Measuring The Impact of Aerobic Exercise Training on Blood Lipids With Quantitative Analysis

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Declaration

I declare that this work has not been and is not being submitted for any other degree to this or any other University. To the best of my knowledge it does not contain any materials previously published or written by another person except where due reference is made in the text; and all substantive contributions by others to the work presented, including jointly authored publications is clearly acknowledged.

Signed: [redacted] Dated: 08/09/2020

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Thesis Format

This thesis is presented as a thesis by publication. As such, some overlap between chapters exists. Chapter manuscripts have been submitted to, or accepted and published in, peer reviewed journals, or are in press. The formatting of the chapters is that required by the journals for submission, and hence some formatting discrepancy is a consequence.

Peer reviewed publications included in this thesis:

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No Proof of publication could be located for the following chapters:

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Abbreviations

AET	Aerobic exercise training
Apo	Apolipoprotein
AUD	Australian dollar
BMI	Body mass index
BP	Blood pressure
CI	Confidence interval
CMA	Comprehensive Meta-Analysis (software programme)
CVD	Cardiovascular disease
ES	Effect size
H	Hypertension
HDL	High-density lipoprotein
HDL-C	High-density lipoprotein cholesterol
HIIT	High-intensity interval training
ITT	Intention-to-treat
LDL	low-density lipoprotein
LDL-C	Low-density lipoprotein cholesterol
Lp	Lipoprotein
Lp(a)	Lipoprotein (a)
M	Mean
MA	Meta-analysis
MD	Mean difference
MetS	Metabolic Syndrome

METS	Metabolic equivalents of task
MICT	Moderate-intensity continuous training
mg/dL	milligrams per decilitre
mmol/L	millimoles per litre
MR	Meta-regression
MVMAMR	Multivariate meta-analysis with meta-regression
PA	Physical activity
PRISMA	Preferred reporting items for systematic reviews and meta-analyses
RCT	Randomised controlled trial
SD	Standard deviation
SE	Standard error
SLP	Standard lipid profile
SM	Supplementary material
SR	Systematic review
TC	Total cholesterol
TESTEX	Tool for the Assessment of Study Quality and Reporting in Exercise
TRG	Triglycerides
T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus
US	United States
USD	United States Dollar
VLDL	Very-low-density lipoprotein
VO_{2MAX}	peak oxygen capacity
WHO	World Health Organisation

ABSTRACT

Aerobic exercise training (AET) is recommended for lipid management. Several published government health authority guidelines prescribe minimum-intensity and -duration targets of physical activity intended to positively affect cardiovascular disease (CVD) risk biomarkers, such as the standard lipid profile comprising total cholesterol, triglycerides, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol. These guidelines may be of insufficient dosage to improve the standard lipid profile and lower CVD risk.

The aim of this thesis was to use quantitative methods ie systematic review with meta-analysis, to establish whether an optimal AET prescription for lipid management in adults exists. A literature review revealed that previous quantitative research estimating the effect size of AET on lipids had amalgamated heterogenous populations and AET protocols. This resulted in a large variation between estimated outcome measures as well as inconsistency of significance. The literature review also identified gaps where no research synthesis had been undertaken, such as analysis of the effects of AET on lipoproteins, apolipoproteins, and associated lipid ratios. To reduce the potential for confounding factors to under- or over-estimate effect sizes, a rigorous synthesis and quantification using pre-determined and validated protocols was undertaken. The effect size of AET as an intervention to change lipids was estimated by pooling the outcome data of previously published randomised controlled trials. Intervention covariates, such as the intensity of AET effort, minutes per AET session, number of AET sessions per week, and duration of AET intervention, were investigated to determine if any of these explained the change in lipids. Both AET and population groups were

differentiated: AET effort of intensity and duration of intervention were set at a required minimum for RCTs to be included for review, and RCTs were allocated to one of two reviews according to the health status of the population groups being studied.

Chapter 2 describes the protocol for a systematic review with univariate meta-analysis and meta-regression investigating the effects of AET on the standard lipid profile of adult populations free of chronic disease, and diagnosed either with or without Metabolic Syndrome. Chapter 3 describes the protocol for a systematic review with multivariate meta-analysis and meta-regression on novel lipid biomarkers in adult populations. Chapters 4-7 are the quantitative reviews investigating the impact of AET and intervention covariates on the standard lipid profile and novel lipid biomarkers. Chapter 8 presents the findings of this series of quantitative reviews.

The quantitative comparison of the aerobic exercise training protocols high-intensity interval training and moderate-intensity steady state training found neither protocol exerted more effect on total cholesterol, triglycerides, and low-density lipoprotein than the other, in heterogenous populations. High-density lipoprotein cholesterol was significantly raised by high-intensity interval training in comparison to moderate-intensity continuous training. Aerobic exercise training of a minimum intensity and duration similar to government recommended levels of physical activity significantly and positively impacted the standard lipid profile in adult populations free of chronic disease, resulting in a moderate reduction of CVD risk. In adult populations diagnosed with Metabolic Syndrome or Type 1 or 2 diabetes mellitus, the effect size of AET on the standard lipid profile was both significant and larger, as was the decrease in CVD risk, than that of adult populations free of Metabolic Syndrome or

Type 1 or 2 diabetes mellitus, for similar AET protocols. Intervention covariates were not found to explain change in the latter population for any lipids, except the number of sessions per week explaining change in low-density lipoprotein cholesterol. However, intervention covariates potentially explained some of the change in triglycerides (intensity of AET effort), and some of the change in high- and low-density lipoprotein cholesterol (volume of total AET undertaken), of adult populations diagnosed with Metabolic Syndrome or Type 1 or 2 diabetes mellitus. Emerging lipid biomarkers such as lipoprotein fractions, apolipoproteins, and associated ratios were significantly and positively affected by AET, and intervention covariates explained some of these changes in antiatherogenic lipoproteins and apolipoproteins, as well as atherogenic lipid ratios, independent of population.

No optimal AET protocol was identified for populations free of chronic disease, although an increase in sessions per week may induce larger reductions in low-density lipoprotein cholesterol. However, this thesis has identified the aerobic exercise parameters which can be modified to induce greater effects on the standard lipid profile in populations affected by Metabolic Syndrome and diabetes. In addition, this thesis has identified aerobic exercise parameters which can be modified to induce greater changers in lipoprotein fractions, apolipoproteins, and associated ratios in heterogenous populations. These findings suggest future research is better equipped to discover tailored AET protocols which can better manage lipid profiles.

1 CHAPTER 1 – INTRODUCTION

1.1 Introduction

This thesis aims, by using quantitative methods ie systematic review with meta-analysis, to establish whether an optimal aerobic exercise training (AET) prescription for lipid management in adults can be formulated. As part of this broader work, this chapter details the burden and cost of cardiovascular disease (CVD) and its key risk factor, arguably lipids, globally and in the Australian context. The aetiology and pathophysiology of lipid-related conditions pertinent to CVD are presented. The role of lipids both as risk indicators and as treatable health indices is examined, as well as the pharmaceutical and non-pharmaceutical treatments of lipid conditions which are implicated in the development of CVD.

Concerning non-pharmacological therapies, the prevalence of physical inactivity and its related health-care costs in the Australian context is highlighted. This aspect of the work commences with a definition of the difference between physical activity and AET, and considers the implication of this difference. The different methods of quantifying AET amount, or volume, is described, together with how the dosage precision of this prescribed therapy can be enhanced.

This literature review chapter examines the methodology and findings of previously published, relevant research investigating the impact of AET on lipids. The findings of the literature review inform the research proposals to be pursued in the body of this thesis, see Figure 1.1, which indicates how the research is divided between populations, lipids, and AET intervention protocols, within the context of AET as a therapy for managing lipids. As an outcome of this appraisal, quantitative methods are selected and described as protocols to estimate the effect size of AET on lipids.

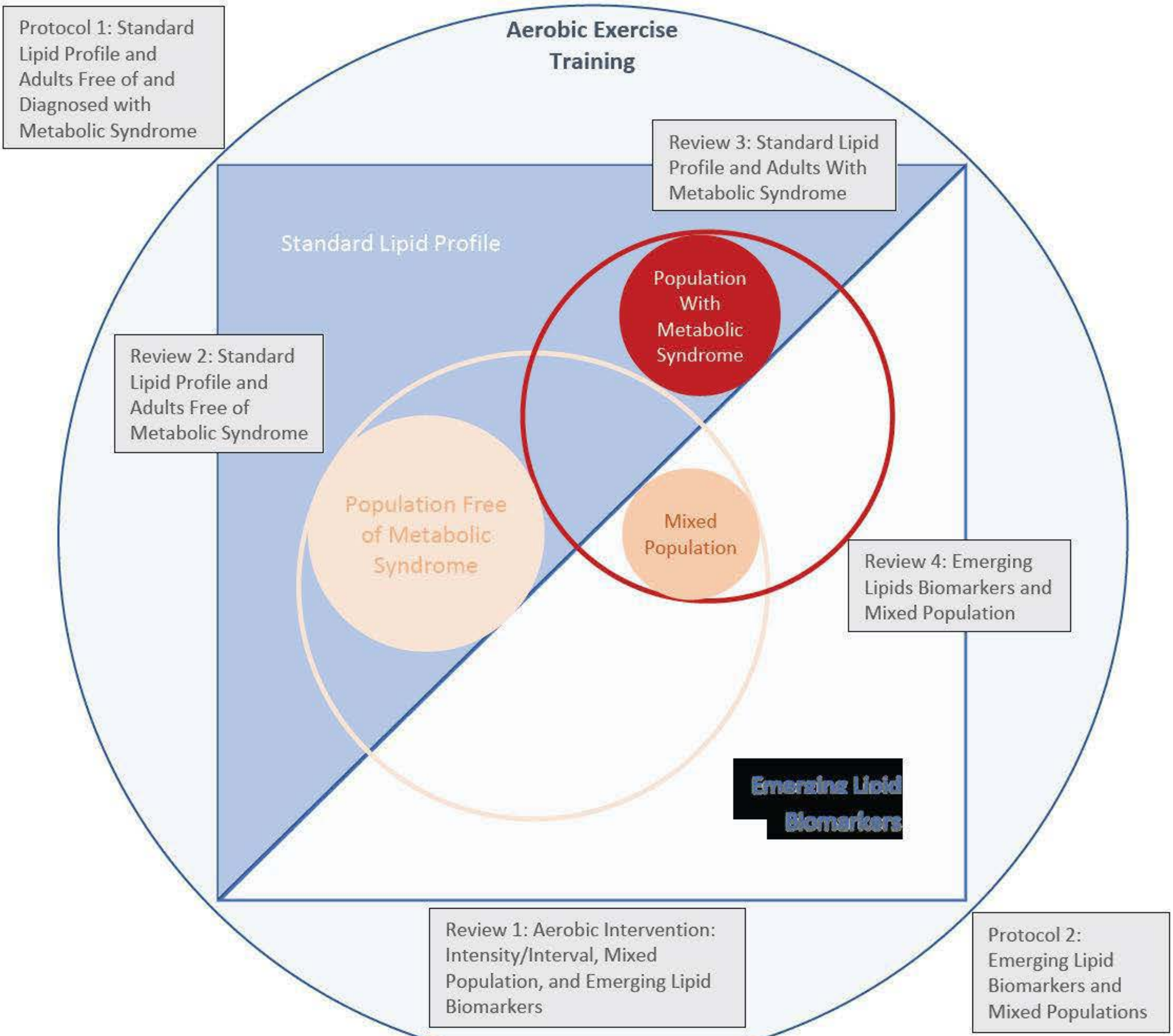


Figure 1.1 Thesis Structure

1.2 Cardiovascular disease and lipids

1.2.1 Epidemiology, prevalence, and cost of cardiovascular disease

As of 2015, an estimated 442.7 million cases of CVD existed throughout the world.(1) An estimated 17.8 million deaths attributable to CVD occurred in 2017, an increase from 2007 of 21%.(2) The main categories of CVD responsible for deaths during this period were ischaemic heart disease and stroke (84.9%).(2) In 2006, using Framingham Heart Study(3) data, the estimated lifetime risk of developing CVD by age 95 for females free of the disease at age 50 was 39.2%, and for males the risk was 51.7%.(4) As total cholesterol (TC) increased (from <4.65 to ≥6.2 mmol/L), the lifetime risk of developing CVD by age 95 commensurately rose to 48.3% for females and to 64.6% for males. Low levels (<1.03 mmol/L in men, <1.29 mmol/L in women) of high-density lipoprotein cholesterol (HDL-C) and obesity (BMI ≥30) were risk factors for developing CVD by age 95. These latter two risk factors were equivalent to the TC risk factor of developing CVD by age 95 at TC levels ≥5.16 mmol/L.(4)

In 2017, high levels (≥3.4mmol/L) of low-density lipoprotein cholesterol (LDL-C) were responsible for 68.9% of ischaemic heart disease deaths amongst adults aged 15-49, for 50.15% amongst adults aged 50-65, and for 35.75% amongst adults ≥70 years.(2,5) Amongst Australian, European, and US populations, progressive incidence of CVD over 30 follow-up years was positively associated with increasing levels of LDL-C and triglycerides (TRG), or non-HDL-C. Non-HDL-C is the measure of cholesterol which remains after subtracting HDL-C from

TC. In women, non-HDL-C levels <2.6 mmol/L were associated with 7.7% incidence of CVD and rose to 33.7% with non-HDL-C levels ≥5.7 mmol/L. In men, non-HDL-C levels <2.6 mmol/L were associated with 12.8% incidence of CVD, rising to 43.6% for non-HDL-C levels ≥5.7 mmol/L. The sharpest increase in the relative hazard ratio associated with non-HDL-C was amongst populations free of CVD, under 45 years, and with non-HDL-C levels ≥5.7 mmol/L.(6) Together, these data illustrate that lipid abnormalities play a major role, if not the major role, in the development of CVD. Moreover, if lipid abnormalities exist in the presence of other CVD risk factors such as hypertension, significant interaction between these CVD risk factors occurs, and the disease process is accelerated.(4) Later sections of this chapter will detail how common lipid abnormalities can be effectively managed. Thus, the capacity to reduce the health and economic burden of lipid abnormalities and resultant CVD on society is large. The total global annual cost of CVD is predicted to rise from USD$863 billion in 2010, to USD$1 044 billion in 2030. Of this annual global cost, 55% will be direct health care costs, and 45% will be cost due to lost productivity (arising from disability or premature death, or time off work). The additive (year-on-year) cost over this 20-year period is estimated to total USD$20 032 billion, or a per capita additive cost of almost USD$3 000.(7)

In 2018, approximately 1.2 million Australians were diagnosed with CVD.(8) In 2015-2016, the total health-care cost attributable to CVD was AUD$10.4 billion.(9) The projected economic cost associated with the loss in productivity from CVD deaths in 2003 is estimated to be AUD$2.7 billion by 2030.(10) More than one management strategy needs to be adopted to reduce costs, mortality, and a diminished quality of life for those diagnosed with or at risk of developing CVD.

1.2.2 What conditions comprise cardiovascular disease?

Atherosclerosis, the principal accepted cause of most forms of CVD, is the hardened accumulation of fatty substances or lipids, including cholesterol, on the vascular intima (inner linings of arteries). Atherosclerosis results in occlusion of the blood supply,(11) causing:

- chronic and/or acute coronary heart disease (angina and heart attack respectively);
- stroke (defined as central nervous system infarction(12));
- heart failure (damage to and resultant weakening of the heart muscle leading to loss of function); and
- peripheral vascular disease (occlusion of blood supply to peripheral organs and limbs).(13,14)

Arrythmia and heart valve disease, although considered to be CVD, are less likely to be a direct result of atherosclerosis.(14) Congenital heart diseases, also belonging to CVD, are heart and blood supply disorders present at birth, and not a result of atherosclerosis.(13,14) Atherosclerosis is thus an underlying condition of the most prevalent forms of CVD. Before turning to the development of atherosclerosis, the following section examines the role of lipids in the body.

1.2.3 The role of lipids in the body

Lipids conserve and furnish energy, act as signalling molecules, and are components of cellular structures.(15) Cholesterol is synthesised in cells as the precursor to steroid hormones and metabolic products such as bile, while TRG are the primary supplier of calories.(15,16) Lipolysis occurs when lipid levels are insufficient to provide energy, and lipogenesis, the inverse process, results in storage in adipose tissue.(17) Triglyceride and cholesterol esters, insoluble in water, are transported by lipoproteins, a fluctuating ratio of macromolecular complexes comprising apolipoproteins (Apo) and other lipids.(16,18) Circulating lipoproteins comprise chylomicrons, HDL (HDL2, HDL3), very-low-density lipoprotein (VLDL), intermediate LDL, and LDL. These circulating lipoproteins vary in size, composition, and density (HDL: HDL_{2a}, HDL_{2b}, HDL_{3a}, HDL_{3b}, HDL_{3c}; LDL: LDL-I, LDL-II, LDL-III, LDL-IV),(19,20) and separate into mainly atherogenic and antiatherogenic Apos,(15,16,18) see Table 1.1.(15,16,18,21-27) The major core lipid of chylomicrons and VLDL is TRG; HDL and LDL are composed primarily of cholesterol.(15,16)

Lipoprotein	**Apolipoprotein**	**Function**	**Atherogenicity**
HDL	A1	Structural component	Antiatherogenic
HDL	A2	Structural component	Antiatherogenic
HDL	A4	Structural component	Antiatherogenic
VLDL	A5	Capillary surface association	Atherogenic
VLDL/LDL	B100	Structural component	Atherogenic
Chylomicrons	B48	Structural component	Atherogenic
VLDL/HDL	C1	Inhibits VLDL receptor	Atherogenic
VLDL/HDL	C2	Lipoprotein lipase activator (LpL)	Antiatherogenic
VLDL/chylo-microns	C3	LpL inhibitor; chylomicron and VLDL remnants hepatic uptake inhibitor	Possible antiatherogenic effects
HDL	D	Multi ligand binder	uncertain
VLDL/HDL	E	LDL ligand receptor	Atherogenic
Lp(a)	Apo(a)	Unknown	Atherogenic

Table 1.1 Lipoproteins, apolipoproteins, function and atherogenicity
(15,16,18,21-27)

The role of lipids in the body is thus critical to the proper functioning and maintenance of cells, hormones, digestion, and provision of energy in the body. The following section examines how atherogenic and antiatherogenic lipids are implicated in the development of atherosclerosis, and hence CVD.

1.2.4 What is the pathophysiology of atherosclerosis?

Atherosclerosis is an inflammatory disease of the arteries.(28) Lesions, in the forms of scarred tissue,(29) calcification,(30) and inflammation,(31) accompany the deposition of lipids on the intima of the arteries, and lead to cardiovascular complications such as blood supply occlusion or embolism.(32,33) This damage to the intima of the arteries appears to arise from a combination of interacting factors:(34) changed lipid metabolism,(35,36) altered endothelial cell function,(37) and inflammation.(38,39)

While it is the interplay of these cellular and biological factors which initiates the development of atherosclerosis, the trigger appears to be the accretion of apolipoprotein B-rich low-density lipoprotein (LDL) in the weakened intima of the endothelium.(40) This condition results from the interruption of atheroprotective shear stress.(41) The process is exacerbated by the oxidisation of the LDL particles(42) and the expression, by macrophages, of scavenger receptors absorbing altered and native lipids,(43,44) including high-density lipoprotein (HDL).(45) The development of atherosclerosis is thus preceded by a progressive disruption of the balance of lipids in the blood, or dyslipidaemia.

1.2.5 Dyslipidaemia: aetiology

Dyslipidaemia, generally a combination of abnormally elevated atherogenic and lowered antiatherogenic lipids or lipoproteins, derives principally from the following secondary(46), not primary, causes:

- tobacco use;(47)
- alcohol use;(48)
- obesity;(49)
- high levels of dietary fat;(50)
- endocrine and autoimmune disorders;(51)
- ingestion of anabolic steroids and progestins;(52,53)
- physical inactivity;(54-56) and
- contra-indicated medication.(57)

Obesity and endocrine disorders are negatively affected by physical inactivity.(58,59) With the exception of disorders arising from genetic predispositions,(60) these secondary causes of dyslipidaemia can be modified by behavioural change. Whether these secondary causes of dyslipidaemia occur singly or grouped, physical inactivity precedes the occurrence of, as well as exacerbates, a disrupted lipid profile.(61)

As well as behavioural change strategies to modify the secondary causes of dyslipidaemia, various therapies exist to manage the condition itself. Before progressing to an examination of the treatment options available to manage dyslipidaemia, the following section discusses lipids as CVD risk factors. Dyslipidaemia is a state of lipids out of balance in the body, and a precursor to atherosclerosis, the principally accepted cause of most forms of CVD. Disrupted lipid profiles, as single lipids or in combination, have been identified as risk factors in the development of CVD.

1.2.6 Lipids as cardiovascular risk factors

Confirmed by later work completed around the world,(62-65) analyses of Framingham Heart Study(3) data indicated TRG, HDL-C, and LDL-C were robust and independent CVD risk predictors.(66) While comprehensive or total risk informs clinical guidelines,(67-69) the quantitative measurement of improvement in lipid levels, inversely correlated with CVD prevalence,(70) has led to desirable or atheroprotective lipid targets. These targets are used for either primary or secondary prevention and segmented according to overall CVD risk.(71) Lipid assessment as a management tool for modifying CVD risk has resulted in the standard lipid profile (or panel) (SLP)(72) and targets, see Table 1.2.(71,73) These target ranges are more aggressive when CVD or other CVD risk factors are present.(71)

Lipid	**Target range** AU: Australian target; EU: European target; US: United States target.(71,73)
TC	< 4.0 mmol/L at risk groups, < 5.5 mmol/L no CVD risk factors present[AU]
TRG	< 2.0 mmol/L[AU]
HDL-C	≥ 1.3 mmol/L for women,[EU/US] ≥ 1.0 mmol/L for men[EU/US]
LDL-C	< 1.8 mmo/L for CVD groups[AU/EU] < 2.0 if no CVD risk factors present[AU]

Table 1.2 Standard Lipid Profile

Non-HDL-C is the concentration of cholesterol transported by LDL and VLDL. Non-HDL-C is a discretionary target (< 2.5 mmol/L) in Australian guidelines when individual TRG levels exceed 2.3 mmol/L, in recognition of the atherogenic aspect of VLDL.(69,71). Ratios such as TC/HDL-C and LDL-C/HDL-C, as well as Apo A or Apo B or the ratio Apo B100/Apo A1 may be recommended for measurement but are not (yet) always included in the SLP.(74) In 1983, as a result of quantitative analysis of lipid and exercise studies, the TC/HDL-C ratio was suggested as being more effective at indicating CVD risk(75). Recent studies suggest emerging lipid biomarkers, such as ratios, HDL-2 and HDL-3, Apo A and Apo B, predict CVD risk with a precision exceeding the SLP.(76-83)

Lipids interact with adipose tissue at the cellular level; obesity presents concurrently with dyslipidaemia.(84,85) Obesity and dyslipidaemia are clustered as a set of continuous cardiometabolic risk factors or precursor conditions to CVD, together with elevated blood pressure, and either the presence of insulin resistance or glucose intolerance, or Type 1 or 2 diabetes mellitus, as the Metabolic Syndrome (MetS).(86) Variation as to the exact definition of MetS exists;(87,88) a composite version was proposed in 2009 and is in use.(89) While the presence of any one of these CVD risk factors represents an increased risk for CVD, when grouped the estimated CVD risk is higher.(87) The presence or pharmacotherapy of three or more of the MetS factors indicated above is sufficient for a diagnosis of MetS.(90) Lipids (TG and HDL-C) constitute two of the core MetS factors, while simultaneously with TC and LDL-C are the strongest lifetime risk factors for the most prevalent forms of CVD.

Lipids, established as risk factors for CVD, are also used as health indices or targets to reduce the incidence of CVD. The most common forms of CVD are primarily a result of atherosclerosis, which arises from dyslipidaemia, or a disrupted lipid profile. Dyslipidaemia derives principally from behaviours, thus termed secondary causes, as identified in section 1.2.5. With the exception of hereditary disorders, these secondary causes of dyslipidaemia are modifiable through behavioural change. A disrupted lipid profile can also be managed via pharmacotherapy. The following section examines behavioural change and pharmaceutical options for managing dyslipidaemia.

1.2.7 Dyslipidaemia: non-pharmacotherapy and pharmacotherapy management

The behavioural phenomenon of physical inactivity underpins or intensifies the impact of secondary causes of dyslipidaemia. A recent metaepidemological review of randomised controlled trials found behavioural change interventions, in the form of raising physical activity levels, to have equal or greater beneficial effects on mortality outcomes (secondary prevention of CVD) compared with pharmaceutical interventions.(91) Despite such a finding, reducing physical inactivity is a behavioural change strategy most often prescribed as a treatment aimed to prevent dyslipidaemia,(32,92,93) even though it is a preferred first treatment option for dyslipidaemia in sub-clinical populations and a concurrent treatment option in clinical populations.(94-98) Pharmacotherapy of dyslipidaemia is prescribed according to the calculated level of CVD risk.(99) This pharmacotherapy prescription results from the classification of CVD risk, the CVD risk indices being evaluated,(97) and the extent to which the response of CVD risk indices to behavioural change and pharmaceutical treatment can be measured.(100) Pharmacotherapy of dyslipidaemia, principally in the form of statins as at the time of writing,(101-103) is quantified by changes in lipid values; decrease in atherogenic lipids and increase in antiatherogenic lipids equates to a decrease in CVD risk.(16) Pharmaceutical trials test specific dosages (fixed or titrating) over a given time period, measure the before-and-after lipid delta, and estimate the CVD risk reduction as a result of changes in lipids.(104) The results of appropriately designed pharmaceutical trials can be quantitively aggregated to derive an estimated effect size (ES) across all pharmaceutical treatments aimed at reducing CVD risk by acting on lipids.(105,106) In contrast, behavioural change as the intervention designed to reduce CVD risk, such as reduction in physical inactivity, is less easily and precisely described, prescribed, and quantified.

The full diminution in risk of ischaemic heart disease is achieved within five years of lowering TC by 0.6 mmol/L.(107) A 1% decrease in LDL-C represents a 1.7% reduction in CVD risk.(108) A 1% decrease in HDL-C raises CVD risk by approximately 3%.(80) An increase in HDL-C of 0.026 mmol/L decreases CVD risk by 2% in males and ≥ 3% in women.(109) Both cholesterol lowering medication and behavioural change strategies require a minimum period to show effects, however trials of pharmacological intervention(110) are generally conducted for longer periods than trials of non-pharmacological intervention.(111) Pharmaceutical intervention is not without negative side effects.(112,113) An analysis of the VOYAGER database demonstrated that pharmacotherapy can decrease HDL-C,(114) thus increasing CVD risk. Pharmacotherapy also imposes a financial cost on health systems.(115-117) Non-pharmacotherapy, such as behavioural change strategies designed to raise physical activity levels, represents an opportunity to treat a disrupted lipid profile.

1.3 Aerobic exercise training

1.3.1 The financial cost of physical inactivity in Australia

Despite increasing evidence of the benefits of aerobic exercise training (AET) on health indices such as lipids, global levels of physical inactivity amongst adults have continued to stagnate, showing little change during the previous three decades.(118) During 1993-94 in Australia, 18% or AUD$161 million of the cost of treating coronary heart disease was directly attributable to physical inactivity.(119) Between 1989 and 2011, physical inactivity amongst Australians remained unchanged, and was responsible for 21.2% of CVD prevalence.(120) In 2014-15, 52% of self-reporting adults aged 18-64 were sedentary or physically inactive, as were 75% of adults ≥65 years.(121) The true contribution of sedentariness to Australian health-care costs due to CVD, and thus in large part, to a disrupted lipid profile, is at least AUD$2.2 billion, as of 2016. Reducing levels of physical inactivity and increasing levels of physical activity is a means to reduce Australian health-care costs due to CVD, as well as improve lipid profiles.

1.3.2 Why not call aerobic exercise training "physical activity" (PA)?

The term "physical activity" refers to musculature contraction requiring an increase in energy expenditure above the basal metabolic level, occurring spontaneously during regular quotidian tasks, or recreational and leisure activities, without the specific goal of contributing to or enhancing elements of physical fitness.(122) With the advent of mechanisation and automation, opportunities for occupational activity as a component of PA have declined.(123) "Exercise" is a subcategory of PA, and defined as planned, structured movement intended to increase or maintain physical fitness or health.(122)

Given that government health authorities globally report and are aware of the level of physical inactivity amongst populations, PA guidelines have been developed to reduce sedentariness in the populace.(124-126) Government health authority guidelines published in Europe,(125) the US,(126) and Australia(124) refer to PA and recommend PA targets of "moderate intensity aerobic" or "vigorous intensity aerobic". These health authority guidelines suggest PA combinations of session duration and frequency of sessions in a given time period, typically a week, of accumulated moderate or vigorous intensity.(124-126) The PA recommendations made in these health authority guidelines imply the planning and structure associated with AET, and the basis for undertaking AET is to achieve an improvement in physical fitness.(122)

Government health authority guidelines provide examples of how to incorporate PA in quotidian tasks, such as walking briskly for 30 minutes instead of catching the bus, cycling at a given speed to the office for 45 minutes rather than driving the car, walking up the stairs rather than using lifts or escalators.(124) The behavioural change message of these guidelines, by providing such examples, is to encourage the adoption of PA on a daily basis ie ‘anything is better than nothing’,(124) rather than promote an aggressive AET behavioural change strategy. These examples of including PA in normal daily activities are generalised and not prescriptive, instead being offered for the individual to adapt and adopt. In addition, these examples are not formulated so that the amount of PA (time spent or effort level accomplished) being undertaken is expected to be monitored or recorded. Thus, these example PA formulations are unable to be assessed with respect to determining the effects of sporadic PA on health indices such as lipids. This intention to increase the level of PA in populations is unsuited to testing hypotheses regarding AET dose-response relationships. Aerobic exercise training dose-response trials follow a planned and structured protocol of specified dose variables to which the intervention group must adhere. In order to test the effect of AET, AET variables must be explicitly pre-defined. Hence the use of the term AET.

1.3.3 What are aerobic exercise training dose variables?

Manipulable AET dose variables are frequency, intensity, and time, which together constitute volume, as well as type and progression.(127) Frequency is the number of times in a given period a bout of AET is performed eg 3 times/week; time is the length of time taken for a single bout of AET eg 30 minutes, and type refers to the activity eg walking, jogging, or swimming. Aerobic exercise training intensity ranges can be described using an absolute range ie the metabolic cost of performing a single bout of AET. Alternatively, the relative range uses a percent measure of maximal capacity.(123) A program of AET commences at a given volume and intensity and as physical fitness improves, the program advances to a higher volume and/or intensity, hence progression.(127) Cardioprotective benefits are associated with effort levels above light intensity,(128,129) and debate exists as to the potential benefits of AET performed at intensities above vigorous,(129,130) hence government health authority guidelines recommend moderate-to-vigorous intensity. (124-126)

The moderate-intensity aerobic range, defined using an absolute criterion such as metabolic equivalent of task (METS), is the equivalent of 3-6 metabolic equivalents METS; the vigorous-intensity aerobic range using an absolute criterion is defined as the equivalent of 6-9 METS. Relative measures of moderate-intensity aerobic range from 40<60% of heart rate reserve (HRR) or maximal oxygen uptake (VO_{2MAX}); 55<70% of maximal heart rate (MHR); or rate of perceived effort (RPE) of 11-13 on the Borg scale. Relative measures of vigorous-intensity aerobic range from 60<85% HRR or VO_{2MAX}; 70<90% MHR; or RPE of 14-16 on the Borg scale.(130) In less fit populations, the METS definition of moderate intensity, by using an absolute range, equates to a vigorous level of intensity measured using relative range, hence the general preferred usage of relative ranges to measure intensity when prescribing AET.(129,130)

Aerobic exercise training, whether measured using electronic devices as the cardiovascular output arising from activities such as dancing or participation in team games, or prescribed with a set protocol of minutes per session, sessions per week, and intensity per session, varies by two factors during its execution: effort (measured by intensity) and effort-to-recovery ratio (determined by the period spent exercising at one intensity interspersed with a period spent exercising at a different intensity).(131) Thus, AET protocols can be varied by manipulating each of the intervention covariates indicated above. Providing the baseline level of fitness of a given population is established prior to an intervention, the dose-response relationship of a prescribed combination of AET intervention covariates can be investigated to determine a specific physiological effect, such as measuring change in lipids in response to AET.

1.3.4 Optimising aerobic exercise training prescription for lipid management

Aerobic exercise training is a therapeutic intervention.(132) As a therapeutic intervention, its effect can be quantified through observing pre- and post-intervention changes in measurable biomarkers. A considerable body of evidence exists examining the physiological effects of AET,(123) which underpins global recommendations.(67,96) Early exploratory work examining the effect of AET on lipids in CVD patients found significant positive effects.(133) Subsequent landmark works observing sub-clinical groups and reporting lipids as the primary outcome suggested a minimum volume of AET (>180 minutes per week at >40% VO_{2MAX} or >1200 kcal/week) were necessary to induce positive changes to lipids.(134,135) Later studies showed AET at specific thresholds (high-intensity endurance or 500kcal/session) improves the standard lipid panel (SLP) and antiatherogenic lipoprotein in sub-clinical and clinical populations.(136,137) A recent meta-review of systematic reviews (SR) and meta-analyses (MA) found AET to have more impact on lipids than resistance training or combined aerobic and resistance training.(138) Just as steadily increasing dosages of cholesterol-reducing medication result in greater improvements to lipids,(98,139,140), higher dosages of AET also significantly improve lipids. Lipids appear sensitive to optimisation of dose-response relationships. Optimising AET protocols is possible by manipulating intervention covariates such as intensity, frequency, time spent training, and duration.

The main focus of this thesis is to establish whether an optimised AET protocol can be formulated and prescribed to positively manage lipids. The publication of several new studies since the early exploratory and landmark works may challenge, confirm and/or augment previous findings, namely that lipids are positively affected by AET, and that energy expenditure above 500kcal/session improves the SLP and raises antiatherogenic lipoprotein in certain populations. In order to inform later chapters of this thesis, an up-to-date systematic literature search has been conducted to identify SRs and MAs which pooled trials investigating the effect of AET on lipids and reported a lipid outcome. The next section details this search and the subsequent qualitative appraisal of these SRs and MAs. The appraisal of these SRs and MAs was intended to identify potential questions which could animate the research proposal.

1.4 Existing quantitative, synthesised evidence of the effects of aerobic exercise training on lipids – Literature Review

1.4.1 Objective of the review of to-date SRs and MAs of AET interventions reporting lipids

A qualitative review of SRs and MAs pooling trials of the effects of AET on lipids in populations free of chronic disease (but not MetS, component MetS factors such as blood pressure, or Type 1 or 2 diabetes mellitus, since these are CVD pre-cursors) was conducted. This review was expected to achieve the following three objectives:

1. classifying what and how research on this topic has been executed;
2. discovering the direction and magnitude of previously estimated changes in lipids which occurred as a result of AET interventions; and
3. identifying the potential to update or augment existing research.

To achieve these objectives, the following methodology was adopted:

1. identifying possible questions to be asked and answered regarding the effect of AET on lipids
2. selecting sources of relevant material;
3. setting search, inclusion, and exclusion criteria;
4. fixing the end date of first searches to 31st March 2018;
5. collating results from points 1-3; and
6. identifying gaps in research syntheses.

1.4.2 Selection of sources of relevant material

Online English-language searches of the Cochrane Database of Systematic Reviews, Pubmed, Web of Science, and EBSCO databases were conducted to identify potential SRs with MA examining the effect of AET on lipids. Search term combinations included but were not limited to “meta-analysis”, “aerobic exercise”, “aerobic training”, “cholesterol”, “lipoproteins”, “apolipoproteins”, “triglycerides”, “lipids”, “adults”, and delimiters included “cancer”, “stroke”, “NAFLD”, “renal”, “claudication”, “polycystic”, “pregnant”, “lactating”, “HIV”, “depression”. Recently published SRs and MAs were also searched for reference to earlier published SRs and MAs.

1.4.3 Search, inclusion, and exclusion criteria

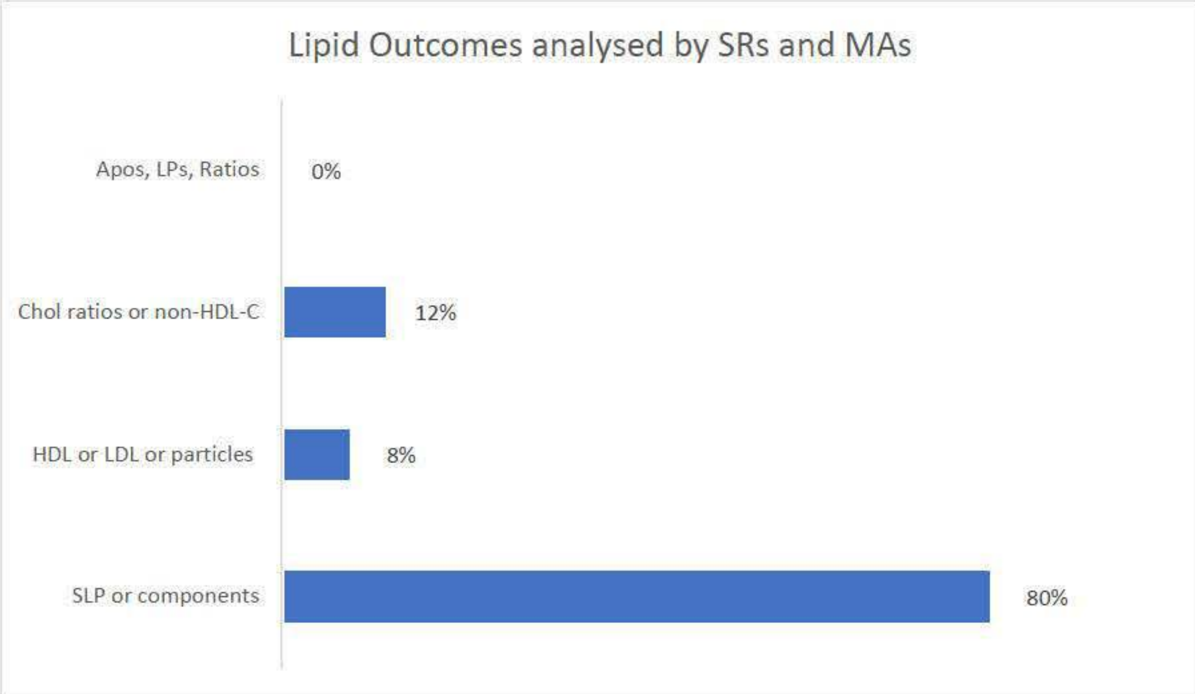
Peer-reviewed, published SRs with MAs were required to have pooled a minimum of 3 studies. These pooled studies were then required to have the following characteristics:

- measured the effects of AET on lipids;
- reported on at least one lipid (common to at least 3 pooled studies reporting that lipid), as either a primary or secondary outcome;
- conducted trials of adults free of chronic disease (and not survivors of chronic disease events) except for MetS factors, MetS, Type 1 or 2 diabetes mellitus;
- used only structured AET protocols with a prescribed measure of aerobic intensity ie not progressive accumulation of PA, not multi-factor lifestyle interventions, not self-selected intensity, not resistance or strength training, not unconventional modes such as Qi Gong or Tai Chi; and
- compared an AET intervention against a non-exercising intervention, or different AET interventions were to be compared eg HIIT vs MICT; and not comparing combined

diet and AET, resistance training and AET, or pharmacotherapy and AET interventions, against control groups.

1.4.4 Presentation of results – findings of existing pooled evidence

The searches undertaken to inform the research proposal were completed by 31st March 2018 (subsequent searches have been conducted until July 31st, 2020). These initial searches identified 23 quantitative SRs satisfying selection criteria, details of which are provided in Appendix 1 Table 1. Of these, the most recently identified SR and MA(141) searched for eligible studies until July 2017; the latest published pooled trial data included in this SR and MA was dated 2016. One of the included SR with MA was a Cochrane Review.(142) Included SRs with MAs were published between 1985 and January 2018, with pooled effect measures of the standard lipid profile; three SRs with MA included the TC/HDL-C ratio, one included non-HDL-C, one included HDL-C2 and C3, and one included lipoprotein particles, see Figure 1.2. Several SRs with MA included trials other than RCTs, and performed neither study quality analysis nor sensitivity analysis using study quality (either as meta-regression or as sub-analysis).



SLP: Standard Lipid Profile; Apos, LPs, Ratios: apolipoproteins, lipoproteins, and ratios; Chol: cholesterol; HDL: high-density lipoprotein; LDL: low-density lipoprotein

Figure 1.2 Lipid outcomes analysed by systematic reviews and meta-analyses published to 31st March 2018.

Aerobic exercise training interventions identified in the included quantitative reviews consisted of walking, jogging, running, circuit training, ergocycling, swimming, team games, and dancing. One SR with MA(143) included aerobic interventions with stretching and resistance components (stretching typically forms part of warm up and cool down protocols, circuit training can include aerobic resistance components), but the reported sensitivity analysis did not change the estimated outcome measures. Aerobic intensity, when the included SRs and MAs reported this variable, showed the inclusion of studies with effort levels from less than moderate, to high. Intervention duration ranged from 2-156 weeks, 3 MAs reported no duration length, and 16 included trials of length <12 weeks.

The health status of populations investigated in the pooled studies and reported in the included SRs with MAs ranged from healthy active to sedentary with CVD (not all SRs with MA discriminated for health status in selection criteria, nor activity status pre-intervention), see Figure 1.3. Ages ranged from young adult to elderly, four studies reported no age range. Four of the SRs with MA were gender specific (3 female, one male), and 2 did not indicate the population gender of included trials.

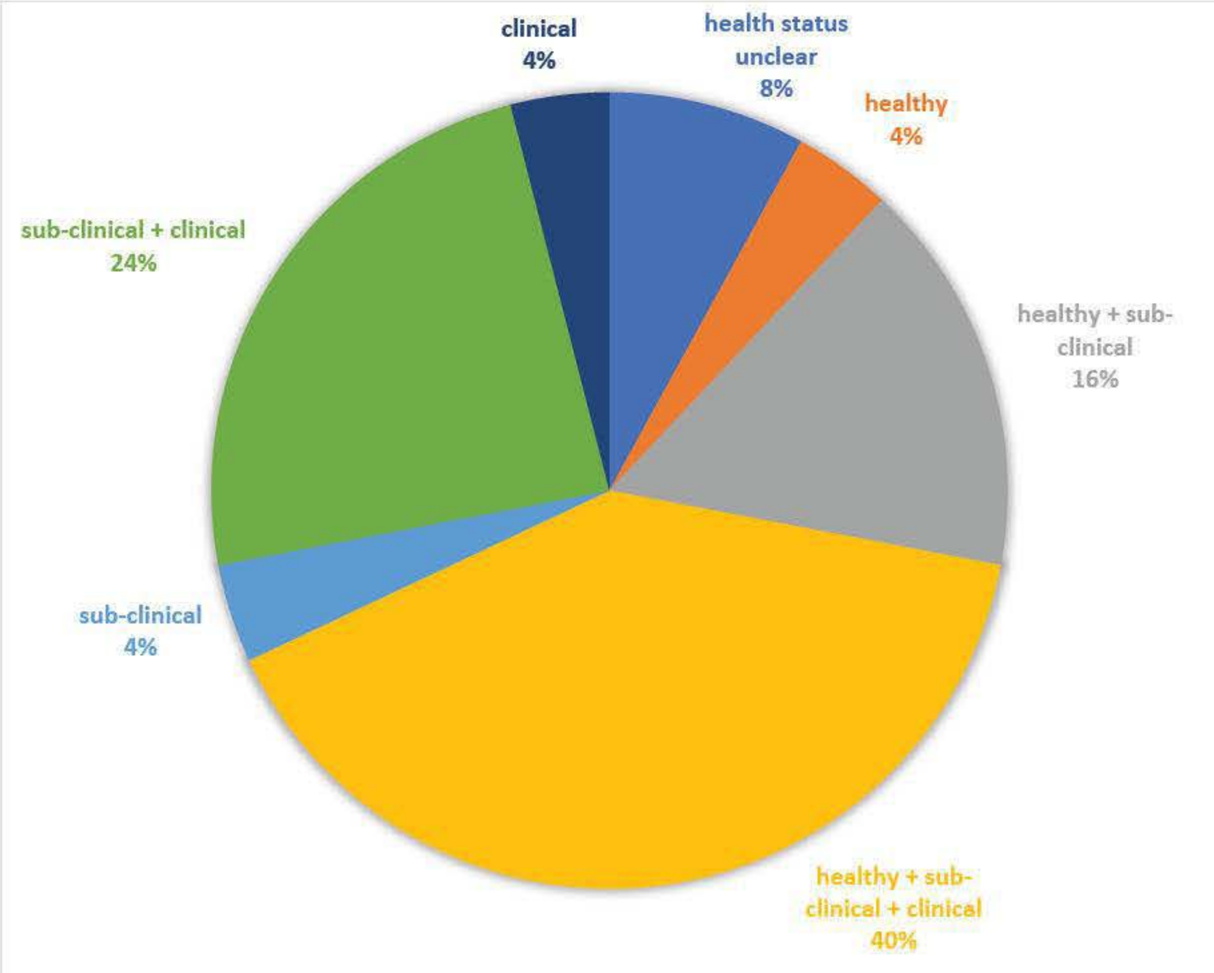


Figure 1.3 Health status of populations combined in systematic reviews and meta-analyses published to 31st March 2018

The main hypotheses being tested by previously published SRs with MAs attempt to determine whether AET or AET intervention covariates affect lipids. The findings of these previous SRs and MAs are inconclusive and lack agreement as to size or direction of change, see Table 1.3.

Cohort	Hypothesis being tested	Findings	Systematic review with meta-analysis
Mixed healthy, sub-clinical, and clinical	AET affects lipids	AET significantly affects TG only	Chudyk 2011(144);
		AET significantly affects LDL-C only	Kelley 2007(145)
		AET does not significantly affect lipids	Hwang 2011(146), Qui 2014(147)
	AET affects lipids by gender (M; F)	AET significantly affects lipids by gender	Kelley 2006a(148); Kelley 2004(149)
	AET affects lipids by gender (F)	AET significantly affects TC and TRG, but not HDL-C and LDL-C, in females	Lokey 1989(150)
		No clear result whether AET affects lipids in females	Zhang 2016(151)
	AET affects non-HDL-C	AET significantly affects non HDL-C	Kelley 2005b(152)
	AET affects antiatherogenic lipoproteins	AET does not significantly affect antiatherogenic lipoproteins except for HDL-C2	Kelley 2006b(153)
	AET affects lipoproteins	The significant effect of AET on lipoprotein depends on particle size and lipoprotein (inconsistent)	Sarzynski 2015(154)
AET covariates Mixed healthy, sub-clinical, and clinical	Intensity influences the effect of AET on lipids (HIIT vs MICT)	Intensity does not significantly influence the effect of AET on lipids	De Nardi 2018(141)
	AET intervention variables influence the effect of AET on lipids	Above a pre-specified threshold, AET intervention variables significantly influence the effect of AET on lipids;	Fikenzer 2018(155);
		AET intervention variables significantly influence the effect of AET on TRG and HDL-C, but not TC and LDL-C	Hespanhol Junior 2015(156)
	AET intervention variables influence the effect of AET on lipoproteins	The significance of AET variables influencing the effect of AET on lipoproteins depends on particle size and lipoprotein (inconsistent)	Sarzynski 2015(154)
Sub-clinical	AET affects lipids	AET significantly affects HDL-C only	Fagard 2006(157) ;
		AET significantly affects TRG only	Kelley 2012(158)
		AET significantly affects lipids, but not LDL-C	Halbert 1999(159)
		AET does not significantly affect lipids	Ruppar 2014(143)
	AET affects HDL-C only	AET significantly affects HDL-C only	Kodama 2007(160)
MetS, clinical	AET affects lipids	AET significantly affects lipids	Kelley 2005a(161)
	AET affects lipids	AET significantly affects lipids, but not HDL-C	Ostman 2017(162)
		AET significantly affects lipids, but not TC	Shaw 2006 (142)
Weight change	Non-specific exercise affects lipids with weight change	Non-specific exercise significantly affects lipids in the presence of weight loss or weight stability but not weight gain	Tran 1985(163)

Table 1.3 Findings of previous systematic reviews with meta-analyses to 31st March 2018.

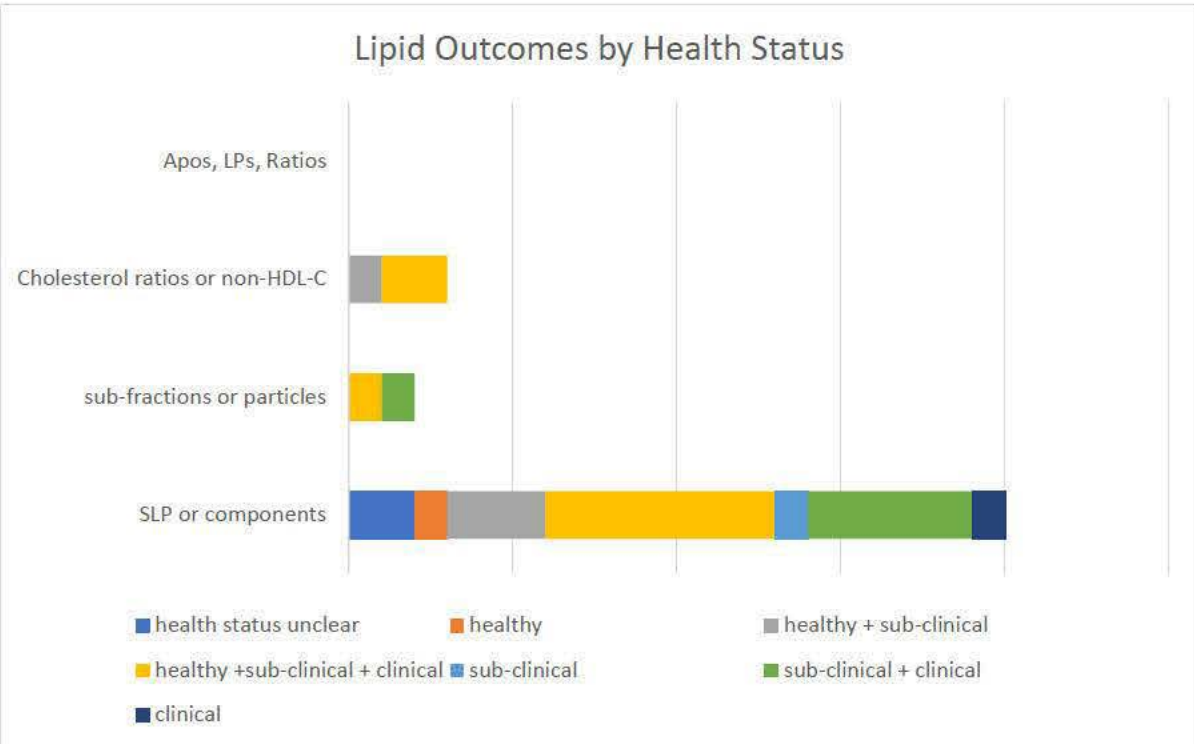
Previous SRs with MAs investigating the impact of AET on lipids reported estimated ES with 95% confidence intervals that crossed the line of null effect (no significant change), see

Appendix 1 Table 1. Thus, no improvement in any of the lipid measures analysed can be expected. Unless the trials included in these SRs with MAs were reporting lipids as the primary outcome, one explanation for the lack of significance of either the trials or the SRs with MAs is inadequate statistical power. Another reason for the incongruity of results may be the variety of AET protocols aggregated for comparison; shorter duration of included trials and the range of intensities could account for differing impacts on lipids. Alternatively, the amalgamation of effect measures calculated from trials using healthy participants as well as those diagnosed with chronic cardiometabolic diseases such as MetS, Type 1 or 2 diabetes mellitus, and in several instances, the inclusion of CVD populations (incidental and not specifically targeted), might explain the variation. The reported heterogeneity amongst pooled trials suggests the presence not only of statistical heterogeneity, but clinical and treatment heterogeneity could also account for the disparity between size and direction of effect measures.(164) These results suggest a different approach is required to reduce noise and heterogeneity. Such an approach would focus on collating and comparing different AET protocols by covariates, with minimum duration and intensity thresholds, and seek to minimise the confounding effects of health status by comparing similar populations.

Subsequent searches conducted until 31st July, 2020 for quantitative reviews satisfying the aforementioned inclusion criteria found three SRs with MAs published since 31st March, 2018, see Appendix 1 Table 2. These later SRs with MAs focused on estimating an effect measure for T2DM(165) and overweight/obesity,(166) or comparing two AET protocols in overweight/obese populations(166) and mixed health populations.(167) The former qualitative SR with MA that differentiated for intensity and interval found no between-group significance on the SLP, (166) however the latter found that HDL-C responded significantly to higher-intensity interval training, and that participant characteristics appeared to influence the size of the estimated effect measure.(166)

1.5 Identified Research Gaps

No quantitative SRs satisfying the selection criteria described above could be found that had pooled trial data to determine the effects of AET on HDL, VLDL, LDL, Apos, and associated ratios, for healthy, sub-clinical, healthy + sub-clinical, and clinical populations, see Figure 1.4.



SLP: Standard Lipid Profile; Apos, LPs, Ratios: apolipoproteins, lipoproteins, and ratios; Chol: cholesterol; HDL: high-density lipoprotein; LDL: low-density lipoprotein

Figure 1.4 Lipid outcomes by health status of systematic reviews and meta-analyses published to 31st March 2018

From searches ending 31st March 2018, included SRs with MA reporting the SLP and dating from 2013 focused on mixed health populations(155), diabetic and MetS populations,(141,162), and running studies of healthy populations,(156) see Table 1.4. Quantitative SRs from the same period reporting individual lipids focused on healthy combined with sub-clinical(143) and clinical populations(147), or reported the TC/HDL-C ratio for healthy combined with sub-clinical populations,(143) or LP particles for sub-clinical combined with clinical populations,(154) see Table 1.4. In the three decades previously, only one SR with MA using mixed health populations has reported on HDL subfractions,(153), or the TC/HDL-C ratio,(145) see Table 1.4.

This review of synthesised, quantitative evidence to 31st March 2018, undertaken to identify research questions necessary to inform the research proposal, suggests a number of areas for consideration:

1. re-examining whether intensity, or other intervention covariates, might play a role in explaining the change in lipids;
2. developing protocols for and conducting SRs and MAs which:
    a. examine the effect of AET of a minimum duration of 12 weeks, with a minimum intensity of at least moderate effort, on the SLP of sedentary, sub-clinical populations (free of a MetS and Type 1 or 2 diabetes mellitus diagnosis) without chronic disease;
    b. examine the effect of AET of a minimum duration of 12 weeks, with a minimum intensity of at least moderate effort, on the SLP of sedentary clinical populations free of chronic disease except for MetS and Type 1 or 2 diabetes mellitus;
    c. examine the effect of AET of a minimum duration of 12 weeks, with a minimum intensity of at least moderate effort, on emerging lipid biomarkers such as

apolipoproteins, lipoprotein sub-fractions, and associated ratios in populations as above; and

3. updating the existing literature.

Participant health status in pooled studies / Lipid outcomes reported in pooled studies	Health status not reported	Healthy*	Healthy + subclinical	Healthy + subclinical + clinical	Subclinical	Subclinical + clinical	Clinical
Standard lipid profile or components	Lokey 1989 (SLP) Tran 1985 (SLP)	Hespanhol 2015 (SLP)	Fagard 2006 (SLP) Halbert 1999 (SLP) Ruppar 2014 (TC, HDL-C, LDL-C)	Fikenzer 2015 (SLP) Hwang 2011 (TRG, HDL-C) Kelley 2004; 2005a; 2006a; 2007 (SLP) Zhang 2016 (TC, HDL-C, LDL-C)	Shaw 2006 (TC, TRG, HDL-C)	Chudyk 2011 (TRG, HDL-C, LDL-C) De Nardi 2018 (SLP) Kelley 2012 (SLP) Kodama 2007 (HDL-C) Qui 2014 (HDL-C, LDL-C)	Ostman 2017 (TRG, HDL-C, LDL-C)
Lp subfractions (by core lipid or particle)				Kelley 2006b (HDLC2, C3)		Sarzynski 2015 (VLDL-P, LDL-P; HDL-P)	
Cholesterol ratios or non-HDL-C			Ruppar 2014 (TC/HDL-C)	Kelley 2005b (non-HDL-C); 2007 (TC/HDL-C)			
Apos, Lps, Ratios							

* includes populations in the intervention group who were active prior to the trial, or trials of active participants, otherwise refers to sedentary participants with no sub-clinical or clinical conditions present. F: females; Lp:Lipoprotein

Table 1.4 Systematic reviews with meta-analyses (published as of 31st March 2018) measuring the effects of AET on lipids and clustered by lipid outcome and participant health status

1.6 Aims of this research

This thesis aims to:

1. determine the current state of SR and MA research examining the impact of AET on the SLP and associated lipid biomarkers of populations free of chronic disease other than cardiometabolic conditions such as MetS and Type 1 or 2 diabetes mellitus, with the intent to identify knowledge gaps and research synthesis opportunities;
2. develop robust protocols for conducting quantitative SRs of the effects of AET on the SLP and associated lipid biomarkers of these populations;
3. undertake synthesis of RCTs investigating the impact of AET on the SLP and emerging lipid biomarkers of these populations using quantitative SRs as the research methodology;
4. estimate the ES of AET for lipid indices of importance to the prediction of CVD risk;
5. identify factors likely to impact the ES of AET; and
6. indicate whether an optimal AET protocol can be formulated.

1.7 Conclusion

This chapter has traced how lipids are critical in the development of CVD, as well as combating CVD. As the leading global cause of death and reduction in quality of life, CVD exacts a heavy financial and social cost. The prime condition underlying the commonest types of CVD is atherosclerosis. The pathophysiology of atherosclerosis has been explored, as well as the aetiology and management of dyslipidaemia. The development of dyslipidaemia is predicated upon secondary factors sensitive to, and worsened by behaviours, principally physical inactivity. Dyslipidaemia is treated mainly by pharmacotherapy, although non-specific physical activity (which encompasses generic movement as well as dose-response prescribed aerobic exercise training) is encouraged as a treatment option. The role of lipids in the body and the assignment of CVD risk using lipid values and risk factor cut offs has been appraised. Metabolic Syndrome is described as the presence of 3 or more of a cluster of cardiometabolic biomarkers at specific levels, or pharmacotherapy for any 3 of these. Two of these biomarkers are HDL-C and TRG. Lipids, via dyslipidaemia and atherosclerosis, are arguably the biggest contributing lifetime risk factor for developing CVD, or attributable to CVD deaths.

This chapter reviewed AET. Physical inactivity in Australia accounts for at least one fifth of the health-care costs associated with CVD, estimated at AUD$2.2 billion as of 2016. Less than half the Australian population achieves sufficient PA targets. The earliest studies investigating the effect of AET on lipids demonstrated that AET lowers TC, TRG, and LDL-C, and raises HDL-C. Prescribed volumes and intensities of AET are now commonplace in global government health authority guidelines for managing lipids and other CVD risk biomarkers. Further research has sought to quantify the impacts of different AET protocols on CVD risk biomarkers, including lipids. Metaepidemiological research suggests that PA has equal or greater benefits on cardiovascular mortality outcomes in comparison with pharmaceutical interventions, and a recent meta-review suggests that amongst different forms of PA, AET confers the most benefit on lipids. Aerobic exercise training protocols appear to be manipulable, by varying intervention covariates such as intensity or volume to determine dose-response relationships. The effect of AET on lipids is able to be quantitatively estimated by precisely describing these intervention covariates and obtaining pre- and post-intervention measures of lipids during AET trials investigating the effect of AET on lipids. Thus, it may be possible to formulate an optimal AET prescription for lipid management as a result of pooling such trials and estimating an ES of AET on lipids, and determining which intervention covariates might explain the change in ES.

Finally, this chapter has qualitatively synthesised and examined the quantitative evidence investigating the effects of AET on lipids in populations free of chronic disease other than CVD, MetS and Type 1 or 2 diabetes mellitus. This qualitative appraisal has identified research questions to inform the course of this research proposal, which the following chapters now pursue. Chapter 2 develops a protocol describing the research methodology for estimating the ES of AET on the standard lipid profile in adults free of, and diagnosed with MetS and Type 1 or 2 diabetes mellitus. Chapter 3 develops a protocol describing the research methodology for determining the ES of AET on emerging lipid biomarkers amongst heterogenous populations. Turning to an investigation of whether intensity influences the effect of AET on lipids, Chapter 4 is a comparison of AET intensities and interval types (long steady state vs repeated short): HIIT vs MICT, on the SLP and TC/HDL-C ratio amongst heterogenous populations. Chapters 5-6 are quantitative SRs following the protocol developed and presented in Chapter 2. Chapter 5 estimates the ES of AET on the SLP of a relatively homogenous population, a group free of MetS and Type 1 or 2 diabetes mellitus, and other chronic disease. In addition, Chapter 5 explores whether study and intervention covariates help explain change in lipids. Chapter 6 estimates the ES of AET on the SLP on a group diagnosed with MetS and/or Type 1 or 2 diabetes, but otherwise free of chronic disease, and indicates which study and intervention covariates might help explain change in lipids. Chapter 7 is a quantitative SR following the protocol developed and presented in Chapter 3. Chapter

7 estimates the ES of AET on multiple emerging lipid biomarkers in heterogenous populations, free of chronic disease but diagnosed with and without MetS, and/or Type 1 or 2 diabetes mellitus. Study and intervention covariates explaining change in the estimated ES of these emerging lipid biomarkers are identified. Chapter 8 draws together the results of the four quantitative reviews investigating the effects of AET on the SLP and emerging lipid biomarkers, and indicates a possible path for future research.

