-hip ratio and then cardiorespiratory fitness (Table 5.3).

Study factor(s) grouped into collections with the highest association with exercise diastolic BP are reported in Appendix Table 5.3. The response in exercise diastolic BP with a one-unit change in each study factor(s) in the mutually adjusted multivariable analysis and the total effects in the SEM are reported in Appendix Table 5.4. The direct and indirect effects between each study factor and exercise diastolic BP from the SEM are reported in Appendix Table 5.5 and visually illustrated in Appendix Figure 5.4. Details for why urine creatinine was excluded from the mutually adjusted multivariable analysis and SEM are reported in the supplementary material (Appendix D).

Table 5.3. Multivariable linear regression and structural equation models indicating cardiovascular risk factors most-strongly associated with exercise systolic BP.

Study factor	Study factor SD	Mutually adjusted multiple linear regression	Structural equation model	
		Effect of a one-unit change (95% CI)	Effect of a one-unit change (95% CI)	Effect of a one SD change (95% CI)
Age, years	2.67	0.53 (-0.41, 1.46)	0.60 (0.33, 0.86) *	1.60 (0.89, 2.30) *
Female sex	0.50	3.70 (0.19, 7.20) *	-4.02 (-7.27, -0.77) *	-2.00 (-3.63, -0.38) *
Body mass index, kg/m ²	4.58	-0.02 (-0.35, 0.31)	0.58 (0.43, 0.73) *	2.66 (1.96, 3.36) *
Waist-to-hip ratio	0.08	49.93 (21.96, 77.90) *	58.60 (30.59, 86.61) *	4.91 (2.56, 7.26) *
HOMA1-IR	0.81	0.65 (-1.18, 2.48)	0.32 (0.12, 0.51) *	0.26 (0.10, 0.42) *
LDLC, mmol/L	0.82	0.24 (-1.19, 1.68)	0.15 (0.02, 0.27) *	0.12 (0.01, 0.23) *
Triglycerides, mmol/L	0.56	-1.05 (-3.31, 1.27)	1.58 (0.44, 2.72) *	0.89 (0.25, 1.53) *
Cardiorespiratory fitness unadjusted for lean body mass, Watts	74.25	-0.02 (-0.04, -0.002) *	-0.04 (-0.06, -0.02) *	-2.88 (-4.25, -1.51) *
High sensitivity c-reactive protein, mg/L	2.44	-0.25 (-0.78, 0.27)	0.11 (0.04, 0.17) *	0.26 (0.10, 0.41) *
Resting heart rate, bpm	0.01	0.14 (-0.003, 0.28)	0.14 (0.07, 0.20) *	0.001 (0.0004, 0.001) *
Clinic BP, mmHg	14.15	0.63 (0.53, 0.73) **	0.66 (0.57, 0.75) *	9.35 (8.04, 10.67) *

BP, blood pressure; CI, confidence interval; HOMA1-IR, Homeostatic model assessment of insulin resistance; LDLC, low-density lipoprotein cholesterol; SD, standard deviation. * denotes statistical significance (p<0.05)

5.5 DISCUSSION

This study aimed to quantify the direct and indirect pathways of associations between CVD risk factors and exercise BP, to determine the CVD risk factor/s most-strongly related to exercise BP. The results indicated that many CVD risk factors are associated with exercise systolic BP, mostly with indirect effects via clinic BP. The study factors that were most-strongly associated with exercise systolic BP were clinic BP, waist-to-hip ratio and cardiorespiratory fitness. Thus, lifestyle modification of these CVD risk factors is likely a primary strategy to decrease BP-related CVD risk.

The statistical methods used in this study are distinctly different to those in previous studies that have investigated the relationship between exercise BP and various CVD risk factors via traditional linear models (i.e. Pearson's correlation or regression) [124,144,220]. A limitation of previous findings and traditional statistical methods is that the association between exercise BP and a CVD risk factor may be indirect via a relation with another factor. The SEM utilised in this study has, for the first time, enabled multiple pathways of association between exercise BP and CVD risk factors to be tested simultaneously. For example, the SEM showed that while waist-to-hip ratio had a direct relationship with exercise BP, this association was also simultaneously present via relations with multiple blood-related CVD risk factors, resting heart rate and clinic BP. Thus, the results from the SEM in the present study have enabled the interrelationships between CVD risk factors and exercise BP to be understood.

High BP is not always correctly identified with the traditional measurement of BP taken under resting conditions in clinical settings [17], which is why home or ambulatory BP monitoring is recommend for a definitive diagnosis [16]. In the absence of out-of-office BP, the measurement of exercise BP may also be used in clinical

settings to screen for high BP. Indeed, an abnormal exercise BP response, such as an HRE, is likely a signal of high BP [10,69,221]. Those with an HRE likely also have slightly raised clinic BP (i.e. pre-hypertension) [46,144], which may still be a signal of elevated BP-related CVD risk [46]. This aforementioned evidence could support why exercise BP was most-strongly associated with clinic BP, and why this relationship also mediated via other CVD risk factors, which typically appear with high BP [148,149,213]. However, an HRE can still occur even when clinic BP is normal [10,69]. The results of the current study also support this idea because exercise BP was associated with age, sex, waist-to-hip ratio and cardiorespiratory fitness independently of clinic BP. Thus, these results highlight that the measurement of exercise BP could offer an opportunity to identify individuals at high BP-related CVD risk that may have been otherwise missed under resting conditions.

It is well known that there is a complex interplay between body composition and cardiorespiratory fitness in relation to CVD risk. Whilst raised body ‘fatness’ is associated with increased risk of CVD, this relationship can be reduced with higher cardiorespiratory fitness levels [234]. Moreover, the poor CVD risk profile related to elevated body fatness can be improved, but not fully eliminated, with an increase in cardiorespiratory fitness [235]. Exercise BP also had a stronger positive association with elevated body fatness compared to its independent negative relationship with cardiorespiratory fitness in this study. These findings are consistent with other cross-sectional studies where exercise systolic BP was higher among individuals with elevated body fatness irrespective of cardiorespiratory fitness [138,236]. A decrease in exercise BP has also been found to be independently associated with a reduction in waist circumference and improvement in cardiorespiratory fitness following an exercise intervention [237]. The current study also expands on this understanding between exercise BP, body fatness and cardiorespiratory fitness and shows these

relationships were partly mediated via relations with general CVD risk factors, suggesting other contributory factors may also influence the BP response. Indeed, another potential contributory factor associated with exercise BP is raised arterial stiffness [220], which also shares a relationship with elevated body fatness parameters, low cardiorespiratory fitness and a poorer metabolic- and lipid-related CVD risk profile [214,215,238]. Overall, the results in this study may suggest that lifestyle modification of CVD risk factors could be a primary strategy to decrease CVD risk related to exercise BP.

Strengths and limitations. A strength of this study was that exercise BP can be interpreted free from the influence of cardiorespiratory fitness because it was measured during a standardised fixed and submaximal workload rather than at a specific intensity [239]. This study included a large national representative sample of middle-aged adults but may not be generalisable to younger or older populations. In the absence of the gold-standard measurements, cardiorespiratory fitness and body fatness were estimated in this study. However, the methods used to estimate cardiorespiratory fitness and body fatness are recognised to be appropriate for large scale field-based studies that do not require expensive training and equipment [134]. Behavioural variables (e.g. physical activity and diet) may also influence the BP response to exercise, as well as one or more CVD risk factors that were included in the current study. Self-reported behavioural factors can be unreliable and inaccurately estimate objective measures [240,241], which is why these factors were excluded from the current analyses. An analysis with longitudinal data would improve the understanding of the different causal relationships between exercise BP and different CVD risk factors compared to this cross-sectional study. Nevertheless, the direction of each relationship and total effect (i.e. the combined direct and indirect associations) between exercise BP and individual CVD risk factors in the SEM were as hypothesised

in the original model specification, and thus, likely represent biologically plausible pathways to be tested in future studies. Moreover, the SEM in this study was sufficiently powered to evaluate the multiple pathways of association between exercise BP and different CVD risk factors simultaneously, which cannot be undertaken with a multivariable linear regression model. Future studies are encouraged to use an SEM approach to better understand the possible pathways of association between exercise BP, different CVD risk factors and clinically meaningful outcomes (such as target organ damage markers or CVD events and mortality).

Conclusions There are many pathways of association between exercise BP and different CVD risk factors, mostly that occur via an indirect relation with clinic BP. Clinic BP, body composition and cardiorespiratory fitness were shown to be most-strongly associated with exercise BP, suggesting lifestyle modification of these risk factors may have independent and additive effects to decrease exercise BP-related CVD risk.

5.6 CONTRIBUTION OF STUDY TO THESIS AIMS

Prior to Study 4, it remained unknown whether and how individual CVD risk factors could interact with one another to influence the exercise BP response. In Study 4, several pathways of association were found between exercise BP and individual CVD risk factors. Most CVD risk factors shared a relationship with exercise BP via an association with clinic BP. However, age, sex, waist-to-hip and cardiorespiratory fitness are also associated with exercise BP independently of clinic BP.

6 IMPROVEMENT IN FUNCTIONAL CAPACITY WITH SPIRONOLACTONE MASKS THE TREATMENT EFFECT ON EXERCISE BLOOD PRESSURE.

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6.1 ABSTRACT

Objectives. A hypertensive response to submaximal exercise is associated with CVD but this relationship is influenced by functional capacity. Spironolactone improves functional capacity, which could mask treatment effects on exercise blood pressure (BP). This study sought to examine this hypothesis, with additional consideration of the role of aortic stiffness on changes in exercise BP following treatment.

Design. Retrospective analysis of a randomised clinical trial.

Methods. 102 participants (54 ± 9 years; 52% male) with a hypertensive response to maximal exercise (systolic BP ≥ 210 mmHg men; ≥ 190 mmHg women) were randomized to 3-months spironolactone 25 mg daily ($n=53$) or placebo ($n=49$). Submaximal exercise BP was measured during low-intensity cycling (50, 60 or 70% age-predicted maximal heart rate). Functional capacity was measured as maximal oxygen capacity obtained during a maximal treadmill exercise test, and (resting) aortic stiffness by carotid-to-femoral pulse wave velocity.

Results. Spironolactone improved submaximal exercise systolic BP vs. placebo (-4 ± 16 vs. 2 ± 15 mmHg, $p=0.045$, Cohen's $d=0.42$), and had a small (but non-statistically significant) improvement in functional capacity (0.64 ± 5.10 vs. -1.43 ± 5.04 ml/kg/min, $p=0.06$, Cohen's $d=0.4$). When treatment effects were expressed as the change in submaximal exercise systolic BP relative to the change in functional capacity, a larger effect size was observed (-0.3 ± 1.1 vs. 0.3 ± 1.1 mmHg/ml.kg.min⁻¹, $p=0.01$, Cohen's $d=0.58$), but was not explained by improved aortic stiffness.

Conclusions. Spironolactone reduces submaximal exercise BP, but this treatment effect may be hidden by improved functional capacity and a non-fixed workload. Exercise BP should be measured at a low intensity and fixed workload where the influence of fitness on exercise BP is removed. Subsequently the effects of therapy on exercise BP can be appreciated.

6.2 INTRODUCTION

Blood pressure (BP) is routinely measured during clinical exercise testing. Hypertensive BP responses during submaximal exercise intensity can occur in some individuals and are associated with an elevated risk of cardiovascular mortality,[9,242] future hypertension,[11] and reveal high BP undetected by the measurement of resting BP.[10,69,205] Therefore, the BP response at submaximal exercise may be an important clinical signal for identifying hypertension-related CVD risk beyond current strategies focussed on resting BP.

Independent of BP, the potassium sparing diuretic spironolactone can improve aortic stiffness and left ventricular systolic strain,[165,174,243] as well as improve left ventricular diastolic volume.[173,176,244] These factors which unload pressure on the left ventricle and improve cardiac function may contribute to increased functional capacity.[165,173,244] Higher functional capacity enables individuals to achieve greater workloads at an exercise intensity relative to maximal heart rate, but this is also associated with increased maximal exercise BP.[98] On the other hand, these individuals have lower BP and heart rate response when the workload is fixed during submaximal exercise.[46,139,144] Therefore, the assessment of exercise BP without considering changes in functional capacity brought about by any intervention (including medications such as spironolactone), may lead to clinical misinterpretation of exercise BP. To our knowledge the effect of spironolactone on exercise BP after considering (correcting for) functional capacity has never been examined and was the aim of this study. We hypothesised that the treatment effect of spironolactone on exercise BP may be masked by changes in functional capacity.

6.3 METHODS

Data were analyzed retrospectively from a randomized double-blind controlled clinical trial of spironolactone (25 mg/d) compared with identical placebo over three months (<http://www.anzctr.org.au>; clinical trial ID: ACTRN12609000835246), which the primary outcomes have been published.[165] Participants included people who had a hypertensive systolic BP response to maximal exercise (≥ 210 mmHg in men; ≥ 190 mmHg in women).[42] Participants were excluded from the trial if an exercise stress test echocardiogram was positive for ischemia, uncontrolled resting BP $\geq 140/90$ mmHg, previous diagnosis for hypertension or were already on antihypertensive medication, had renal dysfunction defined as serum creatinine >2 mg/dl, had a history of gynecomastia, had been prescribed regular nonsteroidal inflammatory medication or were pregnant. Of the 110 participants who were included in the original trial, 102 participants (49 in the control group and 53 in the spironolactone group) had the measurement of BP taken during a submaximal exercise cycling test at baseline and follow up and were included in this analysis. In addition, 88 participants (39 in the control group and 49 in the spironolactone group) had functional capacity measured during a separate treadmill test at baseline and follow-up. The Princess Alexandra Hospital Research Ethics Committee provided approval for this trial, and all participants gave written informed consent.

Submaximal and maximal exercise BP was measured in duplicate using mercury sphygmomanometry by a trained technician according to recommendations.[7] Submaximal exercise BP was measured while participants were cycling at a steady state heart rate after three-to-five minutes at the same exercise intensity and workload. Participants began cycling at a cadence of 50 rpm and a workload of 50 Watts. The workload was adjusted until each participant reached 50, 60 or 70% of age-predicted maximum heart rate ($220 - \text{age} \times \text{target percentage of heart rate}$). This exercise

intensity was chosen because it is at the same intensity where exercise BP is associated with elevated BP-related CVD risk. Moreover, exercise BP measured at a steady-state heart rate was attained while cycling because it was not possible during the Bruce treadmill protocol with workloads increasing every three minutes. Submaximal exercise BP was measured at the same intensity while cycling at baseline and follow-up. Maximal exercise BP was measured upon maximal exhaustion of a Bruce treadmill exercise test.

Maximal oxygen capacity was obtained as a measure of functional capacity using indirect calorimetry (Vmax29c; SensorMedics, Yorba Linda, CA) during a graded treadmill stress test to exhaustion (Bruce protocol).

Central BP and aortic stiffness were measured in duplicate at supine rest by carotid-to-femoral pulse wave velocity using applanation tonometry (SphygmoCor 7.1. AtCor Medical Pty Ltd, Sydney, Australia).

Statistical analyses were performed on participants with measures completed at pre- and post-intervention timepoints. All data are presented as the mean \pm standard deviation (SD). Variable distributions were assessed using a Shapiro-Wilk test, Levene's test of equality of variance, and visually assessed using Q-Q plots. Outliers were assessed using Q-Q plots and defined as observations greater than 3.3 or less than -3.3 standardized residuals.[245] Baseline and change from baseline to follow-up comparison between treatment groups were assessed using t-tests for normally distributed data and Mann-Whitney U tests for non-normally distributed data. The quotient of the changes in exercise BP and functional capacity was used to determine the treatment effect on exercise BP taking into consideration changes in functional capacity. Chi-Squared tests were used to assess baseline differences between treatment groups for categorical variables. Multiple linear regression was performed to compare

the change between treatment groups after adjusting for confounding variables. Effect size was calculated to determine the magnitude of the difference between treatment groups using Cohen's d (0.3-0.5 small effect size, 0.5-0.8 moderate effect size, and ≥ 0.8 large effect size).[246] A p-value ≤ 0.05 was considered statistically significant. Data were analysed using R for Windows (version 3.5.1, Boston, Massachusetts).

6.4 RESULTS

On average, participants were of middle-to-older age, male, non-smokers with a raised body mass index and low functional capacity (Table 6.1). There was no difference in participant characteristics between treatment groups, except the spironolactone group had a higher percentage of participants who self-reported being diagnosed with type 2 diabetes mellitus compared to the placebo group. There was no difference between control and treatment groups in the number of participants that cycled at 50, 60 and 70% of age-predicted maximal heart rate (n=4 and 5; n=19 and 17; n=26 and 31, respectively; p=0.77).

Table 6.1. Baseline and follow up clinical characteristics of study participants by treatment group.

Variable	Placebo (n = 49)		Spironolactone (n = 53)		P-value between groups	
	Pre-treatment	Post-treatment	Pre-treatment	Post-treatment	Pre-treatment	Post-treatment
Age, years	55 (8)	-	54 (9)	-	0.507	-
Male sex, n (%)	27 (55)	-	31 (59)	-	0.730	-
Height, cm	171.4 (9.4)	-	171.3 (9.8)	-	0.968	-
Weight, kg	84.4 (15.8)	85.5 (16.1)	88.1 (15.4)	87.3 (15.1)	0.228	0.524
Body mass index, kg/m ²	28.6 (3.9)	28.8 (4.0)	30.1 (5.2)	28.6 (7.7)	0.112	0.902
Type 2 diabetes mellitus, n (%)	3 (6)	-	10 (20)	-	0.045	-
Smoking status, n (%)	5 (10)	-	1 (3)	-	0.105	-
Resting systolic blood pressure, mmHg	126 (12)	124 (11)	126 (11)	121 (11)	0.942	0.271
Resting diastolic blood pressure, mmHg	73 (7)	74 (8)	74 (8)	72 (7)	0.319	0.176
Total Cholesterol, mmol/L	5.3 (0.9)	5.2 (0.9)	5.3 (1.0)	5.1 (1.0)	0.868	0.755
Triglycerides, mmol/L	1.5 (1.1)	1.4 (1.1)	1.6 (1.2)	1.4 (1.0)	0.481	0.929
High density lipoprotein cholesterol, mmol/L	1.4 (0.4)	1.3 (0.4)	1.3 (0.4)	1.4 (0.4)	0.429	0.667
Low density lipoprotein cholesterol, mmol/L	3.3 (0.8)	3.2 (0.8)	3.3 (1.0)	3.2 (0.9)	0.905	0.622
Fasting glucose, mmol/L	5.9 (2.2)	6.1 (2.5)	6.0 (1.8)	6.1 (2.2)	0.723*	0.473*
HbA1c, %	5.9 (1.0)	5.9 (1.0)	6.0 (1.3)	6.0 (1.4)	0.624*	0.606*
Statin use, n (%)	10 (20)	-	7 (14)	-	0.533	-

Data presented as mean (SD). * represents when the comparison between treatment groups required a Mann Whitney U test to be performed for analysis.

Table 6.2 shows the between-group changes in submaximal and maximal exercise BP from baseline to follow up. Spironolactone improved submaximal exercise systolic BP compared to placebo (-4 ± 16 vs. 2 ± 15 mmHg, $p=0.045$, Cohen's $d=0.42$), and had a small (but non-statistically significant) relative improvement in functional capacity (0.64 ± 5.10 vs. -1.43 ± 5.04 ml/kg/min, $p=0.06$, Cohen's $d=0.4$). When treatment effects were expressed as the change in submaximal exercise systolic BP relative to the change in functional capacity, a larger effect size was observed (-0.3 ± 1.1 vs 0.3 ± 1.1 mmHg/ml.kg.min⁻¹, $p=0.01$, Cohen's $d=0.58$). Spironolactone also improved maximal exercise systolic BP compared to placebo, as well as the ratio of maximal exercise systolic BP to functional capacity. There were no between-group differences in the change in submaximal and maximal exercise diastolic BP or change in the exercise diastolic BP/functional capacity ratio. All observed between-group effects after adjustment for type 2 diabetes mellitus were similar to unadjusted results, except for an increased effect size for the change in submaximal exercise systolic BP.

Change in aortic pulse wave velocity and central BP from baseline to follow up are presented in Table 6.2. Spironolactone improved aortic pulse wave velocity and central BP with a moderate effect size compared to placebo, which remained after adjusting for the presence of type 2 diabetes mellitus. The improvement in aortic pulse wave velocity had a weak association with the decrease in exercise systolic BP at submaximal ($r=0.195$, $p=0.062$) and maximal intensities ($r=0.218$, $p=0.041$). The improvement in aortic pulse wave velocity had no association with the decrease in exercise systolic BP/functional capacity ratio at submaximal ($r=0.012$, $p=0.918$) or maximal exercise ($r=0.005$, $p=0.962$).

Table 6.2. Hemodynamic and arterial stiffness characteristic changes from baseline to follow up between spironolactone and placebo group.

	Placebo (n = 49)				Spironolactone (n = 53)				Between treatment groups			
	n	Baseline	Follow up	Change	n	Baseline	Follow up	Change	Change			
									p-value ^a	Effect size ^a	p-value ^b	Effect size ^b
Submaximal exercise												
SBP, mmHg	49	175 (23)	177 (23)	2 (15)	53	177 (21)	174 (23)	-4 (16)	0.079	0.35	0.045	0.42
DBP, mmHg	49	83 (10)	82 (12)	-1 (10)	53	83 (10)	80 (10)	-3 (9)	0.279	0.22	0.087	0.28
SBP / functional capacity, mmHg/ml.kg.min ⁻¹	39	5.8 (1.6)	6.1 (1.5)	0.3 (1.1)	49	6.1 (1.9)	5.8 (1.7)	-0.3 (1.1)	0.014	0.54	0.014	0.58
DBP / functional capacity, mmHg/ml.kg.min ⁻¹	39	2.7 (0.6)	2.8 (0.7)	0.1 (0.6)	49	2.9 (0.9)	2.7 (0.7)	-0.2 (0.6)	0.017	0.52	0.014	0.54
Maximal exercise												
Functional capacity, ml/kg/min	39	31.8 (7.3)	30.4 (6.1)	-1.4 (5.0)	49	31.3 (8.2)	32.9 (8.1)	0.6 (5.1)	0.06	0.4	0.07	0.4
SBP, mmHg	43	216 (16)	215 (16)	-1 (11)	51	222 (16)	213 (18)	-8 (12)	0.049	0.57	0.044	0.57
DBP, mmHg	43	95 (12)	93 (14)	-2 (9)	51	92 (14)	90 (13)	-2 (12)	0.810	0.05	0.859	0.03
SBP / functional capacity, mmHg/ml.kg.min ⁻¹	39	7.1 (1.6)	7.4 (1.6)	0.3 (1.3)	49	7.5 (2.0)	7.1 (1.7)	-0.5 (1.2)	0.011	0.56	0.016	0.57
DBP / functional capacity, mmHg/ml.kg.min ⁻¹	39	3.1 (0.8)	3.2 (0.8)	0.1 (0.6)	49	3.2 (1.0)	3.0 (0.9)	-0.2 (0.7)	0.077	0.38	0.1	0.38
Aortic pulse wave velocity, m/s	42	8.2 (1.7)	8.6 (2.2)	0.4 (1.0)	50 [†]	8.4 (1.9)	8.1 (1.6)	-0.3 (0.9)	0.022	0.49	0.01	0.55

Resting central SBP	44	114 (10)	113 (11)	-1 (9)	51	113 (11)	109 (10)	-4 (8)	0.04	0.43	0.03	0.44
Resting central DBP	44	74 (7)	75 (8)	1 (7)	51	75 (8)	73 (7)	-2 (6)	0.02	0.50	0.01	0.53

Data presented as mean (standard deviation). BP, blood pressure; DBP, diastolic BP; SBP, systolic BP. Submaximal exercise BP measured at a fixed intensity of 50, 60 or 70% age-predicted maximal heart rate while upright cycling. Maximal exercise BP was measured up upon exhaustion of a Bruce Treadmill test. ^aeffect size unadjusted for the difference in those with type 2 diabetes mellitus between treatment groups; ^beffect size after performing multiple linear regression analyses to adjust for the difference in those with type 2 diabetes mellitus between treatment groups. [†]One participant was considered an outlier and was excluded.

6.5 DISCUSSION

The key finding of this study was that the full treatment effect of spironolactone on submaximal exercise systolic BP was hidden by an improvement in functional capacity. Other studies have reported the effects of antihypertensive therapy on exercise BP separate from the effects on functional capacity[165,173] or exercise test duration.[247–249] To our knowledge, this current study is the first to take into consideration the relative changes in both exercise BP and functional capacity (cardiorespiratory fitness). This is an important step that reveals a potential deficiency relevant to the clinical interpretation of exercise stress test results. Specifically, that a lack of change (decrease) in exercise systolic BP following therapy could be from improved functional capacity, as a result of people exercising at the same relative intensity but at a greater workload, and thereby accompanied by higher exercise BP.[98]

The stronger likelihood of having uncontrolled BP among people with high exercise systolic BP should warrant consideration of initiating or up-titrating antihypertensive treatment, or further investigation to confirm BP control.[10,69,205] However, consideration of fitness is also critical because a hypertensive response to exercise can occur in healthy athletes with high fitness as well as those with disease and low fitness.[43,83,242] Importantly, a hypertensive response to exercise occurs more predominantly towards maximal intensity among individuals with higher fitness because of achieving higher workloads relative to people with lower fitness. Conversely, a hypertensive response to exercise is observed during submaximal intensities and lower exercise workloads among people with low fitness and increased disease burden.[46,145] At lower exercise workloads, people with higher fitness or athletes are working at a much lower intensity relative to people of lower fitness, and thus have lower relative BP.[46,144] These previous data, together with the findings

of this study, emphasize that the most clinically relevant exercise BP occurs at a low intensity and fixed workload (e.g. first or second stage of a Bruce treadmill protocol) where the influence of fitness on exercise BP is removed. This is also where the higher quality exercise BP measures can be recorded without the extra noise and movement artefact that occurs at maximal exercise.[7] Our observations extend on these observations by showing that fitness should also be considered when assessing the effect of treatment on exercise BP.

The small improvement in functional capacity following spironolactone may be explained by several factors. Firstly, spironolactone can improve peak early diastolic velocity, left ventricular filling pressure, untwisting rate, and systolic strain,[173,176,243,244] which in-turn may also increase functional capacity.[173,244] Secondly, spironolactone reduces large artery (aortic) stiffness,[165,174] which will enhance ventricular-vascular interaction, decrease systolic BP and left ventricular afterload, altogether contributing towards improved functional capacity.[250,251] Having said this, such an effect was not statistically evident in the findings of this current study. Thirdly, the higher post-intervention functional capacity may be achieved by improving endothelial function and increasing blood flow (and oxygen supply) to the active muscles.[252,253] Thus, spironolactone has multiple effects that improve cardiovascular function and exercise reserve, increasing the possibility of exercise at higher external workloads despite the same relative exercise intensity, potentiating higher exercise BP.

This study was a retrospective analysis of data recorded within a randomized control trial and the findings will need to be reproduced elsewhere. This includes assessing if findings are similar when exercise BP is normalised with other variables obtained from the cardiopulmonary test, e.g. peak workload and ventilatory threshold, that were

unavailable in this analysis. Exercise BP and functional capacity may also differ when obtained during cycle ergometry compared to treadmill.[31,254] Thus, the results may not be generalized to other exercise modalities beyond the cycling protocol used in this study, nor to other antihypertensive agents, e.g. furosemide or amiloride, that induce a change in BP similar to spironolactone but without vascular remodelling. We also cannot exclude that other medication (such as metformin) may be interacting with spironolactone and be confounding the results of this study. Although this study was a randomized control trial, we could not preclude participants from changing their level of lifestyle activities (such as physical activity) and this could have influenced the results. Finally, aortic stiffness was measured at rest, which may return different results to that measured during exercise,[255] and potentially underappreciating the influence of large artery function on changes in exercise BP.

Conclusion. Spironolactone reduces submaximal exercise BP, but its full treatment effects on BP may be hidden by concomitant increases in functional capacity in the absence of a fixed workload. This highlights that the most clinically relevant exercise BP is at a low intensity and fixed workload (e.g. first or second stage of a Bruce treadmill protocol) where the influence of fitness on exercise BP is removed and the full effects of therapy can be appreciated.

Practical implications

- This study highlights how the effect of treatment on submaximal exercise BP could be masked by a concomitant improvement in functional capacity by the drug.
- Taking into consideration the relative changes in both exercise BP and functional capacity is an important step that reveals a potential deficiency relevant to the clinical interpretation of exercise stress test results.

- Clinicians and researchers should pay attention on exercise BP measured at a low-intensity and fixed workload, where the influence of functional capacity is removed and the full effects of therapy can be appreciated.

6.6 *CONTRIBUTION OF STUDY TO THESIS AIMS*

The effect of an intervention (i.e. lifestyle medication or pharmacotherapy) on exercise BP is varied. However, an intervention may also improve other CVD risk factors that influence the BP response to exercise. The results of Study 5 have shown that three months treatment with spironolactone can decrease exercise BP. However, when the treatment effect of spironolactone was expressed as the change in submaximal exercise systolic BP relative to the change in cardiorespiratory fitness, a larger effect size was observed. This suggests improvement in cardiorespiratory fitness may change the workload at which time exercise BP is measured, i.e., taken at a higher workload relative to intensity (based on age-predicted maximal heart rate). Therefore, from the findings of Study 5, clinicians and allied health professionals should fix the external workload to correctly interpret the effect of treatment on the BP response to exercise.

7 SUMMARY, FUTURE DIRECTIONS AND CONCLUSIONS

7.1 SUMMARY OF RESULTS.

The first section of this thesis has shown that exercise BP is associated with cardiac structure (Chapter 3) and several CVD risk factors (Chapters 4 and 5). Those with an HRE also had a higher risk of LV hypertrophy and a poorer CVD risk profile compared to those without an HRE, irrespective of clinic BP (Chapters 3 and 4). Exercise BP was associated with many CVD risk factors via a relation with clinic BP. However, age, sex, waist-to-hip ratio and cardiorespiratory fitness influenced exercise BP independently of clinic BP (Chapter 5). Taken all together, an HRE is likely indicative of uncontrolled high BP-related CVD risk potentially missed at rest.

The second part of this thesis has highlighted several methodological factors related to exercise BP measurement. In Study 1, the automated measurement of BP during a standard exercise test had good concordance with manual auscultation. Thus, automated measurement of BP may be a suitable alternative to manual measurement of BP during clinical exercise testing among individuals with type 2 diabetes mellitus. In Study 5, the treatment effect of spironolactone on exercise BP was masked by a simultaneous improvement in cardiorespiratory fitness. These data highlight that exercise BP should be measured at a fixed workload to aid appropriate clinical interpretation.

Overall, the original studies in this thesis advance the understanding and highlight the potential importance of measuring exercise BP to identify CVD risk related to high BP.

7.2 IMPLICATIONS OF RESEARCH AND FUTURE DIRECTIONS.

Manual measurement of BP during clinical exercise testing is the recommended standard [6,7,36]. However, automated measurement of BP is also used in clinical

practice [6,7,36]. Data is scarce on whether the measurement of BP during exercise with an automated BP device is concordant with manual auscultation [86,87,94–97]. The results of Study 1 that show the measurement of exercise BP with the Tango+ automated BP device has good-to-excellent concordance with manual auscultation among individuals with type 2 diabetes mellitus and could give clinicians and allied health professionals confidence that the measurement method used during an exercise test may not influence the clinical interpretation of the BP response. However, the results of Study 1 are specific to the Tango+ automated BP device, which may handle noise and movement artifact differently to other devices in order to measure exercise BP. Indeed, the automated BP device used by Modesti et al.[86] uses a spectral analysis of sounds perceived by the microphone during the inflation of the cuff. In contrast, the Colin STBP-680 used by Lightfoot et al.[256] uses the QRS complex from an electrocardiogram to trigger when the device should sample for the Korotkoff sounds. How noise and movement artifact is handled by automated BP devices during clinical exercise tests should be considered in the validation protocols written by peak professional bodies as well as by clinicians and allied health professionals that interpret the BP response during exercise. The exercise testing methods used in Study 1 to investigate the concordance between manual and automated measurement of BP were also different to the various procedures performed in earlier studies (Table 1.2). However, a standard treadmill exercise test that is regularly performed in cardiology departments worldwide was used in Study 1. Future studies could investigate if the automated measurement of BP during exercise tests is concordant with manual auscultation at different (high) intensities consistent between various exercise modalities. This future work would help peak professional bodies develop a standardised approach to investigate the validation of new automated BP devices to measure BP during clinical exercise tests. This future work may also be helpful for

companies that design and produce automated BP devices to accurately measure BP during an exercise test.

Determining the concordance between manual and automated exercise BP is important because an HRE during submaximal intensities is an independent signal of elevated CVD risk and may indicate high BP-related CVD risk missed at rest [9–11]. The findings of Study 1 may give clinicians and allied health professionals the confidence to use the Tango+ automated device to evaluate the BP response to exercise without necessarily confirming the result with manual auscultation. However, whether physiological factors among those with chronic disease, e.g. raised aortic stiffness, influence the measurement of BP during exercise should be determined in future research. Peak professional bodies should also seek to determine a standardised protocol for the validation of an automated BP device during an exercise test.

Chronically high BP can result in structural cardiac damage [73]. Elevated BP-related structural cardiac parameters include LV hypertrophy and left atrial enlargement, which also independently predict the risk of CVD mortality, heart failure and cardiac arrhythmia [257,258]. However, clinicians may not investigate cardiac structure if clinic BP is normal and thus, miss an opportunity to perform other tests to assess CVD risk and intervene with lifestyle modification or pharmacotherapy. The results of Study 2 may encourage clinicians to investigate cardiac structure in individuals with an HRE.

In Study 2, structural cardiac remodelling was similar (elevated) among those with an HRE that were also athletic, apparently healthy or had a chronic disease. To differentiate between a ‘pathological’ and ‘physiological’ BP response to exercise, it is recommended that exercise BP be measured at a submaximal and fixed external workload [239]. This recommendation to interpret the BP response free from the influence of cardiorespiratory fitness may help distinguish between structural cardiac

remodelling that is pathological from a normal physiological response and should be investigated in future research. This future research is potentially important for individuals with extremely high cardiorespiratory fitness with an HRE during maximal intensities that appear to be at elevated risk of future high BP-related CVD [64,259], despite having no difference in ventricular-vascular function or resting cardiovascular abnormalities compared to those without an HRE [45,77,260]. This future work would also help clinicians, allied health professionals, and sports scientists triage individuals (including athletes) with an HRE that requires follow-up care related to high BP-related CVD risk.

In Study 3, those with an HRE had a poorer CVD risk profile compared to those without an HRE, irrespective of clinic BP. As uncontrolled high BP clusters with other CVD risk factors [148,149], allied health professionals that supervise an exercise test and notice an HRE are recommended to report this finding as a red flag, which should prompt the referring clinician to assess BP control with 24-hour ambulatory monitoring to rule out underlying hypertension. This recommendation is consistent with some clinical guidelines for exercise testing [72,261], but is different from international hypertension guidelines because of the lack of standardisation in exercise test methodologies [25]. Therefore, there is a need to standardise the exercise testing methods used between studies to determine a clinically meaningful BP response to exercise. However, the consistent results in Study 3 suggest clinicians and allied health professionals can be confident that an HRE (during any intensity and modality) is an important indicator of elevated CVD risk irrespective of clinic BP. Therefore, the different clinical guidelines written by various peak professional bodies should be harmonised to suggest that an HRE (during any type of exercise test) is an important indicator of elevated CVD risk, which should require follow-up care of BP control. This harmonisation of different clinical guidelines would also decrease the

ambivalence of clinicians and health professionals to use the measurement of exercise BP as a clinical tool for the assessment of CVD risk.

Fifty percent (50%) of those with high BP have one or more other CVD risk factors [149], most commonly type 2 diabetes mellitus, lipid disorders and metabolic syndrome [149]. Whether the poorer CVD risk profile among those with an HRE in Study 3 was above 'clinically meaningful' thresholds is unknown (e.g. HbA1C \geq 6.5%, fasting glucose \geq 7.0 mmol/L, total cholesterol \geq 4.0 mmol/L, low-density lipoprotein cholesterol \geq 2.0 mmol/L or high-density lipoprotein \leq 1.0 mmol/L) [182,262]. Findings of this future work may indicate that those with an HRE are also at elevated risk of other chronic conditions and could incline clinicians to complete blood tests to investigate CVD risk further.

