# PHYSICAL ACTIVITY & MENOPAUSE ON FEMALE CARDIOVASCULAR HEALTH

# PHYSICAL ACTIVITY AND MARKERS OF CARDIOVASCULAR HEALTH: UNDERSTANDING THE INFLUENCE OF MENOPAUSE AND STROKE

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A Thesis Submitted to the School of Graduate Studies in Partial Fulfilment of the Requirements for the Degree Master of Science

McMaster University MASTER OF SCIENCE (2023) Hamilton, Ontario (Rehabilitation Science)

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| TITLE: | THE EFFECT OF EXERCISE AND PHYSICAL ACTIVITY ON TRADITIONAL CARDIOVASCULAR HEALTH MARKERS IN PRE- AND POSTMENOPAUSAL FEMALES WITH AND WITHOUT STROKE |
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| PAGES: | xvi, 137 |

## LAY ABSTRACT

Exercise and physical activity are good for the health of the heart and blood vessels. We do not know how physical activity also benefits females after menopause and females with stroke. This thesis examined the association between physical activity and the health of the heart and blood vessels in females before and after menopause, with and without stroke. The first study reviewed other studies that looked at the effect of aerobic exercise on the health of the heart and blood vessels in females after menopause. We found that after menopause females might benefit from aerobic exercise. We also found that different intensities of exercise may affect the health of the heart and blood vessels better than others, but more research is needed. The second study found that physical activity is related to better health of the heart and blood vessels in females after stroke, and whether a female has undergone menopause does not change this relationship. These studies show that exercise and physical activity may help the health of heart and blood vessels in females after menopause and females with stroke. Together they may help inform future exercise and physical activity guidelines and research to improve the health of the heart and blood vessels in these populations.

## ABSTRACT

In females, menopause-related reductions in estrogen may cause declines in cardiovascular health and increase the risk for stroke. In the event of stroke, cardiovascular health of postmenopausal females may be further worsened. It is well established that physical activity and exercise improves cardiovascular health in the general population and in those with chronic conditions, including stroke. However, the nature and extent of the associations between physical activity and cardiovascular health of pre- and post-menopausal females with, and without, stroke are unclear. This thesis is comprised of two studies to address this knowledge gap.

The first study was a systematic review to examine the effect of aerobic exercise on cardiovascular health of postmenopausal females, and the association with different exercise intensities. Five electronic databases from inception to May 6th, 2022, were searched for randomized-controlled trials of aerobic exercise interventions reporting cardiovascular outcomes in postmenopausal females. Data was synthesized qualitatively, and random-effects meta-analyses and subgroup analyses (for light, moderate, vigorous intensity) were performed. Fifty-six studies (4134 participants;45-78 years of age) were identified. Aerobic exercise interventions varied in frequency (3-21x/week), intensity, type, time (8-60 min/session), and duration (3-52 weeks). Fifty studies (n=3730) were included in the quantitative synthesis. Aerobic exercise improved systolic blood pressure (SBP) (Mean difference(MD)=-3.67mmHg, 95%CI[-6.88,-0.46],p=0.03), resting heart rate (MD=-5.76bpm, 95%CI[-5.76,-1.61],p<0.01), body mass index (BMI)(MD=-0.65kg/$m^2$, 95%CI[-0.99,-0.31],p<0.01), waist circumference (WC) (MD=-2.03cm, 95%CI[-2.65,-1.41],p<0.01), body fat (MD=-2.57kg, 95%CI[-3.65,-1.49],p<0.01), low-density lipoprotein cholesterol (MD=-10.46mg/dL, 95%CI[-16.31,-4.61],p<0.01), high-density

lipoprotein cholesterol (MD=3.28mg/dL, 95%CI[0.20,6.36],p=0.04) and cardiorespiratory fitness (Standardized MD=1.43, 95%CI[1.17,1.70],p<0.01). Subgroup differences in exercise intensity were only present for BMI where light- and vigorous-intensities were beneficial, and moderate intensity had no effect ($X^2$=9.79, df=2,p<0.01), and for blood triglycerides and blood glucose where light intensity showed a beneficial effect and there was no effect of moderate and vigorous intensities (triglycerides $X^2$=7.70, df=2, p=0.02; glucose $X^2$=20.98, df=2, p<0.01).

The second study was a cross-sectional analysis of baseline data from the Canadian Longitudinal Study on Aging that examined the association between physical activity and cardiovascular health in females with stroke, and the interaction with menopause. Generalized linear models with applied sampling weights were used to examine the associations between cardiovascular health, and self-reported physical activity, while controlling for age and smoking history. Subsequent models included an interaction between physical activity and menopausal status. The sample included 1468 females with stroke (103 premenopausal). Physical activity was beneficially associated with SBP (ß = -0.02 (SE=0.01), p=0.04, 95% CI: -0.42 to -0.0005), WC (ß = -0.03 (SE=0.008), p<0.01, 95% CI: -0.05 to -0.02), waist-to-hip ratio (ß = -0.00009 (SE=0.00004), p=0.03, 95% CI: -0.0002 to -0.0000007), C-Reactive protein (ß = -0.007 (SE=0.003), p<0.02, 95% CI: -0.013 to -0.001). There were no interactions between physical activity and menopausal status for all outcomes.

Together, these studies contribute to the development of future guidelines and research to improve cardiovascular health in underrepresented and high-risk populations of postmenopausal females and females with stroke.

## ACKNOLWEDGMENTS

First, I would like to express my deepest thanks to Dr Ada Tang, who has been an exceptional supervisor throughout my MSc. Your unwavering dedication, expertise, and insightful guidance have played a pivotal role in shaping my academic and personal growth. You consistently challenged me to delve deeper into my research, fostering critical thinking and analytical skills that have greatly enriched my academic experience. I extend my sincerest appreciation to you for your outstanding supervision, mentorship, and friendship. My thesis would not have reached its current level of achievement without your unwavering commitment. I am profoundly grateful for the opportunity to work under your guidance and for the lasting impact you have had on my academic journey.

To my supervisory committee, Dr Marla Beauchamp, and Dr Maureen MacDonald, thank you both for your invaluable expertise and insightful contributions to my thesis.
Dr Beauchamp, thank you for your depth of knowledge and the time you have dedicated to providing feedback which has significantly enhanced my quality of work. Dr MacDonald, thanking for welcoming me into your Vascular Dynamics Lab, your warm welcome and openness to collaboration have allowed me to learn from your wealth of experience and work alongside your talented trainees. Your guidance and support have broadened my perspectives and deepened my understanding in this field.

To the MacStroke Canada Lab, thank you for fostering an environment where I am constantly challenged and helping me grow into the best researcher I can be. Thank you to Elise for seeing the potential in me and giving me an opportunity as a research practicum student, I would not be in this position without you. Thank you for your hours of commitment into helping my studies and answering all my questions at any hour of the day. Thank you, Kenny and Kevin,

for being incredible friends and coauthors. Your friendship has been a constant source of support, making the toughest times of my degree more bearable. Your valuable insights have greatly influenced my research, for the better. To Hanna, thank you for everything you do for the MacStroke Canada Lab! To helping me get settled into the lab back in my second year to assisting with my departure after four and a half years. Your friendship and help have shaped my experience in this lab for the better.

Finally, thank you to my family. To my parents, thank you for your unconditional support and love through everything. You have always been there with me to celebrate my successes and encourage me during adversity. To my brothers, Chris, Phillip, Nathan, and Brian. Thank you all for being the best friends I could ever ask for, knowing you will always have my back has given me courage to take risks and opportunities that have pushed me to be a better person. To Angela, Ariel, Jessica, and Lyanna, thank you for your incredible support and encouragement. Your joy and celebration of my successes have made the journey even more meaningful. Importantly, thank you for taking time to see me every Wednesday and Saturday, these moments not only serve as great memories but were much-needed times to recharge.

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## LIST OF ABBREVIATIONS

| | |
|---|---|
| Beats per minute | bpm |
| Body Mass Index | BMI |
| Canadian Longitudinal Study on Aging | CLSA |
| Cardiorespiratory Fitness | CRF |
| Cardiovascular Disease | CVD |
| Confidence Interval | CI |
| Diastolic Blood Pressure | DBP |
| High-Density Lipoprotein Cholesterol | HDL-C |
| High Sensitivity C-Reactive Protein | hsCRP |
| Hormone Replacement Therapy | HRT |
| Low-Density Lipoprotein Cholesterol | LDL-C |
| Mean Difference | MD |
| Physical Activity Scale for the Elderly | PASE |
| Randomized Controlled Trial | RCT |
| Resting Heart Rate | HR |
| Standard Deviation | SD |
| Standardized Mean Difference | SMD |
| Systolic Blood Pressure | SBP |
| Transient Ischemic Attack | TIA |
| Waist Circumference | WC |
| Waist-to-hip Ratio | WHR |

## DECLARATION OF ACADEMIC ACHIEVEMENT

This thesis was completed by the candidate and recognizes the contributions of Dr Ada Tang, Dr Marla K Beauchamp, and Dr Maureen J MacDonald in providing guidance and insight into the preparation and execution of this thesis. Elise Wiley, Kenneth S Noguchi, Hanna Fang, and Kevin Moncion contributed to data collection and analysis.

# Chapter 1: BACKGROUND

# 1.0 INTRODUCTION

Cardiovascular diseases (CVDs) are the primary cause of disease burden worldwide.[1] Well-established cardiovascular health measures such as blood pressure,[2] heart rate,[3,4] body composition,[5,6] blood lipids,[7-10] blood glucose,[11,12] cardiorespiratory fitness,[13-16] and markers of inflammation[17] enable the quantification of CVD risk and allow for early management.[18] Monitoring cardiovascular health measures may be of importance after substantial events such as menopause and stroke.

Menopause is an event in the life of females that results in substantial reductions of the sex hormone estrogen, and its cardioprotective effects.[19] Postmenopausal females are more likely to present with cardiometabolic conditions such as hypertension, obesity, dyslipidemia and type 2 diabetes.[20-26] The increase in cardiometabolic conditions may contribute to the two-fold increase in CVD risk compared to premenopausal females of the same age,[27] and risk of stroke in the 10-years following menopause.[28]

Stroke is a neurological condition caused by an acute injury to the central nervous system, typically resulting from a vascular cause.[29] Stroke may further impair cardiovascular health via direct effects on the nervous system such as autonomic dysregulation,[30,31] and indirect effects such as physical inactivity.[32,33] Individuals poststroke have two-fold higher CVD risk compared to the general population in the first year after the event,[34] and risk of recurrent stroke is high at 26% within 5 years, and 39% after 10 years.[35] Therefore, targeting measures of cardiovascular health in postmenopausal females and especially those with stroke can reduce the risk of CVD and subsequent stroke.

Physical activity and exercise have been used as non-diet and non-pharmacological methods to improve cardiovascular health in adults,[36] and other chronic populations,[37-41] including

stroke.[42] However, much of the current literature in cardiovascular exercise physiology[43] and stroke[44] underrepresents females, as a majority of participants are male. Moreover, the lack of reporting female-specific factors such as menopausal status may impair the reproducibility of study of beneficial study results and generalizability.[45,46] The current evidence of the influence of exercise and physical activity in postmenopausal females and females with stroke remains unclear.

This thesis focused on the associations between physical activity and the cardiovascular health of pre- and postmenopausal females with, and without, stroke. This thesis is comprised of two studies. First, we examined the effects of aerobic exercise on traditional cardiovascular health measures in postmenopausal females. Second, we examined the association between physical activity and cardiovascular health in females with stroke, and explored differences based on menopausal status.

The current chapter establishes a foundation for this thesis by presenting a comprehensive summary of the literature, covering cardiovascular disease, menopause, stroke, and physical activity. It begins by providing an overview of CVD, its impact, and the measures used to quantify cardiovascular health. The chapter then defines menopause and discusses the impact of estrogen loss on cardiovascular health. It then addresses the burden of stroke, its etiology, and its impact on cardiovascular health. Finally, the chapter defines physical activity and exercise and explores their beneficial effects on cardiovascular health.

## 1.1 Cardiovascular Disease

CVD is an umbrella term encompassing various conditions that effect the heart and blood vessels,[47] such as heart disease, stroke, cardiomyopathy and myocarditis, and atrial fibrillation.[1] Worldwide, CVDs are the primary cause of disease burden.[1] The prevalence of CVD has

increased nearly two-fold from 271 million in 1990 to 523 million in 2019, and the number of deaths due to CVD has increased from 12.1 million to 18.6 million in over the same time span.[1] As a result, disability-adjusted life years, a measure of disease burden in terms of the number of years lost due to illness, disability, or early death, has increased substantially, from 17.7 million to 34.4 million.[1] The current burden of CVD may be attributable to poor management of modifiable risk factors such as blood pressure, diet, blood lipids, body fat, blood glucose, smoking, and low physical activity.[1,48]

### 1.1.1 Measures of Cardiovascular Health

Cardiovascular health measures are used to assess the overall health of an individual's cardiovascular system, to aid in quantifying CVD risk and determining management.[18] There are several traditional measures cardiovascular health including:

#### *Resting Blood Pressure*

Blood pressure is a measure of blood pushing against the walls of arteries and is comprised to two measures, systolic blood pressure (SBP), the pressure in the arteries during systole, and diastolic blood pressure (DBP) the pressure in the arteries when the heart is at rest, or diastole.[49] High SBP is considered the most modifiable risk factor to CVD.[1] As high blood pressure (>120/80) may damage the endothelial lining of blood vessels, including the intracerebral arteries to accelerate the progression of atherosclerotic clots, and increase the risk of stroke.[50] A large review of individuals with and without CVD (n=344,716) concluded that a 5 mmHg decrease in SBP reduces the risk of CVD by about 10% regardless of previous cardiovascular disease, and current blood pressure status.[2] Moreover, a decline in DBP is indicative of increased arterial stiffness.[51] The growing gap between SBP and DBP values can be

indicative of higher CVD risk. When pulse pressure, or the difference between SBP and DBP, exceeds 10 mmHg there is a 12% increase in CVD risk in persons >45 years.[52]

***Resting Heart Rate***

Heart rate (HR) is one of the most frequently measured vital signs and is expressed as the number of beats per minute (bpm).[53] High resting HR may increase CVD risk, as decreased diastolic profusion time and higher myocardial oxygen demand lead to increased shear stress of the coronary arteries, thereby contributing to the development of atherosclerosis.[54] Additionally, high resting HR may lead to increased cardiac noradrenaline synthesis, decreased arterial elasticity, diastolic duration, coronary perfusion time, and induce plaque rupture, increasing heart failure and myocardial infarction risk.[54] In individuals without CVD, increases in resting HR from <60bpm to ≥80bpm results in an 87% increase in CVD risk.[4] Moreover, every 10bpm increase in resting HR, risk of cardiovascular mortality increases by 8%.[3]

***Body Composition***

Body fat is an important component of overall body composition due to its well-established relationship to morbidity and mortality.[55] Visceral fat has a high rate of lipolysis, resulting in an overproduction of fatty acids that may lead to excess intra-hepatic fat and increase the risk of CVD.[56] Additionally, visceral fat secretes growth factors, cytokines, and hormones that are involved in the development of various CVD.[56] Increased size of adipocytes and the infiltration of immune cells lead to a chronic low-grade inflammation which contributes to developing CVD.[57]

Body composition may be measured invasively, or non-invasively using techniques such as computerized tomography, magnetic resonance imaging, which are recognized as the gold standard techniques.[55] Moreover, body composition may be estimated using simple indirect

measurements[55] such as body mass index (BMI),[58] waist circumference (WC), and waist-to-hip ratio (WHR).[59] BMI is often used to classify individuals as underweight, normal weight, overweight or class 1 to 3 obese.[60] Being overweight (BMI≥25kg/m$^2$), obese (BMI≥30kg/m$^2$) or morbidly obese (BMI≥40kg/m$^2$) is associated with a 32%, 85% and 153% increase in risk CVD compared to having a BMI of <25kg/m$^2$, respectively.[5] Furthermore, WC and WHR may be better at predicting risk of CVD compared to BMI.[61] One standard deviation increases in WHR and WC was associated with a 37% and 19% increase in the odds for myocardial infarction, respectively.[61]

***Blood Lipids***

Blood lipids are commonly assessed through a fasted blood draw.[62] Dyslipidemia is often characterized by higher levels of plasma triglycerides and low-density lipoprotein cholesterol (LDL-C), and reductions in high-density lipoprotein cholesterol (HDL-C).[63] The imbalance in lipid profile increases CVD risk as LDL-C is known to deposit in blood vessel walls contributing to the formation of atherosclerosis, whereas HDL-C functions to remove excess cholesterol in the blood to the liver for excretion reducing the progression of atherosclerosis.[64] Plasma triglycerides do not directly contribute to atherosclerosis however are an important biomarker due to its known association with proteins that contribute to atherosclerosis.[10] A 38.7 mg/dL increase in LDL-C is attributed to an increased CVD risk of 16%.[7] Moreover, lower levels of HDL-C and high levels of plasma triglycerides have shown to increase risk for CVD.[8,9]

***Blood Glucose***

The relationship between fasting blood glucose and CVD is well established.[65,66] Increased blood glucose is positively associated with increased reactive oxygen species which exacerbates endothelial dysfunction contributing to increased atherosclerotic risk.[67] Blood

glucose is typically measured using a venous blood draw in a fasted state.[68] Optimal fasting glucose levels are <100 mg/dL, pre-diabetes is >100 mg/dL and individuals with diabetes have a fasting blood glucose level of ≥126 mg/dL.[69] The risk of CVD significantly increases as one transitions from living with prediabetes to type 2 diabetes.[11] Moreover, the incidence of atherosclerotic CVDs, such as ischemic heart disease, myocardial infarction and thrombotic stroke significantly increased as fasting blood glucose increased to >100 mg/dL.[12]

***Cardiorespiratory Fitness***

Cardiorespiratory fitness (CRF) refers to the capability of the circulatory and respiratory systems to supply oxygen to skeletal muscle during physical activity.[70] Evidence has shown that increased CRF has an independent protective effect against cardiovascular morbidity and all-cause mortality.[13-16] The gold standard method of assessing CRF is using a cardiopulmonary exercise test to determine maximal oxygen consumption.[71] Alternatively, several valid and reliable submaximal tests may be used to estimate maximal oxygen consumption and can overcome several limitations associated with maximal exercise testing, thus making them more suitable for individuals with physical impairments or chronic conditions.[72] Predictive submaximal exercise tests include the Modified Bruce Treadmill Test, Single-Stage Submaximal Treadmill Walking Test, Astrand and Rhyming Cycle Ergometer Test, Canadian Aerobic Fitness Test, 20-Meter Shuttle Test, 1-Mile Track Walk Test (Rockport Fitness Test).[72] It has been shown that one metabolic equivalent (3.5 mL/kg/min) increase in CRF results in a 21%[73] and 15%[16] reduction in the risk of heart failure, and in CVD and coronary heart disease, respectively.

***C-Reactive Protein***

High Sensitivity C-reactive protein (hsCRP) is a blood marker of the inflammation of the arterial walls and is a strong biomarker of cardiovascular risk.[17] It is a protein synthesized and

secreted by the liver in response to cytokines such as interleukin-6.[74] hsCRP plays a role in the synthesis of tissue factors, cytokines, and platelet aggregation at areas of endothelial damage, contributing to the development of atherosclerosis.[74] hsCRP, is typically measured through a blood draw.[75] An increase in hsCRP from 0.6 mg/L to 1.9 mg/L is associated with a greater than two-fold increase in CVD risk and an increase to 8.5 mg/L further increases in risk to nearly 4.5 times.[17]

### 1.1.2 Menopause and Cardiovascular Risk

Although females typically have lower lifetime prevalence of CVD compared to males,[76] there is a notable increase in CVD risk coincident with the onset of menopause.[77] It is also known that females have poorer outcomes after a cardiovascular event compared to males.[78]

## 1.2 Menopause

Menopausal transition is a significant biological milestone in the life of females, marking the end of reproductive years and the eventual permanent cessation of menstrual cycles.[79,80] As females enter the early stages of the natural menopausal transition, known as the beginning of the perimenopausal phase, the length of consecutive menstrual cycles begins to vary significantly.[79] During the late stages of perimenopause, the intervals of amenorrhea, or absence of menstrual periods increase to ≥60 days.[79] After a female experiences their final menstrual period, they are not considered postmenopausal until they have had one consecutive year of amenorrhea.[80] Therefore, the confirmation of postmenopausal status occurs retrospectively.[80]

The loss of follicular cells in the ovaries is the central determinant of natural menopause.[81] The allocation of these cells is predetermined prior to birth and gradually diminishes over the course of the lifespan.[81] Ultimately, the depletion of all follicular cells occurs during midlife, typically between the ages of 45 and 55 years,[81] and is marked by a pronounced decline of

approximately 85% to 90% in the primary female sex hormone, estrogen.[82] Data from population-based studies that report the average age of menopause onset to be 50 to 52 years old.[83-87] However, the onset of menopause may vary by one or two years due to factors such as genetics, race, body composition, physical activity levels, diet, socioeconomic status and smoking status.[88,89]

### 1.2.1 Cardioprotective Effects of Estrogen

A consequence of the substantial decrease in estrogen is a loss of its cardioprotective effects. In animal models, estrogen has shown to play an important role in maintaining cardiovascular health by improving mitochondrial function, reducing oxidative stress, regulating extracellular matrix remodelling, protecting against fibrosis, and promoting the formation of new blood vessels.[19]

In humans, decreased estrogen may impair the cardiovascular health of postmenopausal females directly and indirectly. Reduced estrogen directly effects cardiovascular health due to increased activation of the renin-angiotensin system, increased angiotensin II, endothelin-1 and decreased nitric oxide synthase.[89] Estrogen is also a potent vasoactive hormone that promotes vascular remodelling and elasticity, and regulates reactive dilation and inflammatory activity.[90] Moreover, oxidative stress is further augmented by endothlin-1 and angiotensin II, contributing to the development of atherosclerosis, hypertension, arterial stiffness, and endothelial dysfunction,[89] increasing CVD risk. The reduction of estrogen indirectly increases visceral fat,[91] inflammation,[91] insulin resistance,[92] and affects LDL-C and HDL-C balance,[93] contributing to an overall decline in cardiovascular health.[89]

Thus, the reduction of estrogen and its direct and indirect effects on the cardiovascular system is evidenced by impaired cardiovascular health markers and can lead to an overall

increase in CVD risk. In the Framingham Heart Study, postmenopausal females had a twofold increase in relative risk of CVD compared to premenopausal females of the same age.[27] Moreover, in the 10 years following menopause, the risk of stroke nearly doubles.[28] Therefore, postmenopausal females who tend to have suboptimal cardiovascular health profiles are at high risk for stroke, which, in turn, may exacerbate their cardiovascular health and predispose them further to secondary events.

### 1.3 Stroke

Worldwide, stroke is the second most common cause of death and leading cause of long-term disability.[31] In 2019, stroke accounted for a total of 143 million disability-adjusted life years, with 6.55 million deaths and 101 million cases worldwide.[1] In Canada, approximately 878,500 individuals aged over 20 are living with the effects of stroke.[94]

The etiology of stroke can be classified into two categories, hemorrhagic and ischemic strokes. Ischemic strokes are responsible for approximately 80% of all cases and result from the occlusion of a blood vessel leading to the brain.[95,96] Hemorrhagic strokes are responsible for the remaining 20% of all cases and result from the rupturing of a blood vessel in the brain.[95,96] Both types of stroke lead to inadequate oxygen delivery to the brain and neurologic deficit to the corresponding area.[95,96] Additionally, a transient ischemic attack (TIA) is a neurologic deficit that lasts less than 24 hours. It results from a temporary blockage of blood flow to the brain and is often indicative of a future stroke.[96] One in ten individuals with TIA experience a stroke within the next three months and 15% of individuals report a history of TIA before their stroke.[97]

### 1.3.1 Effect of Stroke on Cardiovascular Health

The cardiovascular health profile of individuals are typically poor before stroke[98] and may be exacerbated following stroke, both directly though immediate effects to the cardiovascular system and indirectly though physical impairments.