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2 CHAPTER 2 – DETERMINING THE EFFECT SIZES OF AEROBIC EXERCISE TRAINING ON THE STANDARD LIPID PROFILE OF ADULTS FREE OF, AND DIAGNOSED WITH, THE METABOLIC SYNDROME: PROTOCOL FOR TWO SYSTEMATIC REVIEWS WITH UNIVARIATE META-ANALYSES AND META-REGRESSIONS OF RANDOMISED CONTROLLED TRIALS

2.1 Manuscript information – submitted 30th July 2020

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STATEMENT OF AUTHORSHIP

On each occasion that research is made public the forms 'Statement of Authorship' and 'Location of Data' must be filled out, signed and lodged with the Head of the Department of which the principal researcher is a member. If, for any reason, one or more co-authors are unavailable or otherwise unable to sign the statements, the Head of Department may sign on their behalf, noting the reason for their unavailability. Heads of Departments must keep copies of these statements in departmental files.

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(a) conception and design, or analysis and interpretation of data, and
(b) drafting the article or revising it critically for important intellectual content, and
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An author's role in a research output must be sufficient for that person to take public responsibility for at least part of the output in that person's area of expertise. No person who is an author, consistent with this definition, must be excluded as an author without their permission in writing.

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2.2 Statement of authors' contribution

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We, the PhD candidate and the candidate's Principal Supervisor, certify that all co-authors have consented to their work being included in the thesis and they have accepted the candidate's contribution as indicated in the *Statement of Originality*.

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2.4 Full Manuscript as submitted

Determining the effect size of aerobic exercise training on the standard lipid profile of adults free of, and diagnosed with, Metabolic Syndrome: A protocol for two systematic reviews with univariate meta-analyses and meta-regression of randomised controlled trials

Short title: The impact of aerobic exercise training on lipids: Protocol for 2 quantitative reviews

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Declarations

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excluding Abstract (1), References (73), Tables (0), and Legends (0).

ABSTRACT

Objectives To determine the effect size (ES) of aerobic exercise training (AET) on the standard lipid profile of two groups of adults: those with and those free of Metabolic Syndrome (MetS); and determine if study or intervention covariates explain change in outcomes.

Design Systematic review and univariate meta-analyses of randomised controlled trials (RCTs).

Data sources English language searches of online databases.

Eligibility criteria We will include published RCTs of adult humans with intervention and non-exercising control populations ≥10; an AET intervention duration ≥12 weeks of at least moderate intensity (>40% VO_{2MAX}); and reporting pre/post measurements. Trials of elite athletes, subjects with chronic disease (except diabetes mellitus or MetS), or pregnant/lactating, or trials testing diet/medications, or resistance/isometric/unconventional training, will be excluded.

Results We follow the Preferred Reporting Items for Systematic Reviews and Meta-Analysis statement. We will perform univariate meta-analysis to investigate the effects of AET on the standard lipid profile, and use a random raw mean difference, Knapp-Hartung adjusted, 95% confidence interval, model. Heterogeneity will be evaluated using fail-safe N, rank correlation, trim-and-fill, and regression tests, and precision and standard error funnel plots. Multivariate meta-regression will determine if study or intervention variables explain change in outcomes. Analyses will be performed in Comprehensive Meta-Analysis 3.0. Study quality will be evaluated using TESTEX.

Conclusion We aim to estimate the ES of AET of the standard lipid profiles of adults with and free of MetS, and if any study or intervention covariates explain change in outcomes.

PROSPERO ID CRD42019145560 (non-MetS); CRD42020151925 (MetS)

Keywords Lipids, Cholesterol, Triglycerides, Lipoprotein, Physical Activity

1.0 INTRODUCTION

Metabolic Syndrome (MetS) and MetS factors are implicated in cardiovascular disease (CVD).[1] Dyslipidaemia, an abnormally elevated or lowered blood lipid profile, is a significant MetS risk factor of CVD;[2, 3] ischemic stroke;[4] non-alcoholic fatty liver disease (NAFLD);[5] and chronic pancreatitis.[6, 7] Moderate- and vigorous- intensity aerobic exercise training (AET) positively impacts MetS factors, thus lowering CVD risk.[8, 9] Aerobic or moderate intensity is defined as 3-6 metabolic equivalents (METS); 40-60% of heart rate reserve (HRR) or maximal oxygen uptake (VO_{2MAX}); 55-70% of maximal heart rate (MHR); or rate of perceived effort (RPE) of 11-13 on the Borg scale.[10] Aerobic exercise training has been shown to reduce elevated total cholesterol (TC), triglycerides (TRG) and low-density lipoprotein cholesterol (LDL-C), and increases high-density lipoprotein cholesterol (HDL-C) in sub-clinical and clinical populations.[11-14]

A recent metaepidemological review of randomised controlled trials (RCTs) found physical activity interventions to have equal or greater beneficial effects on mortality outcomes (secondary prevention of CVD) compared with pharmaceutical interventions.[15] Aerobic physical activity as a first treatment option for dyslipidaemia in sub-clinical populations and as a concurrent treatment in clinical populations is generally preferred to pharmaceutical intervention,[16-20] since pharmaceutical intervention is not without side effects[21, 22] and represents a financial cost to health systems.[23-25] Lack of aerobic physical activity has negative consequences for lipids.[26]

Various systematic reviews (SRs) have examined the impact of AET on lipids without conducting meta-analyses (MAs).[14, 27-34] Quantitative reviews investigating the impact of AET have focused on single lipids,[35] specific genders,[36-38] change in baseline body-weight,[39] mixed health status,[36, 37, 40, 41] or modalities of AET (running,[42] walking,[43] high intensity intervals versus moderate intensity steady state[40, 41, 44]). One

SR and MA reviewed the effects of aerobic and resistance exercise between normolipidaemic and dyslipidaemic adults.[45] Another SR and MA concentrated on determining the effectiveness, measured by achieved intensity, of AET intervention protocols.[13] A Cochrane Review reported on lipids as a secondary outcome only using 3 studies.[46] The results of these SRs and MAs reveal a range of estimated effect sizes (ES) varying according to participant and intervention characteristics.

Studies have indicated a minimum of AET (>180 minutes per week at >40% VO_{2MAX}, or >1200 kcal/week) may be necessary to induce positive changes to lipids.[47, 48] Some SRs and MAs have concluded longer AET intervention and session duration results in greater effects,[35, 42] and a minimum effective AET volume (>45 minutes per session for 3-4 sessions per week for duration >26 weeks at >65% VO_{2MAX}) results in significant positive changes to lipids.[13] Similarly, cholesterol lowering medication dosages which are steadily increased result in greater effects than fixed dosages on lowering targeted lipids or raising HDL-C.[20, 49, 50] The full reduction in risk of ischaemic heart disease is achieved within five years of lowering TC by 0.6 mmol/L.[51] Both cholesterol lowering medication and AET require a minimum period to show effects, however trials of pharmacological intervention are generally conducted for longer periods[52] than trials of AET intervention.[53]

To the best of our knowledge, no comprehensive SR and MA pooling the outcomes of only RCTs comparing the effects of minimum-intensity AET, with no exercise, on the standard lipid profile[54] of adults diagnosed with, and free of MetS, has been conducted.

We aim to conduct one SR and MA determining the ES of AET on TC, TRG, HDL-C, and LDL-C in non-MetS populations, and one SR and MA for MetS populations. We also wish to discuss our findings in the context of statin therapies, since statins represent 98% of cholesterol lowering medication prescribed.[55]

2.0 METHODS

These SRs and MAs have been designed by GNW and NS and registered in the International Prospective Register of Systematic Reviews (PROSPERO)[56]: CRD42019145560 (non-MetS); CRD42020151925 (MetS). Our results will be presented according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[57]

2.1 Study Eligibility

We will include studies if the study design is that of an RCT comparing an AET intervention against a non-exercising control group. The study must report pre-post intervention and control measurements of the standard lipid profile as primary or secondary outcomes in humans 18 years.

2.1 Data Sources

We will conduct systematic online searches of PubMed, EMBASE, all Web of Science and EBSCO health and medical databases. We will search for RCTs published during this period in English or bilingual journals. Searches will include a mix of Medical Subject Headings (MeSH) and free text terms such as aerobic exercise training, physical activity, endurance exercise, lipids, lipoproteins, triglycerides, and cholesterol. Other SRs and reference lists of papers will be hand searched for additional RCTs.

2.3 Study Selection

Four researchers (GNW, ET, AP, and VN) will search online databases, and review their search results on the basis of title and abstract independently, using Microsoft Excel (MS Excel Version 16.31 2019). The same 4 researchers will independently assess and review the full PDF texts of potentially eligible RCTs. In the event of disagreement over inclusion of RCTs in the final list, NS will be consulted. We will exclude RCTs testing diet and pharmaceutical interventions, and studies of intervention and control group population sample sizes (N) < 10.[58] We will use Endnote X.9 (or later) as the citation management software.

2.3.1 Participants

Studies of participants with chronic disease, other than Type 1 or 2 diabetes mellitus (T1D, T2D) or MetS, will be excluded. We will exclude RCTs of participants that are of pregnant or lactating females, or elite athletes.

2.3.2 Intervention

Since an AET intervention of at least moderate intensity for a period of 12 weeks is considered the minimum time to affect lipid profiles,[45] we will exclude any RCTs for which the AET intervention duration is less. If the RCT describes neither prescribed steady state nor interval AET with an intended minimum moderate intensity effort (> 40% VO_{2MAX}),[10] it will be excluded. We place no restrictions on AET session time or type, however RCTs which include either an isometric, unconventional, resistance- or combined-training intervention, or a dietary or pharmaceutical intervention, will be excluded, unless a separate AET-only group is compared against a non-exercising control group. We will exclude RCTs evaluating different AET interventions unless compared against a non-exercising control group. Studies which fail to provide details of the AET protocol, such as session duration, intensity, number of sessions in the intervention, or other details which will prevent estimation of volume of exercise if not specifically reported, will be excluded.

2.3.3 Comparator

An AET intervention is required to be compared to a non-exercising control group.

2.3.4 Outcomes

Pre- and post-intervention measurements or equivalent, in mass (mg/dL) or molar (mmol/L) units for the standard lipid profile, for each of intervention and non-exercising control groups, will be required to be reported. Where measurements are given in conventional units (mg/dL), these will be multiplied by 0.02586 to convert to the International System (SI) molar unit mmol/L.[59] We will contact lead authors via email regarding missing data or outcome measurement scales as necessary. Outcome data presented graphically will be converted to numerical values using WebPlotDigitzer (Version 4.2, 2019) by AP and VN independently.

2.4 Data Extraction

Pre-established data extraction sheets will be designed by GNW, using Microsoft Excel (Version 16.31 2019). The list of included RCTs will be divided between and randomly distributed to 3 teams comprising AP and TvdT, AM and GNW, and ET and NS. Each team member will extract data independently. Each set of extracted data will be reviewed by the other team member. In the case of discrepancies or disagreement, GNW will be consulted. We will extract the following data for each RCT: 1) author(s), year of publication and study design; 2) demographic and clinical characteristics; 3) AET intervention and control protocols; 4) intervention and control group values before and after intervention for the standard lipid profile. We will extract any of pre- and post mean (M) or mean difference (MD), pre- and post standard deviation (SD) or change in SD, standard error (SE) or change in SE, pre- and post within- or between group *P* values or change in *P* values, and 95% within- or between group confidence intervals (CI) or change in CIs for each found outcome.

2.5 Study Quality

We will assess each RCT using the validated Tool for the Assessment of Study Quality and Reporting in Exercise (TESTEX),[60] a 15-point scale specific to exercise training studies for determining study quality and bias. A score 10 is deemed good study quality and reporting.[61] Within-study risk of bias will be determined by evaluating an additional 7 factors (see Supplementary Materials (SM) Table 1), and awarding either low, medium or high within-study risk of bias scores. The RCTs will be divided between and randomly distributed to 3 researchers (ET, AP, and VN), who will extract the relevant data independently according to the TESTEX criteria. Data sheets of the extracted TESTEX variables will be cross-checked by GNW, TvdT and AM for accuracy. Disputes will be mediated by NS. A study quality sub-analysis of RCTs grouped according to a TESTEX score 10 and a within-study risk evaluation of low-to-medium will be conducted.

2.6 Data Synthesis

Statistical analyses will be performed using Comprehensive Meta-Analysis (CMA) 3.0 (Biostat, Inc., New Jersey, USA). A continuous univariate random effects model[62] with Hartung-Knapp-Sidik-Jonkman adjustment[63] is intended to be used with the effects measure of raw MD, a 5% level of significance, and a 95% CI, to report change in outcome measures. Reported raw MD, SD, and N for each of intervention and control groups will be pooled. If these values are not explicitly reported, we will calculate the missing data if possible. As necessary, the MD will be calculated by subtracting $M_{pre\text{-}treatment}$ from $M_{post\text{-}treatment}$. The SD of the MD was calculated as follows: SD = square root [$(SD_{pre\text{-}treatment})^2 + (SD_{post\text{-}treatment})^2 - (2r \times SD_{pre\text{-}treatment} \times SD_{post\text{-}treatment})$], assuming a correlation coefficient r = 0.5, considered a conservative estimate.[64] Per group outcome data, whether reported for intention-to-treat (ITT) or for non-ITT analysis, will be pooled. The data sets will be divided equally between GNW and NS. These 2 researchers will independently enter the data in CMA, and review each other's entry files for accuracy prior to performing analyses.

2.6.1 Meta-analysis and Sub-analyses

A cumulative random MA will be conducted to assess the impact of AET over time, and RCTs will be sorted chronologically to show the cumulative effect of each.

Sub-analyses will be conducted in CMA for study quality using TESTEX scores (RCTs with a score 10) and within-study bias analysis (low to medium). A leave-one-out (K-1, where K = total number of pooled RCTs, and each RCT is excluded once) sensitivity analysis will be also performed to evaluate the influence of each RCT on the ES of pooled data.[65]

2.6.2 Small-Study Effects

Analysis of small study effects will be conducted using CMA. We will evaluate the risk of small study effects using each of Rosenthal's failsafe N, Duval and Tweedie's trim-and-fill, Egger's regression test, Begg and Mezumdar's rank correlation test, and precision and standard error funnel plots. Data will be entered into CMA by 2 researchers (GNW and NS) independently, and cross-checked for accuracy. A third researcher (MW) will conduct the analyses.

2.6.3 Meta-regression

Multivariate meta-regression will be conducted in CMA without adjustment for *P* values to determine whether any *a priori* covariates might explain a change in statistically significant point estimates. *A priori* AET intervention covariates are: intensity (percentage of VO_{2MAX}); minutes per session; sessions per week; and duration in weeks. These covariates have been shown to influence lipid outcomes.[13, 35, 42] Other *a priori* covariates are: year of publication (potential for improved laboratory testing in recent RCTs); total study participants N (potential for under-powered studies to influence outcomes); and TESTEX study quality and risk of bias scores (potential for better quality RCTs to influence outcomes). Data will be entered in CMA by GNW and validated by NS and MW. Using a random effects maximum likelihood model with a Hartung-Knapp adjustment, we will regress the intercept and each AET covariate against the dependent variable MD. The same regression will be repeated for study covariates.

2.6.4 Heterogeneity

Heterogeneity will be quantified in CMA using the Q statistic, and the corresponding *P* value, τ^2, τ, and I^2.[62] The Q statistic, and the corresponding *P* value, compares the differences among the calculated ES; τ^2 measures absolute between-study heterogeneity and the estimated SD (τ).[62] The relative measure of heterogeneity I^2 ranges from 0% (complete homogeneity) to 100% (complete heterogeneity).[66] If necessary, a further sensitivity analysis, using pooled analysis 95% CI boundaries, will be conducted.[67]

3.0 RESULTS

The search and inclusion process will presented using a PRISMA flow diagram[57]. Data will be extracted, pooled and analysed from the final list of RCTs.

3.1 Study, Participant, and Intervention Characteristics

Participant and intervention details of included RCTs will be presented in table format. Interventions will be described according to duration, number of sessions per week, number of minutes per session, intensity of the intervention (in VO_{2MAX}), as well as type of AET eg walking, swimming, etc.

3.2 Comparative Outcomes

The changes in TC, TRG, HDL-C, and LDL-C will be reported in a tabular format as a point estimate, along with CIs, *P* value, and individual group N and combined total N. Sensitivity analyses (K-1) for statistically significant outcomes will be reported in SM tables. The cumulative random MA of each outcome will be presented chronologically as a table and graphically showing the study name, outcome name, cumulative statistics and sample size, study quality score, CIs, and weights (random and relative). These figures will be generated using CMA.

3.3 Study Quality and Reporting

The TESTEX scores, median and range, and within-study risk of bias scores, will be presented in SM tables. Sub-analyses using TESTEX scores 10 and risk of bias scores of low-medium will test for point estimate significance for each analysed outcome previously shown to be significant using CMA. The cumulative random MA of each outcome that remains (or attains significance) from sub-analysis will be presented graphically showing the study name, outcome name, cumulative statistics and sample size, study quality score, CIs, and weights (random and relative). These figures will be generated using CMA.

3.4 Lipid Extraction Methodology

The lipid extraction method will be examined for adherence to standard accepted methods (fasted, rested, seated or supine position for blood draw).

3.5 Small Study Effects

The number of included studies will be compared to the minimum number required to perform small study effect analyses.[68] Data will be presented as tables and graphically in SM. The figures and tables will be generated using CMA.

3.6 Meta-regression

Tables will be generated using CMA and presented in SM.

3.7 Heterogeneity

The degree of absolute between-study (τ^2) and relative heterogeneity (I^2) for each analysed outcome will be calculated and presented.

4.0 DISCUSSION

Aerobic exercise training has been shown to raise HDL-C and lower TC, TRG, and LDL-C. We will report whether our analysis of changes in the lipid profile reflects previous work analysing the effect of AET. We will discuss our findings in the context of the effects of statin therapies. We will indicate whether independent intervention variables contribute to a change in outcomes, as others suggest.[13, 35, 42, 47, 48] On the basis of the TESTEX analysis of study quality, we will indicate how researchers might better present their findings.

4.1 Strengths and Limitations of this Quantitative Review

To the best of our knowledge, these SRs and MAs are the first that seek to compare the effects of AET differentiated by a minimum required intensity and duration against no exercise on the standard lipid profile of separate non-MetS and MetS populations. We will follow a rigorous inclusion/exclusion protocol to ensure minimisation of confounding factors amongst the RCT populations.[69]

A potential limitation of our work is the reliance on aggregated RCT data and not individual subject data.[70, 71] Secondly, we will search only using English language terms, reducing the pool of available studies for selection and possibly introducing small study effects. We intend to exclude studies with intervention and comparison groups of N < 10, unless we have too few studies to perform an SR and MA, and it is possible that intervention duration will be skewed closer to the minimum of 12 weeks, which may decrease the ES. Heterogeneity may show that our results should not be pooled and small study effects may find that our results are due to the presence of bias. The inclusion of AET protocols starting from the minimum of moderate intensity (> 40% VO_{2MAX}) may elicit very small changes in lipids,[13] and measurement bias (digital vs analog) of achieved AET volume in the included RCTs may impact ES. Since we exclude unconventional AET protocols such as yoga, the ES may be impacted.

5.0 CONCLUSION

Our SRs and MAs intend to pool data and determine the effect size of AET programs of a minimum intensity and duration on the standard lipid profile in adults diagnosed with, and free of, MetS. We intend to identify whether any or all covariates influence the change in outcomes. We hope to augment the evidence suggesting AET mitigates CVD risk through positively impacting the standard lipid profile.

Supplementary Materials

Author Year	Study non-randomised or randomised	Minimum compliance level set	Habitual medication use reported	Dropout reason reported	Baseline fitness and effort determined	> 50% sessions supervised	Effort monitoring and measurement device	Risk of bias assesment low, medium, or high

SM Table 2.1Within-study Risk of Bias Factors Score Table

Methodology:

We award either of low or high for the following factors as per SM Table 2.1:

1. Study non randomised or randomised low if randomised, high if non randomised;[1]
2. For intervention groups, a minimum level of compliance to be counted as having participated in the intervention group or control group low if a minimum level of compliance was set or reported, high if there was no minimum compliance level;
3. Habitual medication use reported low if reported, high if not reported;
4. Drop-out reasons given low if reported, high if not reported;
5. Baseline fitness and effort determined low if baseline fitness and effort was measured, high if not determined;
6. > 50% of sessions supervised low if50% of sessions were supervised, high if not; and
7. Effort monitoring and measurement devices low if digital recording devices were used, high if analog or no device.

Studies are to be scored overall low, medium, or high risk of bias according to the number of times either "low" or "high" is awarded. A low risk of bias is scored for 0 2 instances of "high", a medium risk of bias is scored for 3-4 instances of "high", and a high risk of bias is scored for 5-7 instances of "high". All factors are equally weighted.

[1] All studies eligible for inclusion must be randomised, but we record as a confirmation measure.

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3 CHAPTER 3 – THE EFFECTS OF AEROBIC EXERCISE TRAINING ON LIPOPROTEIN SUB-FRACTIONS, APOLIPOPROTEINS, AND ASSOCIATED RATIOS: PROTOCOL FOR A SYSTEMATIC REVIEW WITH MULTIVARIATE META-ANALYSIS AND META-REGRESSION OF RANDOMISED CONTROLLED TRIALS

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On each occasion that research is made public the forms 'Statement of Authorship' and 'Location of Data' must be filled out, signed and lodged with the Head of the Department of which the principal researcher is a member. If, for any reason, one or more co-authors are unavailable or otherwise unable to sign the statements, the Head of Department may sign on their behalf, noting the reason for their unavailability. Heads of Departments must keep copies of these statements in departmental files.

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Authorship is defined as substantial participation, where all the following conditions are met:

(a) conception and design, or analysis and interpretation of data, and
(b) drafting the article or revising it critically for important intellectual content, and
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3.2 Statement of authors' contribution

Higher Degree Research Thesis by Publication
University of New England

STATEMENT OF AUTHORS' CONTRIBUTION

We, the PhD candidate and the candidate's Principal Supervisor, certify that all co-authors have consented to their work being included in the thesis and they have accepted the candidate's contribution as indicated in the *Statement of Originality*.

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We, the PhD candidate and the candidate's Principal Supervisor, certify that the following text, figures, diagrams, tables, labels, keys and legends are the candidate' original work.

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3.4 Full manuscript as submitted

The effects of aerobic exercise training on lipoprotein sub-fractions, apolipoproteins, and lipid ratios: A protocol for a systematic review and multivariate meta-analysis and meta-regression of randomised controlled trials.

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Declarations

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ABSTRACT

Background and aims Compared with the standard lipid profile, lipoprotein sub-fractions, apolipoproteins, and associated ratios more effectively predict cardiovascular disease risk. We aim to describe a protocol for a systematic review and multivariate meta-analysis determining the effects of aerobic exercise training (AET) on, and identify covariates associated with change in, these biomarkers.

Methods We will search online databases from inception to June 2020 for published RCTs of adult humans with intervention and non-exercising control populations 10; an AET intervention duration 12 weeks of at least moderate intensity (> 40% VO_{2MAX}); and reporting pre/post measurements. Subjects with chronic disease (except diabetes mellitus Type 1-2) or pregnant/lactating, as well as trials testing diet/medications, or resistance/isometric/ unconventional training, will be excluded. We will join outcomes according to atherogenicity and use a random raw mean difference, Knapp-Hartung adjusted, 95% confidence interval, model. Heterogeneity will be evaluated using classic and fail-safe N, rank correlation, trim-and-fill, and regression tests, and precision and standard error funnel plots. Multivariate meta-regression will determine if study or intervention covariates explain change in outcomes. Analyses will be performed in Comprehensive Meta-Analysis 3.0. Study quality will be evaluated using TESTEX.

Results We will report RCT and intervention characteristics; RCT quality; small study effects; estimated effect sizes, confidence intervals, *P* values, and absolute and relative heterogeneity for each biomarker outcome; as well as goodness of fit for explanatory covariates.

Conclusion We hope to provide evidence of the effect of AET on lipoprotein sub-fractions, apolipoproteins, and associated ratios.

PROSPERO ID CRD42020151925.

Keywords Lipids, Cholesterol, Triglycerides, Lipoprotein, Apolipoprotein, Aerobic Exercise

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Key Points

1. Lipoprotein sub-fractions, apolipoproteins, and associated ratios more effectively predict cardiovascular risk than the standard lipid profile, which does not include these biomarkers.

2. Aerobic exercise training positively impacts the standard lipid profile. We wish to determine how aerobic exercise training affects apolipoproteins, lipoprotein sub-fractions, and ratios.

3. A multivariate meta-analysis is appropriate for correlated or non-independent outcomes, or for missing outcomes, when a large number of studies are to be analysed.

1.0 INTRODUCTION

The standard lipid profile biomarkers used to evaluate cardiovascular (CVD) risk comprise total cholesterol (TC), triglycerides (TRG), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C).[1] Dyslipidaemia, an abnormally elevated or lowered lipid profile, is a risk factor of CVD;[2, 3] ischemic stroke;[4] non-alcoholic fatty liver disease (NAFLD);[5] and chronic pancreatitis.[6, 7] A recent 17-year follow-up study of females concluded TC/HDL-C was a potent predictor of CVD events.[8] A systematic review (SR) collating data from several large observational studies found CVD risk was better predicted by TC/HDL-C and LDL-C/HDL-C ratios than by the standard lipid profile biomarkers.[9]

Apolipoproteins (Apo) A1 and A2 are the largest protein constituent of HDL.[10] The Apo B100 contains an LDL-receptor responsible for the uptake of LDL, and serves to assemble and secrete VLDL.[11] Raised levels of Apo A1 and A2 are considered to be antiatherogenic, while increased levels of Apo B100 and VLDL are atherogenic.[12] Apolipoproteins and the Apo B100/Apo A1 ratio have been investigated as biomarkers more sensitive to identifying CVD risk than TC, TRG, and LDL-C.[13-15] Systematic reviews have examined the risk prediction power of Apo A1, A2, and B100 for cardiovascular risk and found Apo B100 and the Apo B100/Apo A1 ratio improved prediction.[16-18] Lowered levels of lipoprotein sub-fractions HDL2 and HDL3 are considered to increase CVD risk, although HDL3 may be less protective in the presence of Metabolic Syndrome (MetS).[19] Sub-fractions of HDL-C may be more relevant in identifying CVD risk than HDL-C.[15]

Lack of aerobic physical activity has negative consequences for lipids.[20] Aerobic exercise training (AET) positively impacts dyslipidaemia,[21-24] thus lowering CVD risk.[25, 26] Aerobic exercise training of moderate intensity is defined as 3-6 metabolic equivalents (METS); >40% of heart rate reserve (HRR) or maximal oxygen uptake (VO_{2MAX}); 55-70% of maximal heart rate (MHR); or rate of perceived effort (RPE) of 11-13 on the Borg scale.[27]

Various SRs, with and without meta-analysis (MA), have examined the impact of AET on the standard lipid profile biomarkers.[23, 24, 28-47] Studies have found AET of at least 180 minutes per week at >40% VO_{2MAX} or >1200 kcal/week is necessary to induce positive changes to TC, TRG, HDL-C, LDL-C.[48, 49] Quantitative SRs have concluded longer AET intervention and session duration results in greater effects,[33, 38] and a minimum effective AET volume (>45 minutes per session for 3-4 sessions per week for duration >26 weeks at >65% VO_{2MAX}) results in significant positive changes to the standard lipid profile.[23]

To the best of our knowledge, no comprehensive SR with MA and meta-regression (MR) has investigated the effects of AET on lipoprotein sub-fractions, Apo A1, A2, and B100, and lipid and Apo ratios in adults. This may be a result of the under-reporting of apolipoproteins, or reporting in differing units of measurement, thus limiting the number of pooled analyses. A meta-analytical technique, appropriate for large numbers of studies with missing or multiple correlated and non-independent outcomes, is multivariate (MV) MA.[50, 51]

We aim to conduct an SR and multivariate meta-analysis/meta-regression (MVMAMR) comparing the effects of AET achieving a minimum aerobic intensity (> 40% VO_{2MAX}) or equivalent, against non-exercising control groups on lipoprotein sub-fractions, apolipoproteins, and associated ratios. Further, we intend to investigate whether RCT study covariates such as year of publication, number of RCT participants, study quality score, and number of extracted outcomes, as well as AET intervention covariates such as volume, intensity, frequency, session duration and intervention duration, explain change in outcome measures.

2.0 METHODS

This SR and MVMAMR has been designed by GNW and NS and registered in the International Prospective Register of Systematic Reviews (PROSPERO)[52] CRD42020151925. Our results will be presented according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[53]

2.1 Study Eligibility

We will include studies if the study design is that of an RCT comparing an AET intervention against a non-exercising control group. The study must report pre-post intervention and control measurements of lipid and Apo ratios, lipoprotein sub-fractions, and apolipoproteins as primary or secondary outcomes in humans 18 years.

2.2 Data Sources

We will conduct systematic online searches of PubMed, EMBASE, all Web of Science and EBSCO health and medical databases from inception of the database until June 2020. We will search for RCTs published during this period in English or bilingual journals. Searches will include a mix of MeSH and free text terms such as aerobic exercise training, physical activity, endurance exercise, lipids, lipoproteins, apolipoproteins, triglycerides, and cholesterol. Other SRs and reference lists of papers will be hand searched for additional RCTs.

2.3 Study Selection

Four researchers (GNW, ET, AP, and VN) will search online databases, and review their search results on the basis of title and abstract independently, using Microsoft Excel (MS Excel Version 16.31 2019). The same 4 researchers will independently assess and review the full

PDF texts of potentially eligible RCTs. In the event of disagreement over inclusion of RCTs in the final list, NS will be consulted. We will exclude RCTs testing diet and pharmaceutical interventions, and studies of intervention and control group population sample sizes (N) < 10.[54] We will use Endnote X.9 (or later) as the citation management software.

2.3.1 Participants

Studies of adult participants with no chronic disease, other than Type 1 or 2 diabetes mellitus or Metabolic Syndrome (MetS), will be included. We will exclude RCTs of participants that are of pregnant or lactating females, or elite athletes.

2.3.2 Intervention

Since an AET intervention of at least moderate intensity for a period of 12 weeks is considered the minimum time to affect lipid profiles,[32] we will exclude any RCTs for which the AET intervention duration is less. If the RCT describes neither prescribed steady state nor interval AET with an intended minimum moderate intensity effort (> 40% VO_{2MAX}),[27] it will be excluded. We place no restrictions on AET session time or type, however RCTs which include either an isometric, unconventional, resistance- or combined-training intervention, will be excluded, unless a separate AET-only group is compared against a non-exercising control group. We will exclude RCTs evaluating different AET interventions unless compared against a non-exercising control group. Studies which fail to provide details of the AET protocol, such as session duration, intensity, number of sessions in the intervention, or other details which will prevent estimation of volume of exercise if not specifically reported, will be excluded.

2.3.3 Comparator

An AET intervention is required to be compared to a non-exercising control group.

2.3.4 Outcomes

Pre- and post-intervention measurements or equivalent, in mass (mg/dL) or molar (mmol/L) units for lipoprotein sub-fractions and apolipoproteins, and associated ratios and lipid ratios, for each of intervention and non-exercising control groups, will be required to be reported. Where lipid sub-fraction measurements are given in mass as mg/dL, these will be multiplied by 0.02586 to convert to the International System (SI) molar unit mmol/L.[55] Apolipoprotein measurements, whether reported using SI or conventional units, will remain unconverted. We will contact lead authors via email regarding missing data or outcome measurement scales as necessary. Outcome data presented graphically will be converted to numerical values using WebPlotDigitzer (Version 4.2, 2019) by AP and VN independently.

2.4 Data extraction

Pre-established data extraction sheets will be designed by GNW, using Microsoft Excel (Version 16.31 2019). The list of included RCTs will be divided between and randomly distributed to 3 teams comprising AP and TvdT, AM and GNW, and ET and NS. Each team member will extract data independently. Each set of extracted data will be reviewed by the other team member. In the case of discrepancies or disagreement, GNW will be consulted. We will extract the following data for each RCT: 1) author(s), year of publication and study design; 2) demographic and clinical characteristics; 3) AET intervention and control protocols; 4) intervention and control group values before and after intervention for any Apo or lipoprotein sub-fractions, and associated ratios. We will extract any of pre- and post mean (M) or mean difference (MD), pre- and post standard deviation (SD) or change in SD, standard error (SE) or change in SE, pre- and post within- or between group *P* values or change in *P* values, and 95% within- or between group confidence intervals (CI) or change in CIs for each found outcome.

2.5 Study Quality

We will assess each RCT using the validated Tool for the Assessment of Study Quality and Reporting in Exercise (TESTEX),[56] a 15-point scale specific to exercise training studies for determining study quality and bias. A score 10 is deemed good study quality and reporting.[57] Within-study risk of bias will be determined by evaluating an additional 7 factors (see Supplementary Materials (SM) Table 3.1) and awarding either low, medium or high within-study risk of bias scores. The RCTs will be divided between and randomly distributed to 2 researchers (ET and GNW), who will extract the relevant data independently according to the TESTEX criteria. Data sheets of the extracted TESTEX variables will be cross-checked between ET and GNW for accuracy. The results will be independently reviewed by a third researcher (AM). Disputes will be mediated by NS. A study quality sub-analysis of RCTs grouped according to a TESTEX score 10 and a within-study risk evaluation of low-to-medium will be conducted.

2.6 Data Synthesis

Statistical analyses will be performed using Comprehensive Meta-Analysis (CMA) 3.0 (Biostat, Inc., New Jersey, USA). To allow for multiple missing and correlated outcomes,[50, 51] a continuous multivariate random effects model[58] with Hartung-Knapp-Sidik-Jonkman adjustment[59] is intended to be used with the effects measure of raw MD, a 5% level of significance, and a 95% CI, to report change in outcome measures. Outcomes will be joined according to atherogenicity, change of effect size (ES) direction, and unit of measurement (mmol/L or mg/dL). Outcomes unable to be joined will be analysed with a univariate model as described above. Reported raw MD, SD, and N for each of intervention and control groups will be pooled. If these values are not explicitly reported, we will calculate the missing data if possible. As necessary, the MD will be calculated by subtracting $M_{pre\text{-}treatment}$ from $M_{post\text{-}}$

$_{treatment}$. The SD of the MD was calculated as follows: SD = square root [$(SD_{pre\text{-}treatment})^2 + (SD_{post\text{-}treatment})^2 - (2r \times SD_{pre\text{-}treatment} \times SD_{post\text{-}treatment})$], assuming a correlation coefficient r = 0.5, considered a conservative estimate.[60] Per group outcome data, whether reported for intention-to-treat (ITT) or for non-ITT analysis, will be pooled. The data sets will be divided equally between GNW and NS. These 2 researchers will independently enter the data in CMA, and review each other's entry files for accuracy prior to performing analyses.

2.6.1 Meta-analysis and Sub-analyses

A cumulative random MVMA will be conducted for joint outcomes to assess the impact of AET over time. The CMA software package allows outcomes to be joined by using the mean of the outcomes reported on a per RCT basis, which assists in avoiding Type 1 errors. In each cumulative random MVMA, RCTs will be sorted chronologically to show the cumulative effect of each RCT. For outcomes unable to be joined (eg ES direction, unit of measurement), a cumulative random univariate MA will be used to the impact of AET over time with RCTs sorted chronologically.

Sub-analyses will be conducted in CMA for study quality using TESTEX scores (RCTs with a score 10) and within-study bias analysis (low to medium). A leave-one-out (K-1, where K = total number of pooled RCTs, and each RCT is excluded once) sensitivity analysis will be also performed to evaluate the influence of each RCT on the ES of pooled data.[61]

2.6.2 Small-Study Effects

Analysis of small study effects will be conducted using CMA. We will evaluate the risk of small study effects using each of Rosenthal's failsafe N, Orwin's failsafe N, Duval and Tweedie's trim-and-fill, Egger's regression test, Begg and Mezumdar's rank correlation test, and precision and standard error funnel plots. Data will be entered into CMA by 2 researchers

(GNW and NS) independently, and cross-checked for accuracy. A third researcher (MW) will conduct the analyses.

2.6.3 Meta-regression

Meta-regression will be conducted in CMA without adjustment for *P* values to determine whether any *a priori* covariates might explain a change in statistically significant point estimates. *A priori* AET intervention covariates are: intensity (percentage of VO_{2MAX}); minutes per session; sessions per week; and duration in weeks. These covariates have been shown to influence lipid outcomes.[23, 33, 38] Other *a priori* covariates are: year of publication (potential for improved laboratory testing in recent RCTs); total study participants N (potential for under-powered studies to influence outcomes); number of extracted relevant outcomes (changes in similar outcomes are correlated); and TESTEX study quality and risk of bias scores (potential for better quality RCTs to influence outcomes). Data will be entered in CMA by GNW and validated by NS and MW. Using a random effects maximum likelihood model with a Hartung-Knapp adjustment, we will regress the intercept and each AET covariate against the dependent variable MD. The same regression will be repeated for study covariates.

2.6.4 Heterogeneity

Heterogeneity will be quantified in CMA using the Q statistic, and the corresponding *P* value, τ^2, τ, and I^2.[58] The Q statistic, and the corresponding *P* value, compares the differences among the calculated ES; τ^2 measures absolute between-study heterogeneity and the estimated SD (τ).[58] The relative measure of heterogeneity I^2 ranges from 0% (complete homogeneity) to 100% (complete heterogeneity).[62]

3.0 RESULTS

The search and inclusion process will presented using a PRISMA flow diagram[53]. Data will be extracted, pooled and analysed from the final list of RCTs.

3.1 Study, Participant, and Intervention Characteristics

Participant and intervention details of included RCTs will be presented in table format. Interventions will be described according to duration, number of sessions per week, number of minutes per session, intensity of the intervention (in VO_{2MAX}), as well as type of AET eg walking, swimming, etc.

3.2 Comparative Outcomes

The outcomes extracted for ratios, sub-fractions, and apolipoproteins will be reported. Whether outcomes were joined on the basis of atherogenicity, ES direction and/or unit of measurement, will be indicated. Change in each outcome will be reported in a tabular format as a point estimate, along with CIs, *P* value, and individual group N and combined total N. Sensitivity analyses (K-1) for statistically significant outcomes will be reported in SM tables. The cumulative random MVMA of each outcome will be presented chronologically as a table and graphically showing the study name, outcome name, cumulative statistics and sample size, study quality score, CIs, and weights (random and relative). These figures will be generated using CMA.

3.3 Study Quality and Reporting

The TESTEX scores, median and range, and within-study risk of bias scores, will be presented in SM in tables. Sub-analyses using TESTEX scores 10 and risk of bias scores of low-medium will test for point estimate significance for each analysed outcome previously shown to be significant using CMA. The cumulative random MVMA of each outcome that remains (or attains significance) from sub-analysis will be presented graphically showing the study name, outcome name, cumulative statistics and sample size, study quality score, CIs, and weights (random and relative). These figures will be generated using CMA.

3.4 Lipid Extraction Methodology

The lipid extraction method will be examined for adherence to standard accepted methods (fasted, rested, seated or supine position for blood draw).

3.5 Small Study Effects

The number of included studies will be compared to the minimum number required to perform small study effect analyses.[63] Data will be presented as tables and graphically in SM. The figures and tables will be generated using CMA.

3.6 Meta-regression

Tables will be generated using CMA and presented in SM.

3.7 Heterogeneity

The degree of absolute between-study (τ^2) and relative heterogeneity (I^2) for each analysed outcome will be calculated and presented. If the heterogeneity results indicate that data should not be pooled, we will perform univariate meta-analysis provided at least two effects measures are reported for each found outcome, and repeat the previous analyses.

4.0 DISCUSSION

Aerobic exercise training of at least moderate intensity has been shown to raise HDL-C and lower TC, TRG, and LDL-C. We will report whether our analysis of changes in lipoprotein sub-fractions, apolipoproteins, associated ratios, reflects previous work analysing the effect of AET on standard lipid profile biomarkers. We will indicate whether independent intervention variables contribute to a change in outcomes, as others have found.[23, 33, 38, 48, 49] On the basis of the TESTEX analysis of study quality, we will indicate how researchers might better present their findings.

4.1 Strengths and Limitations of this Quantitative Review

To the best of our knowledge, this SR and MVMAMR is the first that seeks to compare the effects of AET against no exercise on lipid sub-fractions, ratios, and apolipoproteins. We will follow a rigorous inclusion/exclusion protocol to ensure minimisation of confounding factors amongst the RCT populations.[64]

A potential limitation of our work is the reliance on aggregated RCT data and not individual subject data.[65, 66] We will search using English language terms only which may reduce the pool of available studies for selection and introduce small study effects. We intend to exclude studies with intervention and non-exercising control groups of N < 10, unless we have too few studies to perform an SR and MA, and it is possible that intervention duration will be skewed closer to the minimum of 12 weeks, which may decrease the ES. Heterogeneity may show that our results should not be pooled and small study effects may find that our results are due to the presence of bias. The inclusion of AET protocols starting from the minimum of moderate intensity (>40% VO_{2MAX}) may elicit very small changes in lipids,[23] and measurement bias (digital vs analog) of achieved AET volume in the included RCTs may impact ES. Since we exclude unconventional AET protocols such as yoga, the ES may be impacted.

5.0 CONCLUSION

Our MVMAMR intends to pool data and determine whether AET programs of moderate intensity with a minimum 12 week duration improve atherogenic and anti-atherogenic lipid outcomes in adults. We intend to identify whether any or all covariates influence the change in outcome. Our results may help to establish lipid and Apo ratios, lipoprotein sub-fractions, and apolipoproteins as being sensitive to AET and thus useful for indicating the success of AET in mitigating CVD risk.

Supplementary Materials

Author Year	Study non-randomised or randomised	Minimum compliance level set	Habitual medication use reported	Dropout reason reported	Baseline fitness and effort determined	> 50% sessions supervised	Effort monitoring and measurement device	Risk of bias assesment low, medium, or high

SM Table 3.1 Within-study Risk of Bias Factors Score Table

Methodology:

We award either of low or high for the following factors as per SM Table 3.1:

1. Study non-randomised or randomised – low if randomised, high if non-randomised;[1]
2. For intervention groups, a minimum level of compliance to be counted as having participated in the intervention group or control group – low if a minimum level of compliance was set or reported, high if there was no minimum compliance level;
3. Habitual medication use reported – low if reported, high if not reported;
4. Drop-out reasons given – low if reported, high if not reported;
5. Baseline fitness and effort determined – low if baseline fitness and effort was measured, high if not determined;
6. > 50% of sessions supervised – low if50% of sessions were supervised, high if not; and
7. Effort monitoring and measurement devices – low if digital recording devices were used, high if analog or no device.

Studies are to be scored overall low, medium, or high risk of bias according to the number of times either "low" or "high" is awarded. A low risk of bias is scored for 0-2 instances of "high", a medium risk of bias is scored for 3-4 instances of "high", and a high risk of bias is scored for 5-7 instances of "high". All factors are equally weighted.

[1] All studies eligible for inclusion must be randomised, but we record as a confirmation measure.

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4 Chapter 4 – Peer reviewed publication: HIIT is not superior to MICT in altering blood lipids: a systematic review and meta-analysis

4.1 Manuscript information – published 17th December 2019

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On each occasion that research is made public the forms 'Statement of Authorship' and 'Location of Data' must be filled out, signed and lodged with the Head of the Department of which the principal researcher is a member. If, for any reason, one or more co-authors are unavailable or otherwise unable to sign the statements, the Head of Department may sign on their behalf, noting the reason for their unavailability. Heads of Departments must keep copies of these statements in departmental files.

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Authorship is defined as substantial participation, where all the following conditions are met:

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(b) drafting the article or revising it critically for important intellectual content, and
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Authorship (*refer to definition given above*)
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Statement by the responsible or principal author(s):-

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4.2 Statement of authors' contribution

Higher Degree Research Thesis by Publication
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STATEMENT OF AUTHORS' CONTRIBUTION

We, the PhD candidate and the candidate's Principal Supervisor, certify that all co-authors have consented to their work being included in the thesis and they have accepted the candidate's contribution as indicated in the *Statement of Originality*.

	Author's Name (please print clearly)	**% of contribution**
Candidate	Gina Nadine Wood	70
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4.3 Statement of originality

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STATEMENT OF ORIGINALITY

We, the PhD candidate and the candidate's Principal Supervisor, certify that the following text, figures, diagrams, tables, labels, keys and legends are the candidate' original work.

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All text, figures, diagrams, tables, labels, keys and legends in the Chapter **except** the referenced PRISMA diagram and the SM Table 4.1 TESTEX Assessment of Study Quality.	pp 103-115; pp 117-147; pp 149-164

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4.4 Full manuscript as submitted

HIIT is not superior to MICT in altering blood lipids: A systematic review and meta-analysis

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Statements:

1. The authors declare no competing interests.
2. Gina Wood (GW) and Neil Smart NS) designed the systematic review and meta-analysis, and performed searches. Tom van der Touw (TvdT) reviewed search results. Data extraction was performed by GW and Anna Murrell (AM). Data validation was performed by GW, AM, NS, and TvdT. Data synthesis was performed by GW and AM. The article was written by GW with revisions suggested by AM, NS, and TvdT.
3. This systematic review and meta-analysis used pooled data from previously published peer-reviewed articles for which the corresponding ethics approval was obtained by the authors of these previously published studies.
4. There are no acknowledgements to be made regarding contributors who do not meet the author requirements.
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ABSTRACT

Objective To compare the effects of moderate intensity continuous training (MICT) and high intensity interval training (HIIT) on adult lipid profiles; to identify training or participant characteristics that may determine exercise-induced change in total cholesterol (TC), triglycerides (TRG), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C).

Design Systematic review and meta-analysis.

Data sources English language searches of several databases were conducted from inception until September 2019.

Eligibility criteria for excluding studies Inclusion: 1) published randomised controlled human trials with group population N 5; 2) intervention duration 4 weeks; 3) comparing HIIT with MICT; and 4) reporting pre-post intervention lipid measurements. Exclusion: subjects with chronic disease, <18 years, pregnant/lactating, in elite athletic training; and studies with a dietary or pharmaceutical intervention component.

Results Twenty-nine data sets (mmol/L) of 823 participants were pooled and analysed. Neither HIIT nor MICT was better in decreasing (raw mean differences (MD), 95% confidence intervals (CI) mmol/L) TC (MD 0.10 [CI -0.06, 0.19], P=.12, I^2=0%), TRG (MD -0.05 [CI -0.11, 0.01], P=.10, I^2=0%), LDL-C (MD 0.05 [CI -0.06, 0.17], P=.37, I^2=0%), or the ratio TC/HDL-C (MD -0.03 [CI-0.36, 0.29], P=.85, I^2=0%). HIIT significantly raised HDL-C (MD 0.07 [CI 0.04, 0.11], P<0.001, I^2=0%) compared to MICT.

Conclusion Neither HIIT nor MICT is superior for altering TC, TRG, or LDL-C, or TC-HDL-C ratio. Compared to MICT, HIIT appeared to significantly improve HDL-C. Clinicians may prescribe either protocol to encourage participation in exercise and reduce cardiovascular risk. To raise HDL-C, HIIT may result in a larger effect size compared to MICT.

PROSPERO ID CRD42019136722

Keywords Lipids, Cholesterol, Triglycerides, Lipoprotein, Exercise Training, Exercise Intensity

SUMMARY BOX

What is already known?

- Aerobic physical activity positively impacts blood lipids, however lack of time and enjoyment are cited as impediments to exercising.
- High-intensity interval training (HIIT) appears to offer greater benefits compared to moderate-intensity continuous training (MICT). Protocols are formulated to require less time spent training, however higher intensity may negatively impact enjoyment.
- Sufficient volume of aerobic physical activity is necessary to induce changes to blood lipids, however little agreement exists as to whether the shorter session duration of high-low intensity intervals or the moderate intensity of longer session steady-state exercise best changes effect size.

What are the new findings?

- HIIT does not out-perform MICT in positively affecting TC, TRG, LDL-C and the TC/HDL-C ratio. However, MICT seems to be inferior to HIIT for inducing positive changes to HDL-C.
- Participant (age, gender, and presence of MetS or MetS factors/risk) and intervention (weight-bearing) characteristics do appear to influence effect size.
- The multiplicity of HIIT protocols is an obstacle to endorsing a specific HIIT regime most effective for positively impacting blood lipids while accounting for time and enjoyment needs, although HIIT could be chosen in preference to MICT for improving HDL-C.

INTRODUCTION

An abnormally elevated or lowered blood lipid profile, known as dyslipidaemia, is a significant risk factor of cardiovascular disease (CVD);[1,2] ischemic stroke;[3] non-alcoholic fatty liver disease (NAFLD);[4] and chronic pancreatitis.[5,6] Dyslipidaemia frequently coexists with other Metabolic Syndrome (MetS) factors such as obesity (Ob)[7] and Type 2 diabetes (T2D);[8, 9] and MetS is implicated in CVD risk.[10] Moderate- and vigorous- intensity aerobic physical activity positively impacts MetS factors, thus lowering CVD risk.[11, 12] Studies[13, 14] and systematic reviews[15, 16] have shown aerobic exercise reduces elevated total cholesterol (TC), triglycerides (TRG) and low-density lipoprotein cholesterol (LDL-C) and increases high-density lipoprotein cholesterol (HDL-C) in sub-clinical and clinical populations.

Much published work has examined and confirmed the beneficial physiological effects of aerobic physical activity or moderate intensity (55-70% of maximal heart rate (MHR), rate of perceived effort (RPE) of 11-13 on the Borg scale)[17] continuous training, known as MICT. The World Health Organization (WHO) recommends a minimum of 150 minutes per week of aerobic physical activity at moderate continuous intensity, or 75 minutes at higher intensity, to maintain or achieve health. However, WHO reports insufficient aerobic physical activity levels amongst adults18 years.[18] Poor adherence to such recommended aerobic activity or MICT protocols results from lack of time,[19] and lack of support.[20] Although enjoyment of exercise is positively associated with incidence of physical activity in adults, absence of enjoyment has not been significant in explaining lack of exercise, and attitudes towards exercise lack positive association with incidence of aerobic physical activity.[21] Such findings have prompted searches for alternatives to MICT in order to address continuing insufficient aerobic physical activity levels.

High-intensity interval training (HIIT) is a protocol of short work intervals <60 seconds–8 minutes[22] of vigorous (70–90% MHR or RPE Borg scale 14–16)[17] to high intensity (≥90% MHR or RPE Borg scale 17)[17] interspersed with active (40-70% MHR or RPE Borg scale 8-13)[17] or passive (cessation of movement) recovery periods of 1–5 minutes.[22]. HIIT has been employed since the mid-twentieth century to improve athletic exercise performance.[22] Contemporary protocols developed for non-athletes are intended to reduce session time and provide a greater stimulus for physiological and psychological adaptation compared to MICT.

HIIT has been shown to increase peak oxygen consumption (VO_{2MAX} or VO_{2PEAK}) compared to MICT in CVD populations,[23] despite VO_{2MAX} being only one component of positive changes to cardiorespiratory fitness.[24] Studies indicate that a positive impact on biomedical health indices is protocol dependent in clinical[25] and healthy[26] populations.

To encourage individuals to undertake aerobic physical activity, both HIIT[27] and MICT[28] are promoted as enjoyable and effective, although no consensus exists as to which aerobic exercise protocol is more so. Studies have shown a minimum volume of weekly aerobic exercise for a minimum duration[29] and a weekly aerobic exercise energy expenditure (EEE) threshold of 1200-2200 kcal[30] is necessary to induce positive changes to lipids. Systematic reviews and meta-analyses of the effect of aerobic physical activity on lipid levels have established that longer intervention and session duration results in greater effects.[31, 32]

A systematic review comparing HIIT against MICT found no difference on blood lipids in healthy and clinical populations, but no meta-analysis was conducted.[33] A pooled analysis comprising only 3 studies and consisting of CVD, MetS, and overweight populations unsurprisingly showed equivocal effects on serum lipids.[34] Other systematic reviews[16, 35-36] and meta-analyses [15, 37-40] have investigated the effect of exercise on lipids, but have not compared HIIT against MICT. Thus no previously published meta-analysis exists that has examined the effects of HIIT versus MICT on lipids in sub-clinical populations.

The aim of this study was therefore to conduct a systematic review and meta-analysis comparing the effects of HIIT and MICT on TC, TRG, HDL-C, LDL-C, and TC/HDL-C in sub-clinical populations and to examine whether one protocol surpassed the other.

METHODS

This systematic review and meta-analysis was registered in the International Prospective Register of Systematic Reviews (PROSPERO).[41] Its results are presented according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.[42]

Search Strategy GNW and NAS conducted systematic English-language searches of PubMed, all EBSCO health and medical databases including SPORTDiscus, MEDLINE and CINAHL, as well as Web of Science and EMBASE from inception to September 2019.

Searches included a mix of MeSH and free text terms relevant to the concepts of: exercise training intensity eg (high OR HIIT OR sprint OR SIT OR vigorous AND moderate continuous OR MICT OR MICE OR CME); interval training eg (intermittent OR interval OR reps AND training OR exercise); intervention duration eg (weeks NOT single bout); exercise-induced lipid metabolism; metabolic syndrome eg (metabolic syndrome OR MetS OR T2D OR diabetes OR hypertension OR overweight OR obese); and blood lipids eg (lipids OR cholesterol OR lipoprotein OR triglycerides). Searches excluded for pregnancy, lactation, elite athletes, juveniles, CVD, stroke, cancer, and NAFLD. Systematic reviews and reference lists of papers were hand searched for additional studies.

Participants and Interventions Inclusion/Exclusion Criteria Sub-clinical (healthy or overweight (Ov) or MetS or MetS factors such hypertensive (H)), and clinical (Ob and T2D) participants taking usual medications, and with a sample size population of N 5 in HIIT and MICT were included.

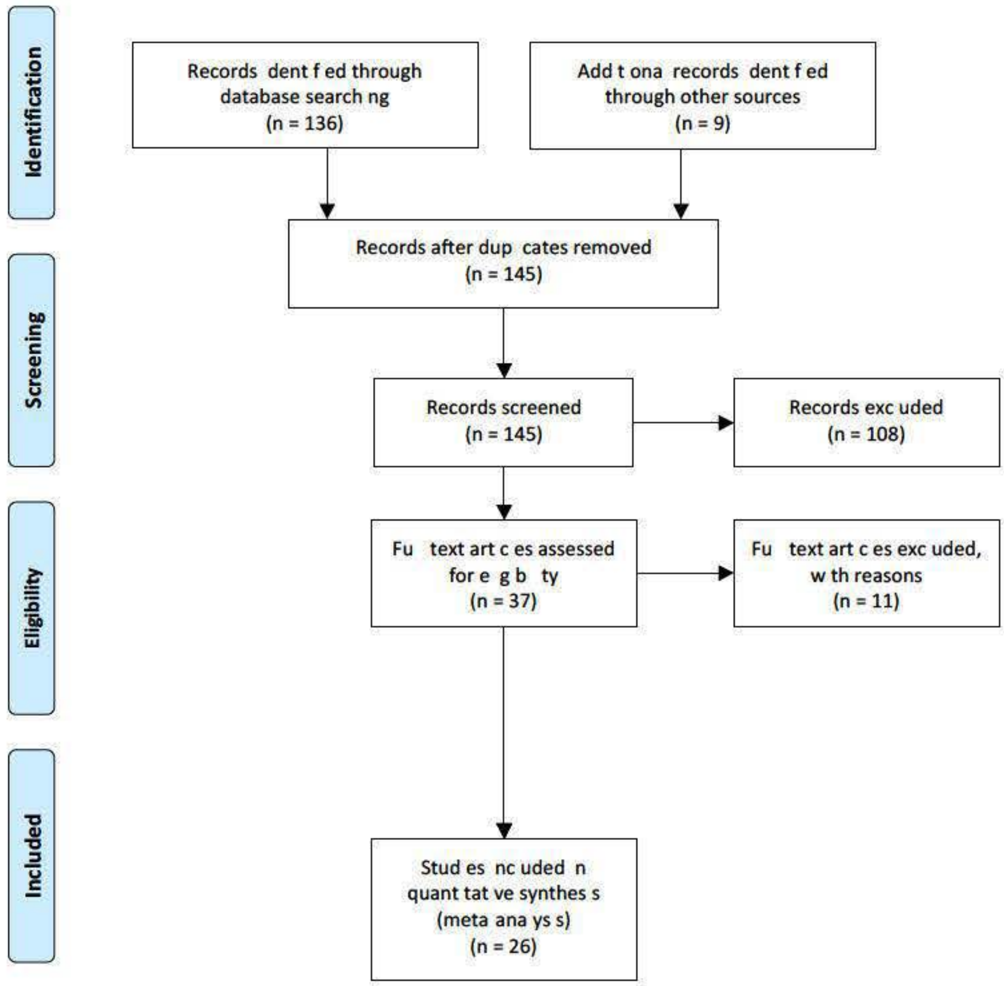
Two distinct exercise protocols differentiated by effort as per established guidelines[17] and described as either steady state (MICT) or higher effort plus active or passive recovery intervals (HIIT), separate to warm up and cool-down, were required. No restrictions were placed on exercise session time, number and time length of work and recovery intervals or exercise type. Levels and measurement of effort such as percentage of VO_{2peak} or VO_{2MAX}, percentage of peak heart rate (HR_{PEAK}) or MHR or heart rate reserve (HRR) or individual anaerobic threshold heart rate (HR_{IAT}), Borg scale, metabolic equivalent (MET), or percentage of workload or watts (W_{MAX} or W_{PEAK}) were required. Resistance- or combined- training interventions without separate HIIT and MICT interventions as comparators were excluded.

Comparator HIIT protocols as the intervention were compared against MICT protocols as the control for differentiated impacts on blood lipids.

Outcomes Pre-post intervention lipid measurements reported as mmol/L or mg/dL for any of TC, TRG, HDL-C, LDL-C or TC/HDL-C were required.

Study Selection GNW and NAS assessed the resulting titles and abstracts of randomised controlled trials (RCTs) lasting ≥4 weeks, which compared HIIT and MICT protocols, and reported pre-post intervention lipid measurements in humans ≥18 years. Subsequently, the full text of potentially eligible studies was reviewed according to participant, intervention, and outcome inclusion and exclusion criteria. TvdT was consulted to resolve disputes. The flow of papers through the search and inclusion process is presented in Figure 4.1[42]

PRISMA 2009 Flow Diagram



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For more information, visit www.prisma-statement.org.

Figure 4.1 PRISMA flow diagram

Data extraction GNW and AM extracted the data to a pre-established extraction form and NS and TvdT confirmed the data extraction. For each study the following information was extracted: 1) author(s), year of publication and study design characteristics, 2) demographic and clinical characteristics, 3) HIIT intervention and MICT control protocols, 4) values before and after HIIT intervention and MICT control for any of TC, TRG, HDL-C, LDL-C or TC/HDL-C ratio and expressed as mean (M) or mean difference (MD), standard deviation (SD) or converted to SD (standard error (SE) using SD = square root (Sample Size) x SE), as well as main findings concerning lipids.

Data Synthesis Statistical analyses were performed using Revman 5.3 (The Nordic Cochrane Centre, Copenhagen, Denmark) for continuous data by using the raw MD and SD of the MD. Where the MD and SD of the MD were not reported, the raw MD was calculated by subtracting the pre-intervention M from the post-intervention M. The SD of the MD was calculated as follows: SD = square root $[(SD_{pre\text{-}treatment})^2 + (SD_{post\text{-}treatment})^2 – (2r \times SD_{pre\text{-}treatment} \times SD_{post\text{-}treatment})]$, assuming a correlation coefficient (r) = 0.5, considered a conservative estimate.[43] Revman 5.3 also enabled calculations of the SD of the MD using group sample size and *P* values or 95% confidence intervals (CIs) when provided. Where data was not presented in text or tables and authors could not be reached, data presented in figures was extracted where possible.

Data were pooled for meta-analysis when two or more studies measured the same outcome and provided data in a format suitable for pooling. Where a study included multiple HIIT groups, data were entered separately for each group and the sample size of the MICT group was divided by the number of HIIT groups to eliminate inflation of the sample size. GNW entered the data in Revman 5.3; TvdT reviewed the data entry for accuracy. A random effects inverse variance model was used with the effects measure of MD, a 5% level of significance, and a 95% CI to report change in outcome measures. This model was chosen to allow for different effect sizes achieved across selected studies.[44]

Meta-analysis and Sub-analyses For meta-analysis of the 4 cholesterol fractions and single ratio, all included studies were grouped under each fraction and data was pooled. Sub-analyses were conducted according to: age; gender; presence or absence of MetS risk and/or factor(s) or T2D; and weight-bearing or non weight-bearing exercise.

Sensitivity Analysis In order to evaluate the influence of each study on the overall effect size of pooled data, we conducted iterative leave-one-out sensitivity analyses.[45] Where sub-analyses gave rise to significance, iterative leave-one-out analysis (K-1, where K = the number of studies, and each study is excluded from the pool analysis one at a time) was also conducted.

Heterogeneity and Publication Bias Heterogeneity was quantified using the I^2 test where heterogeneity values range from 0% (homogeneity) to 100% (complete heterogeneity).[46] Visual inspection of funnel plots was used to assess risk of publication bias.[47] If the 95% CIs of a study were outside the pooled 95% CIs, the study was removed as an outlier.[48]

Study Quality Study quality was assessed by AM and GNW and reviewed by NS and TvdT, using the validated Tool for the Assessment of Study Quality and Reporting in Exercise (TESTEX),[49] a 15-point scale specific to exercise training studies. A score ≥10 indicates a better study quality and reporting. In the case of discrepancies NS was consulted. A study quality sub-analysis of studies grouped according to TESTEX scores (≥10, <10) was also conducted.

RESULTS

Combined searches generated a total of 126 articles. After removal of duplicates and exclusion of articles based on abstract and title, 37 full-text articles remained for screening. One study using a non HIIT protocol,[50] two studies using dietary intervention,[51, 52] two studies of increasing intensity not high-intensity intervals,[13, 53] one study with no MICT group,[54] one study reporting only pre-intervention values,[55] one study combining outcome measures of both protocols,[56] and a feasibility study[57] were excluded. One study tested two HIIT protocols, one of which was excluded.[58] Two further excluded studies were non-RCTs.[59-60] Three studies[61-63] tested two HIIT protocols against the same group of MICT participants, hence after screening, a total of 29 data sets from 26 studies [24-25, 58, 61-82] met the stated inclusion criteria.