Future work that aims to determine thresholds of exercise BP that denote increased CVD risk could be integrated into the algorithm of automated BP devices and act as a warning signal to alert clinicians to provide follow-up care. The threshold of an HRE during a submaximal workload, such as the first or second stage of a Bruce treadmill test, is likely more important than when BP is measured during maximal/peak exercise intensities for several reasons. Firstly, an HRE at submaximal (rather than maximal) intensities is associated with higher risk of cardiovascular mortality and incident hypertension [9,11]. Secondly, there is no difference in the mean difference in cardiac structure or CV risk factors between those with and without an HRE when exercise BP was measured at submaximal or maximal intensities (Studies 2 and 3). Thirdly, submaximal exercise BP is likely less influenced by noise and movement artifact and can reveal the presence of hypertension undetected at rest [10]. Fixing the workload during submaximal exercise intensities would also remove the influence of cardiorespiratory fitness on the interpretation of exercise BP [239]. The Exercise Stress Test Collaboration Project is currently underway and aims to determine thresholds of

exercise BP associated with acute and long-term CVD risk amongst a large clinical set of exercise test results from around Australia. The results of this study will enable supervising medical and health professionals to provide appropriate follow-up care to reduce the acute and long-term risk of CVD. The results of this future research will also be additive to current exercise science and hypertension guidelines, which tend to only include evidence on the prognostic value of an HRE at maximal/peak intensities. Individuals in low-income countries are at higher risk of BP-related CVD compared to those in high-income countries [3,263]. Moreover, BP control is still poorly screened and managed in low-income countries with only ~10% individuals reported to have controlled BP [264]. Therefore, there is a need to improve the detection and treatment strategies to better control BP in low-income countries. Exercise tests are performed in hospitals in low-income countries [265]. Therefore, exercise BP may be an opportunity to improve the screening of high BP with no additional cost to the healthcare service. Future research should aim to better understand whether the exercise BP may improve the detection of high BP-related CVD risk in low-income countries.

In Study 4, clinic BP, waist-to-hip ratio and cardiorespiratory fitness were most strongly associated with exercise BP. This finding may suggest that clinicians and allied health professionals recommend lifestyle modification to most effectively decrease the CVD risk associated with exercise BP. The different pathways of association found in Study 4 may also help understand how other interventions (i.e. pharmacotherapy and surgery) can decrease exercise BP. For example, an intervention with a beta-blocker medication may decrease exercise BP via a reduction in heart rate and clinic BP, whilst surgical interventions that improve body composition (e.g. body mass index and waist-to-hip ratio) could reduce exercise BP via a decline in blood-related CVD risk factors, heart rate, and clinic BP. These possible causal relationships

between exercise BP and different CVD risk factors could be further investigated in future studies with longitudinal or clinical trial data. Taken all together, this future work could help guide and inform public health services, clinicians and other health professionals on what prevention and treatment interventions could most effectively decrease exercise BP and its associated CVD risk.

Historically, the association between CVD outcomes and different exposures have been assessed with statistical methods such as Pearson's correlation or linear regression. Indeed, these traditional statistical methods are helpful to understand the direct (and independent) associations between an outcome and an exposure. However, the relationship between an outcome and an exposure via a second (or third) exposure cannot be quantified. In Study 4, exercise BP was associated with body composition and cardiorespiratory fitness via a relationship with several CVD risk factors (including clinic BP), which only became apparent with the SEM. An SEM is extensively used in sociological and general epidemiological research but is still hardly used in medical research. Therefore, more medical and health researchers are encouraged to use SEM to understand the possible and various pathways of association between different CVD outcomes and risk factors. This work would also guide prevention and treatment strategies to decrease the burden of high BP-related CVD risk.

In Study 5, the full treatment effect of spironolactone on submaximal exercise systolic BP was hidden by the improvement in cardiorespiratory fitness. This finding may explain why the effects of lifestyle modification and antihypertensive medication on exercise BP has varied. Indeed, an intervention that improves cardiorespiratory fitness could lead to a greater workload being achieved and increase exercise BP. If the external workload is fixed, then the effect of treatment on exercise BP may be correctly interpreted by individuals supervising the exercise tests. This interpretation of exercise

BP with the consideration of cardiorespiratory fitness may be achieved during submaximal fixed workloads (e.g. first or second stage of a Bruce treadmill protocol), where there is good test-retest reliability [88], and where higher quality BP measurements can be made [7]. Future studies should further investigate the influence of cardiorespiratory fitness on submaximal exercise BP following treatment, and with the relationship with CVD outcomes.

Because the focus of this thesis was on BP measured during exercise, how these results may apply to BP measured after exercise (post exercise BP) is unknown. Future studies could investigate whether the physiological mechanisms are different between exercise BP and post-exercise BP. Future research could also investigate if post-exercise BP differs by mode of exercise, body position, or exercise intensity. This research may help clinicians and allied health professionals use the BP response during an exercise test to better evaluate risk of CVD.

7.3 CONCLUSIONS

This thesis has identified several clinically relevant results related to the understanding of exercise BP. Exercise BP was found to share a relationship with several CVD risk factors and different structural cardiac parameters. These results were also consistent irrespective of clinic BP. These results may further highlight that exercise BP may be useful for the identification of high BP and its related CVD risk otherwise missed at rest. There appears to be good concordance between manual and automated measurement of exercise BP, suggesting the type of method used to measure exercise BP may not influence clinical interpretation. The assessment of exercise BP without considering changes in cardiorespiratory fitness brought about by an intervention may mask treatment effects on exercise BP. Therefore, measurement of exercise BP should

be at a fixed submaximal workload where the effect of changes in cardiorespiratory fitness are removed.

The findings in this thesis inform that the different clinical guidelines should include information on the high BP-related CVD risk associated with the BP response to exercise. This thesis has also discussed several methodological factors that clinicians and other health professionals should consider for the correct interpretation of an HRE and its related CVD risk. Ultimately, this research highlights the potential opportunity the measurement of exercise BP has for the identification of high BP-related CVD risk beyond standard clinic BP, which may assist in decreasing the global burden of CVD.

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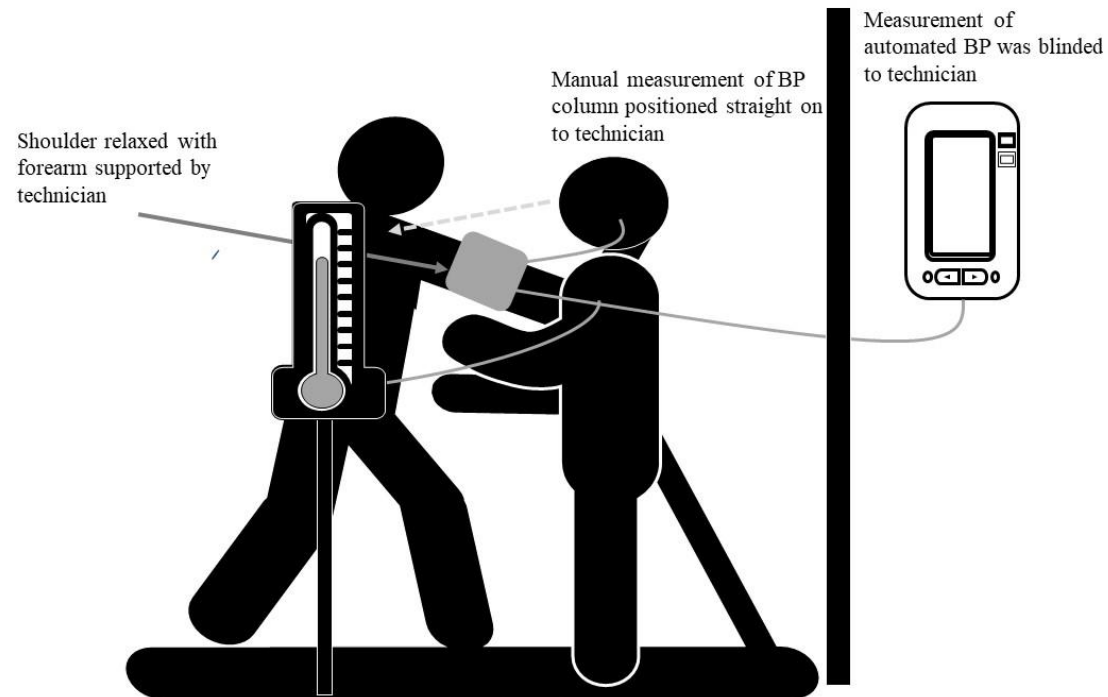
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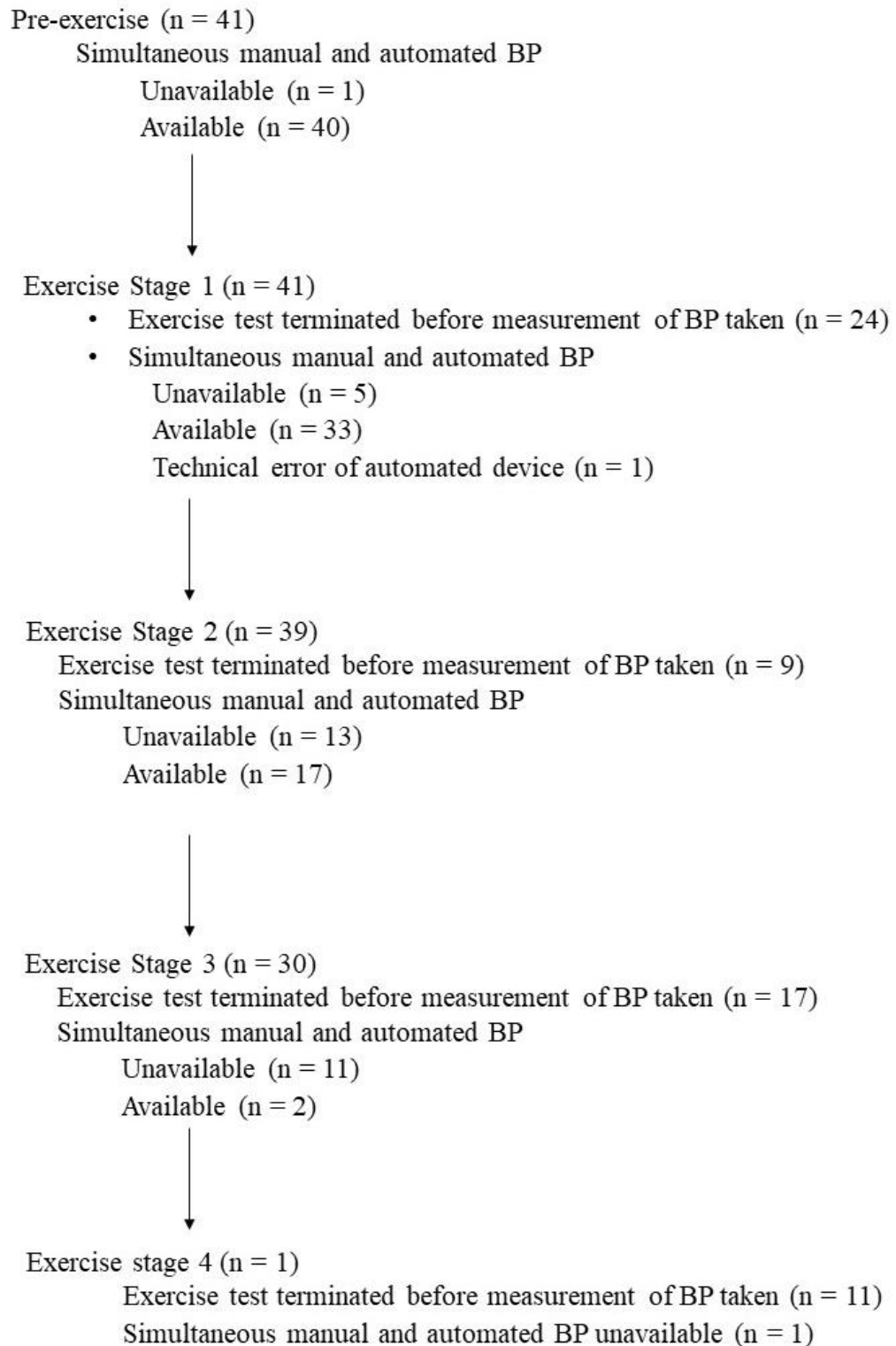
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Appendix A. SUPPLEMENTARY MATERIAL FOR CHAPTER 2.



Appendix Figure 2.1. Illustration of the simultaneous manual and automated exercise BP measurement by trained technician blinded to the automated device.



Appendix Figure 2.2. Flow of participants and comparisons between manual and automated measurement of blood pressure (BP) across different stages of a Bruce treadmill exercise test.

Appendix Table 2.1. Comparison between manual and automated auscultatory delta blood pressure from pre-exercise to different stages of a Bruce treadmill exercise test.

Comparisons	Pre-exercise to Exercise Stage 1	Pre-exercise to Exercise Stage 2
	n=32	n=16
Δ Systolic blood pressure (mmHg)		
Automated	38 \pm 23	48 \pm 30
Manual	38 \pm 19	50 \pm 19
Mean Difference	0 \pm 16°	-2 \pm 17
ICC (95% confidence intervals)	0.841 (0.672-0.923)*	0.881(0.661-0.959)*
Δ Diastolic blood pressure (mmHg)		
Automated	3 \pm 14	5 \pm 14
Manual	0 \pm 8	-1 \pm 11
Mean Difference	2 \pm 13	6 \pm 11
ICC (95% confidence intervals)	0.529 (0.045-0.759)**	0.747(0.294-0.911)**
Δ Pulse pressure (mmHg)		
Automated	35 \pm 21	43 \pm 29
Manual	37 \pm 18	51 \pm 16
Mean Difference	-2 \pm 19°	-8 \pm 21
ICC (95% confidence intervals)	0.715 (0.415-0.861)*	0.735(0.281-0.906)**

Comparisons include the individuals who had manual and automated BP measured both at pre-exercise and at exercise stage 1 and 2. Data represent mean \pm standard deviation unless specified. Mean difference corresponds to automated blood pressure minus manual blood pressure. ICC, intra-class correlation. °, comparison between manual and automated exercise BP assessed using Mann-Whitney U test. *, $p < 0.001$. ** $p < 0.05$

Appendix Table 2.2. Percentage of cases in which the absolute difference between manual and automated auscultatory blood pressure fall within specific thresholds at pre-exercise and different stages of a Bruce treadmill exercise test.

Comparisons	Pre-exercise n=40	Exercise Stage 1 n=33	Exercise Stage 2 n=17	All Stages [†] n=90	Exercise Stages only [‡] n=50
Systolic blood pressure					
≤5 mmHg	72.5	39.4	29.4	52.0	36.0
≤10 mmHg	80.0	60.6	58.8	68.9	60.0
≤15 mmHg	87.5	78.8	82.4	83.3	80.0
Diastolic blood pressure					
≤5 mmHg	65.0	54.5	58.8	60.0	56.0
≤10 mmHg	87.5	84.8	76.5	84.4	82.0
≤15 mmHg	92.5	87.9	82.4	88.0	86.0
Pulse pressure					
≤5 mmHg	57.5	36.3	43.8	47.2	38.8
≤10 mmHg	72.5	57.6	58.8	64.4	58.0
≤15 mmHg	82.5	63.6	64.7	72.2	64.0

All data represents percentage respective to the available number of comparisons between manual and automated blood pressure at each exercise test stage. [†] pre-exercise to exercise stage 2. [‡] exercise stage 1 to stage 2 only (excluding pre-exercise).

APPENDIX B. SUPPLEMENTARY MATERIAL FOR CHAPTER 3.

Supplementary methods for Chapter 3.

Data extraction. Tsiachris et al. [80] indexed LV mass by body surface area and height^{2.7} separately, which were both extracted for meta-analyses. Two studies[91,266] did not report estimates for cardiac structure between those with and without an HRE within the text, so data was extracted from figures using extraction software.[267] For studies that reported exercise systolic BP using more than two categories, the lowest and highest exercise systolic BP categories were extracted, with the highest category of exercise BP defined as an HRE and lowest category representing the reference group (no HRE). Pearson correlation coefficients at the lowest exercise intensity were extracted for studies that reported unadjusted associations between exercise systolic BP and cardiac structure at multiple exercise intensities. Nine studies reported a correlation with cardiac structure with exercise systolic BP at both submaximal and peak intensities.[46,205,268–274] As such, correlations between structural cardiac variables and submaximal exercise systolic BP were extracted from studies because it is more representative of 24-hour ambulatory BP than peak exercise systolic BP,[69] and thus hypertension-related cardiac remodelling.

Data not extracted from specific studies included: 1) the data reported by Markovitz et al. [200] because the number of participants with and without an HRE was not stated; 2) LV wall thickness reported by Caselli et al. [45] because there was no indication of whether this variable was LV posterior or interventricular wall thickness; 3) difference in interventricular septal and posterior wall thickness between those with and without an HRE reported by Molina et al. [275] because these two structural cardiac variables had been indexed by body surface area; 4) unadjusted correlation between exercise BP and cardiac structures that had been indexed by body surface area reported by Mazic et al.;[276] 5) associations between exercise systolic BP and cardiac structure reported

in Molina et al. [275] because Spearman's rather than Pearson's correlation was performed.

Statistical analysis. A single sample size, mean and standard deviation was calculated for those with and without an HRE in the six studies that separated results by sex.[42,91,200,277,278] A single sample size, mean and standard deviation was also calculated for the five studies that included two groups with and/or without an HRE.[205,207,266,279,280] The two separate associations between exercise systolic BP and structural cardiac parameters reported by Karjalainen et al. [75] were combined to form a single correlation estimate using a sample-wise-adjusted-weighted procedure.[281] Units reported for left atrial diameter and LV end-diastolic and end-systolic dimension by Bitigen et al. [74] were converted to allow direct comparison with other studies.

Studies not included within individual meta-regressions included Douglas et al. [282] did not report resting BP status and was excluded from meta-regression analyses across different BP classifications. Vriend et al. [91] was also excluded from meta-regression analyses across different resting BP classifications because BP status was not based on resting BP.

Supplementary results for Chapter 3.

Meta-regressions

Resting BP status. The pooled unadjusted correlation between exercise systolic BP and LV relative wall thickness was lower in those without hypertension compared to populations with a “mixed” BP status ($p=0.002$, $R^2=100\%$). The pooled mean difference in all secondary structural cardiac variables between those with and without an HRE was similar among study populations with or without resting hypertension (Appendix Table 3.4).

Health status. The pooled unadjusted correlation between exercise systolic BP and all secondary cardiac structural variables was similar among populations with different health status (Appendix Table 3.3). The pooled mean difference in individual secondary structural cardiac variables between those with and without an HRE was similar among study populations with different health status (Appendix Table 3.4).

The exercise intensity at which time BP was measured. The pooled unadjusted correlation between exercise systolic BP and LV posterior wall thickness was similar between studies that measured BP at submaximal and peak intensity ($p=0.06$; $R^2=100\%$; Appendix Table 3.3). Studies that measured exercise systolic BP during submaximal intensities compared to those that measured during peak exercise systolic BP had a higher pooled unadjusted correlation interventricular septal thickness ($p=0.01$, $R^2=100\%$). The mean difference in individual secondary structural cardiac variables between those with and without an HRE was also similar among studies that measured BP during submaximal and peak exercise intensities (Appendix Table 3.4).

Exercise modality. The pooled unadjusted correlation between exercise systolic BP and relative wall thickness was similar irrespective of the exercise modality of the

included studies ($p=0.793$, $R^2=9\%$; Appendix Table 3.3). Studies using treadmill testing had a similar mean difference in LV relative wall thickness ($p=0.883$, $R^2=0\%$), LV end-systolic dimension ($p=0.019$, $R^2=77\%$), and left atrial size ($p=0.226$, $R^2=21\%$) compared to cycling. Studies using treadmill testing had a higher pooled mean difference in LV posterior wall thickness ($p=0.01$, $R^2=35\%$), interventricular septal thickness ($p=0.005$, $R^2=32\%$), and LV end-systolic dimension ($p=0.018$, $R^2=77\%$; Appendix Table 3.4) compared to cycling.

Study quality. Meta-regression analyses indicated that study quality explained the heterogeneity in the pooled unadjusted correlation between exercise systolic BP and LV relative wall thickness ($p<0.01$, $R^2=100$), interventricular septal thickness ($p=0.33$, $R^2=41\%$) and LV posterior wall thickness ($p=0.64$, $R^2=23\%$; Appendix Table 3.3). There was a positive association between study quality and mean difference in LV relative wall thickness ($\beta = 0.01$, 95% CI: 0, 0.01; $p=0.03$, $R^2=51\%$), and negative association with the mean difference of LV end-systolic dimension ($\beta = -2.07$, 95% CI: -3.84, -0.27; $p=0.02$, $R^2=79\%$) and LV end-diastolic dimension ($\beta = -1.00$, 95% CI: -1.84, -0.17; $p=0.02$, $R^2=46\%$).

Appendix Table 3.1. A search of three online databases (Medline via Ovid, Scopus and Embase) was conducted from the earliest available records to August 18th 2020.

Medline via Ovid	<ol style="list-style-type: none"> 1. Blood Pressure/ or Arterial Pressure/ or Hemodynamics/ or Blood Pressure Determination/ or hypertension/ or hypotension/ 2. (h?emodynamic or blood pressure or arterial pressure or hypertensi* or hypotensi*).tw. 3. Exercise/ or Exercise Test/ or Exercise Tolerance/ or Ergometry/ or Running/ or Walking/ 4. (cardiopulmonary test or stress test or exercise or running or walking or treadmill or cycling).tw. 5. ((h?emodynamic or (blood pressure or arterial pressure) or (hypertensi* or hypotensi*)) adj5 (cardiopulmonary test or stress test or exercise or running or walking or cycling)).tw. 6. 1 and 3 7. 1 and 4 8. 2 and 3 9. 5 or 6 or 7 or 8 10. Ventricular Remodeling/ or Cardiomyopathies/ or Cardiomegaly/ 11. (left ventric* adj2 (hypertrophy or wall thickness or structure or mass or mass index)).tw. 12. 10 or 11 13. Atherosclerosis/ or Pulse Wave Analysis/ or Carotid Intima-Media Thickness/ or Vascular stiffness/ or Vascular resistance/ or Vascular calcification/ 14. (Atherosclerosis or Pulse Wave Analysis or Carotid Intima-Media Thickness or vascular stiffness or vascular resistance or vascular calcification or pulse wave velocity or arterial compliance or arterial stiffness or endothelial function or vascular function or endothelial dysfunction or vascular dysfunction or carotid stiffness or coronary calcium score or ankle-to-brachial index).tw. 15. 13 or 14 16. Glucose/ or Blood Glucose/ or Cholesterol/ or Cholesterol, HDL/ or Cholesterol, LDL/ or Lipoproteins/ or Triglycerides/ or Glycated Hemoglobin A/ or Creatinine/ or Glomerular Filtration Rate/ or Aldosterone/ or Insulin/ or Renin-Angiotensin System/ or Renin/ or Proteinuria/ 17. (glucose or cholesterol or lipoprotein or triglyceride or glycated hemoglobin or glycated haemoglobin or hba1c or creatinine or Glomerular Filtration Rate or Aldosterone or Insulin or Renin or Proteinuria or albuminuria).tw. 18. 16 or 17 19. 12 or 15 or 18 20. 9 and 19 21. exp animals/ not humans.sh. 22. 20 not 21
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	23. exp adolescent/ or exp child/ or exp infant/
	24. 23 not Adults/
	25. 22 not 24
	26. limit 25 to English language
Scopus	<p>((((TITLE-ABS(Exercise OR "exercise test" OR "exercise tolerance" OR "stress test" OR "Cardiopulmonary test" OR ergometry or "running" or "walking" or "cycling")))) AND ((TITLE-ABS("blood pressure" OR "arterial pressure" OR "haemodynamic" OR "hemodynamic" OR "hypertensi*" OR "hypotensi*")))) AND (((TITLE-ABS(cardiomyopathies OR cardiomyopathy OR cardiomegaly OR ("left ventric*" W/2 (hypertrophy OR mass OR "wall thickness" OR structure OR remodeling)))))) OR ((TITLE-ABS("Pulse wave velocity" OR "pulse wave analysis" OR "Carotid Intima-Media Thickness" OR atherosclerosis OR "atherosclerotic plaque" OR "vascular stiffness" OR "arterial stiffness" OR "Vascular resistance" OR "arterial compliance" OR ((endothelial OR vascular) W/2 (function OR dysfunction)) OR "Vascular calcification" OR "coronary calcium score")))) OR ((TITLE-ABS(glucose OR "Blood glucose" OR cholesterol OR lipoprotein OR Triglycerides OR "Glycated Hemoglobin A" OR HbA1c OR Creatinine OR "Glomerular Filtration Rate" OR eGFR OR Aldosterone OR "Renin-Angiotensin System" OR Renin OR Proteinuria)))) AND (LIMIT-TO (SRCTYPE,"j")) AND (LIMIT-TO (SUBJAREA,"MEDI")) AND (LIMIT-TO (DOCTYPE,"ar")) AND (LIMIT-TO (LANGUAGE,"English")) AND (LIMIT-TO (EXACTKEYWORD,"Human") OR LIMIT-TO (EXACTKEYWORD,"Adult"))</p>
Embase via OVID	<p>1. blood pressure/ or arterial pressure/ or hemodynamics/ or blood pressure measurement/ or blood pressure monitoring/ or hypertension/ or elevated blood pressure/</p> <p>2. (blood pressure or arterial pressure or h?emodynamics or hypertensi* or hypotensi*).tw.</p> <p>3. exercise test/ or aerobic exercise/ or exercise/ or cardiopulmonary exercise test/ or dynamic exercise/ or exercise tolerance/ or running/ or walking/ or cycling/</p> <p>4. (exercise or exercise test or cardiopulmonary test or stress test or running or walking or treadmill or cycling).tw.</p> <p>5. 1 and 3</p> <p>6. 1 and 4</p> <p>7. 2 and 3</p> <p>8. ((blood pressure or arterial pressure or h?emodynamics or hypertensi* or hypotensi*) adj5 (exercise or exercise test or cardiopulmonary test or stress test or running or walking or treadmill or cycling)).tw.</p> <p>9. 5 or 6 or 7 or 8</p> <p>10. cardiomegaly/ or cardiomyopathy/ or heart ventricle remodeling/ or heart ventricle hypertrophy/</p> <p>11. (cardiomegaly or cardiomyopathy or (ventric* adj2 (hypertrophy or wall thickness or structure or mass or mass index or remodeling))).tw.</p>

12. 10 or 11
 13. atherosclerotic plaque/ or atherosclerosis/ or coronary artery atherosclerosis/ or aortic atherosclerosis/ or carotid atherosclerosis/ or pulse wave/ or arterial wall thickness/ or arterial stiffness/ or vascular resistance/ or artery compliance/ or vascular endothelium/ or vascular fibrosis/ or blood vessel calcification/ or coronary artery calcium score/
 14. (Atherosclerosis or Pulse Wave Analysis or Carotid Intima-Media Thickness or vascular stiffness or vascular resistance or vascular calcification or pulse wave velocity or arterial compliance or arterial stiffness or aortic stiffness endothelial function or vascular function or endothelial dysfunction or vascular dysfunction or carotid stiffness or coronary calcium score or ankle-to-brachial index).tw.
 15. 13 or 14
 16. glucose blood level/ or glucose/ or blood glucose monitoring/ or glucose level/ or glucose intolerance/
 17. cholesterol blood level/ or cholesterol level/ or low density lipoprotein cholesterol/ or high density lipoprotein cholesterol/ or low density lipoprotein cholesterol level/ or cholesterol/ or high density lipoprotein cholesterol level/ or total cholesterol level/
 18. triacylglycerol/
 19. glycosylated hemoglobin/ or hemoglobin A1c/
 20. creatinine blood level/ or creatinine/
 21. glomerulus filtration rate/
 22. renin angiotensin aldosterone system/ or aldosterone/ or aldosterone blood level/
 23. renin/ or plasma renin activity/
 24. proteinuria/
 25. albuminuria/
 26. (glucose or cholesterol or lipoprotein or triglyceride or glycated hemoglobin or glycated haemoglobin or hba1c or creatinine or Glomerular Filtration Rate or Aldosterone or Insulin or Renin or Proteinuria or albuminuria).tw.
 27. 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26
 28. 12 or 15 or 27
 29. 9 and 28
 30. limit 29 to "humans only (removes records about animals)"
 31. limit 30 to english
 32. limit 31 to (adult <18 to 64 years> or aged <65+ years>)
-

Appendix Table 3.2. Characteristics of 49 studies reporting exercise blood pressure and cardiac structure.

#	first author, year	Population type	Participant , n	Male, n (%)	Age (years)
1	Bitigen 2007	Non-hypertensive apparently healthy without an HRE	20	11 (55)	47.8 (5)
		Non-hypertensive apparently healthy with an HRE	32	17 (53)	48.7 (7)
2	Campbell 1999	Mixed BP status otherwise apparently healthy males with an HRE	746	746 (100)	58 (11)
		Mixed BP status otherwise apparently healthy males without an HRE	1470	1470 (100)	58 (12)
		Mixed BP status otherwise apparently healthy females with an HRE	573	0	61 (11)
		Mixed BP status otherwise apparently healthy females without an HRE	656	0	57 (12)
3	Cardillo 1996	Hypertensive otherwise apparently healthy	63	43 (68)	46.6 (8.8)
		Non-hypertensive apparently healthy	32	22 (69)	43.8 (7.3)
4	Caselli 2016	Non-hypertensive athletic with an HRE	142	1190 (63)	26 (6)
		Non-hypertensive athletic without an HRE	1734		24 (6)
5	Chang 2003	Non-hypertensive apparently healthy without an HRE	35	66 (94)	45.4 (8.1)
		Non-hypertensive apparently healthy with an HRE	35		
6	Chang 2004	Non-hypertensive apparently healthy without an HRE	25	23 (92)	46.7 (8.7)
		Non-hypertensive apparently healthy with an HRE	25	23 (92)	44.7 (8.8)
7	Currie 2017	Non-hypertensive endurance-trained athletes with an HRE	22	16 (73)	56 (6)
		Non-hypertensive endurance-trained athletes without an HRE	11	8 (73)	55 (5)
8	Douglas 1986	Ultra-endurance athletes	14		
9	Duyuler 2017	Non-hypertensive apparently healthy without an HRE	44	28 (64)	48.0 (7.0)
		Non-hypertensive apparently healthy with an HRE	40	20 (50)	47.7 (10.0)
10	Fagard 1995	Non-hypertensive or borderline hypertension otherwise apparently healthy	92	92 (100)	22 (4)
11	Fazio 1995	Non-hypertensive apparently healthy without an HRE	20	14 (70)	40 (6)
		Prehypertensive otherwise apparently healthy without an HRE	11	8 (73)	38 (7)
		Prehypertensive otherwise apparently healthy with an HRE	9	6 (67)	41 (9)
12	Giaconci 1989	Borderline hypertension otherwise apparently healthy	18	18 (100)	45 (range: 33- 59)
13	Gosse 1989	Non-hypertensive apparently healthy	23	14 (61)	25 (5)

14	Gottdiener 1990	Non-hypertensive apparently healthy with an HRE	22	39 (100)	44.6 (8.5)
		Non-hypertensive apparently healthy without an HRE	17		
15	Grossman 1994	Untreated Essential hypertension otherwise apparently healthy	60	47 (78)	40 (2)
16	Herkenhoff 1997	Non-hypertensive apparently healthy with an HRE	20	20 (100)	44 (3)
		Non-hypertensive apparently healthy without an HRE	20	20 (100)	43 (3)
17	Karjalainen 1997	Prehypertensive otherwise apparently healthy endurance athletes	32	32 (100)	26 (3)
		Prehypertensive otherwise apparently healthy sedentary	15	15 (100)	26 (3)
18	Kilicaslan 2015	Non-hypertensive suspected coronary artery disease with an HRE	33	14 (47)	45.3 (10.3)
		Non-hypertensive suspected coronary artery disease without an HRE	33	17 (52)	40.7 (9.6)
19	Knutsen 1991	Moderate hypertension with no signs of secondary hypertension, renal disease/damage.	87	87 (100)	45 (range: 22-64)
20	Kokkinos 2007	Prehypertensive otherwise apparently healthy with an HRE	430	408 (52)	52 (10)
		Prehypertensive otherwise apparently healthy without an HRE	360		
21	Kop 2000	Non-hypertensive apparently healthy	36	13 (36)	33.9 (9.4)
22	Lauer 1992	Non-hypertensive apparently healthy males with an HRE	122	860 (100)	41 (9)
		Non-hypertensive apparently healthy males without an HRE	738		
		Non-hypertensive apparently healthy females with an HRE	67	0 (0)	
		Non-hypertensive apparently healthy females without an HRE	1051		
23	Lim 2001	Hypertensive otherwise apparently healthy	49	32 (65)	45(12)
24	Malek 2019	Normotensive endurance athletes without an HRE	17	30 (100)	39 (range: 36.3-43.0)
		Normotensive endurance athletes with an HRE	3		
		High-normal BP endurance athletes without an HRE	7		43 (range: 42.0-48.3)
		High-normal BP endurance athletes with an HRE	3		
25	Markovitz 1996	Non-hypertensive apparently healthy black males only	781	781 (100)	29.3 (3.7)
		Non-hypertensive apparently healthy white males only	945	945 (100)	30.5 (3.8)
		Non-hypertensive apparently healthy black female only	992	0 (0)	29.5 (3.9)
		Non-hypertensive apparently healthy white female only	1024	0 (0)	30.6 (3.4)

26	Martinez-Vea 2004	Non-hypertensive with polycystic kidney disease with an HRE	6	9 (50)	24.1 (6)
		Non-hypertensive with polycystic kidney disease without an HRE	12		
		Non-hypertensive apparently healthy with an HRE	5	9 (50)	24.5 (6)
		Non-hypertensive apparently healthy without an HRE	13		
27	Michelsen 1990	Non-hypertensive apparently healthy	95	95 (100)	44 (range: 21-69)
28	Mazic 2015	Non-hypertensive apparently healthy	95	95 (100)	23 (5)
29	Miyai 2005	Non-hypertensive apparently healthy with an HRE	27		39.9 (1)
		Non-hypertensive apparently healthy without an HRE	27	54 (100)	40.0 (1)
30	Mizuno 2016	Hypertensive otherwise apparently health with an HRE	40	25	62.0 (4.6)
		Hypertensive otherwise apparently health without an HRE	63	36	61.6 (4.3)
31	Molina 1999	Non-hypertensive apparently healthy with an HRE	43	43 (100)	42.44 (7.85)
		Non-hypertensive apparently healthy without an HRE	275	275 (100)	36.95 (8.60)
32	Mottram 2004	Hypertensive with mixed health conditions and with an HRE	22	9 (41)	58 (11)
		Prehypertensive with mixed health conditions with an HRE	19	9 (47)	53 (9)
		Non-hypertensive with mixed health conditions without an HRE	17	6 (35)	53 (5)
33	Naimark 1990	Non-hypertensive apparently healthy males with an HRE	98	98 (100)	43.0 (1.1)
		Non-hypertensive apparently healthy males without an HRE	64	64 (100)	45.1 (1.4)
		Non-hypertensive apparently healthy females with an HRE	24	0	54.8 (2.4)
		Non-hypertensive apparently healthy females without an HRE	110	0	42.1 (1.0)
34	Naimark 1991	Apparently healthy with normotension (77%) or hypertension (23%)	77	77 (100)	46 (11)
35	Oh 2018	Non-hypertensive apparently healthy	7923	5498 (69.4)	50.0 (7.5)
36	Papademetrio 1989	Mild-to-moderate hypertension otherwise apparently healthy	19	NR	NR
37	Pierson 2004	Sedentary overweight with untreated high normal blood pressure or stage 1-2 hypertension (resting BP: 130-180/85-110 mmHg)	80	37 (46)	46.2 (8.3)
38	Polonia 1992	Non-hypertensive apparently healthy without an HRE	60	60 (100)	50 (8)
		Non-hypertensive apparently healthy with an HRE	60	60 (100)	50 (8)
		Hypertensive apparently healthy with an HRE	40	60 (100)	51 (10)

39	Ren 1985	Hypertensive otherwise apparently healthy	67	26 (39)	NR
40	Schmieder 1990	Mild-to-moderate hypertension apparently healthy	73	73 (100)	NR
41	Scott 2008	Non-hypertensive with an HRE (includes people with Type 2 diabetes mellitus)	54		
		Non-hypertensive without an HRE (includes people with Type 2 diabetes mellitus)	92	91 (62.3)	NR
42	Sharman 2011	Individuals with masked hypertension	42	29 (69)	54 (9)
		Individuals with normotension	30	14 (47)	54 (9)
43	Shim 2008	Not hypertensive and apparently healthy with an HRE	36	18 (50)	50 (16)
		Not hypertensive and apparently healthy without an HRE	36	50 (50)	50 (16)
44	Smith 1992	Uncomplicated essential mild-to-moderate hypertension otherwise apparently healthy	65	65 (65)	
45	Sung 2003	Untreated high normal BP (130-139/85-89 mmHg) or mild hypertension (140-159/90-99 mmHg) otherwise apparently health.	77	34 (44)	Male: 62 (5); female: 65 (6)
46	Takamura 2008	Not hypertensive without an HRE	30	30 (100)	60 (7)
		Not hypertensive with an HRE	25	25 (100)	65 (7)
		Hypertensive with an HRE	74	74 (100)	64 (7)
47	Tsiachris 2010	Untreated hypertensive otherwise apparently healthy with an HRE	36	18 (50)	55.4 (9)
		Untreated hypertensive otherwise apparently healthy without an HRE	63	43 (68)	48 (9.4)
48A	Vriend 2004	Post-coarctectomy with mixed BP status	144	91 (63)	31.5 (11.2)
48B	Vriend 2004	Non-hypertensive post-coarctectomy males with an HRE	13	48 (100)	
		Non-hypertensive post-coarctectomy males without an HRE	5		
49	Yang 2014	Non-hypertensive apparently healthy with an HRE	19	15 (79)	48 (11)
		Non-hypertensive apparently healthy without an HRE	152	82 (54)	48 (8)

Appendix Table 3.2 cont.