Stroke impairs the central nervous system, which contains the brain, and may cause excitotoxic and necrotic cell death of brain tissue within minutes of a stroke.[99] Damage to the brain impacts the peripheral nervous system branch, the autonomic nervous system.[30,31] Dysregulation of the autonomic nervous system can be observed acutely after stroke which manifests as increased sympathetic nerve activity and decreased parasympathetic nerve activity.[31,100] This results in higher amounts of circulating norepinephrine even at resting conditions,[101] increasing heart rate, blood pressure, risk of future secondary cardiovascular events, and poststroke morbidity and mortality.[31] Although deficits reduce with time, the autonomic nervous system is shown to be significantly impaired compared to adults without stroke.[31,100]

Deficits in somatic sensations, including touch, temperature, pain, and proprioception, as well as motor impairments, such as muscle weakness, changes in muscle tone, and impaired motor control are common poststroke.[32] These deficits may contribute to physical inactivity,[32,33] impairing CRF[14-16] to levels that are 50% of individuals without stroke matched for age and sex.[102]

The direct and indirect effects of stroke in individuals with an already compromised cardiovascular health profile may contribute to increased risk of subsequent cardiovascular events. Following stroke, the risk of a recurrent event is high; 26% experiencing a second stroke within 5 years, and 39% after 10 years of the initial event.[35] Moreover, a study of 93,627 older

Canadian males and females with ischemic stroke revealed that females faced a 25.1-fold greater risk and males a 23.4-fold greater risk in the 30 days following ischemic stroke.[34] Even after a one-year, the risk of adverse cardiovascular events remained elevated, with females and males experiencing a 2.1- and 2.0-fold higher risk compared to the general population.[34]

To mitigate the elevated cardiovascular risk in postmenopausal females and individuals with stroke, especially those risk factors that are modifiable, various interventions may be employed. Lifestyle modifications such as diet, smoking cessation, and physical activity have shown to have significant benefits on improving cardiovascular health.[103]

## 1.4 Physical Activity on Cardiovascular Health

*Physical activity* is any bodily movement produced by skeletal muscles that results in energy expenditure.[104] It is the sum of energy at rest, physical activity during household tasks, sports, exercise and at work.[104] *Exercise* is a subcategory of physical activity which refers to planned, structured bodily movement to improve or maintain physical fitness.[104] One form of exercise training is *aerobic exercise* which uses large muscle groups in a rhythmic nature for an extended period of time.[105]

Physical activity and aerobic exercise have been supported as non-pharmacological, non-diet interventions to mitigate CVD risk in older adults,[36] and in chronic disease populations such as individuals living with coronary heart disease,[37] heart failure,[38] obesity,[39] diabetes mellitus,[40] hypertension,[41] and stroke.[42]

### 1.4.1 Mechanisms Underlying Physical Activity on Markers of Cardiovascular Health

The mechanisms underlying the effect of physical activity and exercise on markers of cardiovascular health have been hypothesized to be linked to blood pressure, heart rate, body

composition, blood lipids, blood glucose, cardiorespiratory fitness, and inflammation and will be described in more detail below.

***Resting Blood Pressure***

The effect of physical activity on SBP can be attributed to both neurohormonal mechanisms and structural factors. Neurohormonal mechanisms such as the reduction in sympathetic nerve activity may lead to long-term peripheral vasodilation.[106] Moreover, after periods of physical activity, there is a reduction in the vasoconstrictor endothelin-1, and an increase in the potent vasodilator nitric oxide.[106] The increase in nitric oxide bioavailability, is thought to elicit long-term structural adaptations such as an overall increase in lumen diameter.[107] Next, increased physical activity may attenuate the age-related decreases in arterial elasticity and compliance through increased pulse pressures and mechanical distension of collagen fibres, this may contribute to a reduced SBP.[106,108]

***Resting Heart Rate***

Similarly, long-term physical activity leads to a decreased sympathetic tone,[106] and increased parasympathetic tone[109] at rest. Dominant parasympathetic activity is caused by greater stimulation of the vagus nerve which serves to lower resting heart rate.[110] Moreover, structural factors such as increased stroke volume via non-pathological left ventricular hypertrophy from long-term physical activity or exercise training may reduce HR.[111]

***Body Composition***

Physical activity may increase total energy expenditure,[112] causing the body to rely on adipose tissue for energy.[113] Epinephrine is released in this process, which begins adipose tissue lipolysis via the activation of enzymes that break down adipose tissue into free fatty acids and glycerol.[113] These free fatty acids are released into the bloodstream and taken up by skeletal

muscle, where they are transported into the mitochondria and undergo a process to produce adenosine triphosphate, the body's primary energy source.[113] The increased fat metabolism due to increased activity may decrease overall body fat reducing the development of cardiovascular disease and inflammation.[56,57]

***Blood Lipids***

The mechanisms underlying physical activity-induced blood lipid changes may be due to increase enzyme and gene activity. Physical activity may increase the signaling molecule cyclic adenosine monophosphate,[114,115] which in turn increases the expression of lipoprotein lipase,[116] which is responsible for the hydrolysis of plasma triglycerides.[115] Reductions in LDL-C due to physical activity may be attributed to reduced Proprotein Convertase Subtilisin/Kexin Type 9 levels,[117] allowing for more LDL-C to be absorbed and excreted by the liver.[118] Lastly, increased physical activity may induce a cascade of events that subsequently upregulate the ATP-binding cassette transporter A1 gene which has a strong effect on the formation of HDL-C.[118,119]

***Blood Glucose***

Similar to insulin, physical activity increases skeletal muscle glucose uptake, resulting in reduced blood glucose, through increased movement of glucose transporter 4.[120] Additionally, studies have shown that aerobic exercise training may increase mitochondrial content contributing to decreases in blood glucose.[120]

***Cardiorespiratory Fitness***

Regular physical activity improves CRF by increasing cardiac output, primarily through increase in stroke volume and blood volume.[111,121] Additionally, the arteriovenous oxygen content difference is improved following exercise training due to increases in total hemoglobin mass, which is responsible for transporting oxygen in the blood to the muscles.[121]

***C-Reactive Protein***

Physical activity training may reduce resting levels of pro-inflammatory cytokines such as interleukin-6 and Tumor Necrosis Factor-alpha, ultimately reducing hsCRP production.[122] This may occur by decreasing body fat and leptin levels while increasing adiponectin and insulin sensitivity.[122] Additionally, physical activity has antioxidant effects and can mitigate inflammation through decreasing the susceptibility of LDL-C to oxidize, preventing endothelial injury and reducing oxidative stress.[122]

### 1.4.2 Physical Activity on Cardiovascular Health Postmenopause

Given the elevated risk of CVD after menopause, effective strategies such as increased physical activity to manage traditional cardiovascular health markers are warranted. Evidence supports aerobic exercise for improving cardiovascular health after menopause. A review (17 studies, 792 postmenopausal females) reported that aerobic and resistance exercise improved body fat, WC, blood triglycerides, LDL-C and HDL-C but had no effect on BMI.[123] Another review (15 studies, 1110 postmenopausal females) reported beneficial effects of aerobic exercise on WC, blood glucose, and $\dot{V}O_2max$.[124] While these reviews were important for providing the first synthesized evidence of the effectiveness of exercise to support cardiovascular health after menopause, their findings may have limited generalizability. The authors were careful to include only studies that explicitly confirmed postmenopausal status but may thus have excluded a large body of exercise studies with older females who were of menopausal age but did not report menopausal status. Additionally, these reviews only included postmenopausal females without chronic conditions, yet conditions such as metabolic syndrome,[20] including hypertension,[21] diabetes mellitus,[22,23] obesity,[24,25] and dyslipidemia[26] are highly prevalent after menopause and individuals with these conditions may benefit from exercise.

### 1.4.3 Physical Activity on Cardiovascular Health Poststroke

In a high-CVD risk population such as postmenopausal females, stroke can further increase cardiovascular risk. Thus, therapeutic interventions such as physical activity are especially warranted. Currently, aerobic exercise training is recognized as a key component in stroke rehabilitation.[125] In stroke and TIA, systematic review evidence has supported use of aerobic exercise for improving markers of cardiovascular health including SBP, blood glucose, insulin, HDL-C,[42] and $\dot{V}O_2$max.[126] However, the current evidence is limited as results have not been disaggregated by sex and no studies to date have examined the association between physical activity and cardiovascular health nor considered the interaction of menopausal status in females living with stroke.

## 1.5 Overall Thesis Aim and Specific Objectives

The overall aim of this thesis was to examine the effectiveness of physical activity and exercise on the cardiovascular health of postmenopausal females, and the interaction between menopause and physical activity on cardiovascular health in females with stroke. This thesis is written in manuscript style and contains two distinct yet complementary studies to address the overall aim.

### 1.5.1 STUDY 1: The Effects of Aerobic Exercise on Cardiovascular Health in Postmenopausal Females: A Systematic Review and Meta-Analysis

This was a systematic review and meta-analysis of RCTs with the purpose of examining the effectiveness of aerobic exercise interventions compared to control on traditional cardiovascular health measures in postmenopausal females.

The objective of this review was two-fold:

- Primary objective: The primary objective of this study was to examine the effectiveness of aerobic exercise compared to control on traditional cardiovascular health measures (resting SBP and DBP, HR, BMI, WC, WHR, absolute body fat, LDL-C, HDL-C, plasma triglycerides, blood glucose, and CRF) in postmenopausal females.

*Hypotheses:* It was hypothesized that aerobic exercise interventions would improve all traditional measures of cardiovascular health compared to control in postmenopausal females.

- Secondary objective: The secondary objective of this study was to examine the association between aerobic exercise intensity (light, moderate, vigorous) and traditional cardiovascular health measures in postmenopausal females.

  *Hypothesis:* It was hypothesized that greater aerobic exercise intensities would elicit greater effects on traditional cardiovascular health measures in postmenopausal females. We expected vigorous intensity exercises to have a greater effect compared to moderate and light intensities and moderate intensity to have a greater effect compared to light intensity.

### 1.5.2 STUDY 2: Examining the Associations Between Cardiovascular Health, Physical Activity and Menopausal Status in Pre- And Post-menopausal Females Living With Stroke and Transient Ischemic Attack: A Cross-Sectional Analysis of Baseline Data From the Canadian Longitudinal Study on Aging

This was a cross-sectional analysis of baseline data from the Canadian Longitudinal Study on Aging with two objectives:

- Primary objective: The primary objective of this study was to assess the association between self-reported physical activity and measures of cardiovascular health (SBP, DBP, HR, WC, WHR, and hsCRP) in Canadian females living with stroke.

  *Hypothesis:* It was hypothesized that higher levels of self-reported physical activity would be negatively associated with measures of cardiovascular health.

- Secondary objective: The secondary objective of this study was to evaluate the interaction between menopausal status and the association between self-reported physical activity and measures of cardiovascular health.

  *Hypothesis:* It was hypothesized there will be an interaction between physical activity and menopausal status on all associations with cardiovascular health.

# Chapter 2: The Effects of Aerobic Exercise on Cardiovascular Health in Postmenopausal Females: A Systematic Review and Meta-Analysis

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**Abstract**

***Background.*** After menopause, the reductions in estrogen and its cardioprotective effects increases the risk of cardiovascular disease two-fold. Aerobic exercise training has been shown to reduce cardiovascular risk in older adults, but its effectiveness in postmenopausal females is unclear. This review examined: 1) the overall effectiveness of aerobic exercise training, and 2) the association between exercise intensity and cardiovascular health outcomes in postmenopausal females.

***Methods.*** Five electronic databases were searched for randomized-controlled trials of aerobic exercise training interventions reporting cardiovascular outcomes in postmenopausal females from inception to May 6$^{th}$, 2022. Data was synthesized qualitatively and, random-effects meta-analyses and subgroup analyses (for light, moderate, vigorous intensity) were performed.

***Results.*** Fifty-six studies (4134 participants; 45-78 years) were identified. Aerobic exercise interventions varied in frequency (3-21x/week), intensity, type, time (8-60 min/session), and duration (3-52 weeks). Fifty studies (n=3730) were included in the quantitative synthesis. Aerobic exercise decreased systolic blood pressure (Mean difference(MD)=-3.67 mmHg, 95%CI[-6.88,-0.46], p=0.03), resting heart rate (MD=-5.76 bpm, 95%CI[-5.76,-1.61], p<0.01), body mass index (BMI)(MD=-0.65 kg/m$^2$, 95%CI[-0.99,-0.31], p<0.01), waist circumference (MD=-2.03 cm, 95%CI[-2.65,-1.41], p<0.01), body fat (MD=-2.57 kg, 95%CI[-3.65,-1.49], p<0.01), low-density lipoprotein cholesterol (MD=-10.4 6mg/dL, 95%CI[-16.31,-4.61], p<0.01), and increased high-density lipoprotein cholesterol (MD=3.28 mg/dL, 95%CI[0.20,6.36], p=0.04) and cardiorespiratory fitness (Standardized MD=1.43, 95%CI[1.17,1.70], p<0.01). Subgroup differences in exercise intensity were only present for BMI where light- and vigorous-intensities were beneficial, and moderate intensity had no effect ($X^2$=9.79, df=2, p<0.01), and for blood

triglycerides and blood glucose where light intensity showed a beneficial effect and there was no effect of moderate and vigorous intensities (triglycerides $X^2$=7.70, df=2, p=0.02; glucose $X^2$=20.98, df=2, p<0.01).

***Conclusion***. Aerobic exercise may improve cardiovascular health outcomes in postmenopausal females and may be useful in primary prevention of cardiovascular disease. Furthermore, all exercise intensities showed similar effects for most health outcomes apart from BMI, blood triglycerides and blood glucose which warrants further investigation.

## Introduction

Menopause is defined as a permanent cessation of menstruation due to ovarian follicular depletion.[80,127] Females are considered postmenopausal after 12 consecutive months of amenorrhoea or the absence of menstrual periods.[80,127] Thus, menopause is identified retrospectively.[80,127] Following menopause, there is a reduction in the sex hormone estrogen, which has been shown to have several cardioprotective mechanisms.[19] The reduction in estrogen can lead to poor cardiovascular health, characterized by increased blood pressure, body fat, sympathetic tone, endothelial dysfunction, vascular inflammation, irregular plasma lipids and reduced glucose tolerance.[128] As such, postmenopausal females are at a two-fold higher risk for CVD compared to premenopausal females[27] and the risk of stroke nearly doubles in the 10 years following menopause.[28]

It is important to examine strategies to improve cardiovascular health in postmenopausal females. Aerobic exercise can be one such strategy, as evidenced by systematic-review level evidence in the general population and in people with chronic conditions. For instance, a review of 93 trials and 5,223 adult males and females with normal blood pressure, prehypertension and hypertension found that exercise, including aerobic exercise, decreases systolic and diastolic

blood pressure.[129] Other reviews have shown that aerobic exercise is effective for improving systolic blood pressure (SBP),[130] diastolic blood pressure (DBP),[131] body composition,[130-132] high-density lipoprotein cholesterol (HDL-C),[131] serum triglycerides,[130,131] blood glucose,[131] and cardiorespiratory fitness (CRF)[131] in individuals who are overweight or obese,[132] living with metabolic syndrome[131] and type 2 diabetes.[130]

To date, only two systematic reviews have focused specifically on postmenopausal females and reported that aerobic and resistance interventions were effective in improving $\dot{V}O_2$max (n=398 postmenopausal females),[124] waist circumference (WC) (n=711),[123,124] and blood glucose (n=568).[124] These reviews, however, did not include females living with chronic conditions commonly seen postmenopause such as metabolic syndrome,[20] hypertension,[21] diabetes mellitus,[22,23] obesity,[24,25] and dyslipidemia,[26] and thus are limited in generalizability. Further, while these reviews were careful to use stringent definitions of post-menopausal status (i.e. confirmed/self-reported postmenopausal status), they may have missed a larger body of evidence of studies involving older females who may not have confirmed postmenopausal status but are of postmenopausal age.

There is an opportunity to build upon these previous reviews by including a broader body of literature including older females at postmenopausal ages and by including females with common metabolic conditions. Thus, the purpose of this systematic review was to examine the effects of aerobic exercise on traditional cardiovascular health measures in a broad population of postmenopausal females. The American College of Sports Medicine suggests that *intensity* may be the most important exercise parameter for improving fitness.[133] Therefore, the secondary objective was to examine the effects of different aerobic exercise intensities on traditional cardiovascular health measures.

## Methods

This systematic review and meta-analysis was reported based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[134] The protocol is registered in the PROSPERO International Prospective Register of Systematic Reviews (CRD42022313350).

### Eligibility Criteria

This review was restricted to peer-reviewed, published randomized controlled clinical trials in English. Non-randomized trials, conference abstracts, cross-sectional studies, study protocols and ongoing trials were excluded.

In this review, we considered the study sample to represent postmenopausal females if they met at least 1 of the following 3 criteria: 1) if studies explicitly confirmed participants to be postmenopausal (e.g., via self-report); 2) if postmenopausal status was not explicitly reported but age range was, with a conservative criterion of the lower bound of age ≥55 years old, or 3) if age range was not reported, mean age ≥63 years old. The latter 2 criteria were based on data from large population-based studies that report the average age of menopause to be 50 to 52 years old,[83-87] with onset of menopause varying by one or two years due to factors such as race, body composition, physical activity levels, diet, socioeconomic status, and smoking.[88] Furthermore, a mean age of 63 with an estimated standard deviation (SD) of 4 years yields a 95% confidence interval (CI) with a lower limit age of 55 years. Lastly, to increase generalizability of our findings, we included studies of participants with hypertension, diabetes mellitus, obesity, and dyslipidemia, as these metabolic conditions are common postmenopause.[20-26] Participants with history of overt cardiovascular events were excluded (e.g. stroke, myocardial infarction).

Included trials were aerobic exercise interventions (i.e., activities that use large muscle groups that is maintained continuously and in a rhythmic nature)[135] that reported at least two of

the following training parameters: frequency, intensity, type and duration. There was no restriction to the frequency, intensity, type, and duration of aerobic interventions. Non-aerobic exercise interventions were excluded, such as, resistance training, co-interventions, yoga, tai chi, virtual reality, pharmacological or nutritional interventions.

Control groups included non-exercise, non-diet, or non-pharmacological interventions, such as health education or stretching.

Trials were included if the following traditional cardiovascular health outcomes were measured:

**Resting Blood Pressure.** Resting SBP and DBP were included as outcomes of interest, as hypertension is the most prominent modifiable risk factor for CVD in females.[136,137] Although antihypertensive medications are commonly used to reduce blood pressure, there is a maximal effect after 12 months and the effectiveness slowly attenuates after that.[138] Thus, alternative strategies to sustain long-term blood pressure reductions are needed.[138]

**Resting Heart Rate.** Resting heart rate (HR) was included as an outcome of interest due to its well-established positive association with CVD risk.[3,139]

**Body Composition.** Due to the known association between obesity and CVD,[140,141] body mass index (BMI),[142] body fat,[143] waist-to-hip ratio (WHR), and waist circumference[144] were considered as outcomes of interest.

**Blood Lipids.** Dyslipidemia is highly prevalent in females postmenopause[145] and is associated with increased cardiovascular risk.[7,8,146] Thus, low-density lipoprotein cholesterol (LDL-C),[7] HDL-C,[8] and blood triglycerides[146] levels were considered as outcomes of interest.

**Fasting Glucose.** Compared to normoglycaemia, individuals with hyperglycemia are at an increased risk for CVD.[65,66] The risk significantly increases as an individual transitions from

prediabetes to type 2 diabetes.[11] Therefore, fasting blood glucose levels were considered as an outcome of interest.

**Cardiorespiratory Fitness.** Poor CRF is related to an increased incidence of CVD.[14-16] Thus, measures of cardiorespiratory fitness, such as $\dot{V}O_2$max and other submaximal cardiorespiratory fitness tests, were included as outcomes of interest.

Studies not reporting at least one of these traditional cardiovascular outcomes were excluded.

**Information Sources**

Six electronic databases (OVID MEDLINE, EMBASE, CINAHL, CENTRAL, SPORTDiscus and Web of Science) were searched from inception to May 5th, 2022. The search strategy was developed in consultation with a research librarian. Terms related to "cardiovascular health", "aerobic exercise", "older adults" and "menopause" were used, final search strategies are displayed in Appendix 1.

**Data Extraction**

Two sets of independent reviewers (E.H and E.W, E.H and K.S.N) assessed study eligibility based on titles and abstracts followed by full-text review. All reviewers (E.H, E.W, K.S.N) piloted title and abstract screening by independently screening two sets of abstracts (n=100). Disagreements were resolved by discussion between the two independent reviewers and if necessary, resolution with a third reviewer (A.T).

Qualitative and quantitative data was extracted into Covidence systematic review manager (Covidence systematic review software, Veritas Health Innovation, Melbourne, Australia) by three sets of independent reviewers (E.H and E.W, E.H and K.S.N, E.H and H.F) and included lead author name, year of publication, summary of participant eligibility criteria, population characteristics, control group characteristics, exercise intervention parameters (i.e.,

frequency, intensity, type, duration), qualitative summary of effect on cardiovascular health, sample size and change in outcome (pre- to post-intervention) in intervention and control groups, respectively.

**Statistical Analysis**

To assess the effects of aerobic exercise training on measures of cardiovascular health (objective 1), random-effects meta-analyses and inverse variance-weighted estimation were used. Mean difference (MD) or standardized mean difference (SMD) in change-scores from pre- to post-intervention with 95% CIs were used to determine the effect of aerobic exercise training on outcomes of interest.[147] Pooled standard deviations were calculated. Studies that contained two or more intervention groups were combined, outcome measures reported in median (interquartile range), mean (standard error) or mean (95% CI) were transformed to mean and SDs, and SDs for change scores were calculated per Cochrane guidelines.[147] Corresponding authors were contacted for studies with missing pre- and post-intervention means and SDs; otherwise, these studies were excluded. Forest plots were created to visually display the overall effects of aerobic exercise on outcomes of interest.

*A priori* subgroup analyses were conducted to compare the individual effects of different intensities (light, moderate, vigorous) of aerobic exercise on cardiovascular health (objective 2). Subgroups were based on categorization from the American College of Sport Medicine using %HR reserve, %$\dot{V}O_2$ reserve, %HR max, %$\dot{V}O_2$max.[105] To preserve number of studies in each intensity category, categories of very-light and light, and vigorous and near-maximal to maximal were combined. Moreover, for studies that incorporated intensity progressions throughout the intervention period, categorization was based on the intensity performed at ≥50% of the total intervention duration.

The robustness of the findings was tested with four *a priori* sensitivity analyses excluding studies of 1) older age females without confirmed postmenopausal status; 2) females with reported chronic conditions; 3) outliers where high heterogeneity was observed; and 4) comparator groups of stretching, health education, relaxation, and placebo drug interventions.

Heterogeneity was assessed using Higgins $I^2$ statistic[147] and all analyses were conducted using Review Manager (RevMan version 5.3).