Study, Participant, and Intervention Characteristics Summarised descriptions of studies, participants, and interventions included in trials are provided in Table 4.1 below and detailed descriptions in Supplementary Materials (SM) Table [4.2].

Study (A-Z)	Participants N, status, gender	Exercise Type, HIIT work interval intensity, MICT intensity	Sessions Week^{-1}	Weeks	Outcomes
Ciolac, et al. 2010	22 healthy ♀	Treadmill walking or running HIIT: 80–90% VO_{2MAX}, MICT: 60–70% VO_{2MAX}	3	16	TC, TRG, HDL-C, LDL-C
Connolly, et al. 2017	30 healthy ♀	Ergocycle HIIT: 30–<100% sprint, MICT: 70–85% HR_{PEAK}	3	12	TC, TRG, HDL-C, LDL-C, TC/HDL-C
Cuddy, et al. 2019	27 Ov-Ob ♀♂	Ergocycle HIIT: 100% sprint; MICT: 40–65% HRR	HIIT: 2-4 MICT: 3-5	8	TRG, HDL-C
Fisher, et al. 2015	23 Ov-Ob ♂	Ergocycle HIIT: 85% sprint, MICT: 55–65% VO_{2PEAK}	HIIT: 3 MICT: 5	6	TC, TRG, HDL-C, LDL-C
Hwang, et al. 2016	29 Ov ♀♂	All-extremity ergometer HIIT: 90% HR_{PEAK}, MICT: 70% HR_{PEAK}	4	8	TC, TRG, HDL-C, LDL-C
Keating, et al. 2014	22 Ov ♀♂	Ergocycle HIIT: 120% VO_{2PEAK}, MICT: 50-65% VO_{2PEAK}	3	12	TC, TRG, HDL-C, LDL-C
Kemmler, et al. 2014	65 Ov-MetS ♂	Running HIIT: 95–110% HR_{IAT}*, MICT: 70–82.5% HR_{IAT}*	2-4	16	TRG, HDL-C
Kong, et al. 2016	26 Ob ♀	Ergocycle HIIT: max VO_{2PEAK}, MICT: 60–80% VO_{2PEAK}	4	5	TC, TRG, HDL-C, LDL-C
Lee, et al. 2016 a	20 healthy ♂	Ergocyle HIIT: 85–90% VO_{2MAX}, MICT: not stated	3	4	TC, TRG, HDL-C, LDL-C
Lee, et al. 2016 b	18 healthy ♂	Ergocycle HIIT: 85–90% VO_{2MAX}, MICT: not stated	3	4	TC, TRG, HDL-C, LDL-C
Lira, et al. 2019	20 healthy ♂	Treadmill HIIT: 100% sVO_{2PEAK} ,MICT: 70% sVO_{2PEAK}	3	5	TC, TRG, HDL-C
Maillard, et al. 2016	16 Ov-Ob, T2D ♀	Ergocycle HIIT: 80% MHR, MICT: 55–60% target HR	2	16	TC, TRG, HDL-C, LDL-C, TC/HDL-C
Matsuo, et al. 2015	26 Ov-MetS ♂	Ergocycle HIIT: 85% VO_{2PEAK}, MICT: 60-65% VO_{2PEAK}	3	8	TC, TRG, HDL-C, LDL-C, TC/HDL-C
Mohr, et al. 2014	42 H, Ov ♀	Free-style swimming HIIT: 85–95% MHR, MICT: 72–79% MHR	3	15	TC, HDL-C, LDL-C
Morales-Palermo, et al. 2019 a	50 MetS ♀♂	Ergocycle HIIT4: 90% MHR, MICT: 70% MHR	3	16	TC, TRG, HDL-C, LDL-C
Morales-Palermo, et al. 2019 b	49 MetS ♀♂	Ergocycle HIIT1:100% MHR, MICT: 70% MHR	3	16	TC, TRG, HDL-C, LDL-C
Moreira, et al. 2008	16 Ob ♀♂	Ergocycle HIIT: 60–72% VO_{2MAX}, MICT: 55–66% VO_{2MAX}	3	12	TC, TRG
Nybo, et al. 2010	17 healthy ♂	Running HIIT: 85% VO_{2MAX}, MICT: 65% VO_{2MAX}	3	12	TC, HDL-C, LDL-C, TC/HDL-C
Ramos, et al. 2016	32 MetS, T2D ♀♂	Walking/running, ergocycle/cycling, swimming HIIT: 85–95% HR_{PEAK}, MICT: 60–70% HR_{PEAK}	HIIT: 3 MICT: 5	16	TRG, HDL-C
Ruffino, et al. 2017	16 Ov-Ob, T2D ♂	Ergocycle, walking HIIT: 80%–90% MHR, MICT: 50–55% HRR	HIIT: 3 MICT: 5	8	TRG, HDL-C, LDL-C
Sawyer, et al. 2016	18 Ob ♀♂	Ergocycle HIIT: 90–95% MHR, MICT: 70–75% MHR	3	8	TC, TRG, HDL-C, LDL-C
Shepherd, et al. 2015	78 Ov ♀♂	Ergocycle HIIT: >90% MHR, MICT: 70% MHR	HIIT: 3 MICT: 5	10	TC, TRG, HDL-C, LDL-C, LDL-C/HDL-C
Thomas, et al. 1985 a	14 healthy ♂	Running HIIT: 90–100% MHR, MICT: 75–85% MHR	3	11	TC, HDL-C
Thomas, et al. 1985 b	14 healthy ♂	Running HIIT: 90–100% MHR, MICT: 75–85% MHR	3	11	TC, HDL-C
Tjønna, et al. 2008	19 MetS ♀♂	Treadmill walking and running HIIT: 90% MHR, MICT: 70% MHR	3	8	TRG, HDL-C
Vella, et al. 2017	17 Ov-Ob ♀♂	Treadmill, ergocycle, elliptical HIIT: 75–80% HRR, MICT: 55–59% HRR	4	8	TC, TRG, HDL-C, LDL-C
Winding, et al. 2018	25 Ov, T2D ♀♂	Ergocycle HIIT: 95% W_{PEAK}, MICT: 50% W_{PEAK}	3	11	TC, TRG, HDL-C, LDL-C
Winn, et al. 2018	16 Ob ♀♂**	Treadmill walking and running HIIT: 80% VO_{2PEAK}, MICT: 55% VO_{2PEAK}	4	4	TC, TRG, HDL-C, LDL-C
Zhang, et al. 2015	24 Ob ♀	Treadmill running HIIT: 50–95% HR_{PEAK}, MICT: 60–70% HR_{PEAK}	4	12	TC, TRG

Key: *HR_{IAT} – HR at individual aerobic threshold IAT (minimum lactate 2.0 mmol/L). ** Assumed. Gender not specified.

Table 4.1 Study Characteristics and PICO

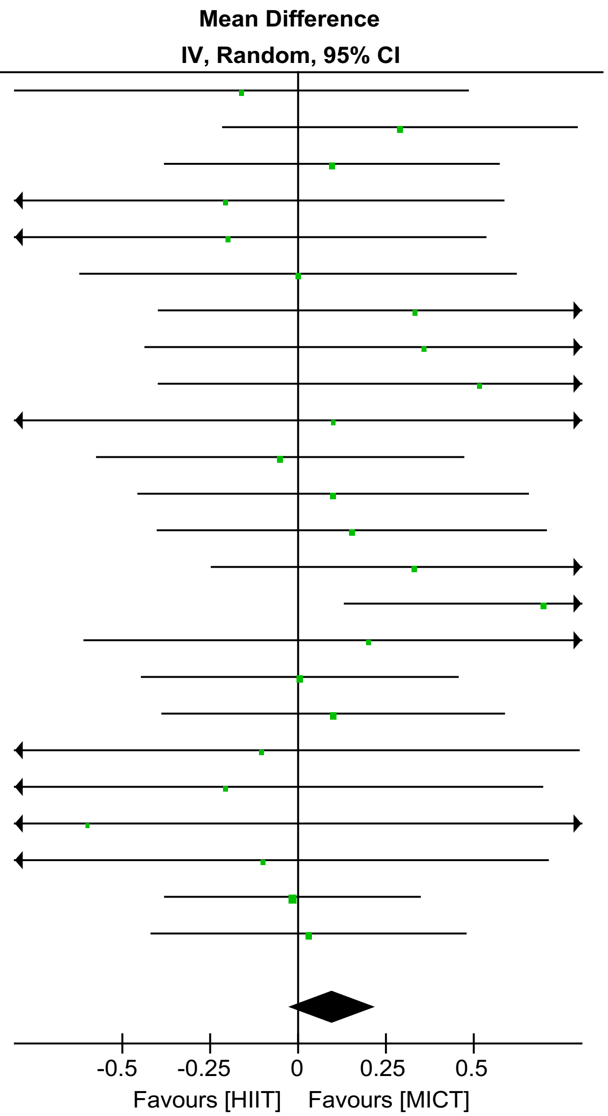
Comparative Outcome Measures

Total Cholesterol Twenty-one studies of 24 data sets with a total of 653 (352 HIIT, 301 MICT) subjects reported on TC MD (0.10 mmol/L [-0.03, 0.22], P=.12, I^2=0%), shown in Figure [4.2]. No significance was found. Sensitivity analysis (K-1) did not change results. Sub-analyses did not change significance, see SM Table [4.3].

	HIIT			MICT				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI
C o ac 2010	-0.233	0.6568	11	-0.072	0.8704	11	3.6%	-0.16 [-0.81, 0.48]
Conno y 2017	0.15	0.7732	15	-0.14	0.626	15	6.0%	0.29 [-0.21, 0.79]
F sher 2015	-0.238	0.5828	15	-0.334	0.6853	13	6.7%	0.10 [-0.38, 0.57]
Hwang 2016	-0.31	1.0552	15	-0.103	1.1159	14	2.4%	-0.21 [-1.00, 0.58]
Keat ng 2014	0	0.9539	13	0.2	0.9539	13	2.8%	-0.20 [-0.93, 0.53]
Kong 2016	0	0.9	13	0	0.7	13	3.9%	0.00 [-0.62, 0.62]
Lee CL 2016 a	0.16	0.6645	13	-0.173	0.8551	7	2.8%	0.33 [-0.40, 1.06]
Lee CL 2016 b	0.186	0.7104	12	-0.173	0.8551	6	2.4%	0.36 [-0.43, 1.15]
L ra 2019	-0.207	0.931	10	-0.724	1.1428	10	1.8%	0.52 [-0.40, 1.43]
Ma ard 2016	-0.1	1.2329	8	-0.2	0.8485	8	1.4%	0.10 [-0.94, 1.14]
Matsuo 2015	0.052	0.7255	13	0.103	0.6271	13	5.6%	-0.05 [-0.57, 0.47]
Mohr 2014	-0.1	0.9165	21	-0.2	0.9165	21	4.9%	0.10 [-0.45, 0.65]
Mora es-Pa omo 2019 a	-0.01	0.8419	32	-0.163	1.0158	18	5.0%	0.15 [-0.40, 0.71]
Mora es-Pa omo 2019 b	0.168	0.9094	32	-0.163	1.0158	17	4.6%	0.33 [-0.25, 0.91]
More ra 2008	0	0.4927	8	-0.698	0.6496	8	4.7%	0.70 [0.13, 1.26]
Nybo 2010	-0.1	0.5657	8	-0.3	1.0817	9	2.3%	0.20 [-0.61, 1.01]
Sawyer 2016	0.129	0.3899	9	0.124	0.5667	9	7.5%	0.01 [-0.44, 0.45]
Shepherd 2015	-0.3	1.347	46	-0.4	0.9868	44	6.4%	0.10 [-0.39, 0.59]
Thomas 1985 a	-0.052	0.3862	8	0.052	0.9837	5	1.9%	-0.10 [-1.01, 0.80]
Thomas 1985 b	-0.155	0.6739	9	0.052	0.9837	6	1.9%	-0.21 [-1.11, 0.69]
Ve a 2017	-0.7	5.8611	8	-0.1	5.9844	9	0.0%	-0.60 [-6.24, 5.04]
W nd ng 2018	-0.2	1.0536	13	-0.1	1.0149	12	2.3%	-0.10 [-0.91, 0.71]
W nn 2017	-0.078	0.4034	8	-0.062	0.3336	8	11.5%	-0.02 [-0.38, 0.35]
Zhang 2015	-0.5	0.6453	12	-0.53	0.4564	12	7.6%	0.03 [-0.42, 0.48]
Total (95% CI)			**352**			**301**	**100.0%**	**0.10 [-0.03, 0.22]**

Heterogene ty: Tau² = 0.00; Ch ² = 11.03, df = 23 (P = 0.98); I² = 0%

Test for overa effect: Z = 1.55 (P = 0.12)



Key: MD and SD expressed as mmol/L; Total = number of participants.

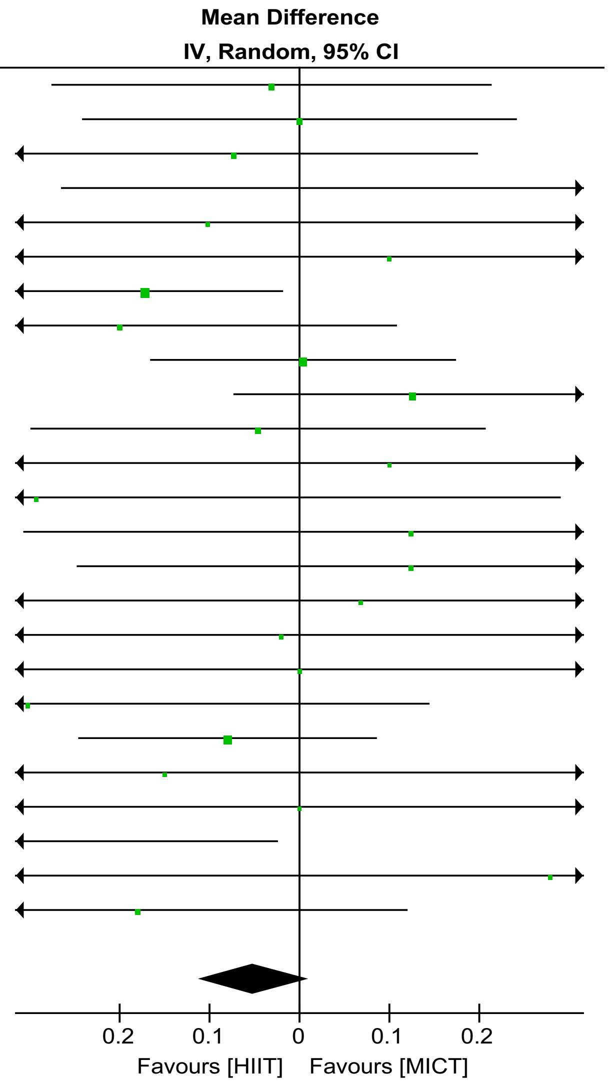
Figure 4.2 Total Cholesterol Forest Plot

Triglycerides Twenty-three studies of 25 data sets with a total of 736 (392 HIIT, 344 MICT) subjects reported on TRG MD (-0.05 mmol/L [-0.11, 0.01], P=.10, I^2=0%), shown in Figure [4.3]. No significance was found. Sensitivity analysis (K-1) did not alter significance. Sub-analyses changed significance in favour of HIIT for 1) age grouping 35 – 55 years (-0.10 mmol/L [-0.19, -0.01], P=.03, I^2=0%); 2) Mets or MetS factors/risk (-0.10 mmol/L [-0.18, -0.02],P=.01, I^2=0%); and 3) weight-bearing protocols (-0.11 mmol/L [-0.21, -0.00], P=.04, I^2=0%). Sensitivity analysis (K-1) of these sub-analyses resulted in no significance with the removal of one study,[24] see SM Table [4.3].

	HIIT			MICT				Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**Weight**	**IV, Random, 95% CI**
C o ac 2010	0.008	0.309	11	0.023	0.2733	11	6.3%	0.03 [0.27, 0.21]
Conno y 2017	0.05	0.3915	15	0.05	0.2706	15	6.4%	0.00 [0.24, 0.24]
Cuddy 2019	0.154	0.3602	12	0.081	0.3517	15	5.1%	0.07 [0.34, 0.20]
F sher 2015	0.173	0.5845	15	0.535	1.0152	13	0.9%	0.36 [0.26, 0.99]
Hwang 2016	0.079	0.8027	15	0.023	0.6379	14	1.3%	0.10 [0.63, 0.42]
Keat ng 2014	0	0.6245	13	0.1	0.6245	13	1.6%	0.10 [0.38, 0.58]
Kemm er 2014	0.224	0.3026	33	0.052	0.3252	32	15.9%	0.17 [0.32, 0.02]
Kong 2016	0.1	0.4	13	0.1	0.4	13	3.9%	0.20 [0.51, 0.11]
Lee CL 2016 a	0.012	0.1599	13	0.008	0.1958	7	13.0%	0.00 [0.17, 0.17]
Lee CL 2016 b	0.134	0.2152	12	0.008	0.1958	6	9.5%	0.13 [0.07, 0.32]
L ra 2019	0.023	0.3255	10	0.023	0.2442	10	5.9%	0.05 [0.30, 0.21]
Ma ard 2016	0	1.2329	8	0.1	0.2828	8	0.5%	0.10 [0.78, 0.98]
Matsuo 2015	0.316	0.5671	13	0.023	0.9093	13	1.1%	0.29 [0.88, 0.29]
Mora es Pa omo 2019 a	0.131	0.8579	32	0.255	0.6732	18	2.0%	0.12 [0.31, 0.55]
Mora es Pa omo 2019 b	0.131	0.5397	32	0.255	0.6732	17	2.7%	0.12 [0.25, 0.49]
More ra 2008	0.011	1.302	8	0.079	0.9266	8	0.3%	0.07 [1.04, 1.18]
Ramos 2016	0.13	1.1953	22	0.11	0.845	21	1.0%	0.02 [0.64, 0.60]
Ruff no 2017	0.1	0.755	8	0.1	0.8185	8	0.6%	0.00 [0.77, 0.77]
Sawyer 2016	0.036	0.5178	9	0.266	0.444	9	1.9%	0.30 [0.75, 0.14]
Shepherd 2015	0.13	0.4041	46	0.05	0.3947	44	13.7%	0.08 [0.25, 0.09]
Tjønna 2008	0.05	0.2948	11	0.2	1.1863	8	0.5%	0.15 [0.99, 0.69]
Ve a 2017	0.1	1.6746	8	0.1	1.9514	9	0.1%	0.00 [1.72, 1.72]
W nd ng 2018	0.5	1.3892	13	0.4	0.781	12	0.5%	0.90 [1.77, 0.03]
W nn 2017	0.25	0.7587	8	0.029	0.4177	8	1.0%	0.28 [0.32, 0.88]
Zhang 2015	0.07	0.3148	12	0.11	0.4249	12	4.2%	0.18 [0.48, 0.12]
Total (95% CI)			**392**			**344**	**100.0%**	**-0.05 [-0.11, 0.01]**

Heterogene ty: Tau² = 0.00; Ch ² = 18.31, df = 24 (P = 0.79); I² = 0%

Test for overa effect: Z = 1.63 (P = 0.10)



Key: MD = mean difference and SD = standard deviation expressed as mmol/L; Total = number of participants.

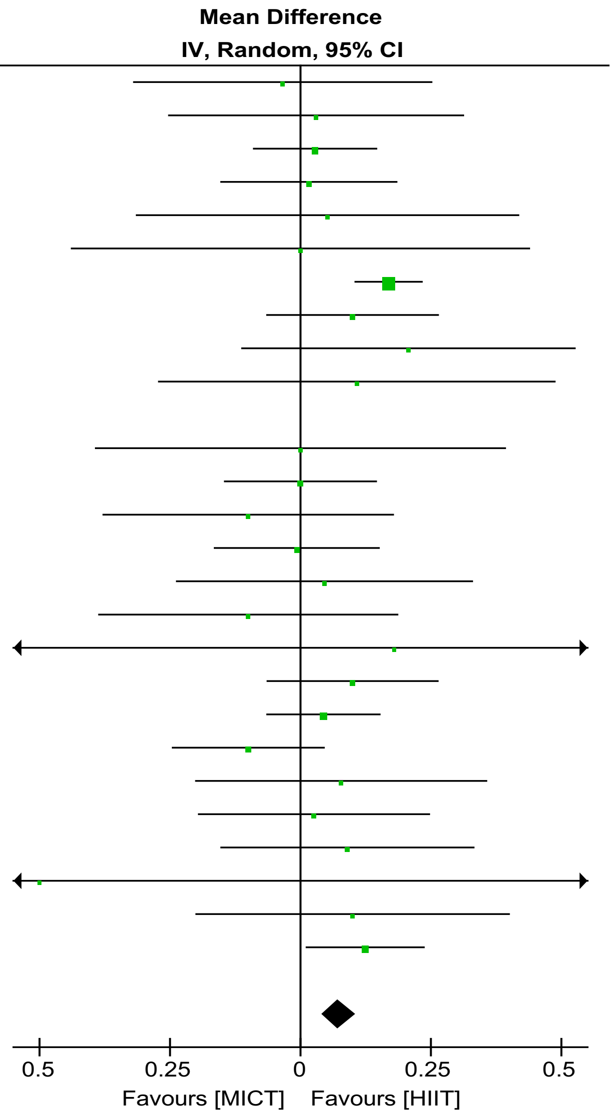
Figure 4.3 Triglycerides Forest Plot

High-density Lipoprotein Cholesterol Twenty-six studies comprising 28 data sets with a total of 739 (384 HIIT, 355 MICT) subjects reported on HDL-C MD (0.07 [0.04, 0.11], P<0.0001, I^2=0%), as shown in Figure [4.4], and favoured HIIT. Removal of one outlier [70] did not alter significance. Sensitivity analysis (K-1) resulted in insignificance with the removal of one study,[24] HDL-C MD (0.04 mmol/L [-0.00, 0.08], P=.06, I^2=0%), see SM Table [4.3] With the exception of age (all) and gender (females), sub-analyses remained significant for HIIT. Applying sensitivity analysis (K-1) to sub-analyses resulted in insignificance for the weight-bearing grouping only, see SM Table [4.3].

	MICT			HIIT				Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**Weight**	**IV, Random, 95% CI**
C o ac 2010	0.059	0.4259	11	0.093	0.226	11	1.4%	0.03 [0.32, 0.25]
Conno y 2017	0.04	0.3759	15	0.07	0.4104	15	1.4%	0.03 [0.25, 0.31]
Cuddy 2019	0.072	0.1515	12	0.044	0.158	15	8.1%	0.03 [0.09, 0.15]
F sher 2015	0.036	0.2467	15	0.052	0.2064	13	4.0%	0.02 [0.15, 0.18]
Hwang 2016	0	0.6009	15	0.052	0.387	14	0.8%	0.05 [0.31, 0.42]
Keat ng 2014	0	0.7211	13	0	0.3606	13	0.6%	0.00 [0.44, 0.44]
Kemm er 2014	0.228	0.1371	33	0.059	0.1241	32	27.7%	0.17 [0.11, 0.23]
Kong 2016	0.1	0.3009	13	0.0001	0.0006	13	4.2%	0.10 [0.06, 0.26]
Lee CL 2016 a	0.158	0.2723	13	0.049	0.3808	7	1.1%	0.21 [0.11, 0.53]
Lee CL 2016 b	0.059	0.3986	12	0.049	0.3808	6	0.8%	0.11 [0.27, 0.49]
L ra 2019	0.26	0.144	10	0.052	0.1293	10		Not est mab e
Ma ard 2016	0.1	0.2828	8	0.1	0.4899	8	0.7%	0.00 [0.39, 0.39]
Matsuo 2015	0.078	0.1696	13	0.078	0.2053	13	5.3%	0.00 [0.14, 0.14]
Mohr 2014	0	0.4583	21	0.1	0.4583	21	1.5%	0.10 [0.38, 0.18]
Mora es Pa omo 2019 a	0.03	0.2482	32	0.023	0.2846	18	4.5%	0.01 [0.16, 0.15]
Mora es Pa omo 2019 b	0.023	0.3582	8	0.023	0.2846	17	1.4%	0.05 [0.24, 0.33]
Nybo 2010	0	0.2828	8	0.1	0.3	8	1.4%	0.10 [0.39, 0.19]
Ramos 2016	0.08	0.346	22	0.1	1.7299	9	0.1%	0.18 [0.96, 1.32]
Ruff no 2017	0.1	0.2	8	0	0.2	21	4.2%	0.10 [0.06, 0.26]
Sawyer 2016	0.026	0.1104	9	0.018	0.1221	9	9.7%	0.04 [0.06, 0.15]
Shepherd 2015	0.04	0.3367	46	0.14	0.3618	44	5.3%	0.10 [0.24, 0.04]
Thomas 1985 a	0	0.2725	8	0.078	0.2327	5	1.4%	0.08 [0.20, 0.36]
Thomas 1985 b	0.052	0.181	9	0.078	0.2327	6	2.3%	0.03 [0.19, 0.25]
Tjønna 2008	0.15	0.2948	11	0.06	0.2417	8	1.9%	0.09 [0.15, 0.33]
Ve a 2017	0.3	1.7942	8	0.2	1.431	9	0.0%	0.50 [2.06, 1.06]
W nd ng 2018	0	0.3606	13	0.1	0.4	12	1.2%	0.10 [0.20, 0.40]
W nn 2017	0.088	0.1448	8	0.036	0.0724	8	8.9%	0.12 [0.01, 0.24]
Total (95% CI)			**384**			**355**	**100.0%**	**0.07 [0.04, 0.11]**

Heterogene ty: Tau² = 0.00; Ch ² = 23.85, df = 25 (P = 0.53); I² = 0%

Test for overa effect: Z = 4.32 (P < 0.0001)



Key: MD = mean difference and SD = standard deviation expressed as mmol/L; Total = number of participants.

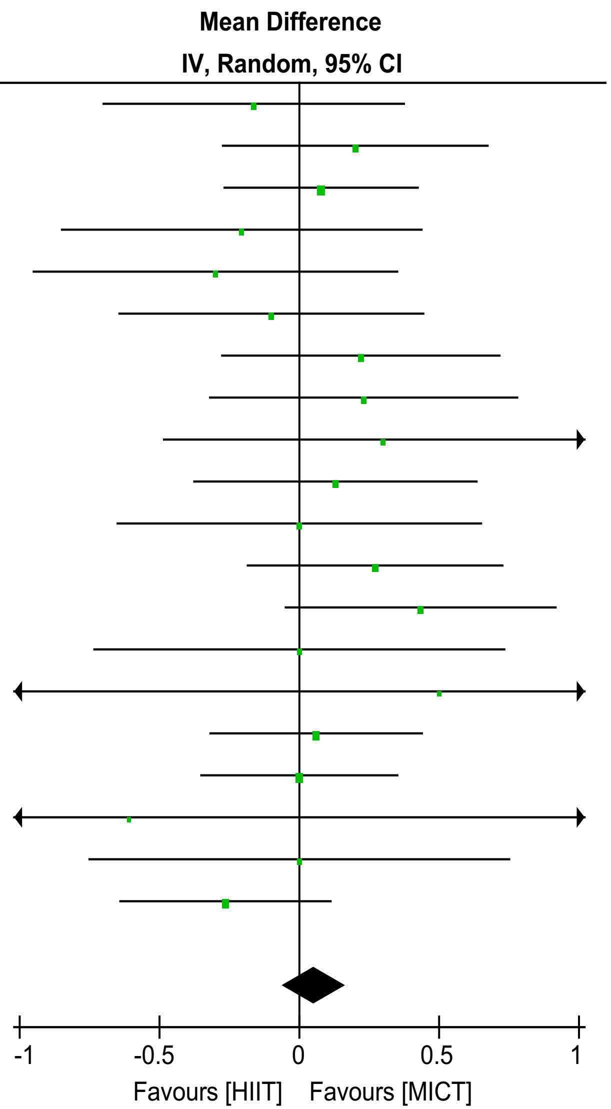
Figure 4.4 High-density Lipoprotein Cholesterol Forest Plot

Low-density Lipoprotein Cholesterol Twenty data sets of 580 (313 HIIT, 267 MICT) subjects reported on LDL-C MD (0.05 mmol/L [-0.06, 0.17], P=.37, I^2=0%), shown in Figure [4.5]. No significance was found. Sensitivity analysis (K-1) did not change significance. Sub-analyses did not change significance, see SM Table [4.3].

	HIIT			MICT				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI
C o ac 2010	-0.318	0.4988	11	-0.155	0.7602	11	4.6%	-0.16 [-0.70, 0.37]
Conno y 2017	0.12	0.8073	15	-0.08	0.4729	15	5.9%	0.20 [-0.27, 0.67]
F sher 2015	-0.124	0.4727	15	-0.202	0.4595	13	11.1%	0.08 [-0.27, 0.42]
Hwang 2016	-0.284	0.7011	15	-0.078	1.024	14	3.2%	-0.21 [-0.85, 0.44]
Keat ng 2014	0	0.7211	13	0.3	0.9539	13	3.1%	-0.30 [-0.95, 0.35]
Kong 2016	-0.1	0.8	13	0	0.6	13	4.5%	-0.10 [-0.64, 0.44]
Lee CL 2016 a	-0.041	0.512	13	-0.261	0.5543	7	5.4%	0.22 [-0.28, 0.72]
Lee CL 2016 b	-0.031	0.5724	12	-0.261	0.5543	6	4.4%	0.23 [-0.32, 0.78]
Ma ard 2016	0.1	0.8485	8	-0.2	0.7483	8	2.2%	0.30 [-0.48, 1.08]
Matsuo 2015	0.129	0.6857	13	0	0.6271	13	5.2%	0.13 [-0.38, 0.63]
Mohr 2014	-0.1	0.9165	21	-0.1	1.2124	21	3.1%	0.00 [-0.65, 0.65]
Mora es-Pa omo 2019 a	0.041	0.6747	32	-0.23	0.8467	18	6.4%	0.27 [-0.18, 0.73]
Mora es-Pa omo 2019 b	0.204	0.7113	32	-0.23	0.8467	16	5.7%	0.43 [-0.05, 0.92]
Nybo 2010	-0.1	0.7483	8	-0.1	0.7937	9	2.5%	0.00 [-0.73, 0.73]
Ruff no 2017	0.3	1.7521	8	-0.2	1.4526	8	0.5%	0.50 [-1.08, 2.08]
Sawyer 2016	0.127	0.2863	9	0.067	0.5032	9	9.3%	0.06 [-0.32, 0.44]
Shepherd 2015	-0.3	1.0102	46	-0.3	0.6578	44	10.8%	0.00 [-0.35, 0.35]
Ve a 2017	-0.6	3.8277	8	0.01	4.15	9	0.1%	-0.61 [-4.40, 3.18]
W nd ng 2018	-0.1	1.0149	13	-0.1	0.9	12	2.4%	0.00 [-0.75, 0.75]
W nn 2017	-0.277	0.4396	8	-0.013	0.3181	8	9.4%	-0.26 [-0.64, 0.11]
Total (95% CI)			**313**			**267**	**100.0%**	**0.05 [-0.06, 0.17]**

Heterogene ty: Tau² = 0.00; Ch ² = 10.96, df = 19 (P = 0.93); I² = 0%

Test for overa effect: Z = 0.90 (P = 0.37)



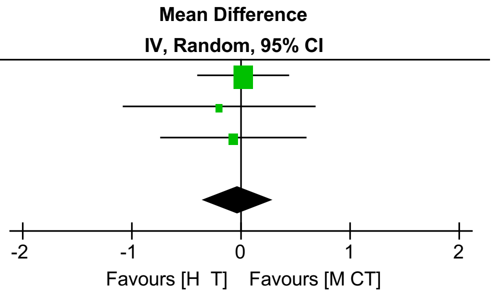
Key: MD = mean difference and SD = standard deviation expressed as mmol/L; Total = number of participants.

Figure 4.5 Low-density Lipoprotein Cholesterol Forest Plot

TC/HDL-C Ratio As shown in Figure [6], 3 studies with a total of 72 subjects reported on the TC/HDL-C ratio MD (-0.03 mmol/L [-0.36, 0.29], P=.85, I^2=0%).

	HIIT			MICT				Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**Weight**	**IV, Random, 95% CI**
Connolly 2017	0 08	0 5951	15	0 06	0 5611	15	62 0%	0 02 [-0 39 0 43]
Maillard 2016	-0 4	1 0198	8	-0 2	0 7483	8	13 8%	-0 20 [-1 08 0 68]
Matsuo 2015	-0 24	0 6509	13	-0 17	1 0312	13	24 2%	-0 07 [-0 73 0 59]
Total (95% CI)			**36**			**36**	**100.0%**	**-0.03 [-0.36, 0.29]**

Heterogeneity Tau² = 0 00 Chi² = 0 21 df = 2 (P = 0 90) ² = 0%
Test for overall effect Z = 0 19 (P = 0 85)



Key: MD = mean difference; SD = standard deviation; Total = number of participants.
Figure 4.6 Total Cholesterol/High-density Lipoprotein Cholesterol Ratio Forest Plot

Heterogeneity and Publication Bias Meta-analyses indicated zero heterogeneity for all lipid fractions, and the TC/HDL-C ratio. Visual inspection of funnel plots showed moderate-to-high likelihood of publication bias for TC and TRG, and low-to-moderate likelihood for HDL-C and LDL-C, see SM Figures [4.7-4.11].

Study Quality and Reporting A median TESTEX score of 11 out of 15 was obtained (range 7 to 13). TESTEX scores (≥10 or <10) did not alter significance and heterogeneity, moreover sensitivity analysis (K-1) did not affect these results, see SM Table [4.4]. No study was excluded based on its TESTEX score.

Lipid Assessment Lipid assay details are provided in SM Table [4.5]. No study was excluded based on lipid assay reporting.

DISCUSSION

Meta-analysis This systematic review and meta-analysis aimed to compare the effects of HIIT and MICT on adult blood lipid profiles in sub-clinical populations and to examine whether one protocol was superior to the other. Our review is the first to include more than 8 trials and compare the effect size of intermittent high-low intensity and continuous moderate intensity in positively altering TC, TRG, HDL-C, LDL-C, and the ratio of TC/HDL-C in sub-clinical populations. Our analysis, of 29 data sets from 26 studies, assessed the effects on lipids of weight-bearing and non-weight bearing HIIT and MICT exercise therapies excluding concurrent dietary or pharmaceutical interventions. Although HIIT and MICT appear to induce positive changes, our analysis did not demonstrate that intermittent high-intensity out-performed continuous moderate-intensity protocols in achieving better lipid outcomes.

Outcome Measures

Total Cholesterol We found no statistically significant evidence showing a benefit in favour of HIIT or MICT in reducing TC. Our results are similar to a previous qualitative review comparing exercise with no exercise.[33] Our results differ from the findings of others[38-40] whose works did not differentiate for continuous or interval protocols. We also included papers with intervention duration of 4-6 weeks; these are arguably of insufficient duration to effect change.[33] MICT has been shown to prioritise fat as a primary substrate fuel in sub-clinical populations,[83] hence it could be reasonably expected that MICT would outperform HIIT. However, a weekly energy expenditure[30] or volume[15, 29, 31] is required before impacts on lipids can be observed, and a number of included protocols likely fell short of this threshold. We excluded studies including dietary intervention which may have impacted our results.[84]

Triglycerides We found no difference in effect size between HIIT and MICT in positively altering TRG except for sub-analyses. Our results broadly agree with a recent meta-analysis,[85] although we excluded trials of cardiac patients. Our results also agree with a previous qualitative review.[33] We differ from the work of others,[38-40] possibly because we included mixed populations or because we differentiated for protocol and intensity. A systematic review suggested TRG responded favourably to increased exercise intensity in

MetS populations,[16] agreeing with a previous meta-analysis,[39] and our sub-analysis (MetS or MetS factors/risk) found HIIT significantly lowered TRG more than MICT.

High-Density Lipoprotein Cholesterol HIIT showed significance compared to MICT for affecting HDL-C, however sensitivity analysis (K-1) contradicted this result. Our findings agree with a previous meta-analysis,[39] although this work compared exercise with no exercise only and focused on overweight and obese populations. We also agree with the results of a recent meta-analysis comparing intensity, although this work focused on studies of subjects with cardiovascular conditions.[85] Our results are dissimilar to other systematic reviews,[16, 33, 36] and two (one female and one male) meta-analyses,[38, 40] although none of these works compared for intensity. Given the greater impact on cardiorespiratory fitness of HIIT compared to MICT,[23, 55] our result is not unexpected, as HIIT would most likely outperform MICT in optimising lipid transport via an improved microvascular capillary network. However, both HIIT and MICT have been shown to equally improve muscle microvascular density.[86]

Low-Density Lipoprotein Cholesterol We found no significance for preferring HIIT to MICT for positively changing LDL-C. Our findings agree with other meta-analyses.[39, 85] We differ from two meta-analyses comparing exercise with no exercise and examining general populations,[38, 40] as well as a meta-analysis comparing intensity and examining LDL-C in overweight and obese populations.[87] We surmise this is a corollary of our inclusion of studies with healthy participants, although our sub-analyses of clinical and sub-clinical participants did not affect significance. Previous work showing that LDL-C falls when accompanied by weight loss has been corroborated by a later meta-analysis comparing exercise with no exercise in overweight and obese groups.[30, 39] A recent meta-analysis of HIIT compared to MICT in these populations showed no preference for either protocol in achieving weight loss.[86, 88] Existing higher base levels of lipids in these populations[7] may have led to sufficient decrease in LDL-C to demonstrate significance for HIIT protocols.[14] According to one systematic review, increasing intensity is required to impact LDL-C,[16] hence MICT by its nature should have shown inferiority to HIIT. Insufficient intervention duration and probable similar overall intensity in the protocols of included studies may have obfuscated our results.

Total Cholesterol/High-Density Lipoprotein Cholesterol Ratio HIIT and MICT were equivalent in reducing TC/HDL-C ratio.

Clinical Significance and Future Research Our meta-analysis results indicate HIIT seems to be superior to MICT in affecting HDL-C. Either HIIT or MICT can be prescribed to positively affect TC, TRG, LDL-C and the TC/HDL ratio, as part of efforts to increase exercise participation to meet current aerobic physical activity guidelines.[18] Previous studies and reviews suggest a weekly minimum EEE of >1200 kcals and time commitment >150 minutes of aerobic physical activity at vigorous intensity is necessary to positively impact lipids.[26, 30-31, 33] These indicative minimum requirements exceed current weekly aerobic physical activity guidelines of 150 minutes at moderate intensity or 75 minutes at vigorous intensity.[90] Sharing the results of these studies and reviews may motivate some demographics to participate in and/or increase aerobic physical activity.

Based on the number of HIIT or MICT sessions per week, our included studies generally met the minimum weekly time requirements of current aerobic physical activity guidelines.[90] The EEE, effort, session duration and frequency achieved in several studies were unlikely to meet the levels required to positively impact lipids.[26, 30-31, 33] We propose that future research should address the following criteria to ascertain whether HIIT or MICT is better in inducing desirable changes in TC, TRG, and LDL-C for varying populations: interventions should aim for duration8 weeks (excluding familiarity sessions) as previously established;[31, 33] protocols should achieve a weekly EEE threshold >1200 kcals,[30] or minimum session duration and frequency;[26] and HIIT interventions should ensure that the overall effort (work:recovery ratio and repetitions) remains at or close to vigorous intensity per session, since higher intensity has been shown to impact more favourably on lipids than lower intensity.[13, 26]

Strengths and Limitations in the Systematic Review and Meta-analyses This review has a number of strengths. To our knowledge, this review and quantitative meta-analysis is the first to compare the effects of intermittent high-intensity and continuous moderate-intensity weight-bearing and non-weight bearing protocols on cholesterol fractions and the TC/HDL-C ratio in healthy, sub-clinical and clinical adult populations.

Previous systematic reviews did not use the validated exercise study evaluation tool TESTEX[48] to measure the quality of included studies. We followed a rigorous inclusion and exclusion protocol to ensure minimisation of confounding factors amongst the study populations.[91]

A major limitation of this review is the relatively small number of studies used in our sub-analyses. This is compounded by the varying populations studied and the different exercise protocols (number and length of effort and recovery intervals, intensities, session and intervention duration, session frequency, and energy expenditure) used for comparing HIIT against MICT. Some studies did not report all lipid fractions. In addition, reporting of protocol adherence and intensity used objective eg electronic devices as well as subjective measures eg Borg scale, self-reported HR, log books, denoted by different indices of intensity (energy expenditure, VO2Max, MHR, METs, Borg scale).

Aerobic physical activity protocols mainly consisted of running, swimming, walking, or cycling, which could have influenced results. While the majority of studies included in the analysis specified intervention duration ≥8 weeks, a small number of included studies used an intervention duration of 4-6 weeks, which may have weakened results.

With respect to data pooling, we measured the difference between pre- and post-intervention means; in cases where the MD SDs were not available, we imputed the SD using pre-post SDs, *P* values, and 95% CIs, and hence statistical analyses depended on extrapolated data. Our imputation was conservative, and sensitivity analyses (leave-one-out) were conducted. This approach may have weakened results.

The results of our analysis may have been affected because some of the studies measured lipids as secondary and not as primary outcomes. We therefore infer that some studies were perhaps not designed with the primary goal of lipid lowering. In the paragraph on clinical significance above, we have demonstrated that earlier reviews suggest a minimum weekly EEE of >1200 kcals, thus some of the studies that met our inclusion criteria may have failed to meet the minimum applicable EEE, session duration, and session frequency required to positively impact lipids.

CONCLUSION

Pooled analysis indicated that aerobic physical activity intensity did not influence effect size for change in TC, TRG, LDL-C, and TG/HDL-C. Change in the effect size of lipids seems to be sensitive to physical activity volume rather than intensity. The exception to this appears to be HDL-C, which improved more with HIIT than MICT. Our findings suggest that HIIT protocols do not confer greater improvements in lipid profiles over MICT protocols. Clinicians and allied health specialists should therefore endeavour to encourage people to undertake aerobic physical activity at or above the minimum threshold (about 1200 kcal weekly) as a treatment or prevention strategy likely to be effective in managing lipid profiles and reducing CVD risk.

Supplementary Materials

Study (alphabetical order)	Participants (number, gender, age, health status, dropout)	Exercise Protocols (frequency, intensity, time, type, volume, progression, study duration, exercise equipment, session supervision, physiological monitoring; work or energy matching)	Pre- and Post Lipid Outcomes
(Ciolac, et al. 2010)	Recruited (R) 44♀; Analysed (A) HIIT: 11, MICT: 11, CON: 12; HIIT: 24.4 ± 3.8 years MICT: 26.6 ± 4.9 years CON: 25.3 ± 3.7 years; Status: healthy; HIIT dropout: 5 (1 non compliant) MICT dropout: 5 (2 non compliant) CON dropout: 0 Completion compliance minimum: 70%	Treadmill walking or running; 3 sessions per week; 16 weeks duration; Weight-bearing; 5 min warm-up (intensity unspecified); 15 min calisthenics cool down (intensity unspecified); HIIT: (2 min walking 50–60% of VO_{2MAX} + 1 min walking/running at 80–90% of VO_{2MAX}) x 13; MICT: 40 min walking 60–70% VO_{2MAX}; Cardiovascular workload matched; Exercise time matched; Supervised; HR monitoring device; VO_{2MAX} established at baseline; treadmill incline adjusted throughout duration of study for training adaptations;	Measurements taken during follicular phase of subject's cycle, pre-post intervention; 12-hour fasted state, seated position; mg dL^{-1} Lipid fractions similar between groups at baseline and follow-up; Lipid changes: TC: ↓HIIT>↓MICT; TRG: ↓HIIT>↑MICT; HDL-C: ↑MICT>↑HIIT; LDL-C: ↓HIIT>↓MICT; not statistically significant;
(Connolly, et al. 2017)	R 48♀; A HIIT: 15, MICT: 15, CON: 15 HIIT: 44 ± 7 years MICT: 43 ± 7 years CON: 45 ± 7 years; Status: healthy; HIIT dropout: 1 MICT dropout: 1 CON dropout: 1	Ergocycle; 3 sessions per week; 12 weeks duration; Non weight-bearing; 5 min warm-up 50W; 5 min cool-down 50W; HIIT: (30-20-10 sec) ie: 30 sec LI (~30% of max effort) + 20 sec MI (~50–60% of max effort) + 10 sec HI (>90% max effort) x 5 + 2 min passive recovery) x 5; MICT: 50 min 70-85% HR_{peak}; Not work/energy matched; Supervised; HR monitoring device, RPE 10 point scale; self-selection of intensity (pedal cadence or flywheel resistance increase) and self-adjustment for training adaptation;	Time of measurement pre intervention not indicated; post not < 96 hours after final exercise session; Overnight fasted state, seated position; mmol/L Lipid fractions similar between groups at baseline and follow-up; Lipid changes: TC: ↓MICT>↑HIIT; TRG: ↑MICT=↑HIIT; HDL-C: ↓HIIT<↓MICT; LDL-C: ↓MICT>↑HIIT; TC/HDL-C: ↑MICT<↑HIIT; not statistically significant;
(Cuddy, Ramos and Dalleck 2019)	R: 16♀, 16♂ A HIIT: 12, MICT: 15,	Ergocycle HIIT: 2-3-4 sessions per week;	Measurements taken pre-post training (48-72 hours after last training session); Fasted state;

	HIIT: 40.8 ± 10.8 years MICT: 42.2 ± 9.7 years Status: Ov, Ob HIIT dropout: 4 MICT dropout: 1	MICT: 3-4-5 sessions per week 8 weeks duration; Non-weight bearing; HIIT: 3 min warm-up, 3 min cool-down MICT: unspecified (included in 30 mins) HIIT: Wk 1-2: 20 sec sprint + 3 min slow recovery + 20 secs sprint ≈ 4 mins of HIIT protocol per session 2 days Wk 3-4: as above 3 days Wk 5-8: as above 4 days MICT (unspecified aerobic exercise): Wk 1: 40-50% HRR 3 days 25min Wk 2: 50-55% HRR 4 days 30 min Wk 3-4: 55-60% HRR 4 days 30 min Wk 5-6: 55-60% HRR 5 days 30 min Wk 7-8: 60-65% HRR 5 days 30 min HRR; Exercise energy expenditure unmatched; Supervised; MHR and VO_{2MAX} estimated at baseline; HIIT intensity adjusted, MICT not stated; HIIT: HR monitoring device, MICT not stated;	Seated position; mg dL^{-1} Lipid fractions similar between groups at baseline; Lipid changes: TRG:↓HIIT>↓MICT; HDL-C: ↑HIIT>↑MICT; Statisitically significant within group from baseline for HIIT and MICT but not between groups;
(Fisher, et al. 2015)	R 28♂; A HIIT: 13, MICT: 10; 20 ± 1.5 years; Status: Ov, Ob; HIIT dropout: 2 MICT dropout: 3;	Ergocycle; HIIT: 3 sessions per week; MICT: 5 sessions per week; 6 weeks duration; Non weight-bearing; Warm-up/cool-down not indicated; HIIT: (((4 min 15% Max-AP + 30 sec 85% Max-AP) x 4) + 2 min 15% Max-AP) x 2; MICT: 45-60 min 55-65% VO_{2peak}; Exercise energy expenditure match not indicated; Supervised; HR monitoring device; Maximum Anaerobic Power (Max A-P) and VO_{2peak} established at baseline; adjustment of effort during sessions not indicated;	Measurements taken 24-72 hours after last day of training; Overnight fasted state; Seated position; mg dL^{-1} Lipid fractions similar between groups at baseline; Lipid changes: TC*: ↓MICT>↓HIIT; TRG*: ↓MICT>↓HIIT; *Statistically significant for test of change over time within groups; HDL-C: ↓HIIT<↓MICT; LDL-C: ↓MICT>↓HIIT Not statistically significant

(Hwang, et al. 2016)	R 51; A HIIT: 15(5♂), MICT: 14(7♂), CON: 14(5♂); HIIT: 64.8 ± 1.4 years MICT: 65.6 ± 1.8 years CON: 63.8 ± 1.6 years; Aged; Status: Ov; HIIT dropout: 2(1♂) MICT dropout: 4(2♂) CON dropout: 2(1♂);	All-extremity ergometer; 4 sessions per week; 8 weeks duration; Non weight-bearing; 10 min warm-up 70% HR_{peak}; 2-min cool-down 70% HR_{peak}; HIIT: (4 min 90% HR_{peak} + 3 min 70% HR_{peak}) x 4; MICT: 32 min 70% HR_{peak} Exercise energy expenditure closely matched; Supervised; HR monitoring device; HR_{peak} established at baseline, individuals self-adjusted to reach target HR;	Measurements taken pre intervention. Post intervention blood samples obtained 31.8 ± 6.1 and 24.7 ± 3.9 hours following last exercise training session for HIIT and MICT; Fasted state; Position not indicated; mg dL^{-1} Lipid fractions similar between groups at baseline and followup; Lipid changes: TC: ↓HIIT>↓MICT; TRG: ↓HIIT>↑MICT; HDL-C: ↓MICT>∆HIIT; LDL-C: ↓HIIT>↓MICT; Not statistically significant
(Keating, et al. 2014)	R 38 (7♂); A HIIT: 11(3♂), MICT: 11(2♂), CON: 11(2♂); HIIT: 41.8 ± 9.7 years MICT: 44.1 ± 6.9 years CON: 42.9 ± 9.4 years Status: Ov HIIT dropout: 2(0♂) MICT dropout: 2(0♂) CON dropout: 1(0♂)	Ergocycle; 3 ssessions per week 12 weeks duration; Non-weight bearing; HIIT: 6 min total warm-up/cool-down (intensity unspecified) HIIT: Wks 1-4 (120% VO_{2peak} + <40% VO_{2peak}) x 4 ≈ 12.5-16.5mins per session (work:recovery ratio = 16.7-37.5), Wks 5-12 (120% VO_{2peak} + <40% VO_{2peak}) x 6 ≈ 18mins per session (work:recovery ratio 50%); MICT: 3-6 min total warm-up/cool down (intensity unspecified) MICT: Wks 1-2 50-60% VO_{2peak} 30-40 mins, Wks 3-12 65% VO_{2peak} 45 mins Energy expenditure/workload unmatched; Supervised; HR monitoring device, RPE 6-20 point scale; VO_{2peak} estimated at baseline; effort increased to maintain intensity targets;	Measurements taken pre-post invention; 10-hour overnight fasted state; Position not indicated; mmol/L Lipid fraction dis/similarites between groups at baseline not stated; Lipid changes: TC*: ↑MICT∆HIIT; TRG: ↓MICT∆HIIT; HDL-C: ∆MICT = ∆HIIT; LDL-C*: ↑MICT∆HIIT; Not statistically significant *Statistically significant group x time interaction (P<.05).
(Kemmler, et al. 2014)	R 81♂; A HIIT: 33, MICT: 32, CON: 41; HIIT: 43.9 ± 5.0 years MICT: 42.9 ± 5.1 years CON: 42.5 ± 5.6 years; Status: Ov, MetS; HIIT dropout: 7 MICT dropout: 9 CON dropout: 0;	Running; 2 sessions per week at baseline, 3-4 sessions per week from week 8; 16 weeks duration; Weight-bearing; No warm-up/cool-down specified; HIIT: (90 sec -12 mins 95-110% IAT-HR + 1-3 mins 70-75% IAT-HR) ≈ 30-40 min per session and 25-45 min 95% IAT-HR; MICT: 35-90 min 70–82.5% IAT-HR; Exercise energy expenditure closely matched;	Measurements taken pre-post intervention; 12-hour overnight fasted state; Position not indicated; mg dL^{-1} Lipid fractions similar between groups at baseline; Lipid changes: TRG: ↓HIIT*>↓MICT; HDL-C**: ↑HIIT*>↑MICT* *Significant changes within groups;

		50% sessions per week supervised with HR training device and RPE, individual monthly training log; IAT-HR: HR at individual aerobic threshold IAT (minimum lactate 2.0 mmol/L) established at baseline and adjusted at 8 weeks;	**Significant changes between groups.
(Kong, et al. 2016)	R 31♀; A HIIT: 13, A MICT: 13; HIIT: 21.5 ± 4 years MICT: 20.5 ± 1.9 years Status: Ob; HIIT dropout: 2 MICT dropout: 3	Ergocycle; 4 sessions per week 5 weeks duration; Non weight-bearing; 3 min warm up 50 W; 3 min cool-down 50W; HIIT: (8 sec maximum VO_{2peak} + 12 sec passive recovery) x 60, average workload ≈ 80 ± 7% VO_{2peak}; MICT: 40 min 60% VO_{2peak} first 2 weeks, thereafter 40 min 80% VO_{2peak}; Not work/energy matched; Supervised; HR monitoring device, RPE 6-20 point scale; VO_{2peak} established at baseline; resistance increased after 2 successfully completed sessions at a given resistance by 0.5kg;	Measurements taken 96-144 hours pre-intervention during follicular or late luteal phases of subject's cycle, post-intervention 72-120 hours after last training session; 12-hour fasted state, Position not indicated; mmol/L Lipid fractions similar between groups at baseline and follow-up; Lipid changes: TC: ↓HIIT>↑MICT; TRG: ↓HIIT>↑MICT; HDL-C: ↑HIIT>∆MICT; LDL-C: ↓HIIT>↑MICT; Not statistically significant
(Lee, Hsu and Cheng 2016, a)	R 21♂; (entire study) Comparison a: MICT group split A HIIT: 13, A MICT: 7; HIIT: 21 ± 1 years MICT: 21 ± 3 years Status: healthy; HIIT dropout: 1 MICT dropout: 0	Ergocycle; 3 sessions per week 4 weeks duration; Non weight-bearing; 5 min warm-up 30% VO_{2MAX} 3 min cool-down 30% VO_{2MAX}; HIIT: 2 weeks (60 sec 85% VO_{2MAX} + 120 sec 30% VO_{2MAX}) x 8, 2 weeks (60 sec 90% VO_{2MAX} + 120 sec 30% VO_{2MAX}) x 8; MICT: usual activity with no HIIT component ≈ 6 hours per week; Not work/energy matched; HIIT supervised, MICT unsupervised; HR monitoring not specified, VO_{2MAX} established at baseline;	Measurements taken pre-post intervention; 12-hour fasted state, Position not indicated; mg dL^{-1} Lipid fractions similar between groups at baseline and follow-up; Lipid changes: TC: ↓MICT>↑HIIT; TRG: ↑HIIT>↑MICT; HDL-C: ↑HIIT>↓MICT; LDL-C: ↓MICT>↓HIIT; Not statistically significant
(Lee, Hsu and Cheng 2016, b)	R 21♂; (entire study) Comparison b: MICT group split A HIIT: 12, A MICT: 6; HIIT: 21 ± 1 years MICT: 21 ± 3 years; Status: healthy;	Ergocycle; 3 sessions per week 4 weeks duration; Non weight-bearing; 5 min warm-up 30% VO_{2MAX} 3 min cool-down 30% VO_{2MAX};	Measurements taken pre-post intervention; 12-hour fasted state, Position not indicated; mg dL^{-1} Lipid fractions similar between groups at baseline and follow-up; Lipid changes:

	HIIT dropout: 2 MICT dropout: 1	HIIT: 2 weeks (10 sec 85% VO_{2MAX} + 20 sec 30% VO_{2MAX}) x 48, 2 weeks (10 sec 90% VO_{2MAX} + 20 sec 30% VO_{2MAX}) x 48; MICT: usual activity with no HIIT component ≈ 6 hours per week; Not work/energy matched; HIIT supervised, MICT unsupervised; HR monitoring not specified, VO_{2MAX} established at baseline;	TC: ↓MICT>↑HIIT; TRG: ↑HIIT>↑MICT; HDL-C: ↑HIIT>↓MICT; LDL-C: ↓MICT>↓HIIT; Not statistically significant
(Lira, et al. 2019)	R 20♂; A HIIT: 10, A MICT: 10 HIIT: 26.9 ± 4.7 years MICT: 24.6 ± 3.7 years Status: healthy HIIT dropout: 0 MICT dropout: 0	Treadmill running; 3 sessions per week; 5 weeks duration; Weight-bearing; 5 min warm up 50% sVO_{2PEAK} ≈ maximal aerobic speed 5 min cool down 50% sVO_{2PEAK} HIIT: (1 min 100% sVO_{2PEAK} + 1 min passive recovery) x 10-20 (to equal 5km) MICT: 20-30 mins (to equal 5km) 70% sVO_{2PEAK} Not energy work/matched; Supervised; HR monitoring, VO_{2PEAK} established at baseline, effort increased to maintain intensity targets;	Measurements taken pre-post intervention; 12-hour overnight fasted state; Position not indicated; mg dL^{-1} Lipid fractions similar between groups at baseline and follow-up; Lipid changes: TC: ↓MICT>↑HIIT; TRG: ↓HIIT=↑MICT; HDL-C: ↓MICT >↑HIIT; Not statistically significant
(Maillard, et al. 2016)	R 17♀; A HIIT: 8, A MICT: 8; Age matched HIIT and MICT, 61-80 years, postmenopausal; Status: T2D, Ov, Ob; Aged; HIIT dropout: 0 MICT dropout: 1;	Ergocycle; 2 sessions per week; 16 weeks duration; Non weight-bearing; 5 min warm-up (intensity unspecified) 5 min cool-down (intensity unspecified); HIIT: (8 sec 80% max HR + 12sec 20-30rpm) x 60 MICT: 40 min 55-60% target HR of estimated HRR: Exercise energy expenditure closely matched; Supervised; Mean HR monitored weeks 2, 8, 16, estimated maximum HR (208 - 0.7 x age) and target HR [(est max HR – HR at rest) x target % + HR at rest] calculated at baseline and after 2 months;	Measurements taken one week before first and 5-7 days after last training session; Overnight fasted state; Position not indicated; mmol/L Lipid fractions similar between groups at baseline; at follow-up HIIT TRG higher; Lipid changes: TC: ↓MICT>↓HIIT; TRG*: ↓MICT>↑HIIT; HDL-C: ↑MICT=↑HIIT; LDL-C: ↓MICT>↑HIIT; TC/HDL-C**: ↓HIIT>↓MICT Not statistically significant, *Group effect (HIIT) significant ANOVA P=.03, **Time effect significant ANOVA P=.03;
(Matsuo, et al. 2015)	R 26♂; A HIIT: 13, A MICT: 13; HIIT: 47.5 ± 7 years MICT: 47.4 ± 7.5 years;	Ergocycle; 3 sessions per week; 8 weeks duration; Non weight-bearing;	Measurements taken pre-post intervention; 12-hour fasted state; Position not indicated; mg dL^{-1}

	Status: MetS risk factors, Ov HIIT dropout: 0 MICT dropout: 0;	2 min warm-up 30W 3 min cool-down 30W (MICT only); HIIT: (3 min 85% VO_{2peak} + 2 min 50% VO_{2peak}) x 3; MICT: 40 min 60-65% VO_{2peak} Not work/energy matched; Supervised; HR monitoring not specified, MHR and VO_{2peak} established at baseline and measured at week 4, exercise intensity adjusted at week 4;	Lipid fractions similar between groups at baseline; Lipid changes: TC: ↑MICT>↑HIIT TRG: ↓HIIT>↓MICT HDL-C*: ↑MICT=↑HIIT LDL-C: ↑HIIT>∆MICT TC/HDL-C: ↓HIIT*>↓MICT *Statisically significant;
(Mohr, et al. 2014)	R 62♀; A HIIT: 21, MICT: 21, CON: 20; HIIT: 44 ± 2 years MICT: 46 ± 2 years CON: 45 ± 2 years Status: H, Ov; HIIT dropout: 0 MICT dropout: 0 CON dropout: 0	Free-style swimming; 3 sessions per week 15 weeks duration; Non weight-bearing; HIIT: (30 sec max effort (≈85-95% MHR) + 2 min passive recovery) x 6-10 ≈ 15-25 mins; MICT: 60 min aiming for max distance ≈ 72-79% MHR; Not work/energy matched; Supervised; HR monitored week 1 and week 15, swimming distances recorded each session, MHR established at baseline, intervals increased at 6 and 12 weeks for HIIT participants, and MICT participants were encouraged to swim further at each session if possible;	Measurements taken pre-post intervention without reference to menstrual cycle; Overnight fasted state; Resting position; mmol/L Lipid fractions were similar between groups at baseline and follow-up; Lipid changes: TC: ↓MICT*>↓HIIT; HDL-C: ↑MICT>∆HIIT; LDL-C: ↓MICT=↓HIIT; Not statistically significant, *statistically significant for sub-group with baseline TC >= 5.5 mmol/L;
Morales-Palermo, et al. 2019 a	R: 132 (entire study) Comparison a: MICT, CON groups split A HIIT: 32 (35%♀), MICT: 18 (37%♀), CON: 11 (36%♀); HIIT: 55 ± 8 years MICT: 57 ± 7 years Status: MetS HIIT dropout: 3 MICT dropout: 4 CON dropout: 0 Compliance set at 90% of sessions	Ergocycle 3 sessions per week; 16 weeks duration; Non weight-bearing; HIIT 10 min 70% MHR warm-up/5 min 70% cool-down MICT warm-up/cool down included in session HIIT: (4 min 90% MHR + 3 min 70% MHR) x 4 MICT: 50 min 70% MHR Not work/energy matched; Supervised; HR monitoring, MHR established at baseline, effort increased to maintain intensity targets;	Measurements taken pre- and 48 hours post intervention; Overnight fasted state; Position not indicated; mg dL^{-1} Lipid fractions similar between groups at baseline; Lipid changes: TC: ↑MICT>↑HIIT TRG: ↓MICT>↓HIIT HDL-C: ↓MICT>↑HIIT LDL-C: ↓MICT>↓HIIT
Morales-Palermo, et al. 2019 b	R: 132 (entire study) A HIIT: 32 (34%♀), MICT: 18 (37%♀), CON: 11 (36%♀); HIIT: 58 ± 8 years	Ergocycle 3 sessions per week; 16 weeks duration; Non weight-bearing;	Measurements taken pre- and 48 hours post intervention; Overnight fasted state; Position not indicated; mg dL^{-1}