#	Outcome measurement method	Exercise test modality	Exercise test protocol	Intensity exercise BP measured	Exercise BP Measurement method
1	M-mode Transthoracic Echocardiograph	Treadmill	Modified Bruce	Peak	Automated
2	Two-dimensional m-mode Echocardiograph	Treadmill	Bruce and modified Bruce	Peak	NR
3	Two-dimensional m-mode Echocardiograph	Bicycle	50W for 5 mins then 100W for 5 mins	Peak	NR
4	Two-dimensional Echocardiograph	Bicycle	0.5W/kg / 2 minutes	Peak	Manual
5	Echocardiograph (unclear method)	Treadmill	Bruce	Peak	NR
6	Electrocardiography and echocardiography (unclear method)	Treadmill	Bruce	Peak	NR
7	Two-dimensional transthoracic echocardiography	Treadmill	5-minute warmup (2 minutes at 3mph then 3 minutes at 5mph), the test began at 0% incline and a self-selected constant speed. Grade increased by 2% every 2 minutes until 8 minutes, after which it increased by 1% every minute until volitional exhaustion	Peak	Automated
8	M-Mode Echocardiograph	Bicycle	Steady state at 52% VO _{2max}	Submaximal (52% VO _{2max})	NR
9	Transthoracic echocardiography	Treadmill	Modified Bruce	Peak	NR
10	Two-dimensional m-mode Echocardiograph	Bicycle	20W / minute	Submaximal (40W)	Manual
11	Two-dimensional m-mode Echocardiograph	Bicycle	25W / 2 minutes.	Submaximal (100W)	Manual
12	Echocardiograph (unclear method)	Bicycle	Graded – NR	Submaximal and Peak	Automated

13	Two-dimensional m-mode Echocardiograph	Bicycle	Male: 30 W/ 3 minutes; Female: 20 W/ 3 minutes	Peak	NR
14	Two-dimensional m-mode Echocardiograph	Treadmill	Bruce	Peak	Manual
15	Two-dimensional m-mode Echocardiograph	Treadmill	Bruce	Peak	Manual
16	Two-dimensional m-mode Echocardiograph	Bicycle	Astrand & Rhymin's adapted	Peak	NR
17	Two-dimensional m-mode Echocardiograph	Bicycle	50 W/ 3 minutes.	Peak	Manual
18	Two-dimensional m-mode Echocardiograph	Treadmill	Bruce	Peak	Automated
19	Two-dimensional m-mode Echocardiograph	Bicycle	50W/ 4 minutes	Submaximal (50W)	Manual
20	Echocardiograph (unclear method)	Treadmill	Bruce	Submaximal (5 mets) and Peak	Manual
21	Two-dimensional m-mode Echocardiograph	Treadmill	Bruce	Submaximal (7 mets) and Peak	Automated
22	Two-dimensional m-mode Echocardiograph	Treadmill	Bruce	Peak	NR
23	Two-dimensional m-mode Echocardiograph	Treadmill	Bruce	Submaximal (Stage 1) and Peak	Manual
24	Magnetic resonance imaging	Treadmill	NR	Peak	NR
25	Two-dimensional m-mode Echocardiograph	Treadmill	Nine 2-minute increments. Stage 1: 3.0 miles/hr at 2% grade; stages 2-6 were 3.4miles/hr beginning at a 6% grade and increased by 4% each stage so that stage 6 was at a 22% grade;	Peak	Manual

			stages 7 and 8 were 4.2 miles/hr at 22% and 25% grades; stage 9 was 5.6 miles/hr at 25% grade.		
26	Two-dimensional m-mode Echocardiograph	Treadmill	Bruce	Submaximal (Stage 3) and Peak	Manual
27	m-mode Echocardiography	Bicycle	300 kpm / 4 minutes	Submaximal (300kpm) and Peak	NR
28	Echocardiograph	Treadmill	Graded	Maximal	Manual
29	Two-dimensional m-mode Echocardiograph	Bicycle	25W/3mins	Submaximal (100W)	Manual
30	Two-dimensional m-mode Echocardiograph	Treadmill	Bruce	Peak	Manual
31	Two-dimensional m-mode Echocardiograph	Treadmill	Bruce	Peak	Manual
32	Two-dimensional m-mode Echocardiograph	Treadmill	Bruce	Peak	Manual
33	Electrocardiograph	Treadmill	Balke	Peak	Manual
34	Two-dimensional m-mode Echocardiograph	Bicycle	50W / 6 minutes	Peak	Manual
35	Two-dimensional m-mode Echocardiograph	Treadmill	Bruce	Submaximal (Stage 1) and Peak	Manual
36	Two-dimensional m-mode Echocardiograph	Treadmill	Bruce	Submaximal (Stage 1) and Peak	NR
37	Echocardiograph	Treadmill	Duke-Wake-Forest	Peak	Automated
38	Two-dimensional m-mode Echocardiograph	Treadmill	Bruce	Submaximal (Stage 1) and Peak	NR
39	Two-dimensional m-mode Echocardiograph	Treadmill	Bruce	Peak	Manual

40	Two-dimensional m-mode Echocardiograph	Bicycle	Steady state at 100W	Submaximal (100W)	Manual
41	Two-dimensional m-mode Echocardiograph	Treadmill	NR	Peak	Manual
42	Two-dimensional transthoracic Echocardiograph	Treadmill	Bruce	Peak	Manual
43	Two-dimensional Echocardiograph	Supine Bicycle	25W/3mins	Peak	Automated
44	Two-dimensional m-mode Echocardiograph	Treadmill	Modified Bulke Ware	Peak	Manual
45	Magnetic resonance imaging	Treadmill	Modified Bulke	Peak	NR
46	Transthoracic Echocardiograph	Treadmill	Bruce	Peak	Manual
47	Echocardiograph	Treadmill	Modified Bulke	Maximal	Automated
48	M-mode Echocardiograph	Treadmill	Bruce	Peak	Manual
49	Two-dimensional m-mode Echocardiograph	Treadmill	Bruce	Peak	Manual

Appendix Table 3.2 cont.

#	Hypertensive exercise BP response threshold	Left ventricle hypertrophy threshold	Analysis type	Study quality (Newcastle Ottawa scale)	Included in meta-analysis
1	Male $\geq 210/105$ mmHg; Female $\geq 190/105$ mmHg		Categorical only	5.5	Yes
2	Male: Systolic BP ≥ 210 mmHg; Female: Systolic BP ≥ 190 mmHg	Left ventricular mass index > 143 g/m	Categorical only	6.5	Yes
3	NR		Continuous only	5.5	Yes
4	Male: Systolic BP ≥ 220 mmHg; Female: Systolic BP ≥ 200 mmHg		Categorical only	3.5	Yes
5	Male: Systolic BP ≥ 210 mmHg; Female: Systolic BP ≥ 190 mmHg	Left ventricular mass > 215 g	Categorical only	6.5	Yes

6	Male: Systolic BP \geq 210 mmHg; Female: Systolic BP \geq 190 mmHg	Undefined	Categorical only	6.5	Yes
7	Male: Systolic BP \geq 210 mmHg; Female: Systolic BP \geq 190 mmHg		Categorical only	5	Yes
8	NR		Continuous only	7	Yes
9	Male: Systolic BP \geq 210 mmHg; Female: Systolic BP \geq 190 mmHg		Categorical only	6	Yes
10	NR		Continuous only	2.5	Yes
11	Systolic BP \geq 192 mmHg (values > mean exercise systolic BP in Normotensive group plus 2 standard deviations)		Categorical only	7.5	Yes
12	NR		Continuous only	2.5	No
13	NR		Continuous only	2.5	Yes
14	Systolic BP \geq 210 mmHg	Left ventricular mass index > 134 g/m ²	Categorical and continuous	5	Yes
15	Systolic BP \geq 210 mmHg	left ventricular mass index was >134 g/m ² for men and >110 g/m ² for women	Categorical and continuous	5	Yes
16	Systolic BP \geq 220 mmHg		Categorical only	5.5	Yes
17	NR		Continuous only	7.5	Yes
18	Male: Systolic BP \geq 210 mmHg; Female: Systolic BP \geq 190 mmHg		Categorical only	5.5	Yes
19	NR		Continuous only	6	Yes
20	Systolic BP \geq 150 mmHg		Categorical and continuous	4.5	Yes
21	NR		Continuous only	2.5	Yes
22	Male: Systolic BP \geq 210 mmHg; Female: Systolic BP \geq 190 mmHg		Categorical and continuous	6	Yes
23	NR		Continuous only	4.5	Yes

24	Systolic BP \geq 210 mmHg or change in diastolic BP $>$ 10 mmHg from compared to resting BP		categorical only	5.5	Yes
25	NR		Categorical only	5.5	No
26	Male: Systolic BP \geq 210 mmHg; Female: Systolic BP \geq 190 mmHg		Categorical and continuous	7.5	Yes
27	NA		Continuous only	5	Yes
28	NR		Continuous only	2.5	Yes
29	either systolic BP or diastolic BP above the 95th percentile values		Categorical only	6	Yes
30	Male: Systolic BP \geq 210/105 mmHg; Female: Systolic BP \geq 190/105 mmHg		Categorical only	5	Yes
31	Systolic BP \geq 210 mmHg	Left ventricular mass index $> 134 \text{ g/m}^2$	Categorical and continuous	6	Yes
32	Male: Systolic BP \geq 210/105 mmHg; Female: Systolic BP \geq 190/105 mmHg		Categorical only	5	Yes
33	Systolic BP \geq 200 mmHg	$R_{v5}/R_{v6} = 26\text{mm}$, $R_{aVL} = 11 \text{ mm}$. $R_{v5}/R_{v6} + S_{v1} = 35 \text{ mm}$ or $R_1 + S_3 = 24 \text{ mm}$	Categorical only	4.5	Yes
34	Systolic BP \geq 200 mmHg		Continuous only	3	Yes
35	NR		Continuous only	2.5	Yes
36	NR		Continuous only	2	Yes
37	NR		Continuous only	2.5	No
38	Systolic BP \geq 210 mmHg	Left ventricular mass index $> 134 \text{ g/m}^2$	Categorical only	4.5	Yes
39	Systolic BP \geq 190 mmHg	Left ventricular mass index $> 100 \text{ g/m}^2$	Categorical and continuous	7	Yes
40	\geq 210/110 mmHg		Continuous only	2	Yes

41	Male $\geq 210/105$ mmHg; Female $\geq 190/105$ mmHg	Left ventricular mass index $>49.2 \text{ g/m}^{2.7}$ for men and $>46.7 \text{ g/m}^{2.7}$ for women.	Categorical and continuous	6	Yes
42	Male $\geq 210/105$ mmHg; Female $\geq 190/105$ mmHg		Continuous	6.5	No
43	Difference of peak and baseline systolic BP ≥ 60 mm Hg in men and ≥ 50 mm Hg in women compared to resting BP		Categorical only	5	Yes
44	Systolic BP ≥ 210 mmHg		Continuous only	5	Yes
45	NR		Continuous only	4.5	Yes
46	Male: Systolic BP ≥ 210 mmHg; Female: Systolic BP ≥ 190 mmHg		Categorical only	5.5	Yes
47	Male: Systolic BP $\geq 210/105$ mmHg; Female: Systolic BP $\geq 190/105$ mmHg		Categorical only	5	Yes
48A	Systolic BP ≥ 200 mmHg		Categorical and continuous	2.5	Yes
48B	Systolic BP ≥ 200 mmHg		Categorical only		Yes
49	Male: Systolic BP ≥ 200 mmHg; Female: Systolic BP ≥ 190 mmHg		Categorical only	5.5	Yes

BP, blood pressure; HRE, hypertensive response to exercise; NR, not reported Study populations classified as “hypertensive” based on a resting BP $\geq 140/90$ mmHg or prescribed antihypertensive medication. Study populations were classified “apparently health” include those with no history of chronic disease. Study populations classified a “mixed” status when analyses comprised of individuals with and without resting BP or various health statuses, e.g. analyses including people with and without a chronic disease. Analysis type refers to data being extracted from each study with categorical denoting cardiac structure between those with and without an HRE and continuous denoting the correlation between exercise systolic BP and cardiac structure.

Appendix Table 3.3. Correlation between cardiac structure parameter and exercise blood pressure (BP) across different study populations (based on resting BP and health status), various exercise test modalities (i.e. exercise intensity when blood pressure was measured and exercise modality) and study quality (assessed using the Newcastle-Ottawa Scale).

		Number of studies	Correlation coefficient (r)	95% confidence interval		P-value for correlation	Heterogeneity explained, R ² (%)
Subgroup							
Left ventricle mass							
Resting BP status†	Not hypertensive	5	0.48	0.39	0.57	0.003	48
	Hypertensive	4	0.16	-0.14	0.45		
	Mixed	1	0.36	0.18	0.54		
Health status	Apparently healthy	9	0.33	0.22	0.44	0.002	40
	Athletic	1	0.88	0.76	1		
	Chronic disease	1	0.27	0.12	0.42		
	Mixed	1	0.51	0.29	0.29		
Exercise intensity	Submaximal	6	0.39	0.12	0.66	0.825	0
	Peak	6	0.39	0.27	0.5		
Exercise modality	Treadmill	7	0.38	0.27	0.49	0.762	7
	Bicycle	5	0.39	0.1	0.68		
Study quality		12	0.09	0.04	0.14	<0.01	43
Left ventricle mass indexed by body surface area							
Resting BP status	Not hypertensive	7	0.34	0.25	0.44	0.465	38
	Hypertensive	4	0.42	0.27	0.56		
	Mixed	3	0.32	0.16	0.48		
Health status	Athletic	1	0.17	0.09	0.25	0.123	13
	Apparently healthy	11	0.37	0.29	0.46		
	Mixed	2	0.5	0.34	0.66		
Exercise intensity	Submaximal	6	0.22	0.14	0.29	0.008	51
	Peak	8	0.44	0.3	0.58		
Exercise modality	Treadmill	9	0.3	0.22	0.38	0.014	42
	Bicycle	5	0.47	0.39	0.56		
Study quality		14	0.06	0.02	0.10	<0.01	61
Left ventricle mass indexed by height ^{2,7}							
Resting BP status	Not hypertensive	2	0.47	0.3	0.64	0.248	31
	Hypertensive	1	0.29	0.11	0.47		
Health status	Apparently healthy	2	0.56	0.43	0.68	0.002	71
	Mixed	1	0.18	0.02	0.34		
Exercise intensity	Submaximal	1	0.67	0.63	0.71	<0.001	100
	Peak	2	0.23	0.11	0.34		
Study quality		3	-0.34	-0.44	0.24	<0.01	100
Relative wall thickness							

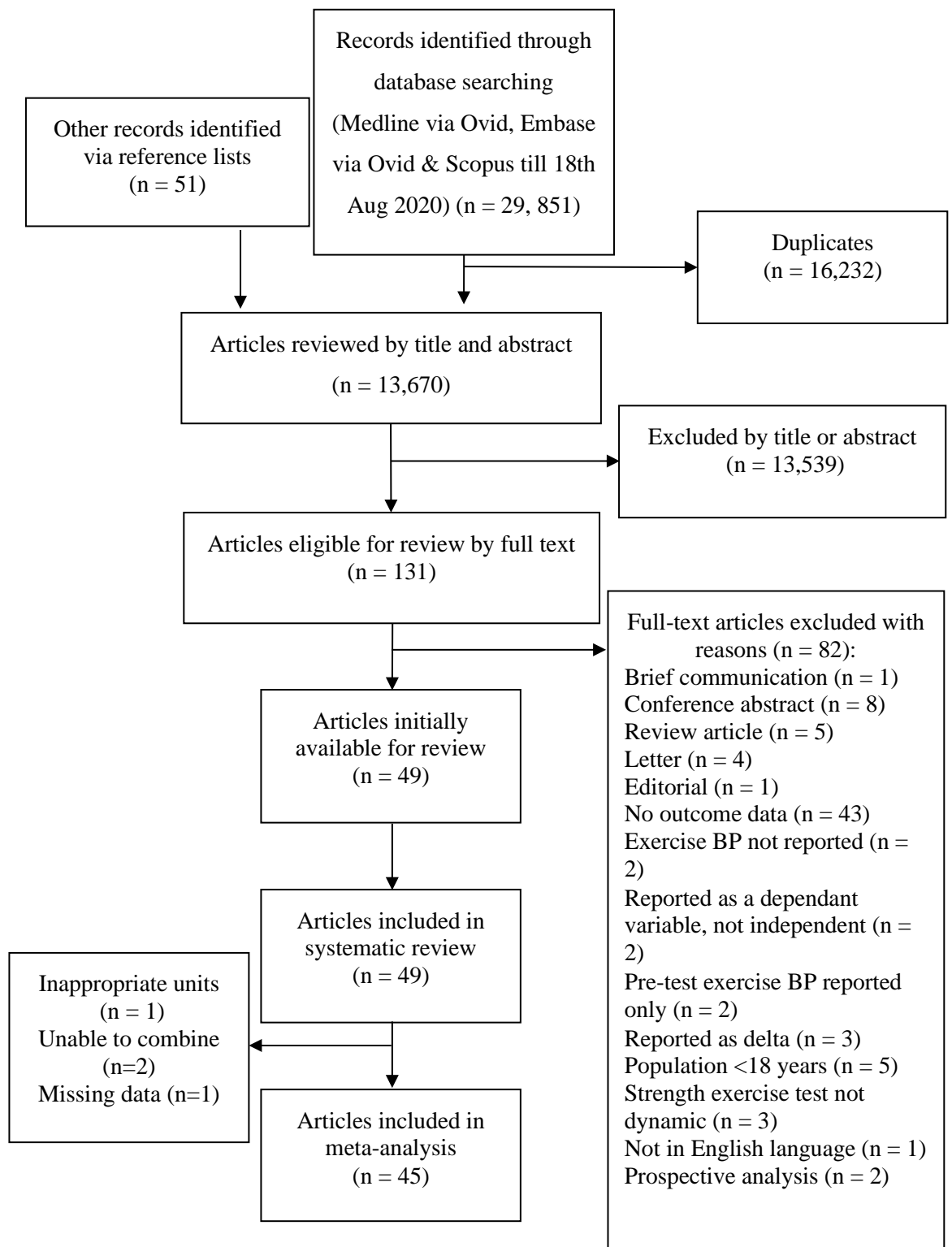
Resting BP status	Not hypertensive	1	0.33	0.18	0.48	0.002	100
	Mixed	2	0.07	-0.02	0.17		
Exercise modality	Treadmill	2	0.17	-0.01	0.35	0.793	9
	Bicycle	1	0.21	0.02	0.4		
Study quality		3	0.29	0.13	0.46	<0.01	100
Posterior wall thickness							
Health status	Athletic	1	0.56	0.19	0.93	0.227	92
	Apparently healthy	3	0.31	0.13	0.5		
Exercise intensity	Submaximal	3	0.44	0.27	0.62	0.062	100
	Peak	1	0.15	-0.1	0.4		
Study quality		4	-0.03	-0.13	0.08	0.64	23
Interventricular septal thickness							
Exercise intensity	Submaximal	2	0.48	0.3	0.67	0.01	100
	Peak	1	0.07	-0.18	0.32		
Study quality		3	-0.09	-0.26	0.09	0.33	41
†two of the 12 available studies did not report a resting BP status and were excluded from meta-regressions							

Appendix Table 3.4. Mean difference in cardiac structure parameter between those with and without a hypertensive response to exercise across different study populations (based on resting blood pressure [BP] and health status), various exercise test modalities (i.e. exercise intensity when blood pressure was measured and exercise modality) and study quality (assessed using the Newcastle-Ottawa Scale).

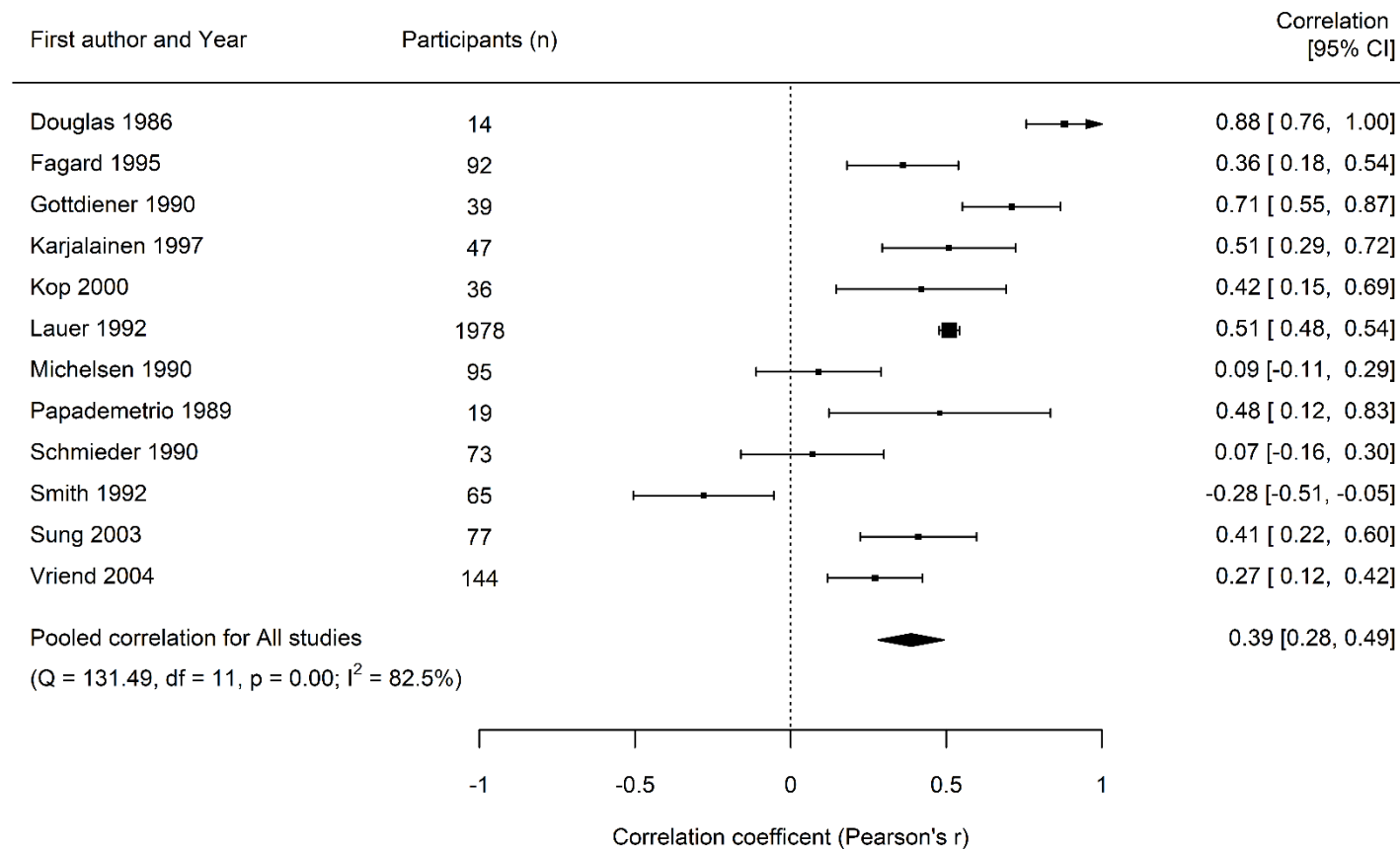
		Number of studies	Mean difference or risk ratio	95% confidence interval		P-value for difference	Heterogeneity explained, R ² (%)
Subgroup							
Left ventricle mass (g)							
Health status	Apparently healthy	3	54.32	38.59	70.06	0.002	40
	Chronic disease	2	20.79	0.28	41.3		
Exercise intensity	Submaximal	1	43	38.47	47.53	0.825	0
	Peak	4	48.26	24.07	72.46		
Study quality		5	0.58	-22.06	23.22	0.96	0
Left ventricle mass indexed by body surface area (g/m ²)							
Resting BP status	Not hypertensive	16	8.04	4.48	11.6	0.055	13
	Hypertensive	3	0.14	-3.42	3.69		
Health status	Athletic	3	5.32	2.08	8.56	0.759	0
	Apparently healthy	13	7.09	2.95	11.24		
	Chronic disease	2	6.15	-2.31	14.6		
	Mixed	2	9.52	1.8	17.24		
Exercise intensity	Submaximal	2	1.33	-8.37	11.03	0.108	0
	Peak	17	8.47	4.56	12.38		
Exercise modality	Treadmill	15	9.43	4.4	14.46	0.065	0
	Bicycle	5	3.06	0.04	6.07		
Study quality		20	-1.75	-5.11	1.61	0.31	0
Left ventricle mass indexed by height ^{2.7} (g/m ^{2.7})							
Resting BP status	Not hypertensive	2	8.8	-0.21	17.8	0.427	17
	Hypertensive	1	2.5	0.03	4.97		
Exercise intensity	Submaximal	1	13.2	11.99	14.41	<0.001	100
	Peak	2	2.93	0.84	5.02		
Study quality		3	-7.05	-13.57	-0.53	0.03	77
Left ventricle hypertrophy (risk ratio)							
Resting BP status	Not hypertensive	7	2.71	2.11	3.49	0.468	0
	Hypertensive	2	2.74	0.24	30.72		
	Mixed	1	1.7	1.19	2.42		
Health status	Apparently healthy	9	2.85	1.93	4.22	0.296	0
	Chronic disease	1	1.7	1.19	2.42		

Study quality		10	0.03	-0.23	0.29	0.82	0
Relative wall thickness							
Resting BP status	Not hypertensive	8	0.02	0.01	0.03	0.061	15
	Hypertensive	2	0	-0.03	0.03		
Health status	Athlete	1	0.01	0	0.02	0.201	0
	Apparently healthy	7	0.02	0.01	0.03		
	Mixed	2	0.04	0.02	0.06		
Exercise intensity	Submaximal	2	0.03	0.03	0.03	0.072	50
	Peak	8	0.02	0.01	0.03		
Exercise modality	Treadmill	5	0.02	0	0.04	0.883	0
	Bicycle	5	0.02	0.01	0.03		
Study quality		10	0.01	0.00	0.01	0.03	51
Posterior wall thickness (mm)							
Resting BP status	Not hypertensive	7	0.82	0.38	1.26	0.351	0
	Hypertensive	1	-0.1	-0.52	0.32		
	Mixed	1	1.47	0.91	2.03		
Health status	Apparently healthy	7	0.69	0.24	1.13	0.331	0
	Mixed	2	1.18	0.59	1.77		
Exercise intensity	Submaximal	3	0.65	0.04	1.27	0.631	0
	Peak	6	0.89	0.16	1.61		
Exercise modality	Treadmill	6	1.11	0.61	1.61	0.01	35
	Bicycle	3	0.23	-0.09	0.54		
Study quality		9	-0.33	-0.71	0.04	0.08	29
Interventricular septal thickness (mm)							
Resting BP status	Not hypertensive	8	0.78	0.41	1.16	0.501	0
	Hypertensive	1	0.1	-0.27	0.47		
	Mixed	1	1.65	0.99	2.3		
Health status	Athletic	1	0.88	-1.09	2.85	0.099	5
	Apparently healthy	7	0.64	0.27	1.02		
	Mixed	2	1.36	0.83	1.88		
Exercise intensity	Submaximal	3	0.62	0.16	1.09	0.474	0
	Peak	7	0.95	0.29	1.61		
Exercise modality	Treadmill	7	1.1	0.69	1.51	0.005	32
	Bicycle	3	0.22	-0.16	0.6		
Study quality		10	-0.3	-0.66	0.06	0.1	11
Left ventricle end-diastolic dimension (mm)							
Resting BP status	Not hypertensive	12	0.83	-0.25	1.91	0.895	0
	Hypertensive	1	0.7	-0.62	2.02		
	Mixed	1	0.48	-1.09	2.05		
	Athlete	1	2	1.14	2.86	0.725	0

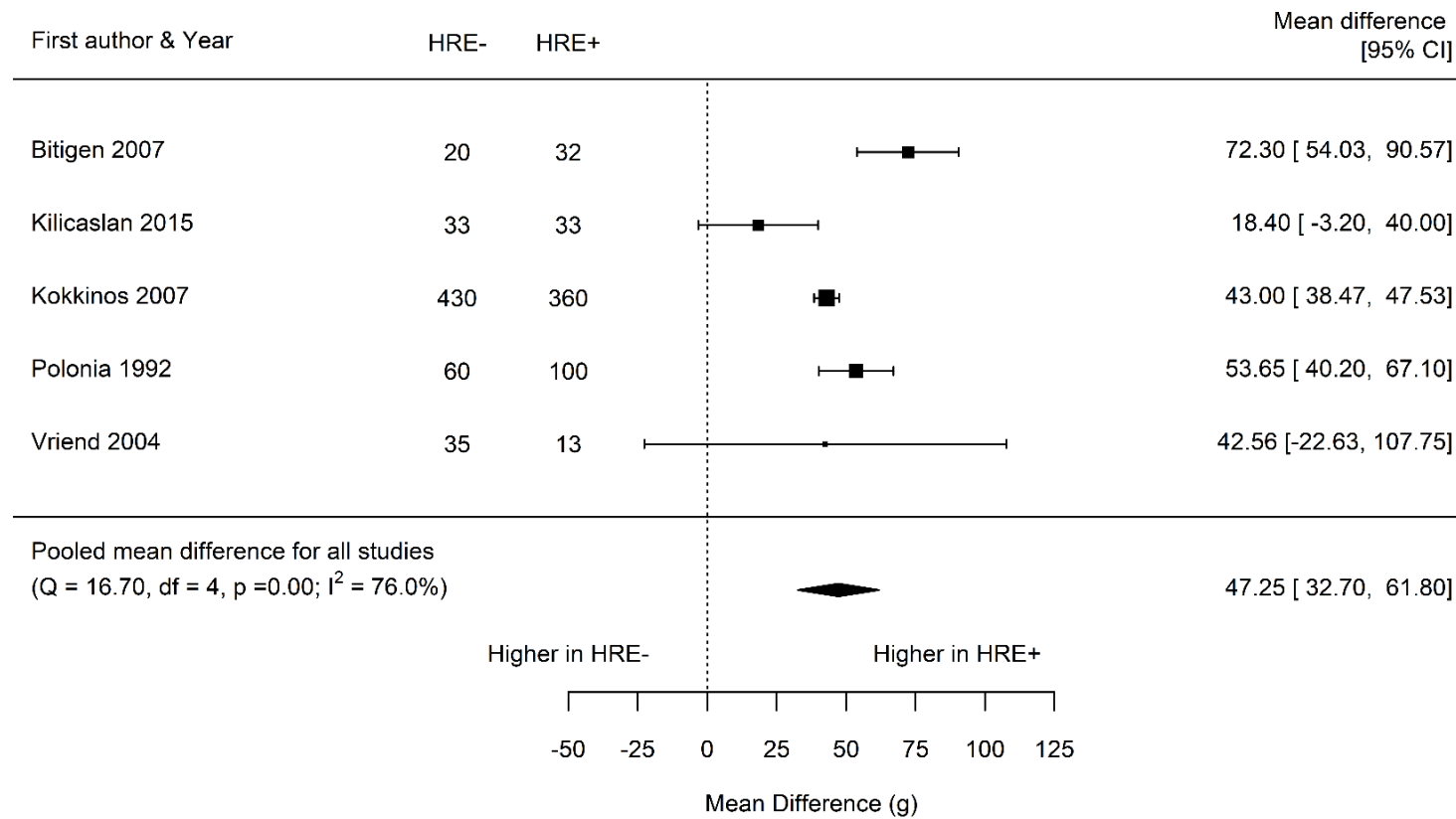
Health status	Apparently healthy	10	0.6	-0.63	1.83		
	Chronic disease	1	1.2	-1.14	3.54		
	Mixed	2	0.77	-0.53	2.08		
Exercise intensity	Submaximal	3	0.03	-2.86	2.92	0.504	0
	Peak	11	1.02	0.44	1.59		
Exercise modality	Treadmill	10	1.35	0.48	2.22	0.055	40
	Bicycle	4	-0.4	-2.09	1.29		
Study quality		14	-1	-1.84	-0.17	0.02	46
Left ventricle end-systolic dimension (mm)							
Resting BP status	Not hypertensive	6	0.7	-1.76	3.16	0.594	0
	Mixed	1	-1.07	-2.6	0.45		
Health status	Apparently healthy	5	0.74	-2.02	3.51	0.639	0
	Chronic disease	1	0.5	-1.35	2.35		
	Mixed	1	-1.07	-2.6	0.45		
Exercise intensity	Submaximal	2	-0.1	-5	4.8	0.767	0
	Peak	5	0.65	-0.57	1.87		
Exercise modality	Treadmill	6	1.03	-0.22	2.29	0.018	77
	Bicycle	1	-2.6	-3.08	-2.12		
Study quality		6	-2.07	-3.86	-0.27	0.02	79
Left atrial size (mm)							
Resting BP status	Not hypertensive	7	2.05	1	3.1	0.281	9.218
	Mixed	1	3.73	1.97	5.48		
Health status	Apparently healthy	4	2.89	1.75	4.02	0.937	0
	Athletic	2	0.73	-0.39	1.84		
	Chronic disease	1	1.8	-0.06	5.48		
	Mixed	1	3.73	1.97	3.66		
Exercise modality	Treadmill	7	2.52	0.53	0.53	0.226	21
	Bicycle	1	1	0.32	1.68		
Study quality		7	0.03	-1.39	1.44	0.97	0



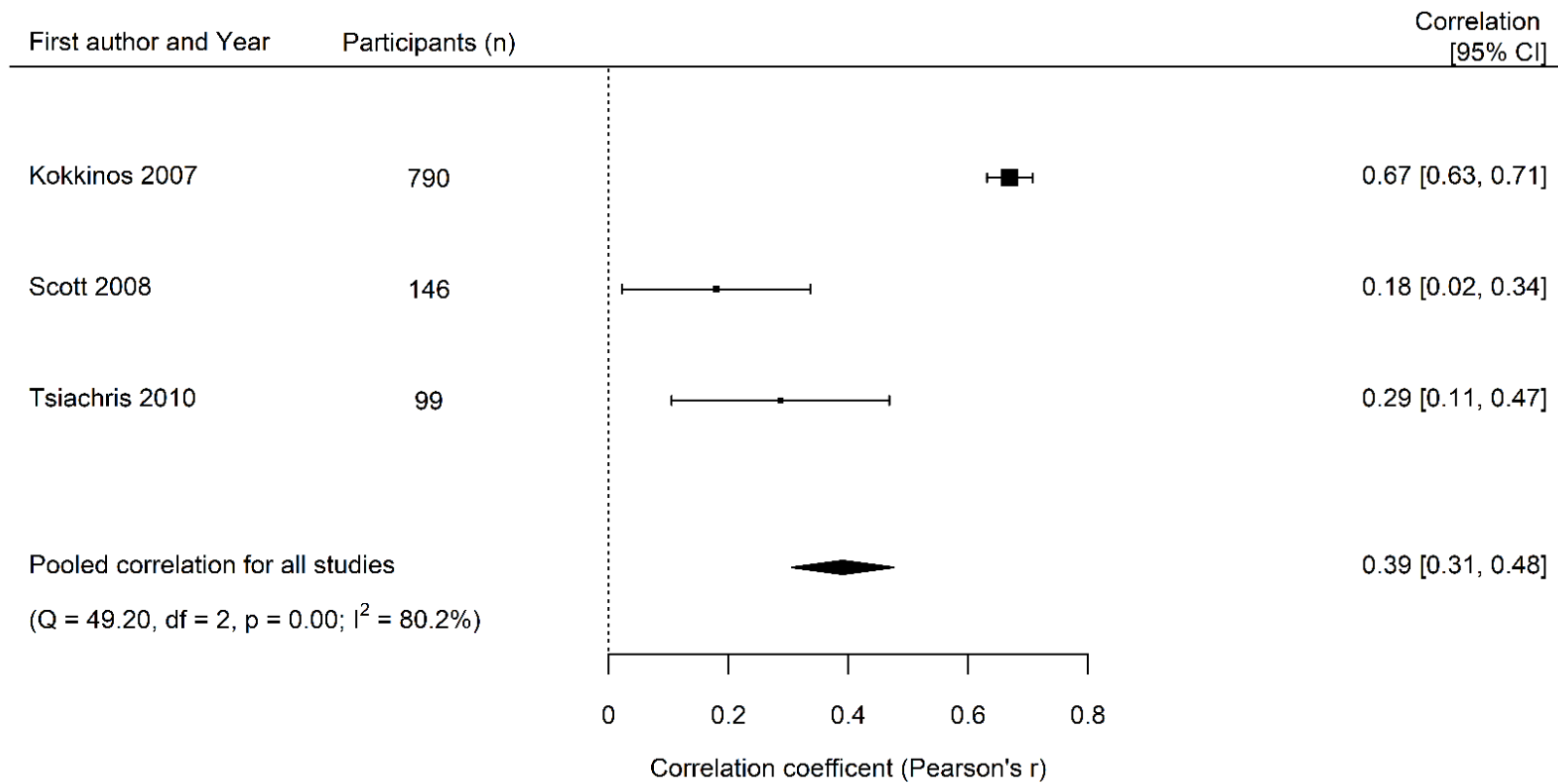
Appendix Figure 3.1. PRISMA flow chart of literature search and selection of articles included in the systematic review and meta-analysis.