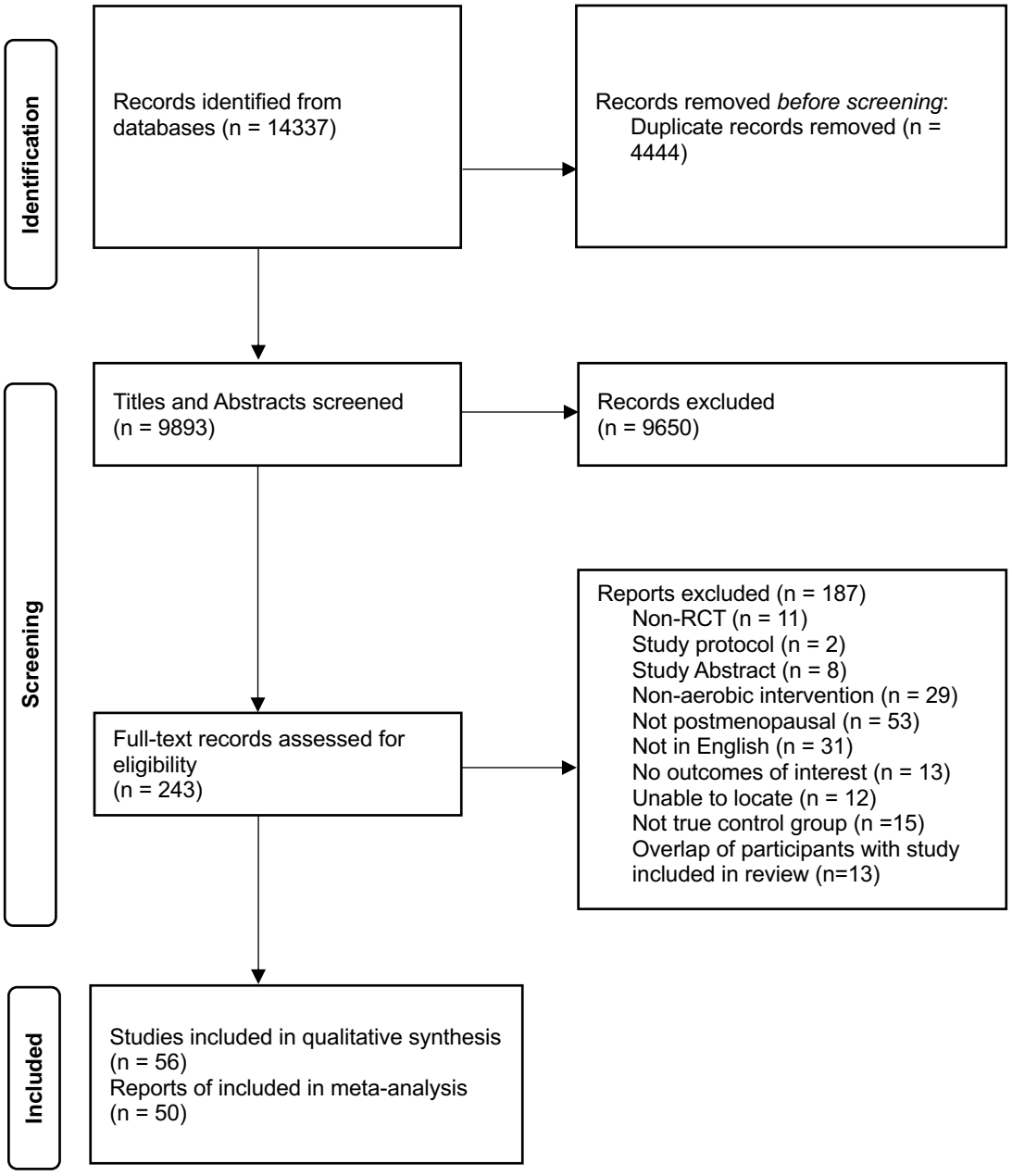
**Quality Appraisal**

The methodological quality of included studies was evaluated by three sets of two independent reviewers (E.H and E.W, E.H and K.S.N, E.H and H.F) using the Cochrane Risk of Bias 2 tool[148] (low, high, some concerns) for domains of random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data and selective reporting. Certainty of evidence was evaluated using the Grading of Recommendation, Assessment, Development and Evaluations (GRADE) tool for high, moderate, low, or very low certainty, based on assessments of risk of bias, imprecision, inconsistency, indirectness, and publication bias.[149] Publication bias was assessed using visual inspection of funnel plots and the Egger's test conducted using. Stata statistical software (Version 16.1, Stata CorpLLC, College Station, Texas, USA). Disagreements were resolved by discussion and if necessary, resolution with a third reviewer (A.T).

## Results

Study flow diagram is displayed in Figure 2.1. Fifty-six articles[150-205] from 54 trials were included in this review; 50 articles[156-205] from 48 trials were included in the meta-analysis. Thirteen articles[206-218] were not included in meta-analyses as they were represented by the trial's primary article which had the largest sample and reported outcomes of interest.

**Figure 2.1. Study flow diagram**




## Qualitative Synthesis

Details of all included studies is summarized in Appendix 2.

**Participant Characteristics.** A total of 4,134 participants were included in this review, with study sample sizes ranging from 14[159] to 464 participants.[196] Participants' ages ranged from 45 years old[164] to 78 years old.[184] Forty-seven studies (84%) reported menopausal status, and 9 studies were included based on age criteria.[153,157,159,162,170,184,192,195,199] Additionally, 38 studies (68%) studies included sedentary postmenopausal females without chronic disease, and 18 studies included postmenopausal females living with one or more cardiometabolic conditions.[150,151,158,162,163,167,177-180,185,186,191,195,196,199,201,204]

**Aerobic Exercise Intervention.** Aerobic exercise intervention durations ranged from 3[187] to 52 weeks,[177,181,189-191,197,198] with 8 to 60 minutes per session, except 4 studies[178,196,202,203] that had a calorie or step goal. Interventions took place 3 to 21 times per week (3 times/day x 7 days). Aerobic interventions consisted of treadmill or cycle ergometer training, aquatic aerobic training, outdoor walking, and bench stepping. Forty-six studies (82%) contained one aerobic intervention group, whereas 10 studies[150,169,178,181,183,194,196,202-204] contained multiple intervention groups that varied in intensity, duration, or type.

**Comparator.** Fifty studies compared aerobic exercise with no intervention (maintain usual diet and activity), and 6 studies used stretching,[168,202,203] health education,[151] relaxation in water,[195] or placebo drug interventions[156] as the control group.

**Outcomes.** All studies reported at least one cardiovascular outcome of interest. Specifically, SBP[150,156-158,161,163,166,169,171,173,174,181,183,184,186,187,194,196,199,201,204,205,219] and DBP[150,156-158,161,163,166,169,171,173,174,181,183,184,186,187,194,196,199,201,204,205,219] were investigated in 23 of 56 studies (41%), while 14 studies (25%) examined HR.[153,156-158,171,176,179,183-185,187,201,204,205] Among body anthropometric measures, BMI was the most frequently investigated outcome (n=36, 64%),[150,151,154,156-158,160-162,164,166,167,169-171,173,174,180-183,186-189,191,192,194,198-205] followed by body fat

(n=15, 27%),[157,158,162,167,171,172,175,180,188,189,191,193,199-201] WC (n=13, 23%),[150,162,168,172,180,186,189,191,194,196,199,201,204] and WHR (n=6, 11%).[158,162,167,169,172,175,180,201,204] Regarding blood lipids, 19 studies (34%) investigated LDL-C[156,160,162,164,168,169,171,172,174,181,188,192-196,199,204,205] and 21 studies (38%) investigated HDL-C and blood triglycerides.[150,156,160,162,164,168,169,171,172,174,181,188,192-196,199,204,205,219] Blood glucose was investigated in 11 studies (20%),[150,162,168,174,176,177,188,193,194,196,219] whereas CRF was investigated in 32 studies (57%).[151,152,156,158-160,165,166,168-170,173,175,178-184,190-192,194,196,197,199-203,219]

**Quality Assessment**

Summary of quality assessment using Cochrane Risk of Bias 2 tool is summarized in Appendix 3. Most studies were declared as high risk of bias due to failure to report participant attrition data (drop-out, reasons for drop-out) or had missing outcome data with failure to estimate intervention effects (intention-to treat analyses).

**Adverse Events**

Of the 56 studies included in our review, 29 (52%)[150,152-154,156,157,159,161,164-167,169-171,175-177,179,182,184-187,192,193,201,204,219] did not report monitoring of adverse events. Of the studies that monitored adverse events, 19 (34%)[158,160,162,163,168,172-174,180,183,188-191,194,195,198-200] reported no occurrence of adverse events, 3 (5%)[178,196,203] studies reported adverse events unrelated to the exercise intervention, 2 (4%)[151,205] studies reported adverse events but did not specify its relation to the intervention, and 3 (5%)[181,197,202] studies reported adverse events due to the intervention.

**Quantitative Synthesis**

Of the 56 studies included in the qualitative synthesis, 6 studies were excluded from the quantitative synthesis: four due to incomplete reporting of means and SDs,[150,151,154,219] and two due to incomplete reporting of SDs.[152,153] Thus, fifty studies (n=3,730 participants) were

included in the quantitative analysis. Nine studies included in the quantitative synthesis reported outcome data from two or more intervention groups, these groups were combined and compared to the control group in the meta-analysis. All outcomes were reported as MD, except CRF where 9 studies[152,159,160,179,182,190,192,199,200] measured CRF using different submaximal tests (e.g. 1-mile walk test, Astrand test, Blake test) and therefore was reported as SMD.

Table 2.1 provides a summary of findings from the meta-analyses to examine the exercise-related effects on cardiovascular outcomes of interest. There were beneficial effects of aerobic exercise on all measures of cardiovascular health except DBP, WHR, blood triglycerides, or blood glucose. Forest plots for beneficial effects are displayed in Figures 2.2-2.9; non-significant findings are displayed in Appendix 4. All outcomes were downgraded from high to very low quality due to multiple factors, including 'very serious' or 'serious' risk of bias, heterogeneity, indirectness, imprecision, and the suspicion of publication bias (Table 2.2).

Positive effects in all outcomes were maintained following sensitivity analyses removing studies of 1) older age females without confirmed postmenopausal status; 2) females with reported chronic conditions; 3) outliers where high heterogeneity was observed; and 4) comparator groups of stretching, health education, relaxation, and placebo drug interventions.

**Table 2.1** Effect of Aerobic Exercise on Traditional Cardiovascular Health Measures in Postmenopausal females

| Cardiovascular Health Measure | Studies | n participants | Mean Difference [95% CI] | *p* |
|---|---|---|---|---|
| Systolic blood pressure | 20 | 1155 | -3.67 mmHg [-6.88, -0.46] | *0.03 |
| Diastolic blood pressure | 20 | 1155 | -2.17 mmHg [-4.75, 0.40] | 0.10 |
| Resting Heart Rate | 12 | 432 | -3.68 bpm [-5.76, -1.61] | *<0.01 |
| Body Mass Index | 33 | 1887 | -0.65 kg/m$^2$ [ -0.99, -0.31] | *<0.01 |
| Waist Circumference | 12 | 1254 | -2.03 cm [-2.65, -1.41] | *<0.01 |
| Waist-to-hip Ratio | 6 | 196 | -0.01 [-0.02, 0.00] | 0.06 |
| Body Fat | 15 | 1008 | -2.57 kg [-3.65, -1.49] | *<0.01 |
| Low-density Lipoprotein Cholesterol | 19 | 1079 | -10.46 mg/dL [-16.31, -4.61] | *<0.01 |

| | | | | |
|---|---|---|---|---|
| High-density Lipoprotein Cholesterol | 19 | 1079 | 3.28 mg/dL [0.20, 6.36] | *0.04 |
| Blood Triglycerides | 19 | 1079 | -11.59 mg/dL [-25.82, 2.65] | 0.11 |
| Blood Glucose | 10 | 875 | -0.92 mg/dL [-2.79, 0.95] | 0.33 |
| Cardiorespiratory Fitness | 29 | 2565 | Standardized mean difference: 1.43 [1.17, 1.70] | *<0.01 |