	MICT: 57 ± 7 years Status: MetS HIIT dropout: 4 MICT dropout: 4 CON dropout: 0 Compliance set at 90% of sessions	HIIT 5 min 70-75% MHR warm-up/5 min 70% cool-down MICT warm-up/cool down included in session HIIT : (1 min 100%MHR + 1.5 min 65%MHR) x 10 MICT: 50 min 70% MHR Not work/energy matched; Supervised; HR monitoring, MHR established at baseline, effort increased to maintain intensity targets;	Lipid fractions similar between groups at baseline; Lipid changes: TC: ↑MICT>↓HIIT TRG: ↓MICT>↓HIIT HDL-C: ↑HIIT=↓MICT LDL-C: ↑HIIT>↓MICT
(Moreira, et al. 2008)	R: 30 (gender unspecified); A 22 (8♂) HIIT: 8, MICT: 8, CON: 6; Status: Ob Age: 40 ± 8 years Total dropout (gender, group unspecified): 7 stated in tables, 8 stated in text;	Ergocycle 3 sessions per week; 12 weeks duration; Non-weight bearing; Warm-up/cool down unspecified; HIIT: (2 mins [Anaerobic Threshold+(AT x 20%)] + 1 min passive recovery) x 20* MICT: 60* mins [AT-(AT x 10%)] Exercise time matched; HR monitoring device; Anaerobic Threshold (AT) established at baseline, training target intensity maintained; *Commencing in week 1 with 20 mins per session and incrementally adjusting time until week 6 with 60 mins per session.	Measurements pre-post intervention within 7 day period; 10-hour fasted state; Position not indicated; $mg\ dL^{-1}$ Lipid fractions similar between groups at baseline. Lipid changes‡: TC: ↓MICT 182 ± 29 – 155 ± 15*>∆HIIT 163 ± 11 - 163 ± 22 TG: ↓MICT 204 ± 80 - 197 ± 84>↓HIIT 207 ± 130 - 206 ± 90 *Statistically significant pre/post MICT values. ‡measurements determined from graphic
(Nybo, et al. 2010)	R 36♂; A HIIT: 8; MICT: 9; Strength (STR): 8; CON: 11; HIIT: 37 ± 3 years MICT: 31 ± 2 years STR: 36 ± 2 years CON: 30 ± 2 years; Status: Healthy HIIT dropout: 0 MICT dropout: 0 STR dropout: 0 CON dropout: 0	Running; 3 sessions per week; 12 weeks duration; Weight-bearing; HIIT: 5 min warm-up 65% HRR + [(2 min finishing at 90-95% MHR (85% VO_{2MAX}) + 1 min recovery (effort unspecified)] x 5 MICT: 60 mins 80% MHR (65% VO_{2MAX}) Not work/energy matched; Supervision not indicated; Monitoring not indicated; MHR and VO_{2MAX} established at baseline, training target intensity maintained;	Measurements taken pre-post intervention; Overnight fasted state; Resting position; mmol/L Lipid fractions similar between groups at baseline; Lipid changes: TC: ↓MICT>↓HIIT; HDL-C: ↑MICT>∆HIIT; LDL-C: ↓MICT=↓HIIT; TC/HDL-C ratio: ↓MICT*>∆HIIT Not statistically significant *Statistically significant pre-post intervention
(Ramos, et al. 2016)	R 43 (♂ and ♀ as percentage); A HIIT: 22(55%♂), MICT: 10(71%♂) HIIT: 56 ± 10 years MICT: 57 ± 9 years	Ergocycle or treadmill per supervised sessions, unsupervised sessions e.g. running, swimming, walking, rowing; HIIT: 3 sessions per week; MICT: 5 sessions per week; 16 weeks duration;	Measurements were taken pre-post intervention 12-hour fasted state; mmol/L Lipid fractions were similar between groups at baseline and follow-up;

	Status: H, MetS, T2D; HIIT dropout: 7 (gender unspecified) MICT dropout: 4 (gender unspecified)	Weight- and non weight-bearing HIIT: (4 min 85-95% HR_{peak} + 3 min 50-70% HR_{peak}) x 4; 10 min warm-up 60-70% HR_{peak} MICT: 30 min 60-70% HR_{peak} including warm-up and cool-down 60-70% HR_{peak} Not work/energy matched; Two sessions per week supervised; HR monitoring device, Borg 6-20 ratings measured, training log; VO_{2MAX} established at baseline using either ergocycle or treadmill, training target intensity maintained;	Lipid changes: TRG: ↓HIIT>↓MICT HDL-C: ↑MICT=↑HIIT Not statistically significant
(Ruffino, et al. 2017)	R: 21♂ A: 8 HIIT; 8 MICT 55 ± 5 years; Status: T2D, Ob, Ov HIIT dropout: 2 MICT dropout: 3 Compliance requirement: miss >20% of the total training sessions or 3 consecutive sessions, or the final session before post-intervention testing for either HIIT or MICT;	HIIT: Ergocycle; MICT: walking HIIT: 3 sessions per week; MICT: 5 sessions per week 8 weeks duration HIIT: (3 mins warm up 25W, 10-20 secs sprint 86±6%-88±6% MHR, 3 minutes recovery 25W, 10-20 secs sprint 86±6%-88±6% MHR, 3 minutes cool down 25W) x 1. Sprints 10 secs in sessions 1–4, 15 secs in sessions 5–12, and 20 secs in last 12 sessions. MICT: 30-min walking at 40% HHR Wk 1-2, 50% HRR Wk 3-4, 55% HRR Wk 5–8 HIIT: non-weight bearing; MICT: weight-bearing; HIIT: all sessions supervised; MICT: 3 sessions supervised; HR monitoring device, RPE (6-20 Borg scale) recorded each final session every week;	Measurements taken pre intervention and 3 days post intervention; Overnight fasted state; Seated position; mmol/L Lipid fractions were similar between groups at baseline and follow-up; Lipid changes: TRG: ↓MICT=↓HIIT HDL-C: ↑HIIT>ΔMICT LDL-C: ↑HIIT>↓MICT Not statistically significant
(Sawyer, et al. 2016)	R 22; A HIIT: 9(5♂); MICT: 9(4♂) HICT: 35.6 ± 8.9 years MICT: 34.8 ±7.7 years Status: Ob HIIT dropout: 2 (gender unspecified) MICT dropout: 2 (gender unspecified)	Ergocycle; 3 sessions per week; 8 weeks duration; Non weight-bearing; HIIT and MICT: 5 min warm-up 50-60% MHR HIIT: 4 min cool-down 50-60% MHR MICT: 5 min cool-down 50-60% MHR HIIT: (1 min 90-95% MHR + 1 min active recovery 25-50 Watts) x 10 MICT: 30 min 70–75% MHR Not work/energy matched; Supervised; HR monitoring device; VO_{2MAX} established at baseline and measured at end of Weeks 4 and 8, training target intensity maintained;	Measurements taken 72 hours pre/post first/last exercise session 10-hour fasted state; Position not indicated; mg dL^{-1} Lipid fractions were similar between groups at baseline and follow-up; Lipid changes: TC: ↑HIIT>↑MICT TRG: ↑MICT>↓HIIT HDL-C: ↑HIIT>↓MICT LDL-C: ↑HIIT>↑MICT Not statistically significant

(Shepherd, et al. 2015)	R 90; A HIIT: 42(12♂, 30♀) MICT: 36(14♂, 22♀) HIIT: 42 ± 11 years MICT: 43 ± 11 years Status: Ov HIIT dropout: 4 (3♂) MICT dropout: 8 (1♂)	Ergocycle; HIIT: 3 sessions per week MICT: 5 sessions per week 10 weeks duration; Non weight-bearing; HIIT 5 min warm-up and cool-down MICT warm up and cool-down included in session; HIIT: 15-60 sec >90% MHR + 45-120 sec passive recovery ≈ 22 min session MICT: 30-45 min progression over 10 weeks 70% MHR; Not work/energy matched; 3 instructor-led sessions per week; HR monitoring device, participants self-monitored HR and adjusted effort levels, individual training log; VO_{2MAX} established at baseline;	Measurements taken pre and 48-120 hours after last training session post intervention 10-hour fasted state; Resting position; mmol/L Lipid fractions were similar between groups at baseline and follow-up; Lipid changes: TC: ↓MICT>↓HIIT TRG: ↓HIIT>↓MICT HDL-C: ↑MICT>↑HIIT LDL-C: ↓HIIT=↓MICT LDL-C/HDL-C: ↓MICT>↓HIIT Not statistically significant
(Thomas, et al. 1985, a)	R 48♂ (entire study); A 36 (entire study) Comparison a (MICT, CON groups split): HIIT: 8 ; MICT 6; CON: 4; HIIT: 23.1 ± 1.9 years MICT: 23 ± 1.2 years CON: 21.9 ± 1 years Status: healthy Dropout: 6 Compliance minimum: 90%	Running; 3 sessions per week; 11 weeks duration; Weight-bearing; Warm up cool down not indicated; HIIT: (4 min 90-100% MHR + 4 min < 50% MHR) x 6 MICT: 60 mins 75-85% MHR Work matched; Supervised; HR monitoring with radial artery palpation; VO_{2MAX} established at baseline, MICT progressed to and maintained 12km/h speed (approximating 85% MHR).	Measurements taken pre-, mid-, and post-intervention, 12-hour fasted state; Position not stated; mg dL^{-1} Lipid fractions were similar between groups at baseline and follow-up; Lipid changes: TC: ↑MICT=↓HIIT HDL-C: ↓MICT>ΔHIIT Not statistically significant
(Thomas, et al. 1985, b)	R 48♂(entire study) A 36 Comparison b (MICT, CON groups split): HIIT: 9; MICT 5; CON: 4 HIIT: 22.8 ± 1.1 years MICT: 23 ±1.2 years CON: 21.9 ± 1 years Status: healthy Dropout: 6 Compliance minimum: 90%	Running; 3 sessions per week; 11 weeks duration; Weight-bearing; Warm up cool down not indicated; HIIT: (2 min 90-100% MHR + 3 min <50% MHR) x 8 MICT: 60 mins 75-85% MHR Work matched; Supervised; HR monitoring with radial artery palpation;	Measurements taken pre-, mid-, and post-intervention, 12-hour fasted state; Position not stated; mg dL^{-1} Lipid fractions were similar between groups at baseline and follow-up; Lipid changes: TC: =↓HIIT >↑MICT HDL-C: ↓MICT>↓HIIT Not statistically significant

		VO_{2MAX} established at baseline, MICT progressed to and maintained 12km/h speed (approximating 85% MHR).	
(Tjønna, et al. 2008)	R 32; A HIIT: 11(4♂); MICT: 8(4♂); CON: 9(5♂) HIIT: 55.3 ± 13.2 years MICT: 52 ± 10.6 years CON: 49.6 ± 9 years Status: MetS HIIT dropout: 1 (gender unspecified) MICT dropout: 2 (gender unspecified) CON dropout: 1 (gender unspecified)	Inclined treadmill walking/running 3 sessions per week; 8 weeks duration; Weight-bearing; HIIT 10 min warm-up, 2 min cool down MICT warm- up and cool-down included in session; HIIT: (4 min 90% MHR + 3 min active recovery 70% MHR) x 4 MICT: 47 min 70% MHR; Exercise energy matched; Supervision not indicated; HR monitoring device; VO_{2MAX} established at baseline, training target intensity maintained;	Measurements taken pre-post intervention Fasted state; Position not stated; mmol/L Lipid fractions were similar between groups at baseline and TRG at follow-up; Lipid changes: TRG: ↑MICT>↑HIIT HDL-C: ↑HIIT*>↑MICT Not statistically significant, *Statistically significant from baseline and between groups.
(Vella, Taylor and Drummer 2017)	R 19; A HIIT: 8(2♂); MICT 9(5♂); HIIT: 23.1 ± 6.6 years MICT: 28.9 ± 8.1 years Status: Ov, Ob; HIIT dropout: 1 MICT dropout: 1	Treadmill, ergocycle, elliptical; 4 sessions per week; 8 weeks duration; Weight- and non weight-bearing; 5 min warm-up 35-40% HRR; 5 min cool-down 35-40% HRR; HIIT: (1 min 75-80% HRR + 1 min active recovery 35-40% HRR) x 10 MICT: 20min 55-59% HRR; Exercise energy matched; First 3 weeks, per week 3 sessions 1-1 supervised, 4th session unsupervised. Last 5 weeks all sessions unsupervised; HR monitoring device, individual training log; VO_{2PEAK} established at baseline, progressive workload adjustment;	Measurements taken pre and >48 hours after last exercise session post intervention, 12-hour fasted state; Position not stated; mmol/L Lipid fractions were similar between groups at baseline; Lipid changes: TC: ↓HIIT>↓MICT TRG: ↑HIIT=↑MICT HDL-C: ↑MICT >↓HIIT* LDL-C: ↓HIIT*>∆MICT Not statistically significant, *Signficantly significant from baseline and between groups
(Winding, et al. 2018)	R 35; A HIIT: 13(7♂); MICT: 12(7♂); CON: 7(5♂); HIIT: 54 ± 6 years MICT: 58 ± 8 years CON: 57 ± 7 years; Status: T2D, Ov; HIIT dropout: 2 (gender unspecified) MICT dropout: 0 (gender unspecified)	Ergocycle; 3 sessions per week; 11 weeks duration; Non weight-bearing; 5 min warm-up 40% peak workload (W_{peak}) no cool-down specified; HIIT: (1 min 95% W_{peak} + 1 min active recovery 20% W_{peak}) x 20 MICT: 40 min 50% W_{peak}; Not work/energy matched;	Measurements taken pre-post intervention 24-72 hours prior to first and 24-120 hours after last training session 10-hour fasted state; Position not stated; mmol/L Lipid fractions were similar between groups at baseline; Lipid changes: TC: ↓HIIT>↓MICT TRG: ↓HIIT>↑MICT

	CON dropout: 1 (gender unspecified)	Supervision not indicated; HR monitoring device; VO_{2PEAK} established at baseline, measured during weeks 4 and 8, training target intensity maintained;	HDL-C: ↓MICT>ΔHIIT LDL-C: ↓MICT=↓HIIT Not statistically significant
(Winn, et al. 2018)	R 23; (gender assumed mixed) A 21; HIIT: 8; MICT: 8; CON: 5 HIIT: 41 ± 14 years MICT: 46 ± 9 years CON: 51 ± 13 years Status: Ob HIIT dropout: 1 MICT dropout: 1 CON dropout: 0	Treadmill 4 sessions per week; 4 weeks duration; Weight-bearing; Warm-up/cool-down not stated; HIIT: 4 min 80% VO2peak + 3 min 50% VO2peak approx 60min MICT: 60 mins 55% VO2peak approx 60 min Exercise energy expenditure matched; Supervised; HR monitoring device; VO_{2PEAK} established at baseline, measured every 4th session, training target intensity maintained;	Measurements taken pre and 36-48 hours after last training session post intervention, 10-hour fasted state; Position not stated; mg dL^{-1} Lipid fractions were similar between groups at baseline and follow-up; Lipid changes: TC: ↓HIIT>↓MICT TRG: ↓HIIT>↓MICT HDL-C: ↑HIIT >↓MICT LDL-C: ↓HIIT>↓MICT Not statistically significant
(Zhang, et al. 2015)	R 43♀; A 35: HIIT: 12, MICT: 12, CON: 11; HIIT: 21.0±1.0 years MICT: 20.6±1.2 years CON: 20.9±1.0 years Status: Ob HIIT dropout: 2 MICT dropout: 3 CON dropout: 3	Treadmill running; 4 sessions per week 12 weeks Weight-bearing 10-minute warm-up and 5-minute cool down 50–60% of HR_{peak} HIIT: (4 min 85–95% HR_{peak} + 3 min 50–60% HR_{peak} + 7 min passive recovery) x 4. Week 1-2 85%, week 3-4 90%, week 5+, 95% HR_{peak} MICT: 33 mins 60–70% HR_{peak}. Week 1-2 60% HR_{peak}, Week 3-4 65%, Week 5+ 70% HR_{peak}; Oxygen cost matched; Supervised; HR monitoring device; VO_{2MAX} established at baseline, running speed maintained after week 5;	Measurements taken one week pre-intervention and 3 days post intervention; Overnight fasted state; Resting position; mmol/L Lipid fractions were similar between groups at baseline; Lipid changes: TC*: ↓MICT>↓HIIT TRG: ↓HIIT>↑MICT *Statistically significant from baseline. Not statistically significant.

Key: CON = control; H =hypertensive; HR = heart rate; mg/dL = milligrames per decilitre; mmol/L = millimoles per litre; Ob = obese; Ov = overweight; T2D = type 2 diabetes mellitus

SM Table 4.2 Detailed characteristics of included studies

Studies	Number of studies	Participant totals	Effect Estimate MD (IV, RE, 95% CI)*	P value	I^2
1.1 Total Cholesterol	24	653	0 10 0 03, 0 22]	0 12	0%
1 2 TC Sub ana yses	24	653			
1 2 1 Age > 55	5	169	0 11 0 20, 0 42]	0 5	0%
1 2 2 Age 35 55	9	281	0 10 0 07, 0 28]	0 24	0%
1 2 3 Age < 35	10	203	0 08 0 12, 0 29]	0 43	0%
1 2 4 Fema es on y	6	160	0 07 0 16, 0 31]	0 54	0%
1 2 5 Ma es on y	8	157	0 12 0 13, 0 36]	0 34	0%
1 2 6 MetS or MetS factors/r sk	16	498	0 08 0 06, 0 22]	0 28	0%
1 2 7 Testex Score >=10	16	478	0 09 0 06, 0 24]	0 22	0%
1 2 8 Testex Score < 10	8	175	0 11 0 11, 0 33]	0 34	0%
1 2 9 We ght bear ng	8	144	0 01 0 21, 0 23]	0 94	0%
Test for subgroup d fferences: Ch ^{2} = 0 67, df = 8 (P = 1 00), ^{2} = 0%					
1.3 Triglycerides	25	736	0 05 0 11, 0 01]	0 1	0%
1 4 TRG Sub ana yses	25	736			
1 4 1 Age > 55	6	212	0 00 0 21, 0 22]	0 97	0%
1 4 2 Age 35 55	12	366	0 10 0 19, 0 01]	0 03	0%
1 4 2 Age 35 55 (K 1**)	11	301	0 06 0 17, 0 05]	0 27	
1 4 3 Age < 35	7	158	0 01 0 10, 0 08]	0 84	0%
1 4 4 Fema es on y	5	118	0 08 0 21, 0 05]	0 24	0%
1 4 5 Ma es on y	7	193	0 03 0 14, 0 09]	0 64	26%
1 4 6 MetS or MetS factors/r sk	20	626	0 10 0 18, 0 02]	0 01	0%
1 4 6 MetS or MetS factors/r sk (K 1)**	19	561	0 07 0 17, 0 02]	0 13	
1 4 7 Testex Score >=10	20	621	0 04 0 11, 0 03]	0 28	0%
1 4 8 Testex Score < 10	5	115	0 11 0 24, 0 03]	0 13	0%
1 4 9 We ght bear ng	8	226	0 11 0 21, 0 00]	0 04	0%
1 4 9 We ght bear ng (K 1)**	7	161	0 05 0 19, 0 09]	0 45	
Test for subgroup d fferences: Ch ^{2} = 3 37, df = 8 (P = 0 91), ^{2} = 0%					
1.5 HDL Cholesterol	26	739	0 07 0 04, 0 11]	0 001	0%
1 6 HDL C Sub ana yses	27	739			
1 6 1 Age > 55	6	176	0 02 0 09, 0 14]	0 67	0%
1 6 2 Age 35 55	12	405	0 06 0 00, 0 12]	0 06	42%
1 6 3 Age < 35	9	178	0 10 0 01, 0 20]	0 07	49%
1 6 4 Fema es on y	5	136	0 03 0 08, 0 14]	0 6	0%
1 6 5 Ma es on y	10	250	0 11 0 03, 0 19]	0 007	52%
1 6 5 Ma es on y (K 1)**	9	185	0 09 0 01, 0 19]	0 07	54%
1 6 6 MetS or MetS factors/r sk	19	605	0 06 0 02, 0 11]	0 002	14%
1 6 6 MetS or MetS factors/r sk (K 1)**	18	540	0 04 0 00, 0 08]	0 08	0%
1 6 7 Testex Score >=10	20	598	0 08 0 03, 0 14]	0 003	40%
1 6 8 Testex Score < 10	7	161	0 02 0 05, 0 10]	0 52	0%
1 6 9 We ght bear ng	10	234	0 13 0 06, 0 21]	0 0006	37%
1 6 9 We ght bear ng (K 1)**	9	169	0 11 0 00, 0 21]	0 05	43%
Test for subgroup d fferences: Ch ^{2} = 7 00, df = 8 (P = 0 54), ^{2} = 0%					
1.7 LDL Cholesterol	20	580	0 05 0 06, 0 17]	0 37	0%
1 8 LDL C Sub ana yses	20	580			
1 8 1 Age > 55	5	168	0 21 0 05, 0 47]	0 11	0%
1 8 2 Age 35 55	9	281	0 02 0 18, 0 15]	0 84	0%
1 8 3 Age < 35	6	131	0 06 0 14, 0 26]	0 58	0%
1 8 4 Fema es on y	5	136	0 03 0 22, 0 29]	0 81	0%
1 8 5 Ma es on y	6	125	0 14 0 08, 0 35]	0 21	0%
1 8 6 MetS or MetS factors/r sk	15	473	0 03 0 10, 0 17]	0 61	0%
1 8 7 Testex Score >=10	16	473	0 08 0 05, 0 20]	0 23	0%
1 8 8 Testex Score < 10	4	107	0 08 0 38, 0 22]	0 59	0%
1 8 9 We ght bear ng	4	72	0 20 0 48, 0 08]	0 17	0%
Test for subgroup d fferences: Ch ^{2} = 6 64, df = 8 (P = 0 58), ^{2} = 0%					

*MD = Mean D fference, V = nverse Var ance, RE = Random Effects, C = Conf dence nterva

**Kemm er 2014

SM Table 4.3 Sub-analyses by lipid

STUDY	E g b ty cr ter a spec f ed	Random sat on spec f ed	A ocat on concea ment	Groups s m ar at base ne	B nd ng of assessor[a]	Outcomes measures assessed n 85% pat ents[b]	Intent on-to-treat ana ys s	Between-group stat st ca compar sons[c]	Po nt measures and measures of var ab ty for a reported outcome measures	Act v ty mon tor ng n contro groups[d]	Re at ve exerc se ntens ty rema ned	Exerc se vo ume and energy expend ture	Overa TESTEX (/15)
C o ac 2010	1	0	0	1	1	1	0	2	1	1	0	1	9
Conno y 2017	0	0	1	0	1	2	0	2	1	1	1	1	10
Cuddy 2019	1	0	0	1	1	1	0	2	1	1	1	0	9
F sher 2015	1	1	1	1	1	0	1	2	1	1	0	1	11
Hwang 2016	1	1	1	1	1	2	0	1	1	1	1	1	12
Keat ng 2014	1	1	0	0	1	3	1	2	1	1	1	1	13
Kemm er 2014	0	1	1	1	1	2	0	1	1	1	1	0	10
Kong 2016	1	0	1	0	1	0	0	2	1	1	0	1	8
Lee CL 2016	1	0	1	1	1	1	0	2	1	1	1	1	11
L ra 2019	1	0	0	1	1	2	1	1	1	1	1	0	10
Ma ard 2016	1	0	0	1	1	2	0	2	1	1	1	1	11
Matsuo 2015	1	1	1	1	1	2	1	2	1	1	1	1	14
Mohr 2014	0	0	0	0	1	2	1	1	1	1	0	0	7
Mora es-Pa ermo 2019	1	1	0	1	1	3	0	2	1	1	1	1	13
More ra 2008	1	0	0	1	1	0	0	2	1	1	1	1	9
Nybo 2010	0	0	0	0	1	3	1	1	1	1	1	0	9
Ramos 2016	1	1	1	1	1	2	0	1	1	1	1	1	12
Ruff no 2016	1	1	0	1	1	2	0	2	1	1	1	0	11
Sawyer 2016	1	0	1	1	1	1	0	2	1	1	1	1	11
Shepherd 2015	1	0	1	1	1	1	1	2	1	1	1	0	11
Thomas 1985	1	0	0	1	1	1	0	1	1	1	1	1	8
Tjønna 2008	1	0	1	0	1	2	0	2	1	1	1	1	11
Ve a 2017	0	0	1	1	1	3	0	2	1	1	1	1	12
W nd ng 2018	1	1	1	0	1	2	0	2	1	1	1	1	12
W nn 2018	1	0	1	1	1	3	0	2	1	1	1	1	13
Zhang 2015	0	0	0	1	1	1	0	2	1	1	1	1	9

Key: tota out of 15 po nts.
Legend: [a]B ood p d measurement s automated so a stud es were awarded 1. [b]Three po nts poss b e—one po nt f adherence >85%, one po nt f adverse events reported, one po nt f exerc se attendance s reported. [c]Two po nts poss b e—one po nt f pr mary outcome s reported, one po nt f a other outcomes reported. [d]MICT s treated as the contro for th s meta-ana ys s, so a stud es were awarded 1 because act v ty mon tor ng was done.

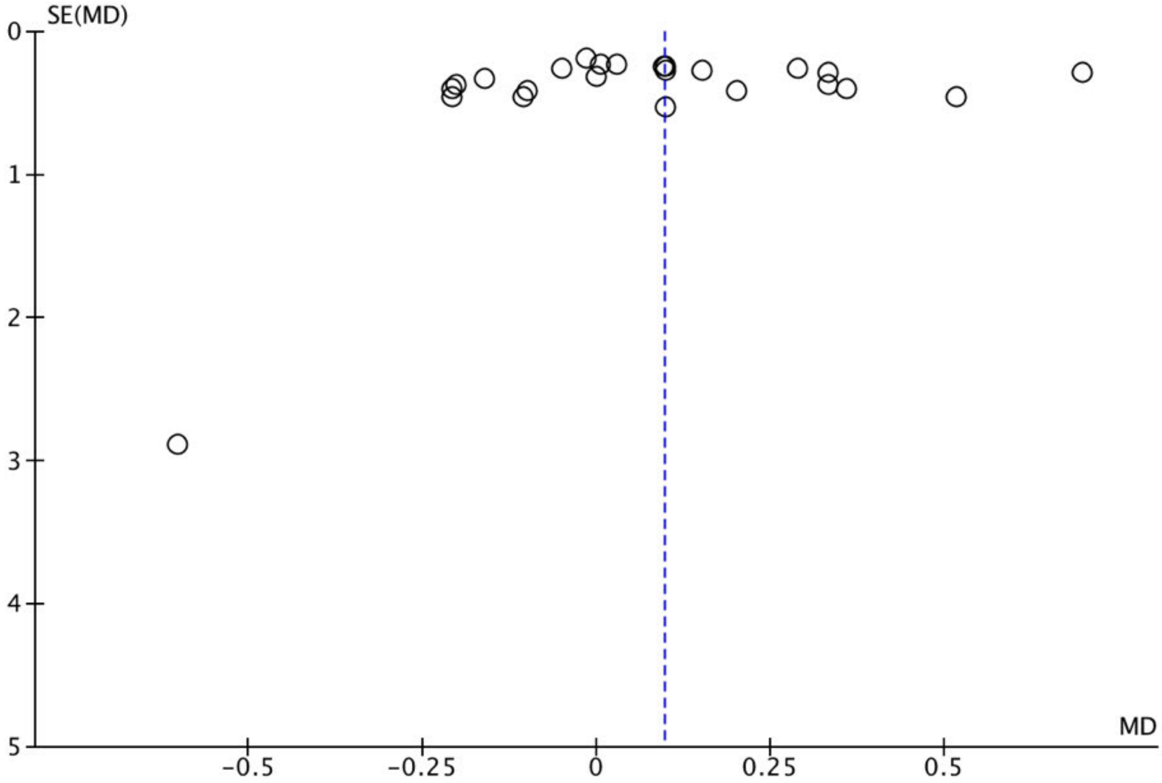
SM Table 4.4 TESTEX Assessment of Study Quality

Study	Lipid Assessment Methodology
(Ciolac, et al. 2010)	Total cholesterol, fractions, and triglycerides: standard methods analysis using a Dimension RXL Max automatic analyser (Dade Behring, Newark, DE, USA).
(Connolly, et al. 2017)	Samples were analysed using an automatic analyser (Roche Modular P-module, Roche Diagnostics, Indianapolis, IN) for HDL-C (coefficient of variation (CV) 2.1%), total cholesterol (CV 2.3%) and triglycerides (CV 2.4%). LDL-C was derived using the Friedewald formula (Friedewald et al. 1972),
(Cuddy, Ramos and Dalleck 2019)	Samples were analysed via a Cholestech LDX System according to strict standardized operating procedures. The LDX Cholestech measured the total cholesterol, high density lipoprotein (HDL) cholesterol, low density lipoprotein (LDL) cholesterol, triglycerides, and blood glucose in the fingerstick blood. A daily optics check was performed on the LDX Cholestech analyzer used for the study.
(Fisher, et al. 2015)	Total cholesterol, HDL-C, and triglycerides were measured using a SIRRUS analyzer (Stanbio Laboratory, Boerne, TX); LDL-C was calculated using the method of Friedewald et al. 1972.
(Hwang, et al. 2016)	Blood lipids were assessed using spectrophotometry.
(Keating, et al. 2014)	The whole blood sample was stored at 4°C for 2-3h prior to analysis by an accredited commercial laboratory (Douglass Hanly Moir Pty Ltd., Sydney, Australia). Analysis was performed on the same day as that of collection of lipids including triglycerides (TRG), total cholesterol (TC), high density lipoprotein cholesterol (HDL-C), and low density lipoprotein cholesterol (LDL-C)).
(Kemmler, et al. 2014)	Total cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides, (Olympus Diagnostica GmbH, Hamburg, Germany) were determined.
(Kong, et al. 2016)	Serum lipids, including high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), total cholesterol (TC) and total triglyceride (TG), were measured by using an automatic biochemical analyzer (Olympus AU400, Japan). The intra-assay coefficients of variation (CV) for blood lipid assays were all within 5%.
(Lee, Hsu and Cheng 2016)	Serum was analyzed for TG, TC, HDL-C, and LDL-C; the inter-assay CV values were 1.8%, 1.8%, 2.0%, and 2.1%, respectively.
Lira, et al. 2019)	The concentrations of TRG, TC, and HDL-c were determined by a colorimetric method according to specific kits (Labtest, Brazil). In addition, the non-HDL cholesterol (nHDL-c) was calculated by subtracting total cholesterol to HDL-c concentrations. All results were adjusted for individual changes in plasma volume.
(Maillard, et al. 2016)	Plasma concentrations of total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C) and triglycerides (TG) were measured (Synchron Clinical System UniCel DxC analyzer, Beckman Coulter, Brea, CA, USA), with a cholesterol oxidase method for TC (CHOL reagent), a direct homogeneous method for HDL-C (HDLD reagent) and a lipase/glycerol kinase method for TG (GPO reagent). The low-density lipoprotein (LDL) fraction was indirectly quantified using the equation described by Friedewald et al. 1972.
(Matsuo, et al. 2015)	Automated laboratory methods were used to measure serum lipids. LDL cholesterol was calculated according to Friedewald's formula. The inter- and intra-assay CV were <5% for all blood parameters.
(Mohr, et al. 2014)	Serum analyzed by an automatic analyzer (Cobas Fara, Roche, France) using enzymatic kits (Roche Diagnostics, Germany) for determination of total cholesterol, LDL-cholesterol, HDL-cholesterol, and triglyceride levels.
(Morales-Palomo, et al. 2019)	High-density lipoprotein cholesterol (HDL-c) using accelerator selective detergent method (iCV, 1.7%-2.9%). Blood TG with glycerol-3-phosphate oxidize method (iCV, 0.8%-1.7%). Total serum cholesterol by an enzymatic method with a single aqueous reagent (iCV, 1.1%-1.4%). Low-density lipoprotein-cholesterol (LDL-c) was calculated as proposed by Friedewald. All of the above analyses were run in an automated Mindray BS 400 Chemistry Analyzer (Mindray Medical Instrumentation, Shenzhen, China).
(Moreira, et al. 2008)	Total cholesterol and triglyceride were measured by 50-µL blood samples drawn from the earlobe in heparinized capillary tubes and the blood deposited in specific reagent strips for each determination performed in the Accutrend GCT portable instrument (Roche).
(Nybo, et al. 2010)	Plasma fatty acid, HDL cholesterol, and plasma triacylglycerol concentrations were measured by commercial kits (Wako Chemicals, Neuss, Germany) on a Hitachi autoanalyzer (Roche Diagnostic, Basel, Switzerland). The analytical variations (CV) for these measures were reported to be less than 1.5%. LDL cholesterol was calculated in accordance with the Friedewald–Levy–Fredrickson equation as total cholesterol minus HDL cholesterol and one-fifth of total plasma triacylglycerol.
(Ramos, et al. 2016)	The fasting lipid profile (triglyceride, total cholesterol (TC), HDL cholesterol (HDL-C), and LDL cholesterol (LDL-C)) levels were measured via a finger-prick blood sample analyzed using a Cholestech LDX system.
(Ruffino, et al. 2017)	Baseline plasma samples were analysed for triglycerides, low-density lipoprotein, and high-density lipoprotein (Randox RX Daytona Co.).
(Sawyer, et al. 2016)	Total cholesterol, high-density lipoprotein cholesterol (HDL-c), low-density lipoprotein cholesterol (LDL-c), triglycerides, and glucose were measured in plasma with an automated chemistry analyzer (Cobas C111; Roche Diagnostics, Indianapolis, IN) using colorimetric enzymatic reagents. Measured intra-assay coefficient of variation (CV) values were 1.4% for total cholesterol, 0.9% for HDL-C, 1.1% for LDL-C, and 1.6% for triglycerides.
(Shepherd, et al. 2015)	An ILab-600 semi-automatic spectrophotometric analyser was used to determine fasting serum non-esterified fatty acid (NEFA), triglyceride (TG), total cholesterol (TC), LDL-cholesterol (LDL-C) and HDL- cholesterol (HDL-C) concentrations, in combination with the appropriate assay kit (all obtained from Instrumentation Laboratory Ltd UK, Warrington, UK, except for the NEFA assay, which was obtained from Randox, London, UK).

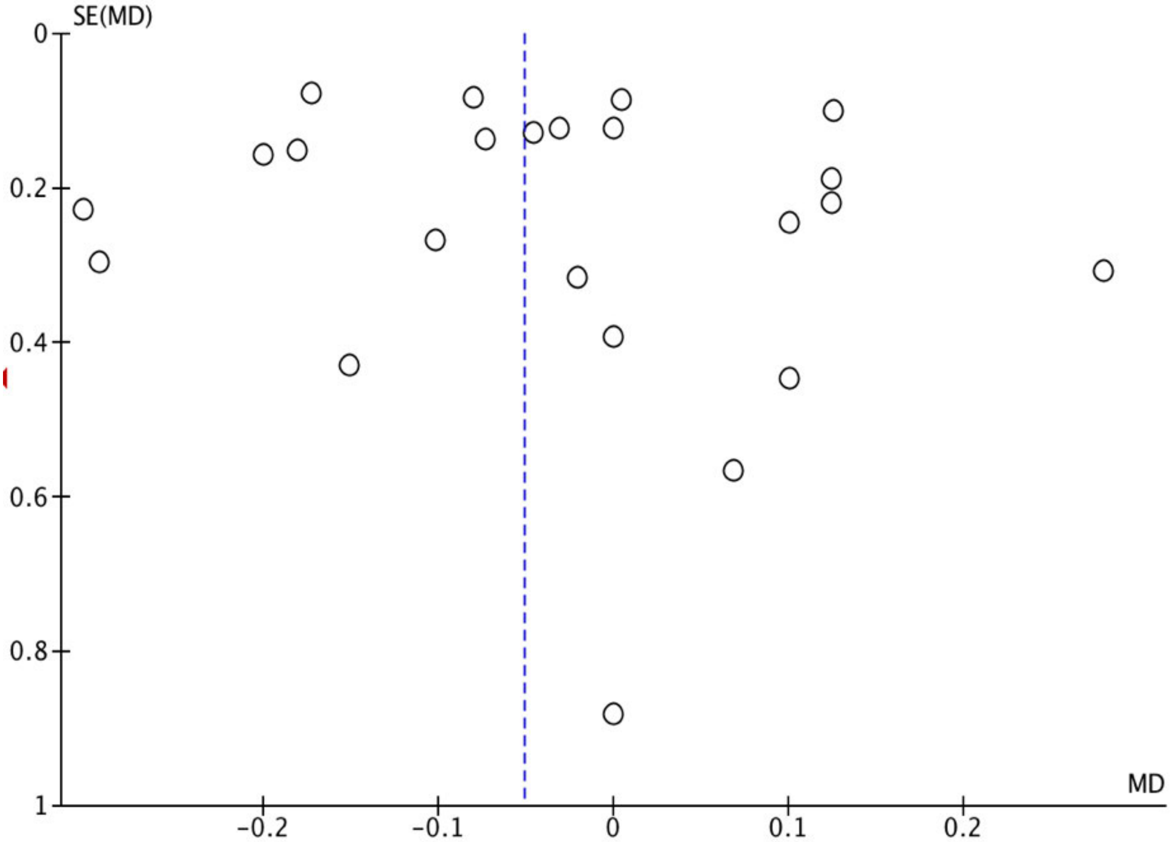
(Thomas, et al. 1985)	HDL-C and TC were analyzed immediately according to the microprocedure of Bonzert and Brewer (1977). This technique requires separation of HDL using phosphotungstate MgCl, ultracentrifugation with a Beckman Airfuge, and an enzymic analysis of TC using a Beckman Cholesterol Analyzer with oxygen electrode. Within assay reliability was assessed y calculating the mean coefficient of variation from duplicate or triplicate samples run during the study. The mean within coefficient of variation for TC = 2.1% and HDL-C = 1.5%. Between assay reliability was assessed by analyzing standards from a stored plasma pool (-70°C) on separate days. The coefficient of variation for TC = 3.6% and HDL-C = 2.5%.
(Tjønna, et al. 2008)	All blood analyses were performed with standard local procedures.
(Vella, Taylor and Drummer 2017)	High-density lipoprotein (HDL), low-density lipoprotein (LDL), total cholesterol, and triglycerides were measured using a Dimension RxL Max Integrated Chemistry System (Siemens, Erlangen, Germany) HDL cholesterol was assessed using the polyethylene glycol direct method with a minimum sensitivity of 0.3 mmol/L and an intra-assay CV of 0.9%. LDL cholesterol was measured using the direct method with a minimum sensitivity of 0.13 mmol/L and an intra-assay CV of 1.4%. Total cholesterol was measured via cholesterol oxidase, esterase, and peroxidase, and had a minimum sensitivity of 0.39 mmol/L and an intra-assay CV of 1.1%. Triglycerides were measured using the enzymatic endpoint method and had a minimum sensitivity of 0.6 mmol/L and an intra-assay CV of 1.2%.
(Winding, et al. 2018)	Baseline blood samples were collected for determination of plasma lipids.
(Winn, et al. 2018)	Serum lipids and aminotransferases (e.g. cholesterol, TG, HDL-C, and LDL-C) were determined by a commercial laboratory (Boyce and Bynum Pathology Laboratories, Columbia, MO, USA).
(Zhang, et al. 2015)	Commercially available kits (Shanghai Kehua Bio-engineering, China) were used with an automatic chemistry analyser (7180, HITACHI, Japan) to determine triglycerides (TG) and total cholesterol (TC). The inter- and intra-coefficients of variance for the measures were as follows: TG (5%, 6%) and TC (4%, 3%).

SM Table 4.5 Included Studies' Lipid Assessment Reporting

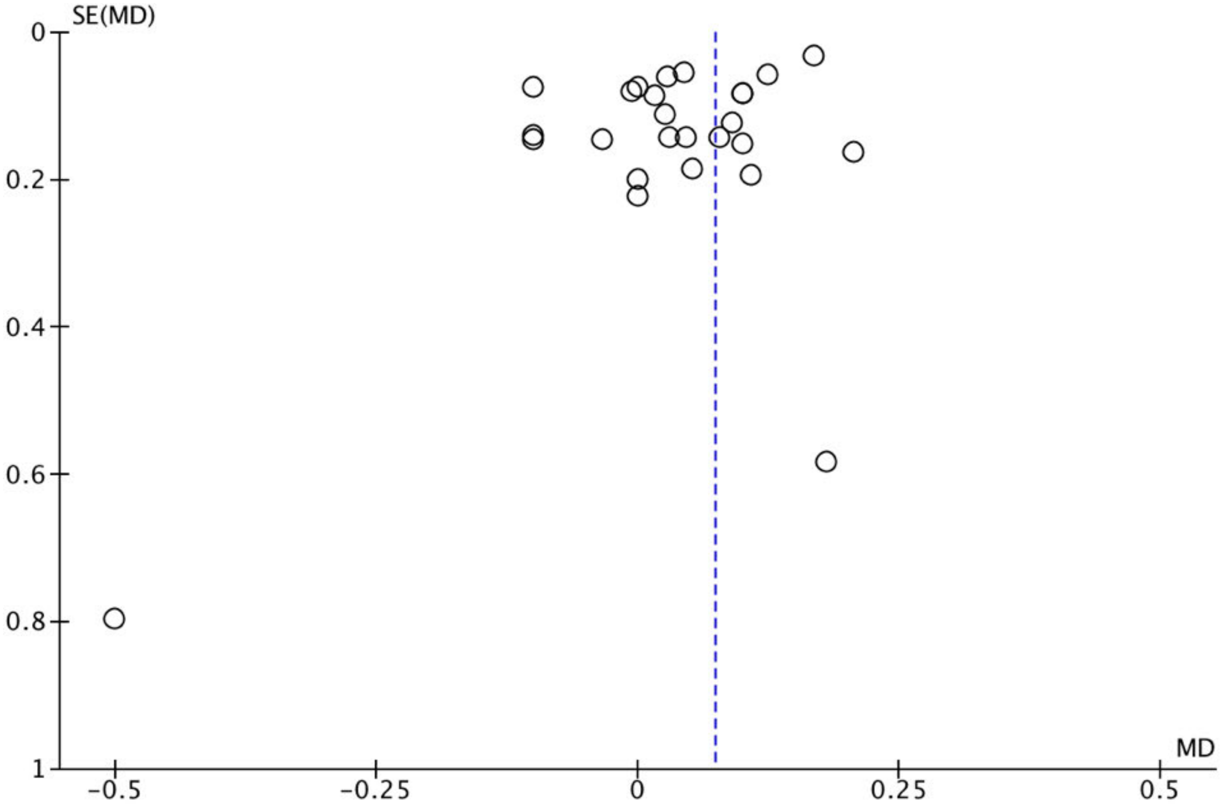
Funnel Plots generated with Revman 5.3:



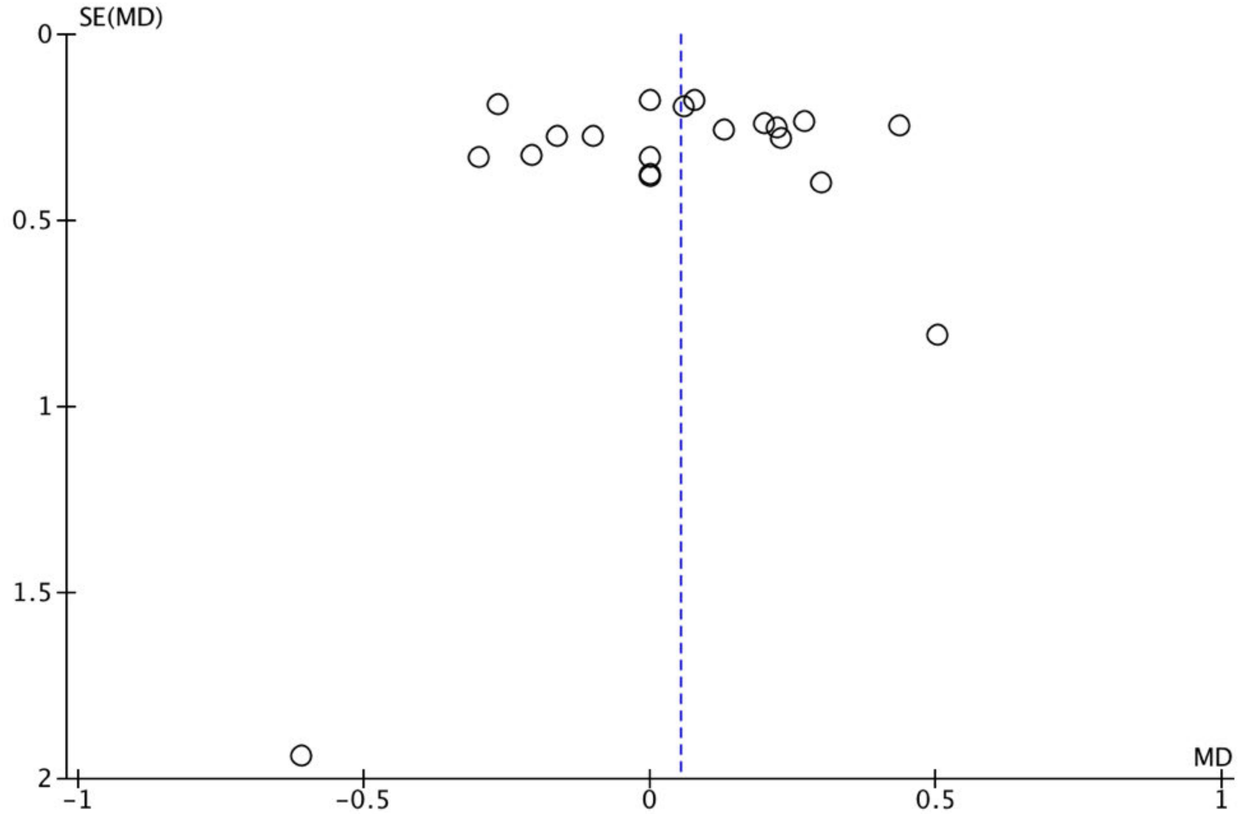
SM Figure 4.7 Total Cholesterol



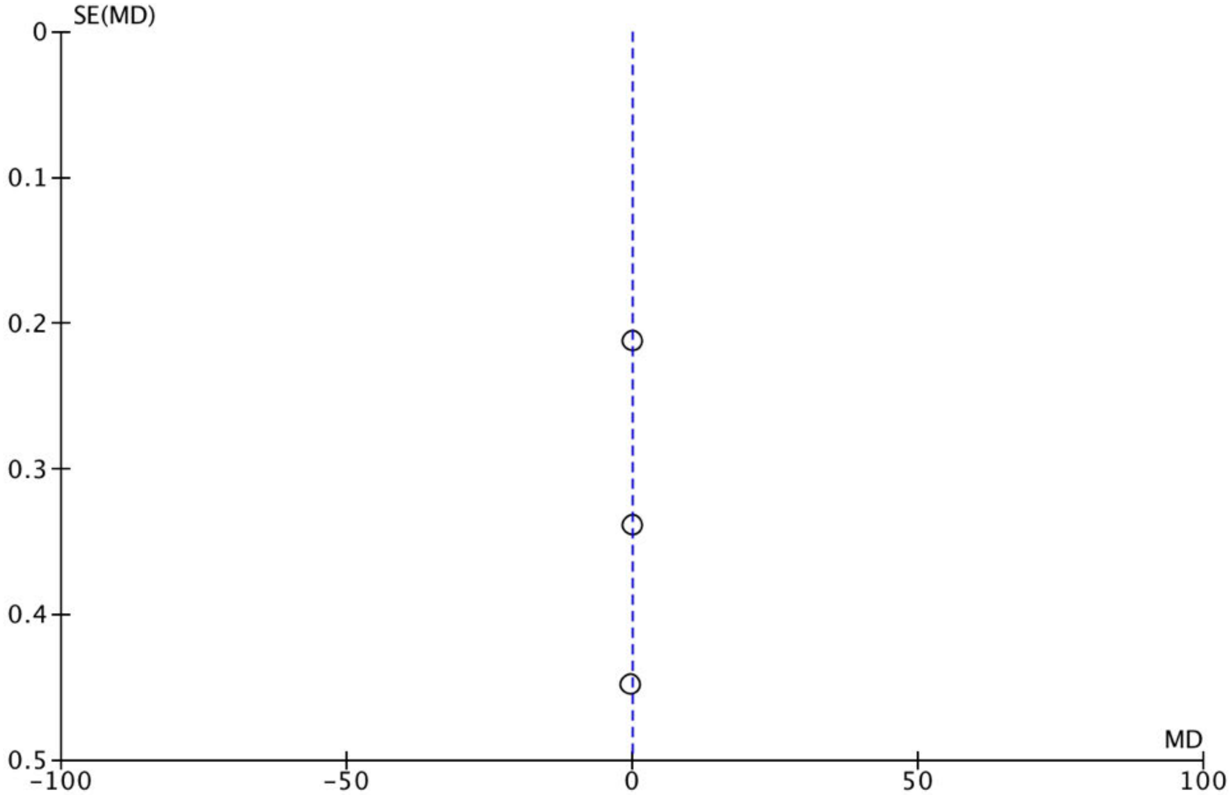
SM Figure 4.8 Triglycerides



SM Figure 4.9 High-density Lipoprotein Cholesterol



SM Figure 4.10 Low-density Lipoprotein Cholesterol



SM Figure 4.11 Total Cholestrol/High-density Lipoprotein Cholesterol Ratio

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5 Chapter 5 – Determining the Effect Size of Aerobic Exercise Training on Blood Lipids in Adults Free of Metabolic Syndrome: A Systematic Review with Meta-analysis and Meta-regression of Randomised Controlled Trials

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5.2 Statement of authors' contribution

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STATEMENT OF AUTHORS' CONTRIBUTION

We, the PhD candidate and the candidate's Principal Supervisor, certify that all co-authors have consented to their work being included in the thesis and they have accepted the candidate's contribution as indicated in the *Statement of Originality*.

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Determining the effect size of aerobic exercise training on blood lipids in adults free of Metabolic Syndrome: A systematic review and meta-analysis of randomised controlled trials.

Short Title: **The impact of aerobic exercise on blood lipids in non-MetS adults: A systematic review and meta-analysis of RCTs.**

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Declarations

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ABSTRACT

Objectives To estimate the effect size of aerobic exercise training (AET) on blood lipid profiles in sub-clinical adults free of Metabolic Syndrome (MetS).

Design Systematic review and random effects meta-analysis.

Data sources English language searches of electronic databases (PubMed, EMBASE, Web of Science, and all EBSCO health databases) were conducted from inception until August 2019.

Eligibility criteria for excluding studies Inclusion: 1) published randomised controlled human trials (RCTs) with per group population size N≥10; 2) intervention duration ≥12 weeks and intensity ≥40% VO_{2MAX}; and 3) reporting pre-post intervention lipid measurements as a primary or secondary outcome. Exclusion: subjects with chronic disease, diagnosed with MetS or type 1 or 2 diabetes, <18 years, pregnant/lactating, in elite athletic training, concurrently testing either a dietary or pharmaceutical intervention, and using resistance, isometric or unconventional exercise interventions.

Results Eighty-two data sets from 70 RCTs of 5872 participants were analysed. Pooled data showed AET significantly improved lipids (mmol/L, mean difference, 95% confidence intervals): reducing total cholesterol (-0.20 [-0.25, -0.15]) *P*<.0001, I^2=21%), triglycerides (-0.13 [-0.16, -0.1] mmol/L, *P*<.0001, I^2=0%), low-density lipoprotein cholesterol (-0.15 [-0.19, -0.11], *P*<.0001, I^2=0%), and raising high-density lipoprotein cholesterol (0.05 [0.04,0.06]) *P*<.0001, I^2=0%). The intervention covariate sessions per week partially explained change in low-density lipoprotein cholesterol.

Conclusion AET positively impacted the blood lipid profile of adults free of chronic disease and not diagnosed with MetS. AET appears to improve high-density lipoprotein cholesterol in non-MetS populations more than common cholesterol-lowering medications. The change in total cholesterol, triglycerides, and low-density lipoprotein cholesterol following AET is

smaller than would be expected from medication.

PROSPERO ID CRD42019145560

Keywords Lipids, Cholesterol, Triglycerides, Lipoprotein, Aerobic Exercise, Medication, Statins

Key Points

1. Aerobic exercise training (AET) positively affects blood lipids in adults free of Metabolic Syndrome (MetS).

2. The training covariate sessions per week appeared to influence the change in low-density lipoprotein cholesterol.

3. The positive change in high-density lipoprotein cholesterol following AET is at least the equivalent of the effect size of statin treatments in non-MetS adults.

1.0 INTRODUCTION

Metabolic Syndrome (MetS) and MetS factors are implicated in cardiovascular disease (CVD).[1] Dyslipidaemia is an abnormally elevated or lowered blood lipid profile and is a significant MetS risk factor of CVD;[2, 3] ischemic stroke;[4] non-alcoholic fatty liver disease (NAFLD);[5] and chronic pancreatitis.[6, 7] Moderate- and vigorous- intensity aerobic exercise training (AET) positively impacts MetS factors, thus lowering CVD risk.[8, 9] Studies and systematic reviews have shown aerobic or moderate intensity (3-6 metabolic equivalents (METS); 40-60% of heart rate reserve (HRR) or maximal oxygen uptake (VO_{2MAX}); 55-70% of maximal heart rate (MHR); or rate of perceived effort (RPE) of 11-13 on the Borg scale)[10] continuous training (MICT) reduces elevated total cholesterol (TC), triglycerides (TRG) and low-density lipoprotein cholesterol (LDL-C) and increases high-density lipoprotein cholesterol (HDL-C) in sub-clinical and clinical populations.[11-14]

A recent metaepidemological review of randomised controlled trials (RCTs) found physical activity interventions to have equal or greater beneficial effects on mortality outcomes (secondary prevention of CVD) compared with pharmaceutical interventions.[15] Aerobic physical activity as a first treatment option for managing lipids in sub-clinical populations and as a concurrent treatment in clinical populations is generally preferred to pharmaceutical intervention,[16-20] since pharmaceutical intervention is not without side effects[21, 22] and represents a financial cost to health systems.[23-25] Lack of aerobic physical activity has profound negative consequences on lipids.[26]

Studies have shown a minimum of AET (>180 minutes per week at >40% VO_{2MAX}, or >1200 kcal/week) is necessary to induce positive changes to lipids.[27, 28] Systematic reviews (SRs) and meta-analyses (MAs) have established longer AET intervention and session duration results in greater effects,[29, 30] and a minimum effective AET volume (>45 minutes per session for 3-4 sessions per week for duration >26 weeks at >65% VO_{2MAX}) results in significant changes to lipids.[13] Similarly, cholesterol lowering medication dosages which are steadily increased result in greater effects than fixed dosages on lowering targeted lipids or raising HDL-C.[31, 32, 20] The full reduction in risk of ischaemic heart disease is achieved within five years of lowering TC by 0.6 mmol/L.[33] Both cholesterol lowering medication and AET require a minimum period to show effects, however trials of pharmacological intervention are generally conducted for longer periods[34] than trials of AET intervention.[35]

Various SRs have examined the impact of AET on lipid profiles without conducting MAs.[36, 37, 14, 38-43] With one exception,[44] SRs including MAs of the impact of AET have focused on single lipids,[30] or specific genders,[45-47] or change in health indices in groups of mixed health status [48-51] or modalities of AET (running,[29] walking,[52] high intensity intervals versus moderate intensity steady state[50, 53, 54]). One SR and MA reviewed the effects of aerobic and resistance exercise between normolipidaemic and dyslipidaemic adults.[55] Another SR and MA concentrated on determining the effectiveness, measured by achieved intensity, of AET intervention protocols.[13] A Cochrane Review reported on lipids as a secondary outcome using only 3 studies.[56] These previous works combined health statuses ranging from chronic disease such as presence of CVD to healthy. To the best of our knowledge, no comprehensive SR and MA has yet been completed which investigated the pooled outcomes of only RCTs comparing various AET modes with no exercise while holding health status constant ie for sub-clinical adult populations free of chronic disease and not diagnosed with MetS.

We aimed to conduct an SR and MA comparing the effects of AET achieving an estimated minimum intensity of >40% VO_{2MAX} or equivalent, against control groups performing no exercise or maintenance of usual habits, on TC, TRG, HDL-C, and LDL-C in sub-clinical sedentary adults not diagnosed with MetS. Following the estimation of the effect size (ES) for each lipid fraction, we wished to discuss these ES with respect to the reported estimated ES of statin interventions, since statins represent 98% of cholesterol lowering medication prescribed,[57] using a comparative and qualitative approach.[58, 59]

2.0 METHODS

This SR and MA was designed by GW and NS and registered in the International Prospective Register of Systematic Reviews (PROSPERO) CRD42019145560.[60] Its results are presented according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[61]

2.1 Search Strategy and Study Selection Potential studies were identified by undertaking systematic English-language searches of PubMed, EMBASE, and all EBSCO health and medical databases from inception to August 2019 for randomised controlled trials (RCTs) lasting ≥12 weeks investigating AET protocols and reporting pre-post intervention lipid measurements in humans ≥18 years.

Searches included a mix of MeSH and free text terms relevant to the concepts of: AET; intervention duration; exercise-induced lipid metabolism; and blood lipids (see Table 5.1 Search Strategy example). Searches excluded for pregnancy, lactation, elite athletes, juveniles, CVD, stroke, cancer, NAFLD, and diet and pharmaceutical interventions. Other SRs and reference lists of papers were hand searched for additional RCTs.

Pubmed example search	(((((exercise[Title/Abstract] OR training[Title/Abstract] OR activity[Title/Abstract] OR endurance[Title/Abstract] OR HIIT[Title/Abstract] OR MICT[Title/Abstract] OR SIT[Title/Abstract] OR HIT[Title/Abstract]) AND (lipids[Title/Abstract] OR cholesterol[Title/Abstract] OR triglycerides[Title/Abstract] OR lipoprotein[Title/Abstract] OR apolipoprotein[Title/Abstract] OR lipase[Title/Abstract])) NOT (juvenile[Title/Abstract] OR adolescent[Title/Abstract] OR child[Title/Abstract])) NOT (supplement[Title/Abstract] OR supplementation[Title/Abstract])) NOT (diet[Title/Abstract] OR pharmaceutical[Title/Abstract] OR *statin[Title/Abstract])) NOT (juice[Title/Abstract] OR oil[Title/Abstract] OR extract[Title/Abstract]) NOT (athlete[Title/Abstract] OR elite[Title/Abstract]) AND (Randomized Controlled Trial[ptyp] AND hasabstract[text] AND "humans"[MeSH Terms] AND "adult"[MeSH Terms])

Table 5.1 Search Strategy example

GNW, ET and AP conducted the searches and assessed titles and abstracts of identified studies. Subsequently, the full text of potentially eligible RCTs was reviewed by GNW, ET, AP, and AM. NS and TvdT were consulted to resolve disputes.

2.2 Participants Studies of healthy (no condition reported) or sub-clinical (overweight (Ov) defined as body mass index (BMI) <30, mildly hypertensive (MH) defined as ≤ 135/85 mmHg, or fewer than three MetS health indices) participants were included. Studies in which participants continued with usual medications were included, unless the medication use in >50% of participants and in the presence of other MetS factors resulted in a diagnosis of MetS, in which case the RCT was excluded. Studies were excluded if the population sample size (N) for the intervention or control groups was N<10.[62]

2.3 Intervention The duration for including RCTs was an AET intervention ≥12 weeks, the minimum time to affect lipid profiles.[55] We included RCTs of either prescribed steady state or interval AET which employed a moderate intensity effort of at least 40% VO_{2MAX} since 40-49% VO_{2MAX} is a recommended starting intensity for unfit individuals.[63] No restrictions were placed on AET session time or type, and we included RCTs where effort levels could be estimated if not specifically reported. Studies including either a resistance- or combined-training intervention without separate AET interventions as comparators were excluded. Studies comparing AET protocols without a control group as comparator were excluded. Studies testing a dietary or pharmaceutical component combined with aerobic exercise were excluded.

2.4 Comparator We evaluated the impact of AET compared to no exercise or usual sedentary habits or usual care on blood lipids.

2.5 Outcomes Studies were eligible for inclusion if pre- and post-intervention lipid measurements for intervention and control groups were reported, whether as mmol/L or mg/dL, the latter being converted to the former as required (multiplication by the conversion factors 0.02586 for TC, HDL-C, and LDL-C, and 0.1129 for TRG). Not all RCTs included values for all of TC, TRG, HDL-C, or LDL-C; if one or more measurements were reported, the RCT was included for the relevant lipid.

2.6 Data Extraction ET, AM, and AP extracted the data to a pre-established data extraction form and GW, NS, and TvdT reviewed the extracted data for accuracy. For each study the following information was extracted: 1) author(s), year of publication and study design; 2) demographic and clinical characteristics; 3) AET intervention protocols; 4) values before and after intervention for any of TC, TRG, HDL-C, or LDL-C expressed as mean (M) or mean difference (MD), standard deviation (SD) or converted to SD from the standard error (SE) using SD = [square root (N) x SE], and main findings concerning lipids.

2.7 Data Synthesis Statistical analyses were performed using Comprehensive Meta-analysis (CMA) 3.0 (Biostat, Inc., New Jersey, USA) for continuous data by using MD, SD, and N. Where the MD and SD of the MD were not reported, the MD was calculated by subtracting $M_{pre-treatment}$ from $M_{post-treatment}$. The SD of the MD was calculated as follows: SD = square root

$[(SD_{pre\text{-}treatment})^2 + (SD_{post\text{-}treatment})^2 - (2r \times SD_{pre\text{-}treatment} \times SD_{post\text{-}treatment})]$, assuming a correlation coefficient r = 0.5, considered a conservative estimate.[64]. Where data was not presented in text or tables and authors could not be reached, data presented in figures was extracted where possible.