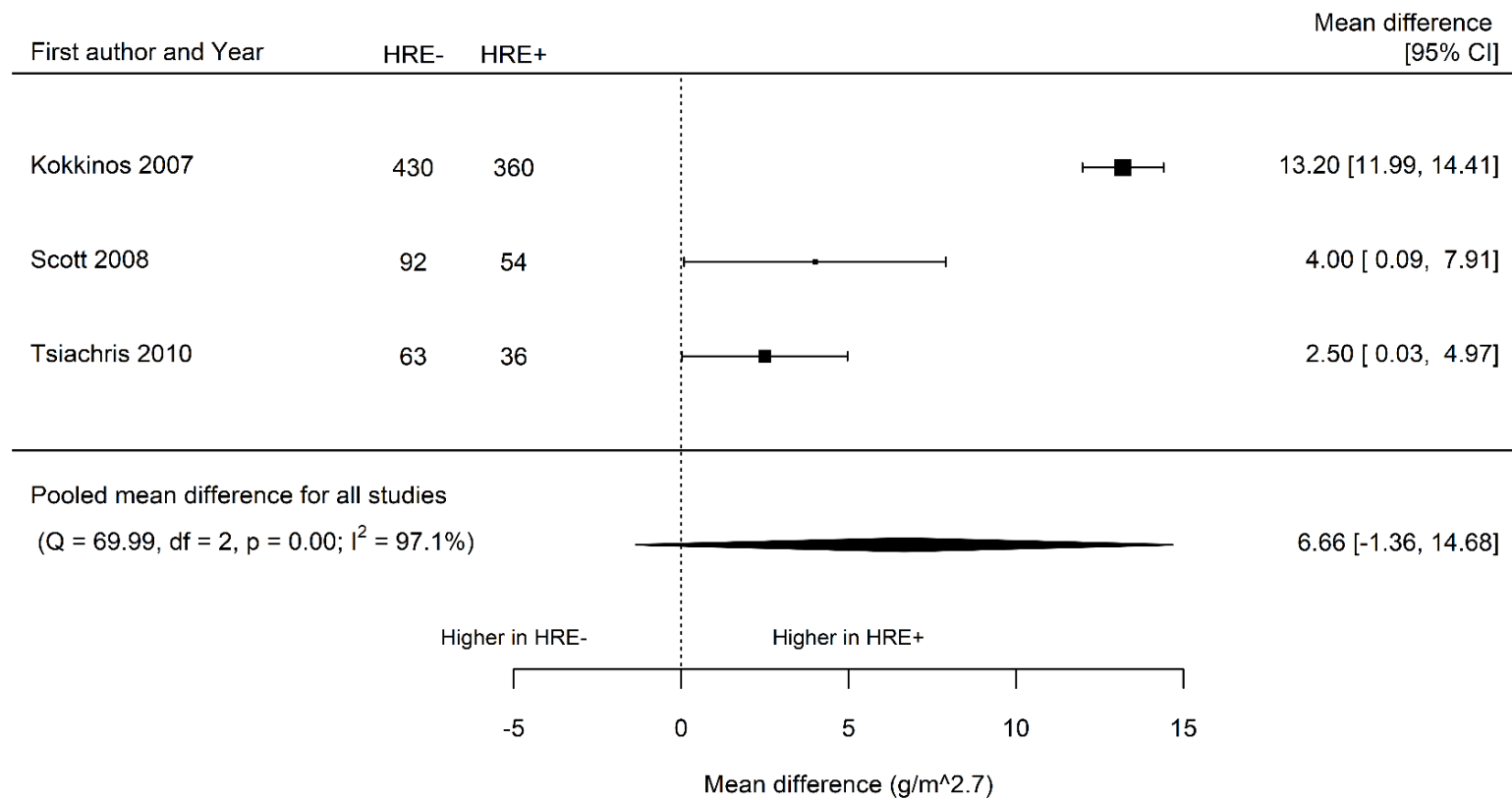
Appendix Figure 3.2. Random effect estimate for the unadjusted strength of association and 95% confidence intervals (CI) between exercise blood pressure and left ventricle mass.



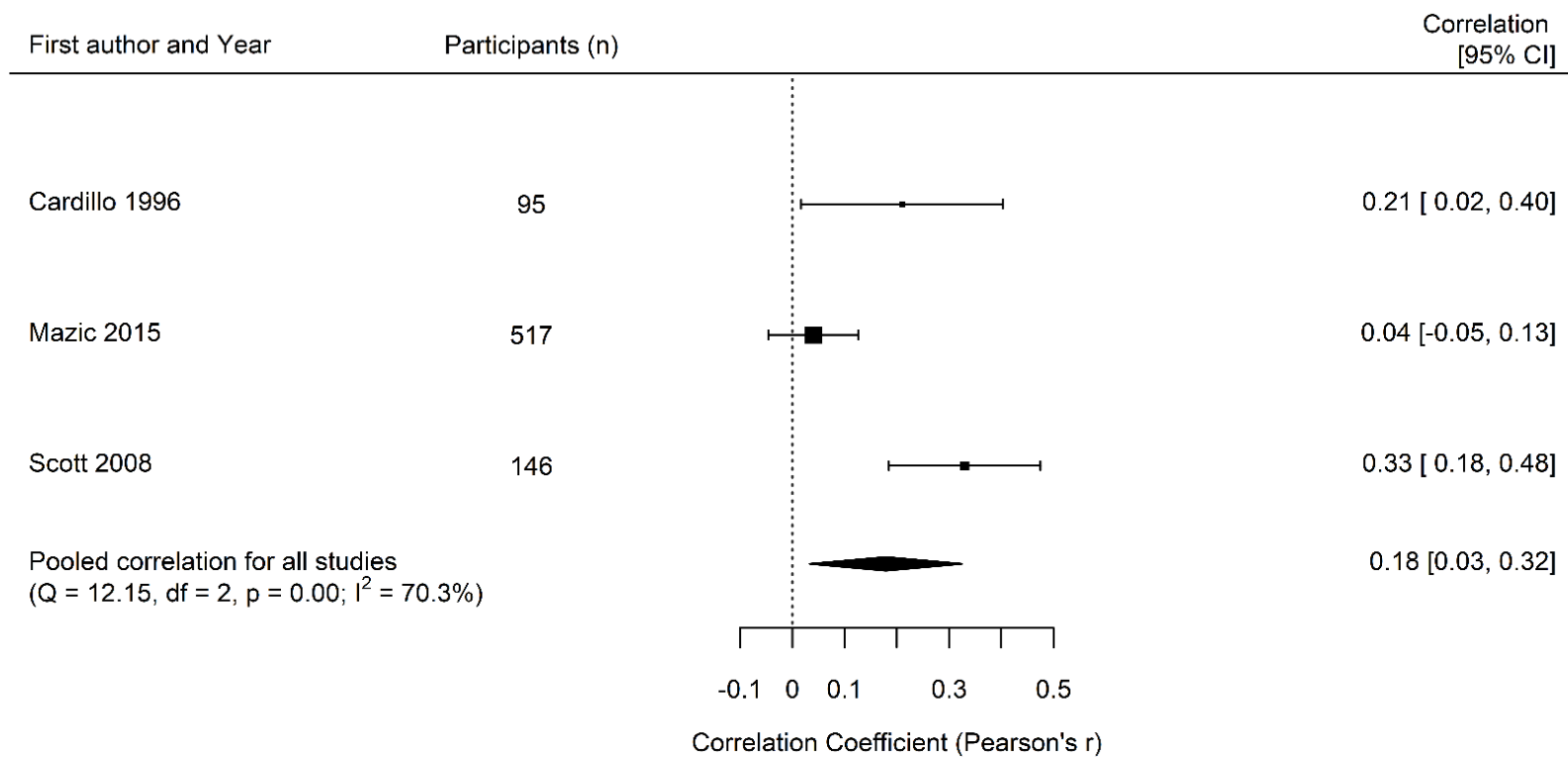
Appendix Figure 3.3. Random effect estimate for the mean difference and 95% confidence intervals (CI) in left ventricle mass between individuals with and without a hypertensive response to exercise (HRE) across all eligible studies.



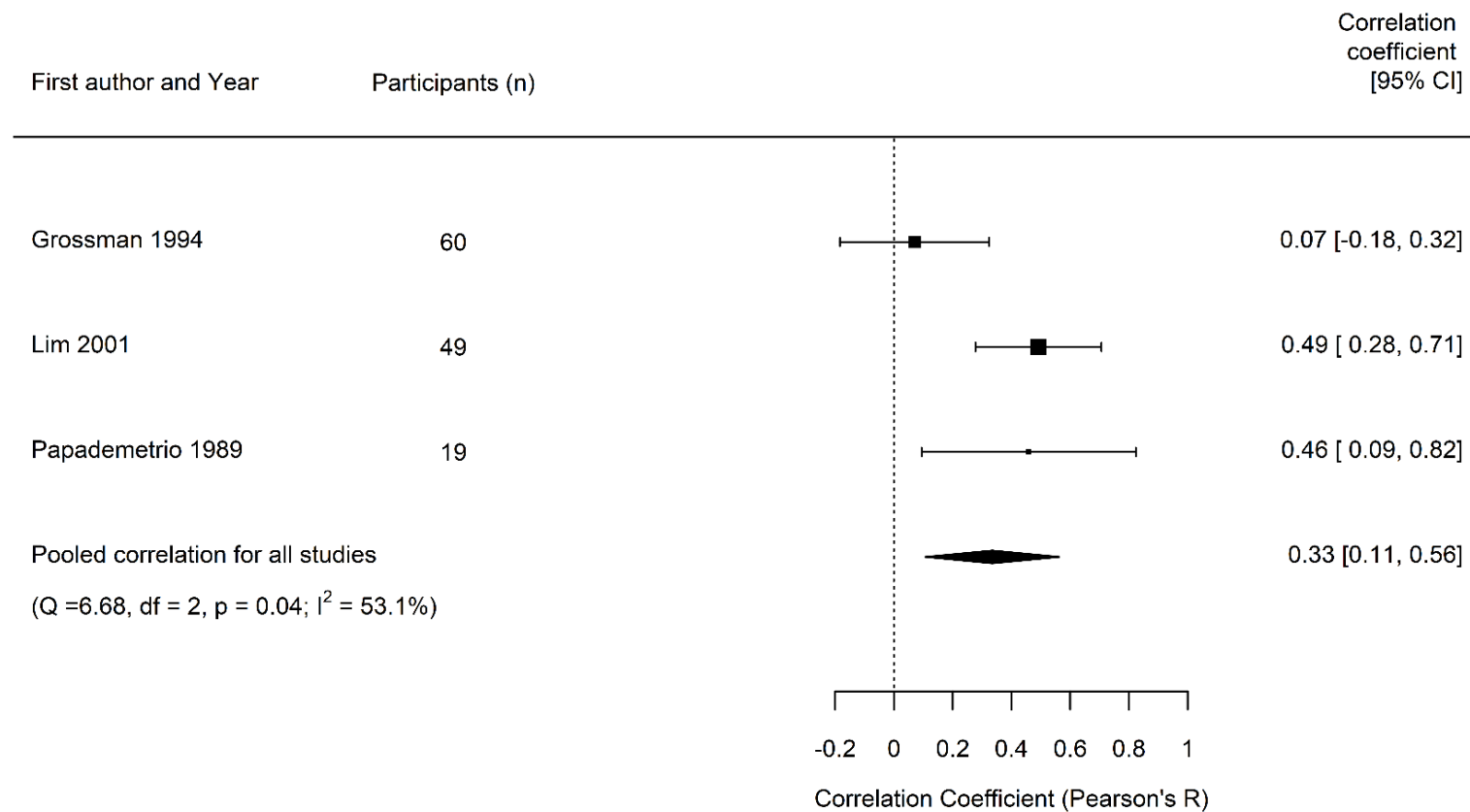
Appendix Figure 3.4. Random effect estimate for the unadjusted strength of association between exercise blood pressure and left ventricle mass indexed by height^{2.7}.



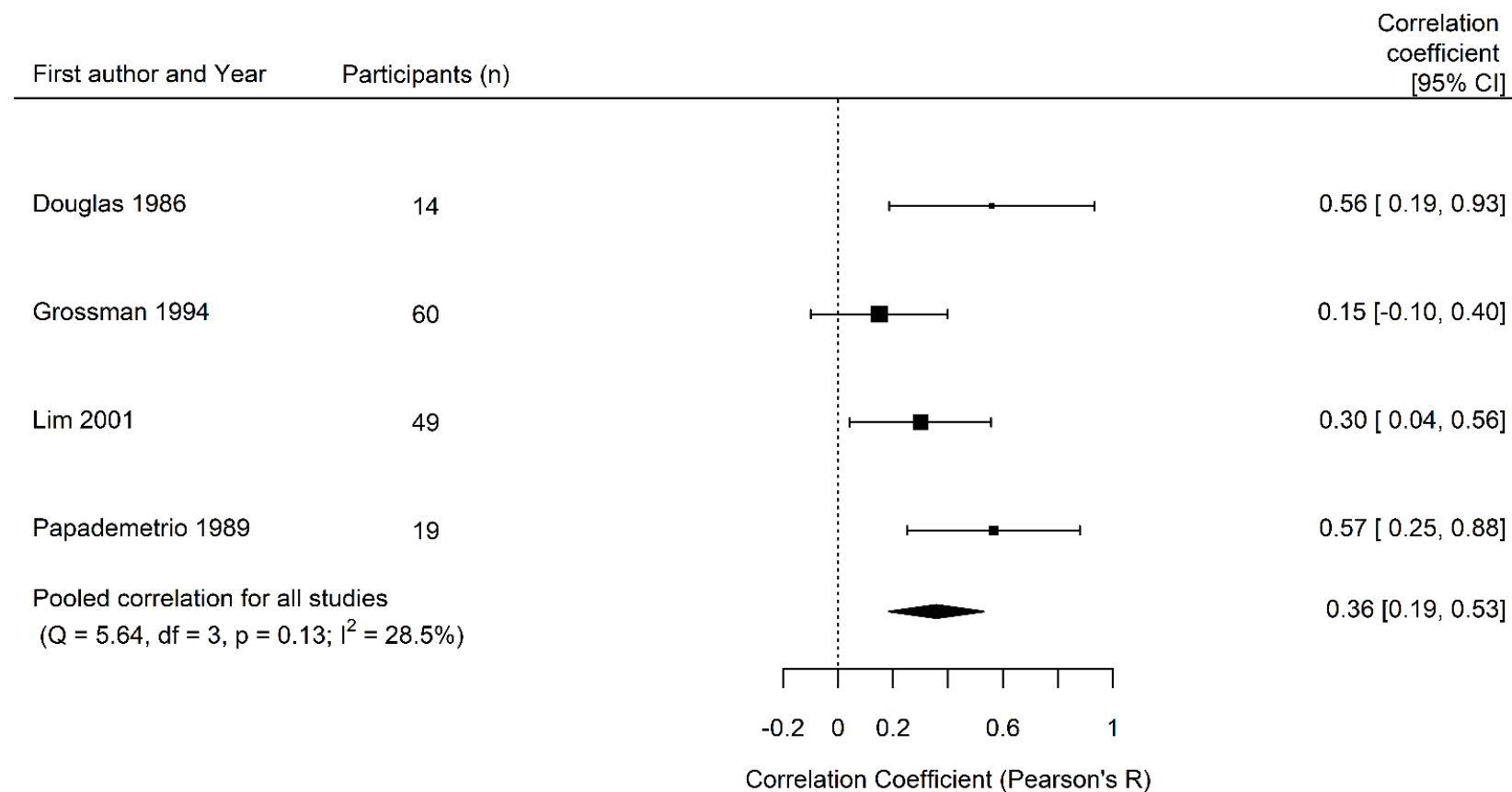
Appendix Figure 3.5. Random effect estimate for the mean difference and 95% confidence intervals (CI) in left ventricle mass indexed by height^{2.7} between individuals with and without a hypertensive response to exercise (HRE) across all eligible studies.



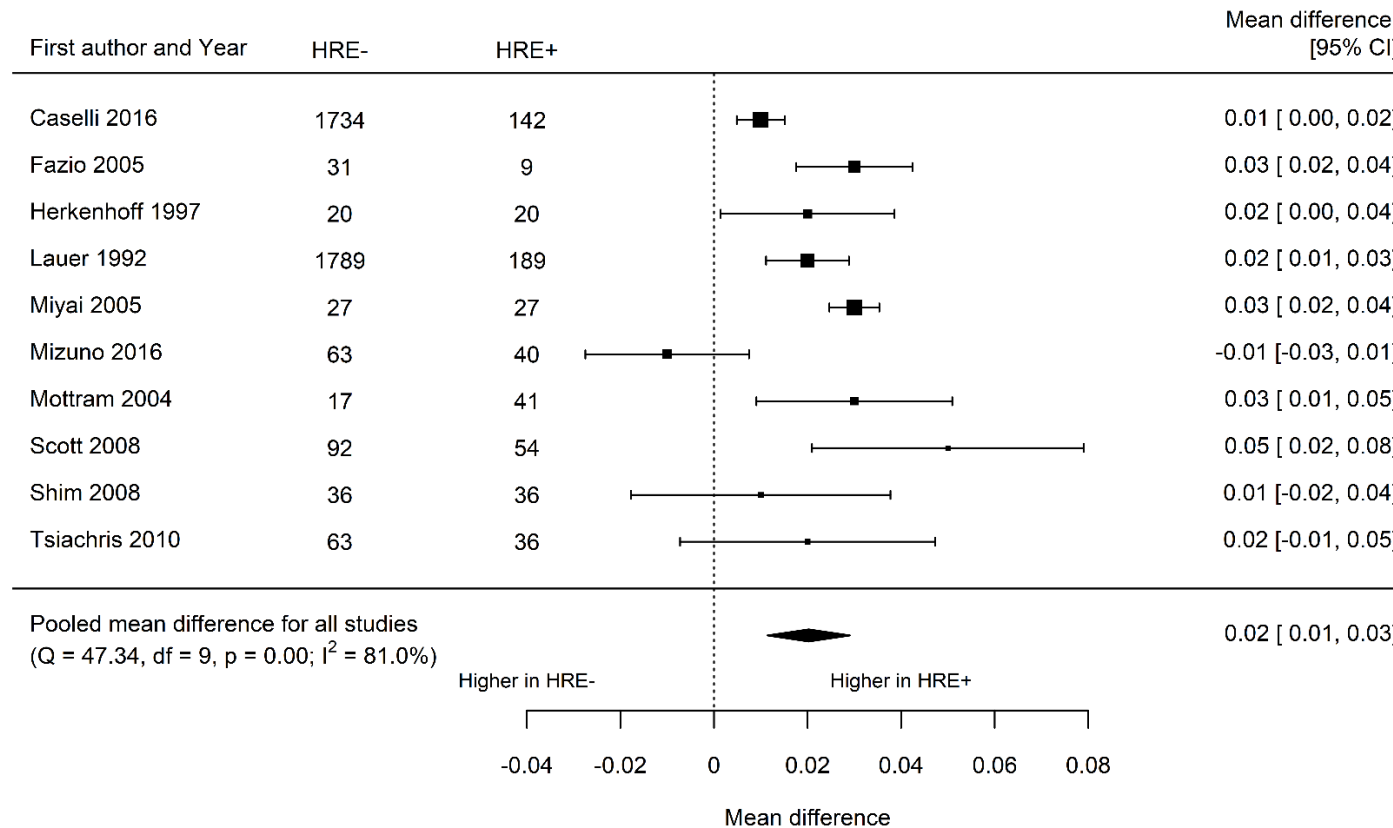
Appendix Figure 3.6. Random effect estimate for the unadjusted strength of association and 95% confidence intervals (CI) between exercise blood pressure and relative wall thickness.



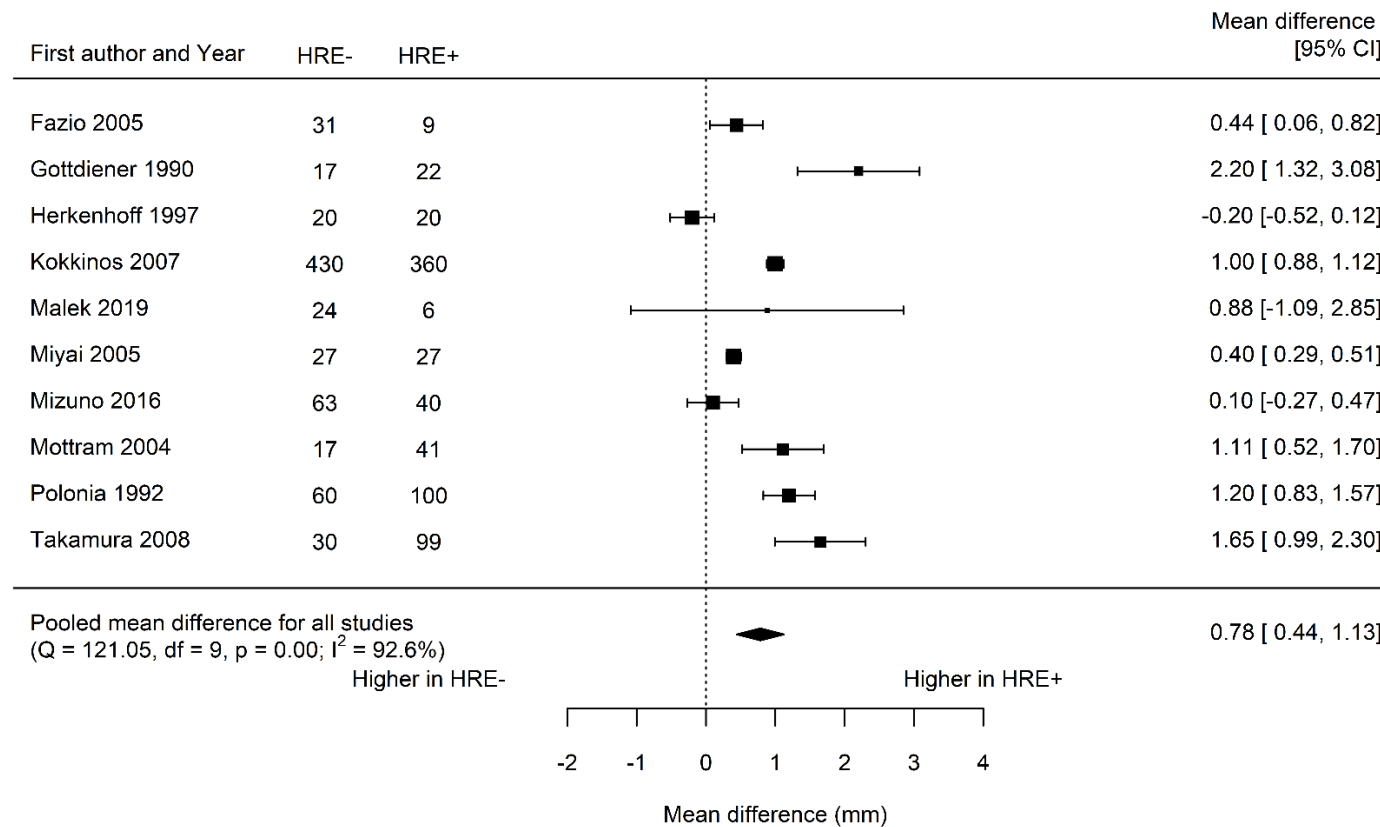
Appendix Figure 3.7. Random effect estimate for the unadjusted strength of association and 95% confidence intervals (CI) between exercise blood pressure and interventricular septal thickness.



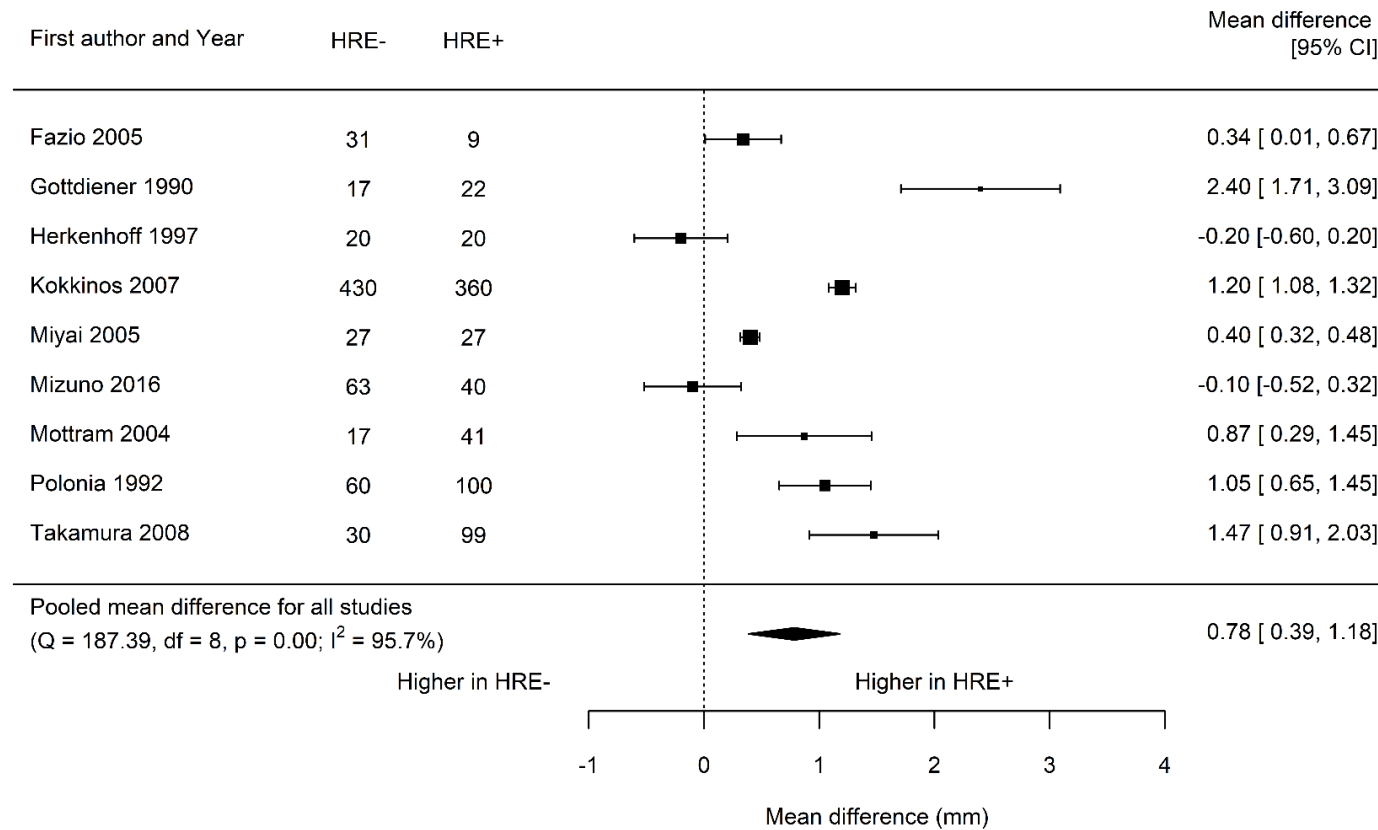
Appendix Figure 3.8. Random effect estimate for the unadjusted strength of association and 95% confidence intervals (CI) between exercise blood pressure and posterior wall thickness.



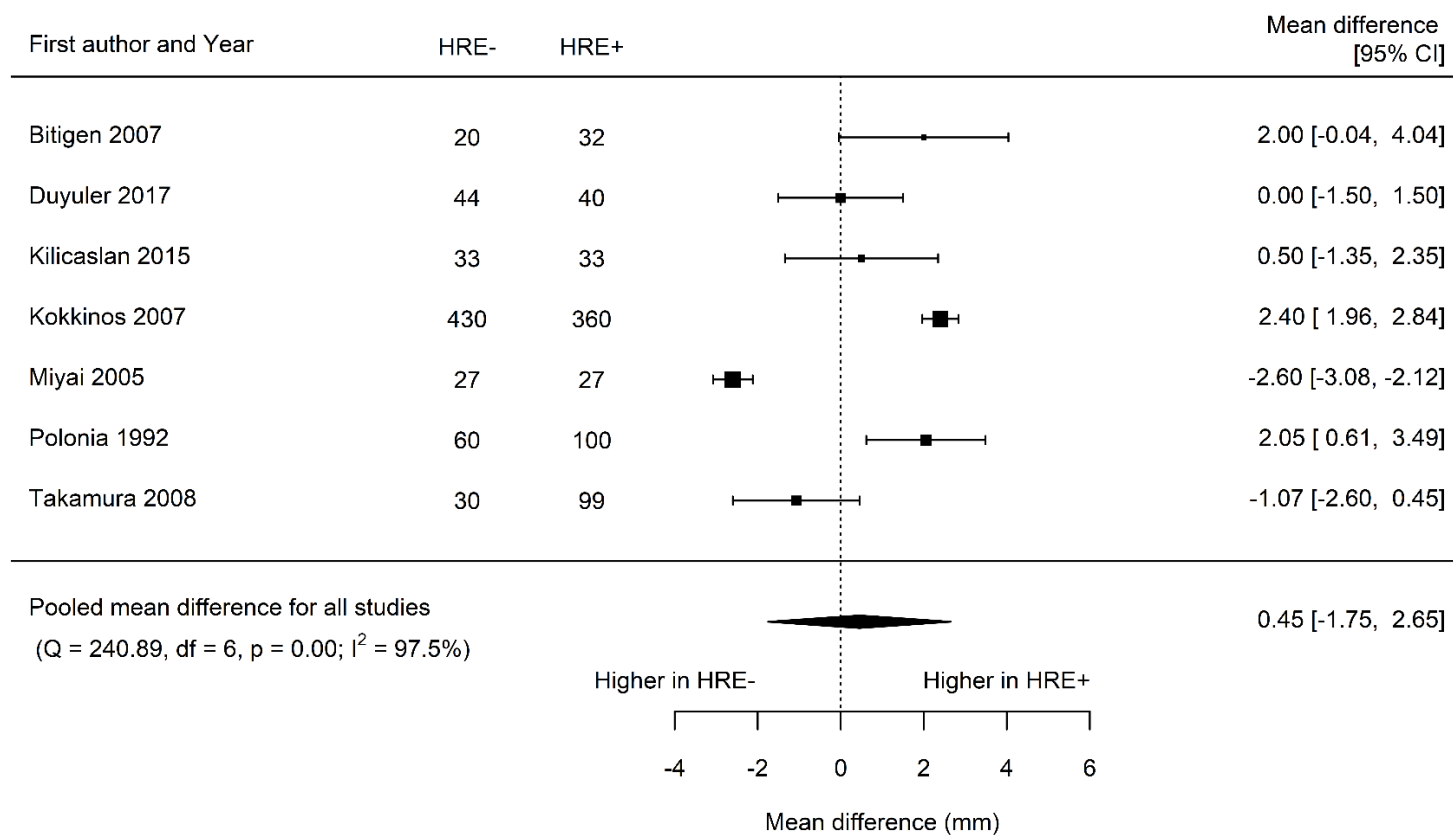
Appendix Figure 3.9. Random effect estimate for the mean difference and 95% confidence intervals (CI) in relative wall thickness between individuals with and without a hypertensive response to exercise (HRE) across all eligible studies.



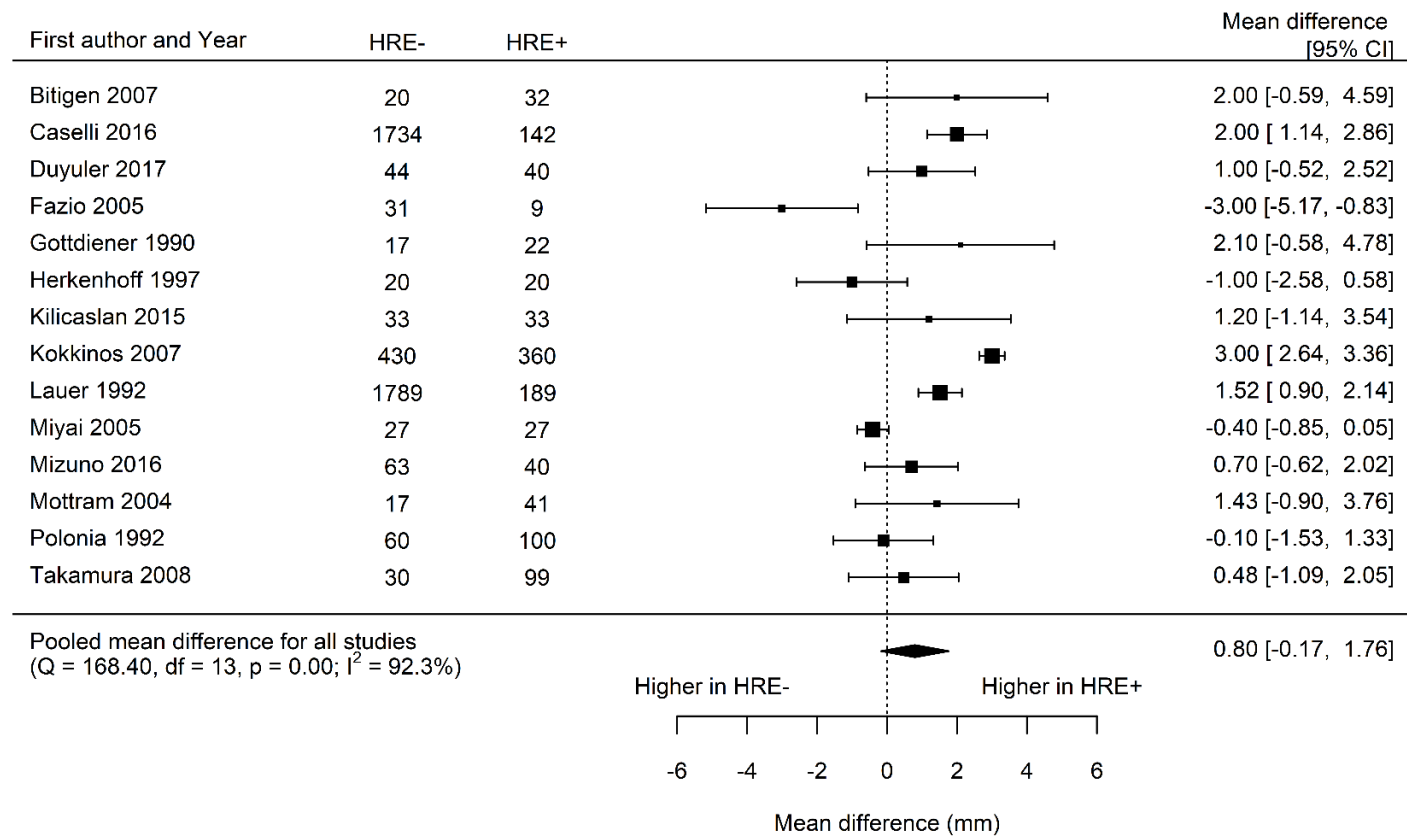
Appendix Figure 3.10. Random effect estimate for the mean difference and 95% confidence intervals (CI) in interventricular septal thickness between individuals with and without a hypertensive response to exercise (HRE) across all eligible studies



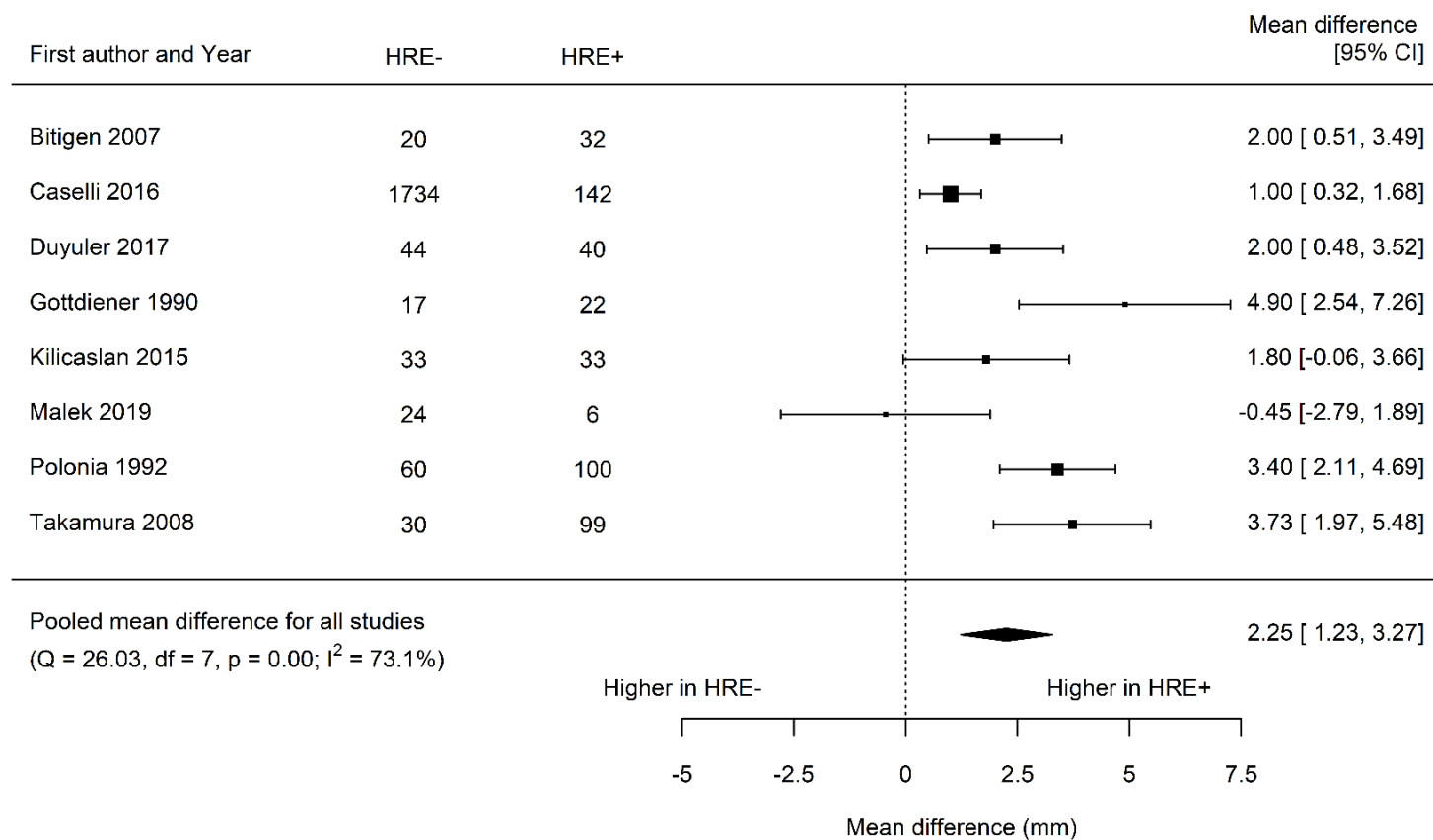
Appendix Figure 3.11. Random effect estimate for the mean difference and 95% confidence intervals (CI) in posterior wall thickness between individuals with and without a hypertensive response to exercise (HRE) across all eligible studies.