95% CI – 95% Confidence Interval
*denotes p<0.05

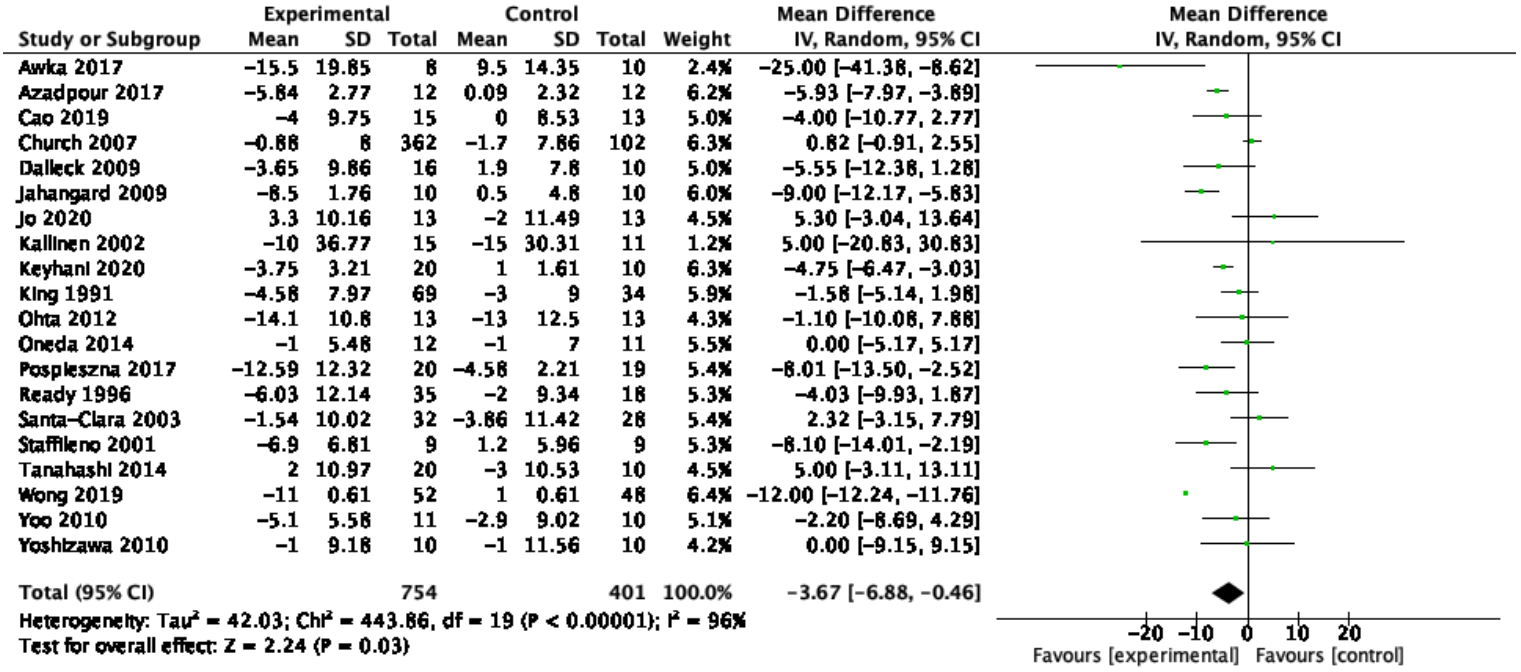



**Figure 2.2: Forest plot of the effect of aerobic exercise on systolic blood pressure**

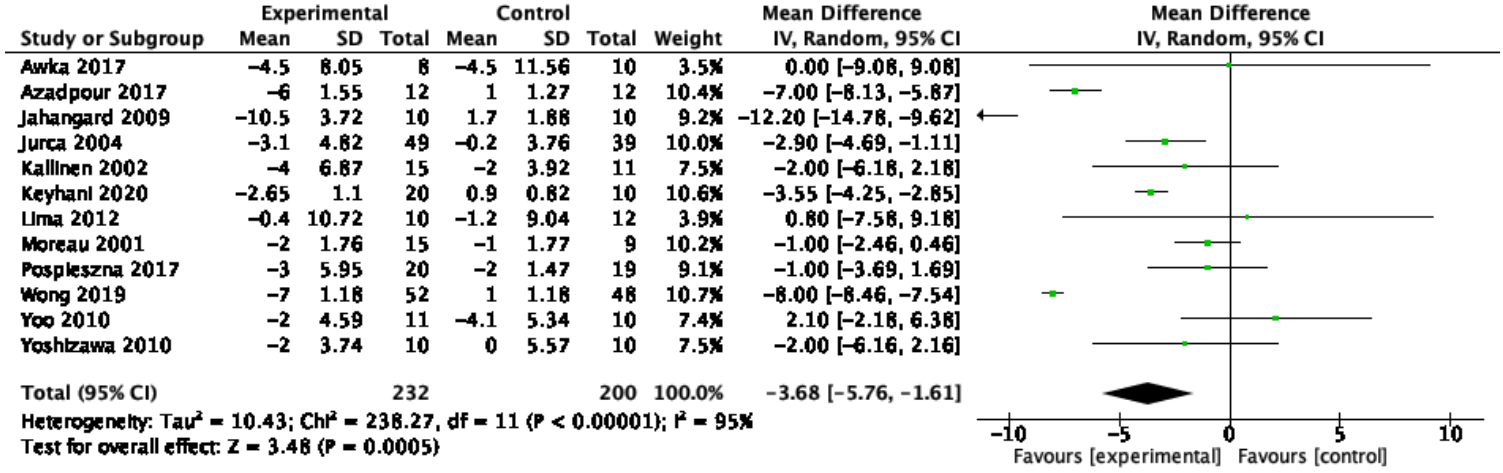



**Figure 2.3: Forest plot of the effect of aerobic exercise on resting heart rate**

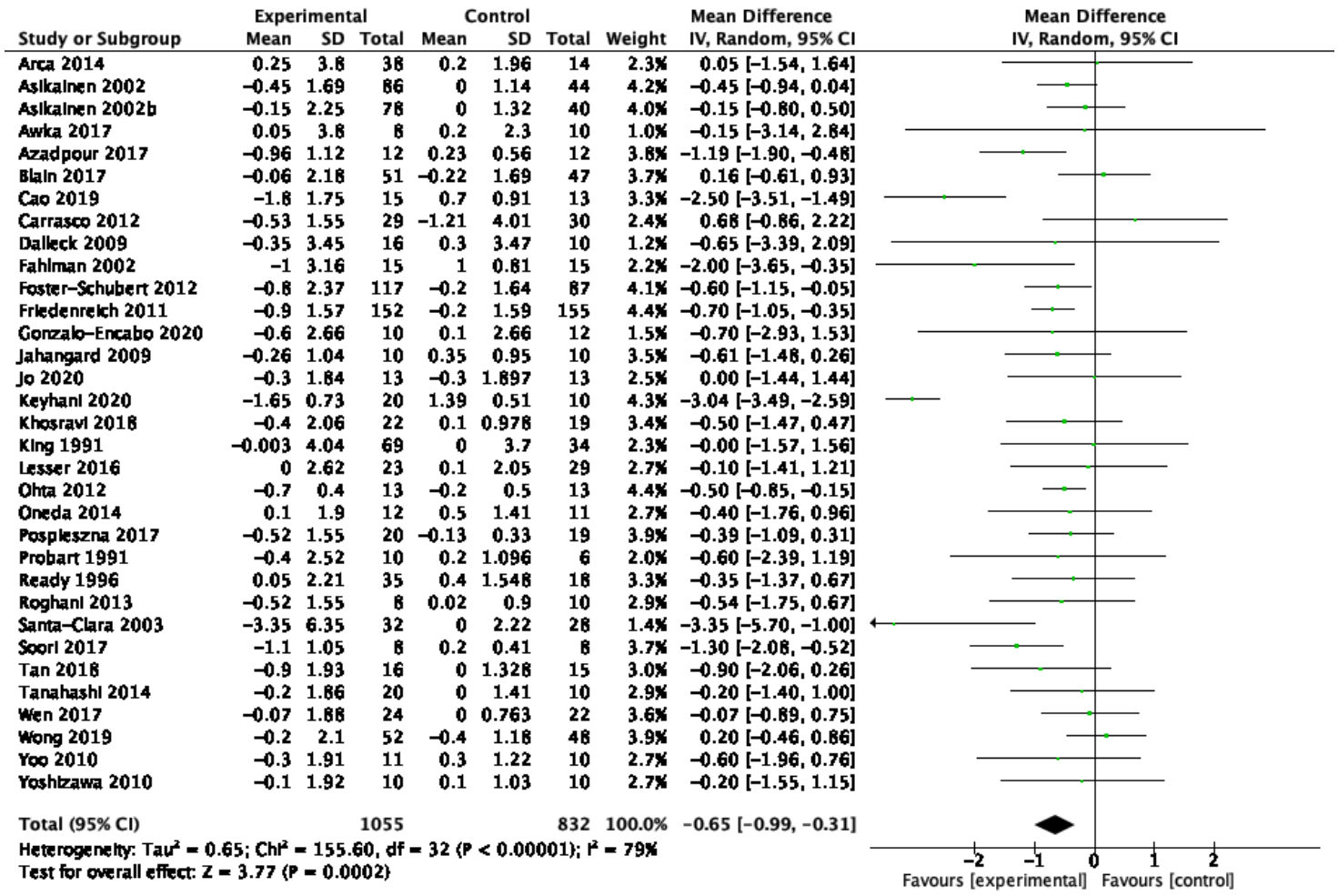



**Figure 2.4: Forest plot of the effect of aerobic exercise on body mass index**

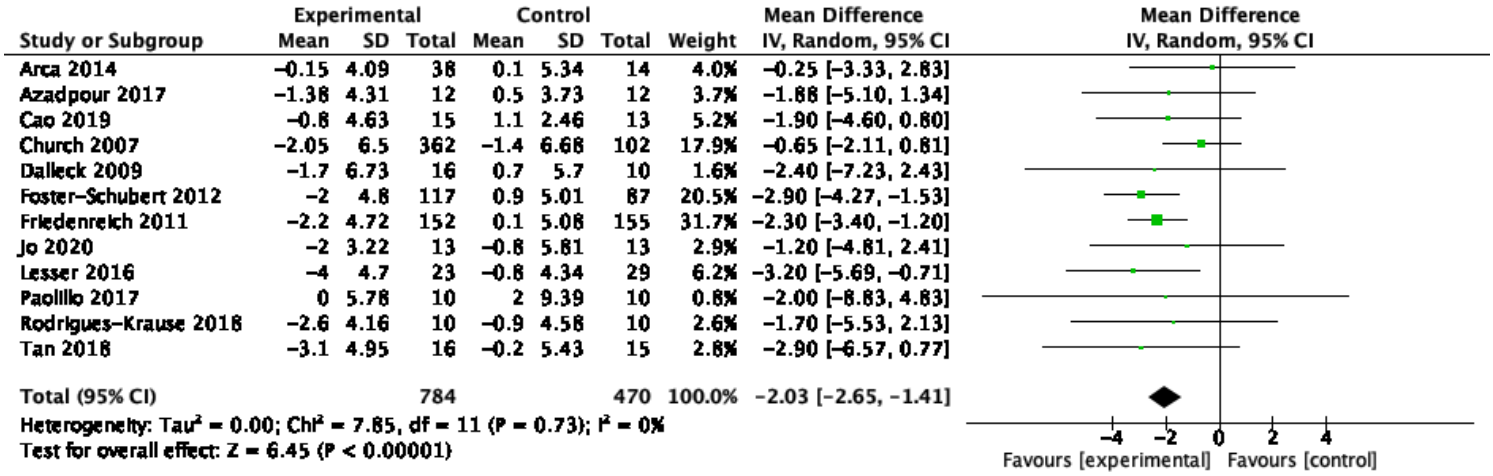



**Figure 2.5: Forest plot of the effect of aerobic exercise on waist circumference**

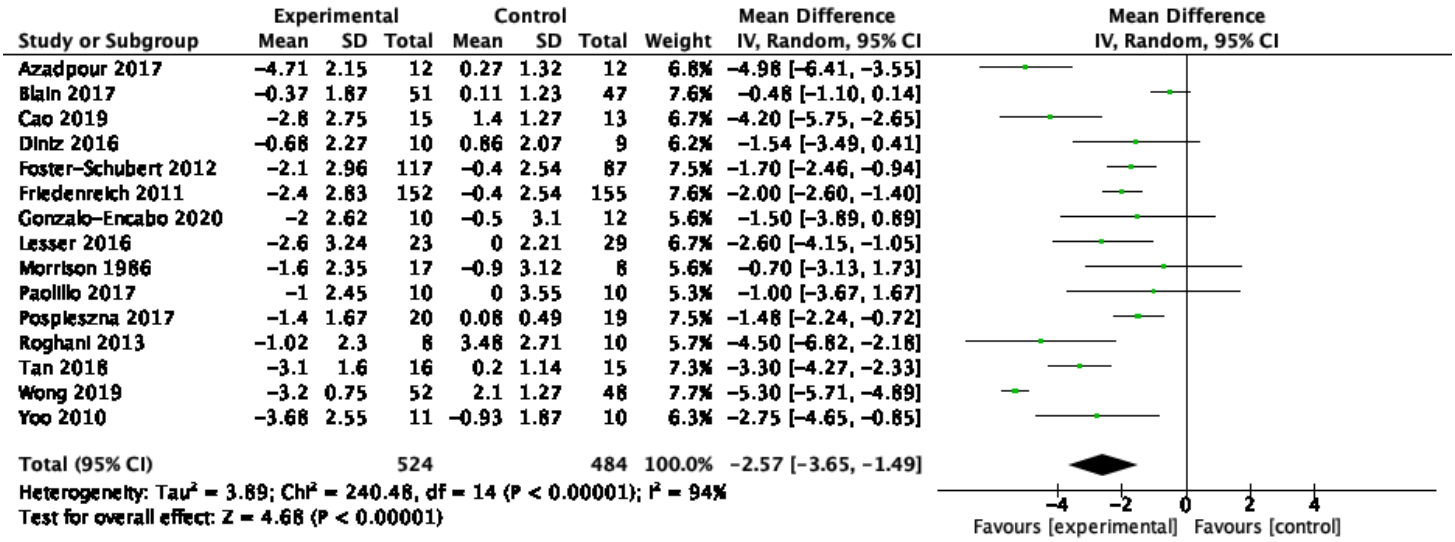



**Figure 2.6: Forest plot of the effect of aerobic exercise on body fat**

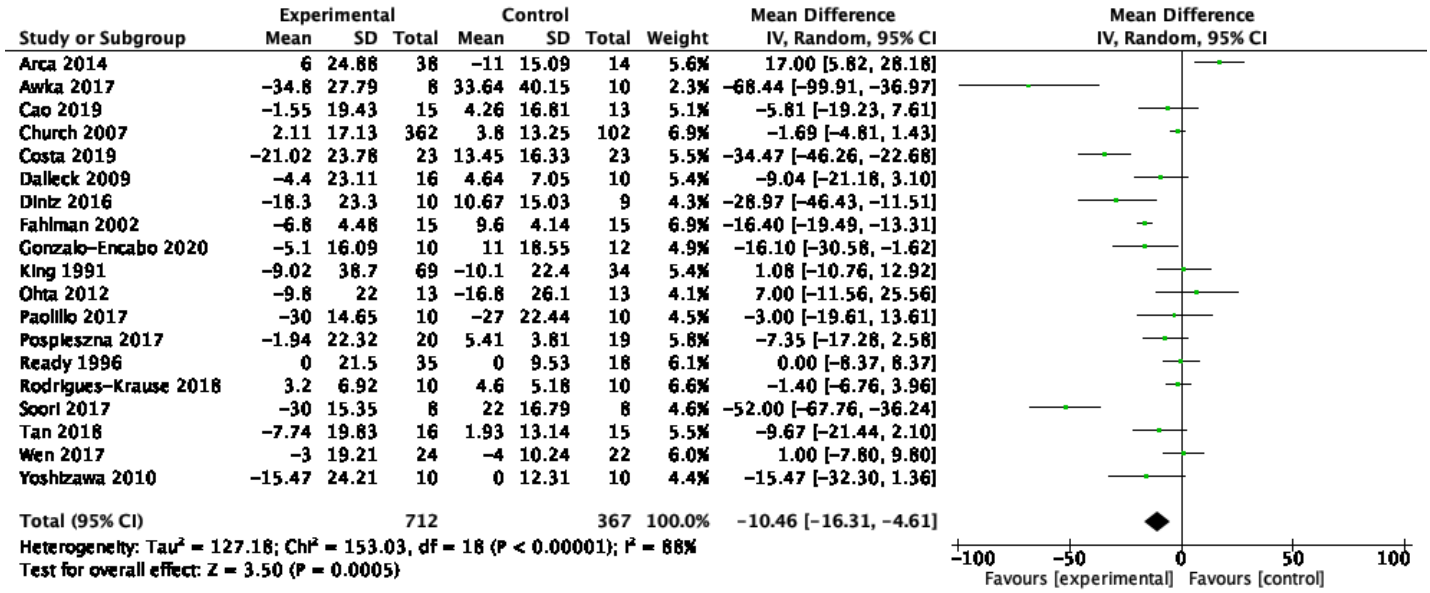



**Figure 2.7: Forest plot of the effect of aerobic exercise on low-density lipoprotein cholesterol**

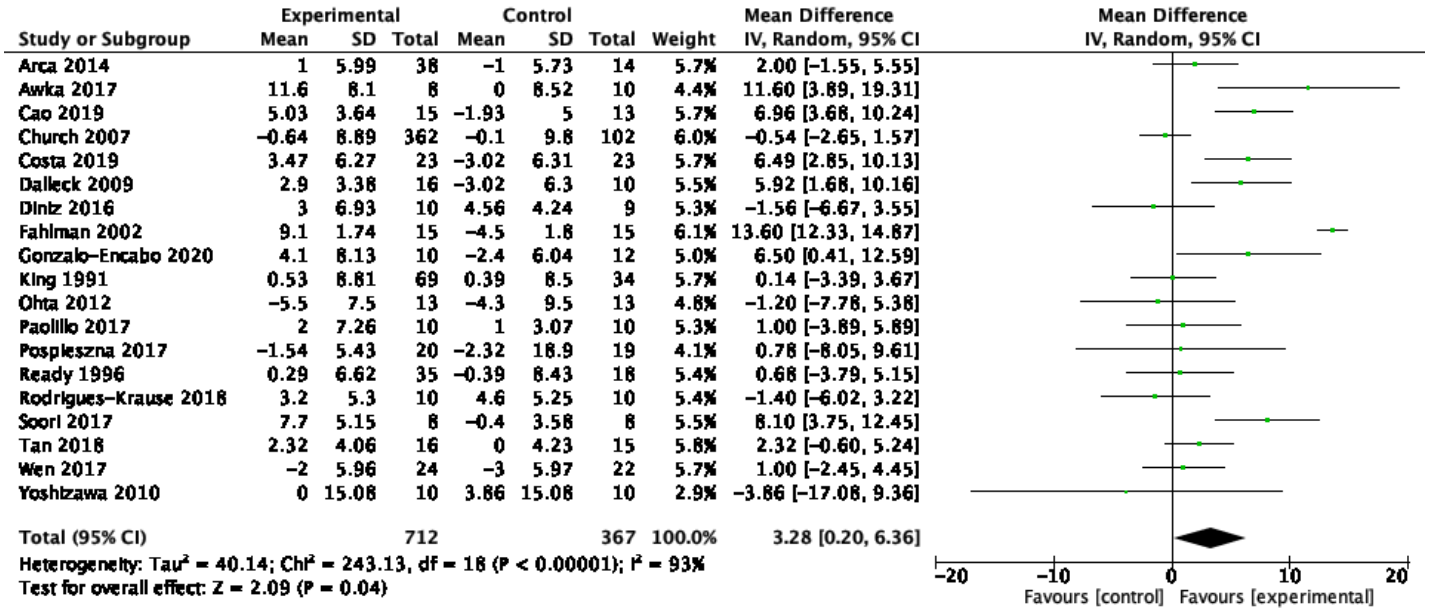



**Figure 2.8: Forest plot of the effect of aerobic exercise on high-density lipoprotein cholesterol**

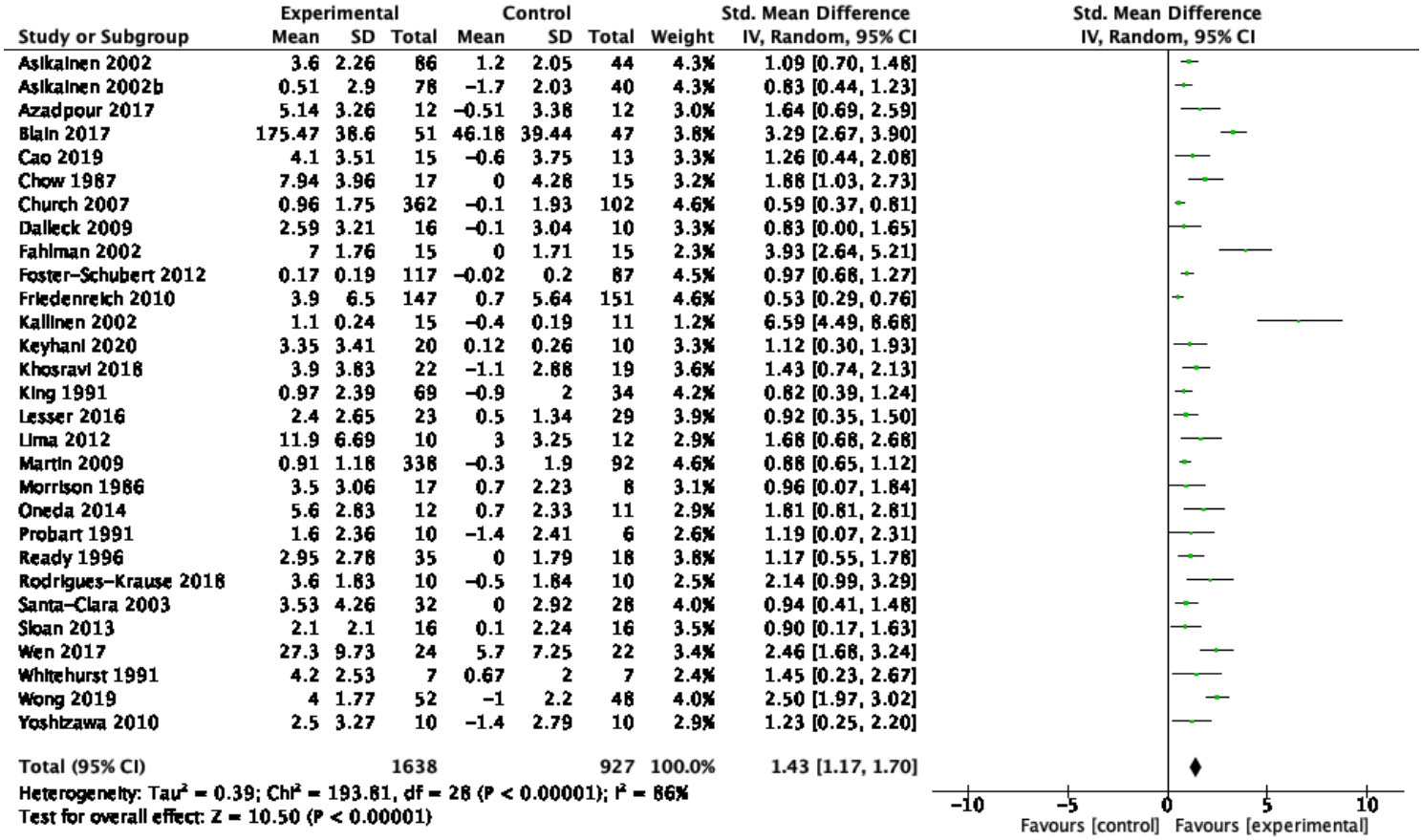



**Figure 2.9: Forest plot of the effect of aerobic exercise on cardiorespiratory fitness**

**Table 2.2.** Quality Appraisal of Included Studies Using GRADE Tool

| Outcome | Number of Studies (n participants) | Certainty Assessment | | | | | Effect (95% CI) | Certainty |
|---|---|---|---|---|---|---|---|---|
| | | Risk of Bias | Inconsistency | Indirectness | Imprecision | Publication Bias | | |
| Systolic Blood Pressure | 20 studies (n=1155) | Very Serious[a] | Serious[c] | Very Serious[e] | Not Serious | None | MD=-3.67 mmHg (-6.88 to -0.46) | ⨁◯◯◯ Very Low |
| Diastolic Blood Pressure | 20 studies (n=1155) | Very Serious[a] | Serious[c] | Very Serious[e] | Very Serious[f] | None | MD=-2.25 mmHg (-4.75 to 0.40) | ⨁◯◯◯ Very Low |
| Resting Heart Rate | 12 studies (n=432) | Very Serious[a] | Serious[c] | Very Serious[e] | Serious[g] | Highly Suspected[i] | MD=-2.84 bpm (-5.76 to -1.61) | ⨁◯◯◯ Very Low |
| Body Mass Index | 33 studies (n=1887) | Very Serious[a] | Serious[c] | Very Serious[e] | Not Serious | Highly Suspected[i] | MD=-0.65 kg/m$^2$ (-0.99 to -0.31) | ⨁◯◯◯ Very Low |
| Waist Circumference | 12 studies (n=1254) | Serious[b] | Not serious | Very Serious[e] | Not Serious | None | MD=-2.03 cm (-2.65 to -1.41) | ⨁◯◯◯ Very Low |
| Waist-to-hip Ratio | 6 studies (n=196) | Serious[b] | Serious[c] | Very Serious[e] | Very Serious[f] | None | MD=-0.01 (-0.02 to 0.00) | ⨁◯◯◯ Very Low |
| Body Fat | 15 studies (n=1008) | Very Serious[a] | Very Serious[d] | Very Serious[e] | Serious[g] | None | MD=-2.57 kg (-3.65 to -1.49) | ⨁◯◯◯ Very Low |
| Low-density Lipoprotein Cholesterol | 19 studies (n=1079) | Serious[b] | Very Serious[d] | Very Serious[e] | Not Serious | Highly Suspected[i] | MD=-10.46 mg/dL (-16.31 to -4.61) | ⨁◯◯◯ Very Low |
| High-density Lipoprotein Cholesterol | 19 studies (n=1079) | Very Serious[a] | Very Serious[d] | Very Serious[e] | Serious[g] | None | MD=3.28 mg/dL (0.2 to 6.36) | ⨁◯◯◯ Very Low |
| Blood Triglycerides | 19 studies (n=1079) | Very Serious[a] | Very Serious[d] | Very Serious[e] | Very Serious[f] | None | MD=-11.59 mg/dL (-25.82 to 2.65) | ⨁◯◯◯ Very Low |
| Blood Glucose | 10 studies (n=875) | Serious[b] | Very Serious[d] | Very Serious[e] | Serious[h] | None | MD=-0.92 mg/dL (-2.79 to 0.95) | ⨁◯◯◯ Very Low |
| CRF | 29 studies (n=2565) | Very Serious[a] | Very Serious[d] | Very Serious[e] | Not Serious | Highly Suspected[i] | SMD=1.43 (1.17 to 1.70) | ⨁◯◯◯ Very Low |

[a]Downgraded for high risk of bias in majority of RoB-2 domains including attrition bias; [b]downgraded for "some concerns" in majority of RoB-2 domains; [c]downgraded for high statistical heterogeneity with overlapping Confidence Intervals (CIs); [d]downgraded for high statistical heterogeneity with minimal overlapping CIs; [e]downgraded due to heterogeneity in population and heterogeneity in comparison groups; [f]downgraded for large 95%CI and crosses line of no effect; [g]downgraded for large 95%CI, but sample >400 participants; [h]downgraded for crossing line of no effect but narrow 95% CI and sample >400 participants; [i]downgraded for evidence of publication bias from Egger test and visual funnel plot assessment.

**Subgroup Analyses**

To conduct subgroup analyses based on intensity, 24 (51%)[156,158,159,163,165,167-171,178-180,184,187,194-196,198,200,202-205] studies were categorized as moderate intensity, 18 (38%)[157,160,166,172,173,175,177,181,183,186,188-193,197,201] as vigorous intensity, and only 5 (11%)[162,164,182,185,199] as light intensity. Forest plots for the subgroup analyses are displayed in Appendix 5. There was no difference in effect between studies of light, moderate and vigorous aerobic exercise intensities for any outcome except BMI ($X^2$=9.79, df=2, p<0.01), blood triglycerides ($X^2$=7.70, df=2, p=0.02), and blood glucose ($X^2$=20.98, df=2, p<0.01). Light (n=5 studies, MD=-1.17kg/m$^2$, 95%CI[-1.88, -0.47], p<0.01) and vigorous (n=12 studies, MD=-1.02kg/m$^2$, 95%CI[-1.74, -0.29], p<0.01) intensities were beneficial at reducing BMI while there was no effect of moderate intensity (n=14 studies, MD=-0.21kg/m$^2$, 95%CI[-0.45, -0.03], p=0.09). Light intensity also showed a significant effect for blood triglycerides (n=3 studies, MD=-35.39mg/dL, 95%CI[-57.09, -13.70], p<0.01) and blood glucose (n=1 study, MD=-18.36mg/dL, 95%CI[-26.04, -10.68], p<0.01); there was no effect observed for moderate (blood triglycerides: n=9 studies, MD=-3.11mg/dL, 95%CI[-10.78,-4.57], p=0.43) (blood glucose: n=4 studies, MD=0.40mg/dL, 95%CI[-2.72, 3.51], p=0.80) and vigorous (blood triglycerides: n=6 studies, MD=-12.75mg/dL, 95%CI[-44.03, -18.53], p=0.42) (blood glucose: n=3 studies, MD=-0.45mg/dL, 95%CI[-1.52, 0.62], p=0.41) intensities (Table 2.3).

No significant differences in the effects of exercise intensities on BMI and blood triglycerides were found when studies involving females with comorbidities were excluded. Moreover, the results of the subgroup analyses remained consistent after excluding studies that did not explicitly report menopausal status.

**Table 2.3.** Summary of Aerobic Exercise Intensity Subgroups on Cardiovascular Health Measures

| Cardiovascular Health Measure | Studies | n participants | Mean Difference [95% CI] | *p* | Pearson Chi-Square | | |
|---|---|---|---|---|---|---|---|
| | | | | | $X^2$ | Degrees of Freedom | *p* |
| Body Mass Index | | | | | | | |
| Light | 5 | 134 | -1.17 kg/m$^2$ [-1.88, -0.47] | <0.01 | | | |
| Moderate | 14 | 801 | -0.21 kg/m$^2$ [-0.45, -0.03] | 0.09 | 9.79 | 2 | *<0.01 |
| Vigorous | 12 | 896 | -1.02 kg/m$^2$ [-1.74, -0.29] | <0.01 | | | |
| Blood Triglycerides | | | | | | | |
| Light | 3 | 75 | -35.39 mg/dL [-57.09, -13.70] | <0.01 | | | |
| Moderate | 9 | 738 | -3.11 mg/dL [-10.78, -4.57] | 0.43 | 7.70 | 2 | *0.02 |
| Vigorous | 6 | 240 | -12.75 mg/dL [-44.03, -18.53] | 0.42 | | | |
| Blood Glucose | | | | | | | |
| Light | 1 | 31 | -18.36 mg/dL [-26.04, -10.68] | <0.01 | | | |
| Moderate | 4 | 549 | 0.40 mg/dL [-2.72, 3.51] | 0.80 | 20.98 | 2 | *<0.01 |
| Vigorous | 3 | 245 | -0.45 mg/dL [-1.52, 0.62] | 0.62 | | | |

95% CI – 95% Confidence Interval
*denotes p<0.05

## Discussion

This review examined the effects of aerobic exercise on traditional measures of cardiovascular health in postmenopausal females. Based on the quality of evidence, aerobic exercise training may improve SBP, RHR, BMI, WC, absolute body fat, LDL-C, HDL-C and CRF. However, aerobic exercise training may have little to no effect on DBP, WHR, blood triglycerides, and blood glucose, although the evidence is very uncertain. In secondary analyses of the effects of various levels of aerobic exercise intensity, we found differences in effect for

BMI, blood triglycerides and blood glucose but none of the other cardiovascular health measures.

The positive effects of aerobic exercise observed on cardiovascular health measures in postmenopausal females is aligned with previous reviews reporting improvements in body fat, WC, LDL-C, HDL-C, and CRF.[123,124] Our study is the first to report improvements in SBP, HR, and BMI in postmenopausal females. Interestingly, we note that many outcomes demonstrating positive effects had a large proportion of studies with baseline values outside of target levels. For example, baseline values for 68% of studies were in prehypertensive or hypertensive ranges (≥120mmHg) for SBP,[220] 50% with high HR values,[221] 84% with BMI ≥25kg/m$^2$,[59] 91% with WC ≥90cm,[59] 89% with LDL-C ≥100mg/dL[222] and 44% with HDL-C ≤50mg/dL.[223] This may be a product of the broader range of eligible studies used in this review, but enables a more comprehensive representation of postmenopausal females to increase the generalizability of findings, and underscores the benefit of aerobic exercise for individuals at higher risk for CVD.

It is important to acknowledge the effect of aerobic exercise observed is very uncertain based on the GRADE assessment. Nonetheless, we found no negative effects with aerobic exercise, only null or beneficial effects with 95% CIs containing clinical important values for most outcomes. The benefits of aerobic exercise may outweigh potential negative effects to cardiovascular health. Thus, we propose that clinicians should consider recommending aerobic exercise to improve cardiovascular health and mitigate menopause-related increases in cardiovascular risk. Our conservative proposition considered a comprehensive assessment of four key domains 1) the balance between desirable and undesirable outcomes, 2) overall quality of evidence for outcomes, 3) values and preferences of participants, and 4) resource use.[224] Postmenopausal females have also shown interest in physical activity including aerobic exercise

to improve their body composition[225] and subsequently cardiovascular health. Last, aerobic exercise interventions such as walking are both feasible and low in cost making them a practical option to improve cardiovascular health in postmenopausal females.[226]

The physiological mechanisms that underlie the positive effects of aerobic exercise on cardiovascular health is well supported. Decreases in SBP and HR are due to a combination of neurohormonal mechanisms[106] and structural factors.[108] Aerobic exercise decreases sympathetic nerve activity and increases parasympathetic activity leading to long-term peripheral vasodilation.[106] Exercise may also improve SBP by attenuating age-related decreases in arterial elasticity and compliance through increased pulse pressures and mechanical distension of collogen fibres.[108] Moreover, exercise-induced enhancements in stroke volume, leading to increased cardiac output during rest, can potentially contribute to a reduction in HR.[111] Aerobic exercise can improve body composition through increased total energy expenditure,[112] leading the body to rely on adipose tissue for energy.[113] Additionally, the upregulation of Proprotein Convertase Subtilisin/Kexin Type 9 due to aerobic exercise may accelerate the absorption and excretion of LDL-C, and upregulation of the liver X receptor gene has a strong effect on formation of HDL-C.[118] CRF may be increased through changes to cardiac output by improved stroke and blood volumes,[111,121] and arteriovenous oxygen content difference.[121]

The null effect of aerobic exercise on DBP may be attributed to low baseline levels making it challenging to induce further reductions. The age of participants may play a factor; DBP has been observed to increase with age until approximately 58 years for females, after which it tends to decline.[51] Notably, >70% of the studies in our review had a mean age of greater than 58 years old, possibly contributing to the normotensive DBP observed. We also did not observe an effect of aerobic exercise on WHR, although this analysis may have been

underpowered due to the small number of participants. Additionally, considering that adipose tissue typically stored in the gluteofemoral regions for females,[227] it is plausible that simultaneous reductions in both waist and hip circumference may have occurred thus resulting in no change in the overall ratio. Lastly, aerobic exercise did not have an impact on blood triglyceride levels or blood glucose levels which may be explained by baseline values already within target ranges. Mean blood triglyceride were in normolipidemic levels (≤150 mg/dL)[228] at baseline for 68% of studies and blood glucose in normoglycemic levels (63-100 mg/dL) for 70% of studies).[229]

In our secondary analyses, we observed that both light and vigorous intensities were effective in reducing BMI compared to moderate intensity, and light intensity exercise for improving blood triglycerides and blood glucose levels. The unexpected positive findings for light-intensity exercise may be attributed to the well-established dose-response effect of exercise volume.[230-232] Given that the interventions included in this review varied in total volume, this may have influenced the results of the second objective. We also suggest that the small number of studies in this subgroup may contribute to type I error, but findings may also be explained in part by baseline characteristics of the study samples being at elevated levels and thus more responsive to change. For example, we noted that overweight or obese females showed the largest effect in the light intensity group for BMI, 2 out of the 3 studies on blood triglycerides focused on females with hyperlipidemia, and the only study in the light intensity subgroup for blood glucose specifically targeted females with type 2 diabetes mellitus. In sensitivity analyses with studies of overweight and obese females and females with hyperlipidemia removed, subgroup differences of exercise intensity on BMI and blood triglycerides were no longer observed. Hence, the positive effects of light aerobic exercise should be interpreted with caution.

## Limitations

We acknowledge limitations of this review. We only included studies published in English; there may have been potentially eligible studies from the 31 papers published in languages other than English. Moreover, while we used conservative age criteria to ensure with a degree of confidence that the females included were postmenopausal, there is a small possibility of including premenopausal females and excluding postmenopausal females who did not meet our age criteria.

## Conclusion

Aerobic exercise may be an important strategy to mitigate the increased cardiovascular risk that occurs following menopause. Although there is uncertainty surrounding the evidence for aerobic exercise and its effect on cardiovascular health outcomes, the potential benefits may outweigh possible unfavorable effects. Therefore, clinicians should consider recommending aerobic exercise to postmenopausal females as a non-pharmacological and non-diet primary preventative approach for cardiovascular disease.

## Acknowledgments

EH is supported by a Canadian Institute for Health Research-Masters Scholarship. EW is supported by the McMaster Institute for Research on Aging and AGEWELL NCE Inc, a member of the Networks of Centres of Excellence program through an AGE-WELL-MIRA Technology and Aging Doctoral Award. KSN is supported by the Ontario Graduate Scholarship.