Data were pooled for meta-analysis when two or more studies measured the same outcome and provided data in a format suitable for pooling. Where an RCT included multiple AET intervention groups, data were entered separately for each intervention group and the control group N was divided by the number of intervention groups to eliminate inflation. ET, AM, and AP entered the data in CMA data sheets; GW, NS and TvdT confirmed the data entry for accuracy. A random effects inverse variance Knapp-Hartung adjusted model was chosen to allow for different pooled effect sizes,[65] with the effects measure of MD, a 5% level of significance, and a 95% CI to report change in outcome measures.

2.8 Meta-analysis and Sub-analyses For meta-analysis of TC, TRG, HDL-C and LDL-C, all included studies were grouped under each outcome and data was pooled. Sub-analyses were conducted for study quality.

2.8.1 Meta-regression Meta-regression was conducted to determine whether any AET intervention variables (intensity, minutes per session, sessions per week, duration) or study variables (study quality, year of publication, number of total study participants) predicted effect size. The analysis was performed by GNW using CMA and validated by NS. For meta-regression of TC, TRG, HDL-C and LDL-C, all included RCTs were grouped under each outcome. Lipid data (MD and 95% CIs) and intervention data were pooled. We regressed intercept and each variable using a random effects model of restricted maximum likelihood, against the dependent variable MD.

2.8.2 Sensitivity analysis In order to evaluate the influence of each RCT on the overall effect size of pooled data, we conducted iterative leave-one-out (K-1, where K = total number of pooled RCTs, and each RCT is excluded once) sensitivity analyses.[66] If the presence of an outlier RCT was detected, it was removed from the analysis. Where sub-analyses gave rise to significance, iterative leave-one-out (K-1) analysis was also conducted.

2.9 Heterogeneity Heterogeneity was quantified in CMA using the I^2 test where heterogeneity values range from 0% (complete homogeneity) to 100% (complete heterogeneity)[67], as well as a test for absolute between-study heterogeneity (τ^2). In the presence of significant statiscal heterogeneity, outliers were removed using pooled analysis 95% CI boundaries.[68]

2.10 Study Quality Study quality was assessed by ET, AP and GNW and reviewed by AM, NS and TvdT. In the case of discrepancies NS was consulted. We used the validated Tool for the Assessment of Study Quality and Reporting in Exercise (TESTEX),[69] a 15-point scale specific to exercise training studies. A score ≥10 indicates a better study quality and reporting. A study quality sub-analysis of studies grouped according to a TESTEX score ≥10 was also conducted. We further assessed within-study risk of bias by evaluating 7 factors (see Electronic Supplementary Material Table S5.7 for a description), and awarded either low, medium or high within-study risk of bias scores.

2.11 Publication Bias Trim and fill analysis[71] using CMA for the pooled data set of each lipid was performed by GW and confirmed by MW to assess risk of publication bias. Visual inspection of CMA-generated funnel plots was conducted by GNW and MW.

2.12 Comparison of the Estimated Effect Sizes of AET and Pharmaceutical Interventions For the purposes of discussion, we searched Pubmed for published SRs and MAs comparing various statin interventions against no statin intervention in different populations which reported estimated ES. We qualitatively compared the estimated ES of these studies with our estimated ES of AET intervention TC, TRG, HDL-C and LDL-C and noted differences in dosages, intervention time-frames, and population characteristics.

3.0 RESULTS

Combined searches generated a total of 1696 articles. After removal of duplicates and exclusion of articles based on abstract and title, 97 full-text articles remained for screening against inclusion and exclusion criteria. Screening resulted in the inclusion of 70 RCTs[72-141] for data extraction, giving a total of 82 data sets to be pooled. The flow of papers through the search and inclusion process is presented in Figure 5.1.[61]

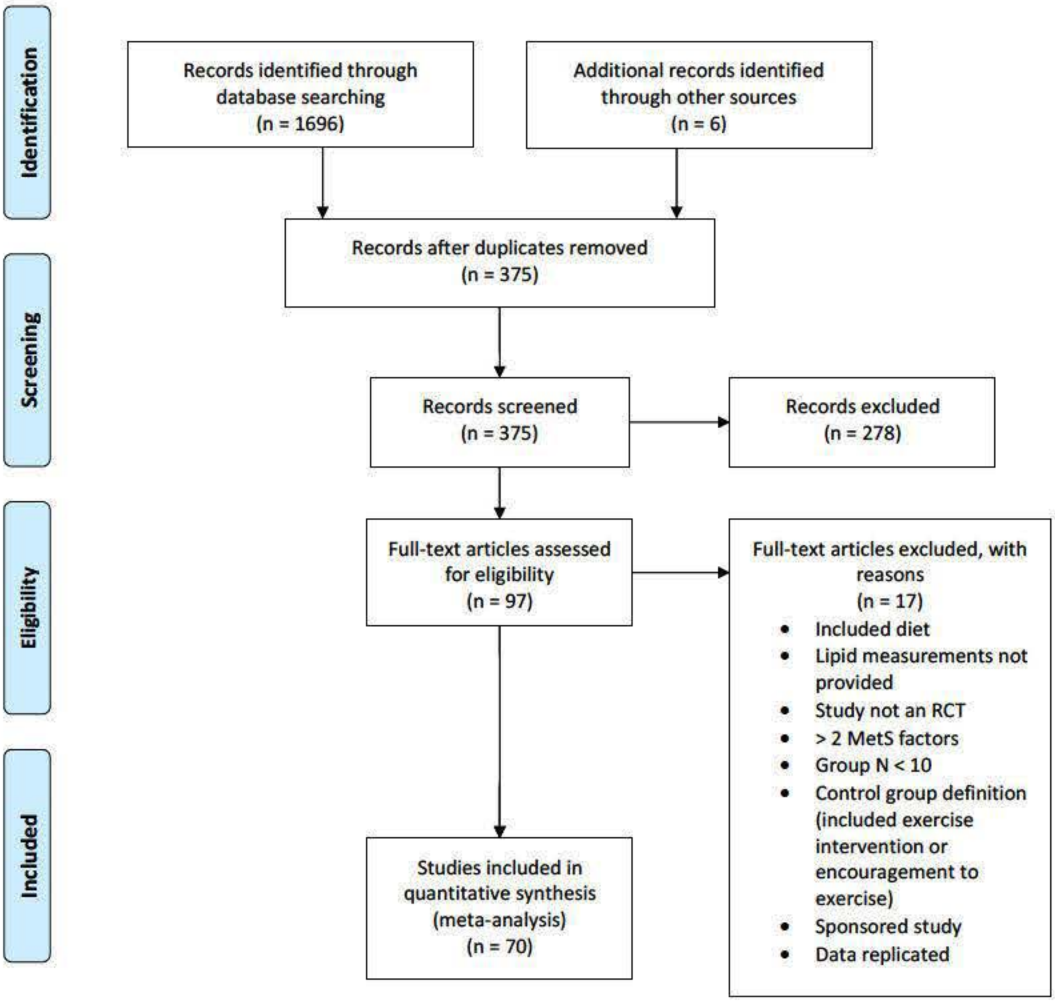


Figure 5.1 PRISMA flow diagram.[61]

3.1 Study, Participant, and Intervention Characteristics Descriptions of participants and interventions detailed in the RCTs chosen for inclusion are provided in Table 5.2.

Study	N	Sex	Age Group	Health Status	Duration weeks	Intensity VO2max	Sessions/ week	Mins/ session	Lipids Measured
Baker 1986	34	M	> 55	1 MetS	20	72%	3.0	48	TC, TRG, HDL-C, LDL-C
Bell 2010 MICT	62	Mx	35 - 55	2 MetS	24	63%	2.8	29	TC, TRG, HDL-C, LDL-C
Bell 2010 walking	66	Mx	35 - 55	1-2 MetS	24	53%	6.4	55	TC, TRG, HDL-C, LDL-C
Bergström 2009	92	F	> 55	sedentary	52	53%	4.5	30	TC, HDL-C, LDL-C
Bhutani 2013	40	Mx	< 35	1 MetS	12	60%	3.0	35	TC, TRG, HDL-C, LDL-C
Blumenthal 1991	63	Mx	> 55	sedentary	16	66%	3.0	30	TC, TRG, HDL-C, LDL-C
Boardley 2007	68	Mx	> 55	1 MetS	16	65%	3.0	35	TC, TRG, HDL-C, LDL-C
Bock 2019 standard	143	Mx	> 55	1 MetS	12	55%	3.0	40	TC, TRG, HDL-C, LDL-C
Bock 2019 video games	140	Mx	35 - 55	1 MetS	12	55%	3.0	40	TC, TRG, HDL-C, LDL-C
Busby 1985	24	F	35 - 55	1 MetS	12	60%	3.0	30	TC, TRG, HDL-C
Costa 2018	40	F	35 - 55	1 MetS	12	60%	2.0	30	TC, TRG, HDL-C, LDL-C
Cunningham 1987	202	M	35 - 55	sedentary	52	70%	2.5	32	TC, HDL-C
Furukawa 2003	45	F	35 - 55	sedentary	12	50%	2.5	30	TC, TRG, HDL-C, LDL-C
Grandjean 1996	37	F	35 - 55	sedentary	24	70%	3.0	40	TC, TRG, HDL-C, LDL-C
Grant 2004	26	F	> 55	2 MetS	12	50%	1.4	25	TC
Hellénius 1993	78	M	35 - 55	1 MetS	26	52%	2.5	43	TC, TRG, HDL-C, LDL-C
Hespel 1988	27	M	35 - 55	1-2 MetS	16	80%	3.0	40	TRG, HDL-C, LDL-C
Hinkleman 1993	36	F	35 - 55	1 MetS	15	62%	5.0	45	TC, TRG, LDL-C
Ho 2012	31	Mx	35 - 55	1 MetS	12	60%	3.4	30	TC, TRG, HDL-C, LDL-C
Hornstrup 2019	26	M	< 35	sedentary	12	73%	1.9	40	TC, TRG, HDL-C, LDL-C
Huttunen 1979	90	M	35 - 55	sedentary	16	50%	3.5	30	TC, TRG, HDL-C, LDL-C
Kemmler 2014	74	M	35 - 55	1-2 MetS	16	65%	4.5	54	TRG, HDL-C
Kiens 1980	37	M	35 - 55	sedentary	12	80%	2.6	45	TC, TRG, HDL-C
King 1991 M (HIT group)	54	M	> 55	sedentary	52	64%	3.0	40	TRG, HDL-C, LDL-C
King 1991 M (HIT home)	56	M	> 55	sedentary	52	64%	3.0	40	TRG, HDL-C, LDL-C
King 1991 M (LIT home)	59	M	> 55	sedentary	52	59%	5.0	30	TRG, HDL-C, LDL-C
King 1991 F (HIT group)	45	F	> 55	sedentary	52	64%	3.0	40	TRG, HDL-C, LDL-C
King 1991 F (HIT home)	47	F	> 55	sedentary	52	64%	3.0	40	TRG, HDL-C, LDL-C
King 1991 F (LIT home)	40	F	> 55	sedentary	52	59%	5.0	30	TRG, HDL-C, LDL-C
Knoepfli-Lenzin 2010	32	M	35 - 55	1 MetS	12	67%	2.5	58	TC, HDL-C, LDL-C
Korshøj 2016	116	Mx	35 - 55	sedentary	16	60%	2.0	30	TC, TRG, HDL-C, LDL-C
Krustrup 2009	20	M	< 35	sedentary	12	70%	2.5	55	TC, HDL-C, LDL-C
Krustrup 2010	31	F	35 - 55	sedentary	16	70%	1.8	52	TC, TRG, HDL-C, LDL-C
Krustrup 2017	31	F	35 - 55	sedentary	52	72%	2.5	48	TC, TRG, HDL-C, LDL-C
Kukkonen-Harjula 1998	108	Mx	35 - 55	1 MetS	15	70%	3.8	45	TC, TRG, HDL-C, LDL-C
Lawton 2008	1089	F	> 55	sedentary	104	50%	4.2	25	TC, HDL-C
LeMura 2000	22	F	< 35	sedentary	16	59%	3.0	30	TC, TRG, HDL-C, LDL-C
Lindheim 1994	45	F	35 - 55	sedentary	26	52%	3.0	30	TC, TRG, HDL-C, LDL-C
Martins 2010	63	Mx	> 55	1-2 MetS	16	60%	3.0	45	TC, TRG, HDL-C, LDL-C
Maruf 2014	120	Mx	> 55	1 MetS	12	50%	2.5	35	TC, TRG, HDL-C, LDL-C
Mawi 2009	62	F	> 55	sedentary	12	45%	4.0	15	TC, TRG, HDL-C, LDL-C
Mohanka 2006	173	F	> 55	1 MetS	52	57%	3.0	45	TC, TRG, HDL-C, LDL-C
Mohr 2014 HIIT	32	F	35 - 55	1 MetS	15	75%	2.9	20	TC, TRG, HDL-C, LDL-C
Mohr 2014 MICT	30	F	35 - 55	2 MetS	15	55%	2.9	60	TC, TRG, HDL-C, LDL-C
Morgan 2010	29	Mx	> 55	sedentary	12	55%	7.0	30	TC, HDL-C
Mosher 2005 continuous	40	F	< 35	1 MetS	12	63%	3.0	35	TC, TRG, HDL-C, LDL-C
Mosher 2005 interval	38	F	< 35	1 MetS	12	63%	3.0	40	TC, TRG, HDL-C, LDL-C
Niederseer 2011	34	Mx	> 55	sedentary	12	55%	2.4	210	TC, TRG, HDL-C, LDL-C
Nieman 1993	30	F	> 55	1-2 MetS	12	55%	5.0	38	TC, TRG, HDL-C, LDL-C
Nieman 2002	43	F	35 - 55	2 MetS	12	65%	4.8	45	TC, TRG, HDL-C, LDL-C
Nualnim 2012	43	Mx	> 55	sedentary	12	65%	3.0	45	TC, TRG, HDL-C, LDL-C
Ohta 2012	26	F	> 55	1-2 MetS	12	65%	2.5	20	TC, TRG, HDL-C, LDL-C
Park 2014	28	Mx	> 55	sedentary	12	60%	2.0	59	TC, TRG, HDL-C, LDL-C
Ready 1995	25	F	> 55	1-2 MetS	26	48%	4.9	54	TC, TRG, HDL-C, LDL-C
Ring-Dimitriou 2007	30	Mx	35 - 55	sedentary	39	75%	1.0	80	TC, TRG, HDL-C, LDL-C
Rossi 2016	33	F	> 55	2 MetS	16	70%	2.0	52	TC, HDL-C, LDL-C
Santiago 1995	27	F	< 35	sedentary	40	55%	4.0	50	TC, TRG, HDL-C, LDL-C
Sarzynski 2018 20 KKW	69	Mx	35 - 55	1 MetS	24	75%	5.0	60	TC, TRG, HDL-C, LDL-C
Sarzynski 2018 8 KKW	70	Mx	35 - 55	1 MetS	24	75%	5.0	30	TC, TRG, HDL-C, LDL-C
Schuit 1998 all round	74	Mx	> 55	active	26	72%	3.0	45	TC, TRG, HDL-C, LDL-C
Schuit 1998 cycling	102	Mx	> 55	active	26	72%	4.0	30	TC, TRG, HDL-C, LDL-C
Short 2003	102	Mx	35 - 55	1-2 MetS	16	52%	3.0	30	TC, TRG, HDL-C, LDL-C
Shou 2019	198	Mx	35 - 55	2 MetS	12	55%	10.5	50	TC, TRG, HDL-C, LDL-C
Sillanpää 2009 M	28	M	35 - 55	sedentary	21	72%	2.0	60	TC, TRG, HDL-C, LDL-C
Sillanpää 2009 F	27	F	35 - 55	sedentary	21	72%	2.0	60	TC, TRG, HDL-C, LDL-C
Sousa 2014	32	M	> 55	sedentary	32	60%	3.0	30	TC, TRG, HDL-C, LDL-C
Stensel 1993	65	M	35 - 55	sedentary	52	60%	7.0	28	TC, TRG, HDL-C, LDL-C

Study	N	Sex	Age Group	Health Status	Duration weeks	Intensity VO2max	Sessions/ week	Mins/ session	Lipids Measured
Sunami 1999	40	Mx	> 55	sedentary	22	50%	3.0	60	TC, TRG, HDL-C, LDL-C
Suter 1990	61	M	35 - 55	sedentary	16	77%	3.0	45	TC, TRG, HDL-C, LDL-C
Suter 1992	32	F	35 - 55	sedentary	16	80%	3.0	40	TC, TRG, HDL-C
Takeshima 2002	30	F	> 55	sedentary	12	67%	3.0	30	TC, TRG, HDL-C, LDL-C
Tiainen 2016	161	F	35 - 55	sedentary	12	65%	4.0	50	TC, TRG, HDL-C, LDL-C
Tsai 2002	23	Mx	35 - 55	1 MetS	12	57%	3.0	30	TC, TRG, HDL-C, LDL-C
Tseng 2013	20	M	< 35	2 MetS	12	50%	5.0	60	TRG, HDL-C
Tully 2007 (= recommended)	52	Mx	35 - 55	1-2 MetS	12	53%	4.2	26	TC, TRG, HDL-C, LDL-C
Tully 2007 (< recommended)	54	Mx	35 - 55	1 MetS	12	53%	4.2	29	TC, TRG, HDL-C, LDL-C
Vainionpää 2007	76	F	35 - 55	sedentary	52	70%	3.0	40	TC, TRG, HDL-C, LDL-C
Vicente-Campos 2012	43	Mx	> 55	2 MetS	35	57%	3.0	50	TC, TRG, HDL-C, LDL-C
von Thiele Schwarz 2008	118	F	35 - 55	sedentary	52	49%	3.0	60	TC, TRG, HDL-C, LDL-C
Wirth 1985	21	M	35 - 55	1 MetS	17	75%	3.0	60	TC, HDL-C, LDL-C
Wood 1983	81	M	35 - 55	sedentary	12	80%	3.0	25	TC, TRG, HDL-C, LDL-C
Zhang 2014	111	F	35 - 55	act/sed	12	60%	3.0	30	TC, TRG, HDL-C, LDL-C

Table 5.2 Study participant and intervention characteristics, and outcomes reported

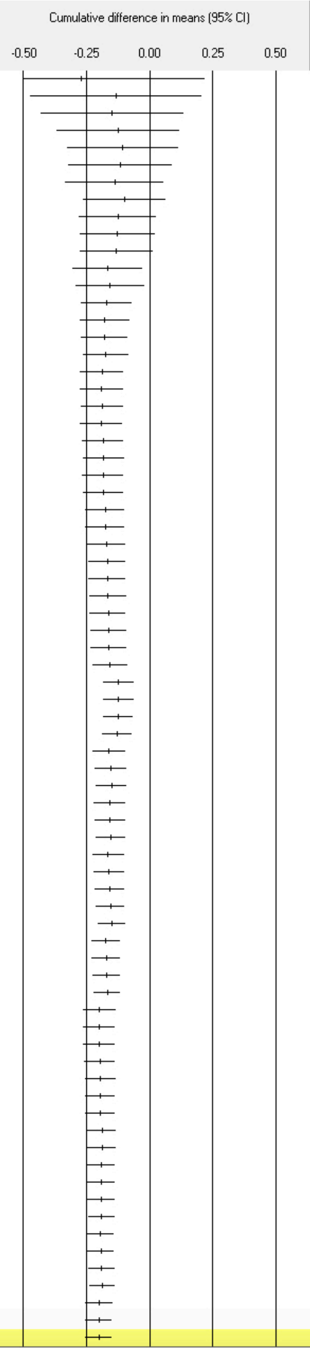
Total participants numbered 5872. Thirty-four RCTs of 2764 participants were female only, 20 RCTs of 1097 participants were male only, and the remaining RCTs of 2011 participants included both genders. Participants below 35 years numbered 233, between 35 – 55 years there were 2836 participants, and 2803 participants were over 55 years. All participants except those in two RCTs [121, 140] were sedentary with either nil or up to two MetS factors.

Control groups were told to maintain usual sedentary habits, or were placed on a no exercise regime. Exercise therapies included weight-bearing activities such as running or walking on treadmills or outdoors, dance or similar, circuit training with no or minimal resistance component, skiing, team sports such as football, and non weight-bearing activities such as swimming, cycling, and ergocycle. Aerobic exercise intensity ranged from 45-80% VO_{2MAX}. Studies included supervised and unsupervised training sessions, with unchanged or progressive effort increments in response to training adaptations, as well as measures of effort monitored in a clinical setting or self-monitored, and reporting via training logs (digital and analog), see Electronic Supplementary Material Tables S5.6-S5.7.

3.2 Estimated Effect Sizes of AET

3.2.1 Total Cholesterol Random effects meta-analysis of 5448 participants (exercise: 2920; control: 2528) showed AET significantly reduced TC mmol/L: MD, 95% CI (-0.20 [-0.25, -0.15]) *P*<.0001, I^2=21%), presented in Figure 5.2.

Study name	Outcome	Cumulative statistics					Cumulative sample size			Study Quality	Weight (Random)	
		Point	Standard error	Lower limit	Upper limit	p-Value	Exercise	Control	Total		Weight (Random)	Relative weight
Huttunen 1979	TC	-0.270	0.252	-0.763	0.223	0.283	44	46	90	11	13.72	1.02
Suter 1990	TC	-0.134	0.174	-0.474	0.206	0.441	83	68	151	9	14.90	2.12
Blumenthal 1991	TC	-0.148	0.145	-0.431	0.136	0.306	114	100	214	9	12.81	3.07
Sunami 1999	TC	-0.122	0.124	-0.365	0.121	0.325	134	120	254	10	14.66	4.15
Suter 1992	TC	-0.107	0.112	-0.327	0.113	0.340	150	136	286	9	12.93	5.11
Kiens 1980	TC	-0.116	0.104	-0.321	0.088	0.265	174	149	323	8	10.71	5.90
Hinkleman 1993	TC	-0.138	0.100	-0.334	0.058	0.167	192	167	359	12	7.92	6.48
Hellénius 1993	TC	-0.099	0.083	-0.262	0.064	0.235	231	206	437	9	30.98	8.78
Ready 1995	TC	-0.126	0.078	-0.278	0.027	0.106	246	216	462	8	17.41	10.06
Nieman 1993	TC	-0.126	0.076	-0.275	0.023	0.097	260	232	492	13	6.95	10.58
Stensel 1993	TC	-0.131	0.074	-0.275	0.014	0.077	302	255	557	11	9.54	11.28
Lindheim 1994	TC	-0.164	0.071	-0.304	-0.025	0.021	322	280	602	9	12.78	12.23
Grandjean 1996	TC	-0.156	0.069	-0.292	-0.021	0.024	342	297	639	11	10.44	13.00
Kukkonen-Harjula 1998	TC	-0.171	0.051	-0.272	-0.071	0.001	395	352	747	12	64.66	17.79
Schuit 1998 all round	TC	-0.179	0.050	-0.277	-0.080	0.000	428	393	821	10	15.23	18.91
Wood 1983	TC	-0.179	0.047	-0.271	-0.087	0.000	461	441	902	9	36.19	21.59
Schuit 1998 cycling	TC	-0.172	0.046	-0.262	-0.083	0.000	522	482	1004	10	21.15	23.15
LeMura 2000	TC	-0.187	0.044	-0.274	-0.101	0.000	532	494	1026	9	25.68	25.05
Takeshima 2002	TC	-0.190	0.044	-0.276	-0.105	0.000	547	509	1056	8	10.64	25.84
Nieman 2002	TC	-0.188	0.043	-0.272	-0.103	0.000	568	531	1099	13	8.81	26.49
Tsai 2002	TC	-0.190	0.043	-0.274	-0.106	0.000	580	542	1122	7	5.00	26.86
Short 2003	TC	-0.184	0.042	-0.267	-0.102	0.000	645	579	1224	8	15.44	28.00
Furukawa 2003	TC	-0.182	0.042	-0.263	-0.100	0.000	666	603	1269	12	15.75	29.17
Grant 2004	TC	-0.184	0.041	-0.266	-0.103	0.000	679	616	1295	8	4.67	29.51
Mosher 2005 continuous step	TC	-0.182	0.041	-0.262	-0.103	0.000	706	629	1335	9	18.42	30.88
Mosher 2005 interval step	TC	-0.176	0.040	-0.254	-0.098	0.000	732	641	1373	9	20.51	32.39
Wirth 1985	TC	-0.176	0.040	-0.254	-0.098	0.000	742	652	1394	8	2.33	32.57
Mohanka 2006	TC	-0.168	0.039	-0.244	-0.093	0.000	827	738	1565	12	28.72	34.69
Vainionpää 2007	TC	-0.165	0.038	-0.239	-0.091	0.000	864	777	1641	10	19.13	36.11
Tully 2007 (less than	TC	-0.167	0.038	-0.240	-0.093	0.000	908	787	1695	13	12.31	37.02
Boardley 2007	TC	-0.165	0.037	-0.238	-0.092	0.000	941	822	1763	9	10.07	37.76
Tully 2007 (= recommended)	TC	-0.163	0.037	-0.236	-0.091	0.000	983	832	1815	13	11.75	38.63
Ring-Dimitriou 2007	TC	-0.163	0.037	-0.235	-0.091	0.000	1003	842	1845	9	2.74	38.83
von Thiele Schwarz 2008	TC	-0.160	0.036	-0.231	-0.090	0.000	1061	902	1963	8	23.19	40.55
Sillanpää 2009 women	TC	-0.156	0.035	-0.225	-0.088	0.000	1076	914	1990	9	36.06	43.22
Lawton 2008	TC	-0.123	0.031	-0.184	-0.063	0.000	1620	1459	3079	12	72.42	48.57
Busby 1985	TC	-0.124	0.031	-0.184	-0.064	0.000	1632	1471	3103	9	5.30	48.97
Sillanpää 2009 men	TC	-0.125	0.030	-0.185	-0.066	0.000	1648	1483	3131	9	18.08	50.30
Krustrup 2009	TC	-0.126	0.030	-0.185	-0.067	0.000	1658	1493	3151	10	4.77	50.66
Mawi 2009	TC	-0.159	0.034	-0.225	-0.094	0.000	1689	1524	3213	10	17.34	51.94
Bergström 2009	TC	-0.153	0.032	-0.216	-0.090	0.000	1737	1568	3305	10	36.53	54.64
Bell 2010 walking	TC	-0.149	0.031	-0.210	-0.088	0.000	1780	1591	3371	11	13.33	55.63
Martins 2010	TC	-0.156	0.032	-0.218	-0.094	0.000	1812	1622	3434	6	14.44	56.70
Krustrup 2010	TC	-0.156	0.031	-0.217	-0.096	0.000	1829	1636	3465	10	12.67	57.63
Knoepfli-Lenzin 2010	TC	-0.153	0.030	-0.212	-0.094	0.000	1844	1653	3497	8	7.50	58.19
Morgan 2010	TC	-0.164	0.032	-0.226	-0.102	0.000	1858	1668	3526	10	4.87	58.55
Santiago 1985	TC	-0.161	0.031	-0.222	-0.101	0.000	1874	1679	3553	8	12.05	59.44
Bell 2010 MICT	TC	-0.157	0.030	-0.216	-0.098	0.000	1914	1701	3615	11	11.35	60.28
Niederseer 2011	TC	-0.154	0.029	-0.211	-0.097	0.000	1932	1717	3649	10	9.32	60.97
Ohta 2012	TC	-0.149	0.028	-0.204	-0.094	0.000	1945	1730	3675	8	13.75	61.99
Vicente-Campos 2012	TC	-0.173	0.029	-0.230	-0.115	0.000	1967	1751	3718	7	52.61	65.88
Ho 2012	TC	-0.171	0.029	-0.228	-0.115	0.000	1982	1767	3749	10	4.77	66.23
Nualmin 2012	TC	-0.170	0.028	-0.225	-0.115	0.000	2006	1786	3792	12	8.37	66.85
Bhutani 2013	TC	-0.165	0.027	-0.218	-0.112	0.000	2030	1802	3832	12	31.07	69.15
Zhang 2014	TC	-0.198	0.033	-0.263	-0.134	0.000	2084	1859	3943	10	46.34	72.58
Mohr 2014 MICT	TC	-0.199	0.032	-0.262	-0.135	0.000	2104	1869	3973	12	5.83	73.01
Baker 1986	TC	-0.200	0.032	-0.262	-0.137	0.000	2124	1883	4007	9	4.86	73.37
Maruf 2014	TC	-0.195	0.031	-0.256	-0.133	0.000	2184	1943	4127	11	30.37	75.61
Sousa 2014	TC	-0.195	0.031	-0.256	-0.135	0.000	2199	1960	4159	9	12.56	76.54
Park 2014	TC	-0.195	0.030	-0.255	-0.135	0.000	2213	1974	4187	11	10.68	77.33
Mohr 2014 HIIT	TC	-0.195	0.030	-0.254	-0.136	0.000	2234	1985	4219	11	9.30	78.02
Tianen 2016	TC	-0.188	0.029	-0.245	-0.131	0.000	2313	2067	4380	11	52.47	81.90
Rossi 2016	TC	-0.188	0.029	-0.244	-0.131	0.000	2328	2085	4413	7	8.84	82.56
Korshøj 2016	TC	-0.190	0.028	-0.245	-0.134	0.000	2385	2144	4529	9	28.70	84.68
Krustrup 2017	TC	-0.192	0.028	-0.247	-0.137	0.000	2404	2156	4560	11	9.27	85.37
Sarzynski 2018 AT1 - 20KKW	TC	-0.193	0.027	-0.247	-0.139	0.000	2450	2179	4629	11	31.01	87.66
Cunningham 1987	TC	-0.189	0.027	-0.242	-0.136	0.000	2551	2280	4831	10	29.23	89.82
Costa 2018	TC	-0.194	0.028	-0.248	-0.140	0.000	2571	2300	4871	10	8.06	90.42
Sarzynski 2018 AT2 - 8 KKW	TC	-0.192	0.027	-0.245	-0.140	0.000	2619	2322	4941	11	35.56	93.05
Bock 2019 video	TC	-0.190	0.026	-0.242	-0.139	0.000	2712	2369	5081	14	24.70	94.88
Bock 2019 standard	TC	-0.187	0.026	-0.237	-0.136	0.000	2808	2416	5224	14	27.22	96.89
Shou 2019	TC	-0.200	0.027	-0.254	-0.146	0.000	2906	2516	5422	9	35.66	99.53
Hornstrup 2019	TC	-0.200	0.027	-0.253	-0.147	0.000	2920	2528	5448	8	6.39	100.00
		-0.200	0.027	-0.253	-0.147	0.000						



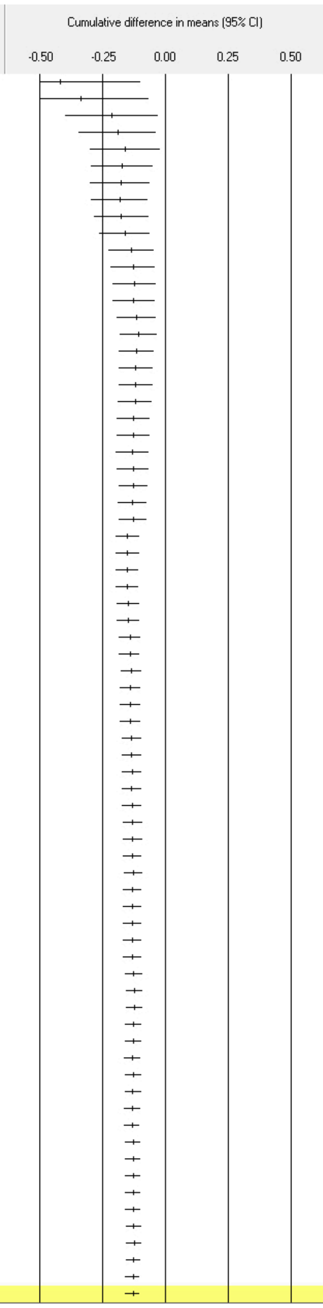
Total = number of participants. Point: estimated mean difference (mmol/L); 95% CI: 95% pooled confidence intervals (mmol/L).

Figure 5.2 Total Cholesterol Random Effects Meta-analysis Forest Plot

Leave-one-out (K-1) analysis did not affect significance and no influencer RCTs were detected (data not shown).

3.2.2 Triglycerides Random effects meta-analysis of 4305 participants (exercise: 2421; control: 1884) showed AET significantly reduced TRG mmol/L: MD 95% CI (-0.13 [-0.16, -0.1] mmol/L, P<.0001, I^2=0%), presented in Figure 5.3.

Study name	Outcome	Cumulative statistics					Cumulative sample size			Study Quality	Weight (Random)	
		Point	Standard error	Lower limit	Upper limit	p-Value	Exercise	Control	Total		Weight (Random)	Relative weight
Huttunen 1979	TRG	-0.420	0.165	-0.743	-0.097	0.011	44	46	90	11	36.80	0.84
Kiens 1980	TRG	-0.336	0.139	-0.608	-0.064	0.016	68	59	127	8	15.01	1.19
Wood 1983	TRG	-0.212	0.094	-0.397	-0.028	0.024	101	107	208	9	91.66	3.29
Busby 1985	TRG	-0.190	0.079	-0.345	-0.035	0.016	113	119	232	9	16.98	3.68
Santiago 1985	TRG	-0.160	0.071	-0.300	-0.019	0.026	129	130	259	8	35.15	4.48
Baker 1986	TRG	-0.173	0.063	-0.297	-0.049	0.006	149	144	293	9	54.97	5.74
Hespel 1988	TRG	-0.179	0.061	-0.299	-0.058	0.004	162	158	320	9	15.74	6.10
Suter 1990	TRG	-0.182	0.058	-0.295	-0.069	0.002	201	180	381	9	35.27	6.91
Blumenthal 1991	TRG	-0.175	0.055	-0.283	-0.067	0.002	232	212	444	9	27.03	7.53
King 1991 HIT group men	TRG	-0.161	0.051	-0.261	-0.061	0.002	272	226	498	9	55.55	8.81
King 1991 HIT group women	TRG	-0.137	0.046	-0.228	-0.046	0.003	306	237	543	9	79.98	10.64
King 1991 HIT home men	TRG	-0.129	0.045	-0.217	-0.040	0.004	348	251	599	9	29.33	11.31
King 1991 HIT home women	TRG	-0.123	0.044	-0.209	-0.037	0.005	383	263	646	9	25.84	11.90
King 1991 LIT home men	TRG	-0.125	0.043	-0.210	-0.041	0.004	428	277	705	9	16.62	12.28
King 1991 LIT home women	TRG	-0.115	0.039	-0.192	-0.037	0.004	457	288	745	9	106.75	14.73
Sunami 1999	TRG	-0.107	0.038	-0.182	-0.033	0.005	477	308	785	10	47.28	15.81
Suter 1992	TRG	-0.115	0.036	-0.185	-0.045	0.001	493	324	817	9	96.05	18.02
Hellénius 1993	TRG	-0.118	0.035	-0.186	-0.050	0.001	532	363	895	9	52.34	19.22
Nieman 1993	TRG	-0.119	0.034	-0.186	-0.052	0.001	546	379	925	13	11.10	19.47
Ready 1995	TRG	-0.121	0.034	-0.188	-0.054	0.000	561	389	950	8	8.75	19.67
Hinkleman 1993	TRG	-0.126	0.034	-0.192	-0.060	0.000	579	407	986	12	26.60	20.28
Stensel 1993	TRG	-0.126	0.034	-0.192	-0.060	0.000	621	430	1051	11	0.70	20.30
Lindheim 1994	TRG	-0.130	0.033	-0.195	-0.065	0.000	641	455	1096	9	14.13	20.62
Grandjean 1996	TRG	-0.129	0.033	-0.193	-0.064	0.000	661	472	1133	11	17.72	21.03
Kukkonen-Harjula 1998	TRG	-0.129	0.030	-0.187	-0.071	0.000	712	526	1238	12	220.87	26.09
Schuit 1998 all round	TRG	-0.130	0.029	-0.187	-0.072	0.000	745	567	1312	10	27.43	26.72
Schuit 1998 cycling	TRG	-0.129	0.029	-0.185	-0.073	0.000	806	608	1414	10	54.26	27.96
LeMura 2000	TRG	-0.151	0.024	-0.198	-0.104	0.000	816	620	1436	9	545.45	40.46
Nieman 2002	TRG	-0.151	0.024	-0.197	-0.104	0.000	837	642	1479	13	16.21	40.83
Takeshima 2002	TRG	-0.151	0.023	-0.197	-0.106	0.000	852	657	1509	8	44.85	41.86
Tsai 2002	TRG	-0.150	0.023	-0.196	-0.105	0.000	864	668	1532	7	37.36	42.72
Furukawa 2003	TRG	-0.148	0.023	-0.193	-0.103	0.000	885	692	1577	12	55.35	43.99
Short 2003	TRG	-0.149	0.023	-0.193	-0.104	0.000	950	729	1679	8	29.33	44.66
Mosher 2005 continuous step	TRG	-0.142	0.022	-0.185	-0.099	0.000	976	741	1717	9	132.11	47.69
Mosher 2005 interval step	TRG	-0.142	0.021	-0.183	-0.100	0.000	1003	754	1757	9	118.65	50.41
Mohanka 2006	TRG	-0.138	0.021	-0.179	-0.096	0.000	1090	840	1930	12	69.76	52.01
Boardley 2007	TRG	-0.139	0.021	-0.180	-0.098	0.000	1123	875	1998	9	20.98	52.49
Ring-Dimitriou 2007	TRG	-0.139	0.021	-0.180	-0.098	0.000	1143	885	2028	9	6.59	52.64
Tully 2007 (less than recommended)	TRG	-0.139	0.021	-0.179	-0.098	0.000	1187	895	2082	13	29.57	53.32
Vainionpää 2007	TRG	-0.134	0.020	-0.174	-0.094	0.000	1224	934	2158	10	87.13	55.31
Tully 2007 (= recommnded)	TRG	-0.134	0.020	-0.173	-0.094	0.000	1266	944	2210	13	23.07	55.84
von Thiele Schwarz 2008	TRG	-0.132	0.020	-0.172	-0.093	0.000	1324	1004	2328	8	54.70	57.10
Mawi 2009	TRG	-0.135	0.020	-0.174	-0.096	0.000	1355	1035	2390	10	39.10	57.99
Sillanpää 2009 men	TRG	-0.133	0.020	-0.172	-0.094	0.000	1371	1047	2418	9	42.86	58.97
Sillanpää 2009 women	TRG	-0.130	0.019	-0.168	-0.092	0.000	1386	1059	2445	9	62.19	60.40
Bell 2010 MICT	TRG	-0.129	0.019	-0.168	-0.091	0.000	1426	1081	2507	11	9.11	60.61
Bell 2010 walking	TRG	-0.130	0.019	-0.168	-0.092	0.000	1469	1104	2573	11	27.46	61.24
Krustrup 2010	TRG	-0.128	0.019	-0.166	-0.090	0.000	1486	1118	2604	10	47.26	62.32
Martins 2010	TRG	-0.130	0.019	-0.167	-0.093	0.000	1518	1149	2667	6	71.49	63.96
Niederseer 2011	TRG	-0.131	0.019	-0.168	-0.095	0.000	1536	1165	2701	10	66.62	65.49
Ho 2012	TRG	-0.132	0.019	-0.168	-0.095	0.000	1551	1181	2732	10	13.35	65.79
Nualmin 2012	TRG	-0.131	0.019	-0.168	-0.095	0.000	1575	1200	2775	12	16.22	66.16
Ohta 2012	TRG	-0.132	0.019	-0.168	-0.095	0.000	1588	1213	2801	8	22.00	66.67
Vicente-Campos 2012	TRG	-0.128	0.017	-0.162	-0.094	0.000	1610	1234	2844	7	385.58	75.51
Bhutani 2013	TRG	-0.124	0.017	-0.157	-0.090	0.000	1634	1250	2884	12	116.06	78.17
Kemmler 2014	TRG	-0.124	0.017	-0.157	-0.091	0.000	1667	1291	2958	12	127.75	81.09
Maruf 2014	TRG	-0.127	0.017	-0.159	-0.094	0.000	1727	1351	3078	11	70.44	82.71
Mohr 2014 HIIT	TRG	-0.129	0.017	-0.161	-0.096	0.000	1748	1362	3110	11	28.87	83.37
Mohr 2014 MICT	TRG	-0.130	0.017	-0.162	-0.098	0.000	1768	1372	3140	12	13.24	83.67
Park 2014	TRG	-0.129	0.017	-0.162	-0.097	0.000	1782	1386	3168	11	22.22	84.18
Sousa 2014	TRG	-0.130	0.016	-0.162	-0.098	0.000	1797	1403	3200	9	22.57	84.70
Zhang 2014	TRG	-0.131	0.016	-0.163	-0.099	0.000	1851	1460	3311	10	62.71	86.14
Korshøj 2016	TRG	-0.131	0.016	-0.163	-0.100	0.000	1908	1519	3427	9	58.61	87.48
Tianen 2016	TRG	-0.128	0.016	-0.159	-0.097	0.000	1987	1601	3588	11	159.45	91.14
Krustrup 2017	TRG	-0.129	0.016	-0.160	-0.098	0.000	2006	1613	3619	11	23.03	91.66
Costa 2018	TRG	-0.129	0.016	-0.160	-0.098	0.000	2026	1633	3659	10	8.52	91.86
Sarzynski 2018 AT1 - 20KKW	TRG	-0.128	0.016	-0.159	-0.098	0.000	2072	1656	3728	11	63.57	93.32
Sarzynski 2018 AT2 - 8KKW	TRG	-0.128	0.015	-0.158	-0.098	0.000	2120	1678	3798	11	99.69	95.60
Bock 2019 standard	TRG	-0.126	0.015	-0.156	-0.096	0.000	2216	1725	3941	14	80.66	97.45
Bock 2019 video	TRG	-0.124	0.015	-0.154	-0.094	0.000	2309	1772	4081	14	51.61	98.63
Hornstrup 2019	TRG	-0.126	0.015	-0.155	-0.096	0.000	2323	1784	4107	8	33.49	99.40
Shou 2019	TRG	-0.129	0.015	-0.159	-0.100	0.000	2421	1884	4305	9	26.18	100.00
		-0.129	0.015	-0.159	-0.100	0.000						



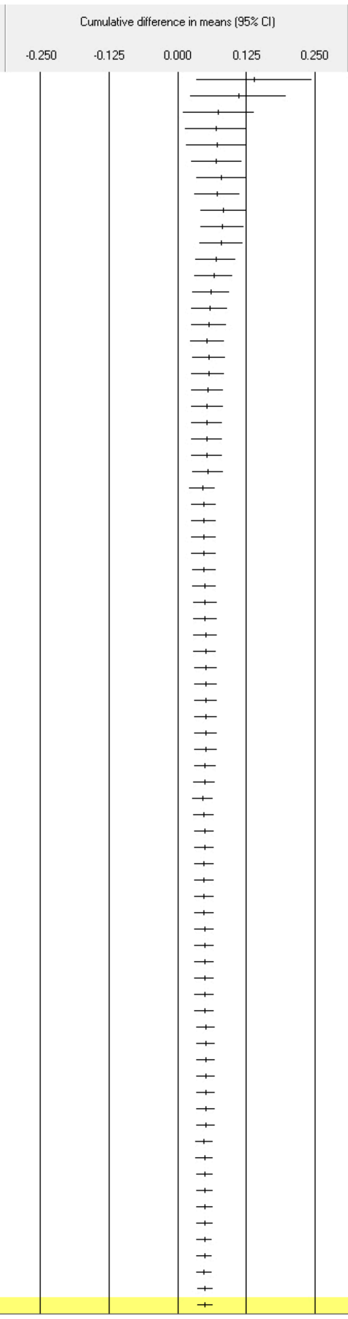
Total = number of participants. Point: estimated mean difference (mmol/L); 95% CI: 95% pooled confidence intervals (mmol/L).

Figure 5.3 Triglycerides Random Effects Meta-analysis Forest Plot Excluding Influencer RCT

Leave one out (K-1) analysis did not affect significance, but identified an influencer RCT,[134]; see Electronic Supplementary Table S5.4 And Figure S5.6.

3.2.3 High-Density Lipoprotein Cholesterol Random effects meta-analysis of 5646 participants (exercise: 3094; control: 2552) showed AET significant increased HDL-C mmol/L: MD, 95% CI (0.05 [0.04,0.06]) *P*<.0001, I^2=0%) presented in Figure 5.4.

Study name	Outcome	Cumulative statistics					Cumulative sample size			Study Quality	Weight (Random)	
		Point	Standard error	Lower limit	Upper limit	p-Value	Exercise	Control	Total		Weight (Random)	Relative weight
Huttunen 1979	HDL-C	0.140	0.054	0.035	0.245	0.009	44	46	90	11	346.19	1.73
Kiens 1980	HDL-C	0.111	0.044	0.024	0.198	0.012	68	59	127	8	161.29	2.54
Wood 1983	HDL-C	0.074	0.033	0.009	0.138	0.025	101	107	208	9	608.54	5.58
Busby 1985	HDL-C	0.071	0.029	0.014	0.128	0.014	113	119	232	9	83.10	5.99
Santiago 1985	HDL-C	0.072	0.028	0.016	0.127	0.011	129	130	259	8	47.21	6.23
Wirth 1985	HDL-C	0.071	0.024	0.025	0.118	0.003	139	141	280	8	532.67	8.89
Baker 1986	HDL-C	0.079	0.023	0.034	0.124	0.001	159	155	314	9	94.00	9.36
Cunningham 1987	HDL-C	0.073	0.021	0.031	0.115	0.001	260	256	516	10	345.60	11.09
Hespel 1988	HDL-C	0.084	0.021	0.042	0.125	0.000	273	270	543	9	142.40	11.80
Suter 1990	HDL-C	0.081	0.020	0.042	0.121	0.000	312	292	604	9	56.83	12.09
Blumenthal 1991	HDL-C	0.080	0.020	0.041	0.119	0.000	343	324	667	9	99.84	12.59
King 1991 HIT group men	HDL-C	0.070	0.018	0.034	0.106	0.000	383	338	721	9	415.23	14.66
King 1991 HIT group women	HDL-C	0.067	0.018	0.031	0.102	0.000	417	350	767	9	171.31	15.52
King 1991 HIT home men	HDL-C	0.062	0.017	0.028	0.095	0.000	459	364	823	9	298.22	17.01
King 1991 HIT home women	HDL-C	0.059	0.017	0.026	0.091	0.000	494	376	870	9	172.51	17.87
King 1991 LIT home men	HDL-C	0.056	0.016	0.025	0.088	0.000	539	390	929	9	302.87	19.38
King 1991 LIT home women	HDL-C	0.054	0.016	0.023	0.085	0.001	568	401	969	9	154.21	20.15
Sunami 1999	HDL-C	0.057	0.016	0.027	0.088	0.000	588	421	1009	10	105.39	20.68
Suter 1992	HDL-C	0.056	0.015	0.026	0.087	0.000	604	437	1041	9	66.71	21.02
Hellénius 1993	HDL-C	0.055	0.015	0.025	0.084	0.000	643	476	1119	9	297.03	22.50
Nieman 1993	HDL-C	0.053	0.015	0.025	0.082	0.000	664	492	1156	13	132.10	23.16
Ready 1995	HDL-C	0.054	0.015	0.025	0.082	0.000	679	502	1181	8	69.19	23.51
Lindheim 1994	HDL-C	0.054	0.014	0.025	0.082	0.000	699	527	1226	9	75.29	23.88
Stensel 1995	HDL-C	0.053	0.014	0.025	0.081	0.000	741	550	1291	11	42.02	24.09
Grandjean 1996	HDL-C	0.056	0.014	0.028	0.084	0.000	761	567	1328	11	91.43	24.55
Kukkonen-Harjula 1998	HDL-C	0.045	0.012	0.022	0.069	0.000	814	621	1435	12	2210.55	35.60
Schuit 1998 all round	HDL-C	0.048	0.012	0.025	0.071	0.000	847	662	1509	10	175.06	36.47
Schuit 1998 cycling	HDL-C	0.049	0.012	0.026	0.071	0.000	908	703	1611	10	262.74	37.79
Nieman 2002	HDL-C	0.047	0.011	0.025	0.069	0.000	936	725	1661	13	283.89	39.21
Takeshima 2002	HDL-C	0.047	0.011	0.025	0.069	0.000	951	740	1691	8	41.31	39.41
Tsai 2002	HDL-C	0.049	0.011	0.027	0.071	0.000	963	751	1714	7	38.05	39.60
Furukawa 2003	HDL-C	0.049	0.011	0.028	0.071	0.000	984	775	1759	12	96.41	40.09
Short 2003	HDL-C	0.051	0.011	0.029	0.072	0.000	1049	812	1861	8	44.68	40.31
Mosher 2005 continuous step	HDL-C	0.050	0.011	0.029	0.072	0.000	1075	824	1899	9	118.77	40.90
Mosher 2005 interval step	HDL-C	0.051	0.011	0.030	0.073	0.000	1102	837	1939	9	119.26	41.50
Mohanka 2006	HDL-C	0.051	0.011	0.030	0.072	0.000	1189	923	2112	12	353.18	43.26
Boardley 2007	HDL-C	0.051	0.011	0.030	0.072	0.000	1222	958	2180	9	89.62	43.71
Ring-Dimitriou 2007	HDL-C	0.052	0.011	0.031	0.072	0.000	1242	968	2210	9	15.66	43.79
Tully 2007 (= recommended)	HDL-C	0.052	0.011	0.031	0.073	0.000	1284	978	2262	13	22.84	43.90
Tully 2007 (less than recommended)	HDL-C	0.052	0.011	0.031	0.073	0.000	1328	988	2316	13	30.99	44.06
Vainionpää 2007	HDL-C	0.052	0.011	0.031	0.073	0.000	1365	1027	2392	10	160.34	44.86
von Thiele Schwarz 2008	HDL-C	0.052	0.010	0.032	0.072	0.000	1423	1087	2510	8	260.01	46.16
Bergström 2009	HDL-C	0.050	0.010	0.030	0.070	0.000	1471	1131	2602	10	637.13	49.35
Krustrup 2009	HDL-C	0.050	0.010	0.030	0.069	0.000	1481	1141	2622	10	50.01	49.60
Lawton 2008	HDL-C	0.046	0.009	0.028	0.065	0.000	2025	1686	3711	12	1249.95	55.84
Sillanpää 2009 men	HDL-C	0.048	0.009	0.029	0.066	0.000	2041	1698	3739	9	251.11	57.10
Sillanpää 2009 women	HDL-C	0.049	0.009	0.031	0.067	0.000	2056	1710	3766	9	107.53	57.64
Bell 2010 MICT	HDL-C	0.049	0.009	0.031	0.067	0.000	2096	1732	3828	11	2.65	57.65
Bell 2010 walking	HDL-C	0.048	0.009	0.030	0.066	0.000	2139	1755	3894	11	222.90	58.76
Knoepfli-Lenzin 2010	HDL-C	0.048	0.009	0.030	0.067	0.000	2154	1772	3926	8	61.28	59.07
Krustrup 2010	HDL-C	0.048	0.009	0.030	0.066	0.000	2171	1786	3957	10	49.04	59.32
Martins 2010	HDL-C	0.049	0.009	0.031	0.066	0.000	2203	1817	4020	6	189.42	60.26
Morgan 2010	HDL-C	0.049	0.009	0.031	0.067	0.000	2217	1832	4049	10	48.60	60.51
Niederseer 2011	HDL-C	0.049	0.009	0.031	0.067	0.000	2235	1848	4083	10	228.17	61.65
Ho 2012	HDL-C	0.049	0.009	0.031	0.067	0.000	2250	1864	4114	10	55.16	61.92
Nualmin 2012	HDL-C	0.049	0.009	0.032	0.067	0.000	2274	1883	4157	12	40.59	62.12
Ohta 2012	HDL-C	0.049	0.009	0.031	0.066	0.000	2287	1896	4183	8	132.65	62.79
Bhutani 2013	HDL-C	0.049	0.009	0.032	0.067	0.000	2311	1912	4223	12	182.38	63.70
Kemmler 2014	HDL-C	0.051	0.009	0.034	0.068	0.000	2344	1953	4297	12	240.44	64.90
Maruf 2014	HDL-C	0.051	0.009	0.034	0.068	0.000	2404	2013	4417	11	193.43	65.87
Mohr 2014 HIIT	HDL-C	0.052	0.009	0.035	0.069	0.000	2425	2024	4449	11	40.85	66.07
Mohr 2014 MICT	HDL-C	0.052	0.009	0.035	0.069	0.000	2445	2034	4479	12	39.72	66.27
Park 2014	HDL-C	0.052	0.009	0.035	0.069	0.000	2459	2048	4507	11	49.99	66.52
Sousa 2014	HDL-C	0.052	0.009	0.036	0.069	0.000	2474	2065	4539	9	111.67	67.08
Zhang 2014	HDL-C	0.052	0.008	0.035	0.069	0.000	2528	2122	4650	10	565.43	69.91
Korshøj 2016	HDL-C	0.049	0.008	0.033	0.065	0.000	2585	2181	4766	9	1153.58	75.67
Rossi 2016	HDL-C	0.049	0.008	0.033	0.065	0.000	2600	2199	4799	7	109.73	76.22
Tianen 2016	HDL-C	0.049	0.008	0.034	0.065	0.000	2679	2281	4960	11	911.95	80.78
Costa 2018	HDL-C	0.050	0.008	0.035	0.066	0.000	2699	2301	5000	10	123.62	81.40
Sarzynski 2018 AT1 - 20KKW	HDL-C	0.050	0.008	0.034	0.065	0.000	2745	2324	5069	11	445.61	83.62
Sarzynski 2018 AT2 - 8KKW	HDL-C	0.049	0.008	0.034	0.064	0.000	2793	2346	5139	11	429.51	85.77
Bock 2019 standard	HDL-C	0.049	0.007	0.035	0.064	0.000	2889	2393	5282	14	1276.27	92.15
Bock 2019 video	HDL-C	0.049	0.007	0.035	0.063	0.000	2982	2440	5422	14	1085.09	97.58
Hornstrup 2019	HDL-C	0.049	0.007	0.035	0.063	0.000	2996	2452	5448	8	63.02	97.89
Shou 2019	HDL-C	0.050	0.007	0.036	0.064	0.000	3094	2552	5646	9	422.03	100.00
		0.050	0.007	0.036	0.064	0.000						



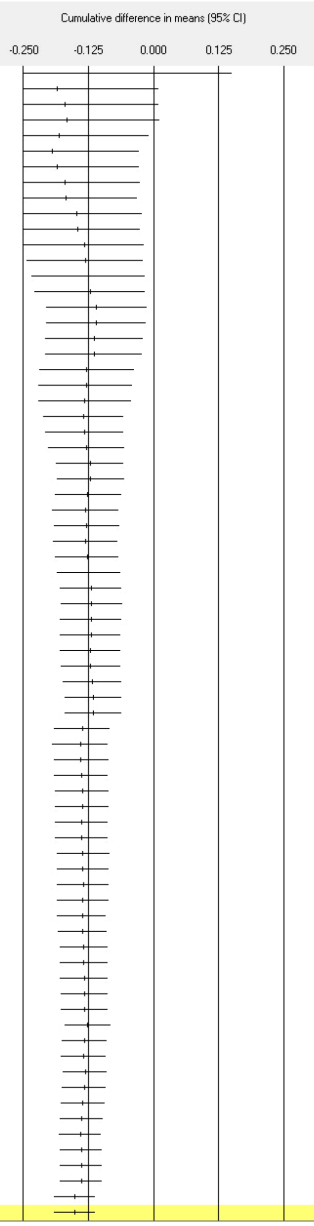
Total = number of participants. Point: estimated mean difference (mmol/L); 95% CI: 95% pooled confidence intervals (mmol/L).

Figure 5.4 High-density Lipoprotein Cholesterol Random Effects Meta-analysis Forest Plot Excluding Outliers

Statistically significant heterogeneity suggested the presence of outliers. The outliers,[98, 101, 105, 134, 136] were detected using pooled 95% CI boundaries and removed, see Electronic Supplementary Material Table S5.5. Leave-one-out (K-1) analysis did not detect the presence of influencer studies (either before or after outliers were removed (data not shown).

3.2.4 Low-density Lipoprotein Cholesterol Random effects meta-analysis of 4303 participants (exercise: 2408; control: 1895) showed AET significantly reduced LDL-C mmol/L: MD 95% CI (-0.15 [-0.19, -0.11], *P*<.0001, I^2=0%), shown in Figure 5.5.

Study name	Outcome	Cumulative statistics: Point	Standard error	Lower limit	Upper limit	p-Value	Cumulative sample size: Exercise	Control	Total	Study Quality	Weight (Random): Weight (Random)	Relative weight
Huttunen 1979	LDL-C	-0.280	0.220	-0.711	0.151	0.203	44	46	90	11	20.64	0.83
Wood 1983	LDL-C	-0.184	0.099	-0.379	0.010	0.064	77	94	171	9	80.51	4.07
Santiago 1985	LDL-C	-0.170	0.092	-0.352	0.011	0.065	93	105	198	8	15.78	4.70
Wirth 1985	LDL-C	-0.165	0.091	-0.344	0.013	0.069	103	116	219	8	3.54	4.85
Baker 1986	LDL-C	-0.181	0.089	-0.356	-0.007	0.041	123	130	253	9	6.02	5.09
Hespel 1988	LDL-C	-0.195	0.086	-0.363	-0.027	0.023	136	144	280	9	9.85	5.49
Blumenthal 1991	LDL-C	-0.185	0.081	-0.345	-0.026	0.022	167	176	343	9	15.07	6.09
King 1991 HIT group men	LDL-C	-0.170	0.074	-0.315	-0.024	0.022	207	190	397	9	30.14	7.30
King 1991 HIT group women	LDL-C	-0.168	0.070	-0.306	-0.030	0.017	241	201	442	9	19.66	8.10
King 1991 HIT home men	LDL-C	-0.147	0.065	-0.274	-0.021	0.023	283	215	498	9	38.06	9.63
King 1991 HIT home women	LDL-C	-0.146	0.062	-0.269	-0.024	0.019	318	227	545	9	16.85	10.31
King 1991 LIT home men	LDL-C	-0.132	0.059	-0.248	-0.016	0.026	363	241	604	9	29.99	11.51
King 1991 LIT home women	LDL-C	-0.130	0.057	-0.242	-0.019	0.022	392	252	644	9	21.45	12.38
Sunami 1999	LDL-C	-0.125	0.055	-0.234	-0.017	0.024	412	272	684	10	18.40	13.12
Suter 1992	LDL-C	-0.121	0.054	-0.227	-0.015	0.026	428	288	716	9	13.73	13.67
Hellénius 1993	LDL-C	-0.110	0.049	-0.206	-0.014	0.025	467	327	794	9	74.65	16.67
Nieman 1993	LDL-C	-0.109	0.049	-0.205	-0.014	0.024	481	343	824	13	8.49	17.01
Ready 1995	LDL-C	-0.114	0.048	-0.208	-0.020	0.017	496	353	849	8	13.04	17.54
Hinkleman 1993	LDL-C	-0.114	0.047	-0.207	-0.021	0.016	514	371	885	12	9.37	17.92
Lindheim 1994	LDL-C	-0.128	0.047	-0.219	-0.036	0.006	534	396	930	9	15.13	18.52
Stensel 1995	LDL-C	-0.129	0.046	-0.220	-0.039	0.005	576	419	995	11	10.75	18.96
Grandjean 1996	LDL-C	-0.132	0.045	-0.221	-0.043	0.004	596	436	1032	11	12.24	19.45
Kukkonen-Harjula 1998	LDL-C	-0.134	0.039	-0.211	-0.057	0.001	647	490	1137	12	170.77	26.32
Schuit 1998 all round	LDL-C	-0.132	0.038	-0.208	-0.057	0.001	680	531	1211	10	22.19	27.21
Schuit 1998 cycling	LDL-C	-0.128	0.038	-0.202	-0.055	0.001	741	572	1313	10	32.49	28.52
LeMura 2000	LDL-C	-0.122	0.033	-0.187	-0.057	0.000	751	584	1335	9	205.83	36.80
Nieman 2002	LDL-C	-0.121	0.033	-0.186	-0.057	0.000	772	606	1378	13	15.22	37.41
Takeshima 2002	LDL-C	-0.126	0.033	-0.190	-0.062	0.000	787	621	1408	8	14.09	37.98
Tsai 2002	LDL-C	-0.130	0.032	-0.194	-0.067	0.000	799	632	1431	7	8.65	38.33
Furukawa 2003	LDL-C	-0.128	0.032	-0.191	-0.066	0.000	820	656	1476	12	22.03	39.22
Short 2003	LDL-C	-0.130	0.032	-0.192	-0.068	0.000	885	693	1578	8	19.66	40.01
Mosher 2005 continuous step	LDL-C	-0.127	0.031	-0.188	-0.065	0.000	911	705	1616	9	28.59	41.16
Mosher 2005 interval step	LDL-C	-0.124	0.031	-0.185	-0.064	0.000	938	718	1656	9	21.72	42.03
Mohanka 2006	LDL-C	-0.120	0.030	-0.179	-0.060	0.000	1025	804	1829	12	43.20	43.77
Boardley 2007	LDL-C	-0.119	0.030	-0.178	-0.060	0.000	1058	839	1897	9	16.64	44.44
Ring-Dimitriou 2007	LDL-C	-0.120	0.030	-0.179	-0.061	0.000	1078	849	1927	9	3.54	44.58
Tully 2007 (= recommended)	LDL-C	-0.120	0.030	-0.178	-0.061	0.000	1120	859	1979	13	11.83	45.06
Tully 2007 (less than recommended)	LDL-C	-0.121	0.030	-0.179	-0.063	0.000	1164	869	2033	13	11.00	45.50
Vainionpää 2007	LDL-C	-0.121	0.029	-0.178	-0.063	0.000	1201	908	2109	10	32.87	46.82
von Thiele Schwarz 2008	LDL-C	-0.118	0.029	-0.174	-0.061	0.000	1257	967	2224	8	53.76	48.99
Bergström 2009	LDL-C	-0.116	0.028	-0.171	-0.061	0.000	1305	1011	2316	10	73.51	51.94
Krustrup 2009	LDL-C	-0.116	0.028	-0.170	-0.062	0.000	1314	1021	2335	10	9.32	52.32
Mawi 2009	LDL-C	-0.137	0.027	-0.191	-0.083	0.000	1345	1052	2397	10	27.18	53.41
Sillanpää 2009 men	LDL-C	-0.141	0.027	-0.194	-0.088	0.000	1361	1064	2425	9	32.36	54.71
Sillanpää 2009 women	LDL-C	-0.139	0.027	-0.191	-0.087	0.000	1376	1076	2452	9	51.60	56.79
Bell 2010 MICT	LDL-C	-0.138	0.026	-0.190	-0.086	0.000	1416	1098	2514	11	15.12	57.40
Bell 2010 walking	LDL-C	-0.137	0.026	-0.188	-0.085	0.000	1459	1121	2580	11	18.78	58.15
Krustrup 2010	LDL-C	-0.136	0.026	-0.188	-0.085	0.000	1476	1135	2611	10	12.26	58.65
Martins 2010	LDL-C	-0.137	0.026	-0.188	-0.086	0.000	1508	1166	2674	6	25.02	59.65
Knoepfli-Lenzin 2010 running	LDL-C	-0.137	0.026	-0.188	-0.086	0.000	1523	1183	2706	8	12.16	60.14
Niederseer 2011	LDL-C	-0.135	0.026	-0.186	-0.085	0.000	1541	1199	2740	10	22.85	61.06
Ho 2012	LDL-C	-0.136	0.026	-0.186	-0.085	0.000	1556	1215	2771	10	6.13	61.31
Nualmin 2012	LDL-C	-0.135	0.026	-0.185	-0.085	0.000	1580	1234	2814	12	8.86	61.67
Ohta 2012	LDL-C	-0.136	0.025	-0.185	-0.086	0.000	1593	1247	2840	8	16.68	62.34
Vicente-Campos 2012	LDL-C	-0.137	0.024	-0.184	-0.090	0.000	1615	1268	2883	7	165.62	69.00
Bhutani 2013	LDL-C	-0.136	0.024	-0.183	-0.089	0.000	1639	1284	2923	12	47.09	70.90
Maruf 2014	LDL-C	-0.134	0.023	-0.180	-0.088	0.000	1699	1344	3043	11	68.80	73.66
Mohr 2014 HIIT	LDL-C	-0.134	0.023	-0.179	-0.088	0.000	1720	1355	3075	11	10.22	74.08
Mohr 2014 MICT	LDL-C	-0.133	0.023	-0.179	-0.087	0.000	1740	1365	3105	12	6.18	74.32
Park 2014	LDL-C	-0.133	0.023	-0.178	-0.087	0.000	1754	1379	3133	11	16.78	75.00
Sousa 2014	LDL-C	-0.133	0.023	-0.178	-0.088	0.000	1769	1396	3165	9	23.61	75.95
Zhang 2014	LDL-C	-0.127	0.022	-0.170	-0.083	0.000	1823	1453	3276	10	108.76	80.32
Korshøj 2016	LDL-C	-0.132	0.022	-0.175	-0.089	0.000	1880	1512	3392	9	57.25	82.63
Rossi 2016	LDL-C	-0.134	0.022	-0.177	-0.091	0.000	1895	1530	3425	7	14.52	83.21
Tianen 2016	LDL-C	-0.131	0.022	-0.173	-0.089	0.000	1974	1612	3586	11	72.47	86.13
Krustrup 2017	LDL-C	-0.132	0.022	-0.175	-0.090	0.000	1993	1624	3617	11	11.51	86.59
Costa 2018	LDL-C	-0.136	0.022	-0.178	-0.094	0.000	2013	1644	3657	10	9.92	86.99
Sarzynski 2018 (AT1 - 20 KKW)	LDL-C	-0.138	0.021	-0.179	-0.096	0.000	2059	1667	3726	11	68.26	89.74
Sarzynski 2018 (AT2 - 8 KKW)	LDL-C	-0.140	0.021	-0.180	-0.099	0.000	2107	1689	3796	11	122.44	94.66
Bock 2019 standard	LDL-C	-0.139	0.021	-0.179	-0.099	0.000	2203	1736	3939	14	26.15	95.72
Bock 2019 video	LDL-C	-0.139	0.020	-0.179	-0.099	0.000	2296	1783	4079	14	21.13	96.57
Hornstrup 2019	LDL-C	-0.139	0.020	-0.179	-0.099	0.000	2310	1795	4105	8	8.88	96.92
Shou 2019	LDL-C	-0.151	0.020	-0.191	-0.112	0.000	2408	1895	4303	9	76.47	100.00
		-0.151	0.020	-0.191	-0.112	0.000						



Total = number of participants. Lack of the 95% CI bar indicates pooled analysis 95% CI boundary outliers. MD and SD expressed as mmol/L.