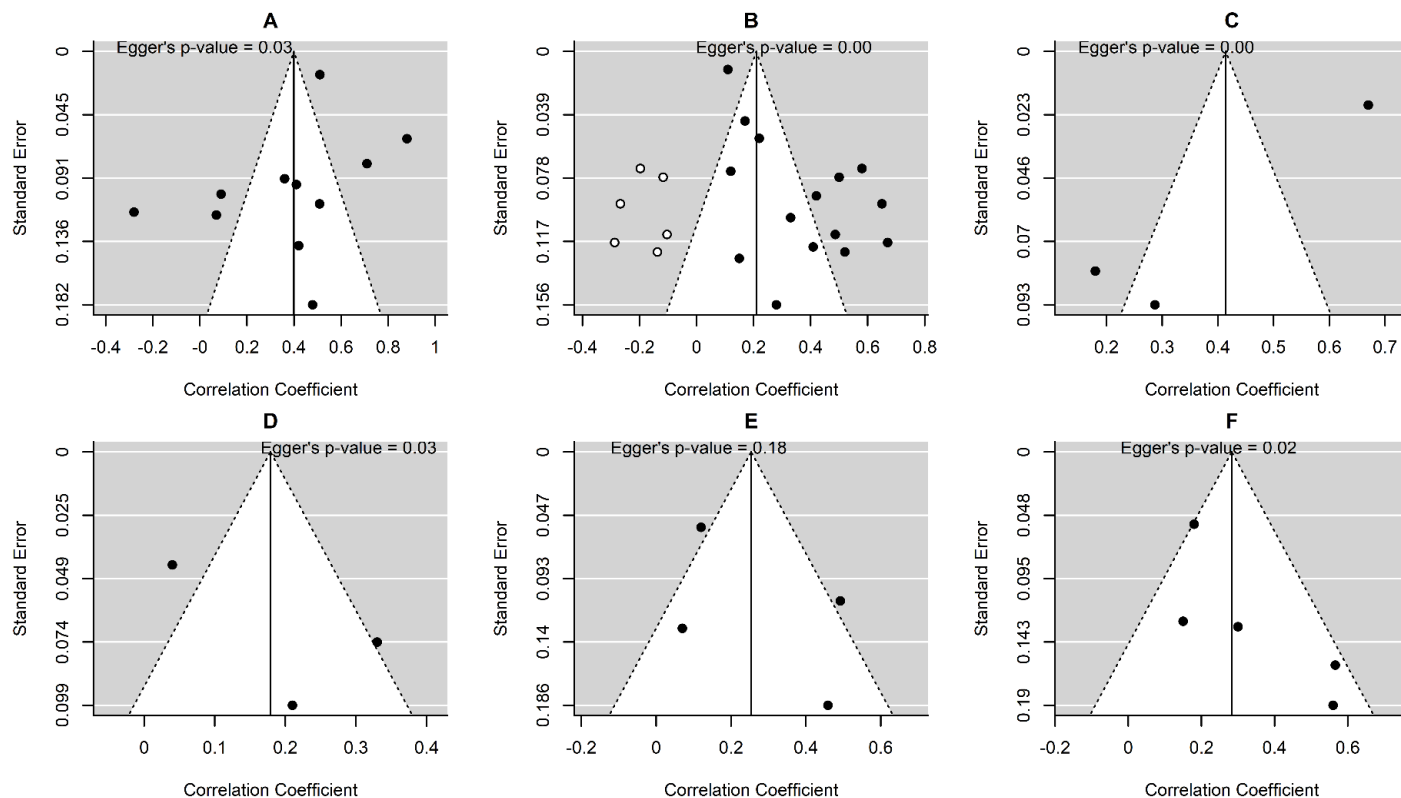
Appendix Figure 3.12. Random effect estimate for the mean difference and 95% confidence intervals (CI) in left ventricle end-systolic dimension between individuals with and without a hypertensive response to exercise (HRE) across all eligible studies.



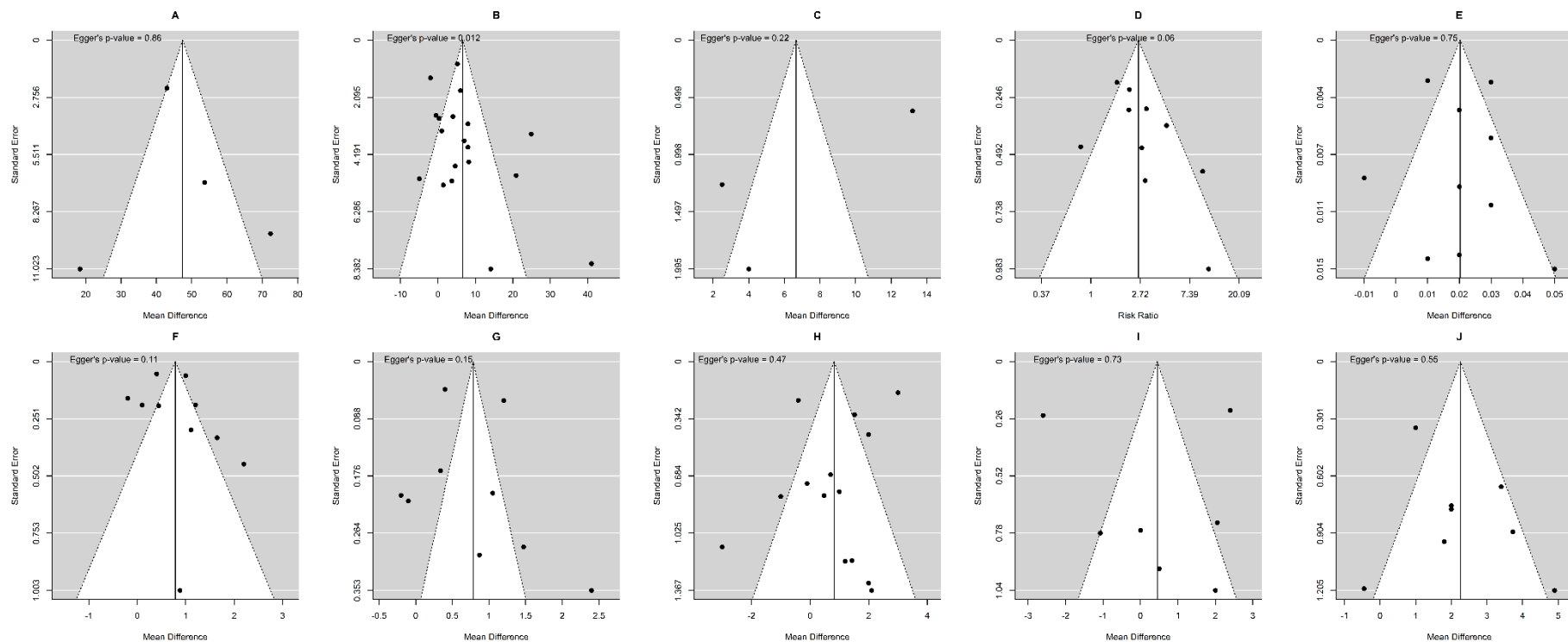
Appendix Figure 3.13. Random effect estimate for the mean difference and 95% confidence intervals (CI) in left ventricle end-diastolic dimension between 4 individuals with and without a hypertensive response to exercise (HRE) across all eligible studies.



Appendix Figure 3.14. Random effect estimate for the mean difference and 95% confidence intervals (CI) in left atrial size between individuals with and without a hypertensive response to exercise (HRE) across all eligible studies.



Appendix Figure 3.15. Funnel plot representing the publication bias for all meta-analyses conducted using continuous data. A) left ventricle mass; B) left ventricle mass indexed by body surface area; C) left ventricle mass indexed by height^{2.7}; D) relative wall thickness; E) interventricular septal thickness and; F) posterior wall thickness. Funnel plots and egger's tests present an absence of publication bias across all outcomes. A trim and fill analysis was also conducted on left ventricle mass, left ventricle mass indexed by body surface area, left ventricle mass indexed by height^{2.7} and relative wall thickness. Filled dots represents the observed studies in the meta-analysis and unfilled dots signify potential studies missing from the meta-analysis.



Appendix Figure 3.16. Funnel plot representing the publication bias for all meta-analyses conducted using categorical data. A) left ventricle mass; B) left ventricle mass indexed body surface area; C) left ventricle mass indexed by height^{2.7}; D) left ventricle hypertrophy; E) relative wall thickness; F) interventricular septal thickness; G) posterior wall thickness; H) left ventricular end-diastolic dimension; I) left ventricular end-systolic dimension and; J) left atrial size. Funnel plots and egger's tests present an absence of publication bias across all outcomes. A trim and fill analysis was also conducted on left ventricle mass indexed body surface area. Filled dots represents the observed studies in the meta-analysis

APPENDIX C. SUPPLEMENTARY MATERIAL FOR CHAPTER 4.

Supplementary methods.

Data extraction. Mundal et al. [124] reported the relationship between total cholesterol and triglycerides across five different exercise systolic BP categories, of which the lowest and highest exercise systolic BP categories were extracted, with the highest category of exercise systolic BP defined as an HRE and lowest category representing the reference group. Sebban et al. [209] assessed the association between exercise systolic BP and aortic pulse wave velocity across different exercise intensities, of which the association at the lowest intensity was extracted for analysis.

Statistical analysis. A single sample size, mean and standard deviation were calculated for the two sub-groups without an HRE reported by Fazio et al. [207] and two sub-groups with an HRE reported by Sharabi et al. [208] The two separate associations between exercise systolic BP and aortic pulse wave velocity reported by Sebban et al. [209] were combined to form a single unadjusted correlation estimate using a sample wise-adjusted procedure.[281]

Appendix Table 4.1. Characteristics of 38 studies reporting exercise blood pressure and cardiovascular risk factor.

#	First author & year	Population type	n	Male, n (%)	Age (years), mean (SD)	Body Mass Index, mean (SD)	Diabetes mellitus, n (%)	Smoking, n (%)
1	Andersen 2003[211]	Not hypertensive and apparently healthy offsprings of two hypertensive parents	25	18 (72)	27.1 (4.5)	24.2 (3.6)	0 (0)	13 (52)
		Not hypertensive and apparently healthy offsprings of two normotensive parents	26	18 (69)	27.0 (5.6)	23.9 (2.1)	0 (0)	6 (23)
2	Bitigen 2007[74]	Not hypertensive apparently healthy with an HRE	32	17 (53)	48.7 (7)	24 (5)	0	0
		Not hypertensive apparently healthy without an HRE	20	11 (55)	47.8 (5)	25 (4)	0	0
3	Bjornholt 2003[212]	Apparently healthy with mixed BP status	1947	1947 (100)	40-59	NR	0 (0)	NR
4	Bratberg 2014[71]	Overweight apparently health with mixed BP statuses with an HRE	25	18 (72)	50.6 (9.3)	33 (4.8)	1 (4)	9 (36)
		Overweight apparently health with mixed BP status with an HRE	52	25 (28)	47.3 (9.8)	32.5 (4.8)	5 (10)	19 (37)
5	Caselli 2016[45]	Not hypertensive athletes with an HRE	142	1190 (63)	26 (6)	23.8 (3.4)	0	1 (1)
		Not hypertensive athletes without an HRE	1734		24 (6)	22.7 (2.36)	0	48 (3)
6	Chang 2003[118]	Not hypertensive apparently healthy with an HRE	35	33 (94)	47 (8)	NR	0 (0)	12 (34)
		Not hypertensive apparently healthy without an HRE	35	33 (94)	44 (8)		0 (0)	15 (43)
7	Chang 2004[117]	Not hypertensive apparently healthy with an HRE	25	23 (92)	44.7 (8.8)	NR	0 (0)	10 (40)

8	Climie 2015[283]	Not hypertensive apparently healthy without an HRE	25	23 (92)	46.7 (8.7)		0 (0)	9 (36)
		Population with type 2 diabetes mellitus with normotension (38%) or high blood pressure (62%)	39	19 (49)	63 (9)	30.5 (4.8)	39 (100)	3 (8)
9	Coner 2019[126]	Not hypertensive apparently healthy with an HRE	31	31 (45)	45.3 (5.8)	29.6 (5.2)	0 (0)	13 (41.9)
10	Cote 2019[128]	Not hypertensive apparently healthy without an HRE	139	86 (61.8)	42.9 (7.1)	26.3 (3.2)	0 (0)	35 (35.2)
		Mixed health and BP status with an HRE	892	620	48.4 (10.4)	29.2 (5.3)	157 (4)	548 (14)
		Mixed health and BP status without an HRE	3021	2012	41.1 (10.8)	26.1 (4.3)		
11	Currie 2017[77]	Athletic without resting hypertension with an HRE	22	16 (73)	56 (6)	23.7 (2.2)	0 (0)	0 (0)
12	Duyuler 2017[120]	Athletic without resting hypertension or an HRE	11	8 (73)	55 (5)	23.2 (1.4)	0 (0)	0 (0)
		Not hypertensive apparently healthy with an HRE	40	20 (50)	47.7 (10)	28.1 (3.9)	5 (13.5)	13 (32.5)
		Not hypertensive apparently healthy without an HRE	44	28 (64)	48 (7)	25.4 (3.8)	2 (4.5)	18 (40.9)
13	Fazio 2005[207]	Not hypertensive apparently healthy prehypertensive with an HRE	9	6 (67)	41 (9)	25 (1)	0 (0)	0 (0)
		Apparently healthy normotensive without an HRE	20	8 (40)	47.7 (10)	25 (1)	0 (0)	0 (0)
		Apparently healthy prehypertensive without an HRE	11	8 (73)	38 (7)	24 (1)	0 (0)	0 (0)
14	Gaudreault 2013[122]	Not hypertensive with metabolic syndrome with an HRE	51	51 (100)	49 (8)	31.1 (3)	0 (0)	0 (0)
		Not hypertensive with metabolic syndrome without an HRE	47	47 (100)	47 (7)	30.6 (2)	0 (0)	0 (0)

15	Hout 2011[138]	Not hypertensive apparently healthy	317	171 (54)	34.8 (12.8)	26.1 (5.2)	0 (0)	79 (24)
16	Jae 2006a[116]	Not hypertensive apparently healthy with an HRE	375	9073 (100)	49.9 (8.9)	25.4 (2.7)	0 (0)	115 (30.7)
		Not hypertensive apparently healthy without an HRE	8698		47.6 (8.8)	24.1 (4.8)	0 (0)	2567 (29.5)
17	Jae 2006b[123]	Not hypertensive apparently healthy with an HRE	43	43 (100)	49.9 (8.9)	25 (2)	0 (0)	17 (40)
		Not hypertensive apparently healthy without an HRE	42	42 (100)	47.6 (8.8)	25 (2)	0 (0)	14 (34)
18	Jae 2018[119]	Not hypertensive apparently healthy with an HRE	152	152 (100)	49.4 (7.8)	25.7 (2.8)	0 (0)	41 (27)
		Not hypertensive apparently healthy without an HRE	4488	4488 (100)	49.1 (7.4)	24.2 (2.5)	0 (0)	862 (19.2)
19	Kilicaslan 2015[78]	Not hypertensive apparently healthy with an HRE	33	14 (47)	45.3 (10.3)	28.6 (4.7)	0 (0)	12 (36)
		Not hypertensive apparently healthy without an HRE	33	17 (52)	40.7 (9.6)	26.8 (4.2)	0 (0)	11 (33)
20	Miyai 2005[284]	Not hypertensive apparently healthy with an HRE	27	54 (100)	39.9 (1)	23.1 (0.6)	0 (0)	11 (40.7)
		Not hypertensive apparently healthy without an HRE	27		40 (1)	23.1 (0.4)	0 (0)	9 (33.3)
21	Mundal 1998[124]	Apparently healthy with mixed BP status and an HRE	289	289 (100)	NR	24.9 (3)	0 (0)	141 (49.25)
		Apparently healthy with mixed BP status without an HRE	489	489 (100)	NR	24 (2.5)	0 (0)	220 (45)
22	Nikolic 2015[112]	Apparently healthy with mixed BP status and an HRE	20	14 (70)	60 (10)	28.9 (5.1)	NR	NR

23	Park 2006[121]	Apparently healthy with mixed BP status without an HRE	44	31 (71)	56 (10)	26.6 (3.4)	NR	NR
		Hypertensive apparently healthy with an HRE	79	38 (48)	56.1 (9.4)	25.7 (3.1)	0 (0)	35 (44.3)
24	Prud-homme 1994[125]	Hypertensive apparently healthy without an HRE	196	106 (54)	53.9 (8.9)	25 (2.9)	0 (0)	78 (39.8)
		Not hypertensive apparently healthy	25	0 (0)	35.1 (6.1)	40.6 (11.2)	NR	NR
25	Scott 2008[43]	Mixed BP and health status with an HRE	54	31 (57)	NR	NR	73	0 (0)
26	Sebban 1981[209]	Mixed BP and health status without an HRE	94	24 (26)				
		Apparently healthy with mixed BP status	13	0 (0)	67 (53-73)	NR	NR	NR
		Apparently healthy with mixed BP status	13	0 (0)	79.5 (56-100)	NR	NR	NR
27	Sharabi 2001[208]	Apparently healthy with mixed BP status and an HRE	18	16 (89)	36.5 (2.8)	25.5 (2.8)	NR	7 (38.9)
		Apparently healthy with mixed BP status without an HRE	81	74 (91)	35 (4.1)	24.2 (2.7)	NR	28 (35)
		Apparently healthy with mixed BP status and an HRE	99	99 (100)	36.8 (4.2)	24.6 (2.9)	NR	34 (34.6)
28	Sharman 2011[70]	Not hypertensive apparently healthy	101	43 (60)	54 (9)	28.6 (3.9)	0 (0)	3 (3)
29	Sharman 2018[107]	Mixed health and BP status with an HRE	4626	2949 (63.96)	60 (6.4)	25.91 (3.7)	217 (4.71)	NR
30	Shim 2008[79]	Mixed health and BP status without an HRE	4350	2542 (58.44)	59 (5.88)	24.18 (3.31)	115 (2.66)	NR
		Not hypertensive apparently healthy with an HRE	36	18 (50)	50 (16)	24.9 (3.1)	4 (11.2)	13 (36.1)
		Not hypertensive apparently healthy without an HRE	36	18 (50)	50 (16)	24.0 (2.6)	2 (5.6)	8 (22.4)

31	Stewart 2004[210]	Apparently healthy with mixed BP status	82	38 (46)	NR	NR	NR	NR
32	Sung 2012[114]	Not hypertensive apparently healthy	2146	1459 (68)	52 (6)	23.5 (2.5)	155 (7.2)	1191 (55.5)
33	Thanassoulis 2012[115]	Mixed health and BP status	2116	991 (47)	59 (9)	27.5 (4.6)	146 (7)	263 (12)
34	Tsiachris 2010[80]	Apparently healthy hypertensive with an HRE	36	18 (50)	55 (9)	27.5 (3.7)	0 (0)	9 (25)
		Apparently healthy hypertensive without an HRE	63	43 (68)	48 (9.4)	27.7 (3.1)	0 (0)	25 (40.3)
35	Tsioufis 2008[93]	Apparently healthy hypertensive with an HRE	48	48 (100)	56 (9)	30.4 (4.9)	0 (0)	16 (33)
		Apparently healthy hypertensive without an HRE	123	123 (100)	50 (9)	28.2 (3.9)	0 (0)	38 (31)
36	Tzemos 2009[68]	Apparently healthy hypertensive with an HRE	11	11 (100)	49 (10)	28 (1)	0 (0)	0 (0)
		Apparently healthy hypertensive without an HRE	11	11 (100)	51 (9)	29 (1)	0 (0)	0 (0)
37	Ugur-Altun 2004[285]	Individuals with Type 2 diabetes and mixed BP status	90	48	49 (6)	>25	90 (100)	24 (27)
38	Yang 2014[127]	Not hypertensive apparently healthy with an HRE	19	15 (79)	48 (11)	24.6 (2)	0 (0)	6 (32)
		Not hypertensive apparently healthy without an HRE	152	82 (54)	48 (8)	23 (2.6)	0 (0)	31 (21)

Appendix Table 4.1 cont.

#	First author & year	Participants on antihypertensive mediation, n	Clinical indications for performing exercise tests	Positive stress- induced myocardial ischemia exercise tests, n (%)	CVD risk factors reported.	Measurement timing of each CVD risk factor in relation to the exercise test
1	Andersen 2003	0	Research	NR	Glucose, Insulin	After - Glucose, Insulin
2	Bitigen 2007	0	Suspicion of coronary artery disease	0	TC, LDLC, HDLC, TG, Glucose, Creatinine	NR - all CVD risk factors reported
3	Bjornholt 2003	0	Participate in a cardiovascular screening survey	NR	TC, TG	Before - TC, TG
4	Bratberg 2014	19	Research	NR	TC, LDLC, HDLC, TG, Glucose, Insulin, Creatinine	Before - all CVD risk factors reported
5	Caselli 2016	0	Medical evaluation before participation in the Olympic Games or other major international events.	0	TC, HDLC, HDLC, TG, Glucose, creatinine	Before - all CVD risk factors reported
6	Chang 2003	0	Admitted to university hospital for health screening	0	TC, LDLC, TG, Glucose, flow-mediated vasodilation	Before - all CVD risk factors reported
7	Chang 2004	0	Admitted to university hospital for health screening	0	TC, HDLC, TG, Glucose, flow-mediated vasodilation	Before - all CVD risk factors reported
8	Climie 2015	25	Research	0	Albumin-creatinine ratio	Before - Albumin- creatinine ratio
9	Coner 2019	0	Research	0	TC, LDLC, HDLC, TG, Glucose, Creatinine, Albumin-creatinine ratio	Before - all CVD risk factors reported
10	Cote 2019	0	Workplace health evaluation.	0	TC, HDLC, LDLC, TG, HbA1c	NR – all CVD risk factors reported

11	Currie 2017	0	Research	0	Aortic PWV,	After - Aortic PWV
12	Duyuler 2017	0	Admitted to research hospital exercise stress test laboratory	0	TC, LDLC, HDLC, TG, Glucose, Creatinine, Insulin, White blood cell count, C- reactive protein, HOMA, HbA1c	NR - all CVD risk factors reported
13	Fazio 2005	0	Evaluation of chest pain or palpitation	0	TC, HDLC, TG	Before - all CVD risk factors reported
14	Gaudreault 2013	0	Research	0	TC, HDLC, LDLC, TG, Glucose, Insulin, HOMA	NR - all CVD risk factors reported
15	Huot 2011	0	Research	0	TC, HDLC, LDLC, TG, Glucose, Insulin	Before - all CVD risk factors reported
16	Jae 2006a	0	Research	0	TC, HDLC, LDLC, Glucose, White blood cell count, HbA1c	Before - all CVD risk factors reported
17	Jae 2006b	0	Research	0	TC, HDLC, LDLC, Glucose, White blood cell coun, HbA1c, C-reactive protein	NR - all CVD risk factors reported
18	Jae 2018	0	Research	0	TC, HDLC, LDLC, Glucose, White blood cell count, Insulin, HOMA, HbA1c, C-reactive protein	NR - all CVD risk factors reported
19	Kilicaslan 2015	0	Suspicion of coronary artery disease	0	TC, HDLC, LDLC, TG, Glucose, C-reactive protein	NR - all CVD risk factors reported
20	Miyai 2005	0	Research	0	TC, TG, Glucose	Before - all CVD risk factors reported
21	Mundal 1998	0	Health survey for detecting prevalence of latent CVD	0	TC, TG	Before - TC, TG

22	Nikolic 2015	18	Suspicion of coronary artery disease	0	Aortic PWV, TC, HDLC, LDLC, TG, Glucose,	After - all CVD risk factors reported
23	Park 2006	0	Research	0	TC, HDLC, LDLC, TG, Glucose, Insulin, HOMA	NR - all CVD risk factors reported
24	Prud-homme 1994	NR	Research	NR	TC, HDLC, LDLC, TG, Insulin	NR - all CVD risk factors reported
25	Scott 2008	25	Research	NR	TG, HbA1c, HOMA	NR - all CVD risk factors reported
26	Sebban 1981	0	Research	NR	Aortic PWV	Before - all CVD risk factors reported
27	Sharabi 2001	0	Periodical medical examination	NR	TC, Glucose	Before - all CVD risk factors reported
28	Sharman 2011	0	Research	0	Aortic PWV, TC, LDL, Glucose, HbA1c,	Before - pulse wave velocity
29	Sharman 2018	1109	Free medical examination every 5 years to working and retired employees	NR	TC, HDLC	After - blood samples NR - blood samples
30	Shim 2008	0	Evaluation of coronary artery disease or exercise-induced diastolic dysfunction as the cause of exertional dyspnea	0	Other – aldosterone, angiotensin, plasma renin activity, epinephrine, norepinephrine	Before - all CVD risk factors reported
31	Stewart 2004	0	Research	0	TC, HDLC, LDLC, TG, Glucose, Flow-mediated vasodilation, aortic PWV	NR – all CVD risk factors reported
32	Sung 2012	0	Research	0	Brachial PWV, LDLC, HDLC, TG, Glucose, C-reactive protein, HbA1c	NR – all CVD risk factors reported

33	Thanassoulis 2012	514	Research	0	Flow-mediated vasodilation	NR – all CVD risk factors reported
34	Tsiachris 2010	0	Referred to outpatient hypertension unit to rule out secondary hypertension	0	Aortic PWV, TC, HDLC, LDLC, TG, Glucose, HbA1c, Creatinine	NR – all CVD risk factors reported
35	Tsioufis 2008	0	Referred to outpatient hypertension unit to rule out secondary hypertension	0	Aortic PWV, TC, HDLC, LDLC, TG, Glucose, HbA1c, Creatinine, Albumin-creatinine ratio	NR– all CVD risk factors reported
36	Tzemos 2009	0	Research	NR	TC, HDLC, LDLC, TG, Glucose, Creatinine	NR – all CVD risk factors reported
37	Ugur-Altun 2004	NR	Research	4 (4.4)	HOMA-index	NR – all CVD risk factors reported
38	Yang 2014	0	Research	NR	TC, LDLC, Glucose	NR – all CVD risk factors reported

Appendix Table 4.1 cont.

#	First author & year	CVD risk factor analysis method	Exercise modality	Exercise protocol	Intensity exercise BP measured	Exercise BP Measurement method
1	Andersen 2003	Glucose – glucose oxidase method. Insulin – enzyme immunoassay.	Bicycle	Graded	Submaximal	Automated
2	Bitigen 2007	All – autoanalyzer	Treadmill	Modified Bruce	Peak	Automated
3	Bjornholt 2003	All – NR	Bicycle	Graded	Peak	Manual
4	Bratberg 2014	All – NR	Treadmill	Graded	Peak	Automated
5	Caselli 2016	All – NR	Bicycle	Graded	Peak	NR
6	Chang 2003	TC, LDLC, TG, Glucose – NR	Treadmill	Bruce	Peak	NR

7	Chang 2004	Flow-mediated vasodilation – B mode ultrasound TC, LDLC, TG, Glucose – NR	Treadmill	Bruce	Peak	NR
8	Climie 2015	Flow-mediated vasodilation – B mode ultrasound Isotope dilution mass spectrometry-aligned technique	Bicycle	Steady-state	Submaximal	Manual
9	Coner 2019	All - NR	Treadmill	Modified Bruce	Peak	Manual
10	Cote 2019	TC, HDLC, LDLC, TG – piccolo xpress chemistry analyzer HbA1c - turbidimetric inhibition immunoassay	Treadmill	Steady-state	Submaximal	Automated
11	Currie 2017	Aortic PWV - tonometry	Treadmill	Graded	Peak	Automated
12	Duyuler 2017	All - NR	Treadmill	Modified Bruce	Peak	Manual
13	Fazio 2005	All - NR	Bicycle	Graded	Submaximal	Manual
14	Gaudreault 2013	All – NR	Treadmill	Bruce	Peak	Automated
15	Huot 2011	Glucose and Insulin – radioimmunoassay with polyethylene glycol separation. TC, HDLC, LDLC, TG - NR	Bicycle	Graded	Submaximal	NR
16	Jae 2006a	TC, HDLC, TG, Glucose – Hitachi 747 analyser. White blood cell count – quantitative automated hematology analyzer. HbA1c – NR	Treadmill	Bruce	Peak	Automated
17	Jae 2006b	TC, HDLC, TG, Glucose – Hitachi 747 analyser.	Treadmill	Bruce	Peak	NR

		White blood cell count – quantitative automated hematology analyzer C-reactive protein - CRP (II) Latax X2 turbidimetric Method. HbA1c - NR				
18	Jae 2018	TC, HDLC, LDLC – enzymatic colorimetric and liquid selective detergent methods. Glucose – Hexokinase, UV method Insulin – immunoradiometric assay White blood cell count – quantitative automated hematology analyzer C-reactive protein - CRP (II) Latax X2 turbidimetric Method. HbA1c - NR	Treadmill	Modified Bruce & Bruce	Peak	Automated
19	Kilicaslan 2015	All - NR	Treadmill	Bruce	Peak	Automated
20	Miyai 2005	All – NR	Bicycle	Graded	Submaximal	Manual
21	Mundal 1998	All – NR	Bicycle	Graded	Submaximal	Manual
22	Nikolic 2015	Aortic PWV - tonometry TC, HDLC, LDLC, TG, Glucose - NR	Bicycle	Steady-state	Submaximal	Manual
23	Park 2006	TC, HDLC, LDLC, TG, Glucose - NR Insulin – immunoradiometric assay	Treadmill	Bruce	Peak	Manual

24	Prud-homme 1994	TC, HDLC, LDLC, TG – Technicon Instrument Autoanalyser II Insulin -immunoradiometric assay	Treadmill	Graded	Submaximal	Manual
25	Scott 2008	TG, HbA1c, HOMA - NR	Treadmill	Graded	Peak	Manual
26	Sebban 1981	Aortic PWV - tonometry	Bicycle	Graded	Submaximal	Manual
27	Sharabi 2001	TC, Glucose - NR	Treadmill	Bruce	Peak	NR
28	Sharman 2011	Aortic PWV - tonometry	Treadmill	Bruce	Peak	Manual
29	Sharman 2018	TC, LDL, Glucose, HbA1c - NR	Step	Self-paced	Submaximal	Manual
30	Shim 2008	TC, HDLC - NR aldosterone, angiotensin, plasma renin activity – radioimmunoassay epinephrine, norepinephrine – high-performance liquid chromatography	Bicycle	Graded	Peak	Automated
31	Stewart 2004	TC, HDLC, LDLC, TG, Glucose - NR Flow-mediated vasodilation - ultrasound aortic PWV - tonometry	Treadmill	Modified Balke	Peak	Manual
32	Sung 2012	Brachial PWV – Colin VP-1000 LDLC, HDLC, TG, Glucose, C- reactive protein, HbA1c - NR	Treadmill	Modified Bruce	Submaximal and peak	Automated
33	Thanassoulis 2012	Flow-mediated vasodilation - ultrasound	Treadmill	Bruce	Submaximal	Manual
34	Tsiachris 2010	Aortic PWV – tonometry TC, HDLC, LDLC, TG, Glucose, HbA1c, Creatinine - NR	Treadmill	Bruce	Peak	Manual

35	Tsioufis 2008	Aortic PWV – tonometry TC, HDLC, LDLC, TG, Glucose, HbA1c – NR Creatinine, Albumin-creatinine ratio – quantitative assay	Treadmill	Bruce	Peak	Manual
36	Tzemos 2009	TC, HDLC, LDLC, TG, Glucose, Creatinine - NR	Step	Dundee	Submaximal	Automated
37	Ugur-Altun 2004	HOMA-index – NR	Treadmill	Bruce	Peak	Manual
38	Yang 2014	TC, LDLC, Glucose - NR	Treadmill	Bruce	Peak	Automated

Appendix Table 4.1 cont.

#	First author & year	HRE threshold (mmHg)	Analysis type	Quality of study (Newcastle Ottawa scale)	In meta- analysis
1	Andersen 2003	NR	Continuous only	4	No
2	Bitigen 2007	Male $\geq 210/105$; Female $\geq 190/105$	Categorical only	5.5	Yes
3	Bjornholt 2003	NA	Categorical only	4.5	No
4	Bratberg 2014	Systolic BP ≥ 200	Categorical only	5.5	Yes
5	Caselli 2016	Male: Systolic BP ≥ 220 ; Female: Systolic BP ≥ 200	Categorical only	3	Yes
6	Chang 2003	Male: Systolic BP ≥ 210 ; Female: Systolic BP ≥ 190	Categorical only	6.5	Yes
7	Chang 2004	Male: Systolic BP ≥ 210 ; Female: Systolic BP ≥ 190	Categorical only	6.5	Yes
8	Climie 2015	NA	Continuous only	5	Yes
9	Coner 2019	Male: Systolic BP ≥ 210 ; Female: Systolic BP ≥ 190	Categorical only	3.5	Yes
10	Cote 2019	Systolic BP $\geq 80^{\text{th}}$ percentile or diastolic BP ≥ 90	Categorical & continuous	4	Yes
11	Currie 2017	Male: Systolic BP ≥ 210 ; Female: Systolic BP ≥ 190	Categorical only	5	Yes
12	Duyuler 2017	Male: Systolic BP ≥ 210 ; Female: Systolic BP ≥ 190	Categorical only	7	Yes
13	Fazio 2005	Systolic BP ≥ 192	Categorical only	7.5	Yes
14	Gaudreault 2013	Systolic BP ≥ 210	Categorical only	4	Yes
15	Huot 2011	NA	Categorical only	2.5	No
16	Jae 2006a	Male: Systolic BP ≥ 210 ; Female: Systolic BP ≥ 190	Categorical only	4	Yes
17	Jae 2006b	Systolic BP ≥ 210	Categorical only	4.5	Yes
18	Jae 2018	Systolic BP ≥ 210	Categorical only	4.5	Yes
19	Kilicaslan 2015	Male: Systolic BP ≥ 210 ; Female: Systolic BP ≥ 190	Categorical only	6.5	Yes
20	Miyai 2005	Either systolic BP or diastolic BP $\geq 95^{\text{th}}$ percentile values	Categorical only	6	Yes
21	Mundal 1998	Systolic BP ≥ 200	Categorical only	3	Yes
22	Nikolic 2015	Male: Systolic BP ≥ 170 ; Female: Systolic BP ≥ 160	Categorical only	6	Yes
23	Park 2006	Male: Systolic BP ≥ 210 ; Female: Systolic BP ≥ 190	Categorical only	4	Yes
24	Prud-homme 1994	NA	Continuous only	1.5	Yes
25	Scott 2008	Male $\geq 210/105$; Female $\geq 190/105$	Continuous only	6	Yes

26	Sebban 1981	NA	Continuous only	1	Yes
27	Sharabi 2001	$\geq 200/100$	Categorical only	3	Yes
28	Sharman 2011	Male $\geq 210/105$; Female $\geq 190/105$	Categorical only	6.5	Yes
29	Sharman 2018	Systolic BP ≥ 150	Categorical only	5	Yes
30	Shim 2008	difference of peak and baseline systolic BP >60 mmHg in men and >50 mmHg in women during exercise	Categorical only	4.5	No
31	Stewart 2004	NA	Continuous only	2	No
32	Sung 2012	NA	Continuous only	2	No
33	Thanassoulis 2012	NA	Continuous only	3	Yes
34	Tsiachris 2010	Male: Systolic BP ≥ 210 ; Female: Systolic BP ≥ 190	Categorical only	5.5	Yes
35	Tsioufis 2008	Systolic BP ≥ 210	Categorical only	3.5	Yes
36	Tzemos 2009	Systolic BP ≥ 200	Categorical only	4	Yes
37	Ugur-Altun 2004	NA	Continuous only	3	Yes
38	Yang 2014	Male: Systolic BP ≥ 210 ; Female: Systolic BP ≥ 190	Categorical only	5.5	Yes

Data reported as mean (standard deviation) or median (range). BP, blood pressure; CVD, cardiovascular disease; HDLC, high-density lipoprotein cholesterol; HOMA, Homeostatic model assessment of insulin resistance; HRE, hypertensive response to exercise; LDLC, low-density lipoprotein cholesterol; n, number; NA, not applicable; NR, not reported; PWV, Pulse wave velocity; TC, Total cholesterol; TG, Triglycerides. Study populations were classified as hypertensive based on a resting BP $\geq 140/90$ mmHg or prescribed antihypertensive medication. Study populations were classified apparently health include those with no history of chronic disease. Study populations classified a mixed status when analyses comprised of individuals with and without high BP at rest or various health statuses, e.g. analyses including people with and without a chronic disease. Exercise BP not measured at peak or maximal intensity was defined as submaximal. Categorical analysis type was when studies reported a difference in CVD risk factor between those with and without an HRE. Continuous analysis type was when studies reported an association between exercise BP and a CVD risk factor.