# Chapter 3: Examining the Associations Between Cardiovascular Health, Physical Activity and Menopausal Status in Pre- And Post-menopausal Females Living With Stroke and Transient Ischemic Attack: A Cross-Sectional Analysis of Baseline Data From the Canadian Longitudinal Study on Aging

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## Abstract

***Background.*** In females, menopause leads to the reduction of estrogen and its cardioprotective effects. Consequently, risk of cardiovascular disease increases two-fold after menopause, and the risk of stroke nearly doubles in the 10 years following menopause. Markers of poor cardiovascular health are prevalent in individuals poststroke, such that risk of recurrent stroke is high after the initial event. Evidence supports engagement in physical activity to improve cardiovascular health in post-menopausal females and individuals post-stroke, but no studies have examined the relationship between physical activity, cardiovascular health, and menopausal status post-stroke. This study examined 1) association between physical activity and cardiovascular health in females with stroke 2) the interacting effect of menopausal status on this association.

***Methods.*** This study used baseline data from the comprehensive cohort of the Canadian Longitudinal Study on Aging (CLSA). Participants in the CLSA were included if they were female with stroke and had available data regarding menopausal status, self-reported physical activity as measured by the Physical Activity Scale for the Elderly, and cardiovascular outcomes of interest and covariates. Generalized linear models with applied analytic weights were used to examine the associations between each measure of cardiovascular health, and self-reported physical activity, while controlling for age and smoking history. Subsequent models included an interaction between physical activity and menopausal status.

***Results.*** The sample included 1468 females with stroke (mean age=67.8 [Linearized Standard Error 0.39]; 103 premenopausal females). Physical activity was beneficially associated with SBP (ß = -0.02 (SE=0.01), p=0.04, 95% CI: -0.42 to -0.0005), WC (ß = -0.03 (SE=0.008), p<0.01, 95% CI: -0.05 to -0.02), waist-to-hip ratio (ß = -0.00009 (SE=0.00004), p=0.03, 95% CI: -0.0002

to -0.0000007), and C-Reactive protein (ß = -0.007 (SE=0.003), p<0.02, 95% CI: -0.013 to -0.001). There were no interactions between physical activity and menopausal status for all outcomes.

***Conclusion***. This study highlights the positive association between physical activity and cardiovascular health in females with stroke regardless of menopausal status. Furthermore, this study lays groundwork for future longitudinal analyses of physical activity on cardiovascular health and for exploring disparities in cardiovascular adaptations between pre- and postmenopausal females with stroke.

## Introduction

In Canada, approximately 878,500 individuals ages 20 and older are living with the effects of stroke.[94] These individuals are at high risk for a recurrent event, with 26% of individuals experiencing a second stroke within 5 years, and 39% after 10 years of initial event.[35]

Stroke disproportionately effects females, which in part may be attributed to the reduction in the sex hormone estrogen during menopausal transition.[233] Menopause is an event in a female's life marked by the cessation of menstruation.[80,127] The result is lower levels of estrogen and its cardioprotective effects,[19] leading to increased blood pressure, sympathetic tone, endothelial dysfunction and vascular inflammation.[128] Consequently, females have two-fold higher risk for cardiovascular disease after menopause compared to before,[27] and two-fold higher risk for stroke in the 10 years following menopause.[28]

Evidence supports the use of physical activity to improve cardiovascular health in pre- and postmenopausal females without stroke,[234,235] and in individuals with stroke.[42] Physical activity refers to any bodily movement that requires energy, encompassing a range of activities including exercise, occupational, sport, and household related tasks.[104] While the evidence

supporting exercise and physical activity after stroke is strong,[42,234-238] females are underrepresented in stroke research trials.[44] Further, the lack of reporting and disaggregation of female-specific cardiovascular risk factors such as menopausal status may reduce the reproducibility and generalizability of study results.[45,46] To date, there have been no studies that have examined the association between physical activity and cardiovascular health in females with stroke while considering the influence of menopausal status.

The primary objective of this study was to assess the association between physical activity and cardiovascular health measures in females with stroke. The secondary objective was to evaluate the interacting effect of menopausal status on the association between physical activity and cardiovascular health in females with stroke. It was hypothesized that higher levels of physical activity would be negatively associated with measures of cardiovascular health. Moreover, it was hypothesized that there will be an interaction between physical activity and menopausal status on all measures of cardiovascular health.

## Methods

### Study Design

This study was a cross-sectional analysis using baseline data from the comprehensive cohort of the Canadian Longitudinal Study on Aging (CLSA). The aim of the CLSA is to investigate the complex process of aging and improve understanding of the transitions and trajectories of healthy aging.[239] The CLSA is a large national research platform that includes participants from all 10 Canadian provinces who will be followed from 2011 until 2033 or death. Baseline data for the comprehensive cohort was acquired between 2011 to 2015 for over 30,000 Canadian adults aged 45-85 years.[240] Approval to access data was obtained from the CLSA

(Application No. T47779) and ethics approval for accessing and analyzing the dataset was granted from the Hamilton Integrated Research Ethics Board (HIREB #13916).

**Participants**

To be included in the present cross-sectional analysis, participants in the CLSA must have: 1) reported being of female sex; 2) reported menopausal status, "Have you gone through menopause, meaning that your menstrual periods stopped for at least one year and did not restart?" (Yes/No); 3) responded "Yes" to any CLSA question regarding being diagnosed with a stroke or TIA by a physician, live with the effects of stroke or TIA as diagnosed by a physician, previous or current drugs/medication use for stroke or TIA, previous or current treatment for stroke or TIA; 4) complete data available on self-reported physical activity; 5) data available for at least one cardiovascular outcome of interest (resting blood pressure, resting heart rate, waist circumference, waist-to-hip ratio, C-reactive protein); 6) available covariate data (age and smoking history). Females with reported hysterectomy were excluded due to missing information regarding type of hysterectomy, which has been reported to affect estrogen levels.[241]

**Independent Variables**

***Physical Activity***

Physical activity levels were measured using a modified version of Physical Activity Scale for The Elderly (PASE). The PASE is a brief and easily scored self-report assessment instrument designed originally to assess physical activity over the past seven days in individuals ages 65 and older,[242] but has also been used in individuals living with stroke,[243-246] and adults <65 years old.[244,247] The PASE is a 12-component questionnaire that combines information regarding leisure (e.g. light, moderate, intense recreational activities; strength and endurance exercises), household (e.g. household work, lawn and yard work, gardening) and work-related

(e.g. paid or volunteer work) activities. The instrument considers the frequency, intensity and duration of each activity to calculate a final score ranging from 0 to 793, with higher scores indicating greater physical activity levels.[242] In the modified version of the PASE used in the CLSA, the frequency and duration of household activities were not examined. The original PASE has shown strong construct validity and test re-test reliability in older healthy adults (r=0.75),[242] and has been validated in older adults living with physical disabilities.[248]

**Dependent Variables**

The cardiovascular health profiles of females with stroke were determined with the following risk factors:

***Blood Pressure and Heart Rate.*** High blood pressure, or hypertension, is the main modifiable risk factor for cardiovascular disease in females.[136,137] Risk for stroke increases when resting blood pressure is >115/75 mmHg and risk for cardiovascular disease doubles with every 20/10 mmHg increase in systolic and diastolic blood pressure, respectively.[249] Anti-hypertensive medications are typically prescribed after stroke to manage blood pressure, but it has been shown that blood pressure remains high despite treatment, leaving these individuals at increased risk for cardiovascular diseases.[250] The association between resting heart rate (HR) and cardiovascular disease risk is also well established,[139] where every 10 beat/min increase in HR increases risk of cardiovascular mortality by 8%.[3] In the CLSA, resting blood pressure and HR were measured simultaneously using an automated blood pressure machine (BpTRU BPM200 Blood Pressure Monitor; VSM MedTech Ltd, Vancouver, British Columbia, Canada) placed over the left brachial artery with the participant in a seated position.[251] The CLSA used the average of 6 readings of systolic and diastolic blood pressures (SBP and DBP, mmHg), and HR (beats/min) values.

***Waist Circumference and Waist-to-hip ratio.*** Waist circumference (WC) and waist-to-hip ratio (WHR), the ratio between the circumference of the waist to the circumference of the hip,[61] are strong surrogate measures of visceral fat[252,253] and stronger markers of cardiovascular risk compared to body mass index.[61,253] In the CLSA, WC (centimeters, cm) was measured with a measuring tape at the level of the "natural indent" in the waist (between the last floating rib and iliac crest).[254] Hip circumference (cm) was measured at the widest part of the hips and buttocks.[254] The WHR was calculated by dividing the WC by the hip circumference.

***C-reactive protein***. High sensitivity C-reactive protein (hsCRP) is a blood marker that indicates both systemic inflammation and inflammation within the arterial walls.[17] It is considered a robust biomarker, particularly for assessing cardiovascular risk.[17,255] In the CLSA, hsCRP (mg/L) was measured from a blood sample,[256] and analyzed at Calgary Laboratory Services using Roche Diagnostics Cobas 8000 series c701.[257]

**Statistical Analyses**

Participant characteristics are presented as mean (linearized standard error) for continuous data, and proportions and linearized standard error for categorical data. For the primary objective, separate generalized linear models were conducted for each measure of cardiovascular health to examine its association with PASE scores in females with stroke. Only participants with available cardiovascular data were included in each respective model. To address the secondary objective, an interaction term between PASE scores and menopausal status was added to each model. To increase generalizability to the broader Canadian population of females living with stroke, we applied analytic weights provided by the CLSA[258] to each generalized linear model. All models were adjusted for covariates known to affect cardiovascular health, regardless of its individual statistical significance. These covariates included age, as

cardiovascular health tends to decline with increasing age,[259] and smoking status, as smoking is a well-established modifiable risk factor for cardiovascular disease.[48] To preserve sample size, Hormone Replacement Therapy (HRT) was not included as a covariate as only 41% of the sample had data available for key HRT parameters known to affect cardiovascular health, such as type, duration of use, and dosage.[260]

All statistical analyses were performed using Stata statistical software (Version 16.1, Stata CorpLLC, College Station, Texas, USA). The significance level was set a priori at $p<0.05$.

## Results

A flow chart of participants included from the CLSA is presented in Figure 3.1. Participant characteristics, combined and stratified by menopausal status, are presented in Table 3.1. In the CLSA at baseline, there were 1468 females living with stroke, of which 103 (7%) were premenopausal and 1365 (93%) were postmenopausal.

**Figure 3.1. Participant Flow Chart**

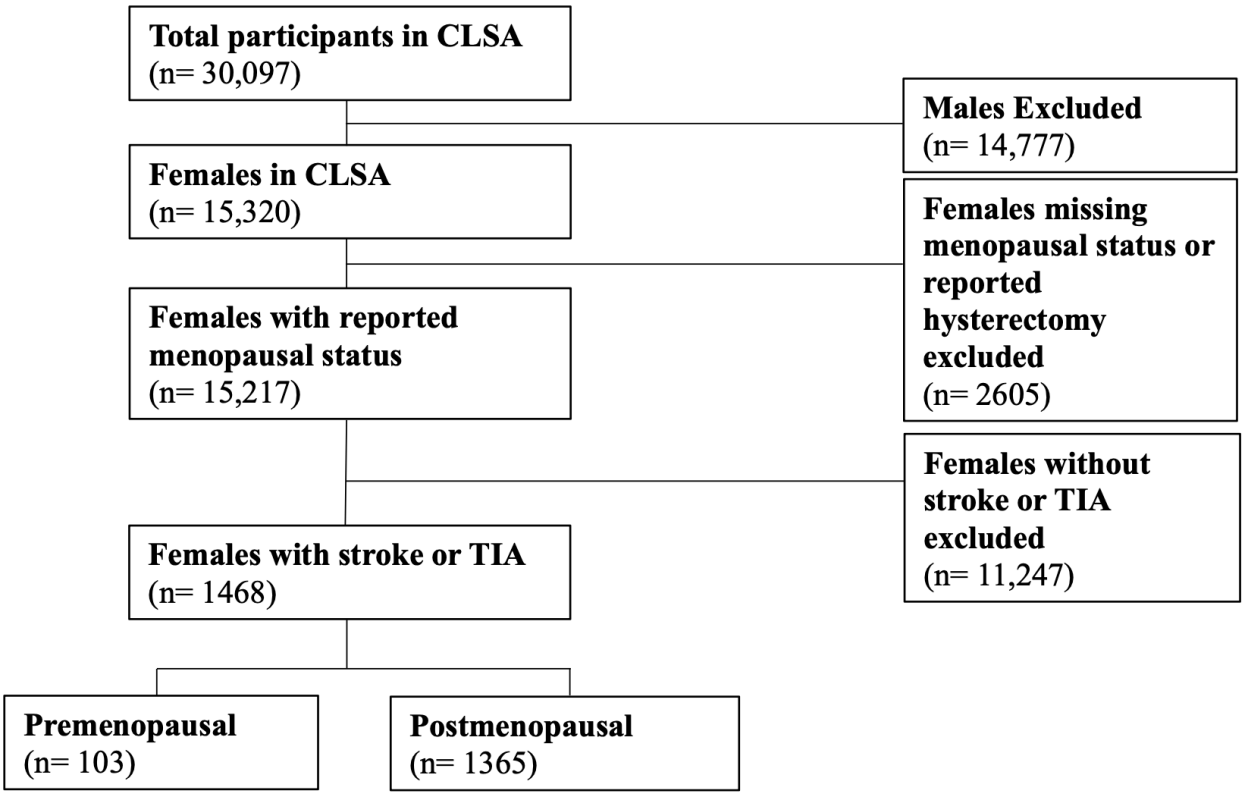


**Table 3.1.** Participant characteristics with analytic weights (n=1468 participants)

| | Total (n = 1468) | Premenopause (n=103) | Postmenopause (n=1365) |
|---|---|---|---|
| Age (years) | 67.8 (0.39) [67.1 to 68.6] | 55.4 (1.03) [53.4 to 57.5] | 69.4 (0.36) [68.7 to 70.1] |
| Physical Activity Scale for the Elderly score | 111.7 (2.39) [107.0 to 116.4] | 129.7 (9.14) [111.6 to 147.9] | 109.5 (2.40) [104.8 to 114.2] |
| Hormone Replacement Therapy* | | | |
| Currently Use/Former Used | 0.40 (0.02) [0.37 to 0.44] | 0.19 (0.04) [0.12 to 0.29] | 0.42 (0.02) [0.39 to 0.47] |
| Never Used | 0.60 (0.02) [0.37 to 0.44] | 0.81 (0.04) [0.71 to 0.88] | 0.57 (0.02) [0.53 to 0.61] |
| Smoking History* | | | |
| Never Smoked | 0.43 (0.02) [0.40 to 0.47] | 0.39 (0.06) [0.28 to 0.50] | 0.44 (0.02) [0.40 to 0.47] |
| Former Smoker | 0.46 (0.02) [0.43 to 0.50] | 0.42 (0.06) [0.31 to 0.53] | 0.47 (0.02) [0.43 to 0.51] |
| Current Smoker | 0.11 (0.01) | 0.19 (0.05) | 0.10 (0.01) |

| | | | |
|---|---|---|---|
| | [0.09 to 0.13] | [0.11 to 0.31] | [0.07 to 0.12] |
| Systolic blood pressure (mmHg) | 126.3 (0.74) | 120.9 (2.12) | 127.0 (0.78) |
| | [124.9 to 127.8] | [116.7 to 125.1] | [125.5 to 128.6] |
| Diastolic blood pressure (mmHg) | 71.6 (0.39) | 74.1 (1.04) | 71.3 (0.42) |
| | [70.8 to 72.4] | [72.0 to 76.1] | [70.5 to 72.1] |
| Resting heart rate (beats/min) | 72.4 (0.38) | 73.9 (1.11) | 72.2 (0.41) |
| | [71.6 to 73.1] | [71.7 to 76.1] | [71.4 to 73.0] |
| Waist Circumference (cm) | 93.6 (0.53) | 93.4 (1.45) | 93.6 (0.56) |
| | [92.6 to 94.7] | [90.6 to 96.3] | [92.6 to 94.7] |
| Waist to Hip Ratio | 0.86 (0.002) | 0.85 (0.01) | 0.86 (0.002) |
| | [0.85 to 0.86] | [0.84 to 0.87] | [0.86 to 0.87] |
| C-Reactive Protein (mg/L) | 2.96 (0.16) | 3.39 (0.54) | 2.91 (0.17) |
| | [2.65 to 3.28] | [2.30 to 4.47] | [2.58 to 3.24] |

Variables are presented as mean (Linearized Standard Error) [95% Confidence Interval]
* - presented proportions (Linearized Standard Error) [95% Confidence Interval]

For objective 1, PASE scores were associated with SBP (ß = -0.02 (SE=0.01), p=0.04, 95% CI: -0.42 to -0.0005), WC (ß = -0.03 (SE=0.008), p<0.01, 95% CI: -0.05 to -0.02), WHR (ß = -0.00009 (SE=0.00004), p=0.03, 95% CI: -0.0002 to -0.0000007), hsCRP (ß = -0.007 (SE=0.003), p<0.02, 95% CI: -0.013 to -0.001) after adjusting for covariates (age, smoking history) (Table 3.2). There was no significant association between physical activity and DBP or HR.

**Table 3.2.** Adjusted generalized linear models examining the associations between cardiovascular health and physical activity levels of females with stroke in the Canadian Longitudinal Study on Aging

| Variable | ß-Coefficient (SE) | 95% CI | p-value |
|---|---|---|---|
| ***Systolic blood pressure*** | | | |
| Physical Activity Scale for the Elderly Scores | -0.02 (0.01) | -0.4223 to -0.0005 | ***0.04** |
| Age | 0.47 (0.08) | 0.32 to 0.62 | <0.01 |
| Smoking Status (ref: current smoker) | | | |
| Never smoked | -0.14 (2.10) | -4.26 to 3.98 | 0.95 |
| Former smoker | 0.46 (2.11) | -3.67 to 4.59 | 0.83 |
| ***Diastolic blood pressure*** | | | |
| Physical Activity Scale for the Elderly Scores | 0.0005 (0.006) | -0.011 to 0.012 | **0.94** |
| Age | -0.22 (0.04) | -0.30 to -0.14 | <0.01 |
| Smoking Status (ref: current smoker) | | | |

| | | | |
|---|---|---|---|
| Never smoked | 0.61 (1.51) | -2.35 to 3.58 | 0.68 |
| Former smoker | 1.28 (1.52) | -1.71 to 4.27 | 0.40 |
| ***Resting heart rate*** | | | |
| Physical Activity Scale for the Elderly Scores | -0.01 (0.006) | -0.0238 to 0.0002 | **0.055** |
| Age | -0.17 (0.04) | -0.25 to -0.09 | <0.01 |
| Smoking Status (ref: current smoker) | | | |
| Never smoked | -0.15 (1.20) | -2.50 to 2.20 | 0.90 |
| Former smoker | 0.42 (1.21) | -1.95 to 2.79 | 0.73 |
| ***Waist Circumference*** | | | |
| Physical Activity Scale for the Elderly Scores | -0.03 (0.008) | -0.05 to -0.02 | ***<0.01** |
| Age | -0.27 (0.05) | -0.37 to -0.16 | <0.01 |
| Smoking Status (ref: current smoker) | | | |
| Never smoked | -0.74 (2.08) | -4.82 to 3.34 | 0.72 |
| Former smoker | 2.08 (2.04) | -1.93 to 6.09 | 0.31 |
| ***Waist to Hip Ratio*** | | | |
| Physical Activity Scale for the Elderly Scores | -0.00009 (0.00004) | -0.0002 to -0.000007 | ***0.03** |
| Age | -0.00006 (0.0003) | -0.0006 to 0.0005 | 0.83 |
| Smoking Status (ref: current smoker) | | | |
| Never smoked | -0.02 (0.009) | -0.037 to -0.003 | 0.02 |
| Former smoker | -0.01 (0.009) | -0.028 to 0.005 | 0.18 |
| ***C-Reactive Protein*** | | | |
| Physical Activity Scale for the Elderly Scores | -0.007 (0.003) | -0.013 to -0.001 | ***0.02** |
| Age | -0.023 (0.02) | -0.06 to 0.01 | 0.18 |
| Smoking Status (ref: current smoker) | | | |
| Never smoked | 0.18 (0.36) | -0.53 to 0.89 | 0.62 |
| Former smoker | 0.16 (0.48) | -0.68 to 1.00 | 0.71 |

SE = Linearized Standard Error
*denotes p<0.05

For objective 2, no interactions between physical activity and menopausal status were observed for any cardiovascular outcomes, after adjusting for covariates (Table 3.3).

**Table 3.3.** Adjusted generalized linear models examining the interaction between physical activity levels and menopausal status on markers cardiovascular health in females with stroke in the Canadian Longitudinal Study on Aging

| Variable | ß-Coefficient (SE) | 95% CI | p-value |
|---|---|---|---|
| ***Systolic blood pressure*** | | | |

| | | | |
|---|---|---|---|
| Physical Activity Scale for the Elderly Scores | -0.02 (0.01) | -0.046 to -0.001 | 0.045 |
| Age | 0.47 (0.08) | 0.31 to 0.63 | <0.01 |
| Smoking Status (ref: current smoker) | | | |
| Never smoked | -0.17 (2.09) | -4.28 to 3.93 | 0.93 |
| Former smoker | 0.43 (2.10) | -3.68 to 4.55 | 0.84 |
| Premenopause | -1.84 (4.34) | -10.35 to 6.68 | 0.67 |
| Premenopause* PASE Scores | 0.01 (0.03) | -0.04 to 0.07 | 0.66 |
| ***Diastolic blood pressure*** | | | |
| Physical Activity Scale for the Elderly Scores | 0.001 (0.007) | -0.01 to 0.01 | 0.84 |
| Age | -0.23 (0.04) | -0.32 to -0.14 | <0.01 |
| Smoking Status (ref: current smoker) | | | |
| Never smoked | 0.60 (1.50) | -2.35 to 3.56 | 0.69 |
| Former smoker | 1.25 (1.52) | -1.73 to 4.23 | 0.82 |
| Premenopause | 0.03 (2.27) | -4.42 to 4.48 | 0.99 |
| Premenopause* PASE Scores | -0.007 (0.01) | -0.04 to 0.02 | 0.65 |
| ***Resting heart rate*** | | | |
| Physical Activity Scale for the Elderly Scores | -0.01 (0.006) | -0.024, 0.001 | 0.08 |
| Age | -0.17 (0.04) | -0.25 to -0.08 | <0.01 |
| Smoking Status (ref: current smoker) | | | |
| Never smoked | -0.15 (1.20) | -2.49 to 2.20 | 0.90 |
| Former smoker | 0.43 (1.20) | -1.93 to 2.78 | 0.72 |
| Premenopause | 0.03 (2.48) | -4.83 to 4.89 | 0.99 |
| Premenopause* PASE Scores | 0.001 (0.01) | -0.03 to 0.03 | 0.92 |
| ***Waist Circumference*** | | | |
| Physical Activity Scale for the Elderly Scores | -0.04 (0.01) | -0.05 to -0.02 | <0.01 |
| Age | -0.31 (0.06) | -0.42 to -0.20 | <0.01 |
| Smoking Status (ref: current smoker) | | | |
| Never smoked | -0.86 (2.05) | -4.88 to 3.16 | 0.67 |
| Former smoker | 1.93 (2.02) | -2.03 to 5.89 | 0.34 |
| Premenopause | -4.98 (3.02) | -10.90 to 0.94 | 0.10 |
| Premenopause* PASE Scores | 0.01 (0.02) | -0.03 to 0.06 | 0.57 |
| ***Waist to Hip Ratio*** | | | |
| Physical Activity Scale for the Elderly Scores | -0.00011 (0.00004) | -0.0002 to 0.00003 | <0.01 |
| Age | -0.0002 (0.0003) | -0.007 to 0.0004 | 0.56 |
| Smoking Status (ref: current smoker) | | | |
| Never smoked | -0.02 (0.009) | -0.038 to -0.003 | 0.02 |
| Former smoker | -0.01 (0.008) | -0.029 to 0.005 | 0.16 |
| Premenopause | -0.03 (0.01) | -0.06 to -0.002 | 0.04 |
| Premenopause* PASE Scores | 0.0002 (0.0001) | -0.00003 to 0.0004 | 0.09 |
| ***C-Reactive Protein*** | | | |

| | | | |
|---|---|---|---|
| Physical Activity Scale for the Elderly Scores | -0.006 (0.003) | -0.013 to 0.0002 | 0.06 |
| Age | -0.023 (0.02) | -0.06 to 0.01 | 0.19 |
| Smoking Status (ref: current smoker) | | | |
| Never smoked | 0.17 (0.37) | -0.55 to 0.89 | 0.64 |
| Former smoker | 0.15 (0.42) | -0.68 to 0.97 | 0.73 |
| Premenopause | 0.17 (0.88) | -1.56 to 1.90 | 0.85 |
| Premenopause* PASE Scores | -0.003 (0.005) | -0.01 to 0.01 | 0.53 |

SE = Linearized Standard Error
PASE = Physical Activity Scale for the Elderly

## Discussion

This study reported beneficial associations between self-reported physical activity and measures of cardiovascular risk in females with stroke, but contrary to our hypothesis, we did not observe an interaction between menopause and physical activity for any of our cardiovascular health markers of interest. Nonetheless, these results provide sex-specific evidence supporting the association between physical activity engagement and improved cardiovascular health for females with stroke, regardless of menopausal status. Although ß-coefficients in our models were relatively small for all outcomes, our findings suggest that any incremental increase in physical activity may be associated with an overall improvement in cardiovascular health.