Figure 5.5 Low Density Lipoprotein-Cholesterol Random Effects Meta-analysis Forest Plot

Leave-one-out (K-1) analysis did not affect significance and no influencer RCTs were detected (data not shown).

3.3 Meta-regression Meta-regression modelling suggested that the study covariate TESTEX study quality score partially explained change in the ES of AET for TC. The intervention covariate sessions per week influenced the effect size of AET on LDL-C in the participants of the included RCTs (R^2=1.00, τ^2=0.00, *P*<0.001). For TRG, meta-regression was performed with the influencer study excluded, and for HDL-C, meta-regression was performed with the 5 outlier studies excluded.

3.4 Heterogeneity Statistically significant relative heterogeneity was present for HDL-C; after removal of outliers relative heterogeneity fell to zero, see Table 5.3. Neither the degree of absolute between-study heterogeneity (τ^2) or the relative heterogeneity (I^2) for each analysed lipid outcome indicated that RCTs should not be pooled, or that significance testing of pooled RCTs should not be undertaken. Heterogeneity for TRG was unchanged (0%) when the influencer study was included (data not shown).

Lipid	MD	Lower CI	Upper CI	Heterogeneity				τ^2			
				Q-value	df (Q)	*P* value	I^2%	τ^2	Standard Error	Variance	τ
TC	-0.20	-0.25	-0.24	91.1	72	.06	21	0.01	0.008	0.000	0.098
TRG*	-0.13	-0.16	-0.10	45.57	71	.99	0	0.00	0.003	0.000	0.000
HDL-C†	**0.08**	**0.06**	**0.10**	**180.25**	**79**	**<.0001**	**56**	**0.003**	**0.002**	**0.000**	**0.054**
HDL-C	0.05	0.04	0.06	44.84	74	>.99	0	0.00	0.001	0.000	0.000
LDL-C	-0.15	-0.19	-0.11	66.77	72	.07	0	0.00	0.005	0.000	0.000

MD: mean difference; CI: confidence interval; df: degrees of freedom

Table 5.3 Heterogeneity statistics for each lipid (*excluding influencer study, †outliers retained)

3.5 Lipid Assessment and Reporting The included RCTs reported standard lipid extraction methodology in fasted states in either resting or supine positions (data not shown).

3.6 Study Quality and Reporting A median TESTEX score of 9.5 (from a maximum score of 15; range 6 to 14) was determined for each included RCT, shown in Electronic Supplementary Material Table S5.6. Within-study risk of bias of the included RCTs was scored as mainly low or medium; only two studies[83, 92] scoring high, see Electronic Supplementary Material Table S5.7.

Sub-analyses (including RCTs with TESTEX scores ≥10 and excluding RCTs with a within-study risk of bias score of high) conducted for each lipid did not change significance and minimally reduced the estimated ES, see Electronic Supplementary Material Figures S5.8-S5.11. Leave-one-out (K-1) analysis of the RCTs grouped for TESTEX scores ≥10 for each lipid outcome did not alter significance (data not shown).

3.7 Publication Bias Duval and Tweedie's trim-and-fill analysis showed some publication bias was likely to be present in the meta-analysis of each lipid, see Electronic Supplementary Material Figures S5.12-S5.15. Publication bias was also suggested by Egger's regression test and Begg and Mezumdar's rank correlation test, see Electronic Supplementary Material Table S5.8. The differences between the imputed estimated ES and 95% CIs and the observed estimated ES and of AET on each lipid were insufficient to invalidate the meta-analysis results, see Electronic Supplementary Material Table S5.8. Publication bias was performed in CMA with the influencer study excluded for TRG, and the outlier studies excluded for HDL-C.

4.0 DISCUSSION

Our work compared the effects of at least 12 weeks of weight-bearing and non-weight bearing AET performed at >40% VO_{2MAX}, against control groups performing no exercise or maintenance of usual habits, on TC, TRG, HDL-C, and LDL-C in adults not diagnosed with MetS and free of chronic disease such as CVD. Using 82 data sets from 70 RCTs of 5823 participants, we estimated significant ES of AET interventions for each lipid, and found that intervention covariates are unlikely to predict change in these ES as a result of AET interventions.

4.1 Estimated Effect Sizes of AET Compared to Previous Works

4.1.1 Total Cholesterol We found statistically significant evidence of AET reducing TC, similar to one previous study investigating the effect of AET on an equivalent population with a significant ES, [55] unlike other previous works with insignificant estimated ES.[29, 56, 143-145]

4.1.2 Triglycerides We found statistically significant evidence for AET in reducing TRG, with an ES similar to one previous SR and MA.[144] Two other previous works reported larger and significant ES, one focused on running studies only,[29] the other pooled only three outcomes.[56] One other previous work found no significant effect of AET on TRG.[143]

4.3 High-Density Lipoprotein Cholesterol We found statistically significant evidence for AET in increasing HDL-C with an ES in accordance with 4 previous SRs and MAs examining AET interventions.[29, 30, 56, 143] Other previous works found no significance.[55, 144, 145]

4.4 Low-Density Lipoprotein Cholesterol We found statistically significant evidence for AET in decreasing LDL-C, unlike previous works investigating the effect of AET on LDL-C in equivalent populations.[29, 55, 143-145]

Previous works, where heterogeneity was reported, found moderate to high heterogeneity for all lipids. We applied pooled 95% CI boundary outlier tests for heterogeneity which may explain the difference between the results of our review and those of others. Unlike the findings of previous reviews linking intensity to effect size, our meta-regression results did not suggest that AET intensity predicted a greater effect size for non-MetS populations. This may be a corollary of including RCTs with AET intensity <60% VO_{2MAX} and not excluding RCTs with AET protocols below recommended weekly AET volume.[16-19]

4.3 Estimated Effect Sizes of AET Compared with Reported Estimated Effect Sizes of Statin Interventions

4.3.1 Total Cholesterol Examining pharmacological interventions, an SR and MA of 91 double-blinded RCTs (active ie two different statin treatments or statin versus other lipid-lowering drug, and placebo ie statin versus no medication) lasting from 12 weeks and up to 5 years calculated the ES of common statins prescribed at fixed and titrating doses ranging from 2.5mg (Simvastatin) to 80mg (Fluvastatin, Lovastatin, and Simvastatin) in sub-clinical (non-familial hypercholesterolaemic, mean baseline value range mmol/L a) TC 6.1-7.5; b) LDL-C 4.0-5.3) and clinical (CVD, at risk of CVD) populations on TC, TRG, HDL-C and LDL-C. The review reported an absolute weighted mean change range for TC (for all doses across all statins) of –(1.2-2.2) mmol/L from a baseline range of 6.1-7.5 mmol/L.[146] A subset study of CVD patients from the EUROASPIRE III database found that achieved targeted TC levels showed a significant trend in statin dose increase.[57]

These reported estimated ES of statin treatments show statin dosages, which are steadily increased, achieve a greater effect amongst clinical populations, and sub-clinical populations with higher base-line TC values, than the estimated ES of AET on populations with baseline TC values at normal-risk levels for CVD, such as those included in our work, who were also free of MetS and CVD. We suggest that the ES of AET in such populations would thus be lower than statin interventions in populations either with higher baseline TC values, or belonging to MetS or CVD groups.

4.3.2 Triglycerides The SR and MA investigating the effect of common statins on lipids described above reported an absolute weighted mean change range for TRG (for all doses across all statins) of –(0.2-0.4) mmol/L from a baseline range of 1.8-2.0 mmol/L.[146] An RCT investigating the effects of treatment with four common statins on LDL-C and TRG levels of normolipidaemic and dyslipidaemic participants at usual prescribed dosages found that at low baseline TRG levels, there was little to no change in TRG; effective changes in TRG were significantly dependent on a high TRG baseline level.[147]

These larger reported ES of statin interventions indicate that statins achieve a greater effect size amongst populations with higher base-line TRG values or CVD populations. Few of the RCT populations included in our MA had baseline TRG values >1.8 mmol/L (MetS factor ≥1.7 mmol/L), and CVD was an exclusion criterion, thus we suggest the ES of AET in normolipidaemic and non-CVD populations would be lower than statin interventions in clinical and MetS populations.

4.3.3 High-Density Lipoprotein Cholesterol The SR and MA investigating the effect of common statins on lipids described above reported an absolute weighted mean change for HDL-C (for all doses across all statins) of 0.1 mmol/L from a baseline range of 1.0-1.3 mmol/L.[146] No statistically significant change in HDL-C was found in a study investigating statin dosages sufficient to lower LDL-C in sub-clinical populations.[148] An SR and MA of 37 RCTs investigated the effects of 3 common statins with dose ranges of 10-80mg on HDL-C levels in dyslipidaemic populations without CVD and found changes in HDL-C were independent of changes in LDL-C.[149] At the lowest dose of one statin, in populations with baseline HDL-C >1.52 mmol/L, HDL-C decreased by 0.2%, and at the highest dose in the same population with a different statin, HDL-C decreased by 0.5%.[149] Low baseline HDL-C and high baseline TRG levels were strong and independent predictors of increases in HDL-C with statin therapy, and increases in statin dosages corresponded with increases in HDL-C for 2 of the 3 statins studied.[149] The maximum increase in HDL-C was 14.3% with an 80mg dose in the population with baseline HDL-C <1.00 mmol/L, and the presence of T2D except in conjunction with the highest statin dose resulted in non-significant change to HDL-C.[149]

The reported ES of statin dosages which are steadily increased on HDL-C in CVD populations or populations with low baseline HDL-C (MetS factor for males <1.0 mmol/L and <1.3 mmol/L for females) and/or high baseline TRG is comparably larger than our estimated ES of AET in normolipidaemic and non-CVD populations. Unlike the effect of AET on sub-clinical populations demonstrated in our work, statin interventions in sub-clinical populations achieve no statistically significant change in HDL-C. Statin interventions in normolipidaemic populations appear to decrease HDL-C,[149] contrary to the effect demonstrated by AET as shown in our work.

4.3.4 Low-Density Lipoprotein Cholesterol The SR and MA investigating the effect of common statins on lipids described above reported an absolute weighted mean change range for LDL-C (for all doses across all statins) of –(1.2-2.2) mmol/L from a baseline range of 4.0-5.3 mmol/L.[146] A recent large prospective cohort study of 165,411 patients found 51.2% of those studied had sub-optimal LDL-C responses at 24 months after initiating statin therapy, (LDL-C M(SD) mmol/L baseline: 3.8 (1.1); and post: 3.1(1.0)). Those with an optimal therapeutic response received greater dosages.[150]

The reported estimated ES of increasing statin doses in CVD and/or dyslipidaemic populations with high baseline LDL-C ie >4.0 mmol/L is comparably larger than the estimated ES of AET interventions in the non-MetS populations of RCTs included in our analysis, of which less than half the RCTs reported elevated LDL-C (increased CVD mortality risk ≥2.6 mmol/L[154]). Our estimated ES of AET in populations free of MetS and CVD is thus necessarily lower than statin interventions in populations with CVD risk level LDL-C values, or belonging to MetS or CVD groups.

4.4 Clinical Significance and Future Research Our SR and MA results indicate AET programs of >40% VO_{2MAX} undertaken for ≥12 weeks may be prescribed for sub-clinical populations to positively affect TC, TRG, HDL-C, and LDL-C. Comparing the estimated ES of statin therapies with estimated ES of AET demonstrates that statin interventions achieve a larger lipid-improving effect in TC, TRG, and LDL-C for clinical populations,[146] but for sub-clinical populations characterised by medium risk to normolipidaemic baseline values of these lipids, the difference may be minimal,[147, 149] or in respect of HDL-C, detrimental [149]. The estimated ES of statin interventions appears to be significantly correlated with baseline lipid levels[149, 152] and population characteristics (CVD risk, CVD patients),[146] as well as genetic risk.[153] The magnitude of difference in effect between statin prescription/adherence and AET adoption/adherence may also be contingent upon the duration of the studies undertaken to measure the effects of pharmacological and AET interventions. The AET RCTs with the longest duration in our analysis ended after 2 years. Statin study data is collated over periods up to 5 years. Increasing statin dosages increases lipid-improving effect size,[57] [150] with concomitant increases in cost[23-25] and adverse effects. [21, 22, 154] Increasing AET volume to health authority recommended minimum levels of >150 minutes per week of moderate intensity or >75 minutes per week of vigorous intensity in sub-clinical populations[16-19] is not generally associated with increases in cost or adverse effects. Aerobic physical activity has been shown to positively impact a range of health biomarkers upon which statins appear to have minimal effect, such as blood pressure,[155] or dubious effect, such as waist circumference and BMI,[156, 157] or a potential for adverse effect, such as glycaemic control,[158, 159] and cardiovascular fitness via decreased physical activity and mitochondrial dysfunction.[160] We recommend, on the basis of our review findings and evaluation of the effect of statins in clinical populations, that clinicians continue to encourage sub-clinical populations to meet the AET volumes that are recommended by national guidelines of >150 minutes weekly of moderate intensity and >75 minutes weekly of vigorous intensity for general health as a first preventative strategy, and to increase HDL-C. To obtain larger effects on lipids, the volume and intensity of weekly AET may need to be increased above these national guidelines, to >180 minutes per week at >40% VO_{2MAX}, or 135-180 minutes per week at >65% VO_{2MAX}, according to previous works.[13, 14, 28, 36]

We propose that future research should compare a) AET interventions of sufficient duration, intensity and volume known to positively affect lipid levels [13, 14, 28, 36] with b) tolerated dosages of statins against c) control groups (placebo and no exercise) in sub-clinical populations. Combined AET and statin therapy in sub-clinical and clinical populations should also be a research objective. Secondly, given that approximately only 50% of patients adhere to medication,[161] future research should investigate levels of adherence to AET interventions designed to affect lipid levels positively, as well as assess motivation for adherence and reasons for non-compliance in study participants. The results from such research may inform how to better promote AET adoption.

4.5 Strengths and Limitations in this Systematic Review and Meta-analysis Our work has a number of strengths. To our knowledge, although this SR and MA is not the first to have compared the effects of AET against no exercise on diverse populations, it has pooled the largest set of RCT data for different weight-bearing and non-weight bearing AET protocols affecting the standard lipid profile in sedentary populations not diagnosed with MetS and free of chronic disease to date. It may be the first attempt to qualitatively compare AET-induced estimated effects measures with the reported estimated effects measures of statin interventions.

Previous SRs did not use the validated exercise study evaluation tool TESTEX[69] to measure the quality of included studies. We followed a rigorous inclusion and exclusion protocol to ensure minimisation of confounding factors amongst the RCT populations.[162]

A limitation of our work is the reliance on aggregated RCT data and not individual subject data.[163, 164] Secondly, we searched using only English language terms, possibly reducing the pool of available studies for selection and potentially introducing publication bias. Further, we excluded studies whose intervention and comparison group numbers were <10, and this may have reduced the ES of AET for the standard lipid profile. The number of RCTs included with longer durations were few, and we included AET protocols starting from the minimum of moderate intensity (>40% VO_{2MAX}). Such short durations and low intensity may elicit small to zero changes in lipids,[13] and the inclusion of these protocols may have resulted in understated ES. In addition, reporting of protocol adherence and intensity used objective eg electronic devices as well as subjective measures eg Borg scale, self-reported HR, log books, denoted by different indices of intensity (energy expenditure, VO_{2MAX}, MHR, METs, Borg scale) and this may have introduced bias in the measurement of data reported in the included RCTs. Little information regarding the AET protocol or energy expenditure was provided in some included RCTs, and we estimated VO_{2MAX} intensity. Protocols mainly consisted of conventional AET, and a small number of RCTs noted that control groups increased physical activity levels during the duration of the study; this may have negatively influenced results.

With respect to data pooling, we calculated the difference between pre- and post-intervention M; in cases where the SD of the MD, exact p values within groups, or 95% CIs were not available, we imputed the SD of the MD, and hence statistical analyses depended on extrapolated data. Our imputation was conservative and we conducted sensitivity analyses (leave-one-out), however this approach may have weakened results.

We were unable to find an SR and MA directly and quantitatively evaluating the effects of AET against statin interventions on lipids in either sub-clinical or clinical populations. We found SRs and MAs investigating the effects of statin interventions versus no statin intervention in clinical populations, dyslipidaemic, and normolipidaemic populations. The ES of statin dosages on lipid profiles estimated in these reviews are not directly comparable to the ES estimated by our analysis of AET interventions versus no exercise in non-MetS populations free of CVD and other chronic diseases. Our qualitative comparison should be regarded with this caveat.

5.0 CONCLUSION

Pooled data indicated AET programs of moderate intensity with a minimum 12 week duration significantly reduced TC, TRG, LDL-C and increased HDL-C in populations free of chronic disease and not diagnosed with MetS, confirming the results of previous SRs and MAs examining the effects of AET in similar populations. The lipid-improving effect size of statin therapy appears to be dependent on poorer baseline lipid levels and health status as well as increases in dosages, and has limited or even detrimental effect on other MetS factors. Not unexpectedly, the reported estimated effect sizes of statins are larger than those estimated in our meta-analysis of sub-clinical populations and minimum moderate intensity AET interventions for TC, TRG, and LDL-C. However, our results suggest AET raises HDL-C in this cohort, where statins have been reported to decrease HDL-C. Given that aerobic physical activity positively impacts not only lipids but other MetS factors, it should form a primary part of the treatment minimising CVD risk.

Supplementary Materials

Detection of influencer RCTs using K-1 (leave one RCT out) analysis for triglycerides.

Study Name	Mean Difference	Standard Error	Lower CI limit	Upper CI limit	P value
Huttunen 1979	-0.078	0.005	-0.088	-0.069	<.001
Kiens 1980	-0.079	0.005	-0.088	-0.069	<.001
Wood 1983	-0.079	0.005	-0.088	-0.069	<.001
Busby 1985	-0.079	0.005	-0.088	-0.069	<.001
Santiago 1985	-0.079	0.005	-0.088	-0.069	<.001
Baker 1986	-0.078	0.005	-0.088	-0.069	<.001
Hespel 1988	-0.079	0.005	-0.088	-0.069	<.001
Suter 1990	-0.079	0.005	-0.088	-0.069	<.001
Blumenthal 1991	-0.079	0.005	-0.088	-0.069	<.001
King 1991 HIT group men	-0.079	0.005	-0.088	-0.069	<.001
King 1991 HIT group women	-0.079	0.005	-0.088	-0.069	<.001
King 1991 HIT home men	-0.079	0.005	-0.088	-0.069	<.001
King 1991 HIT home women	-0.079	0.005	-0.088	-0.069	<.001
King 1991 LIT home men	-0.079	0.005	-0.088	-0.069	<.001
King 1991 LIT home women	-0.079	0.005	-0.088	-0.069	<.001
Sunami 1999	-0.079	0.005	-0.088	-0.069	<.001
Suter 1992	-0.078	0.005	-0.088	-0.069	<.001
Hellénius 1993	-0.079	0.005	-0.088	-0.069	<.001
Nieman 1993	-0.079	0.005	-0.088	-0.069	<.001
Ready 1995	-0.079	0.005	-0.088	-0.069	<.001
Hinkleman 1993	-0.079	0.005	-0.088	-0.069	<.001
Stensel 1993	-0.079	0.005	-0.088	-0.069	<.001
Lindheim 1994	-0.079	0.005	-0.088	-0.069	<.001
Grandjean 1996	-0.079	0.005	-0.088	-0.069	<.001
Kukkonen-Harjula 1998	-0.078	0.005	-0.088	-0.069	<.001
Schuit 1998 all round	-0.079	0.005	-0.088	-0.069	<.001
Schuit 1998 cycling	-0.079	0.005	-0.088	-0.069	<.001
LeMura 2000	-0.077	0.005	-0.087	-0.068	<.001
Nieman 2002	-0.079	0.005	-0.088	-0.069	<.001
Takeshima 2002	-0.079	0.005	-0.088	-0.069	<.001
Tsai 2002	-0.079	0.005	-0.088	-0.069	<.001
Furukawa 2003	-0.079	0.005	-0.088	-0.069	<.001
Short 2003	-0.079	0.005	-0.088	-0.069	<.001
Mosher 2005 continuous step	-0.079	0.005	-0.088	-0.069	<.001
Mosher 2005 interval step	-0.078	0.005	-0.088	-0.069	<.001
Mohanka 2006	-0.079	0.005	-0.088	-0.069	<.001
Boardley 2007	-0.079	0.005	-0.088	-0.069	<.001
Ring-Dimitriou 2007	-0.079	0.005	-0.088	-0.069	<.001

Study Name	Mean Difference	Standard Error	Lower CI limit	Upper CI limit	P value
Tully 2007 (less than recommended)	-0.079	0.005	-0.088	-0.069	<.001
Vainionpää 2007	-0.079	0.005	-0.088	-0.069	<.001
Tully 2007 (= recommnded)	-0.079	0.005	-0.088	-0.069	<.001
von Thiele Schwarz 2008	-0.079	0.005	-0.088	-0.069	<.001
Mawi 2009	-0.078	0.005	-0.088	-0.069	<.001
Sillanpää 2009 men	-0.079	0.005	-0.088	-0.069	<.001
Sillanpää 2009 women	-0.079	0.005	-0.088	-0.069	<.001
Bell 2010 MICT	-0.079	0.005	-0.088	-0.069	<.001
Bell 2010 walking	-0.079	0.005	-0.088	-0.069	<.001
Krustrup 2010	-0.079	0.005	-0.088	-0.069	<.001
Martins 2010	-0.078	0.005	-0.088	-0.069	<.001
Niederseer 2011	-0.078	0.005	-0.088	-0.069	<.001
Ho 2012	-0.079	0.005	-0.088	-0.069	<.001
Nualmin 2012	-0.079	0.005	-0.088	-0.069	<.001
Ohta 2012	-0.079	0.005	-0.088	-0.069	<.001
Vicente-Campos 2012	-0.078	0.005	-0.088	-0.069	<.001
Bhutani 2013	-0.079	0.005	-0.088	-0.069	<.001
Tseng 2013	**-0.129**	**0.015**	**-0.159**	**-0.100**	**<.001**
Kemmler 2014	-0.078	0.005	-0.088	-0.069	<.001
Maruf 2014	-0.078	0.005	-0.088	-0.069	<.001
Mohr 2014 HIIT	-0.078	0.005	-0.088	-0.069	<.001
Mohr 2014 MICT	-0.079	0.005	-0.088	-0.069	<.001
Park 2014	-0.079	0.005	-0.088	-0.069	<.001
Sousa 2014	-0.079	0.005	-0.088	-0.069	<.001
Zhang 2014	-0.079	0.005	-0.088	-0.069	<.001
Korshøj 2016	-0.079	0.005	-0.088	-0.069	<.001
Tianen 2016	-0.079	0.005	-0.088	-0.069	<.001
Krustrup 2017	-0.079	0.005	-0.088	-0.069	<.001
Costa 2018	-0.079	0.005	-0.088	-0.069	<.001
Sarzynski 2018 AT1 - 20KKW	-0.079	0.005	-0.088	-0.069	<.001
Sarzynski 2018 AT2 - 8KKW	-0.079	0.005	-0.088	-0.069	<.001
Bock 2019 standard	-0.079	0.005	-0.088	-0.069	<.001
Bock 2019 video	-0.079	0.005	-0.088	-0.069	<.001
Hornstrup 2019	-0.078	0.005	-0.088	-0.069	<.001
Shou 2019	-0.078	0.005	-0.088	-0.069	<.001
Random effects meta-analysis	**-0.079**	**0.005**	**-0.088**	**-0.069**	**<.001**

Table S5.4 Triglycerides K-1 Identification of Influencer RCT

Study name	Outcome	Cumulative statistics					Cumulative sample size			Study Quality	Weight (Random)	
		Point	Standard error	Lower limit	Upper limit	p-Value	Exercise	Control	Total		Weight (Random)	Relative weight
Huttunen 1979	TRG	-0.420	0.165	-0.743	-0.097	0.011	44	46	90	11	36.80	0.08
Kiens 1980	TRG	-0.336	0.139	-0.608	-0.064	0.016	68	59	127	8	15.01	0.12
Wood 1983	TRG	-0.212	0.094	-0.397	-0.028	0.024	101	107	208	9	91.66	0.33
Busby 1985	TRG	-0.190	0.079	-0.345	-0.035	0.016	113	119	232	9	16.98	0.37
Santiago 1985	TRG	-0.160	0.071	-0.300	-0.019	0.026	129	130	259	8	35.15	0.45
Baker 1986	TRG	-0.173	0.063	-0.297	-0.049	0.006	149	144	293	9	54.97	0.58
Hespel 1988	TRG	-0.179	0.061	-0.299	-0.058	0.004	162	158	320	9	15.74	0.61
Suter 1990	TRG	-0.182	0.058	-0.295	-0.069	0.002	201	180	381	9	35.27	0.69
Blumenthal 1991	TRG	-0.175	0.055	-0.283	-0.067	0.002	232	212	444	9	27.03	0.76
King 1991 HIT group men	TRG	-0.161	0.051	-0.261	-0.061	0.002	272	226	498	9	55.55	0.88
King 1991 HIT group women	TRG	-0.137	0.046	-0.228	-0.046	0.003	306	237	543	9	79.98	1.07
King 1991 HIT home men	TRG	-0.129	0.045	-0.217	-0.040	0.004	348	251	599	9	29.33	1.13
King 1991 HIT home women	TRG	-0.123	0.044	-0.209	-0.037	0.005	383	263	646	9	25.84	1.19
King 1991 LIT home men	TRG	-0.125	0.043	-0.210	-0.041	0.004	428	277	705	9	16.62	1.23
King 1991 LIT home women	TRG	-0.115	0.039	-0.192	-0.037	0.004	457	288	745	9	106.75	1.48
Sunami 1999	TRG	-0.107	0.038	-0.182	-0.033	0.005	477	308	785	10	47.28	1.59
Suter 1992	TRG	-0.115	0.036	-0.185	-0.045	0.001	493	324	817	9	96.05	1.81
Hellénius 1993	TRG	-0.118	0.035	-0.186	-0.050	0.001	532	363	895	9	52.34	1.93
Nieman 1993	TRG	-0.119	0.034	-0.186	-0.052	0.001	546	379	925	13	11.10	1.95
Ready 1995	TRG	-0.121	0.034	-0.188	-0.054	0.000	561	389	950	8	8.75	1.97
Hinkleman 1993	TRG	-0.126	0.034	-0.192	-0.060	0.000	579	407	986	12	26.60	2.03
Stensel 1993	TRG	-0.126	0.034	-0.192	-0.060	0.000	621	430	1051	11	0.70	2.04
Lindheim 1994	TRG	-0.130	0.033	-0.195	-0.065	0.000	641	455	1096	9	14.13	2.07
Grandjean 1996	TRG	-0.129	0.033	-0.193	-0.064	0.000	661	472	1133	11	17.72	2.11
Kukkonen-Harjula 1998	TRG	-0.129	0.030	-0.187	-0.071	0.000	712	526	1238	12	220.87	2.62
Schuit 1998 all round	TRG	-0.130	0.029	-0.187	-0.072	0.000	745	567	1312	10	27.43	2.68
Schuit 1998 cycling	TRG	-0.129	0.029	-0.185	-0.073	0.000	806	608	1414	10	54.26	2.80
LeMura 2000	TRG	-0.151	0.024	-0.198	-0.104	0.000	816	620	1436	9	545.45	4.06
Nieman 2002	TRG	-0.151	0.024	-0.197	-0.104	0.000	837	642	1479	13	16.21	4.09
Takeshima 2002	TRG	-0.151	0.023	-0.197	-0.106	0.000	852	657	1509	8	44.85	4.20
Tsai 2002	TRG	-0.150	0.023	-0.196	-0.105	0.000	864	668	1532	7	37.36	4.28
Furukawa 2003	TRG	-0.148	0.023	-0.193	-0.103	0.000	885	692	1577	12	55.35	4.41
Short 2003	TRG	-0.149	0.023	-0.193	-0.104	0.000	950	729	1679	8	29.33	4.48
Mosher 2005 continuous step	TRG	-0.142	0.022	-0.185	-0.099	0.000	976	741	1717	9	132.11	4.78
Mosher 2005 interval step	TRG	-0.142	0.021	-0.183	-0.100	0.000	1003	754	1757	9	118.65	5.05
Mohanka 2006	TRG	-0.138	0.021	-0.179	-0.096	0.000	1090	840	1930	12	69.76	5.22
Boardley 2007	TRG	-0.139	0.021	-0.180	-0.098	0.000	1123	875	1998	9	20.98	5.26
Ring-Dimitriou 2007	TRG	-0.139	0.021	-0.180	-0.098	0.000	1143	885	2028	9	6.59	5.28
Tully 2007 (less than recommended)	TRG	-0.139	0.021	-0.179	-0.098	0.000	1187	895	2082	13	29.57	5.35
Vainionpää 2007	TRG	-0.134	0.020	-0.174	-0.094	0.000	1224	934	2158	10	87.13	5.55
Tully 2007 (= recommnded)	TRG	-0.134	0.020	-0.173	-0.094	0.000	1266	944	2210	13	23.07	5.60
von Thiele Schwarz 2008	TRG	-0.132	0.020	-0.172	-0.093	0.000	1324	1004	2328	8	54.70	5.73
Mawi 2009	TRG	-0.135	0.020	-0.174	-0.096	0.000	1355	1035	2390	10	39.10	5.82
Sillanpää 2009 men	TRG	-0.133	0.020	-0.172	-0.094	0.000	1371	1047	2418	9	42.86	5.91
Sillanpää 2009 women	TRG	-0.130	0.019	-0.168	-0.092	0.000	1386	1059	2445	9	62.19	6.06
Bell 2010 MICT	TRG	-0.129	0.019	-0.168	-0.091	0.000	1426	1081	2507	11	9.11	6.08
Bell 2010 walking	TRG	-0.130	0.019	-0.168	-0.092	0.000	1469	1104	2573	11	27.46	6.14
Krustrup 2010	TRG	-0.128	0.019	-0.166	-0.090	0.000	1486	1118	2604	10	47.26	6.25
Martins 2010	TRG	-0.130	0.019	-0.167	-0.093	0.000	1518	1149	2667	6	71.49	6.41
Niederseer 2011	TRG	-0.131	0.019	-0.168	-0.095	0.000	1536	1165	2701	10	66.62	6.57
Ho 2012	TRG	-0.132	0.019	-0.168	-0.095	0.000	1551	1181	2732	10	13.35	6.60
Nualmin 2012	TRG	-0.131	0.019	-0.168	-0.095	0.000	1575	1200	2775	12	16.22	6.64
Ohta 2012	TRG	-0.132	0.019	-0.168	-0.095	0.000	1588	1213	2801	8	22.00	6.69
Vicente-Campos 2012	TRG	-0.128	0.017	-0.162	-0.094	0.000	1610	1234	2844	7	385.58	7.57
Bhutani 2013	TRG	-0.124	0.017	-0.157	-0.090	0.000	1634	1250	2884	12	116.06	7.84
Tseng 2013	TRG	-0.077	0.005	-0.087	-0.068	0.000	1644	1260	2904	8	39143.60	97.81
Kemmler 2014	TRG	-0.077	0.005	-0.087	-0.068	0.000	1677	1301	2978	12	127.75	98.10
Maruf 2014	TRG	-0.078	0.005	-0.087	-0.068	0.000	1737	1361	3098	11	70.44	98.27
Mohr 2014 HIIT	TRG	-0.078	0.005	-0.087	-0.068	0.000	1758	1372	3130	11	28.87	98.33
Mohr 2014 MICT	TRG	-0.078	0.005	-0.087	-0.068	0.000	1778	1382	3160	12	13.24	98.36
Park 2014	TRG	-0.078	0.005	-0.087	-0.068	0.000	1792	1396	3188	11	22.22	98.41
Sousa 2014	TRG	-0.078	0.005	-0.087	-0.068	0.000	1807	1413	3220	9	22.57	98.47
Zhang 2014	TRG	-0.078	0.005	-0.088	-0.069	0.000	1861	1470	3331	10	62.71	98.61
Korshøj 2016	TRG	-0.078	0.005	-0.088	-0.069	0.000	1918	1529	3447	9	58.61	98.74
Tianen 2016	TRG	-0.078	0.005	-0.088	-0.069	0.000	1997	1611	3608	11	159.45	99.11
Krustrup 2017	TRG	-0.078	0.005	-0.088	-0.069	0.000	2016	1623	3639	11	23.03	99.16
Costa 2018	TRG	-0.078	0.005	-0.088	-0.069	0.000	2036	1643	3679	10	8.52	99.18
Sarzynski 2018 AT1 - 20KKW	TRG	-0.078	0.005	-0.088	-0.069	0.000	2082	1666	3748	11	63.57	99.33
Sarzynski 2018 AT2 - 8KKW	TRG	-0.078	0.005	-0.088	-0.069	0.000	2130	1688	3818	11	99.69	99.56
Bock 2019 standard	TRG	-0.078	0.005	-0.088	-0.069	0.000	2226	1735	3961	14	80.66	99.74
Bock 2019 video	TRG	-0.078	0.005	-0.087	-0.069	0.000	2319	1782	4101	14	51.61	99.86
Hornstrup 2019	TRG	-0.078	0.005	-0.088	-0.069	0.000	2333	1794	4127	8	33.49	99.94
Shou 2019	TRG	-0.079	0.005	-0.088	-0.069	0.000	2431	1894	4325	9	26.18	100.00
		-0.079	0.005	-0.088	-0.069	0.000						

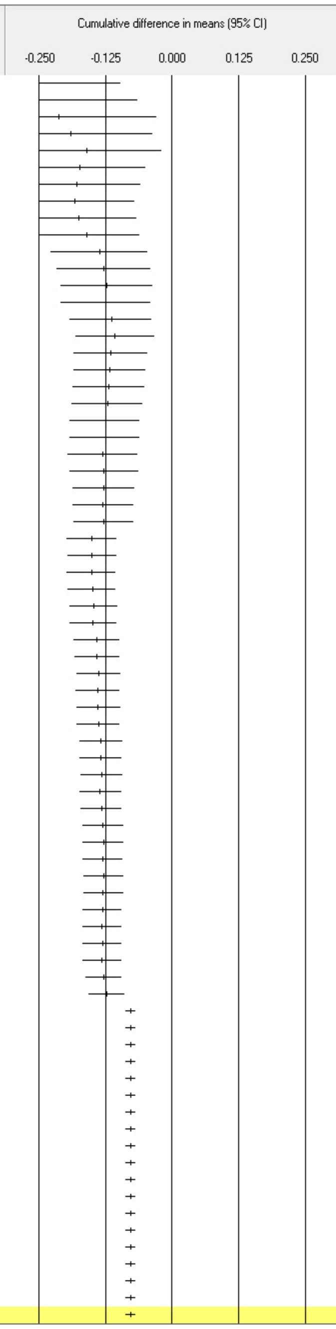


Figure S5.6 Triglycerides Forest Plot Showing Influencer RCT

Detection of pooled 95% confidence interval (CI) boundary outliers for high-density lipoprotein cholesterol (HDL-C), shown in Table S5.5. The lower CI limit for each study was compared with the pooled upper CI limit, and the upper CI limit of each study was compared with the pooled lower CI limit. This enabled detection of RCTs with CIs lying outside the estimated pooled CI.

Study Name	MD	Variance	Lower limit	Upper limit	P value	Exercise N	Control N	Total
LeMura 2000	0.20	0.04	**0.12**	0.28	<.001	10	12	22
Tseng 2013	0.13	0.01	**0.12**	0.14	<.001	10	10	20
Vicente-Campos 2012	0.21	0.03	**0.15**	0.27	<.001	22	21	43
Krustrup 2017	0.40	0.12	**0.17**	0.63	<.001	19	12	31
Mawi 2009	0.50	0.07	**0.36**	0.64	<.001	31	31	62
Pooled meta-analysis	0.08	0.01	0.06	**0.10**	<.001	92	86	178

Table S5.5 Identification of Pooled 95% CI Boundary Outliers (High-density Lipoprotein Cholesterol)

Study name	Outcome	Cumulative statistics					Cumulative sample size			Study Quality	Weight (Random)	
		Point	Standard error	Lower limit	Upper limit	p-Value	Exercise	Control	Total		Weight (Random)	Relative weight
Huttunen 1979	HDL-C	0.140	0.054	0.035	0.245	0.009	44	46	90	11	171.35	1.81
Kiens 1980	HDL-C	0.111	0.044	0.024	0.198	0.012	68	59	127	8	109.32	2.96
Wood 1983	HDL-C	0.074	0.033	0.009	0.138	0.025	101	107	208	9	217.84	5.26
Busby 1985	HDL-C	0.071	0.029	0.014	0.128	0.014	113	119	232	9	66.75	5.97
Santiago 1985	HDL-C	0.072	0.028	0.016	0.127	0.011	129	130	259	8	41.44	6.40
Wirth 1985	HDL-C	0.071	0.024	0.025	0.118	0.003	139	141	280	8	207.27	8.59
Baker 1986	HDL-C	0.079	0.023	0.034	0.124	0.001	159	155	314	9	73.61	9.37
Cunningham 1987	HDL-C	0.073	0.021	0.031	0.115	0.001	260	256	516	10	171.21	11.17
Hespel 1988	HDL-C	0.084	0.021	0.042	0.125	0.000	273	270	543	9	100.30	12.23
Suter 1990	HDL-C	0.081	0.020	0.042	0.121	0.000	312	292	604	9	48.68	12.75
Blumenthal 1991	HDL-C	0.080	0.020	0.041	0.119	0.000	343	324	667	9	77.14	13.56
King 1991 HIT group men	HDL-C	0.070	0.018	0.034	0.106	0.000	383	338	721	9	186.72	15.53
King 1991 HIT group women	HDL-C	0.067	0.018	0.031	0.102	0.000	417	350	767	9	113.83	16.73
King 1991 HIT home men	HDL-C	0.062	0.017	0.028	0.095	0.000	459	364	823	9	158.72	18.41
King 1991 HIT home women	HDL-C	0.059	0.017	0.026	0.091	0.000	494	376	870	9	114.36	19.62
King 1991 LIT home men	HDL-C	0.056	0.016	0.025	0.088	0.000	539	390	929	9	160.02	21.30
King 1991 LIT home women	HDL-C	0.054	0.016	0.023	0.085	0.001	568	401	969	9	106.02	22.42
Sunami 1999	HDL-C	0.057	0.016	0.027	0.088	0.000	588	421	1009	10	80.42	23.27
Suter 1992	HDL-C	0.056	0.015	0.026	0.087	0.000	604	437	1041	9	55.75	23.86
Hellénius 1993	HDL-C	0.055	0.015	0.025	0.084	0.000	643	476	1119	9	158.38	25.53
Nieman 1993	HDL-C	0.053	0.015	0.025	0.082	0.000	664	492	1156	13	95.08	26.54
Ready 1995	HDL-C	0.054	0.015	0.025	0.082	0.000	679	502	1181	8	57.47	27.14
Lindheim 1994	HDL-C	0.054	0.014	0.025	0.082	0.000	699	527	1226	9	61.62	27.79
Stensel 1995	HDL-C	0.053	0.014	0.025	0.081	0.000	741	550	1291	11	37.39	28.19
Grandjean 1996	HDL-C	0.056	0.014	0.028	0.084	0.000	761	567	1328	11	72.02	28.95
Kukkonen-Harjula 1998	HDL-C	0.045	0.012	0.022	0.069	0.000	814	621	1435	12	294.14	32.05
Schuit 1998 all round	HDL-C	0.048	0.012	0.025	0.071	0.000	847	662	1509	10	115.48	33.27
Schuit 1998 cycling	HDL-C	0.049	0.012	0.026	0.071	0.000	908	703	1611	10	148.08	34.83
LeMura 2000	HDL-C	0.064	0.013	0.039	0.090	0.000	918	715	1633	9	209.18	37.04
Nieman 2002	HDL-C	0.062	0.013	0.037	0.086	0.000	946	737	1683	13	154.56	38.67
Takeshima 2002	HDL-C	0.061	0.012	0.037	0.085	0.000	961	752	1713	8	36.83	39.06
Tsai 2002	HDL-C	0.064	0.013	0.039	0.089	0.000	973	763	1736	7	34.21	39.42
Furukawa 2003	HDL-C	0.064	0.013	0.040	0.089	0.000	994	787	1781	12	75.08	40.21
Short 2003	HDL-C	0.066	0.013	0.041	0.091	0.000	1059	824	1883	8	39.48	40.63
Mosher 2005 continuous step	HDL-C	0.065	0.012	0.041	0.089	0.000	1085	836	1921	9	87.97	41.56
Mosher 2005 interval step	HDL-C	0.066	0.012	0.042	0.090	0.000	1112	849	1961	9	88.24	42.49
Mohanka 2006	HDL-C	0.064	0.012	0.041	0.087	0.000	1199	935	2134	12	173.05	44.32
Boardley 2007	HDL-C	0.064	0.011	0.042	0.086	0.000	1232	970	2202	9	70.89	45.07
Ring-Dimitriou 2007	HDL-C	0.063	0.011	0.041	0.085	0.000	1252	980	2232	9	14.97	45.22
Tully 2007 (= recommended)	HDL-C	0.062	0.011	0.041	0.083	0.000	1294	990	2284	13	21.40	45.45
Tully 2007 (less than recommended)	HDL-C	0.062	0.011	0.041	0.083	0.000	1338	1000	2338	13	28.39	45.75
Vainionpää 2007	HDL-C	0.061	0.010	0.040	0.081	0.000	1375	1039	2414	10	108.88	46.90
von Thiele Schwarz 2008	HDL-C	0.060	0.010	0.040	0.080	0.000	1433	1099	2532	8	147.20	48.45
Bergström 2009	HDL-C	0.058	0.010	0.039	0.077	0.000	1481	1143	2624	10	221.39	50.79
Krustrup 2009	HDL-C	0.058	0.010	0.038	0.077	0.000	1491	1153	2644	10	43.58	51.25
Lawton 2008	HDL-C	0.054	0.009	0.035	0.072	0.000	2035	1698	3733	12	266.86	54.07
Mawi 2009	HDL-C	0.076	0.014	0.048	0.104	0.000	2066	1729	3795	10	127.91	55.42
Sillanpää 2009 men	HDL-C	0.076	0.014	0.049	0.104	0.000	2082	1741	3823	9	144.31	56.94
Sillanpää 2009 women	HDL-C	0.078	0.014	0.051	0.106	0.000	2097	1753	3850	9	81.65	57.80
Bell 2010 MICT	HDL-C	0.078	0.014	0.051	0.105	0.000	2137	1775	3912	11	2.63	57.83
Bell 2010 walking	HDL-C	0.076	0.014	0.050	0.103	0.000	2180	1798	3978	11	134.52	59.25
Knoepfli-Lenzin 2010	HDL-C	0.077	0.013	0.050	0.103	0.000	2195	1815	4010	8	51.91	59.80
Krustrup 2010	HDL-C	0.076	0.013	0.050	0.102	0.000	2212	1829	4041	10	42.85	60.25
Martins 2010	HDL-C	0.075	0.013	0.050	0.101	0.000	2244	1860	4104	6	121.56	61.53
Morgan 2010	HDL-C	0.076	0.013	0.051	0.101	0.000	2258	1875	4133	10	42.51	61.98
Niederseer 2011	HDL-C	0.075	0.013	0.050	0.100	0.000	2276	1891	4167	10	136.42	63.42
Ho 2012	HDL-C	0.075	0.012	0.050	0.099	0.000	2291	1907	4198	10	47.44	63.92
Nualmin 2012	HDL-C	0.075	0.012	0.050	0.099	0.000	2315	1926	4241	12	36.25	64.30
Ohta 2012	HDL-C	0.074	0.012	0.050	0.098	0.000	2328	1939	4267	8	95.36	65.31
Vicente-Campos 2012	HDL-C	0.081	0.013	0.055	0.107	0.000	2350	1960	4310	7	264.39	68.10
Bhutani 2013	HDL-C	0.081	0.013	0.055	0.106	0.000	2374	1976	4350	12	118.62	69.35
Tseng 2013	HDL-C	0.083	0.012	0.058	0.107	0.000	2384	1986	4370	8	335.47	72.89
Kemmler 2014	HDL-C	0.084	0.012	0.060	0.108	0.000	2417	2027	4444	12	140.72	74.38
Maruf 2014	HDL-C	0.084	0.012	0.060	0.107	0.000	2477	2087	4564	11	123.20	75.68
Mohr 2014 HIIT	HDL-C	0.084	0.012	0.060	0.107	0.000	2498	2098	4596	11	36.46	76.06
Mohr 2014 MICT	HDL-C	0.084	0.012	0.061	0.108	0.000	2518	2108	4626	12	35.56	76.44
Park 2014	HDL-C	0.084	0.012	0.061	0.108	0.000	2532	2122	4654	11	43.57	76.90
Sousa 2014	HDL-C	0.084	0.012	0.061	0.107	0.000	2547	2139	4686	9	84.02	77.78
Zhang 2014	HDL-C	0.083	0.012	0.061	0.106	0.000	2601	2196	4797	10	212.05	80.02
Korshøj 2016	HDL-C	0.081	0.012	0.058	0.103	0.000	2658	2255	4913	9	262.18	82.79
Rossi 2016	HDL-C	0.081	0.011	0.058	0.103	0.000	2673	2273	4946	7	82.92	83.66
Tianen 2016	HDL-C	0.080	0.011	0.058	0.102	0.000	2752	2355	5107	11	247.29	86.27
Krustrup 2017	HDL-C	0.082	0.011	0.060	0.105	0.000	2771	2367	5138	11	59.94	86.91
Costa 2018	HDL-C	0.083	0.011	0.061	0.105	0.000	2791	2387	5178	10	90.61	87.86
Sarzynski 2018 AT1 - 20KKW	HDL-C	0.082	0.011	0.060	0.103	0.000	2837	2410	5247	11	192.62	89.90
Sarzynski 2018 AT2 - 8KKW	HDL-C	0.081	0.011	0.060	0.102	0.000	2885	2432	5317	11	189.55	91.90
Bock 2019 standard	HDL-C	0.080	0.011	0.059	0.101	0.000	2981	2479	5460	14	268.04	94.73
Bock 2019 video	HDL-C	0.079	0.010	0.058	0.099	0.000	3074	2526	5600	14	258.47	97.45
Hornstrup 2019	HDL-C	0.078	0.010	0.058	0.099	0.000	3088	2538	5626	8	53.15	98.01
Shou 2019	HDL-C	0.079	0.010	0.059	0.099	0.000	3186	2638	5824	9	188.08	100.00
		0.079	0.010	0.059	0.099	0.000						

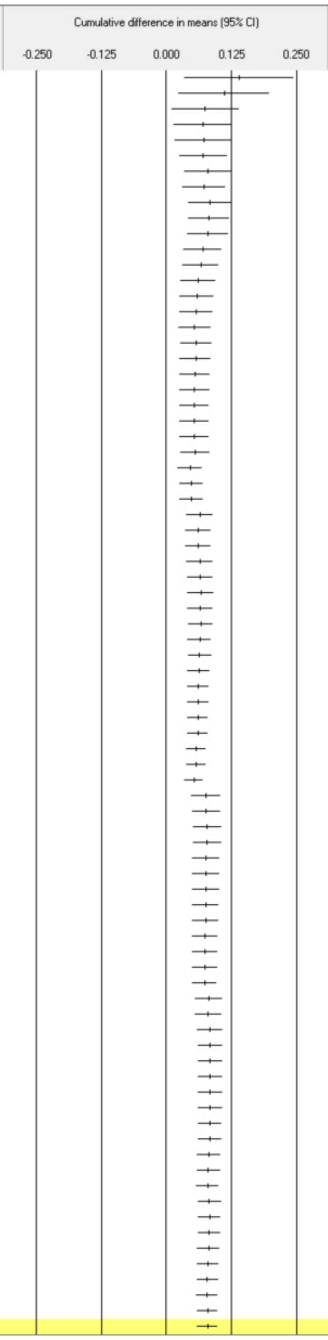


Figure S5.7 High-density Lipoprotein Cholesterol Forest Plot Including 95% CI Boundary Outliers

TESTEX Assessment of Study Quality

Author Year	Eligibility criteria specified	Random -isation specified	Allocation concealment	Groups similar at baseline	Blinding of assessor	Outcomes measures assessed in 85% patients	Adverse events reported	Exercise adherence reported	Intention-to-treat analysis	Between-group statistical comparisons reported	Point measures and measures of variability for primary outcome measures	Point measures and measures of variability for all other outcome measures	Activity monitoring in control groups	Relative exercise intensity remained constant	Exercise volume and energy expenditure	**Overall TESTEX (/15)**
Baker 1986	1	0	0	1	1	1	0	1	0	1	1	1	0	1	0	**9**
Bell 2010 a (MICT)	1	0	1	1	1	0	0	1	0	1	1	1	1	1	1	**11**
Bell 2010 b (walking)	1	0	1	1	1	0	0	1	0	1	1	1	1	1	1	**11**
Bergström 2009	1	1	0	1	1	0	0	1	1	1	1	1	1	0	0	**10**
Bhutani 2013	1	1	0	1	1	0	1	1	1	1	1	1	0	1	1	**12**
Blumenthal 1991	1	0	0	1	1	1	0	1	0	1	1	1	0	1	0	**9**
Boardley 2007	1	0	0	1	1	1	0	1	0	1	1	1	0	1	0	**9**
Bock 2019 standard	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	**14**
Bock 2019 video games	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	**14**
Busby 1985	0	0	1	1	1	1	0	0	0	1	1	1	1	1	0	**9**
Costa 2018	1	1	1	1	1	0	0	1	1	1	1	1	0	0	0	**10**
Cunningham 1987	0	0	0	1	1	1	1	1	1	1	1	1	0	1	0	**10**
Furukawa 2003	1	1	1	0	1	1	0	1	1	1	1	1	1	0	1	**12**
Grandjean 1996	1	0	1	1	1	1	0	0	1	1	1	1	0	1	1	**11**
Grant 2004	1	0	0	0	1	0	1	1	0	1	1	1	0	1	0	**8**
Hellénius 1993	1	0	0	1	1	1	0	1	1	1	1	1	0	0	0	**9**
Hespel 1988	1	0	0	1	1	1	0	1	1	1	1	1	0	0	0	**9**
Hinkleman 1993	1	1	1	0	1	1	1	0	0	1	1	1	1	1	1	**12**
Ho 2012	1	1	1	0	1	0	0	1	0	1	1	1	0	1	1	**10**
Hornstrup 2019	1	0	0	0	1	0	1	1	0	1	1	1	0	0	1	**8**
Huttunen 1979	1	0	1	1	1	1	0	1	0	1	1	1	0	1	1	**11**
Kemmler 2014	1	1	1	1	1	0	0	1	0	1	1	1	1	1	1	**12**
Kiens 1980	1	1	0	0	1	0	0	1	0	1	1	1	0	0	1	**8**
King 1991 mens (HIT group)	1	1	1	0	1	0	0	1	0	1	1	1	1	0	0	**9**
King 1991 mens (HIT home)	1	1	1	0	1	0	0	1	0	1	1	1	1	0	0	**9**
King 1991 mens (LIT home)	1	1	1	0	1	0	0	1	0	1	1	1	1	0	0	**9**
King 1991 womens (HIT group)	1	1	1	0	1	0	0	1	0	1	1	1	1	0	0	**9**
King 1991 womens (HIT home)	1	1	1	0	1	0	0	1	0	1	1	1	1	0	0	**9**
King 1991 womens (LIT home)	1	1	1	0	1	0	0	1	0	1	1	1	1	0	0	**9**
Knoepfli-Lenzin 2010	1	0	0	0	1	0	1	1	0	1	1	1	0	0	1	**8**
Korshøj 2016	1	1	0	1	1	0	0	0	1	1	1	1	0	0	1	**9**
Krustrup 2009	1	0	0	1	1	0	1	1	0	1	1	1	0	1	1	**10**
Krustrup 2010	1	0	0	1	1	0	1	1	0	1	1	1	0	1	1	**10**
Krustrup 2017	1	0	0	1	1	1	1	1	0	1	1	1	0	1	1	**11**
Kukkonen-Harjula 1998	1	1	0	1	1	1	1	1	1	1	1	0	0	1	1	**12**

Author Year	Eligibility criteria specified	Random -isation specified	Allocation concealment	Groups similar at baseline	Blinding of assessor	Outcomes measures assessed in 85% patients	Adverse events reported	Exercise adherence reported	Intention-to-treat analysis	Between-group statistical comparisons reported	Point measures and measures of variability for primary outcome measures	Point measures and measures of variability for all other outcome measures	Activity monitoring in control groups	Relative exercise intensity remained constant	Exercise volume and energy expenditure	**Overall TESTEX (/15)**
Lawton 2008	1	1	1	1	1	1	1	0	1	1	1	1	1	0	0	**12**
LeMura 2000	0	1	0	0	1	1	0	0	0	1	1	1	1	1	1	**9**
Lindheim 1994	1	0	0	0	1	1	0	0	1	0	1	1	1	1	1	**9**
Martins 2010	1	0	0	0	1	0	0	0	0	1	1	1	0	0	1	**6**
Maruf 2014	1	1	0	0	1	0	1	1	1	1	1	1	0	1	1	**11**
Mawi 2009	1	0	1	1	1	1	0	1	1	0	1	1	0	1	0	**10**
Mohanka 2006	1	1	0	1	1	1	0	1	1	1	1	1	1	0	1	**12**
Mohr 2014 HIIT	1	0	0	1	1	1	0	1	1	1	1	1	0	1	1	**11**
Mohr 2014 MICT	1	0	0	1	1	1	1	1	1	1	1	1	0	1	1	**12**
Morgan 2010	1	0	0	1	1	1	0	0	1	1	1	1	1	1	0	**10**
Mosher 2005 continuous step	1	0	0	1	1	1	0	0	0	1	1	1	0	1	1	**9**
Mosher 2005 interval step	1	0	0	1	1	1	0	0	0	1	1	1	0	1	1	**9**
Niederseer 2011	1	0	0	1	1	0	1	1	0	1	1	1	0	1	1	**10**
Nieman 1993	1	0	0	1	1	1	1	1	1	1	1	1	1	1	1	**13**
Nieman 2002	1	0	1	1	1	1	0	1	1	1	1	1	1	1	1	**13**
Nualnim 2012	1	0	0	1	1	1	1	1	0	1	1	1	1	1	1	**12**
Ohta 2012	1	0	0	0	1	0	0	1	0	1	1	1	0	1	1	**8**
Park 2014	0	0	0	1	1	1	0	1	1	1	1	1	1	1	1	**11**
Ready 1995	1	0	0	0	1	0	0	1	0	1	1	1	0	1	1	**8**
Ring-Dimitriou 2007	1	0	0	1	1	0	1	1	0	1	1	1	0	1	0	**9**
Rossi 2016	1	0	0	0	1	0	0	0	0	1	1	1	0	1	1	**7**
Santiago 1995	1	1	0	0	1	0	0	0	0	1	1	1	0	1	1	**8**
Sarzynski 2018 (AT1 - 20 KKW)	1	1	0	1	1	0	0	1	1	1	1	1	0	1	1	**11**
Sarzynski 2018 (AT2 - 8 KKW)	1	1	0	1	1	0	0	1	1	1	1	1	0	1	1	**11**
Schuit 1998 all round	1	1	0	1	1	1	1	1	0	1	1	0	0	0	1	**10**
Schuit 1998 cycling	1	1	0	1	1	1	1	1	0	1	1	0	0	0	1	**10**
Short 2003	1	0	0	0	1	1	0	1	0	1	1	1	0	0	1	**8**
Shou 2019	1	0	0	1	1	1	1	0	0	1	1	1	0	1	0	**9**
Sillanpää 2009 men	1	0	0	1	1	1	0	1	0	1	1	1	0	0	1	**9**
Sillanpää 2009 women	1	0	0	1	1	1	0	1	0	1	1	1	0	0	1	**9**
Sousa 2014	1	0	0	1	1	1	0	1	0	1	1	0	0	1	1	**9**
Stensel 1995	1	0	1	0	1	1	1	1	0	1	1	1	0	1	1	**11**
Sunami 1999	1	0	0	1	1	1	0	1	0	1	1	1	0	1	1	**10**
Suter 1990	1	0	0	1	1	1	0	1	0	1	1	0	0	1	1	**9**
Suter 1992	1	0	0	1	1	1	0	1	0	1	1	0	0	1	1	**9**
Takeshima 2002	1	0	0	0	1	1	1	0	0	1	1	1	0	0	1	**8**

Author Year	Eligibility criteria specified	Random -isation specified	Allocation concealment	Groups similar at baseline	Blinding of assessor	Outcomes measures assessed in 85% patients	Adverse events reported	Exercise adherence reported	Intention-to-treat analysis	Between-group statistical comparisons reported	Point measures and measures of variability for primary outcome measures	Point measures and measures of variability for all other outcome measures	Activity monitoring in control groups	Relative exercise intensity remained constant	Exercise volume and energy expenditure	**Overall TESTEX (/15)**
Tiainen 2016	1	0	0	1	1	1	0	1	0	1	1	1	1	1	1	**11**
Tsai 2002	1	0	0	1	1	0	0	0	0	1	1	0	0	1	1	**7**
Tseng 2013	1	0	0	1	1	1	0	0	0	1	1	1	0	1	0	**8**
Tully 2007 a (= recommended)	1	1	0	1	1	1	1	1	1	1	1	1	1	0	1	**13**
Tully 2007 b (< recommended)	1	1	0	1	0	1	1	1	1	1	1	1	1	1	1	**13**
Vainionpää 2007	1	1	0	1	1	1	0	1	0	1	1	0	0	1	1	**10**
Vicente-Campos 2012	1	0	0	1	1	1	0	0	0	1	1	0	0	0	1	**7**
von Thiele Schwarz 2008	1	0	0	1	1	1	0	0	0	1	1	0	0	1	1	**8**
Wirth 1985	1	0	0	1	1	1	1	0	0	1	1	1	0	0	0	**8**
Wood 1983	1	1	0	1	1	1	0	0	0	1	1	1	0	0	1	**9**
Zhang 2014	1	1	0	1	1	1	0	0	0	1	1	1	0	1	1	**10**

Table S5.6 TESTEX Assessment of Study Quality

Within-Study Risk of Bias Factors and Method

We awarded either of low or high for the following factors:

1. Study non-randomised or randomised – low if randomised, high if non-randomised;[1]
2. For intervention groups, a minimum level of compliance to be counted as having participated in the intervention group or control group – low if a minimum level of compliance was set, high if there was no minimum compliance level;
3. Habitual medication use reported – low if reported, high if not reported;
4. Drop-out reasons given – low if reported, high if not reported;
5. Baseline fitness and effort determined – low if baseline fitness and effort was measured, high if not determined;
6. > 50% of sessions supervised – low if > 50% of sessions were supervised, high if not; and
7. Effort monitoring and measurement devices – low if digital recording devices were used, high if analog or no device.