Appendix Table 4.2. Correlation between cardiovascular risk factor and exercise blood pressure (BP) across different study populations (based on resting BP status and health status) and various exercise test modalities (i.e. exercise intensity when BP was measured and exercise modality).*

		Number of studies	Correlation coefficient (r)	95% confidence interval		P-value for correlation	Heterogeneity explained, R ² (%)
Subgroups							
Aortic pulse wave velocity							
Resting BP status	Not hypertensive	1	0.25	0.07	0.43	0.15	100
	Hypertensive	2	0.32	0.21	0.42		
	Mixed	2	0.48	0.26	0.69		
Exercise intensity	Submaximal	2	0.48	0.26	0.69	0.07	100
	Peak	3	0.30	0.21	0.39		
Exercise modality	Treadmill	3	0.30	0.21	0.39	0.07	100
	Bicycle	2	0.48	0.26	0.69		
Triglycerides							
Resting BP status	Not hypertensive	1	0.02	-0.38	0.42	0.38	48
	Mixed	3	0.21	0.13	0.30		
Health status	Apparently Healthy	3	0.21	0.11	0.31	0.94	4
	Mixed	1	0.21	0.05	0.37		
Exercise intensity	Submaximal	3	0.21	0.11	0.31	0.94	4
	Peak	1	0.21	0.05	0.37		
Exercise modality	Treadmill	2	0.19	0.04	0.33	0.74	1
	Bicycle	2	0.23	0.11	0.34		

*Meta-regressions were not performed to assess the pooled correlation between exercise BP, total cholesterol and albumin-creatinine ratio across different study populations and exercise testing methodologies because there were less than three studies available for analysis.

Appendix Table 4.3. Mean difference in cardiovascular risk factor between those with and without a hypertensive response to exercise across different study populations (based on resting blood pressure [BP] and health status) and various exercise test modalities (i.e. exercise intensity when BP was measured and exercise modality).

			Mean difference or				
Subgroup		Number of studies	standard mean difference	95% confidence interval		P-value for difference	Heterogeneity explained, R ² (%)
Aortic pulse wave velocity (m/s)							
Resting BP status	Not hypertensive	1	0.00	-0.80	0.80	0.300	0
	Hypertensive	1	1.00	0.50	1.50		
	Mixed	1	1.30	0.56	2.04		
Health status	Apparently healthy	2	1.09	0.68	1.51	0.018	100
	Athlete	1	0.00	-0.80	0.80		
Exercise intensity	Submaximal	1	1.30	0.56	2.04	0.395	0
	Peak	2	0.55	-0.42	1.53		
Exercise modality	Treadmill	2	0.55	-0.42	1.53	0.395	0
	Bicycle	1	1.30	0.56	2.04		
Total cholesterol (mmol/L)							
Resting BP status	Not hypertensive	14	0.11	0.03	0.19	0.796	0
	Hypertensive	4	-0.05	-0.28	0.19		
	Mixed	6	0.27	0.12	0.42		
Health status	Apparently Healthy	19	0.15	0.06	0.24	0.910	0
	Athlete	1	-0.10	-0.24	0.03		
	Chronic disease	1	0.20	-0.06	0.46		
	Mixed	3	0.17	0.01	0.32		
Exercise intensity	Submaximal	7	0.16	0.04	0.28	0.578	0
	Peak	17	0.12	0.03	0.21		
Exercise modality	Bicycle	5	0.12	-0.10	0.35	0.496	1
	Treadmill	17	0.18	0.12	0.25		
Low-density lipoprotein cholesterol (mmol/L)							

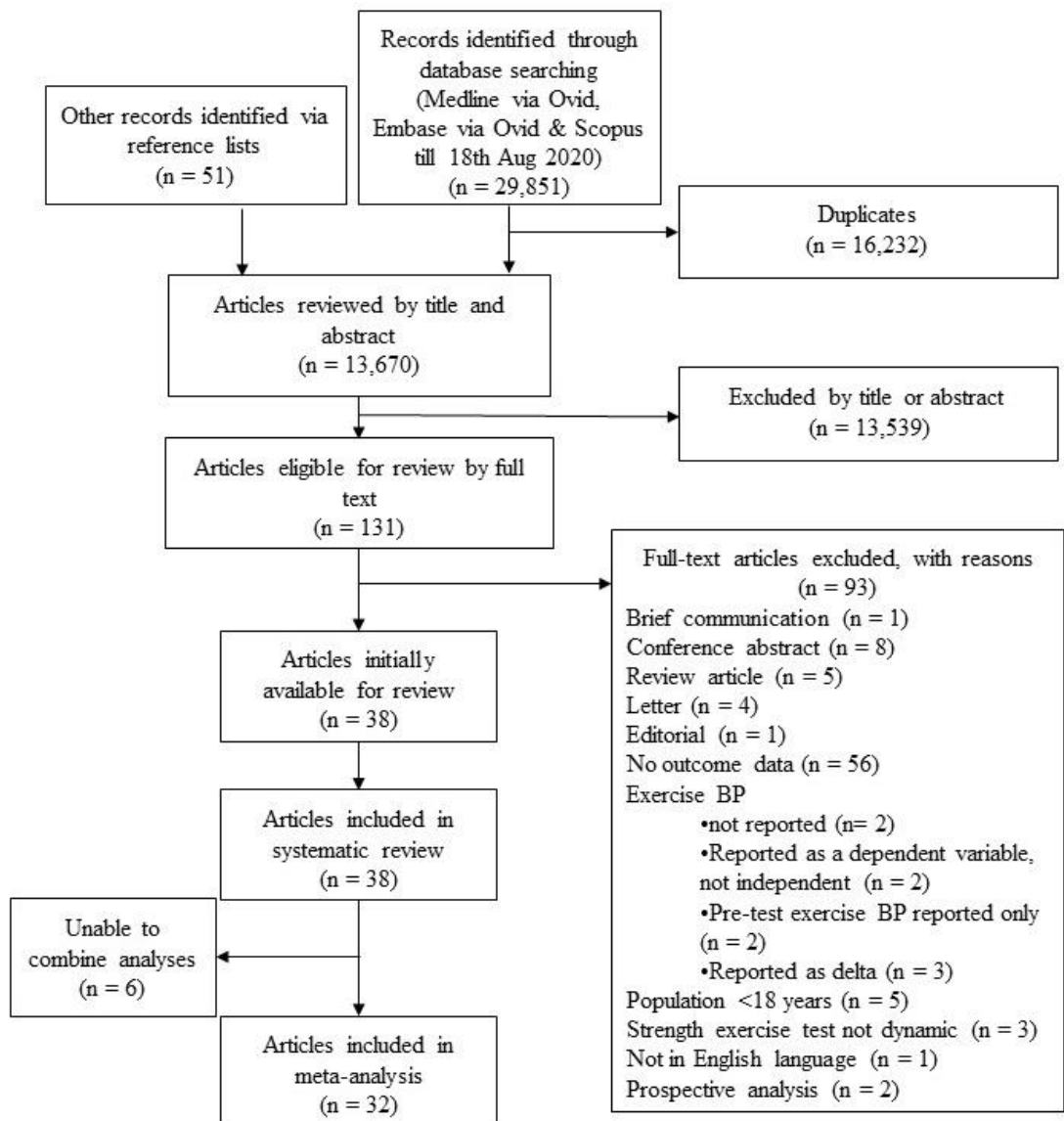
Resting BP status	Not hypertensive	10	0.12	0.03	0.22	0.758	0
	Hypertensive	4	0.15	-0.02	0.31		
	Mixed	3	0.13	0.07	0.18		
Health status	Apparently healthy	13	0.13	0.06	0.20	0.967	0
	Athlete	1	-0.03	-0.14	0.09		
	Chronic disease	1	0.30	0.10	0.50		
Exercise intensity	Mixed	2	0.13	0.07	0.18	0.872	0
	Submaximal	3	0.13	0.08	0.19		
	Peak	14	0.12	0.04	0.20		
Exercise modality	Treadmill	14	0.14	0.08	0.20	0.036	61
	Bicycle	2	-0.02	-0.13	0.09		
	Step	1	0.10	-0.61	0.81		
High-density lipoprotein cholesterol (mmol/L)							
Resting BP status	Not hypertensive	12	-0.05	-0.10	-0.01	0.229	0
	Hypertensive	3	0.00	-0.10	0.10		
	Mixed	4	-0.03	-0.04	-0.01		
Health status	Apparently healthy	14	-0.05	-0.09	-0.01	0.239	0
	Athlete	1	-0.10	-0.18	-0.02		
	Chronic disease	1	0.03	-0.01	0.07		
Exercise intensity	Mixed	3	-0.03	-0.04	-0.04	0.588	0
	Submaximal	5	-0.03	-0.04	-0.04		
	Peak	14	-0.05	-0.09	-0.09		
Exercise modality	Bicycle	3	-0.08	-0.14	-0.14	0.503	0
	Treadmill	14	-0.04	-0.07	-0.07		
	Step	2	-0.01	-0.10	-0.10		
Total Triglycerides (mmol/L)							
Resting BP status	Not hypertensive	10	0.19	0.06	0.32	0.29	48
	Hypertensive	4	0.09	-0.22	0.40		
	Mixed	4	0.34	0.28	0.41		

Health status	Apparently healthy	14	0.25	0.14	0.35	0.895	0
	Athlete	1	0.21	0.00	0.42		
	Chronic disease	1	-0.10	-0.46	0.26		
	Mixed	2	0.33	0.21	0.46		
Exercise intensity	Submaximal	6	0.25	0.13	0.38	0.709	0
	Peak	12	0.22	0.10	0.34		
Exercise modality	Bicycle	5	0.22	0.09	0.34	0.508	6
	Treadmill	12	0.28	0.17	0.40		
	Step	1	0.20	-0.60	1.00		
Glucose (mmol/L)							
Resting BP status	Not hypertensive	11	0.20	0.10	0.30	0.145	0
	Hypertensive	4	0.02	-0.27	0.32		
	Mixed	3	0.02	-0.43	0.47		
Health status	Apparently healthy	15	0.14	0.02	0.25	0.346	0
	Athlete	1	0.06	-0.02	0.13		
	Chronic disease	1	0.30	0.08	0.52		
	Mixed	1	0.40	-0.06	0.86		
Exercise intensity	Submaximal	3	-0.06	-0.50	0.37	0.244	0
	Peak	15	0.18	0.08	0.27		
Exercise modality	Treadmill	14	0.17	0.06	0.29	0.499	0
	Bicycle	3	0.10	-0.15	0.36		
	Step	1	-0.40	-0.96	0.16		
Insulin (standardised mean difference)							
Resting BP status	Not hypertensive	2	0.33	0.18	0.49	0.337	0
	Hypertensive	1	0.62	0.36	0.89		
	Mixed	1	0.00	-0.48	0.48		
Health status	Apparently healthy	2	0.47	0.23	0.72	0.044	80
	Chronic disease	1	0.15	-0.25	0.54		
	Mixed	1	0.00	-0.48	0.48		

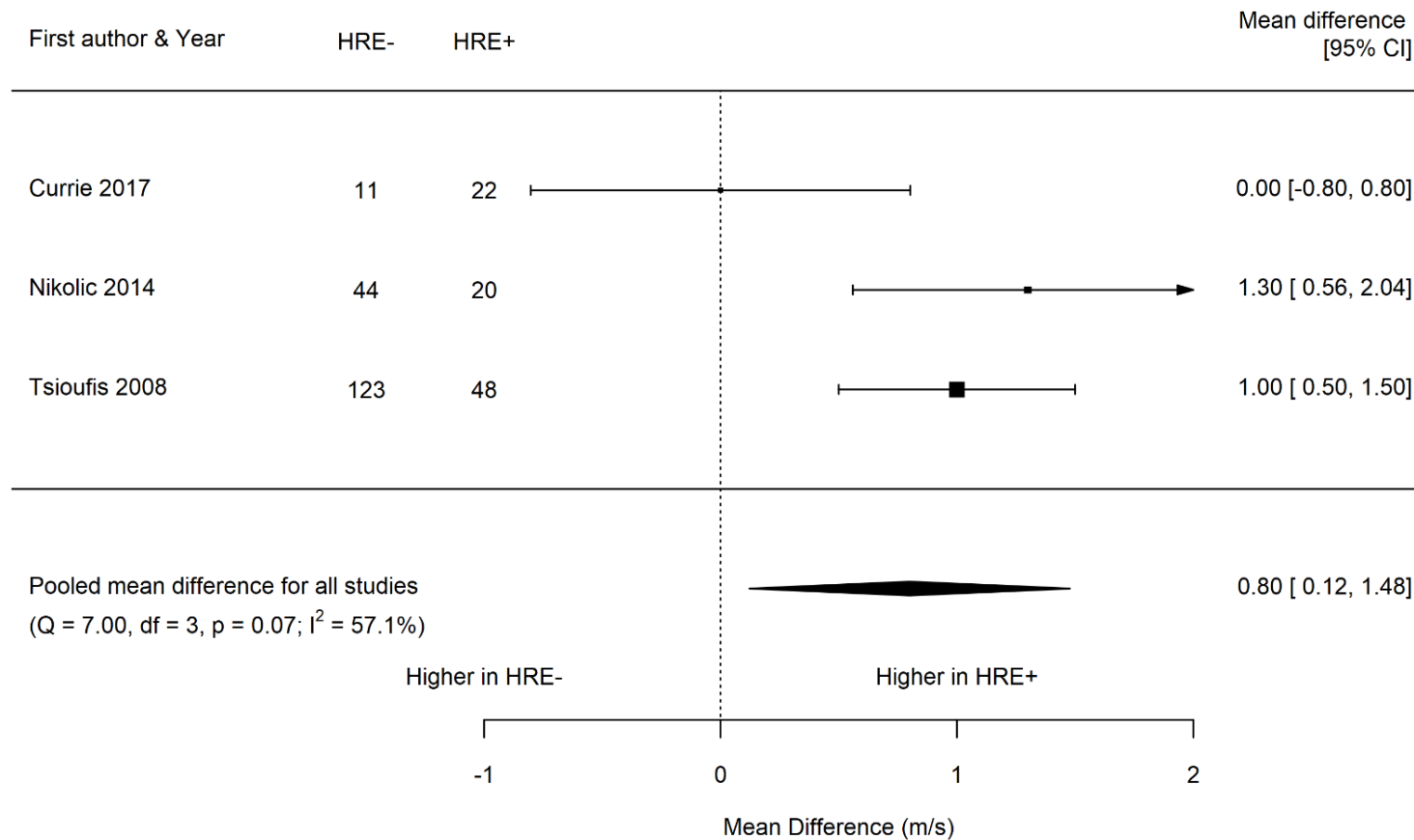
HbA1c (%)							
Resting BP status	Not hypertensive	2	0.08	-0.21	0.37	0.798	0
	Hypertensive	1	0.00	-0.16	0.16		
	Mixed	1	0.26	0.21	0.31		
Health status	Apparently healthy	3	0.06	-0.12	0.24	0.229	0
	Mixed	1	0.26	0.21	0.31		
Exercise intensity	Submaximal	1	0.26	0.21	0.31	0.229	0
	Peak	3	0.06	-0.12	0.24		
Homeostatic model assessment for insulin resistance (IU)							
Resting BP status	Not hypertensive	2	0.38	0.17	0.58	0.029	100
	Hypertensive	1	0.84	0.48	1.20		
Health status	Apparently healthy	2	0.58	0.12	1.04	0.884	0
	Chronic disease	1	0.50	-0.31	1.31		
Creatinine (mmol/L)							
Resting BP status	Not hypertensive	3	0.38	-4.03	4.79	0.722	0
	Hypertensive	3	1.92	-6.28	10.11		
Health status	Apparently healthy	5	1.11	-4.17	6.38	0.913	0
	Athletic	1	1.77	-0.80	4.34		
Exercise intensity	Submaximal	2	5.30	-2.35	12.95	0.115	29
	Peak	4	-0.59	-4.42	3.24		
Exercise modality	Treadmill	4	1.17	-5.24	7.57	0.927	0
	Bicycle	1	1.77	-0.80	4.34		
	Step	1	1.00	-6.12	8.12		

Appendix Table 4.4 Meta-regression analyses assessing the association between exercise blood pressure (as a continuous and dichotomous variable) and individual cardiovascular risk factors with Newcastle Ottawa score.

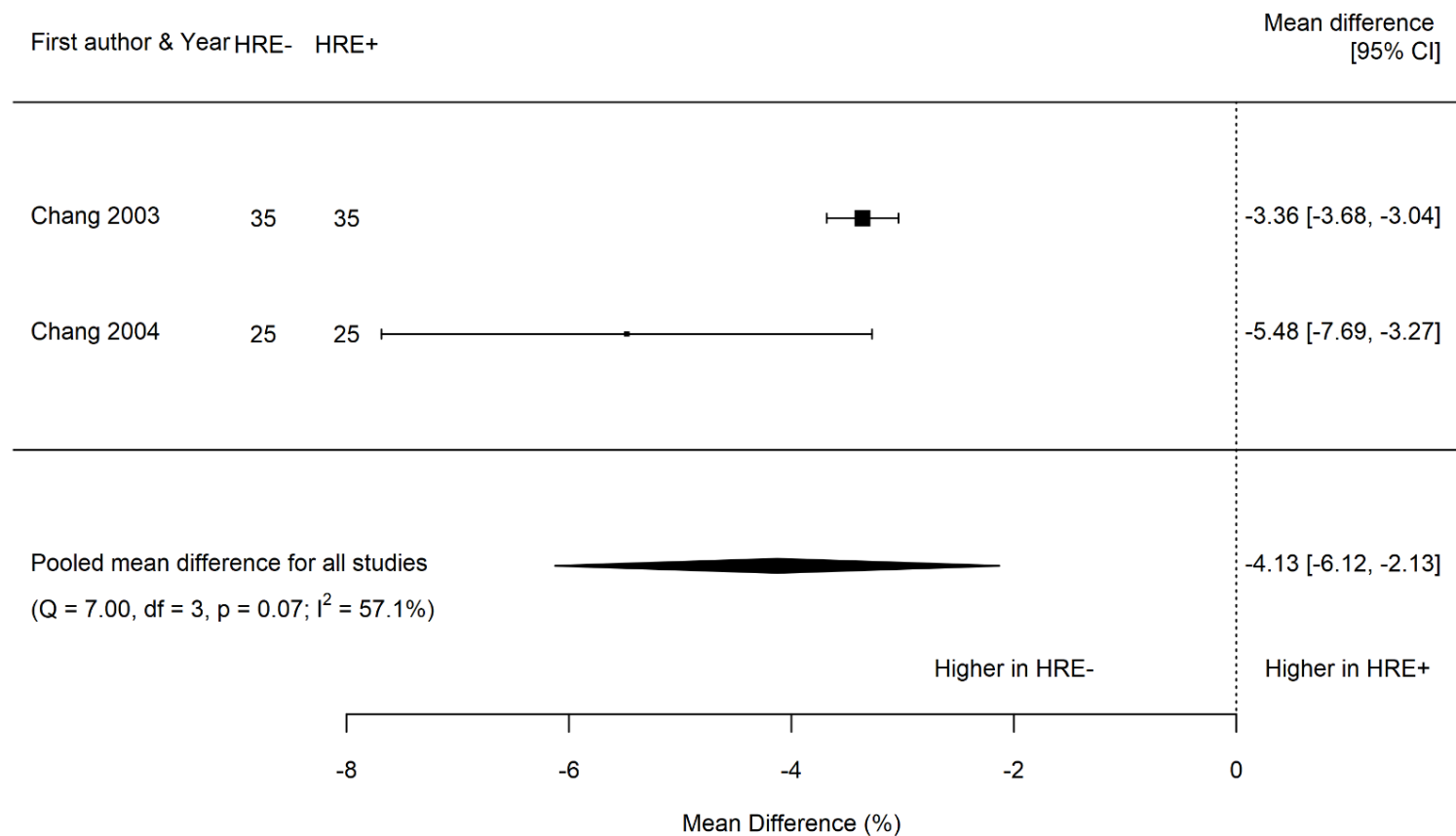
Marker of cardiovascular risk	Beta-coefficient	95% confidence interval		P-value	Heterogeneity explained (R ²)
Pooled mean difference					
Aortic pulse wave velocity	0.05	-0.98	1.07	0.927	0
Total cholesterol	-0.03	-0.08	0.02	0.270	3
Low-density lipoprotein cholesterol	0.02	-0.05	0.09	0.558	0
High-density lipoprotein cholesterol	0.00	-0.02	0.02	0.932	0
Triglycerides	-0.04	-0.09	0.02	0.186	49
Glucose	0.04	-0.04	0.12	0.344	0
Insulin	-0.28	-0.69	0.13	0.177	36
HbA1c	-0.17	-0.31	-0.03	0.020	73
Homeostatic model assessment for insulin resistance	-0.83	-1.61	-0.04	0.039	100
White blood cell count	0.23	-0.08	0.55	0.137	58
Creatinine	-1.91	-4.29	0.47	0.115	17
Pooled correlation					
Aortic pulse wave velocity	-0.04	-0.09	0.00	0.06	100
Triglycerides	-0.26	-0.68	0.16	0.20	100



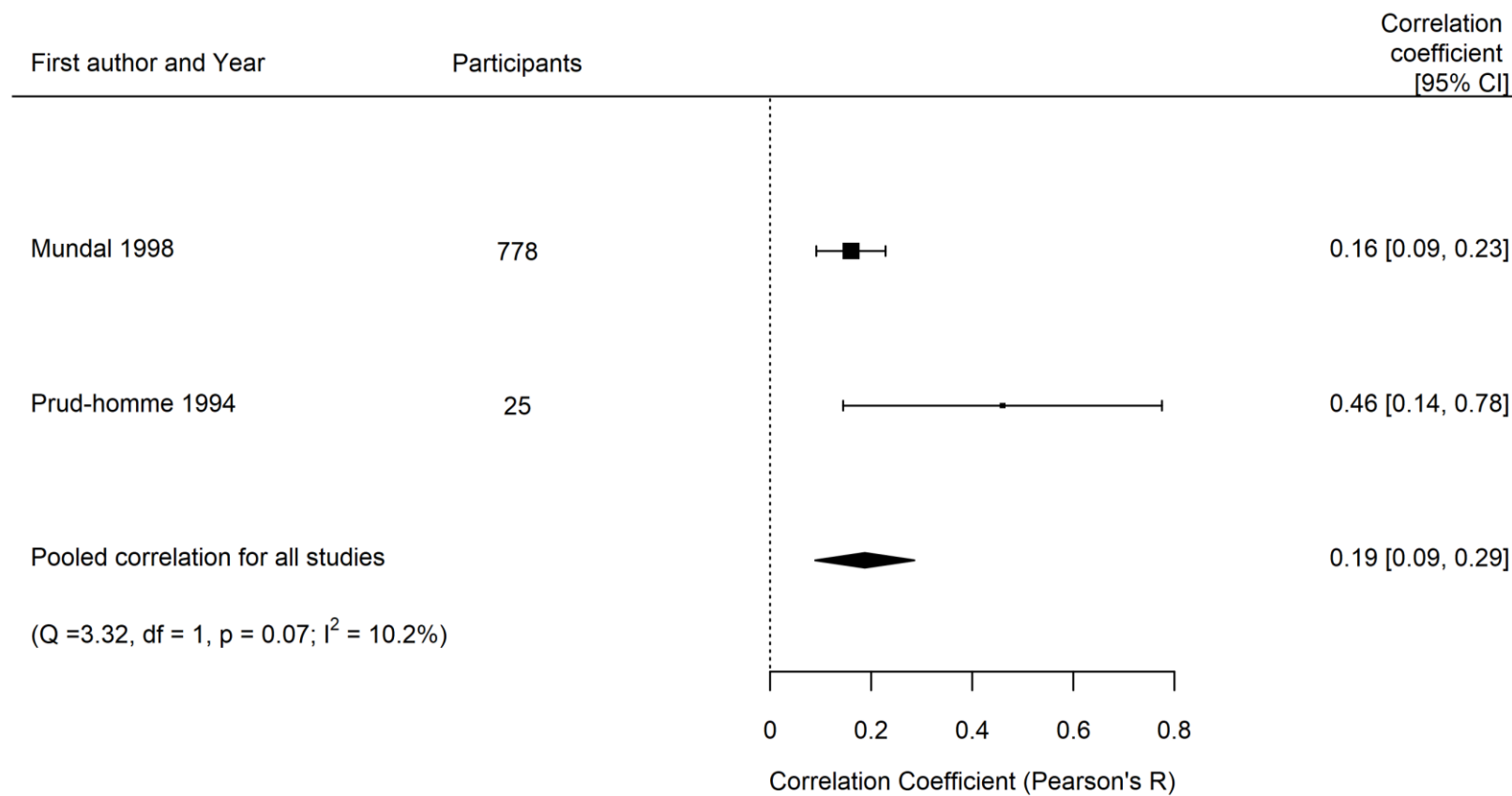
Appendix Figure 4.1. Prisma flow chart.



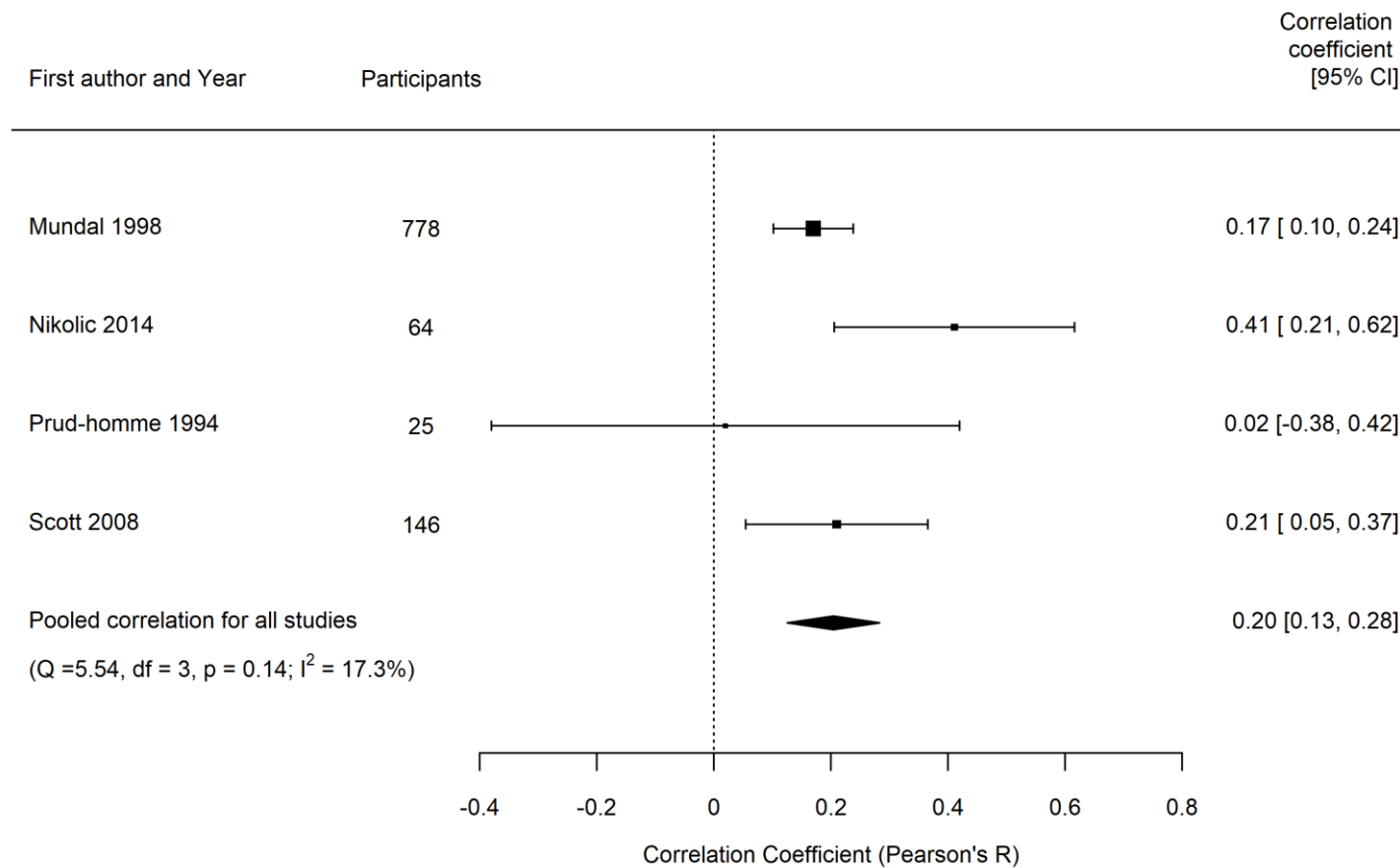
Appendix Figure 4.2. Pooled mean difference in aortic pulse wave velocity between individuals where a hypertensive response to exercise was present (HRE+) or absent (HRE-).



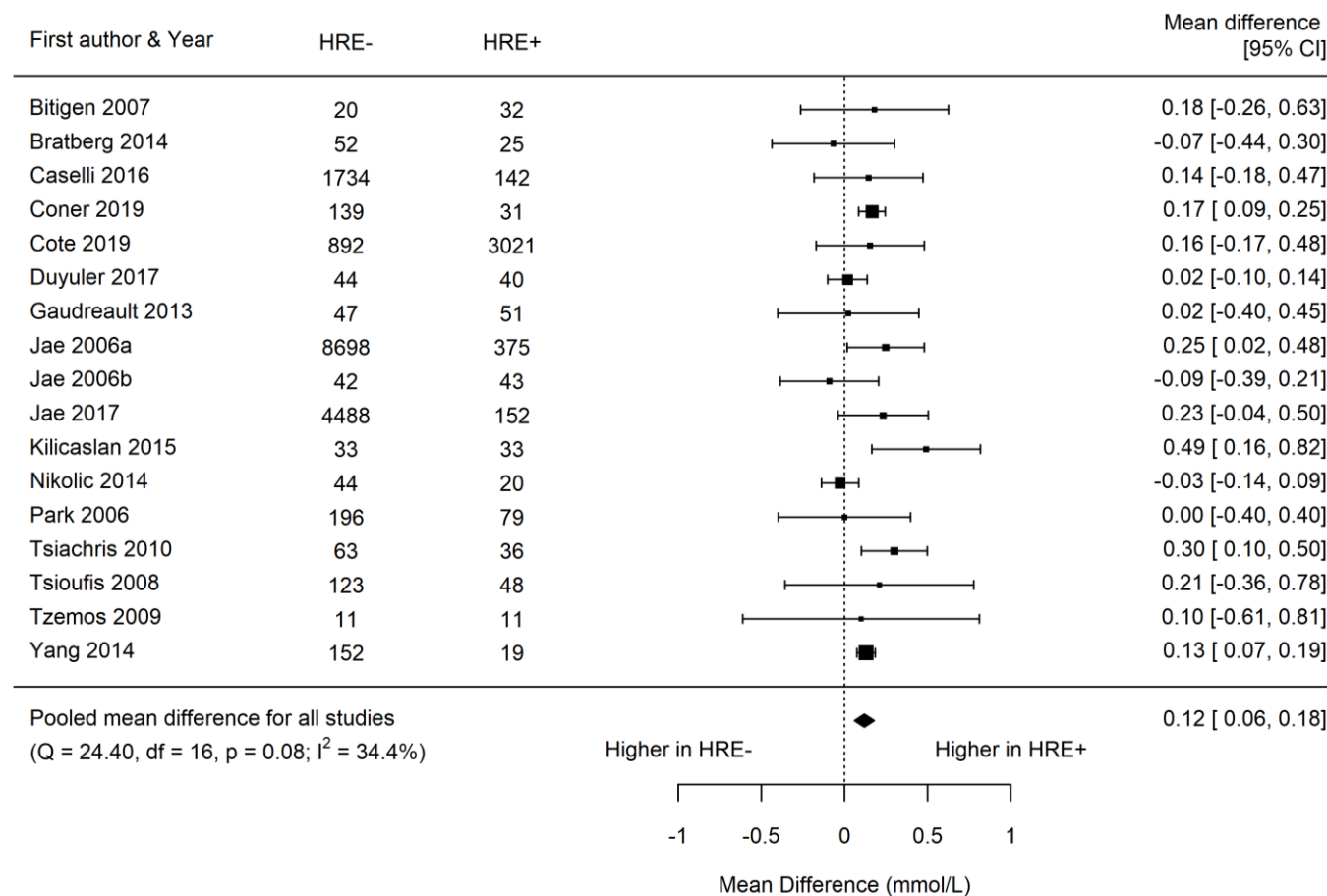
Appendix Figure 4.3. Pooled Mean difference in flow-mediated dilation between individuals where a hypertensive response to exercise was present (HRE+) or absent (HRE-).



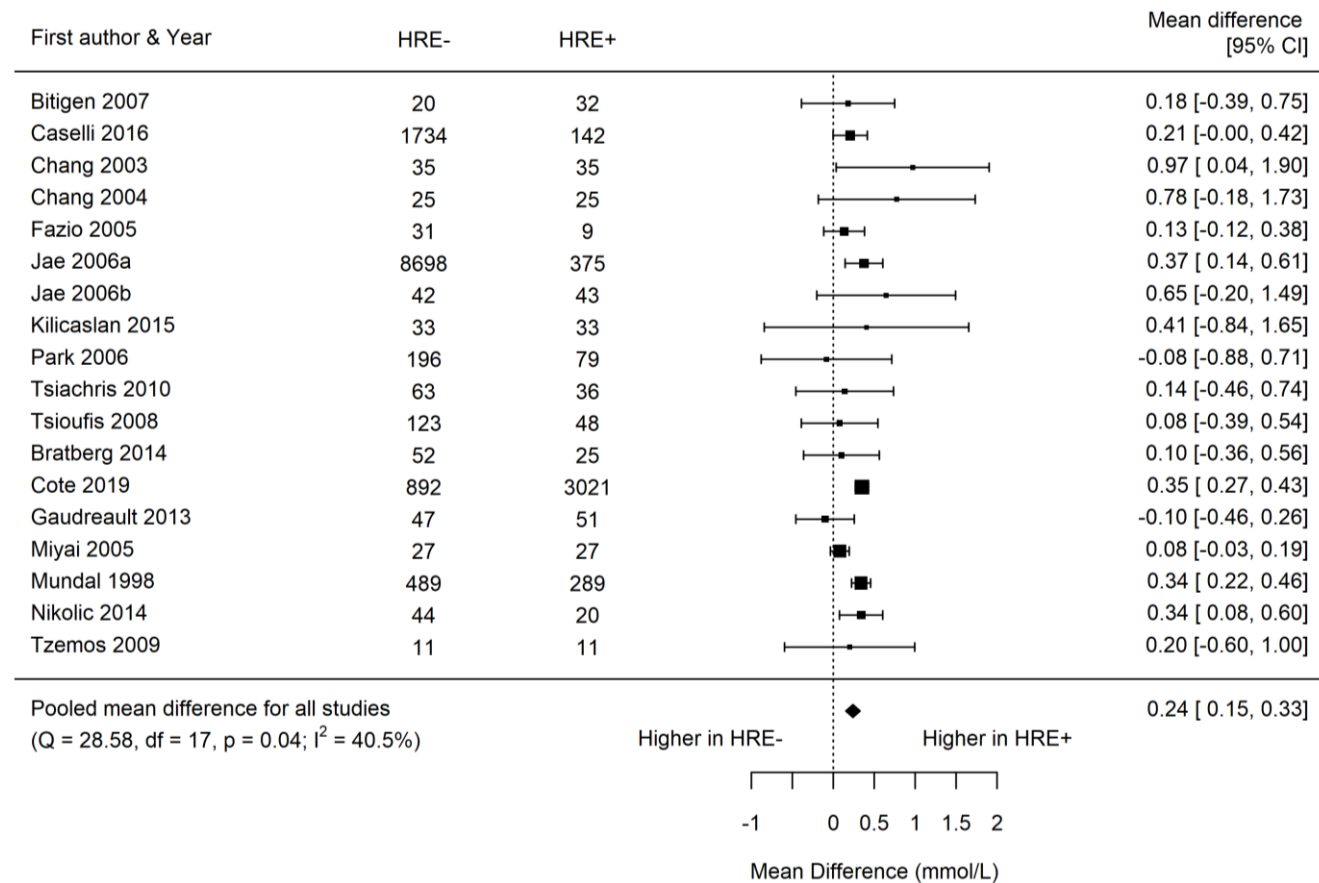
Appendix Figure 4.4. Pooled correlation between exercise blood pressure and total cholesterol.