Physical activity can improve SBP through neurohumoral mechanisms and structural factors. Following periods of physical activity, there is a reduction in the vasoconstrictor endothelin-1 and increase in the vasodilator nitric oxide,[106] which may elicit structural adaptations such as an overall increase in lumen diameter, decreasing blood pressure.[107] Physical activity may also attenuate age-related decreases of arterial elasticity and compliance,[106] due to increased pulse pressures and mechanical distension of the collagen fibres during physical activity.[108] Physical activity decreases abdominal body fat through increased use of body fat for fuel,[113] and measures of inflammation such as hsCRP through decreased leptin levels, cytokine

production in fat, muscle, and mononuclear cells, increased insulin sensitivity, adiponectin levels, endothelial function, and reduced oxidative stress.[122]

We did not observe an association between physical activity and DBP and HR. The absence of association with DBP could be attributed in part to the age of participants included in our analysis. Where the mean age of our sample is 68 years, a recent study demonstrated that DBP increases with age until an inflection point at 58 years old for females, after which it begins to decline.[51] Indeed, mean DBP of our sample was in a normotensive range at 71.6 mmHg. With respect to HR, the absence of association with physical activity may be due to type of activity engaged by participants in this study.[261] In the CLSA, we note that 81% of participants did not perform any strenuous activity in the last 7 days that would provide aerobic stimulus to improve HR.

Our secondary analyses show no interaction between menopausal status and physical activity on SBP, WC, WHR and hsCRP amongst pre- and postmenopausal females with stroke. These findings suggest that clinicians may consider providing similar physical activity recommendations to females with stroke, irrespective of their menopausal status. However, it is important to approach this interpretation with caution given the cross-sectional nature of this analysis. We note that our sample from the CLSA only included 103 premenopausal females and may have been subject to Type II error. Moreover, the variation in hsCRP levels throughout different stages of the menstrual cycle in premenopausal females[262] may have contributed to the wide range of hsCRP values collected, making it more challenging to detect an interaction. Future work examining the interaction between menopausal status and physical activity on cardiovascular health should include a more balanced representation of pre- and postmenopausal females.

We also acknowledge that in the current study HRTs could potentially account for the comparable cardiovascular health profiles observed in pre- and postmenopausal females, thereby reducing the likelihood of an interaction but did not include this in our analysis to preserve sample size. A study comparing postmenopausal females before and after 3-months of HRT to premenopausal females, showed that HRT restored previously impaired endothelial function and other cardiovascular health markers such as cardiorespiratory fitness and anaerobic threshold to levels similar to the premenopausal group.[263] Moreover, results from the Women's Health Initiative trials (n=27,347) show that HRT may increase mean SBP after 1-year follow-up, however, the underlying mechanisms are unclear.[264] Conversely, HRT is associated with decreased adipose tissue,[265] highlighting the potential impact of estrogen on energy intake and expenditure. Premenopausal females exhibited higher energy expenditure when estrogen levels were elevated, compared to lower energy expenditure when estrogen levels were low.[266] Furthermore, in a longitudinal analysis that tracked premenopausal females through the menopausal transition, a substantial 50% decrease in physical activity was observed over a period of 4 years.[267]

**Limitations**

We acknowledge the limitations of this study. First, the cross-sectional nature of this study permits only findings of associations and these findings do not imply causation. The use of the PASE questionnaire only accounts for physical activity in the past 7 days, this may not be reflective of long-term physical activity which is known to be highly associated with improved cardiovascular health.[268] Moreover, the self-report nature of this questionnaire introduces the risk of social desirability and recall bias.[269] Future research should aim to incorporate a combination of self-reported questionnaires and direct measures of physical activity in daily life. This

comprehensive approach could help mitigate potential biases and provide a more accurate representation of physical activity levels over an extended period. Furthermore, we note that our sample was more active,[244] and had healthier blood pressure,[270-272] and HR,[273] compared to previous research, which may limit the generalizability of our findings to the broader stroke population. When investigating the association between physical activity and cardiovascular health in pre- and postmenopausal females, future studies should encompass a larger cohort of premenopausal females. This will increase statistical power and minimize the likelihood of type II errors. Additionally, future research should consider reporting the reproductive age of females using the gold standard Stages of Reproductive Aging Workshop staging system.[79] Implementation of this staging system will help establish potential differences in the associations between physical activity and cardiovascular health at different stages of reproductive aging.

## Conclusion

Our study highlights positive associations between physical activity and SBP, WC, WHR and hsCRP in females with stroke. However, the small magnitude of associations should be interpreted with caution. We also did not observe any interaction between menopausal status and physical activity on cardiovascular health amongst pre- and postmenopausal females with stroke. This study underscores the potential of physical activity to improve cardiovascular health among females with stroke, thereby establishing groundwork for future analyses in the CLSA to investigate the prospective impact of physical activity levels on cardiovascular health and explore possible disparities in cardiovascular adaptations between pre- and postmenopausal females with stroke.

**Acknowledgments**

This research was made possible using the data/biospecimens collected by the CLSA. Funding for the CLSA is provided by the Government of Canada through the Canadian Institutes of Health Research under grant reference: LSA 94473 and the Canada Foundation for Innovation. This research has been conducted using the CLSA dataset using the Baseline Comprehensive data set version 7, under Application Number T47779. The CLSA is led by Drs. Parminder Raina, Christina Wolfson and Susan Kirkland. The opinions expressed in this manuscript are the author's own and do not reflect the views of the Canadian Longitudinal Study on Aging. EH is supported by a Canadian Institute for Health Research-Masters Scholarship. KM is supported by the Ontario Graduate Scholarship. EW is supported by the McMaster Institute for Research on Aging and AGEWELL NCE Inc, a member of the Networks of Centres of Excellence program through an AGE-WELL-MIRA Technology and Aging Doctoral Award. MKB supported by a tier 2 Canada Research Chair in Mobility, Aging, and Chronic Disease.

# Chapter 4: Discussion

# 4.0 DISCUSSION

Elevated CVD mortality rates can largely be attributed to suboptimal management of modifiable risk factors.[274] Both postmenopausal females,[19,89] and females with stroke[95] present with poor cardiovascular health profiles. In the general adult population[36] and in those with other chronic conditions,[38-42] exercise and physical activity have been shown to improve cardiovascular health and reduce risk for CVD, but associations between physical activity, cardiovascular health and menopausal status in females with and without stroke have not been fully examined.

The overall aim of this thesis was to examine the effects of exercise and physical activity on measures of cardiovascular health in pre- and postmenopausal females with, and without, stroke. To achieve this aim, two studies were undertaken.

This chapter provides a summary of the two studies that comprise this thesis, followed by a discussion of the contributions these two studies to the existing literature and their potential influence on clinical recommendations.

## 4.1 Chapter Summaries

### *Study 1: The Effects of Aerobic Exercise on Cardiovascular Health in Postmenopausal Females: A Systematic Review and Meta-Analysis*

This study was a systematic review that examined the effects of aerobic exercise training interventions compared to non-exercise, non-diet, or non-pharmacological controls on traditional cardiovascular health measures in postmenopausal females. Our findings suggest that aerobic exercise training may improve SBP, HR, WC, BMI, absolute body fat, LDL-C, HDL-C and CRF but not DBP, WHR, blood triglycerides, and blood glucose in postmenopausal females. However, based on the GRADE assessment, the evidence has very low certainty. Secondly, our subgroup

analyses revealed that light and vigorous intensity exercises were more effective, compared to moderate intensity, in influencing BMI, but only light intensity was effective in influencing blood triglycerides and glucose.

This review builds on previous reviews by including a broader inclusion criterion to include females at older ages without explicitly reported menopausal status and females living with common chronic conditions. Based on these findings we suggest clinicians recommend aerobic exercise to improve the cardiovascular health of postmenopausal females, as the potential beneficial effects may outweigh the harms.

Our results also suggest that aerobic exercise may have greater benefits in postmenopausal females with poorer cardiovascular health profiles. Future research is needed to examine the benefits of physical activity in females with chronic conditions. In particular, females with elevated CVD risk after menopause, such as those with stroke, may benefit from physical activity. This hypothesis was the basis for study 2.

***Study 2: Examining the Associations Between Cardiovascular Health, Physical Activity and Menopausal Status in Pre- And Post-menopausal Females Living With Stroke and Transient Ischemic Attack: A Cross-Sectional Analysis of Baseline Data From the Canadian Longitudinal Study on Aging***

For Study 2, we conducted a cross-sectional analysis of baseline data from the CLSA to examine the relationship between self-reported physical activity and measures of cardiovascular health in Canadian females living with stroke. Our primary findings demonstrate a positive beneficial association between self-reported physical activity and SBP, WC, WHR, and hsCRP, but not DBP and HR. Our secondary objective demonstrated no interaction between physical activity and menopausal status for any measure of cardiovascular health.

The findings of this study demonstrate that increases in physical activity levels are associated with improvements in cardiovascular health and emphasize the importance physical activity for mitigating cardiovascular risk in females after stroke regardless of menopausal status.

### 4.2 Research Significance

This thesis contributes to our understanding of the interplay between physical activity, cardiovascular health, stroke, and menopausal status. The results of our first study provided empirical evidence supporting the potential benefits of aerobic exercise in enhancing cardiovascular health among a broad range of postmenopausal females. These findings served as a foundation for the second study, which examined the associations between physical activity, cardiovascular health, and menopausal status in females with stroke, a population that may be at even greater CVD-risk. Together, these studies pave the way for future investigations into the effects of physical activity on cardiovascular health in at-risk female populations. They also highlight the potential for randomized controlled trials to explore the effects of exercise training on the cardiovascular health of females with stroke, considering the interaction with menopausal status.

Our studies also address calls to action highlighted in previous research to address the underrepresentation of females in vascular exercise physiology research,[43] females in stroke trials,[44] and lack of reporting female-specific cardiovascular risk factors such as menopausal status.[45,46] Reporting results disaggregated by sex, increasing female representation in vascular exercise physiology and stroke research, and considering female-specific cardiovascular influences such as menopausal status may increase the reproducibility and generalizability of beneficial study results. The studies included in this thesis advance our knowledge in these areas and notably, contribute further to the body of evidence related to stroke.

### 4.3 Clinical Significance

Our systematic review highlights a potential beneficial effect of aerobic exercise on the cardiovascular health in the high-risk population of postmenopausal females including those with comorbid disease such as obesity, hypertension, diabetes mellitus, and dyslipidemia. We propose that clinicians should consider recommending aerobic exercise interventions to improve the cardiovascular health of postmenopausal females. This proposition was based on the GRADE assessment,[224] where we observed that the possible benefits of aerobic exercise may outweigh any potential harm to cardiovascular health. We acknowledge that the strength of our proposition is reduced due to very low quality of evidence for all outcomes. Supporting our proposition, qualitative research has reported postmenopausal females have interest in physical activity interventions that improve their body composition and cardiovascular health, such as aerobic exercise.[225] Lastly, aerobic exercise interventions such as walking or cycling are both feasible and cost-effective,[226] making them a potential therapeutic option to improve cardiovascular health in postmenopausal females. The results from this study may be used to inform aerobic exercise guidelines to improve the cardiovascular health of postmenopausal females.

Subsequently, we extrapolated this evidence and recommendation to females with stroke in our second study. The results of this cross-sectional analysis provide preliminary evidence to support the role of physical activity as a potential lifestyle modification for females poststroke regardless of their menopausal status. Increasing physical activity may be an important low-resource strategy to improve cardiovascular health, reduce the burden of stroke and mitigate the risk of future stroke and other cardiovascular events.

## 4.4 Limitations

We acknowledge the limitations of this thesis. Our systematic review and meta-analysis was limited to studies in English language and studies that disaggregated their data by sex if they included both males and females. Furthermore, the age criteria used in this review ensured the inclusion of postmenopausal females, but there was a possibility of including a small percentage of premenopausal females and excluding postmenopausal females who did not meet our age criteria. Last, the limited number of studies in the light intensity subgroup may have compromised statistical power leading to possible type I or II errors in our subgroup analyses.

In our second study, we used a convivence sample from the CLSA which only included 103 premenopausal females with stroke. This small sample may have contributed to possible Type II errors when examining the interaction between menopausal status and physical activity on cardiovascular health. Moreover, the use of the PASE questionnaire subjects our study to self-reporting biases and may not be reflective of real-world physical activity behaviour.

Our thesis is limited by the available evidence of aerobic exercise trials in females with stroke. As a result, we were unable to conduct a comprehensive systematic review considering the effect of aerobic exercise on the cardiovascular health of females with stroke for study 1, while considering their menopausal status in possible subgroup analyses. This limitation precludes us from being able to inform specific aerobic exercise recommendations tailored to this population.

## 4.5 Future Directions

Future trials should report results disaggregated by sex such that future reviews can perform sex-specific analyses.

Our systematic review provides comprehensive evidence of the potential effects of aerobic exercise on the cardiovascular health of postmenopausal females. This may inform future network meta-analyses to determine the optimal frequency, intensity, type, and duration of aerobic exercise to improve traditional cardiovascular health measures in postmenopausal females.

Our cross-sectional analysis provides valuable preliminary insights that may guide future longitudinal studies to explore the long-term impact of physical activity, on cardiovascular health markers among pre- and postmenopausal females living with stroke. This information can inform the development of randomized controlled trials to explore the effects of exercise training on the cardiovascular health of females with stroke, while considering the interaction with menopausal status. Additionally, future research should explore the potential mediating role of HRT in the association between physical activity and cardiovascular health among pre- and postmenopausal females with stroke. Such studies could inform future longitudinal investigations aiming to identify potential differences in the cardiovascular adaptations to aerobic exercise between pre- and postmenopausal females with stroke and the influence of HRT.

## 4.6 Conclusion

Increasing exercise and physical activity may be an important strategy to mitigate the increased CVD risk that occurs after menopause and stroke. In this thesis, we systematically reviewed the literature regarding the effect of aerobic exercise on traditional cardiovascular health measures in postmenopausal females. Despite the low quality of evidence reported for all cardiovascular outcomes studied, our findings suggest that clinicians may consider recommending aerobic exercise to this population based on its potential beneficial effects relative to any potential unfavorable effects. This suggestion informed our second study, where

we found a positive association between physical activity and all cardiovascular health measures except HR and DBP. These findings suggest clinicians might encourage physical activity among females with stroke, regardless of their menopausal status. Together, these studies provide evidence to support the development of guidelines, and future research to improve the cardiovascular health profile in the underrepresented and high-CVD risk populations of postmenopausal females and females with stroke.

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# APPENDIX 1

# SAMPLE SEARCH STRATEGY

**OVID MEDLINE**

1. exp Exercise/
2. exercis*.mp.
3. exercise/ or endurance training/ or running/ or jogging/ or swimming/ or walking/
4. Bicycling/
5. (run* or walk* or swim* or jog* or bik*).mp.
6. ((aerobic or cardiovascular or endurance) adj2 (exercise* or train*)).mp.
7. or/1-6
8. blood pressure.mp.
9. blood pressure/
10. Blood Glucose/
11. blood glucose.mp.
12. Hypertension/
13. hypertens*.mp.
14. exp hyperglycemia/
15. hyperglyc?emi*.mp.
16. cholesterol/ or cholesterol, hdl/ or cholesterol, ldl/ or cholesterol, vldl/
17. high-density lipoprotein*.mp.
18. low-density-lipoprotein*.mp.
19. very-low-density-lipoprotein.mp. or Lipoproteins, VLDL/
20. (hdl or ldl or vldl).mp.
21. body fat distribution/ or body mass index/ or body weight/ or skinfold thickness/ or waist-hip ratio/
22. (body adj2 (mass or fat or weight)).mp.
23. (skinfold* adj2 (thickness or measur*)).mp.
24. BMI.mp.
25. Waist Circumference/
26. (waist adj2 (hip or ratio or circumference)).mp.
27. Oxygen Consumption/
28. oxygen consumption.mp.
29. Exercise Test/
30. exercise test.mp.
31. max* oxygen uptake.mp.
32. VO2 Max.mp.
33. Cardiorespiratory Fitness/
34. ((cardiorespiratory or cardiovascular) adj2 fitness).mp.
35. or/8-34
36. menopause/ or postmenopause/
37. postmenopaus*.mp.
38. post-menopaus*.mp.
39. menopaus*.mp.
40. 36 or 37 or 38 or 39
41. 7 and 35 and 40
42. randomized controlled trial.pt.
43. controlled clinical trial.pt.
44. randomized.ab.

45. placebo.ab.
46. randomly.ab.
47. trial.ab.
48. groups.ab.
49. or/42-48
50. exp animals/ not humans.sh.
51. 49 not 50
52. 41 and 51

# APPENDIX 2

## QUALITATIVE SUMMARY OF STUIDES INCLUDED IN SYSTEMATIC REVIEW

| Study | Participant Characteristics | Control Group | Aerobic Exercise | | | Outcome Measures |
|---|---|---|---|---|---|---|
| Adams-Campbell et al. (2021) | Total n=213, postmenopausal females with at least two metabolic conditions<br>C: n=70; ≤59 years (n=34), >59 years (n=37)<br>$I_1$:n=73; ≤59 years (n=34), >59 years (n=39) $I_2$:n=69;≤59 years (n=34), >59 years (n=35) | No intervention | | $I_1$ | $I_2$ | NS: SBP, DBP, BMI, WC, HDL-C, TG, BG |
| | | | F: | 3x/wk for 26 wks | 7x/week for 26 wks | |
| | | | I: | 45-65% CRF | 5000 steps/day (week 1) (500 step/day increase until 10 000 steps/day) | |
| | | | T: | Treadmill and/or cycle ergometer | Walking | |
| | | | T: | 75min/week (week 1-3); 150min/week (week 4+) | N/A | |
| Arca et al. (2014) | Total n=52, postmenopausal females with hypertension, 64±7 years<br>C:n=14<br>$I_1$:n=19; $I_2$:n=19 | No intervention | | $I_1$ | $I_2$ | NR: SBP, DBP, HR |
| | | | F: | 3x/wk for 12 wks | | |
| | | | I: | 50-60% HRR – 17 beats | 50-60% HRR | NS: BMI, WC, WHR, LDL-C, HDL-C, TG |
| | | | T: | Deep water running | Cycle ergometer | |
| | | | T: | 20 mins | | |
| Asikainen[a] et al. (2002) | Total n=130, sedentary, healthy postmenopausal females<br>C:n=44; 56.5±4.2 years<br>$I_1$:n=43; 57.8±4.4 years, $I_2$:n=43; 57.6±4.2 years | Attended monthly lectures on health topics and light flexibility exercises | | $I_1$ | $I_2$ | NS: BMI<br>I: CRF |
| | | | F: | 5x/wk for 15wks | 10x/wk (2x/day) for 15 wks | |
| | | | I: | 65% $\dot{V}O_{2max}$ | | |
| | | | T: | walking | | |
| | | | T: | Time to expend 300 kcals | Time to expend 600 kcals | |

| Study | Participant Characteristics | Control Group | Aerobic Exercise | | | | | Outcome Measures |
|---|---|---|---|---|---|---|---|---|
| Asikainen[b] et al. (2002) | Total n=121, sedentary, healthy postmenopausal females<br>C:n=40; 56±3.8 years<br>$I_1$:n=21; 57±3.8 years<br>$I_2$:n=21; 55±3.7 years<br>$I_3$:n=18; 54±3.5 years<br>$I_4$:n=21; 55±4.2 years | Attended monthly lectures on health topics and light flexibility exercises | | $I_1$ | $I_2$ | $I_3$ | $I_4$ | I: BMI, CRF |
| | | | F: | 5x/wk for 24 wks | | | | |
| | | | I: | 55% $\dot{V}O_{2max}$ | 45% $\dot{V}O_{2max}$ | 55% $\dot{V}O_{2max}$ | 45% $\dot{V}O_{2max}$ | |
| | | | T: | walking | | | | |
| | | | T: | Time to expend 1500 kcals/wk | Time to expend 1500 kcals/wk | Time to expend 1000 kcals/wk | Time to expend 1000 kcals/wk | |
| Akwa et al. (2017) | Total n=18, sedentary, healthy postmenopausal females<br>C:n=10; 61.3±7.81 years<br>I:n=8; 61.25±7.45 years | No intervention | F: | 3x/wk for 8 wks | | | | NR: SBP, DBP, HR, BMI, LDL-C, HDL-C, TG |
| | | | I: | Moderate Intensity (NR) | | | | |
| | | | T: | Walking | | | | |
| | | | T: | week 1: 20 min<br>week 2: 25 min<br>week 4: 30 mins<br>week 6: 35 mins<br>week 8: 40 mins | | | | |

| Study | Participant Characteristics | Control Group | Aerobic Exercise | Outcome Measures |
|---|---|---|---|---|
| Azadpour et al. (2017) | Total n=24, obese postmenopausal females with prehypertension<br>C:n=12; 56.58±4.17 years<br>I:n=19; 57.58±4.29 years | No intervention | F: 3x/wk for 10 wks<br>I: Weeks 1-2: 50% HRR<br>Weeks 3-4: 55% HRR<br>Weeks 5-6: 60% HRR<br>Weeks 7-10: 70% HRR<br>T: Treadmill walking/jogging<br>T: Weeks 1-2: 25 mins<br>Weeks 3-4: 30 mins<br>Weeks 5-6: 35 mins<br>Weeks 7-10: 40 mins | I: SBP, DBP, HR, BMI, WC, BF, CRF<br><br>NS: WHR |
| Blain et al. (2017) | Total n=98, sedentary, healthy postmenopausal females<br>C:n=47; 65.78±4.15 years<br>I:n=51; 65.58±4.44 years | No intervention | F: 3x/wk for 26 wks<br>I: 40% to 60-80% HRmax (gradual increase)<br>T: Outdoor walking<br>T: 50 mins | I: CRF<br><br>NS: BMI, BF |
| Cao et al. (2019) | Total n=28, overweight or obese elderly females<br>C:n=13; 64.0±4.6 years<br>I:n=15; 63.8±5.9 years | No intervention | F: 3x/week for 12 weeks<br>I: Individualized FATmax HR<br>T: Walking or jogging<br>T: Week 1: 20 mins<br>Week 2-4: 30 mins<br>Weeks 5-12: 40 mins | I: DBP, BMI, WC, BF, HDL-C, CRF<br><br>NS: SBP, LDL-C, TG |
| Carrasco et al. (2012) | Total n=59, sedentary, healthy postmenopausal females<br>C:n=30; 56.6±6.4 years<br>I:n=29; 58.8±6.5 years | No intervention | F: 2x/wk for 52 wks<br>I: Weeks 1-6: RPE 10-11<br>Weeks 7-52: RPE 11-15<br>T: Swimming<br>T: 35 mins | NR: BMI |

| Study | Participant Characteristics | Control Group | Aerobic Exercise | | | Outcome Measures |
|---|---|---|---|---|---|---|
| Chow et al. (1987) | Total n=32, healthy postmenopausal females<br>C:n=15; 56.33±0.85 years<br>I:n=17; 56.69±0.83 years | No intervention | F: 3x/wk for 52 wks<br>I: 80% HRmax<br>T: Walking/jogging<br>T: 30 mins | | | NR: CRF |
| Church et al. (2007) | Total n=464, sedentary, overweight or obese postmenopausal females with prehypertension<br>C:n=102; 57.2±5.8 years<br>$I_1$:n=155; 57.7±6.6 years, $I_2$:n=104; 57.3±6.6 years, $I_3$:n=103; 56.6±6.6 years | No intervention | | $I_1$ | $I_2$ / $I_3$ | I: SBP, WC, CRF<br><br>NS: DBP, LDL-C, HDL-C, TG, BG |
| | | | F: | 3-4x/wk for 26 wks | | |
| | | | I: | 50% $\dot{V}O_2$peak | | |
| | | | T: | Semi-recumbent cycle ergometers and/or treadmills | | |
| | | | T: | Time to expend 4kcals/kg/wk | Time to expend 8kcals/kg/wk<br><br>Progression: Week 1-expended 4 kcal/kg. Increased energy expenditure by 1kcal/kg a week until prescribed level reached. | Time to expend 12kcals/kg/wk |