Studies were scored overall low, medium, or high risk of bias according to the number of times either "low" or "high" was accorded. A low risk of bias was awarded for 0-2 instances of "high", a medium risk of bias was awarded for 3-4 instances of "high", and a high risk of bias was awarded for 5-7 instances of "high". All factors were equally weighted.

[1] All studies were randomised

Study	Study non-RCT or RCT	Minimum compliance level set	Habitual medication use reported	Dropout reason reported	Baseline fitness and effort determined	> 50% sessions supervised	Effort monitoring and measurement device	Risk of bias assesment low, medium, or high
Baker 1986	low	low	low	low	low	low	high	**low**
Bell 2010 a (MICT)	low	low	low	low	low	low	low	**low**
Bell 2010 b (walking)	low	low	low	low	low	high	high	**low**
Bergström 2009	low	low	low	low	high	high	high	**medium**
Bhutani 2013	low	low	high	low	low	low	low	**low**
Blumenthal 1991	low	low	low	low	low	low	high	**low**
Boardley 2007	low	low	low	high	high	low	high	**medium**
Bock 2019 standard	low	high	high	low	low	low	low	**low**
Bock 2019 video games	low	high	high	low	low	low	low	**low**
Busby 1985	low	high	low	high	low	high	high	**medium**
Costa 2018	low	high	low	low	low	high	high	**medium**
Cunningham 1987	low	high	high	low	low	low	high	**medium**
Furukawa 2003	low	high	high	low	low	high	low	**medium**
Grandjean 1996	low	high	high	high	low	high	high	**high**
Grant 2004	low	high	high	low	low	low	high	**medium**
Hellénius 1993	low	high	high	low	low	high	high	**medium**
Hespel 1988	low	low	low	low	low	low	high	**low**
Hinkleman 1993	low	high	low	low	low	low	low	**low**
Ho 2012	low	low	high	low	high	high	low	**medium**
Hornstrup 2019	low	high	low	low	low	low	low	**low**
Huttunen 1979	low	high	low	low	low	high	high	**medium**
Kemmler 2014	low	low	low	low	low	low	low	**low**
Kiens 1980	low	high	high	high	high	high	low	**high**
King 1991 mens (HIT group)	low	low	high	high	low	low	high	**medium**
King 1991 mens (HIT home)	low	low	high	high	low	high	high	**medium**
King 1991 mens (LIT home)	low	low	high	high	low	high	high	**medium**
King 1991 womens (HIT group)	low	low	high	high	low	low	high	**medium**
King 1991 womens (HIT home)	low	low	high	high	low	high	high	**medium**
King 1991 womens (LIT home)	low	low	high	high	low	high	high	**medium**
Knoepfli-Lenzin 2010	low	low	high	low	low	low	low	**low**
Korshøj 2016	low	high	high	high	low	low	low	**medium**
Krustrup 2009	low	low	low	low	low	low	low	**low**
Krustrup 2010	low	low	low	low	low	low	low	**low**
Krustrup 2017	low	low	low	low	low	low	high	**low**
Kukkonen-Harjula 1998	low	low	low	low	low	low	low	**low**

Study	Study non-RCT or RCT	Minimum compliance level set	Habitual medication use reported	Dropout reason reported	Baseline fitness and effort determined	> 50% sessions supervised	Effort monitoring and measurement device	Risk of bias assesment low, medium, or high
Lawton 2008	low	high	low	low	high	high	high	**medium**
LeMura 2000	low	low	high	high	low	high	low	**medium**
Lindheim 1994	low	high	high	low	low	low	low	**low**
Martins 2010	low	high	low	high	low	low	high	**medium**
Maruf 2014	low	low	low	low	low	low	high	**low**
Mawi 2009	low	low	high	low	high	low	low	**low**
Mohanka 2006	low	low	low	high	low	high	low	**low**
Mohr 2014 HIIT	low	low	low	low	low	low	low	**low**
Mohr 2014 MICT	low	low	low	low	low	low	low	**low**
Morgan 2010	low	low	high	high	low	high	low	**medium**
Mosher 2005 continuous step	low	low	low	low	low	low	high	**low**
Mosher 2005 interval step	low	low	low	low	low	low	high	**low**
Niederseer 2011	low	high	low	high	low	low	low	**low**
Nieman 1993	low	low	low	low	low	low	low	**low**
Nieman 2002	low	low	high	low	low	low	low	**low**
Nualnim 2012	low	low	high	high	low	low	low	**low**
Ohta 2012	low	low	low	low	low	high	high	**low**
Park 2014	low	high	low	low	high	low	low	**low**
Ready 1995	low	low	high	low	low	high	high	**medium**
Ring-Dimitriou 2007	low	high	high	low	low	low	high	**medium**
Rossi 2016	low	low	high	low	high	high	high	**medium**
Santiago 1995	low	high	high	low	low	low	high	**medium**
Sarzynski 2018 (AT1 - 20 KKW)	low	low	low	low	low	low	low	**low**
Sarzynski 2018 (AT2 - 8 KKW)	low	low	low	low	low	low	low	**low**
Schuit 1998 all round	low	low	high	low	low	low	high	**low**
Schuit 1998 cycling	low	low	high	low	low	high	low	**low**
Short 2003	low	low	high	high	low	low	high	**medium**
Shou 2019	low	high	high	high	low	low	high	**medium**
Sillanpää 2009 men	low	low	low	high	low	low	low	**low**
Sillanpää 2009 women	low	low	low	low	low	low	low	**low**
Sousa 2014	low	low	high	low	low	low	high	**low**
Stensel 1995	low	high	low	low	low	high	low	**low**
Sunami 1999	low	low	high	high	low	low	high	**medium**
Suter 1990	low	low	high	high	low	high	low	**medium**
Suter 1992	low	low	high	high	low	high	low	**medium**
Takeshima 2002	low	low	high	high	low	low	low	**low**
Tiainen 2016	low	low	high	low	low	high	low	**low**
Tsai 2002	low	low	high	low	low	low	high	**low**
Tseng 2013	low	high	high	low	low	high	low	**medium**
Tully 2007 a (= recommended)	low	high	high	low	low	high	high	**medium**
Tully 2007 b (< recommended)	low	high	high	low	low	high	high	**medium**
Vainionpää 2007	low	low	high	high	low	low	low	**low**
Vicente-Campos 2012	low	low	high	high	low	low	low	**low**
von Thiele Schwarz 2008	low	low	high	low	low	low	high	**low**
Wirth 1985	low	high	high	low	low	low	high	**medium**
Wood 1983	low	low	high	low	low	low	high	**low**
Zhang 2014	low	low	high	high	low	low	high	**medium**

Table S5.7 Assessed Within-Study Risk of Bias

TESTEX Forest plots

Sub-analysis using study quality: random effects meta-analysis conducted for each lipid, by including those RCTs with a TESTEX score ≥10 and within-study risk of bias score of low to medium only. The influencer RCT was removed for TRG, and the 5 outlier RCTs were removed for HDL-C.

Study name	Outcome	Cumulative statistics					Cumulative sample size			Study Quality	Weight (Random)	
		Point	Standard error	Lower limit	Upper limit	p-Value	Exercise	Control	Total		Weight (Random)	Relative weight
Huttunen 1979	TC	-0.270	0.252	-0.763	0.223	0.283	44	46	90	11	11.55	2.08
Cunningham 1987	TC	-0.097	0.133	-0.358	0.164	0.465	145	147	292	10	20.86	5.85
Sunami 1999	TC	-0.086	0.117	-0.315	0.142	0.460	165	167	332	10	12.21	8.05
Nieman 1993	TC	-0.091	0.111	-0.309	0.127	0.412	179	183	362	13	6.34	9.19
Hinkleman 1993	TC	-0.118	0.106	-0.325	0.089	0.265	197	201	398	12	7.15	10.48
Stensel 1993	TC	-0.127	0.100	-0.322	0.069	0.206	239	224	463	11	8.44	12.00
Kukkonen-Harjula 1998	TC	-0.167	0.061	-0.286	-0.047	0.006	292	279	571	12	34.26	18.19
Schuit 1998 all round	TC	-0.177	0.059	-0.292	-0.061	0.003	325	320	645	10	12.59	20.46
Schuit 1998 cycling	TC	-0.167	0.056	-0.277	-0.056	0.003	386	361	747	10	16.39	23.41
Nieman 2002	TC	-0.163	0.055	-0.272	-0.055	0.003	407	383	790	13	7.86	24.83
Mohanka 2006	TC	-0.151	0.052	-0.253	-0.048	0.004	492	469	961	12	20.60	28.55
Tully 2007 (= recommended)	TC	-0.147	0.051	-0.248	-0.046	0.004	534	479	1013	13	10.12	30.37
Tully 2007 (less than recommended)	TC	-0.151	0.051	-0.250	-0.052	0.003	578	489	1067	13	10.53	32.27
Vainionpää 2007	TC	-0.146	0.049	-0.242	-0.050	0.003	615	528	1143	10	15.15	35.01
Bergström 2009	TC	-0.137	0.046	-0.227	-0.047	0.003	663	572	1235	10	24.33	39.40
Krustrup 2009	TC	-0.139	0.046	-0.229	-0.049	0.002	673	582	1255	10	4.48	40.21
Lawton 2008	TC	-0.096	0.037	-0.169	-0.023	0.010	1217	1127	2344	12	36.32	46.76
Mawi 2009	TC	-0.177	0.063	-0.300	-0.054	0.005	1248	1158	2406	10	14.01	49.29
Bell 2010 MICT	TC	-0.170	0.061	-0.289	-0.051	0.005	1288	1180	2468	11	9.82	51.06
Bell 2010 walking	TC	-0.164	0.058	-0.278	-0.049	0.005	1331	1203	2534	11	11.27	53.09
Krustrup 2010	TC	-0.167	0.056	-0.278	-0.057	0.003	1348	1217	2565	10	10.79	55.04
Morgan 2010	TC	-0.182	0.058	-0.296	-0.068	0.002	1362	1232	2594	10	4.57	55.86
Niederseer 2011	TC	-0.179	0.056	-0.289	-0.068	0.002	1380	1248	2628	10	8.27	57.35
Ho 2012	TC	-0.178	0.055	-0.286	-0.070	0.001	1395	1264	2659	10	4.48	58.16
Nualmin 2012	TC	-0.178	0.054	-0.283	-0.073	0.001	1419	1283	2702	12	7.51	59.51
Bhutani 2013	TC	-0.168	0.051	-0.268	-0.069	0.001	1443	1299	2742	12	21.78	63.44
Maruf 2014	TC	-0.159	0.048	-0.253	-0.065	0.001	1503	1359	2862	11	21.43	67.31
Mohr 2014 HIIT	TC	-0.159	0.047	-0.251	-0.068	0.001	1524	1370	2894	11	8.25	68.80
Mohr 2014 MICT	TC	-0.160	0.046	-0.250	-0.070	0.000	1544	1380	2924	12	5.40	69.77
Park 2014	TC	-0.159	0.045	-0.246	-0.071	0.000	1558	1394	2952	11	9.32	71.46
Zhang 2014	TC	-0.201	0.052	-0.302	-0.100	0.000	1612	1451	3063	10	28.33	76.57
Tianen 2016	TC	-0.191	0.049	-0.286	-0.095	0.000	1691	1533	3224	11	30.50	82.07
Krustrup 2017	TC	-0.196	0.048	-0.291	-0.102	0.000	1710	1545	3255	11	8.22	83.55
Costa 2018	TC	-0.207	0.049	-0.303	-0.112	0.000	1730	1565	3295	10	7.25	84.86
Sarzynski 2018 AT1 - 20KKW	TC	-0.208	0.047	-0.300	-0.116	0.000	1776	1588	3364	11	21.75	88.79
Sarzynski 2018 AT2 - 8 KKW	TC	-0.205	0.045	-0.294	-0.117	0.000	1824	1610	3434	11	23.90	93.10
Bock 2019 standard	TC	-0.198	0.044	-0.284	-0.112	0.000	1920	1657	3577	14	19.82	96.67
Bock 2019 video	TC	-0.194	0.042	-0.277	-0.111	0.000	2013	1704	3717	14	18.45	100.00
		-0.194	0.042	-0.277	-0.111	0.000						

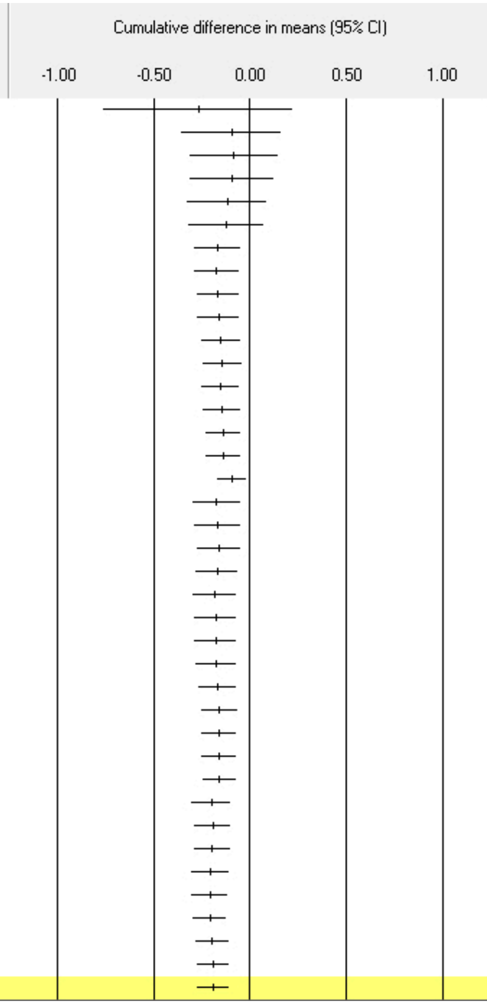


Figure S5.8 TC TESTEX score ≥10 Forest Plot

Study name	Outcome	Cumulative statistics					Cumulative sample size			Study Quality	Weight (Random)	
		Point	Standard error	Lower limit	Upper limit	p-Value	Exercise	Control	Total		Weight (Random)	Relative weight
Huttunen 1979	TRG	-0.420	0.165	-0.743	-0.097	0.011	44	46	90	11	36.80	2.05
Sunami 1999	TRG	-0.208	0.205	-0.609	0.194	0.311	64	66	130	10	47.28	4.68
Nieman 1993	TRG	-0.206	0.144	-0.488	0.076	0.153	78	82	160	13	11.10	5.29
Hinkleman 1993	TRG	-0.218	0.102	-0.418	-0.018	0.033	96	100	196	12	26.60	6.77
Stensel 1993	TRG	-0.211	0.090	-0.388	-0.034	0.019	138	123	261	11	0.70	6.81
Kukkonen-Harjula 1998	TRG	-0.159	0.054	-0.265	-0.053	0.003	189	177	366	12	220.87	19.10
Schuit 1998 all round	TRG	-0.159	0.052	-0.261	-0.057	0.002	222	218	440	10	27.43	20.63
Schuit 1998 cycling	TRG	-0.154	0.049	-0.249	-0.059	0.001	283	259	542	10	54.26	23.64
Nieman 2002	TRG	-0.152	0.048	-0.246	-0.059	0.001	304	281	585	13	16.21	24.55
Mohanka 2006	TRG	-0.133	0.044	-0.220	-0.046	0.003	391	367	758	12	69.76	28.43
Tully 2007 (less than recommended)	TRG	-0.132	0.043	-0.217	-0.048	0.002	435	377	812	13	29.57	30.07
Vainionpää 2007	TRG	-0.115	0.040	-0.194	-0.037	0.004	472	416	888	10	87.13	34.92
Tully 2007 (= recommnded)	TRG	-0.114	0.039	-0.191	-0.037	0.004	514	426	940	13	23.07	36.20
Mawi 2009	TRG	-0.126	0.038	-0.200	-0.051	0.001	545	457	1002	10	39.10	38.38
Bell 2010 MICT	TRG	-0.125	0.038	-0.199	-0.051	0.001	585	479	1064	11	9.11	38.88
Bell 2010 walking	TRG	-0.127	0.037	-0.199	-0.054	0.001	628	502	1130	11	27.46	40.41
Krustrup 2010	TRG	-0.120	0.036	-0.190	-0.049	0.001	645	516	1161	10	47.26	43.04
Niederseer 2011	TRG	-0.126	0.034	-0.194	-0.058	0.000	663	532	1195	10	66.62	46.74
Ho 2012	TRG	-0.127	0.034	-0.194	-0.060	0.000	678	548	1226	10	13.35	47.49
Nualmin 2012	TRG	-0.125	0.034	-0.192	-0.059	0.000	702	567	1269	12	16.22	48.39
Bhutani 2013	TRG	-0.111	0.032	-0.173	-0.048	0.001	726	583	1309	12	116.06	54.85
Kemmler 2014	TRG	-0.114	0.030	-0.173	-0.055	0.000	759	624	1383	12	127.75	61.95
Maruf 2014	TRG	-0.123	0.029	-0.180	-0.066	0.000	819	684	1503	11	70.44	65.87
Mohr 2014 HIIT	TRG	-0.129	0.029	-0.186	-0.073	0.000	840	695	1535	11	28.87	67.48
Mohr 2014 MICT	TRG	-0.132	0.029	-0.188	-0.076	0.000	860	705	1565	12	13.24	68.21
Park 2014	TRG	-0.130	0.028	-0.185	-0.074	0.000	874	719	1593	11	22.22	69.45
Zhang 2014	TRG	-0.132	0.028	-0.186	-0.078	0.000	928	776	1704	10	62.71	72.94
Tianen 2016	TRG	-0.123	0.026	-0.174	-0.072	0.000	1007	858	1865	11	159.45	81.81
Krustrup 2017	TRG	-0.126	0.026	-0.177	-0.075	0.000	1026	870	1896	11	23.03	83.09
Costa 2018	TRG	-0.127	0.026	-0.177	-0.076	0.000	1046	890	1936	10	8.52	83.56
Sarzynski 2018 AT1 - 20KKW	TRG	-0.124	0.025	-0.174	-0.075	0.000	1092	913	2005	11	63.57	87.10
Sarzynski 2018 AT2 - 8KKW	TRG	-0.123	0.025	-0.171	-0.075	0.000	1140	935	2075	11	99.69	92.64
Bock 2019 standard	TRG	-0.118	0.024	-0.165	-0.071	0.000	1236	982	2218	14	80.66	97.13
Bock 2019 video	TRG	-0.115	0.024	-0.161	-0.069	0.000	1329	1029	2358	14	51.61	100.00
		-0.115	0.024	-0.161	-0.069	0.000						

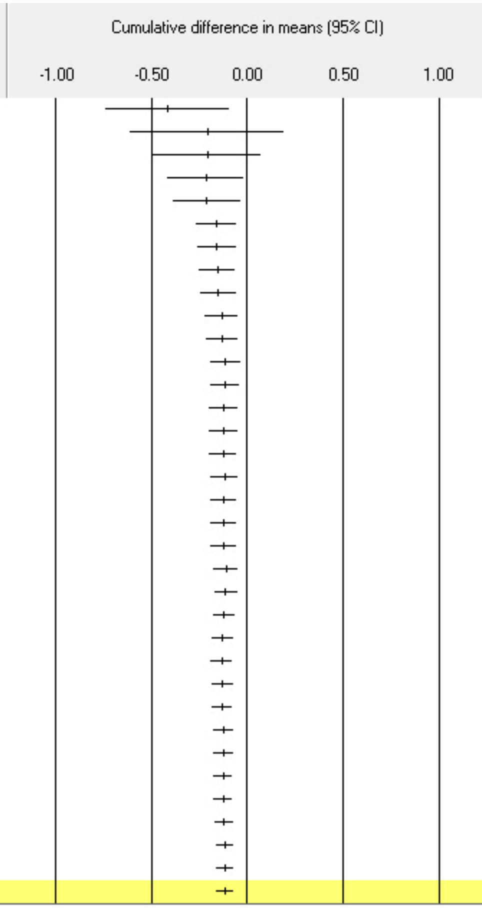


Figure S5.9 TRG TESTEX score ≥10 Forest Plot

Study name	Outcome	Cumulative statistics					Cumulative sample size			Study Quality	Cumulative difference in means (95% CI)	Weight (Random)	
		Point	Standard error	Lower limit	Upper limit	p-Value	Exercise	Control	Total		-1.00 -0.50 0.00 0.50 1.00	Weight (Random)	Relative weight
Huttunen 1979	HDL-C	0.140	0.054	0.035	0.245	0.009	44	46	90	11		346.19	2.74
Cunningham 1987	HDL-C	0.090	0.050	-0.008	0.188	0.072	145	147	292	10		345.60	5.47
Sunami 1999	HDL-C	0.102	0.039	0.026	0.178	0.009	165	167	332	10		105.39	6.31
Nieman 1993	HDL-C	0.088	0.035	0.020	0.155	0.011	186	183	369	13		132.10	7.35
Stensel 1995	HDL-C	0.084	0.032	0.021	0.147	0.009	228	206	434	11		42.02	7.68
Kukkonen-Harjula 1998	HDL-C	0.052	0.025	0.004	0.100	0.034	281	260	541	12		2210.55	25.17
Schuit 1998 all round	HDL-C	0.064	0.026	0.014	0.115	0.013	314	301	615	10		175.06	26.56
Schuit 1998 cycling	HDL-C	0.060	0.021	0.018	0.101	0.005	375	342	717	10		262.74	28.64
Nieman 2002	HDL-C	0.051	0.018	0.015	0.086	0.005	403	364	767	13		283.89	30.88
Mohanka 2006	HDL-C	0.045	0.015	0.015	0.075	0.003	490	450	940	12		353.18	33.68
Tully 2007 (= recommended)	HDL-C	0.045	0.015	0.015	0.075	0.003	532	460	992	13		22.84	33.86
Tully 2007 (less than recommended)	HDL-C	0.047	0.015	0.017	0.076	0.002	576	470	1046	13		30.99	34.10
Vainionpää 2007	HDL-C	0.046	0.015	0.017	0.076	0.002	613	509	1122	10		160.34	35.37
Bergström 2009	HDL-C	0.043	0.014	0.016	0.070	0.002	661	553	1214	10		637.13	40.41
Krustrup 2009	HDL-C	0.043	0.014	0.015	0.070	0.002	671	563	1234	10		50.01	40.81
Lawton 2008	HDL-C	0.038	0.012	0.014	0.063	0.002	1215	1108	2323	12		1249.95	50.70
Bell 2010 MICT	HDL-C	0.038	0.012	0.014	0.063	0.002	1255	1130	2385	11		2.65	50.72
Bell 2010 walking	HDL-C	0.037	0.012	0.013	0.061	0.002	1298	1153	2451	11		222.90	52.48
Krustrup 2010	HDL-C	0.037	0.012	0.013	0.061	0.003	1315	1167	2482	10		49.04	52.87
Morgan 2010	HDL-C	0.038	0.012	0.014	0.062	0.002	1329	1182	2511	10		48.60	53.26
Niederseer 2011	HDL-C	0.038	0.012	0.015	0.062	0.001	1347	1198	2545	10		228.17	55.06
Ho 2012	HDL-C	0.038	0.012	0.015	0.061	0.001	1362	1214	2576	10		55.16	55.50
Nualmin 2012	HDL-C	0.038	0.012	0.015	0.062	0.001	1386	1233	2619	12		40.59	55.82
Bhutani 2013	HDL-C	0.039	0.012	0.016	0.062	0.001	1410	1249	2659	12		182.38	57.26
Kemmler 2014	HDL-C	0.043	0.012	0.020	0.066	0.000	1443	1290	2733	12		240.44	59.16
Maruf 2014	HDL-C	0.044	0.011	0.021	0.066	0.000	1503	1350	2853	11		193.43	60.69
Mohr 2014 HIIT	HDL-C	0.044	0.011	0.022	0.066	0.000	1524	1361	2885	11		40.85	61.02
Mohr 2014 MICT	HDL-C	0.045	0.011	0.022	0.067	0.000	1544	1371	2915	12		39.72	61.33
Park 2014	HDL-C	0.045	0.011	0.023	0.067	0.000	1558	1385	2943	11		49.99	61.73
Zhang 2014	HDL-C	0.045	0.011	0.023	0.066	0.000	1612	1442	3054	10		565.43	66.20
Tianen 2016	HDL-C	0.046	0.010	0.026	0.066	0.000	1691	1524	3215	11		911.95	73.42
Costa 2018	HDL-C	0.047	0.010	0.027	0.068	0.000	1711	1544	3255	10		123.62	74.39
Sarzynski 2018 AT1 - 20KKW	HDL-C	0.047	0.010	0.027	0.066	0.000	1757	1567	3324	11		445.61	77.92
Sarzynski 2018 AT2 - 8KKW	HDL-C	0.046	0.010	0.027	0.066	0.000	1805	1589	3394	11		429.51	81.32
Bock 2019 standard	HDL-C	0.047	0.009	0.028	0.065	0.000	1901	1636	3537	14		1276.27	91.41
Bock 2019 video	HDL-C	0.046	0.009	0.029	0.064	0.000	1994	1683	3677	14		1085.09	100.00
		0.046	0.009	0.029	0.064	0.000							

Figure S5.10 HDL-C TESTEX score ≥10 Forest Plot

Study name	Outcome	Cumulative statistics					Cumulative sample size			Study Quality	Weight (Random)	
		Point	Standard error	Lower limit	Upper limit	p-Value	Exercise	Control	Total		Weight (Random)	Relative weight
Huttunen 1979	LDL-C	-0.280	0.220	-0.711	0.151	0.203	44	46	90	11	18.54	2.10
Sunami 1999	LDL-C	-0.167	0.160	-0.481	0.147	0.297	64	66	130	10	16.71	4.00
Nieman 1993	LDL-C	-0.151	0.145	-0.436	0.133	0.297	78	82	160	13	8.11	4.92
Hinkleman 1993	LDL-C	-0.141	0.133	-0.401	0.119	0.287	96	100	196	12	8.91	5.93
Stensel 1995	LDL-C	-0.151	0.122	-0.389	0.088	0.215	138	123	261	11	10.15	7.09
Kukkonen-Harjula 1998	LDL-C	-0.143	0.065	-0.270	-0.016	0.027	189	177	366	12	87.98	17.08
Schuit 1998 all round	LDL-C	-0.138	0.062	-0.260	-0.017	0.025	222	218	440	10	19.77	19.32
Schuit 1998 cycling	LDL-C	-0.128	0.058	-0.242	-0.013	0.029	283	259	542	10	27.56	22.45
Nieman 2002	LDL-C	-0.126	0.057	-0.237	-0.014	0.027	304	281	585	13	14.04	24.05
Mohanka 2006	LDL-C	-0.111	0.053	-0.216	-0.007	0.037	391	367	758	12	34.89	28.01
Tully 2007 (= recommended)	LDL-C	-0.112	0.052	-0.215	-0.009	0.033	433	377	810	13	11.10	29.27
Tully 2007 (less than recommended)	LDL-C	-0.116	0.052	-0.217	-0.015	0.025	477	387	864	13	10.37	30.45
Vainionpää 2007	LDL-C	-0.116	0.050	-0.213	-0.019	0.020	514	426	940	10	27.83	33.60
Bergström 2009	LDL-C	-0.112	0.046	-0.201	-0.022	0.014	562	470	1032	10	52.32	39.55
Krustrup 2009	LDL-C	-0.112	0.045	-0.200	-0.023	0.014	571	480	1051	10	8.86	40.55
Mawi 2009	LDL-C	-0.182	0.070	-0.319	-0.045	0.009	602	511	1113	10	23.64	43.24
Bell 2010 MICT	LDL-C	-0.173	0.067	-0.304	-0.042	0.009	642	533	1175	11	13.96	44.82
Bell 2010 walking	LDL-C	-0.167	0.063	-0.292	-0.043	0.008	685	556	1241	11	17.02	46.75
Krustrup 2010	LDL-C	-0.165	0.061	-0.284	-0.045	0.007	702	570	1272	10	11.49	48.06
Niederseer 2011	LDL-C	-0.157	0.058	-0.271	-0.043	0.007	720	586	1306	10	20.30	50.36
Ho 2012	LDL-C	-0.158	0.056	-0.268	-0.047	0.005	735	602	1337	10	5.93	51.03
Nualmin 2012	LDL-C	-0.155	0.055	-0.262	-0.048	0.005	759	621	1380	12	8.45	51.99
Bhutani 2013	LDL-C	-0.151	0.051	-0.251	-0.051	0.003	783	637	1420	12	37.39	56.24
Maruf 2014	LDL-C	-0.145	0.047	-0.238	-0.053	0.002	843	697	1540	11	49.89	61.90
Mohr 2014 HIIT	LDL-C	-0.142	0.046	-0.232	-0.052	0.002	864	708	1572	11	9.67	63.00
Mohr 2014 MICT	LDL-C	-0.140	0.045	-0.228	-0.053	0.002	884	718	1602	12	5.98	63.68
Park 2014	LDL-C	-0.138	0.043	-0.222	-0.054	0.001	898	732	1630	11	15.36	65.42
Zhang 2014	LDL-C	-0.126	0.040	-0.205	-0.047	0.002	952	789	1741	10	68.01	73.15
Tianen 2016	LDL-C	-0.120	0.038	-0.193	-0.046	0.002	1031	871	1902	11	51.79	79.03
Krustrup 2017	LDL-C	-0.124	0.037	-0.197	-0.051	0.001	1050	883	1933	11	10.82	80.25
Costa 2018	LDL-C	-0.138	0.041	-0.218	-0.058	0.001	1070	903	1973	10	9.41	81.32
Sarzynski 2018 (AT1 - 20 KKW)	LDL-C	-0.141	0.039	-0.216	-0.065	0.000	1116	926	2042	11	49.60	86.95
Sarzynski 2018 (AT2 - 8 KKW)	LDL-C	-0.143	0.036	-0.213	-0.072	0.000	1164	948	2112	11	73.12	95.26
Bock 2019 standard	LDL-C	-0.139	0.035	-0.208	-0.071	0.000	1260	995	2255	14	22.86	97.85
Bock 2019 video	LDL-C	-0.139	0.034	-0.205	-0.073	0.000	1353	1042	2395	14	18.93	100.00
		-0.139	0.034	-0.205	-0.073	0.000						

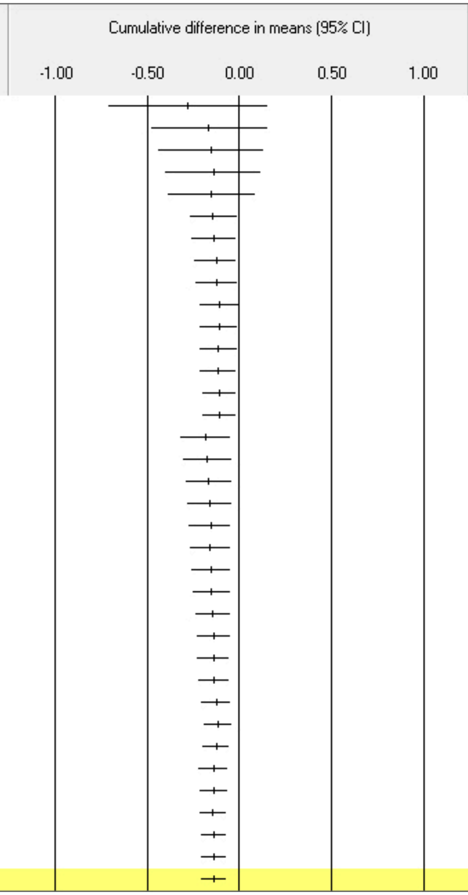


Figure S5.11 LDL-C TESTEX score ≥10 Forest Plot

Publication Bias

Table S5.5 shows Duval and Tweedie's trim-and-fill Analysis statistics for each lipid, and the relevant statistics for Egger's regression test and Begg and Mezumdar's rank correlation test (influencer RCT removed for TRG, 5 outlier RCTs removed for HDL-C). Disagreement between the different statistics arises in the presence of heterogeneity.

Lipid	**MD_ρ**	**95% CI_ρ**	**Q $value_\rho$**	***MD_I***	***95% CI_I***	***Q $value_I$***	***Imputed RCTs (N)***
TC	-0.20	-0.25, -0.15	91.09	-0.24	-0.30, -0.19	121.86	11
TRG excluding influencer	-0.13	-0.16, -0.10	45.57	-0.12	-0.15, -0.09	65.48	6
HDL-C excluding outliers	0.05	0.04, 0.06	44.84	0.04	0.03, 0.05	85.18	19
LDL-C	-0.15	-0.19, -0.11	66.77	-0.16	-0.20, -0.12	69.14	6

Lipid	**Eggers Regression Test**			**Begg and Mezumdar's rank correlation test**	
	Intercept B(0)	95% CI	2-tailed *P*	Kendall's τb	2-tailed *P*
TC	-0.38	-0.99, 0.18	.18	-0.25	.002
TRG excluding influencer	-0.26	-0.66, 0.15	0.21	-0.20	.01
HDL-C excluding outliers	0.67	0.36, 0.98	<.001	0.26	.001
LDL-C	-0.30	-0.80, 0.20	0.24	-0.25	.002

MD_ρ = mean difference (observed)
95% CI_ρ = pooled 95% confidence interval of mean difference (observed)
Q $value_\rho$ = Q value of mean difference (observed)
MD_I = mean difference (imputed)
95% CI_I = pooled 95% confidence interval of mean difference (imputed)
Q $value_I$ = Q value of mean difference (imputed)

Table S5.8 Publication Bias Estimates Using Trim-and-Fill Analysis

Duval and Tweedie's Trim-and-Fill Funnel Plots

For each meta-analysis a funnel plot of the observed and imputed studies was generated using CMA.

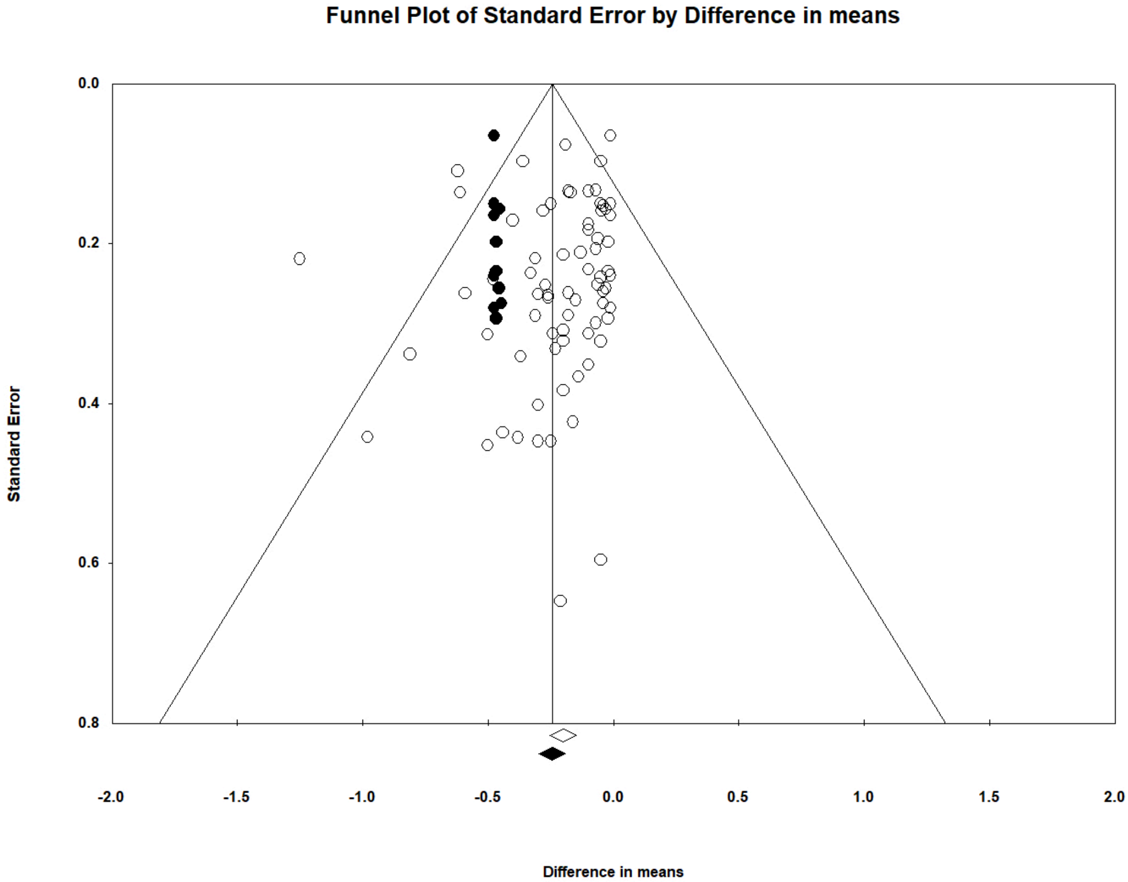


Figure S5.12 TC Funnel Plot (observed and 11 imputed studies)

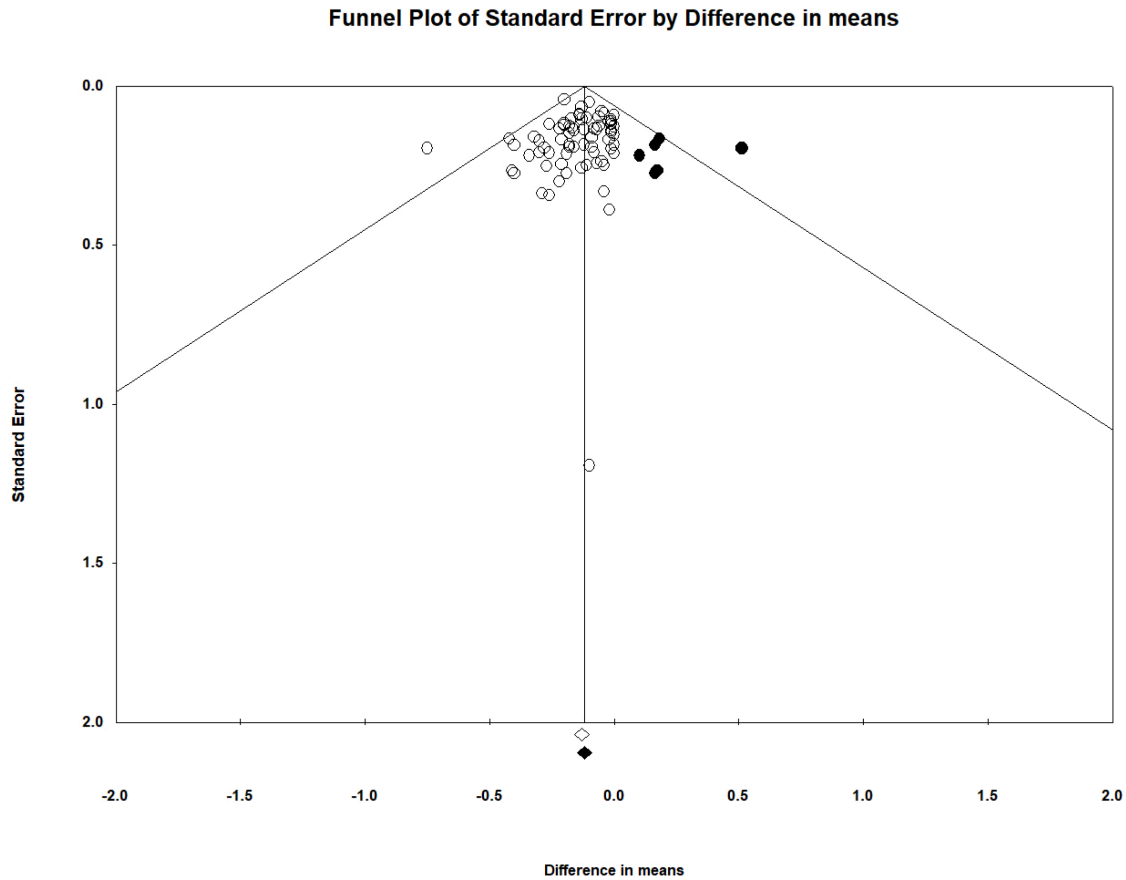


Figure S5.13 TRG Funnel Plot (observed and 6 imputed studies)

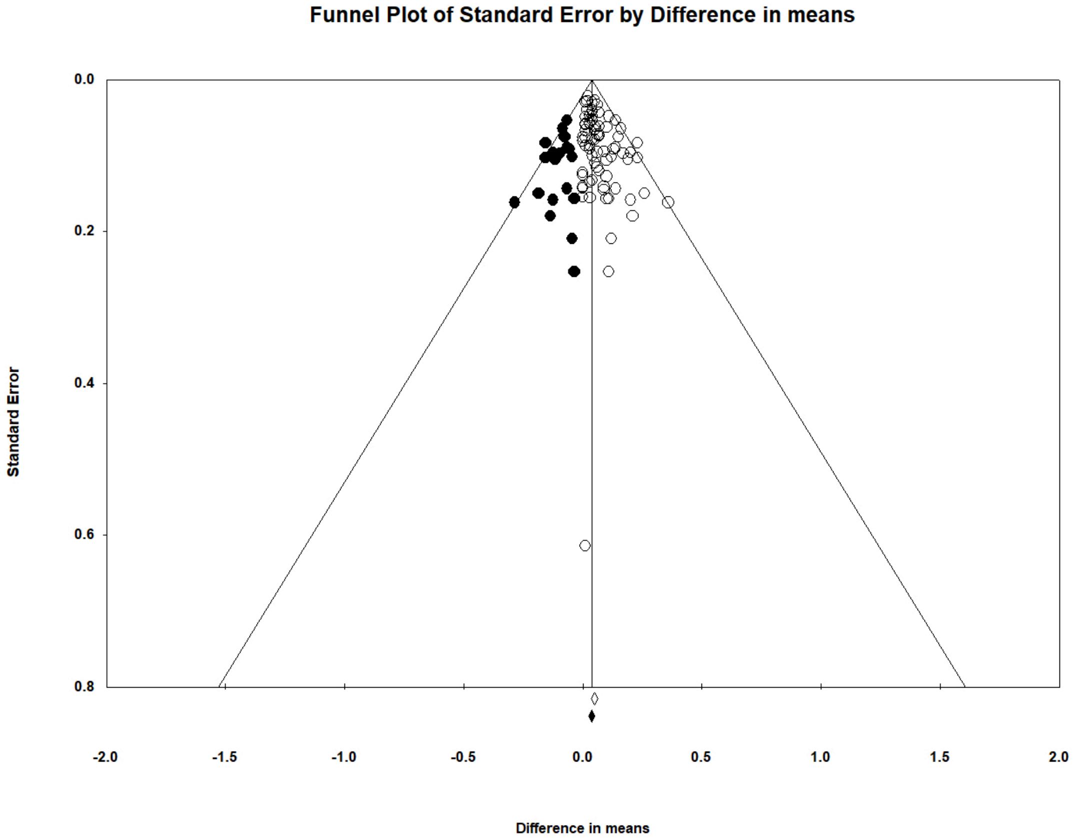


Figure S5.14 HDL-C Funnel Plot (observed and 19 imputed studies)

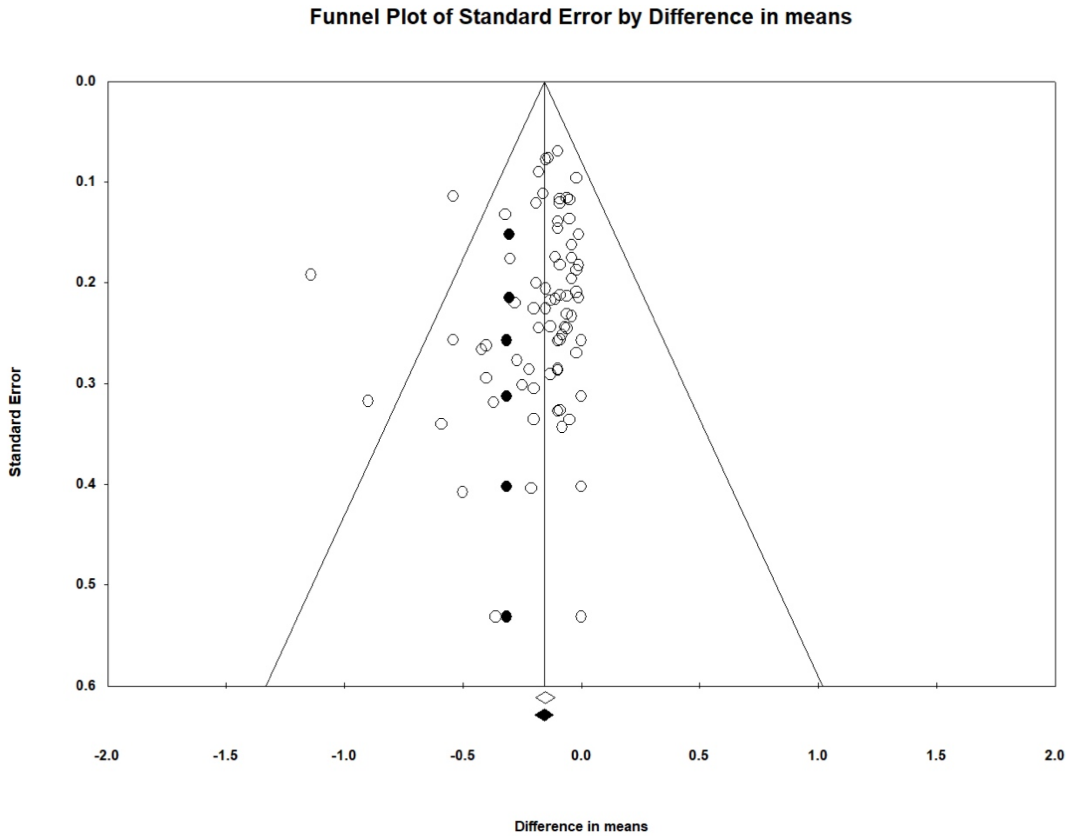


Figure S5.15 LDL-C Funnel Plot (observed and 6 imputed studies)

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6 Chapter 6 – Determining the Effect Size of Aerobic Exercise Training on the Standard Lipid Profile of Adults Diagnosed with Metabolic Syndrome: A Systematic Review with Univariate Meta-analysis and Meta-regression of Randomised Controlled Trials

6.1 Manuscript information – submitted 30th September 2020

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On each occasion that research is made public the forms 'Statement of Authorship' and 'Location of Data' must be filled out, signed and lodged with the Head of the Department of which the principal researcher is a member. If, for any reason, one or more co-authors are unavailable or otherwise unable to sign the statements, the Head of Department may sign on their behalf, noting the reason for their unavailability. Heads of Departments must keep copies of these statements in departmental files.

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Authorship is defined as substantial participation, where all the following conditions are met:

(a) conception and design, or analysis and interpretation of data, and
(b) drafting the article or revising it critically for important intellectual content, and
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An author's role in a research output must be sufficient for that person to take public responsibility for at least part of the output in that person's area of expertise. No person who is an author, consistent with this definition, must be excluded as an author without their permission in writing.

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6.2 Statement of authors' contribution

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STATEMENT OF AUTHORS' CONTRIBUTION

We, the PhD candidate and the candidate's Principal Supervisor, certify that all co-authors have consented to their work being included in the thesis and they have accepted the candidate's contribution as indicated in the *Statement of Originality*.

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We, the PhD candidate and the candidate's Principal Supervisor, certify that the following text, figures, diagrams, tables, labels, keys and legends are the candidate' original work.

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6.4 Full manuscript as submitted

Determining the effect size of aerobic exercise training on the standard lipid profile in sedentary adults with 3 or more Metabolic Syndrome factors: A systematic review and meta-analysis of randomised controlled trials.

Short Title: **The impact of aerobic exercise on lipids in MetS adults: A systematic review and meta-analysis of RCTs.**

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Declarations
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ABSTRACT

Objectives To estimate change in the standard lipid profile (SLP) following aerobic exercise training (AET) of adults diagnosed with ≥3 Metabolic Syndrome (MetS) factors; to determine if this change is clinically important (CIC) for cardiovascular disease risk; and whether study/intervention covariates explain this change.

Design Quantitative review.

Data sources English language searches of online databases from inception until June 2020.

Eligibility criteria 1) published randomised controlled human trials with per group population size ≥10; 2) adults with ≥3 MetS factors or diabetes present but otherwise free of chronic disease, not pregnant/lactating, and sedentary before intervention; 3) AET-only intervention with duration ≥12 weeks; and 4) reporting pre-post intervention SLP outcomes.

Results Various univariate meta-analyses pooled 48 data sets of 2990 participants. Aerobic exercise training significantly (*P*<.001) improved all lipids (mmol/L mean difference ranges, 95% confidence intervals). Total cholesterol: -0.19 (-0.26, -0.12) to -0.29 (-0.36, -0.21); triglycerides: -0.17 (-0.19,-0.14) to -0.18 (-0.24, -0.13); high-density lipoprotein-cholesterol: 0.05 (0.03, 0.07) to 0.08 (0.05, 0.010); low-density lipoprotein-cholesterol: -0.12 (-0.16, -0.9) to -0.20 (-0.25, -0.14). Meta-regression showed that intensity may explain change in triglycerides, and volume for change in high- and low-density lipoprotein-cholesterol.

Conclusion The estimated effect size of AET on the SLP of sedentary adults with ≥3 MetS factors achieved a CIC. For high-density lipoprotein-cholesterol, this CIC is comparable with reported estimated effect sizes of statins. Trials comparing the effect of statins against AET on high-density lipoprotein-cholesterol in this cohort may be warranted. Intervention covariates may be manipulated to potentially increase AET effects on the SLP.

PROSPERO ID CRD42020151925.

Keywords Lipids, Cholesterol, Triglycerides, Lipoprotein, Aerobic Exercise, Clinically Important Change, Statins

Five MCQs

1. Does aerobic exercise training significantly improve the standard lipid profile in sedentary adults free of chronic disease but diagnosed with 3 or more Metabolic Syndrome (MetS) factors?

2. Does this improvement represent a clinically important change such that cardiovascular disease risk may decrease up to 15%?

3. Do any aerobic exercise training intervention covariates potentially explain some change in high-density and low-density lipoprotein cholesterol or triglycerides? If so, which of these covariates, and for which of triglycerides, and the lipoproteins?

4. Does this systematic review and meta-analysis suggest that the estimated effect size of aerobic exercise training impacting high-density lipoprotein cholesterol is worse, equivalent, or better, than the reported effect size of statins for raising high-density lipoprotein cholesterol?

5. Why has this systematic review and meta-analysis presented a range of estimated effect sizes of the impact of aerobic exercise training on lipids rather than one effect size for each outcome? Is the most conservative effect size estimated still clinically important for improving each of the outcomes studied?

1.0 INTRODUCTION

Metabolic Syndrome (MetS) is implicated in cardiovascular disease (CVD).[1] The presence of 3 or more of the following MetS factors (body mass index (BMI) ≥30, hypertensive (H) blood pressure >130/85 mmHg, triglycerides (TRG) ≥1.7 mmol/L, high-density lipoprotein cholesterol (HDL-C) <1.0 mmol/L (males) or HDL-C <1.3 mmol/L (females), fasting blood sugar >5.5 mmol/L or diabetes mellitus, or medication prescribed to manage any of these factors), commonly defines MetS.[2 3] Moderate- and vigorous- intensity aerobic exercise training (AET) positively impacts MetS, thus lowering CVD risk.[4 5] Aerobic exercise training is defined as 3-6 metabolic equivalents (METS); >40% of heart rate reserve (HRR) or maximal oxygen uptake (VO_{2MAX}); 55-70% of maximal heart rate (MHR); or rate of perceived effort (RPE) of 11-13 on the Borg scale.[6]

Dyslipidaemia, an abnormally elevated or lowered lipid profile, is a significant MetS risk factor for CVD.[7-9] Cardiovascular disease risk decreases by 1.7% for every 1% lowering of low-density lipoprotein cholesterol (LDL-C), and CVD risk decreases by 2% in males and ≥ 3% in females for every 0.026 mmol/L increase in HDL-C.[10 11] The incidence of coronary heart disease decreases approximately 2% for every 1% lowering of total cholesterol (TC).[12] The standard lipid profile (SLP)[13] is positively impacted by aerobic exercise training (AET) in sub-clinical and clinical populations.[14-17] Lack of aerobic physical activity has negative consequences for lipids.[18]

A recent metaepidemological review of randomised controlled trials (RCTs) found physical activity interventions to have equal or greater beneficial effects on mortality outcomes (secondary prevention of CVD) compared with pharmaceutical interventions.[19] Aerobic physical activity as a first treatment option for dyslipidaemia in sub-clinical populations and as a concurrent treatment in clinical populations is preferable to pharmaceutical-only interventions.[20-24] Pharmaceutical intervention is a financial cost to health systems[25-27] and not without side effects such as increased risk of diabetes.[28 29]

Studies have shown AET of at least 180 minutes per week at >40% VO_{2MAX} or >1200 kcal/week is necessary to induce positive changes to lipids.[30 31] Systematic reviews and meta-analyses (MAs) have established longer AET intervention and session duration results in greater effects,[32 33] and a minimum effective AET volume (>45 minutes per session for 3-4 sessions per week for duration >26 weeks at >65% VO_{2MAX}) results in significant changes to lipids.[16] Cholesterol-lowering medication dosages which are steadily increased result in greater effects on lowering targeted lipids or raising HDL-C than fixed dosages.[24 34 35] The full reduction in risk of ischaemic heart disease is achieved within five years of lowering TC by 0.6 mmol/L.[36] Medication and AET require a minimum period to show effects, however pharmacological intervention trials are conducted for longer periods[37] than trials of AET intervention.[38]

Various SRs have examined the impact of AET on lipid profiles without conducting MAs.[11 17 39-45] Quantitative reviews examining the impact of AET on lipids have focused on one factor while merging others, such as combined health statuses while examining single lipids,[33 46] single genders,[47-49] and weight change.[50-53]. Other SRs with MA have investigated modalities of AET while combining health statuses: running,[32] walking,[46] intensity,[52-54] and AET effectiveness.[16] A Cochrane Review reported on lipids as a secondary outcome pooling only 3 studies.[55] To the best of our knowledge, no comprehensive SR and MA has yet been conducted which pooled the lipid outcomes of RCTs comparing various AET modes with no exercise for adult populations, while holding health status constant ie examining only those populations diagnosed with MetS and/or Type 1/Type 2 diabetes mellitus (T1DM, T2DM) and free of CVD or other chronic disease.

Our aims were fourfold: 1) to conduct an SR with univariate MA calculating the effect size (ES) of AET interventions of >40% VO_{2MAX} intensity, against non-exercising control groups, on the SLP of sedentary adults diagnosed with MetS and/or T1DM/T2DM; 2) to establish whether our estimated ES represented a clinically important change (CIC) in the SLP; 3) to conduct an exploratory meta-regression investigating whether *a priori* study and intervention covariates might explain change in the SLP; and 4) to discuss our estimated ES with respect to the reported estimated ES of statin therapies, since statins represent 98% of cholesterol lowering medication prescribed.[56]

2.0 METHODS

This SR and MA was designed by GW and NS and registered in the International Prospective Register of Systematic Reviews (PROSPERO) CRD42020151925.[57] Results are presented according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[58]

2.1 Study Eligibility Only RCTs comparing an AET intervention against a non-exercising control group were eligible for inclusion. Studies were required to report pre-post intervention and control SLP or component outcomes in humans ≥18 years.

2.2 Data Sources Potential studies were identified by systematic online searches of PubMed, EMBASE, all Web of Science and EBSCO health and medical databases from inception to June 30, 2020. We searched for RCTs published in English or bilingual journals. Searches included a mix of MeSH and free text terms such as: AET; endurance training; physical activity; lipids; lipoproteins; cholesterol; triglycerides; exercise-induced lipid metabolism; and MetS.

Searches excluded for pregnancy, lactation, elite athletes, juveniles, CVD, stroke, cancer, and diet and pharmaceutical interventions (see Supplementary Materials (SM) Table 6.5). Other SRs and reference lists of papers were hand searched for additional RCTs.

2.3 Study Selection GNW, ET, AP, and VN conducted the online database searches and assessed titles, key words, and abstracts of the search results independently, using Microsoft Excel (Version 16.31 2019). Studies were excluded if the population sample size (N) for the intervention or control groups was N<10.[59] The full text of potentially eligible RCTs was reviewed by GNW, ET, AP and VN. NS was consulted to resolve disputes. We used the citation management software Endnote X.9.3.

2.3.1 Participants Studies of adults who were sedentary prior to intervention with ≥3 MetS indices (including T1DM or T2DM) present in ≥50% of participants were included. Studies of participants either surviving after or presenting with chronic disease were excluded.

2.3.2 Intervention The duration for including RCTs was an AET intervention ≥12 weeks, the minimum time to affect lipid profiles.[60] We included RCTs of either prescribed steady state or interval AET which employed a moderate intensity effort ≥40% VO_{2MAX}. At least 40% VO_{2MAX} is recommended for sedentary individuals.[61 62] No restrictions were placed on AET session time or type. We included RCTs where effort levels could be estimated if not specifically reported. We excluded studies with <50% intervention and control group adherence. Studies using an isometric, resistance- or combined-training intervention, or life-style, dietary or pharmaceutical interventions, without separate AET interventions as comparators against a non-exercising control group, were excluded. Studies comparing multiple AET protocols without a non-exercising control group as comparator were excluded.

2.3.3 Comparator We evaluated AET interventions against a non-exercising control group.

2.3.4 Outcomes Studies were included if pre-post measurements of the SLP for intervention and control groups were reported. Measurements given in mg/dL were converted to mmol/L by using the conversion factors 0.02586 for TC, HDL-C, and LDL-C, and 0.1129 for TRG.[63] We emailed lead authors of included RCTs for missing values of outcomes. Any outcome data presented graphically were converted to numerical values using WebPlotDigitzer (Version 4.2, 2019) by VN and AP independently.

2.4 Data Extraction Included RCTs were randomly divided between two teams (ET and VN; AM and GNW). Each team member independently extracted the data to a pre-established data extraction form designed by GNW. Each team member reviewed the other team member's data extraction for accuracy. GNW was consulted in the case of disagreement. For each RCT the following data was extracted: 1) author(s), year of publication and study design; 2) demographic and clinical characteristics; 3) AET intervention and non-exercising control protocols; 4) intervention and control group pre-post intervention measurements for any SLP components; and 5) main findings. Data extracted included any of pre-post intervention and control group mean (M) or mean difference (MD), standard deviation (SD) or change in SD, standard error (SE) or change in SE, within- or between group *P* values or change in *P* values, and 95% within- or between group confidence intervals (CI) or change in CIs.

2.5 Study Quality Each RCT was assessed for study quality using the validated Tool for the Assessment of Study Quality and Reporting in Exercise (TESTEX),[64] a 15-point scale specific to exercise training studies. A score ≥10 indicates a better study quality and reporting[65]. Within-study risk of bias was determined by evaluating 7 factors (see SM Table 3), and awarded either low, medium or high within-study risk of bias scores. The RCTs were randomly distributed to

ET and GNW for study quality data extraction. Data sheets were cross-checked by ET and GNW for accuracy. The results were reviewed by AM and confirmed.

2.6 Data Synthesis Statistical analyses were conducted in Comprehensive Meta-Analysis (CMA) 3.0 (Biostat, Inc., New Jersey, USA). We used a continuous univariate random effects model[66] with a Hartung-Knapp-Sidik-Jonkman adjustment[67] to estimate change in outcome measures. We estimated the change in SLP outcomes using the effects measures of raw MD, a 5% level of significance, and a 95% CI. Reported effects measures for each of intervention and control groups, whether intention-to-treat or analysis-by-protocol, were pooled when at least two effects measures were provided. Where possible, we calculated these values when not reported. As necessary, the raw MD was calculated by subtracting $M_{pre\text{-}treatment}$ from $M_{post\text{-}treatment}$. The SD of the MD was calculated as follows: SD = square root [$(SD_{pre\text{-}treatment})^2 + (SD_{post\text{-}treatment})^2 - (2r \times SD_{pre\text{-}treatment} \times SD_{post\text{-}treatment})$], assuming a correlation coefficient r = 0.5, considered a conservative estimate.[68]. The data sets were divided equally between GNW and NS who independently entered the data in CMA. GNW and NS then checked each other's CMA files for accuracy prior to performing analyses.