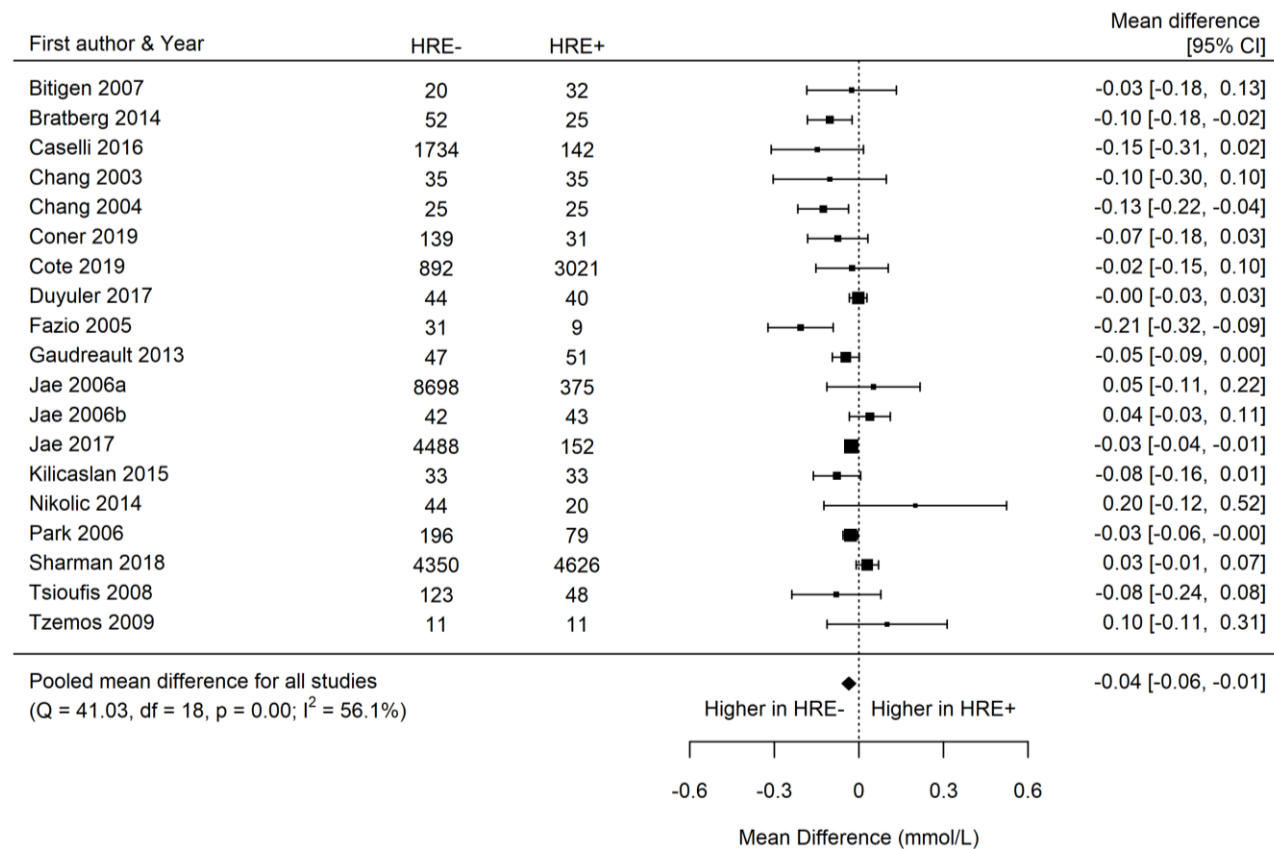
Appendix Figure 4.5. Pooled correlation between exercise blood pressure and triglycerides.



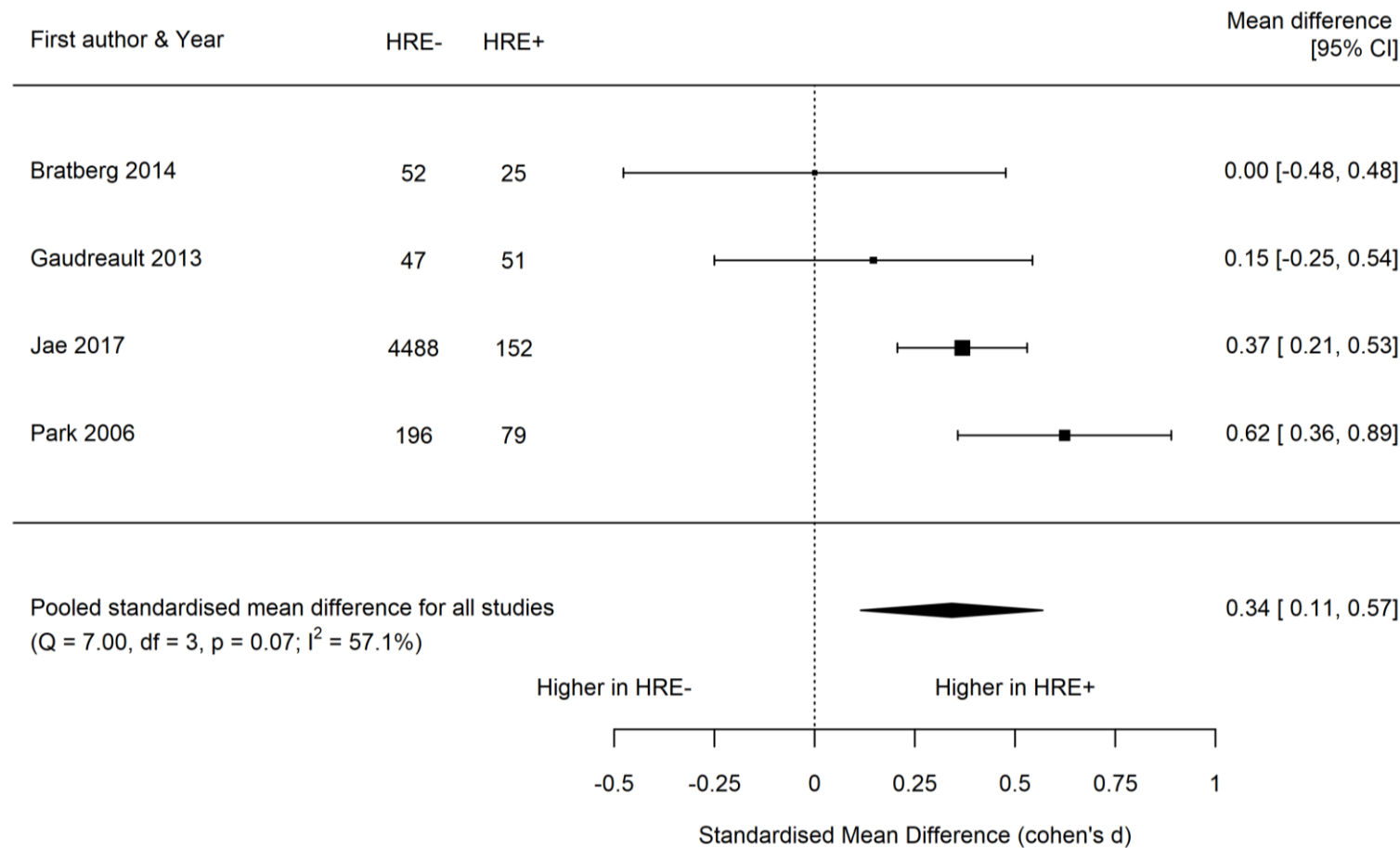
Appendix Figure 4.6. Mean difference in low-density lipoprotein cholesterol between individuals where a hypertensive response to exercise was present (HRE+) or absent (HRE-).



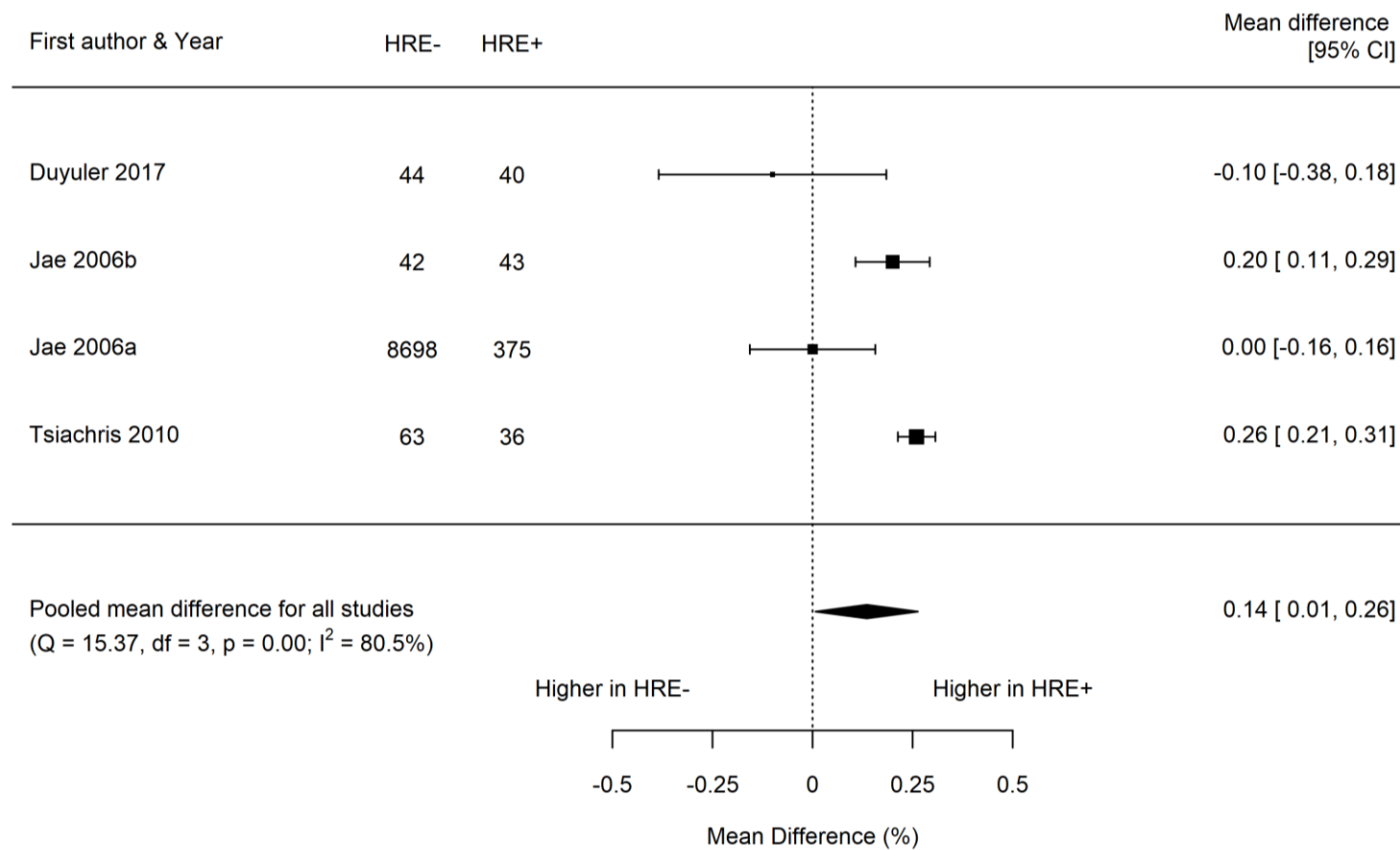
Appendix Figure 4.7. Mean difference in triglycerides between individuals where a hypertensive response to exercise was present (HRE+) or absent (HRE-).



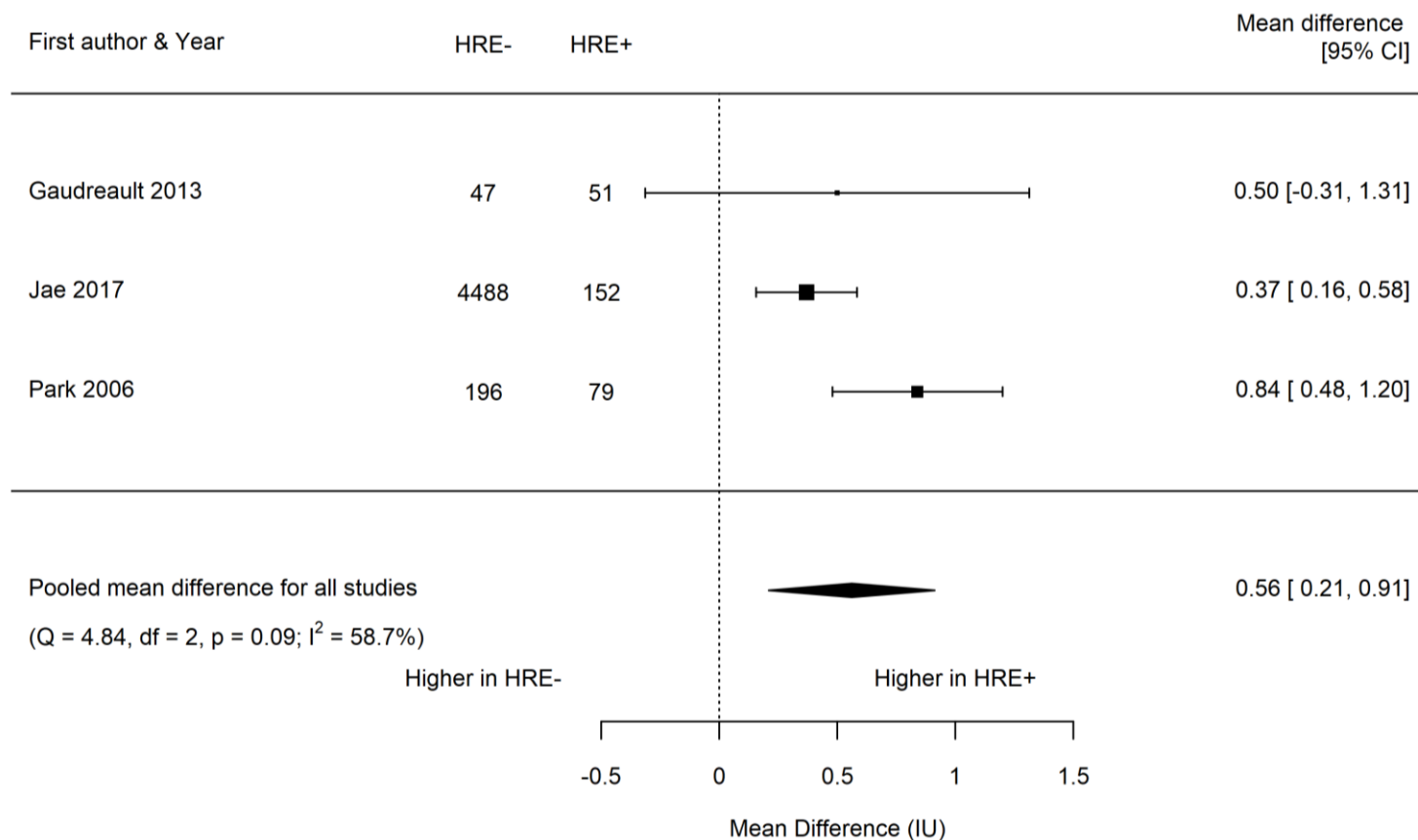
Appendix Figure 4.8. Mean difference in high-density lipoprotein cholesterol between individuals where a hypertensive response to exercise was present (HRE+) or absent (HRE-).



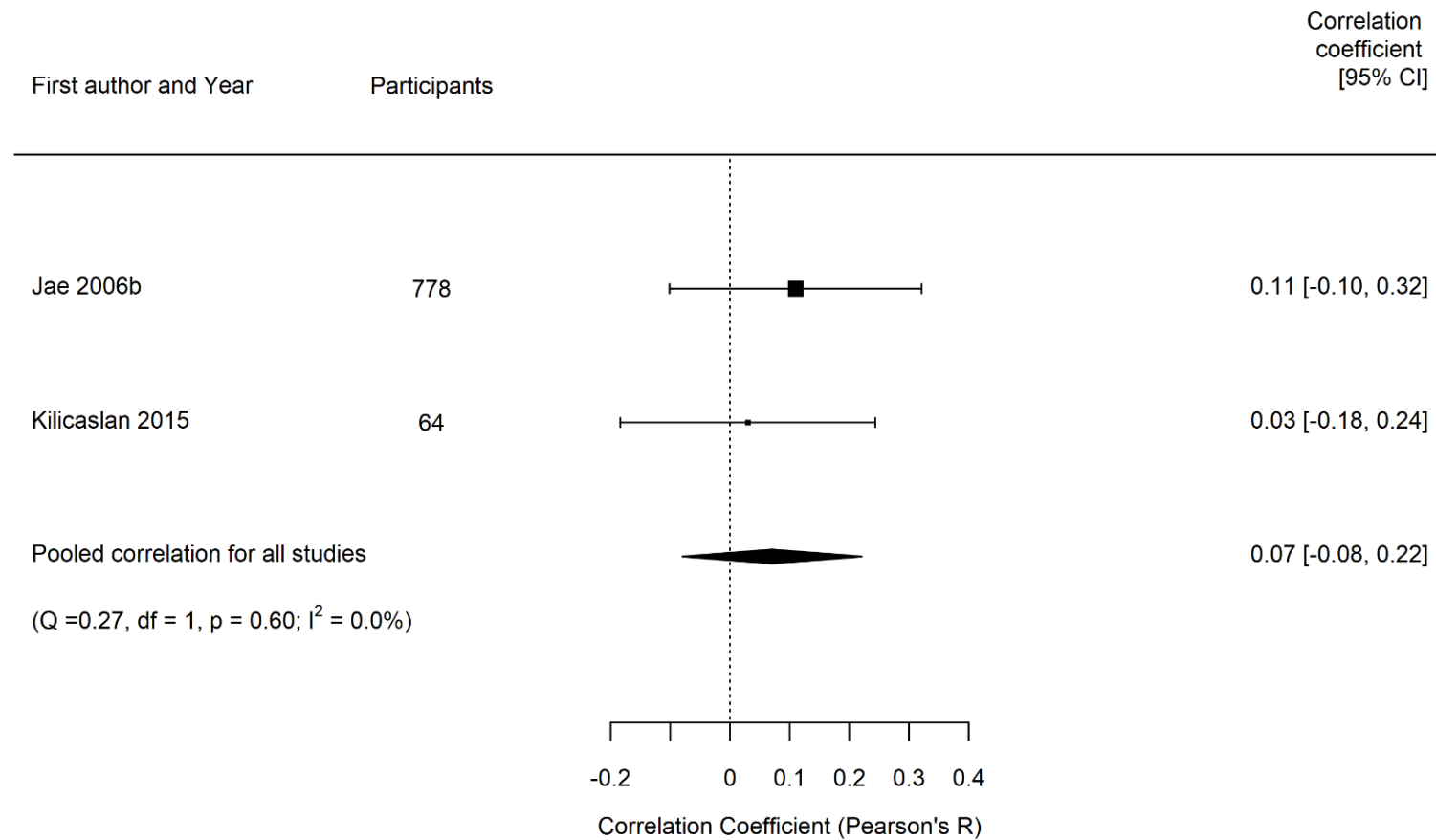
Appendix Figure 4.9. Standardised mean difference in insulin between individuals where a hypertensive response to exercise was present (HRE+) or absent (HRE-).



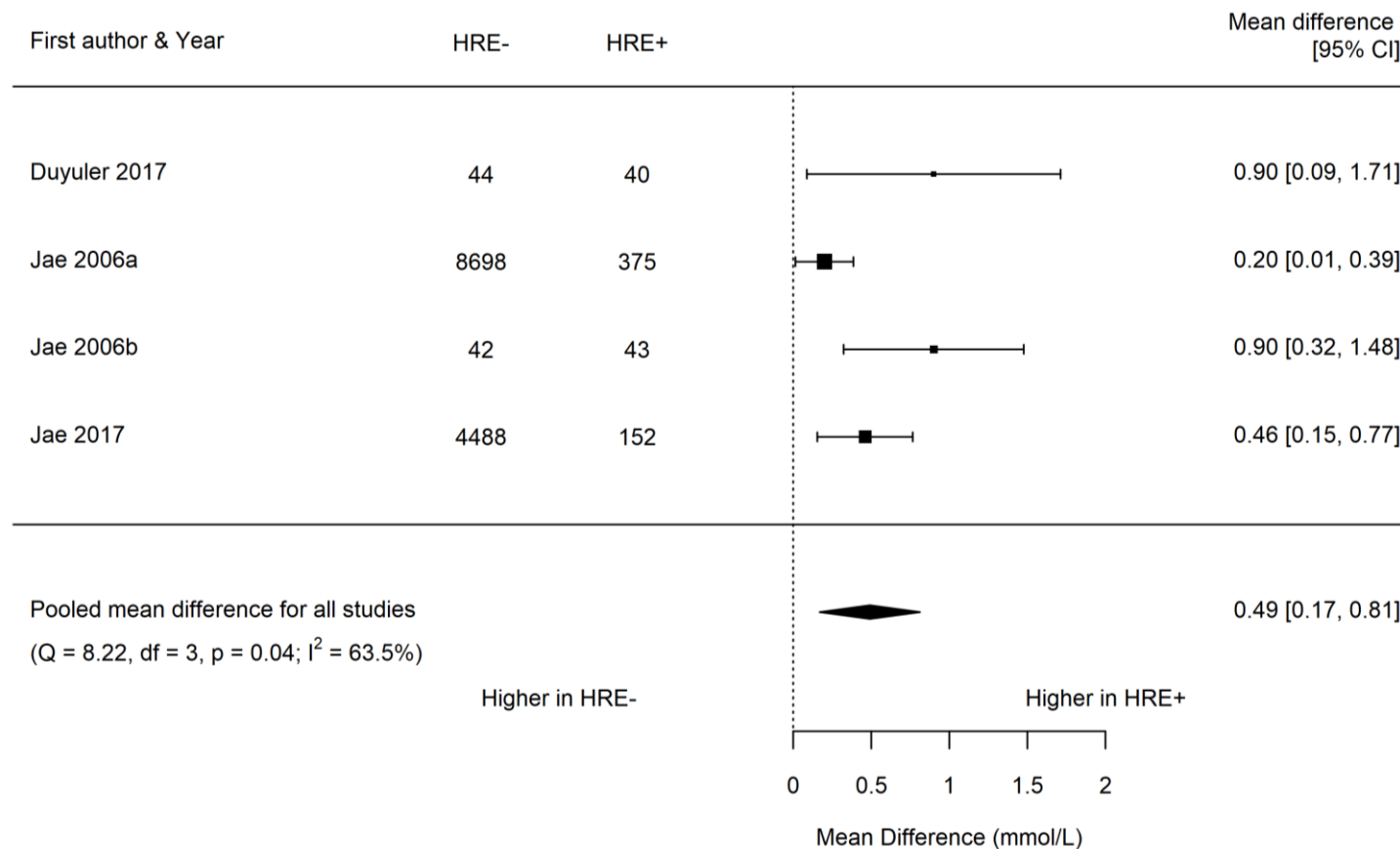
Appendix Figure 4.10. Mean difference in HbA1c between individuals where a hypertensive response to exercise was present (HRE+) or absent (HRE-).



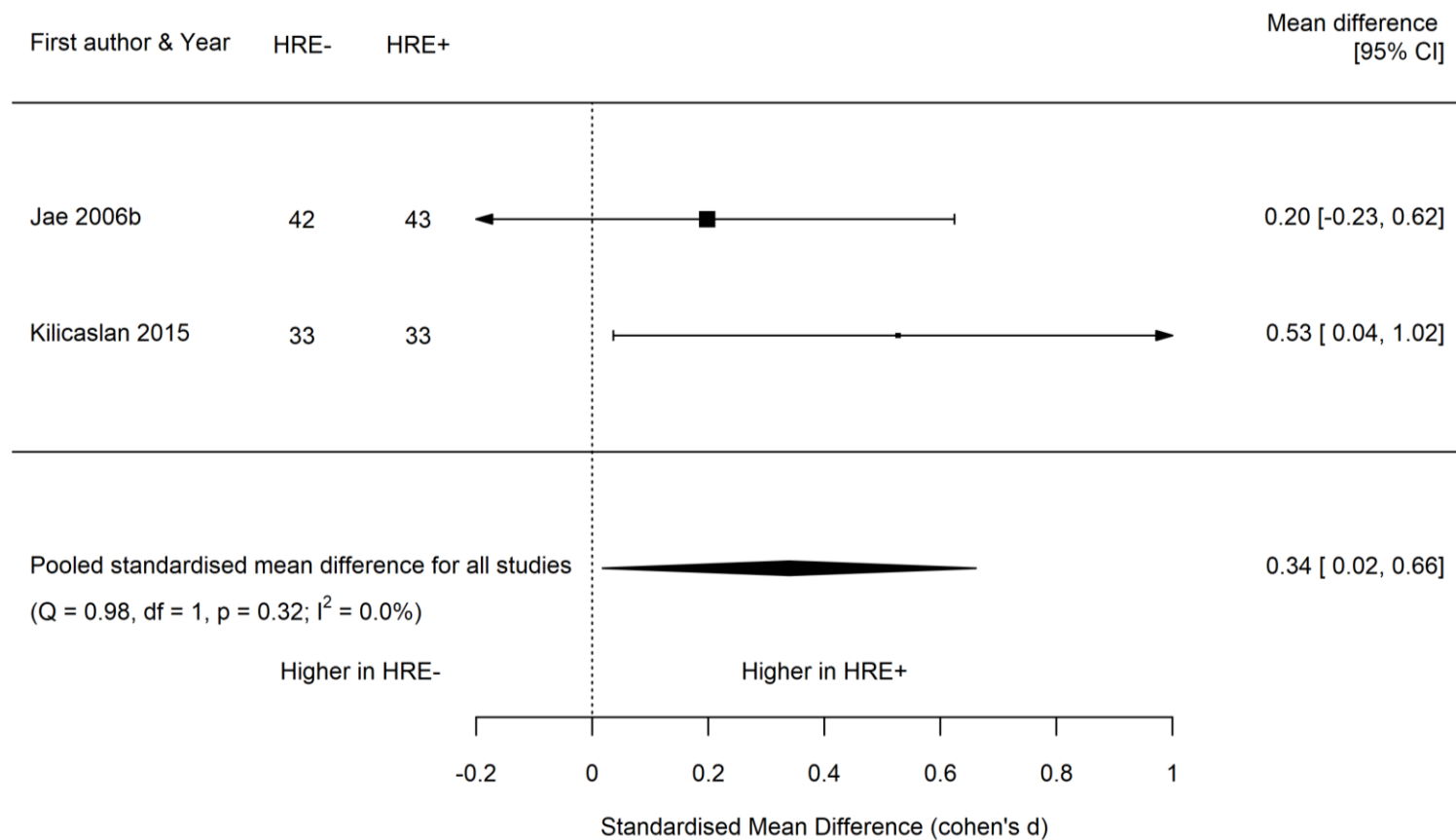
Appendix Figure 4.11. Mean difference in Homeostatic Model Assessment of Insulin Resistance between individuals where a hypertensive response to exercise was present (HRE+) or absent (HRE-).



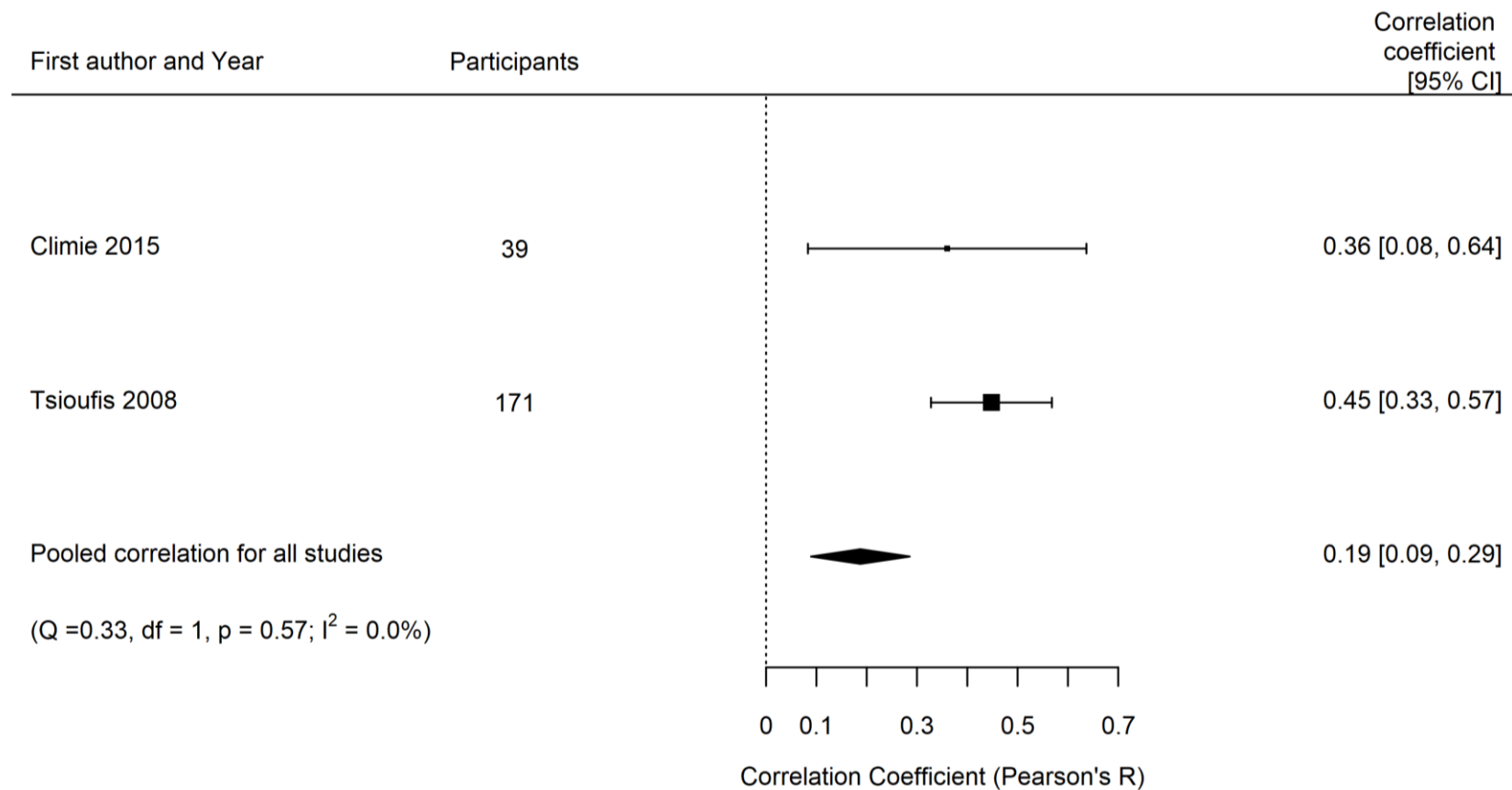
Appendix Figure 4.12. Pooled correlation between exercise blood pressure and c-reactive protein.



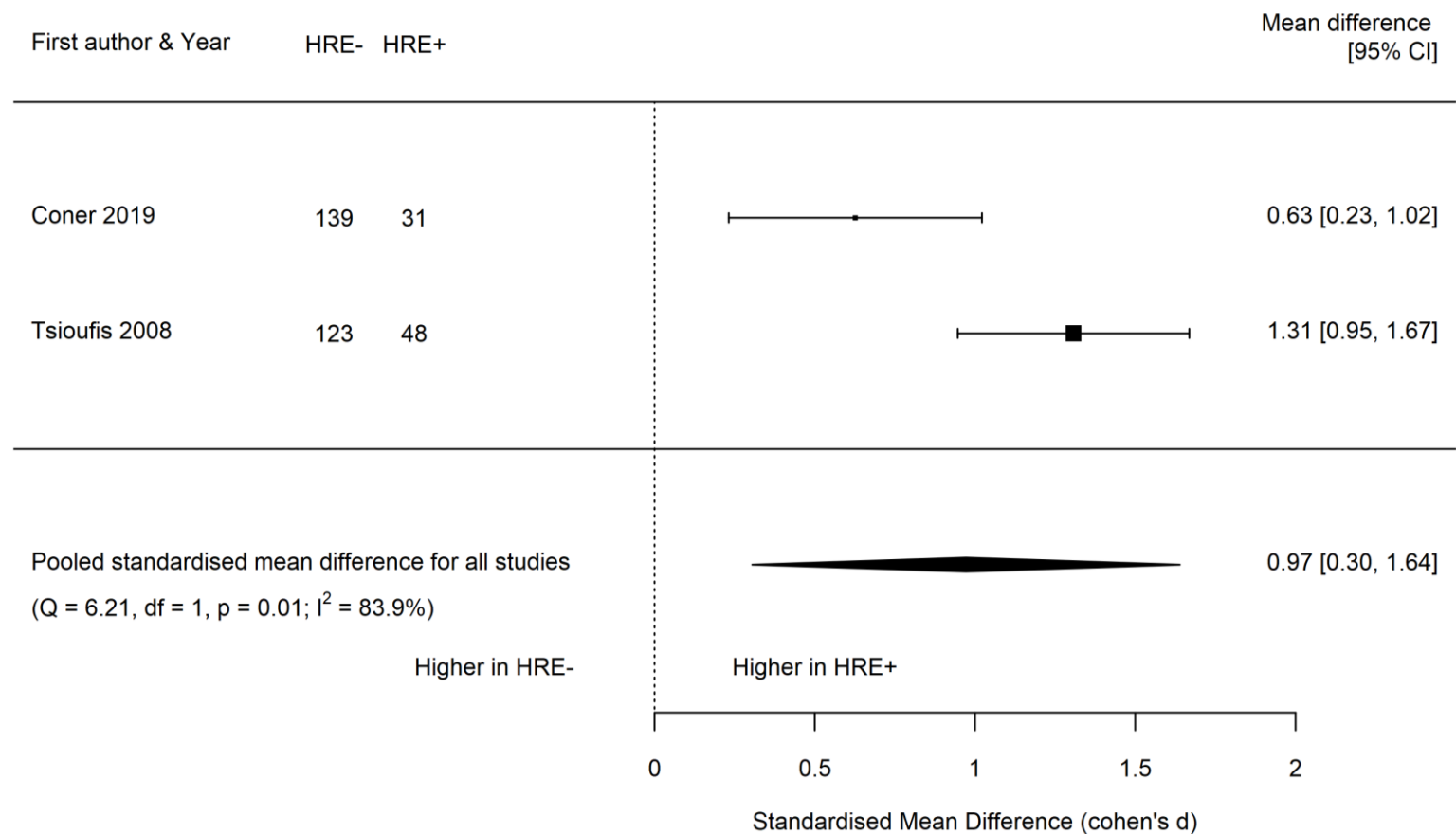
Appendix Figure 4.13. Mean difference in white blood cell count between individuals where a hypertensive response to exercise was present (HRE+) or absent (HRE-).



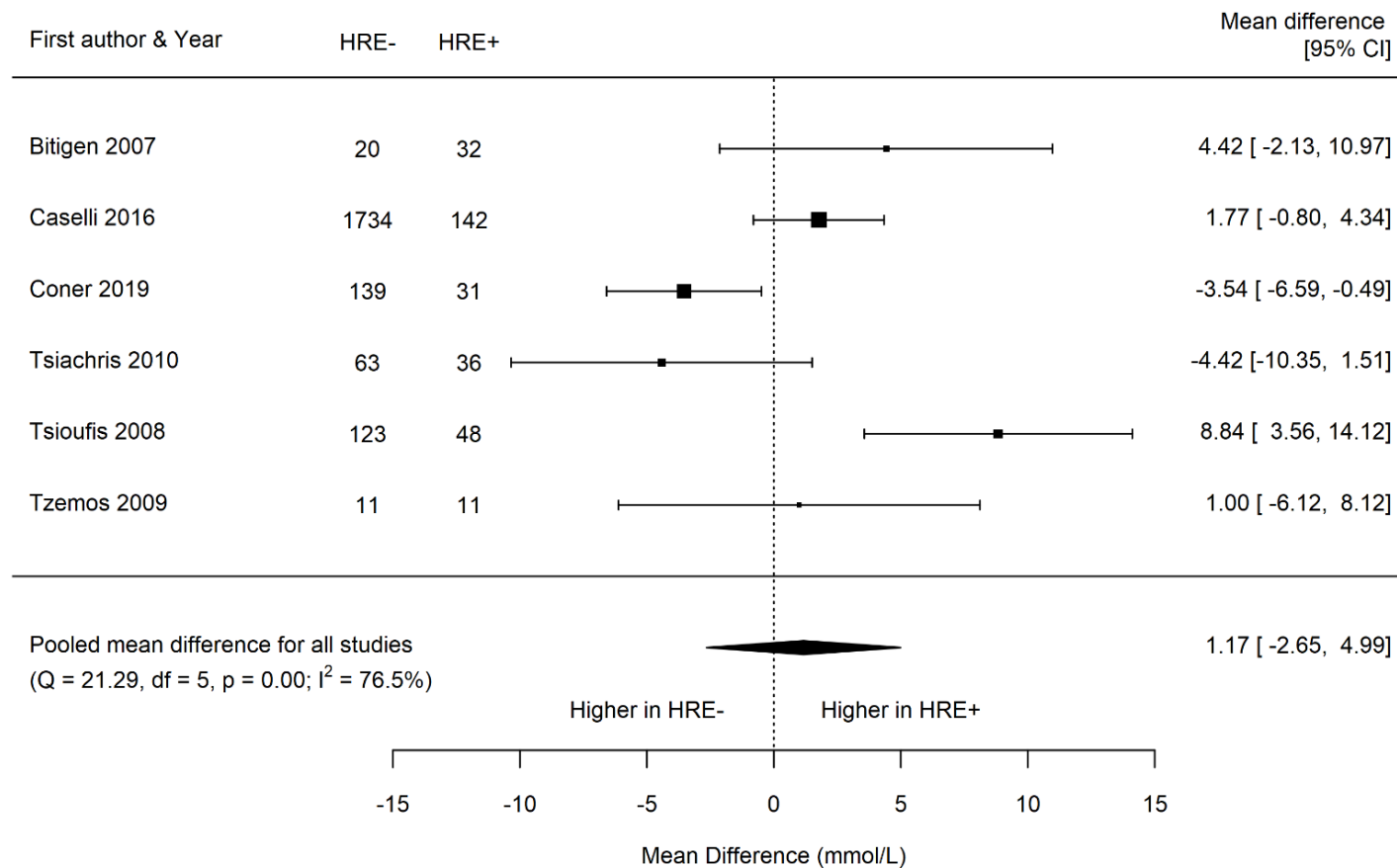
Appendix Figure 4.14. Standardised mean difference in c-reactive protein between individuals where a hypertensive response to exercise was present (HRE+) or absent (HRE-).