| Study | Participant Characteristics | Control Group | Aerobic Exercise | | Outcome Measures |
|---|---|---|---|---|---|
| Coletta et al. (2019) | Total n=33, postmenopausal females at high risk for breast cancer<br>C:n=11; 63.35±7.0 years<br>$I_1$:n=11; 63.73±6.9 years, $I_2$:n=11; 64.62±12.2 years | Received written information related to healthy eating and engaging in regular physical activity | $I_1$ | $I_2$ | I: CRF<br>NS: BMI |
| | | | F: 3x/wk for 12 wks | | |
| | | | I: High:90-100% HRpeak; low:50-70% HRpeak | 60-70% HRpeak | |
| | | | T: HIIT treadmill walking/running | MICT treadmill walking/running | |
| | | | T: 33 mins (4 min high, 3 min low) | 41 mins | |
| | | | Progression: HRpeak was recalibrated at week 6. | | |
| Costa et al. (2019) | Total n=46, elderly females with dyslipidemia<br>C:n=23; 64.63 (62.23 to 67.03) years<br>I:n=23; 66.80 (64.55 to 69.05) years | Relaxation in water immersion | F: 2x/wk for 10 wks<br>I: Week 1-5:<br>High: 90-95% anaerobic threshold point<br>Low: 80-85% anaerobic threshold point<br>Week 6-10:<br>High: 95-100% anaerobic threshold point<br>Low: 85-90% anaerobic threshold point<br>T: Water-based aerobic interval training<br>T: 30 mins | | NR: LDL-C, HDL-C, TG |
| Cowan et al. (1985) | Total n=18, sedentary, healthy postmenopausal females<br>C:n=4; 52±3.6 years<br>I:n=14; 56.7±5.2 years | No intervention | F: 4x/wk for 9 wks<br>I: 80% HRmax<br>T: Walking<br>T: Gradual increase from 17 to 44 mins | | NR: CRF |

| Study | Participant Characteristics | Control Group | Aerobic Exercise | | Outcome Measures |
|---|---|---|---|---|---|
| | | | $I_1$ | $I_2$ | |
| Dalleck et al. (2009) | Total n=26, sedentary, healthy postmenopausal females<br>C:n=10; 57.4±4.6 years<br>$I_1$:n=8; 59.9±3.1 years, $I_2$:n=8; 55.4±3.2 years | No intervention | F: Week 1: 3x; week 2: 4x; week 3: 4x; weeks 4-12: 5x/week<br>I: 50% $\dot{V}O_2R$<br>T: walking<br>T: 30 min exercise group (week 1: 20 min/day; week 2: 25 mins/day; weeks 3-12: 30 min/day) | 45 min exercise group (week 1: 30 min/day; week 2: 35 mins/day; week 3: 40 min/day; weeks 4-12: 45 min/day) | I: BMI($I_2$), WC($I_2$), HDL-C, CRF<br><br>NS: SBP, DBP, LDL-C, TG, BG |
| Diniz et al. (2016) | Total n=19, sedentary, healthy postmenopausal females<br>C:n=9; 62.01±7.83 years<br>I:n=10; 60.26±8.51 years | No intervention | F: Non-consecutive days for 8 wks<br>I: 100% critical velocity<br>T: Walking/jogging<br>T: 50 mins | | I: BF, LDL<br><br>NS: HDL-C, TG, BG |
| Fahlman et al. (2002) | Total n=30, healthy elderly females<br>C:n=15; 74±5 years<br>I:n=15; 76±5 years | No intervention | F: 3x/week for 10 wks<br>I: 70% HRR<br>T: Walking<br>T: Day 1: 20 min, 5-min increase each session until 50 mins (week 3) | | I: HDL-C, TG CRF<br><br>NS: BMI, LDL |

| Study | Participant Characteristics | Control Group | Aerobic Exercise | Outcome Measures |
|---|---|---|---|---|
| Foster-Schubert et al. (2012) | Total n=204, sedentary, overweight or obese postmenopausal females<br>C:n=87; 57.4±4.4 years<br>I:n=117; 58.1±5.0 years | No intervention | F: 5x/week for 52 wks<br>I: 60-85% HRmax<br>Progression: 60-70% HRmax X 15 mins to 70-85% HRmax X 45 mins (week 7)<br>T: Treadmill walking, stationary cycling, other aerobics machines<br>T: 15-45 mins | I: BMI, WC, BF, CRF |
| Friedenreich et al. (2010) | Total n=298, sedentary, healthy postmenopausal females<br>C:n=151; 60.6±5.7 years<br>I:n=147; 61.2±5.4 years | No intervention | F: 5x/week for 52 wks<br>I: At least 70-80% HRR for half the session<br>Progression: from 50-60% HRR X 15-20 mins<br>T: Various aerobic exercises<br>T: >45 mins | I: CRF |
| Friedenreich et al. (2011) | Total n=307, sedentary, healthy postmenopausal females<br>C:n=155; 60.6±5.7 years<br>I:n=152; 61.2±5.4 years | No intervention | F: 5x/week for 52 wks<br>I: At least 70-80% HRR for half the session<br>Progression: from 50-60% HRR X 15-20 mins<br>T: Various aerobic exercises<br>T: >45 mins | I: BMI, WC, BF |

| Study | Participant Characteristics | Control Group | Aerobic Exercise | Outcome Measures |
|---|---|---|---|---|
| Gonzalo-Encabo et al. (2020) | Total n=22, sedentary, healthy postmenopausal females<br>C:n=12; 57 [54.5, 60.5] years<br>I:n=10; 56.5 [55.0, 58.5] years | No intervention | F: 3x/week for 13 wks<br>I: 55-75% HRR<br>T: Treadmill, cycle ergometer, elliptical training<br>T: Week 0: 10-30 mins at 55-60% HRR<br>Week 1-2: 45-60 mins at 60-65% HRR<br>Week 3-4: 60 min at 65-70% HRR<br>Week 5-8: 60 min at 70-75% HRR<br>Week 9-12: 60 min at 70-75% HRR | NR: BMI, BF, LDL-C, HDL-C, TG, BG |
| Hamdorf et al. (1992) | Total n=66, elderly females<br>C:n=36; 64.1±2.6 years I:n=30; 64.1±2.4 years | No intervention | F: 2x/week for 26 wks<br>I: Individualized target HRs<br>T: Progressive walking program<br>T: 16 mins (week 1) progressive increase to 45 mins (week 19+) | I: HR<br><br>NS: SBP, DBP |
| Jahangard et al. (2009) | Total n=20, sedentary, healthy postmenopausal females<br>C:n=10; 50±2 years I:n=10; 50±2 years | No intervention | F: 3x/week for 3 weeks<br>I: 70% HRmax<br>T: Cycle ergometer training<br>T: 20 mins | I: SBP, DBP, HR<br>NS: BMI |
| Jo et al. (2020) | Total n=26, sedentary postmenopausal females with a Framingham CV disease 10-year risk score of >20%<br>C:n=13; 62.5±13.9 years I:n=13; 57.3±8.4 years | No intervention | F: 12 wks<br>I: 60-80% HRR<br>T: Treadmill walking or jogging<br>T: 40 mins | NS: SBP, DBP, BMI, WC |

| Study | Participant Characteristics | Control Group | Aerobic Exercise | Outcome Measures |
|---|---|---|---|---|
| Jurca et al. (2004) | Total n=88, sedentary, overweight or obese postmenopausal females with prehypertension<br>C:n=39; 57.4±6.2 years I:n=49; 56.5±6.2 years | No intervention | F: 3-4x/week for 8 wks<br>I: 50% $\dot{V}O_{2max}$<br>T: Treadmill and recumbent leg ergometer training<br>T: Start at 60 min/week add 15 min/week until 120-165 min/week | NS: HR |
| Kallinen et al. (2002) | Total n=23, elderly females, 76-78 years<br>C:n=11; I:n=12 | No intervention | F: 2-3x/week for 18 wks<br>I: Week 1-5: 50% HRR<br>Week 5+: 80% HRR<br>T: Indoor track walking and step-aerobics<br>T: Walking: 20 mins (week 1-2)<br>Walking: 30 mins (week 3+)<br>Step aerobics: 40 min | NR: SBP, DBP, HR, CRF |

| Study | Participant Characteristics | Control Group | Aerobic Exercise | | | Outcome Measures |
|---|---|---|---|---|---|---|
| Keyhani et al. (2020) | Total n=30, sedentary, healthy postmenopausal females<br>C:n=10; 56.15±0.74 years,<br>$I_1$:n=10; 54.90±0.95 years,<br>$I_2$:n=10; 55.30±0.87 years | No intervention | | $I_1$ | $I_2$ | I: DBP, HR, CRF<br><br>NS: SBP, BMI |
| | | | F: | 3x/week for 8wks | | |
| | | | I: | Week 1-2: High at 70% HRR; low: 45% HRR<br>Week 3: High at 75% HRR<br>Week 4: High at 80% HRR<br>Week 5 & 6: High at 85% HRR<br>Week 7 & 8: high at 90% HRR; low at 50-60% HRR | Weeks 1-2: 50-55% HRR<br>Week 3: 60% HRR<br>Week 4: 65% HRR<br>Weeks 5-6: 70% HRR<br>Weeks 7-8: 75% HRR | |
| | | | T: | HIIT Running | Treadmill running/walking | |
| | | | T: | 30 min (high: 4 mins; low:4 mins) | 30 min | |
| Khosravi et al. (2018) | Total n=41, sedentary, healthy postmenopausal females<br>C:n=19; 55.3±5.2 years I:n=22; 58.8±6.4 years | No intervention | F: | 3x/week for 26 wks | | I: BMI, CRF |
| | | | I: | 45-50% HRmax progressive increase to 70-80% HRmax | | |
| | | | T: | Aerobic Training (not specific) | | |
| | | | T: | 15-20 mins progressive increase to 50 mins | | |

| Study | Participant Characteristics | Control Group | Aerobic Exercise | | | | Outcome Measures |
|---|---|---|---|---|---|---|---|
| King et al. (1991) | Total n=160, sedentary, healthy postmenopausal females, 50 to 60 years<br>C:n=34;<br>$I_1$:n=34; $I_2$:n=35; $I_3$:n=29 | No intervention | | $I_1$ | $I_2$ | $I_3$ | I: CRF<br><br>NR: SBP, DBP, BMI, LDL-C, HDL-C, TG |
| | | | F: | 3x/week for 52 wks | | 5x/week for 52 wks | |
| | | | I: | 73-88% HRpeak | | 60-73% HRpeak | |
| | | | | Progression: gradual increase in HRpeak over initial 6-weeks | | | |
| | | | T | High-intensity group training (treadmill or cycle ergometer) | High-intensity home training (treadmill or cycle ergometer) | Low-intensity home training (treadmill or cycle ergometer) | |
| | | | T | 40 mins | | 30 mins | |
| Lesser et al. (2016) | Total n=51, Sedentary, overweight or obese postmenopausal females with prehypertension<br>C:n=26; 57.7±6.1 years I:n=23; 56.4±6.9 years | No intervention | F: | 3x/week for 12 wks | | | NR: BMI, WC, BF, CRF |
| | | | I: | 55% HRmax increase 10% HRmax every 3 weeks until 85% HRmax | | | |
| | | | T: | Treadmill and cycle ergometer training | | | |
| | | | T: | 40 mins | | | |
| Lima et al. (2012) | Total n=22, Sedentary, postmenopausal females with metabolic syndrome<br>C:n=12; 54.9±1.7 years I:n=10; 52.1±1.6 years | No intervention | F: | 5x/week for 12 wks | | | I: CRF<br><br>NS: HR |
| | | | I: | Week 1: 50% HRmax (3 sessions)<br>Week 2-5: 60% HRmax<br>Week 5+: 60-70% HRmax | | | |
| | | | T: | Aerobic Exercise (not specific) | | | |
| | | | T: | Week 1: 20 minutes<br>Week 2 :30 minutes<br>Week 3-5: 60 minutes | | | |

| Study | Participant Characteristics | Control Group | Aerobic Exercise | | | | Outcome Measures |
|---|---|---|---|---|---|---|---|
| Martin et al. (2009) | Total n=430, sedentary, overweight or obese postmenopausal females with prehypertension<br>C:n=92; 57.1±6.0 years,<br>$I_1$:n=147; 57.9±6.6 years, $I_2$:n=96; 57.7±6.6 years, $I_3$:n=95; 56.5±6.7 years, | No intervention | | $I_1$ | $I_2$ | $I_3$ | NR: CRF |
| | | | F: | 3-4x/wk for 26 wks | | | |
| | | | I: | 50% V̇O2peak | | | |
| | | | T: | Semi-recumbent cycle ergometers and/or treadmills | | | |
| | | | T: | Time to expend 4kcals/kg/wk | Time to expend 8kcals/kg/wk<br><br>Progression: Week 1-expended 4 kcal/kg. Increased energy expenditure by 1kcal/kg a week until prescribed level reached. | Time to expend 12kcals/kg/wk | |
| Mason et al. (2011) | Total n=204, sedentary, overweight or obese postmenopausal females<br>C:n=87; 57.4±4.4 years I:n=117; 58.1±5.0 years | No intervention | F: | 5x/week for 52 wks | | | NS: BG |
| | | | I: | Week 1: 60-70% HRmax progress to 70-85% HRmax by week 7 | | | |
| | | | T: | Treadmill, cycle ergometer, other aerobic machines, outdoor walking | | | |
| | | | T: | Week 1: 15 mins progress to 45 mins (week 7) | | | |

| Study | Participant Characteristics | Control Group | Aerobic Exercise | Outcome Measures |
|---|---|---|---|---|
| Moreau et al. (2001) | Total n=24, sedentary, postmenopausal females<br>C:n=9; 51±1 years I:n=15; 53±2 years | No intervention | F: 7x/week for 24 wks<br>I: 1.4km increase in daily walking; progress 0.5km daily until 3km increase reached<br>T: Walking<br>T: NR | NR: HR, BG |
| Morrison et al. (1986) | Total n=25, healthy postmenopausal females<br>C:n=8; 51.5±3.9 years I:n=17; 51.1±2.8 years | No intervention | F: 3x/week for 35 wks<br>I: 65-75% HRR<br>T: Treadmill training<br>T: 40 mins | I: CRF<br><br>NR: BF |
| Ohta et al. (2012) | Total n=26, healthy postmenopausal females<br>C:n=13; 71.5±7.4 years I:n=13; 72.2±4.2 years | No intervention | F: 21x/week (3x daily) for 12 wks<br>I: 40 steps/min increased 10 steps/min every 4 mins with 2-min of rest Readjusted at week 6<br>T: Bench stepping<br>T: 10-20 mins | I: BMI<br><br>NS: SBP, DBP, LDL-C, HDL-C, TG, BG |
| Oneda et al. (2014) | Total n=23, sedentary, healthy postmenopausal females<br>C:n=11; 50±3 years I:n=12; 50±3 years | No intervention | F: 3x/week for 26 wks<br>I: The initial intensity was HR at anaerobic threshold and progressed gradually until it reached the HR at the respiratory compensation point<br>T: Cycle ergometer training<br>T: 20-50 mins | NR: SBP, DBP, BMI, CRF |

| Study | Participant Characteristics | Control Group | Aerobic Exercise | | Outcome Measures |
|---|---|---|---|---|---|
| Paolillo et al. (2017) | Total n=20, sedentary, healthy postmenopausal females<br>C:n=10; 55±2 years I:n=10; 55±2 years | No intervention | F: 2x/week for 26 wks<br>I: 85-90% HRmax<br>T: Treadmill Training<br>T: 45 mins | | NR: WC, WHR, BF, LDL-C, HDL-C, TG |
| Pospieszna et al. (2017) | Total n=39, sedentary, healthy postmenopausal females<br>C:n=19; 62.0±1.1 years I:n=20; 62.0±3.79 years | No intervention | F: 3x/week for 12 wks<br>I: 90% ventilatory threshold<br>T: Nordic walking<br>T: 50 mins | | NR: SBP, DBP, HR, BMI, BF, LDL-C, HDL-C, TG |
| Probart et al. (1991) | Total n=16, sedentary, healthy elderly females<br>C:n=6; 72.0±0.68 years I:n=10; 72.0±0.60 years | No intervention | F: 3x/week for 26 wks<br>I: 70% HRmax<br>T: Treadmill training<br>T: 20 mins | | I: CRF<br><br>NS: BMI |
| Ready et al. (1996) | Total n=56, sedentary, healthy postmenopausal females, 61.3±5.8 years<br>C:n=18; I:n=10 | No intervention | | $I_1$ | $I_2$ | I: CRF<br><br>NS: SBP, DBP, WHR<br><br>NR: BMI, LDL-C, HDL-C, TG |
| | | | F: | 3x/week for 24 wks | 5x/week for 24 wks | |
| | | | I: | 60% $\dot{V}O_{2max}$ | | |
| | | | T: | Walking | | |
| | | | T: | 60 mins | | |

| Study | Participant Characteristics | Control Group | Aerobic Exercise | Outcome Measures |
|---|---|---|---|---|
| Rodrigues-Krause et al. (2018) | Total n=20, sedentary, healthy postmenopausal females<br>C:n=10; 60 (61-70) years I:n=10; 64 (62-65) years | F: 1x/week for 8 wks<br>I: N/A<br>T: Stretching<br>T: 60 min | F: 3x/week for 8 wks<br>I: 50% $\dot{V}O_2$max (5 mins)<br>65% $\dot{V}O_2$max (30 mins)<br>50% $\dot{V}O_2$max (5 mins)<br>Progression: 60% to 65% $\dot{V}O_2$max at week 5<br>T: Treadmill training<br>T: 40 mins | NR: WC, LDL-C, HDL-C, TG, BG, CRF |
| Roghani et al. (2013) | Total n=18, postmenopausal females with osteoporosis, 45-65 years<br>C:n=10; I:n=8 | No intervention | F: 3x/week for 6 wks<br>I: Week 1-2: 50% HRR<br>Week 3-4: 55% HRR<br>Week 5-6: 60% HRR<br>T: Treadmill training<br>T: 20 mins | NR: BMI, BF |
| Santa-Clara et al. (2003) | Total n=60, sedentary, healthy postmenopausal females<br>C:n=28; 56.14±6.20 years I:n=32; 58.53±5.49 years | No intervention | F: 3-4x/week for 26 wks<br>I: 70-85% HRmax<br>T: Treadmill, cycle ergometer, rowing training<br>T: 45-60 mins | I: CRF<br>NS: SBP, DBP, BMI |
| Sloan et al. (2013) | Total n=32, sedentary, healthy postmenopausal females<br>C:n=16; 54.1±4.9 years I:n=16; 54.1±5.8 years | No intervention | F: 5x/week for 16 weeks<br>I: 75% HRmax<br>T: Home-based walking program<br>T: 30 mins | NR: CRF |

| Study | Participant Characteristics | Control Group | Aerobic Exercise | Outcome Measures |
|---|---|---|---|---|
| Soori et al. (2017) | Total n=16, sedentary, obese postmenopausal females, 45-60 years C:n=8; I:n=8 | No intervention | F: 3x/week for 10 wks<br>I: 40% HRmax increase 5% HRmax biweekly<br>T: Swimming or walking in water<br>T: 45 mins | NR: BMI, WHR, LDL-C, HDL-C, TG |
| Staffileno et al. (2001) | Total n=18, postmenopausal females with hypertension C:n=9; 62.3±8.7 years I:n=9; 57.1±8.7 years | No intervention | F: 5x/week for 8 wks<br>I: 50-60% HRR<br>T: Self-selected aerobic activity (walking/cycling)<br>T: 30 mins | I: SBP, DBP |
| Tan et al. (2018) | Total n=31, elderly females with type 2 diabetes mellitus C:n=15; 62.9±2.6 years I:n=16; 63.0±2.3 years | No intervention | F: 3x/week for 12 wks<br>I: FATmax HR<br>T: Walking or running<br>T: Week 1: 20 mins<br>Week 2-4: 30 mins<br>Week 5-12: 40 mins | I: BMI, WC, WHR, BF, LDL-C, HDL-C, TG, BG |
| Tanahashi et al. (2014) | Total n=30, sedentary, healthy postmenopausal females C:n=10; 61±7years I:n=20; 62±6 years | No intervention | F: >3x/week for 12 wks<br>I: 60% HRmax progress to 65-80% HRmax<br>T: Treadmill or cycle ergometer training<br>T: 30 mins progress to 40-60 mins | NR: SBP, DBP, BMI |

| Study | Participant Characteristics | Control Group | Aerobic Exercise | Outcome Measures |
|---|---|---|---|---|
| Tartibian et al. (2015) | Total n=28, sedentary, healthy postmenopausal females<br>C:n=14; 57.2±2.2years I:n=14; 57.1±7.5 years | No intervention | F: Week 1-8: 3-4x/week<br>Week 9-16: 4-6x/week<br>I: Week 1-8: 44-45% HRmax<br>Week 9-16: 55-65% HRmax<br>T: Treadmill training<br>T: Week 1-8: 25-30 min<br>Week 9-16: 40-55% HRmax | NR: BMI |
| Wang et al. (2014) | Total n=46, sedentary, healthy postmenopausal females<br>C:n=23; 55.1±7.8 years I:n=23; 56.9±6.2 years | No intervention | F: 3x/week for 12 weeks<br>I: 60-80% HRR<br>T: Treadmill training<br>T: 30 mins | NR: SBP, DBP, HDL-C, TG, BG, CRF |
| Wen et al. (2017) | Total n=46, sedentary, healthy postmenopausal females<br>C:n=22; 58.8±3.2years I:n=24; 57.5±3.5 years | No intervention | F: 3x/week for 10 weeks<br>I: 75-85% HRR<br>T: Step exercise<br>Progression: Step height increased from 10cm to 20-25cm<br>T: 35-45 mins | I: CRF<br>NS: BMI, LDL-C, HDL-C, TG |
| Whitehurst et al. (1991) | Total n=14, elderly females, 65.8±8.74 years<br>C:n=22; I:n=24 | No intervention | F: 3x/week for 8 weeks<br>I: 70-80% HRmax<br>T: Cycle ergometer training<br>T: 8-10 min (week 1); 3-5 mins added/session until 35-40 min reached (week 4) | NR: CRF |

| Study | Participant Characteristics | Control Group | Aerobic Exercise | Outcome Measures |
|---|---|---|---|---|
| Wong et al. (2019) | Total n=100, sedentary, postmenopausal females with stage 2 hypertension<br>C:n=48; 73±4 years I:n=52; 74±4 years | No intervention | F: 3-4x/week for 20 weeks<br>I: Week 1-5: 60% HRmax<br>Week 6+: 70-75% HRmax<br>T: Swimming<br>T: 25-30 mins gradual increase to 40-45 min | NR: SBP, DBP, HR, BMI, BF, CRF |
| Yoo et al. (2010) | Total n=21, elderly females<br>C:n=10; 71.1±2.7 years I:n=11; 70.9±2.7 years | No intervention | F: 3x/week for 12 weeks<br>I: 60% HRR<br>T: Weighted walking (2kg)<br>T: 45 mins | NR: SBP, DBP, HR, BMI<br><br>NS: BF |
| Yoshizawa et al. (2010) | Total n=20, sedentary, healthy postmenopausal females<br>C:n=10; 58±1 years I:n=10; 57±1 years | Placebo drug | F: Increased from 3-4 days/week to 4-5 days/week for 8 weeks<br>I: Increased from 60% HRmax to 70-75% HRmax<br>T: Treadmill or cycle ergometer training<br>T: 45 mins | NR: SBP, DBP, HR, BMI, LDL-C, HDL-C, TG, CRF |

Abbreviations: BF, body fat; BG, blood glucose; C, control; CRF, cardiorespiratory fitness; DBP, diastolic blood pressure; BMI, body mass index; HDL-C, high-density lipoprotein cholesterol; HIIT, high-intensity interval training; HR, heart rate; HRR, heart rate reserve; I, favors intervention; $I_1$, intervention 1; $I_2$, intervention 2; $I_3$, intervention 3; $I_4$, intervention 4; LDL-C, low-density lipoprotein cholesterol; MICT, moderate-intensity continuous training; NS, not significant; NR, not reported; HR, resting heart rate; RPE, rating of perceived exertion; TG, blood triglycerides; $VO_2R$, oxygen consumption reserve; $VO_{2max}$, maximal oxygen uptake; SBP, systolic blood pressure; WC, waist circumference;

# APPENDIX 3

# COCHRANE RISK OF BIAS 2 SUMMARY

| Study | Selection Bias | Performance Bias | Detection Bias | Attrition Bias | Reporting Bias | Overall Bias |
|---|---|---|---|---|---|---|
| Adams-Campbell et al. (2021) | Low | Some concerns | Some concerns | High | Some concerns | High |
| Akwa et al. (2017) | Some concerns | Some concerns | Some concerns | High | Some concerns | High |
| Arca et al. (2014) | Some concerns | Some concerns | Some concerns | Low | Some concerns | High |
| Asikainen$_a$ et al. (2002) | Some concerns | Some concerns | Some concerns | Low | Some concerns | High |
| Asikainen$_b$ et al. (2002) | Some concerns | Some concerns | High | Low | Some concerns | High |
| Azadpour et al. (2017) | Some concerns | Some concerns | Some concerns | Low | Some concerns | High |
| Blain et al. (2017) | Low | High | Low | High | Some concerns | High |
| Cao et al. (2019) | High | Some concerns | Some concerns | High | Some concerns | High |
| Carrasco et al. (2012) | Some concerns | High | Some concerns | High | Some concerns | High |
| Chow et al. (1987) | Low | High | Some concerns | High | Some concerns | High |
| Church et al. (2007) | Low | Low | Low | Low | Low | Low |
| Coletta et al. (2019) | Some concerns | Some concerns | Some concerns | Low | Some concerns | High |
| Costa et al. (2019) | Low | Some concerns | Low | Some concerns | Some concerns | High |
| Cowan et al. (1985) | High | High | Some concerns | High | Some concerns | High |
| Dalleck et al. (2009) | High | Some concerns | Some concerns | Some concerns | Some concerns | High |

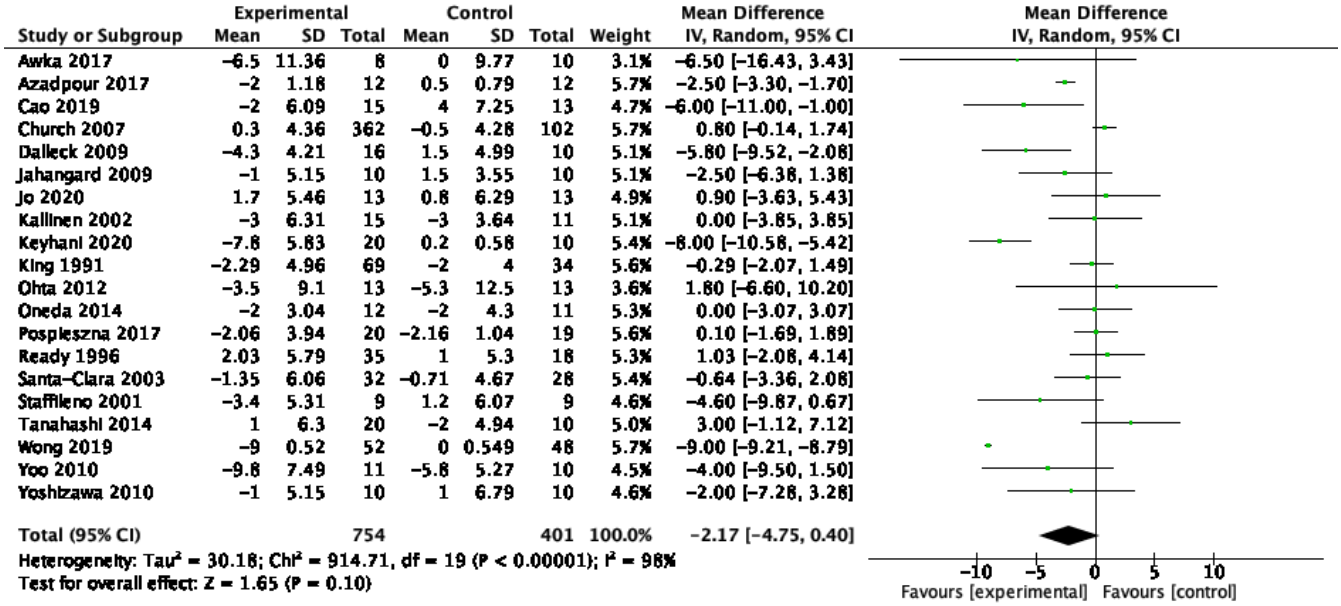
| | | | | | | |
|---|---|---|---|---|---|---|
| Dash et al. (2018) | Low | Low | Low | Low | Some concerns | Some concerns |
| Diniz et al. (2016) | Some concerns | Some concerns | Some concerns | High | Some concerns | High |
| Fahlman et al. (2002) | Some concerns | High | Some concerns | High | Some concerns | High |
| Foster-Schubert et al. (2012) | Some concerns | Low | Low | Some concerns | Some concerns | High |
| Friedenreich et al. (2010) | Low | Some concerns | Low | Low | Some concerns | Some concerns |
| Friedenreich et al. (2011) | Low | Some concerns | Low | Low | Some concerns | Some concerns |
| Gonzalo-Encabo et al. (2020) | Some concerns | Some concerns | Some concerns | High | Some concerns | High |
| Hamdorf et al. (1992) | Some concerns | Some concerns | Some concerns | High | Some concerns | High |
| Jahangard et al. (2009) | Some concerns | Some concerns | Some concerns | High | Some concerns | High |
| Jo et al. (2020) | Some concerns | Some concerns | Some concerns | High | Some concerns | High |
| Jurca et al. (2004) | Some concerns | Some concerns | Low | High | Some concerns | High |
| Kallinen et al. (2002) | Some concerns | Some concerns | Some concerns | High | Some concerns | High |
| Keyhani et al. (2020) | Low | Some concerns | High | Some concerns | Some concerns | High |
| Khosravi et al. (2018) | Some concerns | Some concerns | Low | High | Some concerns | High |
| King et al. (1991) | Some concerns | Some concerns | Low | High | High | High |
| Lesser et al. (2016) | Low | Low | Low | High | Some concerns | High |

| | | | | | | |
|---|---|---|---|---|---|---|
| Lima et al. (2012) | Some concerns | Some concerns | Some concerns | High | Some concerns | High |
| Martin et al. (2009) | Low | Some concerns | Low | High | Low | High |
| Mason et al. (2011) | Some concerns | Some concerns | Low | Some concerns | Some concerns | High |
| Moreau et al. (2001) | Some concerns | Some concerns | Some concerns | Low | Some concerns | High |
| Morrison et al. (1986) | High | High | Low | High | Some concerns | High |
| Ohta et al. (2012) | Some concerns | Some concerns | Some concerns | Low | Some concerns | High |
| Oneda et al. (2014) | Some concerns | Some concerns | Some concerns | Some concerns | Some concerns | High |
| Paolillo et al. (2017) | High | Some concerns | Low | Some concerns | Some concerns | High |
| Pospieszna et al. (2017) | Some concerns | High | Some concerns | High | Some concerns | High |
| Probart et al. (1991) | Some concerns | Some concerns | Some concerns | Low | Some concerns | High |
| Ready et al. (1996) | Some concerns | Some concerns | High | High | Some concerns | High |
| Rodrigues-Krause et al. (2018) | Low | Low | Some concerns | Some concerns | Some concerns | High |
| Roghani et al. (2013) | Some concerns | Some concerns | Some concerns | High | Some concerns | High |
| Santa-Clara et al. (2003) | Some concerns | Some concerns | Some concerns | High | Some concerns | High |
| Sloan et al. (2013) | Some concerns | High | Some concerns | High | Some concerns | High |
| Soori et al. (2017) | Some concerns | Some concerns | Some concerns | High | Some concerns | High |

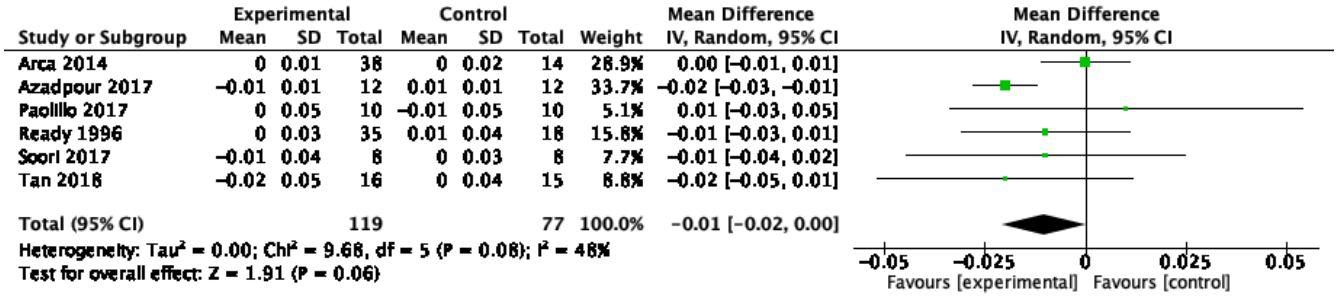
| | | | | | | |
|---|---|---|---|---|---|---|
| Staffileno et al. (2001) | High | Some concerns | Some concerns | Low | Some concerns | High |
| Tan et al. (2018) | Some concerns | Some concerns | Some concerns | Some concerns | Some concerns | High |
| Tanahashi et al. (2014) | High | Some concerns | Some concerns | High | Some concerns | High |
| Tartibian et al. (2015) | Low | Some concerns | Some concerns | High | Some concerns | High |
| Wang et al. (2014) | Some concerns | Some concerns | High | High | Some concerns | High |
| Wen et al. (2017) | Some concerns | Some concerns | Some concerns | Low | Some concerns | High |
| Whitehurst et al. (1991) | Some concerns | Some concerns | Some concerns | High | Some concerns | High |
| Wong et al. (2019) | Low | Some concerns | Low | Low | Some concerns | Some concerns |
| Yoo et al. (2010) | Some concerns | Some concerns | Some concerns | High | Some concerns | High |
| Yoshizawa et al. (2010) | Some concerns | Some concerns | Some concerns | Low | Some concerns | High |

# APPENDIX 4

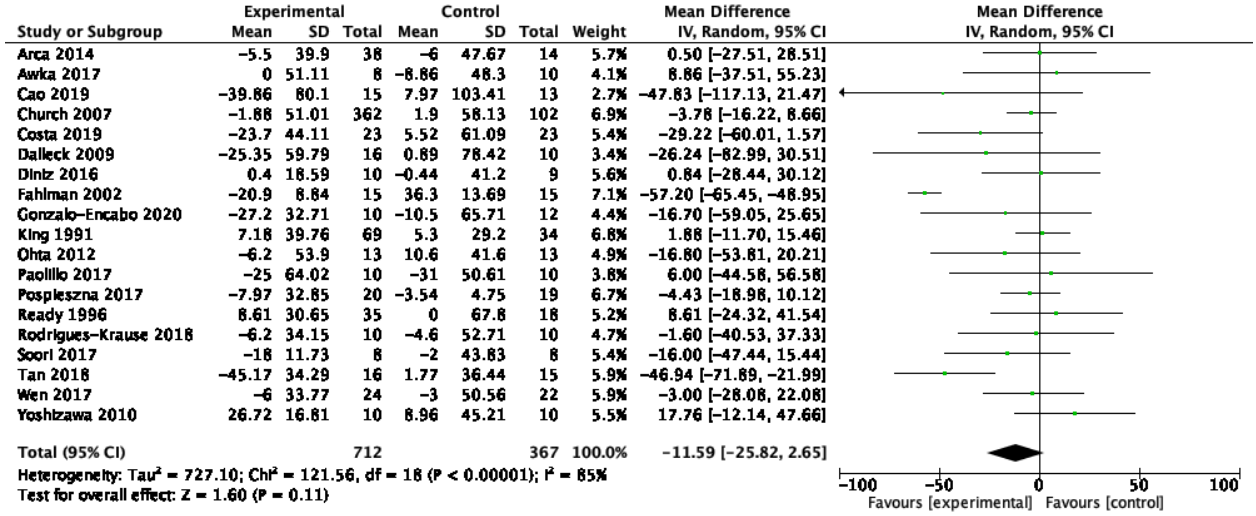
# FOREST PLOTS OF NON-SIGNIFICANT FINDINGS



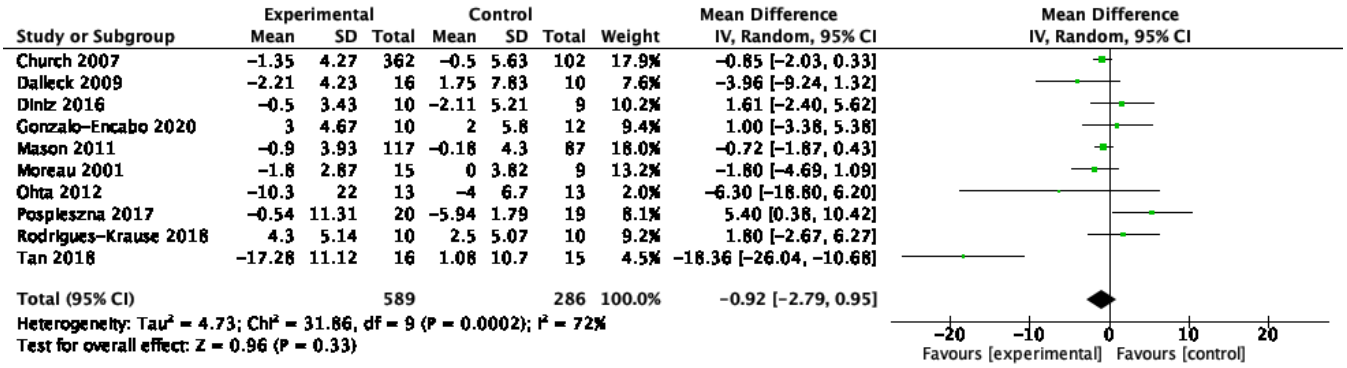

Appendix Figure 1. Effect of aerobic exercise on diastolic blood pressure




Appendix Figure 2. Effect of aerobic exercise on waist-to-hip ratio



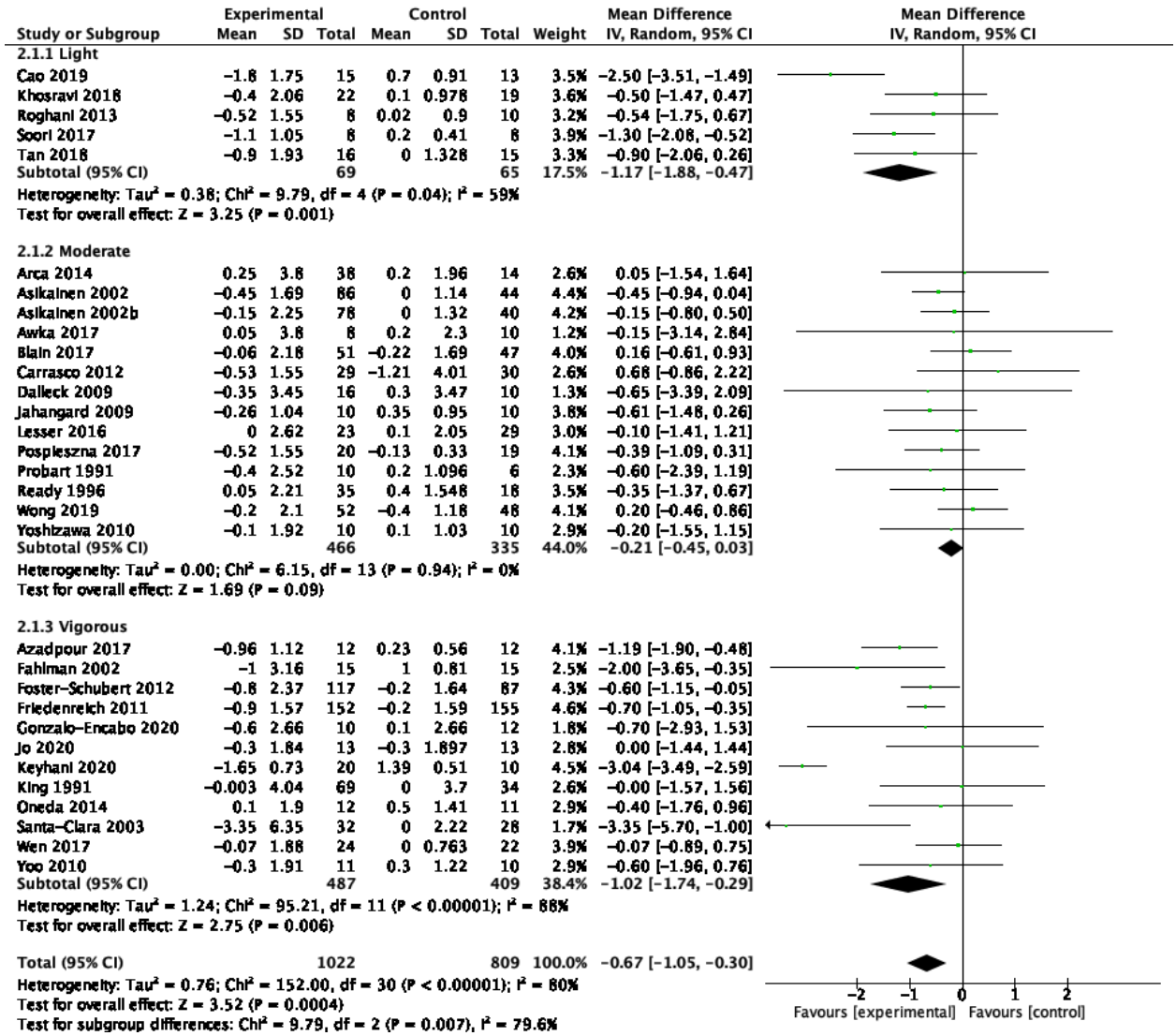

Appendix Figure 3. Effect of aerobic exercise on blood triglycerides



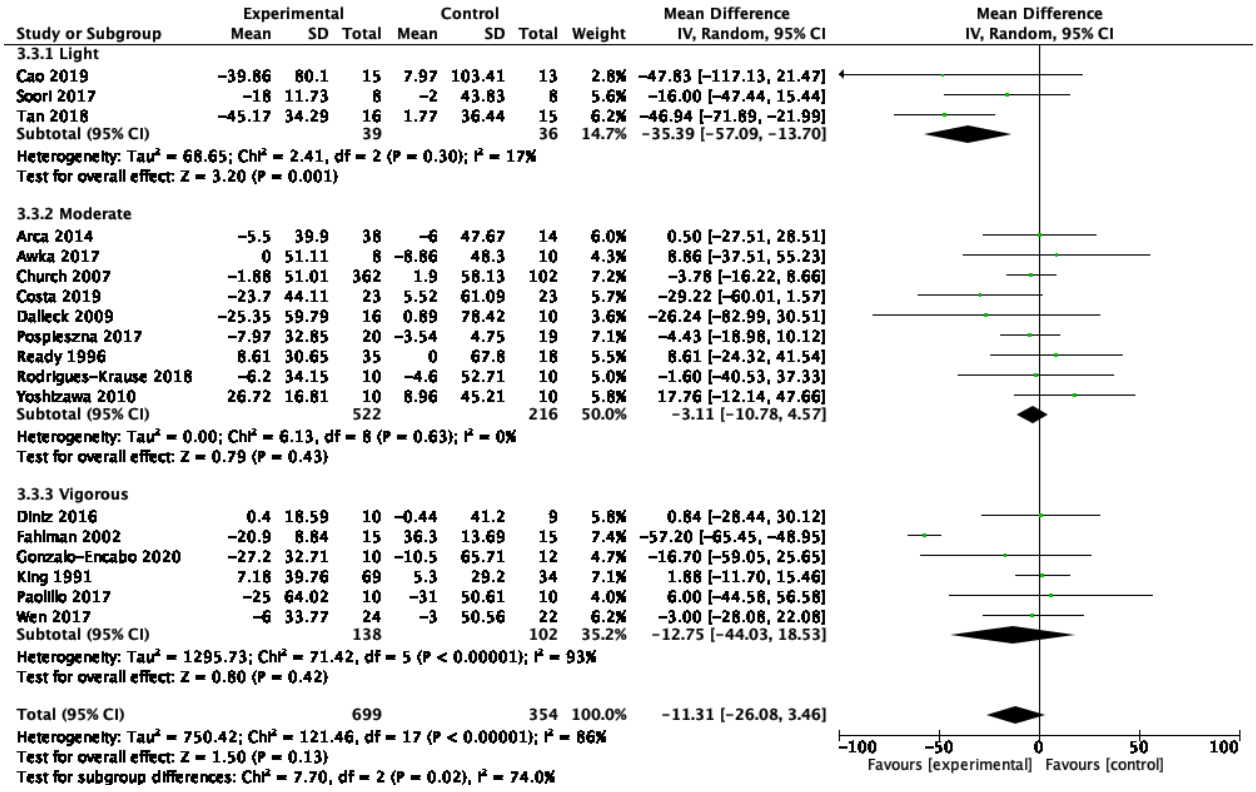

Appendix Figure 4. Effect of aerobic exercise on blood glucose

# APPENDIX 5

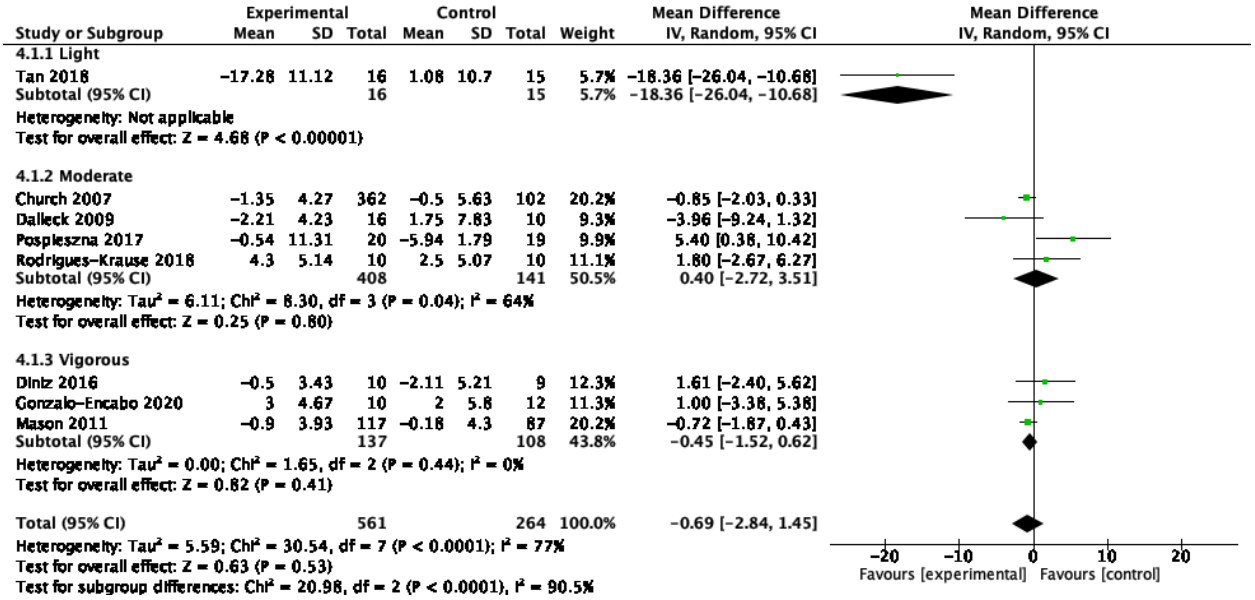
# FOREST PLOTS OF SUBGROUP ANALYSES




Appendix figure 5. Effect of light, moderate and vigorous aerobic exercise on body mass index




Appendix figure 5. Effect of light, moderate and vigorous aerobic exercise on blood triglycerides




Appendix figure 6. Effect of light, moderate and vigorous aerobic exercise on blood glucose