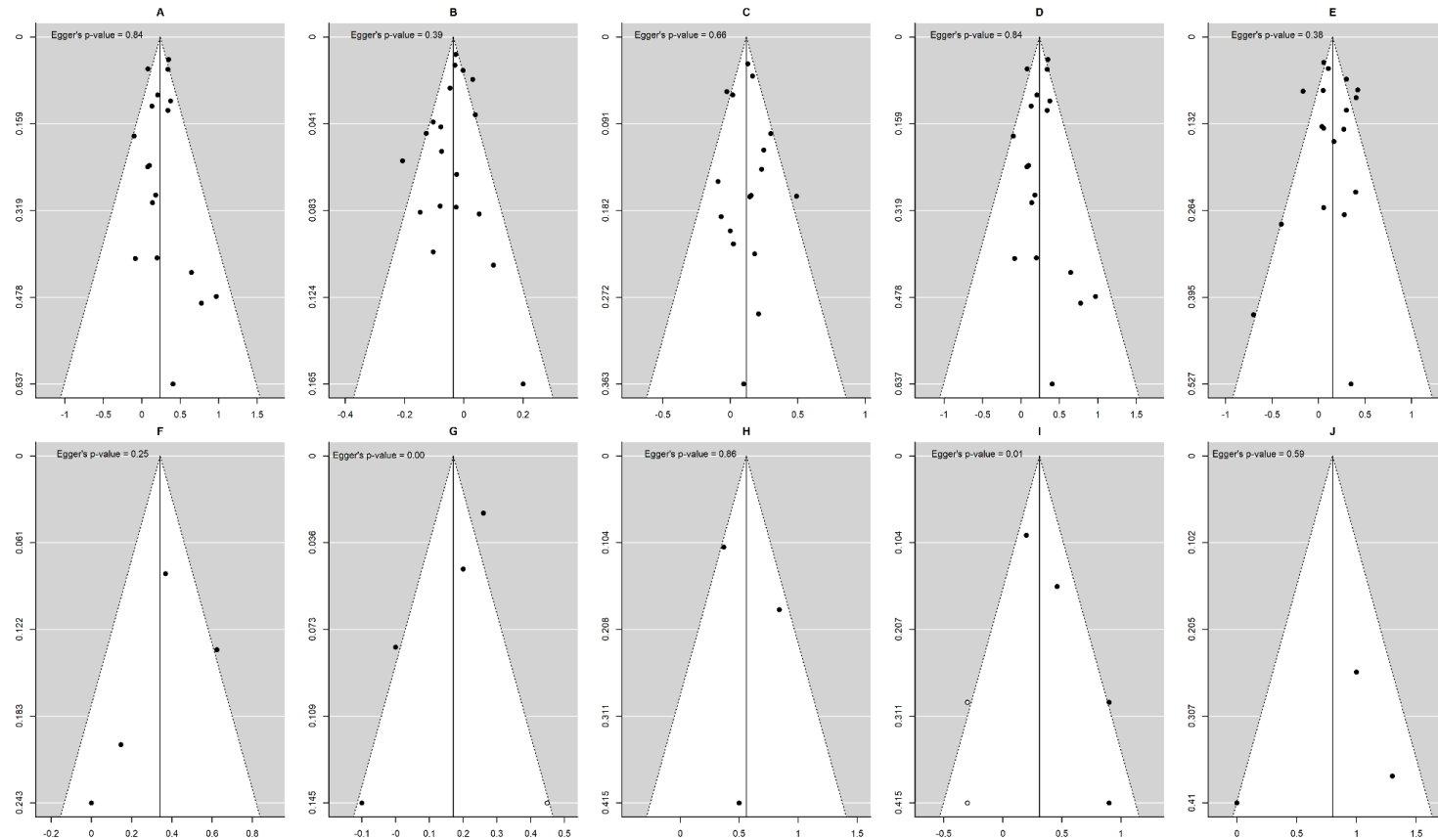
Appendix Figure 4.15. Pooled correlation between exercise blood pressure and albumin-creatinine ratio.



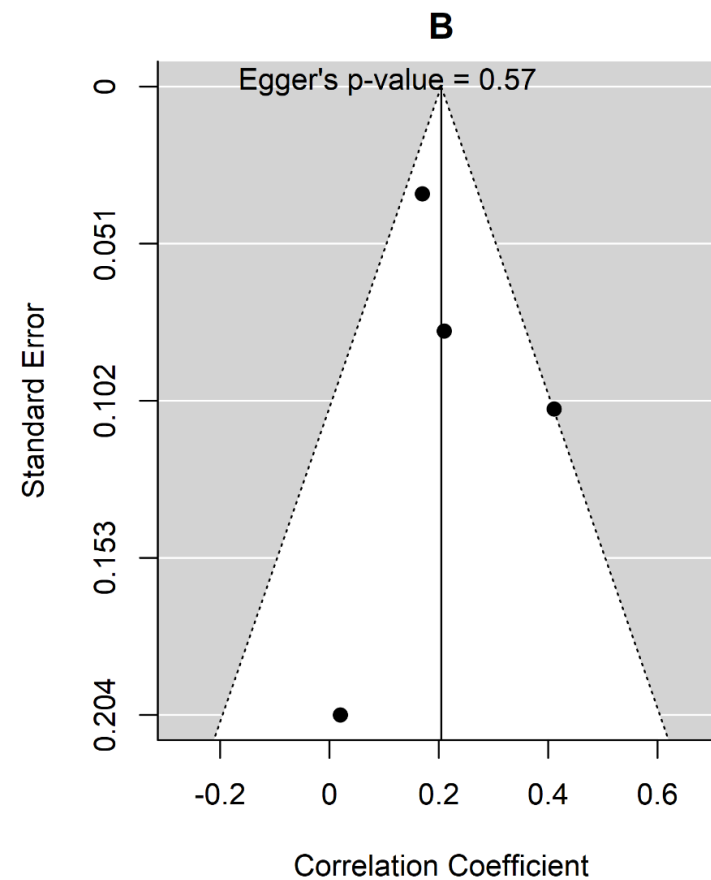
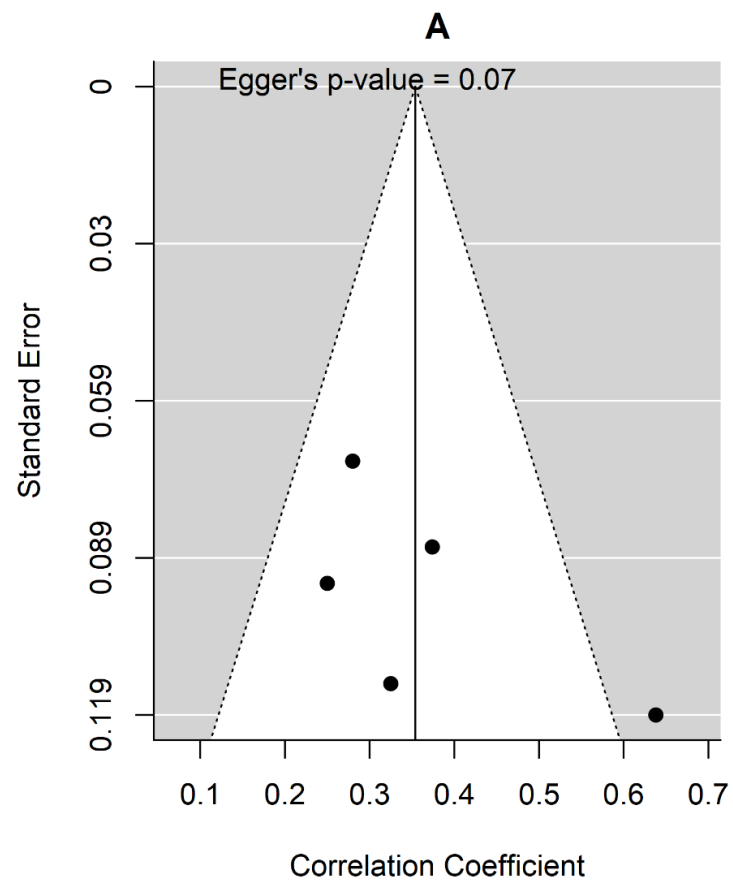
Appendix Figure 4.16. Standardised mean difference in albumin-creatinine ratio between individuals where a hypertensive response to exercise was present (HRE+) or absent (HRE-).



Appendix Figure 4.17. Mean difference in creatinine between individuals where a hypertensive response to exercise was present (HRE+) or absent (HRE-).



Appendix Figure 4.18. Funnel plots representing the publication bias for all meta-analyses conducted using categorical data. A) total cholesterol; B) high-density lipoprotein cholesterol; C) low-density lipoprotein cholesterol; D) triglycerides; E) glucose; F) Insulin; G) HbA1c; H) HOMA-insulin resistance; I) white blood cell count and; J) aortic pulse wave velocity. Funnel plots and egger's tests present an absence of publication bias across all outcomes. Filled dots represent the studies included in systematic review and meta-analysis.



Appendix Figure 4.19. Funnel plots representing the publication bias for all meta-analyses conducted using continuous data. A) Aortic pulse wave velocity and; B) Triglycerides.

APPENDIX D. SUPPLEMENTARY MATERIAL FOR CHAPTER 5.

Supplementary material.

Exercise test. Contraindications for completing the submaximal exercise test included resting systolic BP ≥ 180 mmHg, resting heart rate ≥ 100 bpm, current neck or back pain, been hospitalised in the three months prior to attending the follow-up clinic, knee or hip replacement, a history or family history of CVD or had been prescribed with medication for BP or CVD risk, were more than three months pregnant, any past or present injuries that would be aggravated by cycling, or were weight > 160 Kg.

Blood biochemistry. HOMA was first calculated as the product between glucose and insulin then dividing by 22.5 [286], and this calculation was used to define HOMA1-IR. HOMA was also calculated by a HOMA calculator (HOMA2; version 2.2.3 available from <http://www.dtu.ox.ac.uk/homacalculator>) using fasting glucose and fasting insulin [287]. This HOMA calculator was used to calculate HOMA2-insulin resistance (HOMA2-IR) and beta cell function (HOMA2- β) [288,289]. Participants were included in the calculations for HOMA2-IR and HOMA2- β when fasting glucose levels was 3.5–25 mmol/L (n=1 excluded) and when fasting insulin levels was 20–400 pmol/L (n=47 excluded) because these values were clinically realistic fasting values accepted by the calculator.

Muscular strength. Participants had two attempts to perform each strength measure (i.e. left and right hand grip, shoulder flexion and extension and leg extension), using isometric dynamometers (Smedley's Dynamometer, TTM, Tokyo, Japan). Maximal isometric force that participants exerted while holding the dynamometer in each hand was used to estimate hand grip strength. The hand that participants self-reported to be their dominant hand was used for in analyses of this study. The measures used to estimate shoulder strength (flexion and

extension) were performed with participants holding the dynamometer at chest-level with both hand parallel to the ground. Shoulder flexion was tested by participants simultaneously pushing the bars of the dynamometer medially, with counter-pressure applied by the opposing hand. In contrast, shoulder extension was tested by participants pulling the bars of the dynamometer apart. Leg strength was tested by participants standing flat-footed on the platform of the leg-back dynamometer with a straight back, shoulders and head against a wall. A hand bar was held with an over-hand grip, knees were flexed until an angle of 115° was measured, at which point the bar was attached to the dynamometer by a chain.

Statistical analysis. The interaction of sex and age on each univariable association was assessed using Wald's test. Age- or sex-interactions in the associations of exercise BP with a study factor were considered for reporting if they changed the coefficient of the study factor by more than 10% (an adaption of the change-in-coefficient approach [290]) and could not be attributed to a small number of ill-fitting values (leverage plots, residual plots and Cook's d influence statistic were scrutinised for this purpose). Weight, body mass index, waist and hip circumference, waist-to-hip ratio, fat and fat-free mass and fat mass percentage were grouped as "body composition". Glucose, insulin, HOMA-IR, HbA1c, and diabetes history were grouped as "metabolic". Total cholesterol, low- and high-density lipoprotein cholesterol and triglycerides were grouped as "lipids". Serum creatinine and c-reactive protein were grouped as "inflammation". Urine creatinine and albumin, and albumin-creatinine ratio were grouped as "kidney function". PWC₁₇₀ unadjusted and adjusted for lean body mass were grouped as "cardiorespiratory fitness". Clinic BP, resting heart rate and hypertension history were grouped as "haemodynamic". Dominant hand grip strength, shoulder flexion and extension strength and leg strength were grouped as "muscular strength".

Supplementary Results.

Albumin-creatinine ratio was not independently associated with exercise systolic BP in the mutually adjusted multivariable linear regression model ($p=0.171$), nor was it directly or indirectly associated with exercise systolic BP in the SEM. Therefore, albumin-creatinine ratio was excluded from these models. Urine creatinine was not independently associated with exercise diastolic BP in the mutually adjusted multivariable linear regression model ($p=0.685$), nor was it directly or indirectly associated with exercise diastolic BP in the SEM.

Appendix Table 5.1. Cardiovascular risk factors within groupings most-strongly associated with exercise systolic BP.

Grouping	Study factor	Effect of a one-unit change (95% CI)	R ²
Body composition	Body mass index, kg/m ²	0.58 (0.29, 0.87)	0.14
	Waist-to-hip ratio	65.52 (31.09, 99.95)	
Metabolic	HOMA1-IR	5.00 (3.18, 6.82)	0.10
Lipid	Triglycerides, mmol/L	3.02 (0.57, 5.48)	0.07
	LDLC, mmol/L	1.91 (0.20, 3.61)	
Kidney function	Urine albumin/creatinine ratio	1.10 (0.29, 1.91)	0.06
Fitness	Cardiorespiratory fitness unadjusted for lean body mass, Watts	-0.03 (-0.05, -0.01)	0.06
Inflammation	High-sensitivity c-reactive protein, mg/L	0.74 (0.19, 1.30)	0.06
Haemodynamic	Resting heart rate, bpm	0.23 (0.12, 0.36)	0.31
	Clinic BP, mmHg	0.66 (0.56, 0.75)	

CI, confidence interval; BP, blood pressure; HOMA1-IR, Homeostatic model assessment of insulin resistance; LDLC, low-density lipoprotein cholesterol; PWC₁₇₀, physical work capacity at a heart rate of 170 bpm. All coefficients reported after adjustment for sex and age and have a p-value < 0.05. R² is variance explained in relation to each grouping of study factors.

There was no difference in the R² for exercise systolic BP between HOMA1-IR and HOMA2-IR.

There was no difference in the R² for exercise systolic BP between cardiorespiratory fitness unadjusted or adjusted for lean body mass.

Appendix Table 5.2. Structural equation model indicating the direct and indirect effects of cardiovascular risk factors on exercise systolic BP.

Study factor	Direct effect of a one-unit change (95% CI)	Indirect effect of a one-unit change (95% CI)
Age, years	0.60 (0.33, 0.86) *	-
Female sex	4.19 (0.80, 7.58) *	-7.86 (-9.39, -6.33) *
Body mass index, kg/m ²	-	0.58 (0.43, 0.73) *
Waist-to-hip ratio	52.87 (26.11, 79.63) *	3.53 (1.37, 5.69) *
HOMA1-IR	-	0.32 (0.12, 0.51) *
LDLC, mmol/L	-	0.15 (0.02, 0.27) *
Triglycerides, mmol/L	-	1.58 (0.44, 2.72) *
Cardiorespiratory fitness unadjusted for lean body mass, Watts	-0.03 (-0.05, -0.01) *	-0.01 (-0.014, -0.005) *
High-sensitivity c-reactive protein, mg/L	-	0.11 (0.04, 0.17) *
Resting heart rate, bpm	-	0.14 (0.07, 0.20) *
Clinic BP, mmHg	0.66 (0.57, 0.75) *	-

Indirect effect indicates the effect of a study factor on exercise BP was mediated by one (or more) other study factors in the model. – represents a study factor had no direct or indirect effect on exercise BP. BP, blood pressure; CI, confidence interval; HOMA1-IR, Homeostatic model assessment of insulin resistance; LDLC, low-density lipoprotein cholesterol. * denotes statistical significance (p<0.05)

Appendix Table 5.3. Cardiovascular risk factors within groupings most-strongly associated with exercise diastolic BP.

Grouping	Study factor	Effect of a one-unit change (95% CI)	R ²
Body composition	Waist circumference, cm	0.34 (0.27, 0.41)	0.21
Metabolic	HOMA1-IR	4.99 (3.98, 6.00)	0.17
Lipid	Triglycerides, mmol/L	3.57 (2.07, 7.08)	0.09
	LDLC, mmol/L	1.46 (0.44, 2.49)	
Kidney function	Urine Creatinine, umol/L	0.20 (0.08, 0.33)	0.05
Fitness	Cardiorespiratory fitness unadjusted for lean body mass, Watts	-0.02 (-0.03, -0.01)	0.05
Inflammation	High sensitivity c-reactive protein, mg/L	0.95 (0.61, 1.29)	0.08
Haemodynamic	Resting heart rate, bpm	0.11 (0.05, 0.18)	0.51
	Clinic BP, mmHg	0.65 (0.60, 0.71)	

CI, confidence interval; BP, blood pressure; HOMA1-IR, Homeostatic model assessment 1 of insulin resistance; LDLC, low-density lipoprotein cholesterol; PWC₁₇₀, physical work capacity at a heart rate of 170 bpm. All coefficients reported after adjustment for sex and age and have a p-value <0.01. R² is variance explained in relation to each grouping of study factors.

There was no difference in the R² for exercise systolic BP between HOMA1-IR and HOMA2-IR.

There was no difference in the R² for exercise systolic BP between cardiorespiratory unadjusted or adjusted for lean body mass.

Appendix Table 5.4. Multivariable linear regression and structural equation models indicating cardiovascular risk factors most-strongly associated with exercise diastolic BP.

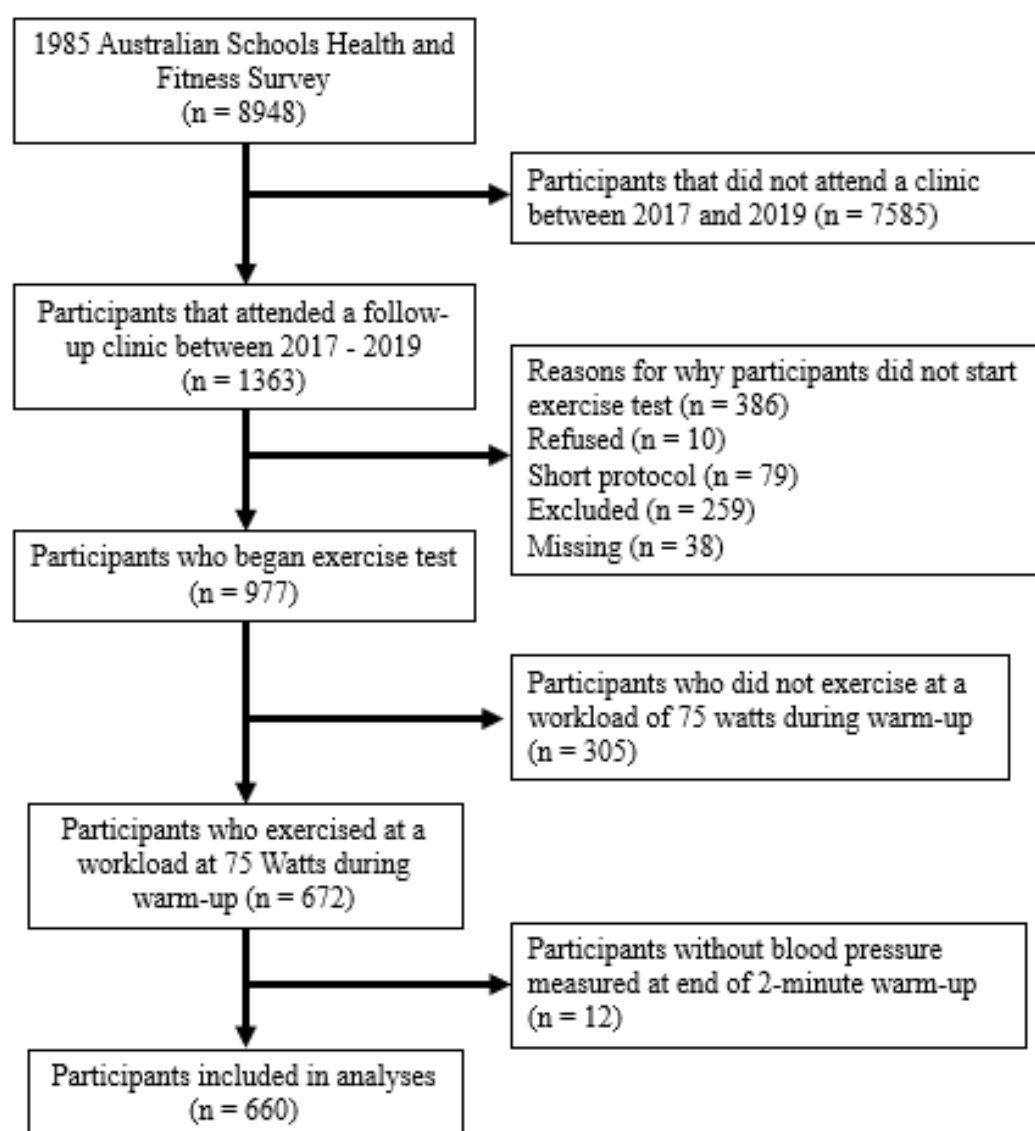
Study factor	SD	Mutually adjusted multiple linear regression	Structural equation model	
		Effect of a one-unit change (95% CI)	Effect of a one-unit change (95% CI)	Effect of a one SD change (95% CI)
Age, years	2.67	0.17 (-0.05, 0.40)	0.21 (0.05, 0.38) *	0.57 (0.14, 1.00) *
Female sex	0.50	-0.75 (-2.37, 0.87)	0.12 (-0.09, 0.33)	0.06 (-0.04, 0.16)
Waist circumference, cm	11.84	0.10 (0.01, 0.17) *	0.44 (0.38, 0.51) *	5.30 (4.54, 6.05) *
HOMA1-IR	0.81	0.65 (-0.34, 1.63)	0.38 (0.20, 0.55) *	0.31 (0.16, 0.45) *
Triglycerides, mmol/L	0.56	-0.17 (-1.39, 1.04)	1.03 (0.19, 1.88) *	0.58 (0.11, 1.05) *
LDLC, mmol/L	0.82	0.14 (-0.63, 0.91)	0.19 (0.04, 0.30) *	0.14 (0.03, 0.25) *
Cardiorespiratory fitness unadjusted for lean body mass, Watts	74.25	-0.01 (-0.02, 0.003)	-0.02 (-0.03, -0.01) *	-1.74 (-2.39, -1.09) *
High sensitivity c-reactive protein, mg/L	2.44	-0.02 (-0.30, 0.26)	0.12 (0.06, 0.18) *	0.09 (0.05, 0.13) *
Resting heart rate, bpm	9.52	0.06 (-0.01, 0.14)	0.16 (0.11, 0.20) *	0.12 (0.08, 0.15) *
Clinic BP, mmHg	10.74	0.60 (0.53, 0.67) *	0.63 (0.56, 0.69) *	6.74 (6.04, 7.44) *

BP, blood pressure; CI, confidence interval; HOMA1-IR, Homeostatic model assessment 1 of insulin resistance; LDLC, low-density lipoprotein cholesterol; SD, standard deviation. * denotes statistical significance (p<0.05)

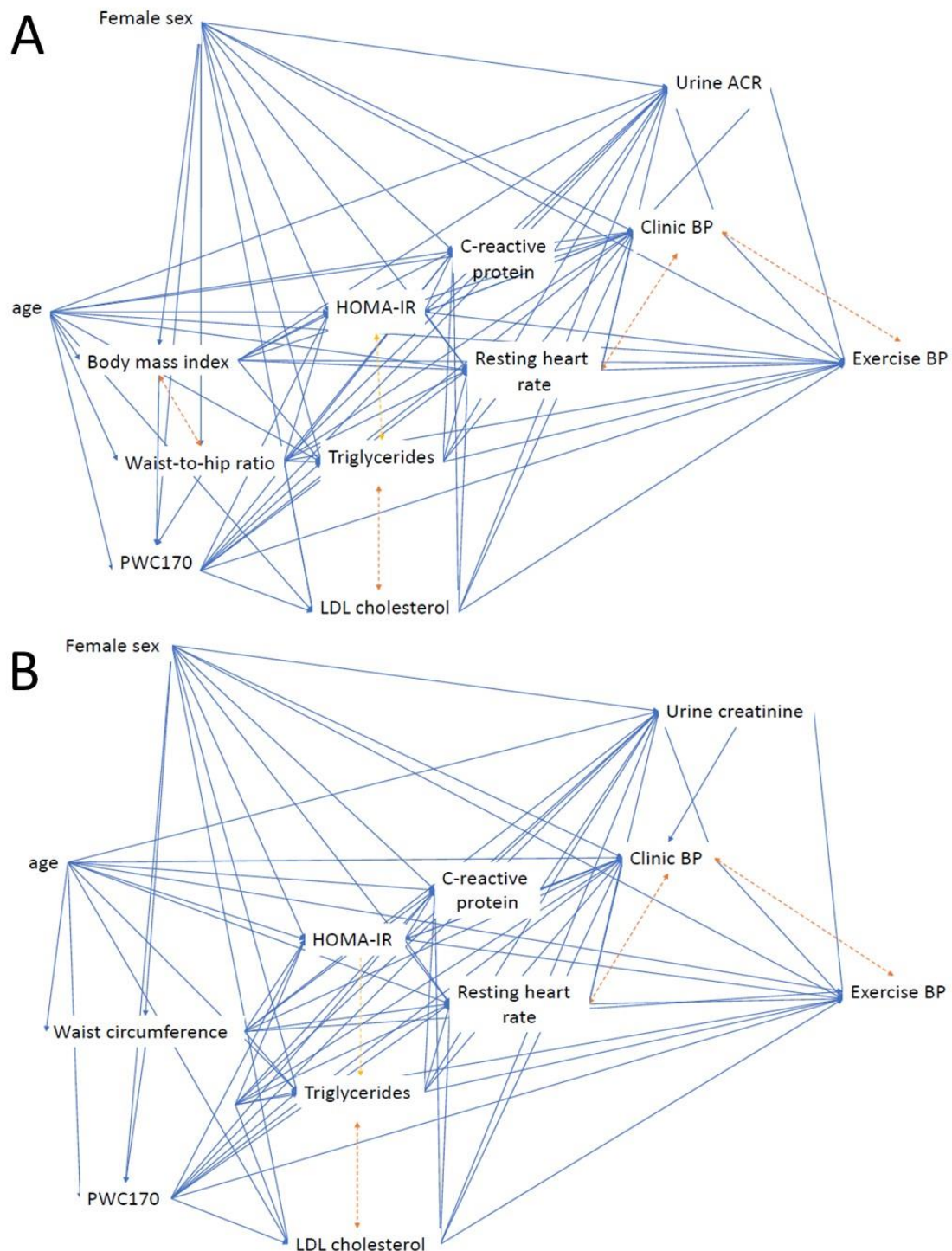
Appendix Table 5.5. Structural equation model indicating the direct and indirect effects of cardiovascular risk factors on exercise diastolic BP.

Study factor	Direct effect of a one-unit change (95% CI)	Indirect effect of a one-unit change (95% CI)
Age, years	-	0.21 (0.05, 0.38) *
Female sex	-	0.12 (-0.09, 0.33)
Waist circumference, cm	0.13 (0.07, 0.19) *	0.32 (0.27, 0.37) *
HOMA1-IR	-	0.38 (0.20, 0.55) *
Triglycerides, mmol/L	-	1.03 (0.19, 1.88) *
LDLC, mmol/L	-	0.19 (0.04, 0.30) *
Cardiorespiratory fitness unadjusted for lean body mass, Watts	-0.014 (-0.022, -0.005) *	-0.01 (-0.013, -0.007) *
High sensitivity c -reactive protein, mg/L	-	0.12 (0.06, 0.18) *
Resting heart rate, bpm	-	0.16 (0.11, 0.20) *
Clinic BP, mmHg	0.63 (0.56, 0.69) *	-

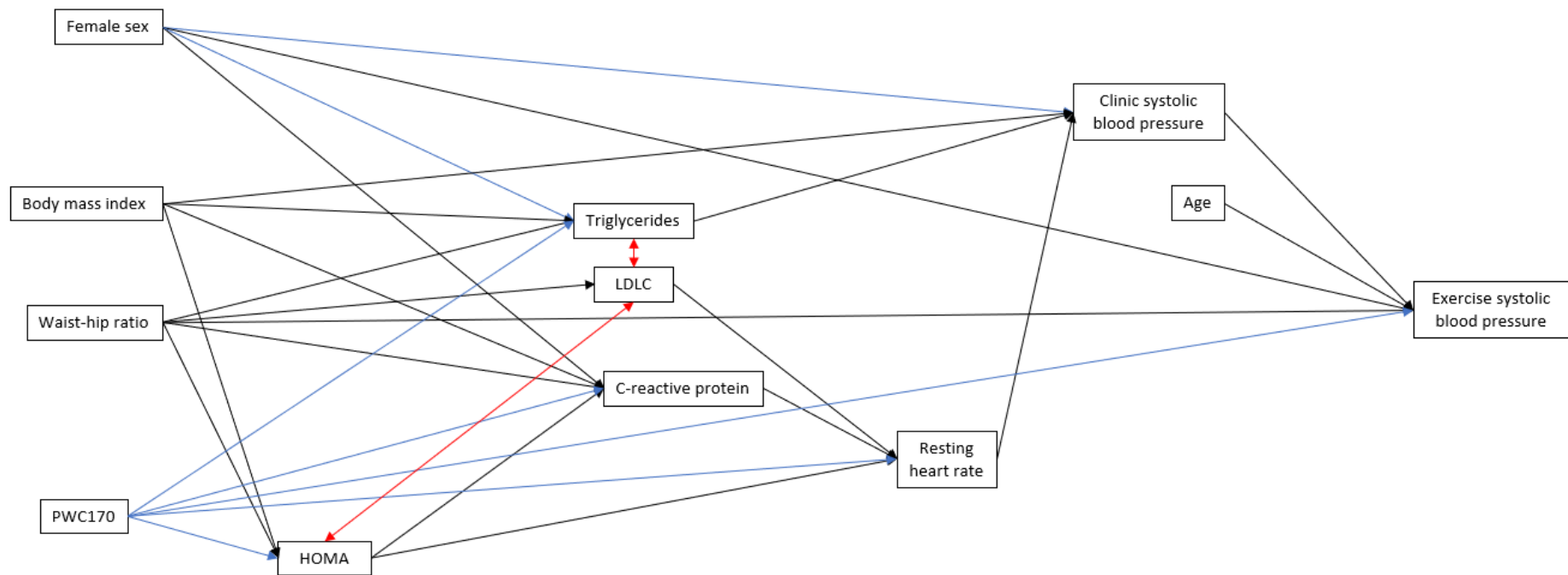
Indirect effect indicates the effect of a study factor on exercise blood pressure was mediated by one (or more) other study factors in the model.
– represents a study factor had no direct or indirect effect on exercise BP. BP, blood pressure; CI, confidence interval; HOMA1-IR, Homeostatic model assessment 1 of insulin resistance; LDLC, low-density lipoprotein cholesterol. * denotes statistical significance (p<0.05)



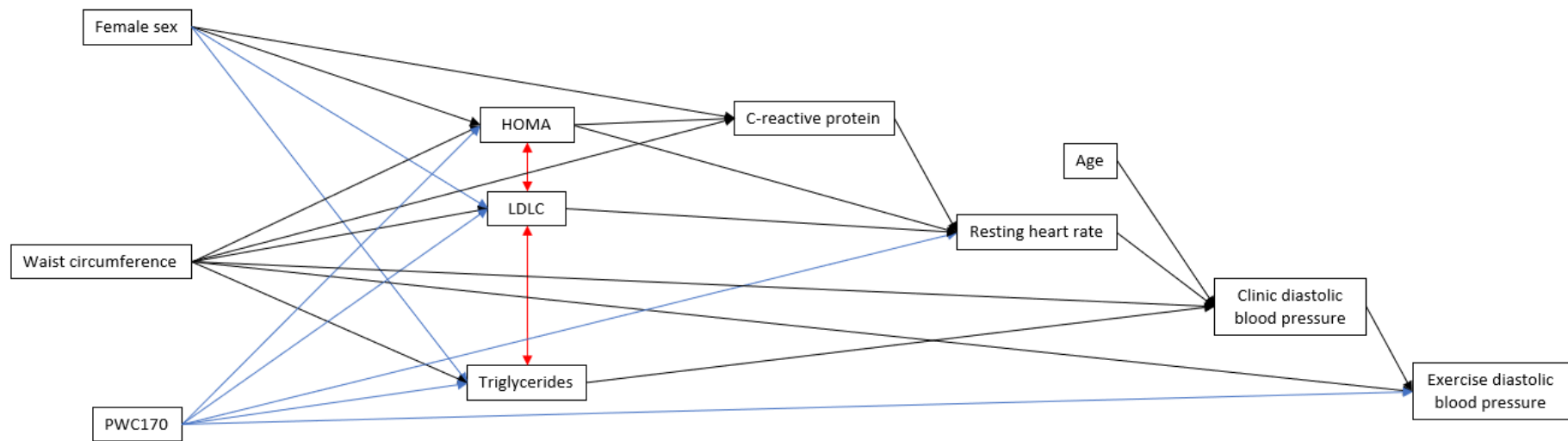
Appendix Figure 5.1. Flow of participants.



Appendix Figure 5.2. Hypothesized pathways of association between different cardiovascular disease risk factors on exercise systolic blood pressure (BP; panel A) and diastolic BP (panel B). Blue lines indicate a hypothesized directional association between two variables included in the structural equation model. Dual head orange arrows indicate a possible shared measurement error between two study factors. HOMA-IR, Homeostatic model assessment of insulin resistance; LDL cholesterol, low-density lipoprotein cholesterol; PWC170, physical work capacity at a heart rate of 170 bpm; ACR, albumin-creatinine ratio



Appendix Figure 5.3. Direct and indirect effects of different cardiovascular risk factors on exercise systolic blood pressure. Black single head arrows indicate a positive effect from one study factor to another. Blue single head arrows indicate a negative effect from one study factor to another. Red dual head arrows indicate a positive association between the measurement errors of two study factors. Overall goodness of model fit: chi-square divided by degrees of freedom = 1.93, root mean square error of approximation = 0.039, comparative fit index = 0.981, and Tucker-Lewis index = 0.963. HOMA, Homeostatic model assessment of insulin resistance; LDLC, low-density lipoprotein cholesterol; PWC170, physical work capacity at a heart rate of 170 bpm.



Appendix Figure 5.4. Direct and indirect effects of different cardiovascular risk factors on exercise diastolic blood pressure. Black single head arrows indicate a positive effect from one study factor to another. Blue single head arrows indicate a negative effect from one study factor to another. Red dual head arrows indicate a positive association between the measurement errors of two study factors. Overall goodness of model fit: chi-square divided by degrees of freedom = 1.93, root mean square error of approximation = 0.039, comparative fit index = 0.981, and Tucker-Lewis index = 0.963. HOMA, Homeostatic model assessment of insulin resistance; LDLC, low-density lipoprotein cholesterol; PWC170, physical work capacity at a heart rate of 170 bpm.