2.6.1 Meta-analysis and Sub-analyses A cumulative random univariate MA was conducted in CMA to estimate the ES over time for each lipid comprising the SLP (TC, TRG, HDL-C, and LDL-C). In each cumulative MA, RCTs were sorted chronologically according to year of publication. Sub-analyses were conducted in CMA for study quality using TESTEX scores (RCTs with a score ≥10) and within-study bias scores (low to medium). A leave-one-out (K-1, where K = total number of pooled RCTs, and each RCT is excluded once) sensitivity analysis for each lipid outcomes was performed to detect the influence of each RCT on the ES of pooled data.[69]

2.6.2 Heterogeneity Using CMA, heterogeneity was quantified for the Q statistic, and the corresponding *P* value, τ^2, τ, and I^2.[66] The Q statistic, and the corresponding *P* value, compared the differences among the calculated ES; τ^2 measured absolute between-study heterogeneity and the estimated SD (τ).[66] The relative measure of heterogeneity I^2 ranges from 0% (complete homogeneity) to 100% (complete heterogeneity).[70] Pooled analysis 95% CI boundaries were used to detect outliers where heterogeneity was statistically signficant.[71]

2.6.3 Small-study Effects We used CMA to examine small-study effects and detect the likelihood of missing studies. Duval and Tweedie's trim-and-fill, Egger's regression test, Begg and Mezumdar's rank correlation test, the Classic Failsafe N, and precision and standard error funnel plots, were used to assess possible small-study effects. Data was entered into CMA by GNW and NS independently and cross-checked for accuracy. MW reviewed the analyses.

2.6.4 Meta-regression Meta-regression was conducted in CMA without adjustment for *P* values using a random effects restricted maximum likelihood model with a Hartung-Knapp adjustment to determine whether any *a priori* covariates could explain changes in statistically significant ES. *A priori* AET intervention covariates included intensity (percentage of VO_{2MAX}), minutes per session, sessions per week, and duration (weeks). These variables have been shown to influence lipid outcomes.[16 32 33] Other *a priori* covariates were year of publication (potential for improved laboratory testing in recent RCTs), total study participants N (potential for under-powered studies to influence outcomes), and TESTEX study quality and risk-of-bias scores (potential for better quality RCTs to influence outcomes). Covariate data was entered in CMA by GNW and validated by NS and MW.

3.0 RESULTS

The flow of papers through the search and inclusion process is presented in Figure 6.1.[58]

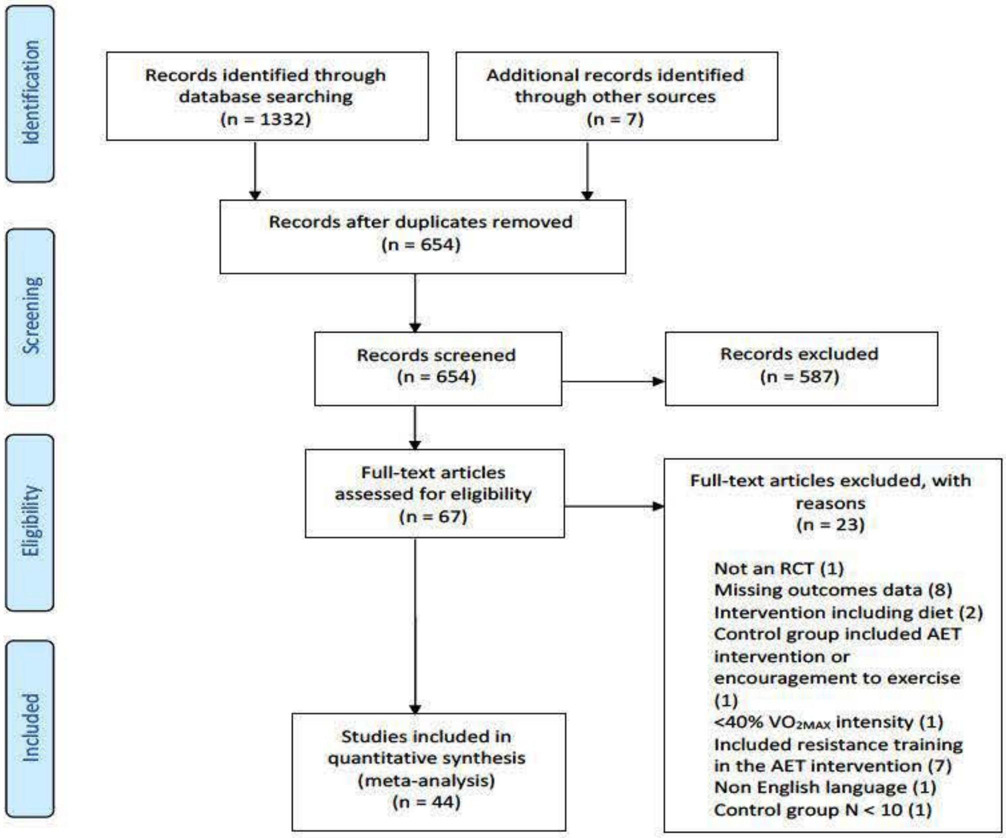


Figure 6.1 PRISMA flow diagram.[58]

Combined searches generated a total of 1339 articles. After removal of duplicates and exclusion of articles based on abstract and title, 67 full-text articles remained for screening against inclusion and exclusion criteria. We contacted 7 lead authors and three provided data as requested. Screening resulted in the inclusion of 44 articles for data extraction,[18 72-112] with 48 data sets to be pooled.

3.1 Study, Participant, and Intervention Characteristics Participant and intervention details of included RCTs are provided in Table 6.1.

Study	Total (N)	Exercise (N)	Control (N)	Gender	Age (years)	Duration (weeks)	Intensity (VO_{2max})	Frequency	Minutes / session
Alvarez 2016	23	13	10	F	35 - 55	16	80%	3.0	29
Anderssen 1995	92	49	43	Mx	35 - 55	52	60%	3.0	60
Arija 2017	364	260	104	Mx	>55	36	50%	2.0	60
Cao 2019	28	13	15	F	>55	12	80%	3.0	60
Chan 2018	164	82	82	Mx	>55	12	50%	3.3	43
Choi 2012	75	38	37	F	35 - 55	12	50%	5.0	60
Conners 2019	26	13	13	Mx	>55	12	48%	3.0	15
Dai 2019	69	34	35	Mx	>55	104	60%	3.0	60
Doğan Dede 2015	60	30	30	Mx	35 - 55	12	68%	3.0	30
Fang 2019	75	37	38	Mx	35 - 55	12	55%	3.0	60
Farag 2019	60	30	30	Mx	35 - 55	12	55%	3.0	60
Farinatti 2016	43	29	14	Mx	35 - 55	64	55%	3.0	30
Gordon 2008	154	77	77	Mx	>55	24	40%	5.0	60
Gram 2010	44	22	22	Mx	>55	16	50%	1.5	45
Jiang 2019 female	24	11	13	F	>55	16	80%	3.0	80
Jiang 2019 male	25	14	11	M	>55	16	80%	3.0	80
Kadoglou 2009	47	23	24	Mx	>55	16	67%	4.0	40
Kang 2016	23	12	11	F	35 - 55	12	52%	5.0	40
Kim 2012	30	15	15	F	35 - 55	16	65%	3.0	60
Laaksonen 2000	42	20	22	M	<35	12	70%	4.0	45
Labrunée 2012	23	11	12	Mx	35 - 55	12	75%	7	30
Lambers 2008	29	18	11	Mx	>55	12	72%	3.0	50
Lavrencic 2000	29	14	15	M	35 - 55	12	67%	3.0	30
Lehmann 1995	29	16	13	Mx	>55	12	50%	3.0	30
Ligtenberg 1997	51	25	26	Mx	>55	26	70%	3.0	50
Madden 2013	52	25	27	Mx	>55	24	60%	3.0	40
Motoyama 1995	30	15	15	Mx	>55	39	50%	5.2	30
Paolillo 2017	20	10	10	F	35 - 55	26	80%	2.0	45
Phing 2017	123	35	88	Mx	35 - 55	16	60%	1.0	60
Raz 1994	38	19	19	Mx	>55	12	65%	2.6	54
Ronnemaa 1988	25	13	12	Mx	35 - 55	17	70%	6.0	45
Shakil-ur-Rehman 2017	102	51	51	Mx	35 - 55	25	60%	3.0	90
Sigal 2007	123	60	63	Mx	35 - 55	22	75%	2.4	45
Slentz 2007 (high vol VICT)	84	66	18	Mx	35 - 55	26	73%	3.6	58
Slentz 2007 (low vol MICT)	72	54	18	Mx	35 - 55	26	48%	3.5	58
Slentz 2007 (low vol VICT)	83	65	18	Mx	35 - 55	26	73%	2.9	43
Smutok 1993	23	13	10	M	35 - 55	20	80%	3.0	30
Stefanick 1998 (females)	88	43	45	F	>55	52	50%	2.5	60

Study	Total (N)	Exercise (N)	Control (N)	Gender	Age (years)	Duration (weeks)	Intensity (VO_{2max})	Frequency	Minutes / session
Stefanick 1998 (males)	93	47	46	M	35 - 55	52	50%	2.5	60
Sykes 2004	36	24	12	Mx	35 - 55	12	50%	1.0	45
Thompson 2010	41	20	21	M	35 - 55	24	59%	3.7	48
Van den Eynde 2020	84	44	40	Mx	>55	12	65%	3.0	45
Venojärvi 2013	79	39	40	M	35 - 55	12	50%	1.9	54
Verissimo 2002	63	31	32	Mx	>55	35	55%	3.0	50
Vinetti 2015	20	10	10	M	>55	52	65%	8.2	25
Watkins 2003	25	14	11	Mx	>55	26	77%	3.4	55
Wedell-Neergaard 2018	27	14	13	Mx	>55	12	50%	3.0	45
Yavari 2012	30	15	15	Mx	35 - 55	52	60%	2.4	40

Age: in years; F: females; M: males; Mx: mixed genders; MetS: metabolic syndrome factors; HDL-C: high-density lipoprotein cholesterol; HIT: high intensity; HIIT: high intensity interval training; KKW: kcal/kg/week; LDL-C: low-density lipoprotein cholesterol; LIT: light intensity; MICT: moderate intensity continuous training; N: number; TC: total cholesterol; TRG: triglycerides; Frequency: sessions per week.

Table 6.1 Study, Participant, Intervention, and Outcomes Attributes

Total participants numbered 2990 (exercise: 1633; control: 1357). Eight RCTs of 311 participants were female only, 8 RCTs of 352 participants were male only, and the remaining RCTs of 2327 participants included both genders. Participants under 35 years numbered 42, between 35–55 years there were 1481 participants, and 1467 participants were over 55 years. Studies stated that all participants were sedentary before starting interventions.

Exercise included weight-bearing activities such as running or walking on treadmills or outdoors, circuit training with no or minimal resistance components, and non weight-bearing activities such as swimming, cycling, and ergocycle. Aerobic exercise intensity ranged from 40-80% VO_{2MAX}. Studies included supervised and unsupervised training sessions, with unchanged or progressive effort increments in response to training adaptations, as well as measures of effort clinically- or self-monitored, and reported via digital device or training logs, see SM Tables 6.6-6.7. Studies reported that control groups were instructed not to exercise.

3.2 Study quality and reporting A median TESTEX score of 10 (from maximum score of 15; range 7 to 15) was derived, see SM Table 6.6. Within-study risk of bias was mainly low or medium, see SM Table 6.7. Sub-analyses using TESTEX scores did not change significance for any lipid, see SM Figures 6.10-6.13.

3.3 Lipid Extraction Methodology The included RCTs extracted blood from individuals in fasted states and in seated or supine positions thus no RCT was excluded (data not shown).

3.4 Estimated Effect Size of AET

3.4.1 Total Cholesterol Aerobic exercise training significantly reduced TC, with a minimum ES of -0.19 mmol/L (95% CI -0.26, -0.12) to a maximum ES of -0.29 mmol/L (95% CI -0.36, -0.21) across all analyses (*P*<.001). Leave-one-out (K-1) analysis did not affect significance, see SM Tables 6.8-6.9. Statistically significant heterogeneity suggested the presence of outliers. Outliers were revealed using pooled analysis 95% CI boundaries, see SM Table 6.10. Removal of outlier RCTs[93 96 113] caused the previously highest weighted study[92] to be re-weighted 83%; this study was also removed to test for significance and ES changes. Sub-analysis using TESTEX scores resulted in no change to significance but reduced ES by 0.02 mmol/L. Summary statistics of the effect of AET on TC according to analysis are presented in Table 6.2. The chronological positive impact of AET on TC is shown in the cumulative random univariate MA of all included RCTs in Figure 6.2, and with influencer and outlier RCTs removed in Figure 6.3.

3.4.2 Triglycerides Aerobic exercise training significantly reduced TRG, with the ES ranging from -0.17 mmol/L (95% CI -0.19,-0.14) to -0.18 mmol/L (95% CI -0.24, -0.13) across all analyses (*P*<.001). Leave-one-out (K-1) analysis did not alter significance, however one study[92] was weighted 79% (see SM Tables 6.8-6.9) and was removed, resulting in an increased ES. Sub-analysis using TESTEX scores resulted in no change to significance nor ES. Summary statistics of the effect of AET on TRG according to analysis are presented in Table 6.2. The chronological positive impact of AET on TRG is shown in the cumulative random univariate MA of all included RCTs in Figure 6.4, and with the influencer RCT removed in Figure 6.5.

3.4.3 High-Density Lipoprotein Cholesterol Aerobic exercise training significantly raised HDL-C, with the ES ranging from 0.05 mmol/L (95% CI 0.03, 0.07) to 0.08 mmol/L (95% CI 0.05, 0.010) across all analyses (*P*<.001). Leave-one-out (K-1) analysis did not affect significance, see SM Tables 6.8-6.9. Statistically significant heterogeneity suggested the presence of outliers. Outliers were revealed using pooled analysis 95% CI boundaries, see SM Table 6.10. Removal of outlier RCTs[77 86 101] caused one study[92] to be weighted 49%. This study was also removed to test for significance and ES changes. Sub-analysis using TESTEX scores resulted in no change to significance but reduced ES by 0.01 mmol/L. Summary statistics of the effect of AET on HDL-C according to analysis are presented in Table 6.2. The chronological positive impact of AET on HDL-C is shown in the cumulative random univariate MA of all included RCTs in Figure 6.6, and with influencer and outlier RCTs removed in Figure 6.7.

3.4.4 Low-density Lipoprotein Cholesterol Aerobic exercise training significantly reduced LDL-C, by -0.12 mmol/L (95% CI -0.16, -0.9) to -0.20 mmol/L (95% CI -0.25, -0.14), across all analyses (*P*<.001). Leave-one-out (K-1) analysis did not alter significance, however one study[92] was weighted 49% (see SM Tables 6.8-6.9) and was removed, resulting in an increased ES. Sub-analysis using TESTEX scores resulted in no change to significance but reduced ES by 0.03 mmol/L. Summary statistics of the effect of AET on LDL-C according to analysis are presented in Table 6.2. The chronological positive impact of AET on LDL-C is shown in the cumulative random univariate MA of all included RCTs in Figure 6.8, and with the influencer RCT removed in Figure 6.9.

Univariate random, raw mean difference, K-H-S-J adjustment, 95% CI, 5% significance		Point Estimate (mmol/L)	Standard Error	Variance	Lower CI (mmol/L)	Upper CI (mmol/L)	*P* value	Exercise N	Control N	Study Quality (median)	Q statistic	I^2	*P* value
TC	SQ TESTEX score ≥ 10*	-0.19	0.04	0.00	-0.26	-0.12	<.001	1159	863	11	13.01	0	>.99
	No outliers, no influencer (K-4)	-0.21	0.03	0.00	-0.27	-0.14	<.001	1298	1000	10.5	19.61	0	.99
	No influencer (K-1)	-0.29	0.04	0.00	-0.37	-0.20	<.001	1424	1127	11	58.39	32	.03
	No outliers (K-3)	-0.31	0.01	0.00	-0.33	-0.28	<.001	1327	1014	10	29.17	0	.88
	All studies (K-0)	-0.29	0.04	0.00	-0.36	-0.21	<.001	1453	1141	10.5	61.03	33	.02
TRG	SQ TESTEX score ≥ 10*	-0.17	0.03	0.00	-0.23	-0.11	<.001	1231	985	11	27.02	0	.57
	No influencer (K-1)	-0.18	0.03	0.00	-0.24	-0.13	<.001	1382	1133	10	31.85	0	.75
	All studies (K-0)	-0.17	0.01	0.00	-0.19	-0.14	<.001	1411	1147	10	32.20	0	.77
HDL-C	SQ TESTEX score ≥ 10*	0.05	0.01	0.00	0.03	0.07	<.001	1189	949	11	33.77	11.08	.29
	No outliers, no influencer (K-4)	0.06	0.01	0.00	0.04	0.07	<.001	1424	1176	10	41.27	3	.41
	No influencer (K-1)	0.08	0.01	0.00	0.05	0.11	<.001	1463	1213	10	94.01	54	<.001
	No outliers (K-3)	0.06	0.01	0.00	0.04	0.07	<.001	1453	1190	10	41.33	1	.46
	All studies (K-0)	0.08	0.01	0.00	0.05	0.10	<.001	1492	1227	10	94.36	53	<.001
LDL-C	TESTEX score ≥ 10*	-0.17	0.03	0.00	-0.23	-0.11	<.001	1159	873	11	14.72	0	.99
	No influencer (K-1)	-0.20	0.03	0.00	-0.25	-0.14	<.001	1409	1114	10	23.91	0	.98
	All studies (K-0)	-0.12	0.02	0.00	-0.16	-0.09	<.001	1438	1128	10	39.24	0	.55

CI: confidence interval; HDL-C: high-density lipoprotein cholesterol; K-H-S-J: Knapp-Hartung-Sidik-Jonkman; N: per group study population; K-1 etc: number of studies removed from all studies; LDL-C: low-density lipoprotein cholesterol; SQ: study quality; TC: total cholesterol; TRG: triglycerides; * conducted with outliers, if present, and influencer removed.

Table 6.2 Effect of AET on the SLP according to pooled analysis by study quality, removal of outliers and influencer RCTs, and including all studies, showing effect size estimate, significance, median study quality TESTEX score, and general heterogeneity statistics

Table [3]

3.5 Heterogeneity Statistically significant relative heterogeneity was present for TC and HDL-C; after removal of outliers relative heterogeneity fell to zero. Neither the degree of absolute between-study heterogeneity (τ^2) or the relative heterogeneity (I^2) for each analysed lipid outcome indicated that RCTs should not be pooled, or that significance testing of pooled RCTs should not be undertaken, see Table 6.3.

Analyses by outcome according to inclusion/ exclusion of RCTs		Heterogeneity				τ^2			
		Q-value	Df [Q]	*P* value	I^2 %	τ^2	Standard Error	Variance	τ
TC	K-4 (no outliers, no influencer)	19.61	37	.99	0	0.00	0.01	0.00	0.00
	K-1 (no influencer)	58.39	40	**.03**	31.50	0.02	0.02	0.00	0.14
	K-3 (no outliers)	29.17	38	.88	0	0.00	0.01	0.00	0.00
	K-0 (all RCTs)	61.03	41	**.02**	32.82	0.01	0.01	0.00	0.11
TRG	K-1 (no influencer)	31.85	38	.75	0	0.00	0.01	0.00	0.00
	K-0 (all RCTs)	32.20	39	.77	0	0.00	0.00	0.00	0.00
HDL-C	K-4 (no outliers, no influencer)	41.27	40	.41	3.09	0.00	0.00	0.00	0.01
	K-1 (no influencer)	94.01	43	**<.001**	54.26	0.00	0.00	0.00	0.01
	K-3 (no outliers)	41.33	41	.46	1	0.00	0.00	0.00	0.00
	K-0 (all RCTs)	94.36	44	**<.001**	53	0.00	0.00	0.00	0.05
LDL-C	K-1 (no influencer)	23.91	40	.98	0	0.00	0.001	0.00	0.00
	K-0 (all RCTs)	39.24	41	.55	0	0.00	0.00	0.00	0.00

HDL-C: high-density lipoprotein cholesterol; K-1 etc: number of studies removed from all studies (K); LDL-C: low-density lipoprotein cholesterol; RCTs: randomised controlled trials; TC: total cholesterol; TRG: triglycerides.

Table 6.3 Relative and absolute between study heterogeneity table showing analyses by lipid outcome and change in heterogeneity measures according to inclusion/exclusion of outlier and influence RCTs.

Model	Study name	Outcome	Cumulative statistics						Cumulative sample size		Study Quality	Weight (Random)	
			Point	Standard error	Variance	Lower limit	Upper limit	p-Value	Exercise	Control		Weight (Random)	Relative weight
	Ronnemaa 1988	TC	-0.270	0.422	0.178	-1.098	0.558	0.523	13	12	8	5.27	0.71
	Smutok 1993	TC	-0.126	0.289	0.083	-0.692	0.440	0.662	26	22	9	5.95	1.51
	Raz 1994	TC	-0.115	0.218	0.048	-0.543	0.313	0.598	45	41	14	8.16	2.60
	Anderssen 1995	TC	-0.057	0.105	0.011	-0.264	0.149	0.585	94	84	11	38.62	7.79
	Motoyama 1995	TC	-0.076	0.100	0.010	-0.272	0.121	0.449	109	99	12	8.26	8.90
	Ligtenberg 1997	TC	-0.088	0.095	0.009	-0.275	0.099	0.357	134	125	11	9.36	10.16
	Stefanick 1998 (females)	TC	-0.101	0.074	0.005	-0.246	0.044	0.172	177	170	12	39.68	15.50
	Stefanick 1998 (males)	TC	-0.081	0.062	0.004	-0.202	0.041	0.193	224	216	12	41.25	21.04
	Laaksonen 2000	TC	-0.086	0.060	0.004	-0.204	0.032	0.153	244	238	11	12.65	22.74
	Lavrencic 2000	TC	-0.086	0.059	0.004	-0.203	0.030	0.147	258	253	10	6.11	23.56
	Verissimo 2002	TC	-0.110	0.058	0.003	-0.223	0.003	0.056	289	285	8	14.72	25.54
	Watkins 2003	TC	-0.111	0.057	0.003	-0.223	0.002	0.054	303	296	10	3.14	25.96
	Sykes 2004	TC	-0.110	0.057	0.003	-0.221	0.001	0.052	327	308	10	8.16	27.06
	Sigal 2007	TC	-0.104	0.053	0.003	-0.208	0.001	0.053	387	371	15	26.38	30.60
	Slentz 2007 (high vol VICT)	TC	-0.111	0.051	0.003	-0.211	-0.012	0.028	451	390	10	25.61	34.05
	Slentz 2007 (low vol MICT)	TC	-0.121	0.049	0.002	-0.217	-0.026	0.013	502	407	10	25.48	37.47
	Slentz 2007 (low vol VICT)	TC	-0.132	0.047	0.002	-0.223	-0.041	0.005	563	425	10	27.07	41.11
	Gordon 2008	TC	-0.170	0.045	0.002	-0.259	-0.082	0.000	640	502	10	21.42	43.99
	Lambers 2008	TC	-0.172	0.045	0.002	-0.260	-0.084	0.000	658	513	12	5.85	44.77
	Kadoglou 2009	TC	-0.202	0.046	0.002	-0.291	-0.112	0.000	681	537	11	30.18	48.83
	Gram 2010	TC	-0.199	0.044	0.002	-0.285	-0.114	0.000	703	559	13	8.47	49.97
	Thompson 2010	TC	-0.193	0.042	0.002	-0.275	-0.110	0.000	723	580	12	11.58	51.52
	Choi 2012	TC	-0.194	0.042	0.002	-0.276	-0.112	0.000	761	617	10	3.12	51.94
	Kim 2012	TC	-0.238	0.049	0.002	-0.334	-0.141	0.000	776	632	11	25.98	55.43
	Labrunée 2012	TC	-0.235	0.048	0.002	-0.329	-0.141	0.000	787	644	9	4.54	56.04
	Yavari 2012	TC	-0.239	0.047	0.002	-0.332	-0.146	0.000	802	659	12	5.88	56.83
	Madden 2013	TC	-0.237	0.046	0.002	-0.327	-0.147	0.000	827	686	13	6.86	57.76
	Venojärvi 2013	TC	-0.240	0.043	0.002	-0.324	-0.156	0.000	866	726	11	31.75	62.02
	Dogan Dede 2015	TC	-0.238	0.041	0.002	-0.319	-0.158	0.000	896	756	12	15.38	64.09
	Vinetti 2015	TC	-0.244	0.042	0.002	-0.325	-0.162	0.000	906	766	9	4.16	64.65
	Alvarez 2016	TC	-0.238	0.040	0.002	-0.316	-0.160	0.000	919	776	12	22.82	67.72
	Farinatti 2016	TC	-0.260	0.035	0.001	-0.330	-0.191	0.000	948	790	10	85.27	79.18
	Arija 2017	TC	-0.264	0.032	0.001	-0.328	-0.201	0.000	1208	894	15	48.10	85.64
	Paolillo 2017	TC	-0.264	0.032	0.001	-0.326	-0.202	0.000	1218	904	9	5.11	86.33
	Chan 2018	TC	-0.268	0.030	0.001	-0.327	-0.209	0.000	1300	986	13	18.06	88.76
	Wedell-Neergaard 2018	TC	-0.272	0.028	0.001	-0.327	-0.216	0.000	1314	999	9	21.25	91.61
	Cao 2019	TC	-0.275	0.027	0.001	-0.327	-0.222	0.000	1327	1014	10	8.00	92.69
	Dai 2019	TC	-0.281	0.039	0.001	-0.357	-0.206	0.000	1361	1049	11	14.54	94.64
	Fang 2019	TC	-0.288	0.038	0.001	-0.362	-0.213	0.000	1398	1087	9	13.64	96.47
	Farag 2019	TC	-0.290	0.037	0.001	-0.363	-0.216	0.000	1428	1117	10	14.01	98.36
	Jiang 2019 (female)	TC	-0.287	0.037	0.001	-0.360	-0.214	0.000	1439	1130	10	6.45	99.22
	Jiang 2019 (male)	TC	-0.286	0.037	0.001	-0.357	-0.214	0.000	1453	1141	10	5.79	100.00
Random			-0.286	0.037	0.001	-0.357	-0.214	0.000					

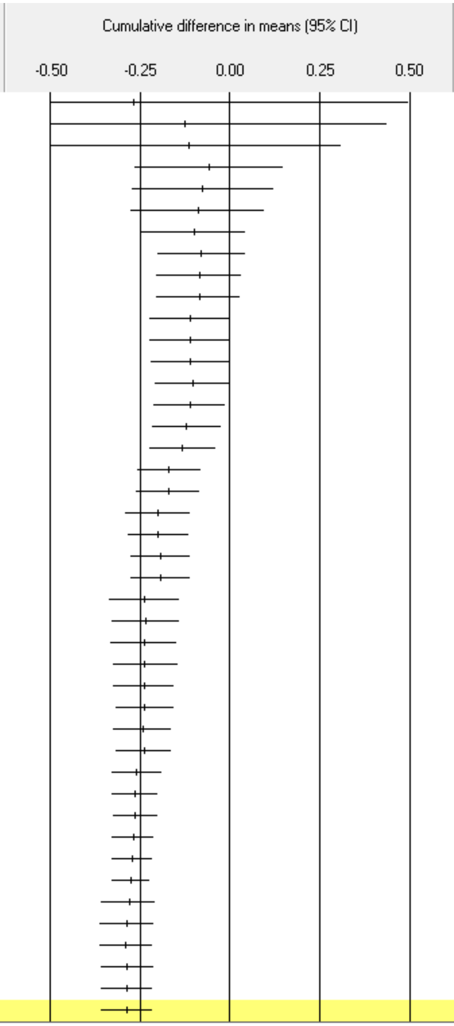


Figure 6.2 Cumulative random effects univariate meta-analysis of TC (K-0: all RCTs)

Model	Study name	Outcome	Cumulative statistics						Cumulative sample size		Study Quality	Weight (Random)	
			Point	Standard error	Variance	Lower limit	Upper limit	p-Value	Exercise	Control		Weight (Random)	Relative weight
	Ronnemaa 1988	TC	-0.270	0.422	0.178	-1.098	0.558	0.523	13	12	8	5.61	0.64
	Smutok 1993	TC	-0.126	0.289	0.083	-0.692	0.440	0.662	26	22	9	6.38	1.36
	Raz 1994	TC	-0.115	0.218	0.048	-0.543	0.313	0.598	45	41	14	9.00	2.38
	Anderssen 1995	TC	-0.057	0.105	0.011	-0.264	0.149	0.585	94	84	11	69.44	10.25
	Motoyama 1995	TC	-0.076	0.100	0.010	-0.272	0.121	0.449	109	99	12	9.13	11.29
	Ligtenberg 1997	TC	-0.088	0.095	0.009	-0.275	0.099	0.357	134	125	11	10.49	12.48
	Stefanick 1998 (females)	TC	-0.101	0.074	0.005	-0.246	0.044	0.172	177	170	12	72.96	20.75
	Stefanick 1998 (males)	TC	-0.081	0.062	0.004	-0.202	0.041	0.193	224	216	12	78.45	29.64
	Laaksonen 2000	TC	-0.086	0.060	0.004	-0.204	0.032	0.153	244	238	11	14.80	31.32
	Lavrencic 2000	TC	-0.086	0.059	0.004	-0.203	0.030	0.147	258	253	10	6.57	32.07
	Verissimo 2002	TC	-0.110	0.058	0.003	-0.223	0.003	0.056	289	285	8	17.72	34.08
	Watkins 2003	TC	-0.111	0.057	0.003	-0.223	0.002	0.054	303	296	10	3.26	34.45
	Sykes 2004	TC	-0.110	0.057	0.003	-0.221	0.001	0.052	327	308	10	9.00	35.47
	Sigal 2007	TC	-0.104	0.053	0.003	-0.208	0.001	0.053	387	371	15	37.86	39.76
	Slentz 2007 (high vol VICT)	TC	-0.111	0.051	0.003	-0.211	-0.012	0.028	451	390	10	36.29	43.87
	Slentz 2007 (low vol MICT)	TC	-0.121	0.049	0.002	-0.217	-0.026	0.013	502	407	10	36.04	47.96
	Slentz 2007 (low vol VICT)	TC	-0.132	0.047	0.002	-0.223	-0.041	0.005	563	425	10	39.29	52.42
	Lambers 2008	TC	-0.134	0.046	0.002	-0.225	-0.044	0.004	581	436	12	6.27	53.13
	Kadoglou 2009	TC	-0.163	0.044	0.002	-0.250	-0.077	0.000	604	460	11	46.21	58.37
	Gram 2010	TC	-0.165	0.044	0.002	-0.251	-0.079	0.000	626	482	13	9.38	59.43
	Thompson 2010	TC	-0.161	0.043	0.002	-0.246	-0.077	0.000	646	503	12	13.36	60.94
	Choi 2012	TC	-0.163	0.043	0.002	-0.247	-0.079	0.000	684	540	10	3.24	61.31
	Labrunée 2012	TC	-0.162	0.043	0.002	-0.246	-0.078	0.000	695	552	9	4.79	61.85
	Yavari 2012	TC	-0.167	0.043	0.002	-0.250	-0.083	0.000	710	567	12	6.30	62.57
	Madden 2013	TC	-0.167	0.042	0.002	-0.250	-0.084	0.000	735	594	13	7.45	63.41
	Venojärvi 2013	TC	-0.178	0.041	0.002	-0.258	-0.099	0.000	774	634	11	49.98	69.08
	Dogan Dede 2015	TC	-0.180	0.040	0.002	-0.259	-0.102	0.000	804	664	12	18.68	71.20
	Vinetti 2015	TC	-0.185	0.040	0.002	-0.263	-0.107	0.000	814	674	9	4.37	71.69
	Alvarez 2016	TC	-0.184	0.039	0.002	-0.260	-0.108	0.000	827	684	12	30.94	75.20
	Arija 2017	TC	-0.197	0.036	0.001	-0.267	-0.126	0.000	1087	788	15	107.53	87.39
	Paolillo 2017	TC	-0.196	0.036	0.001	-0.266	-0.125	0.000	1097	798	9	5.43	88.01
	Chan 2018	TC	-0.199	0.035	0.001	-0.269	-0.130	0.000	1179	880	13	22.79	90.59
	Wedell-Neergaard 2018	TC	-0.202	0.035	0.001	-0.270	-0.134	0.000	1193	893	9	28.11	93.78
	Cao 2019	TC	-0.201	0.035	0.001	-0.269	-0.134	0.000	1206	908	10	8.81	94.78
	Fang 2019	TC	-0.209	0.034	0.001	-0.276	-0.142	0.000	1243	946	9	16.17	96.61
	Farag 2019	TC	-0.213	0.034	0.001	-0.279	-0.146	0.000	1273	976	10	16.70	98.51
	Jiang 2019 (female)	TC	-0.211	0.034	0.001	-0.278	-0.145	0.000	1284	989	10	6.96	99.30
	Jiang 2019 (male)	TC	-0.211	0.034	0.001	-0.277	-0.145	0.000	1298	1000	10	6.20	100.00
Random			-0.211	0.034	0.001	-0.277	-0.145	0.000					

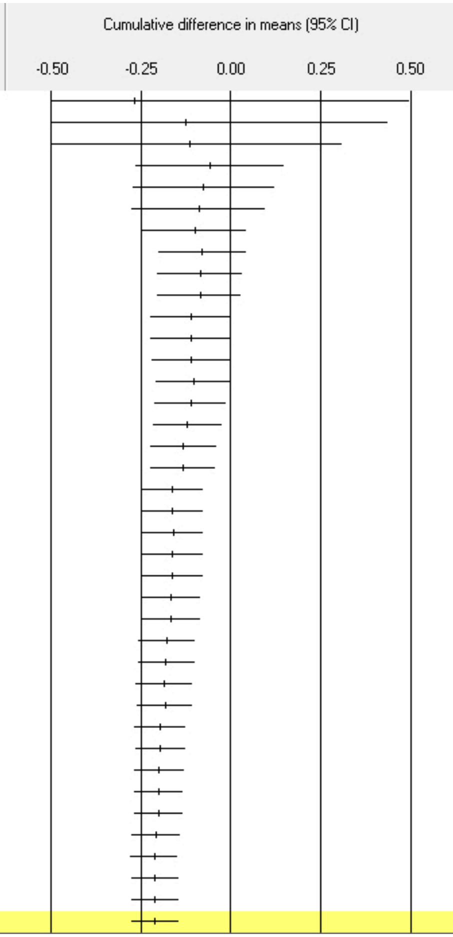
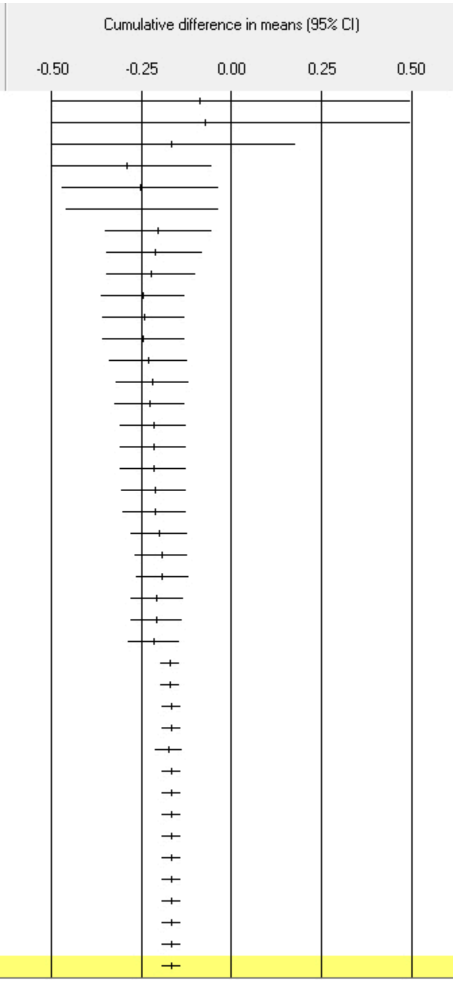


Figure 6.3 Cumulative random effects univariate meta-analysis of TC (K-4: outliers and influencer removed)



Model	Study name	Outcome	Cumulative statistics						Cumulative sample size		Study Quality	Weight (Random)	
			Point	Standard error	Variance	Lower limit	Upper limit	p-Value	Exercise	Control		Weight (Random)	Relative weight
	Ronnemaa 1988	TRG	-0.090	0.393	0.155	-0.861	0.681	0.819	13	12	8	6.46	0.11
	Smutok 1993	TRG	-0.075	0.335	0.112	-0.731	0.582	0.824	26	22	9	2.45	0.15
	Raz 1994	TRG	-0.165	0.176	0.031	-0.511	0.180	0.349	45	41	14	23.24	0.54
	Anderssen 1995	TRG	-0.293	0.122	0.015	-0.532	-0.054	0.016	94	84	11	34.99	1.13
	Motoyama 1995	TRG	-0.255	0.111	0.012	-0.472	-0.038	0.021	109	99	12	14.44	1.38
	Ligtenberg 1997	TRG	-0.248	0.108	0.012	-0.461	-0.036	0.022	134	125	11	3.74	1.44
	Stefanick 1998 (females)	TRG	-0.204	0.075	0.006	-0.352	-0.056	0.007	179	168	12	90.56	2.96
	Stefanick 1998 (males)	TRG	-0.212	0.068	0.005	-0.346	-0.078	0.002	226	214	12	38.51	3.61
	Laaksonen 2000	TRG	-0.224	0.063	0.004	-0.347	-0.101	0.000	246	236	11	39.35	4.28
	Verissimo 2002	TRG	-0.247	0.059	0.003	-0.362	-0.131	0.000	277	268	8	33.53	4.84
	Watkins 2003	TRG	-0.244	0.059	0.003	-0.358	-0.129	0.000	291	279	10	4.49	4.92
	Sykes 2004	TRG	-0.246	0.058	0.003	-0.360	-0.132	0.000	315	291	10	3.34	4.97
	Sigal 2007	TRG	-0.230	0.056	0.003	-0.340	-0.121	0.000	375	354	15	25.30	5.40
	Slentz 2007 (high vol VICT)	TRG	-0.220	0.052	0.003	-0.322	-0.119	0.000	439	373	10	53.27	6.30
	Slentz 2007 (low vol MICT)	TRG	-0.227	0.050	0.003	-0.325	-0.129	0.000	490	390	10	25.93	6.74
	Slentz 2007 (low vol VICT)	TRG	-0.217	0.047	0.002	-0.310	-0.125	0.000	551	408	10	45.83	7.51
	Gordon 2008	TRG	-0.217	0.047	0.002	-0.310	-0.125	0.000	628	485	10	0.40	7.52
	Lambers 2008	TRG	-0.216	0.047	0.002	-0.308	-0.124	0.000	646	496	12	5.42	7.61
	Kadoglou 2009	TRG	-0.214	0.046	0.002	-0.304	-0.123	0.000	669	520	11	13.59	7.84
	Thompson 2010	TRG	-0.213	0.045	0.002	-0.302	-0.124	0.000	689	541	12	19.73	8.17
	Choi 2012	TRG	-0.199	0.040	0.002	-0.279	-0.120	0.000	727	578	10	125.68	10.29
	Kim 2012	TRG	-0.193	0.038	0.001	-0.267	-0.120	0.000	742	593	11	100.33	11.98
	Labrunée 2012	TRG	-0.193	0.037	0.001	-0.267	-0.120	0.000	753	605	9	6.27	12.08
	Yavari 2012	TRG	-0.207	0.037	0.001	-0.279	-0.134	0.000	768	620	12	9.36	12.24
	Venojärvi 2013	TRG	-0.207	0.037	0.001	-0.279	-0.134	0.000	807	660	11	12.50	12.45
	Vinetti 2015	TRG	-0.216	0.036	0.001	-0.287	-0.145	0.000	817	670	9	28.46	12.93
	Farinatti 2016	TRG	-0.171	0.014	0.000	-0.198	-0.145	0.000	846	684	10	4694.33	92.07
	Kang 2016	TRG	-0.171	0.014	0.000	-0.198	-0.145	0.000	858	695	7	10.20	92.24
	Arija 2017	TRG	-0.166	0.013	0.000	-0.192	-0.140	0.000	1118	799	15	160.40	94.94
	Paolillo 2017	TRG	-0.166	0.013	0.000	-0.192	-0.140	0.000	1128	809	9	6.26	95.05
	Phing 2017	TRG	-0.174	0.020	0.000	-0.212	-0.136	0.000	1163	897	10	26.97	95.50
	Chan 2018	TRG	-0.168	0.013	0.000	-0.194	-0.142	0.000	1245	979	13	35.22	96.10
	Wedell-Neergaard 2018	TRG	-0.168	0.013	0.000	-0.194	-0.142	0.000	1259	992	9	15.97	96.37
	Cao 2019	TRG	-0.168	0.013	0.000	-0.194	-0.142	0.000	1272	1007	10	3.66	96.43
	Conners 2019	TRG	-0.167	0.013	0.000	-0.193	-0.142	0.000	1285	1020	14	115.15	98.37
	Dai 2019	TRG	-0.167	0.013	0.000	-0.193	-0.142	0.000	1319	1055	11	9.11	98.52
	Fang 2019	TRG	-0.168	0.013	0.000	-0.193	-0.142	0.000	1356	1093	9	36.01	99.13
	Farag 2019	TRG	-0.168	0.013	0.000	-0.193	-0.142	0.000	1386	1123	10	43.49	99.86
	Jiang 2019 (female)	TRG	-0.168	0.013	0.000	-0.193	-0.142	0.000	1397	1136	10	3.75	99.93
	Jiang 2019 (male)	TRG	-0.168	0.013	0.000	-0.193	-0.142	0.000	1411	1147	10	4.41	100.00
Random			-0.168	0.013	0.000	-0.193	-0.142	0.000					

Figure 6.4 Cumulative random effects univariate meta-analysis of TRG (K-0: all RCTs)

Model	Study name	Outcome	Point	Standard error	Variance	Lower limit	Upper limit	p-Value	Exercise	Control	Study Quality	Weight (Random)	Relative weight
			Cumulative statistics						Cumulative sample size			Weight (Random)	
	Ronnemaa 1988	TRG	-0.090	0.393	0.155	-0.861	0.681	0.819	13	12	8	6.46	0.52
	Smutok 1993	TRG	-0.075	0.335	0.112	-0.731	0.582	0.824	26	22	9	2.45	0.72
	Raz 1994	TRG	-0.165	0.176	0.031	-0.511	0.180	0.349	45	41	14	23.24	2.60
	Anderssen 1995	TRG	-0.293	0.122	0.015	-0.532	-0.054	0.016	94	84	11	34.99	5.42
	Motoyama 1995	TRG	-0.255	0.111	0.012	-0.472	-0.038	0.021	109	99	12	14.44	6.59
	Ligtenberg 1997	TRG	-0.248	0.108	0.012	-0.461	-0.036	0.022	134	125	11	3.74	6.89
	Stefanick 1998 (females)	TRG	-0.204	0.075	0.006	-0.352	-0.056	0.007	179	168	12	90.56	14.21
	Stefanick 1998 (males)	TRG	-0.212	0.068	0.005	-0.346	-0.078	0.002	226	214	12	38.51	17.32
	Laaksonen 2000	TRG	-0.224	0.063	0.004	-0.347	-0.101	0.000	246	236	11	39.35	20.50
	Verissimo 2002	TRG	-0.247	0.059	0.003	-0.362	-0.131	0.000	277	268	8	33.53	23.21
	Watkins 2003	TRG	-0.244	0.059	0.003	-0.358	-0.129	0.000	291	279	10	4.49	23.57
	Sykes 2004	TRG	-0.246	0.058	0.003	-0.360	-0.132	0.000	315	291	10	3.34	23.84
	Sigal 2007	TRG	-0.230	0.056	0.003	-0.340	-0.121	0.000	375	354	15	25.30	25.89
	Slentz 2007 (high vol VICT)	TRG	-0.220	0.052	0.003	-0.322	-0.119	0.000	439	373	10	53.27	30.19
	Slentz 2007 (low vol MICT)	TRG	-0.227	0.050	0.003	-0.325	-0.129	0.000	490	390	10	25.93	32.28
	Slentz 2007 (low vol VICT)	TRG	-0.217	0.047	0.002	-0.310	-0.125	0.000	551	408	10	45.83	35.99
	Gordon 2008	TRG	-0.217	0.047	0.002	-0.310	-0.125	0.000	628	485	10	0.40	36.02
	Lambers 2008	TRG	-0.216	0.047	0.002	-0.308	-0.124	0.000	646	496	12	5.42	36.46
	Kadoglou 2009	TRG	-0.214	0.046	0.002	-0.304	-0.123	0.000	669	520	11	13.59	37.55
	Thompson 2010	TRG	-0.213	0.045	0.002	-0.302	-0.124	0.000	689	541	12	19.73	39.15
	Choi 2012	TRG	-0.199	0.040	0.002	-0.279	-0.120	0.000	727	578	10	125.68	49.30
	Kim 2012	TRG	-0.193	0.038	0.001	-0.267	-0.120	0.000	742	593	11	100.33	57.41
	Labrunée 2012	TRG	-0.193	0.037	0.001	-0.267	-0.120	0.000	753	605	9	6.27	57.91
	Yavari 2012	TRG	-0.207	0.037	0.001	-0.279	-0.134	0.000	768	620	12	9.36	58.67
	Venojärvi 2013	TRG	-0.207	0.037	0.001	-0.279	-0.134	0.000	807	660	11	12.50	59.68
	Vinetti 2015	TRG	-0.216	0.036	0.001	-0.287	-0.145	0.000	817	670	9	28.46	61.98
	Kang 2016	TRG	-0.214	0.036	0.001	-0.284	-0.144	0.000	829	681	7	10.20	62.80
	Arija 2017	TRG	-0.178	0.033	0.001	-0.242	-0.114	0.000	1089	785	15	160.40	75.76
	Paolillo 2017	TRG	-0.177	0.033	0.001	-0.241	-0.113	0.000	1099	795	9	6.26	76.27
	Phing 2017	TRG	-0.196	0.034	0.001	-0.262	-0.130	0.000	1134	883	10	26.97	78.45
	Chan 2018	TRG	-0.189	0.032	0.001	-0.252	-0.127	0.000	1216	965	13	35.22	81.29
	Wedell-Neergaard 2018	TRG	-0.185	0.031	0.001	-0.246	-0.124	0.000	1230	978	9	15.97	82.58
	Cao 2019	TRG	-0.186	0.031	0.001	-0.248	-0.125	0.000	1243	993	10	3.66	82.88
	Conners 2019	TRG	-0.182	0.030	0.001	-0.240	-0.124	0.000	1256	1006	14	115.15	92.18
	Dai 2019	TRG	-0.181	0.029	0.001	-0.239	-0.123	0.000	1290	1041	11	9.11	92.92
	Fang 2019	TRG	-0.182	0.029	0.001	-0.239	-0.125	0.000	1327	1079	9	36.01	95.83
	Farag 2019	TRG	-0.181	0.029	0.001	-0.237	-0.126	0.000	1357	1109	10	43.49	99.34
	Jiang 2019 (female)	TRG	-0.182	0.028	0.001	-0.238	-0.126	0.000	1368	1122	10	3.75	99.64
	Jiang 2019 (male)	TRG	-0.183	0.028	0.001	-0.238	-0.127	0.000	1382	1133	10	4.41	100.00
Random			-0.183	0.028	0.001	-0.238	-0.127	0.000					

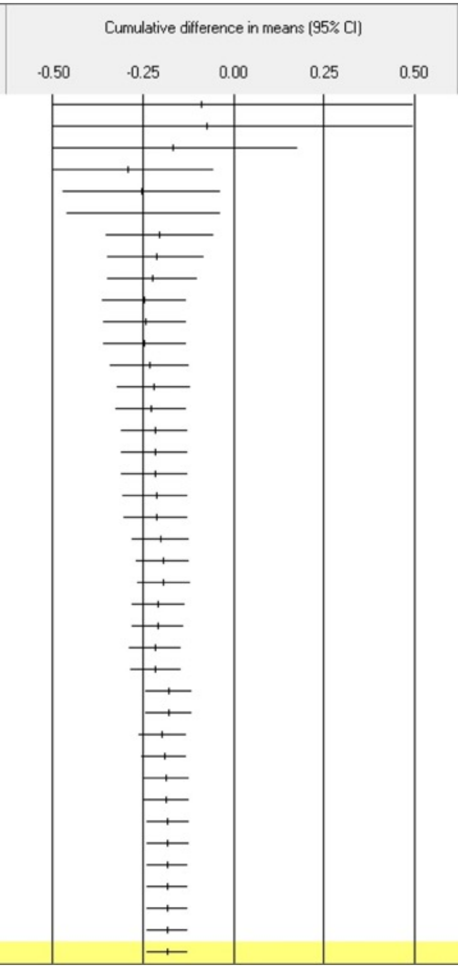


Figure 6.5 Cumulative random effects univariate meta-analysis of TRG (K-1: influencer removed)

Model	Study name	Outcome	Cumulative statistics: Point	Standard error	Variance	Lower limit	Upper limit	p-Value	Cumulative sample size: Exercise	Control	Study Quality	Weight (Random)	Relative weight
	Ronnemaa 1988	HDL-C	0.030	0.135	0.018	-0.235	0.295	0.825	13	12	8	48.67	0.68
	Smutok 1993	HDL-C	0.028	0.084	0.007	-0.136	0.191	0.742	26	22	9	74.09	1.72
	Raz 1994	HDL-C	0.016	0.063	0.004	-0.108	0.140	0.803	45	41	14	85.49	2.91
	Anderssen 1995	HDL-C	0.024	0.024	0.001	-0.023	0.070	0.317	94	84	11	347.58	7.78
	Motoyama 1995	HDL-C	0.085	0.064	0.004	-0.041	0.211	0.188	109	99	12	126.09	9.54
	Ligtenberg 1997	HDL-C	0.081	0.047	0.002	-0.010	0.173	0.081	134	125	11	201.56	12.36
	Stefanick 1998 (females)	HDL-C	0.068	0.034	0.001	0.002	0.135	0.045	177	170	12	288.27	16.39
	Stefanick 1998 (males)	HDL-C	0.057	0.025	0.001	0.009	0.105	0.021	224	216	12	361.28	21.45
	Laaksonen 2000	HDL-C	0.051	0.022	0.000	0.007	0.094	0.022	244	238	11	197.50	24.21
	Lavrencic 2000	HDL-C	0.048	0.021	0.000	0.007	0.089	0.021	258	253	10	78.06	25.30
	Verissimo 2002	HDL-C	0.060	0.022	0.000	0.016	0.103	0.007	289	285	8	136.38	27.21
	Watkins 2003	HDL-C	0.060	0.021	0.000	0.018	0.102	0.005	303	296	10	58.28	28.03
	Sykes 2004	HDL-C	0.061	0.020	0.000	0.020	0.101	0.003	327	308	10	66.80	28.96
	Sigal 2007	HDL-C	0.052	0.019	0.000	0.016	0.089	0.005	387	371	15	283.70	32.93
	Slentz 2007 (high vol VICT)	HDL-C	0.051	0.017	0.000	0.018	0.084	0.003	451	390	10	238.38	36.26
	Slentz 2007 (low vol MICT)	HDL-C	0.047	0.016	0.000	0.016	0.077	0.003	502	407	10	256.57	39.85
	Slentz 2007 (low vol VICT)	HDL-C	0.044	0.014	0.000	0.016	0.072	0.002	563	425	10	232.44	43.11
	Lambers 2008	HDL-C	0.045	0.014	0.000	0.017	0.072	0.001	581	436	12	65.32	44.02
	Kadoglou 2009	HDL-C	0.044	0.013	0.000	0.018	0.069	0.001	604	460	11	206.79	46.91
	Gram 2010	HDL-C	0.043	0.012	0.000	0.019	0.067	0.000	626	482	13	176.49	49.38
	Thompson 2010	HDL-C	0.043	0.012	0.000	0.020	0.066	0.000	646	503	12	149.06	51.47
	Choi 2012	HDL-C	0.043	0.011	0.000	0.022	0.064	0.000	684	540	10	285.94	55.47
	Kim 2012	HDL-C	0.044	0.011	0.000	0.023	0.065	0.000	699	555	11	88.18	56.70
	Labrunée 2012	HDL-C	0.067	0.018	0.000	0.032	0.101	0.000	710	567	9	63.17	57.58
	Yavari 2012	HDL-C	0.065	0.017	0.000	0.031	0.099	0.000	725	582	12	103.85	59.04
	Madden 2013	HDL-C	0.066	0.017	0.000	0.032	0.099	0.000	750	609	13	18.27	59.29
	Dogan Dede 2015	HDL-C	0.063	0.017	0.000	0.031	0.096	0.000	780	639	12	123.21	61.02
	Vinetti 2015	HDL-C	0.063	0.016	0.000	0.031	0.095	0.000	790	649	9	63.22	61.90
	Alvarez 2016	HDL-C	0.073	0.017	0.000	0.039	0.107	0.000	803	659	12	145.15	63.93
	Farinatti 2016	HDL-C	0.067	0.014	0.000	0.039	0.095	0.000	832	673	10	438.44	70.07
	Kang 2016	HDL-C	0.069	0.014	0.000	0.041	0.097	0.000	844	684	7	112.31	71.64
	Arija 2017	HDL-C	0.066	0.013	0.000	0.040	0.093	0.000	1104	788	15	287.48	75.66
	Paolillo 2017	HDL-C	0.065	0.013	0.000	0.039	0.091	0.000	1114	798	9	66.38	76.59
	Phing 2017	HDL-C	0.069	0.013	0.000	0.043	0.094	0.000	1149	886	10	318.51	81.04
	Shakil-ur-Rehman 2017	HDL-C	0.069	0.013	0.000	0.045	0.094	0.000	1200	937	9	260.67	84.69
	Chan 2018	HDL-C	0.068	0.012	0.000	0.044	0.093	0.000	1282	1019	13	127.60	86.48
	Wedell-Neergaard 2018	HDL-C	0.067	0.012	0.000	0.044	0.091	0.000	1296	1032	9	203.14	89.32
	Cao 2019	HDL-C	0.069	0.012	0.000	0.046	0.093	0.000	1309	1047	10	109.26	90.85
	Conners 2019	HDL-C	0.073	0.012	0.000	0.049	0.096	0.000	1322	1060	14	165.70	93.16
	Dai 2019	HDL-C	0.075	0.012	0.000	0.052	0.099	0.000	1356	1095	11	90.75	94.43
	Fang 2019	HDL-C	0.074	0.012	0.000	0.051	0.097	0.000	1393	1133	9	113.68	96.02
	Farag 2019	HDL-C	0.074	0.012	0.000	0.051	0.097	0.000	1423	1163	10	72.89	97.04
	Jiang 2019 (female)	HDL-C	0.076	0.012	0.000	0.053	0.100	0.000	1434	1176	10	44.88	97.67
	Jiang 2019 (male)	HDL-C	0.078	0.012	0.000	0.054	0.101	0.000	1448	1187	10	31.78	98.12
	Van den Eynde 2020	HDL-C	0.076	0.012	0.000	0.053	0.099	0.000	1492	1227	9	134.64	100.00
Random			0.076	0.012	0.000	0.053	0.099	0.000					

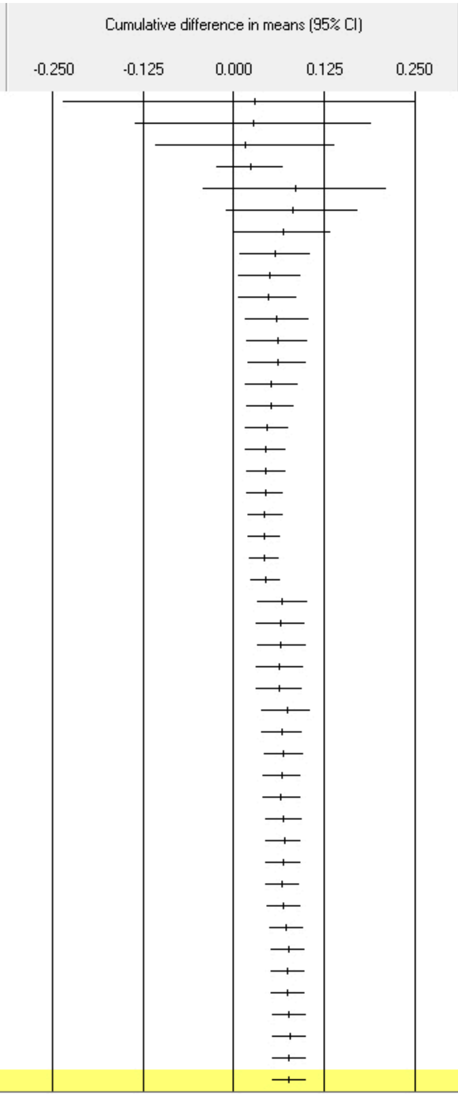


Figure 6.6 Cumulative random effects univariate meta-analysis of HDL-C (K-0: all RCTs)

Model	Study name	Outcome	Cumulative statistics						Cumulative sample size		Study Quality	Weight (Random)	
			Point	Standard error	Variance	Lower limit	Upper limit	p-Value	Exercise	Control		Weight (Random)	Relative weight
	Ronnemaa 1988	HDL-C	0.030	0.135	0.018	-0.235	0.295	0.825	13	12	8	54.30	0.40
	Smutok 1993	HDL-C	0.028	0.084	0.007	-0.136	0.191	0.742	26	22	9	87.98	1.05
	Raz 1994	HDL-C	0.016	0.063	0.004	-0.108	0.140	0.803	45	41	14	104.53	1.82
	Anderssen 1995	HDL-C	0.024	0.024	0.001	-0.023	0.070	0.317	94	84	11	1339.32	11.72
	Ligtenberg 1997	HDL-C	0.032	0.022	0.000	-0.011	0.074	0.143	119	110	11	353.23	14.33
	Stefanick 1998 (females)	HDL-C	0.032	0.018	0.000	-0.004	0.068	0.083	162	155	12	747.04	19.85
	Stefanick 1998 (males)	HDL-C	0.034	0.014	0.000	0.005	0.062	0.020	209	201	12	1568.51	31.45
	Laaksonen 2000	HDL-C	0.032	0.014	0.000	0.005	0.059	0.022	229	223	11	340.97	33.97
	Lavrencic 2000	HDL-C	0.031	0.014	0.000	0.004	0.058	0.023	243	238	10	93.64	34.66
	Verissimo 2002	HDL-C	0.037	0.014	0.000	0.011	0.064	0.006	274	270	8	192.23	36.08
	Watkins 2003	HDL-C	0.038	0.013	0.000	0.012	0.064	0.005	288	281	10	66.55	36.57
	Sykes 2004	HDL-C	0.039	0.013	0.000	0.013	0.065	0.004	312	293	10	77.88	37.15
	Sigal 2007	HDL-C	0.034	0.013	0.000	0.010	0.059	0.007	372	356	15	717.10	42.45
	Slentz 2007 (high vol VICT)	HDL-C	0.035	0.012	0.000	0.012	0.059	0.004	436	375	10	484.37	46.03
	Slentz 2007 (low vol MICT)	HDL-C	0.034	0.012	0.000	0.011	0.057	0.003	487	392	10	565.85	50.21
	Slentz 2007 (low vol VICT)	HDL-C	0.033	0.011	0.000	0.011	0.055	0.003	548	410	10	460.46	53.61
	Lambers 2008	HDL-C	0.034	0.011	0.000	0.012	0.056	0.002	566	421	12	75.88	54.17
	Kadoglou 2009	HDL-C	0.034	0.011	0.000	0.013	0.056	0.002	589	445	11	369.61	56.91
	Gram 2010	HDL-C	0.035	0.011	0.000	0.014	0.056	0.001	611	467	13	282.84	59.00
	Thompson 2010	HDL-C	0.036	0.011	0.000	0.015	0.056	0.001	631	488	12	218.42	60.61
	Choi 2012	HDL-C	0.037	0.010	0.000	0.017	0.057	0.000	669	525	10	731.61	66.02
	Kim 2012	HDL-C	0.038	0.010	0.000	0.018	0.058	0.000	684	540	11	108.58	66.82
	Yavari 2012	HDL-C	0.038	0.010	0.000	0.018	0.058	0.000	699	555	12	133.36	67.81
	Madden 2013	HDL-C	0.038	0.010	0.000	0.018	0.058	0.000	724	582	13	19.01	67.95
	Dogan Dede 2015	HDL-C	0.038	0.010	0.000	0.018	0.057	0.000	754	612	12	167.06	69.18
	Vinetti 2015	HDL-C	0.038	0.010	0.000	0.018	0.057	0.000	764	622	9	73.06	69.72
	Kang 2016	HDL-C	0.039	0.010	0.000	0.020	0.059	0.000	776	633	7	147.64	70.81
	Arija 2017	HDL-C	0.039	0.009	0.000	0.020	0.057	0.000	1036	737	15	741.77	76.29
	Paolillo 2017	HDL-C	0.039	0.009	0.000	0.020	0.057	0.000	1046	747	9	77.31	76.87
	Phing 2017	HDL-C	0.046	0.009	0.000	0.028	0.063	0.000	1081	835	10	990.82	84.19
	Shakil-ur-Rehman 2017	HDL-C	0.048	0.009	0.000	0.031	0.065	0.000	1132	886	9	586.19	88.52
	Chan 2018	HDL-C	0.048	0.009	0.000	0.031	0.065	0.000	1214	968	13	175.24	89.82
	Wedell-Neergaard 2018	HDL-C	0.048	0.009	0.000	0.031	0.065	0.000	1228	981	9	358.12	92.46
	Cao 2019	HDL-C	0.049	0.009	0.000	0.032	0.066	0.000	1241	996	10	142.40	93.52
	Conners 2019	HDL-C	0.052	0.008	0.000	0.035	0.069	0.000	1254	1009	14	256.11	95.41
	Dai 2019	HDL-C	0.053	0.008	0.000	0.037	0.070	0.000	1288	1044	11	112.51	96.24
	Fang 2019	HDL-C	0.053	0.008	0.000	0.036	0.069	0.000	1325	1082	9	150.01	97.35
	Farag 2019	HDL-C	0.053	0.008	0.000	0.037	0.070	0.000	1355	1112	10	86.28	97.99
	Jiang 2019 (female)	HDL-C	0.054	0.008	0.000	0.038	0.071	0.000	1366	1125	10	49.62	98.35
	Jiang 2019 (male)	HDL-C	0.056	0.009	0.000	0.039	0.073	0.000	1380	1136	10	34.09	98.60
	Van den Eynde 2020	HDL-C	0.055	0.009	0.000	0.038	0.072	0.000	1424	1176	9	188.78	100.00
Random			0.055	0.009	0.000	0.038	0.072	0.000					

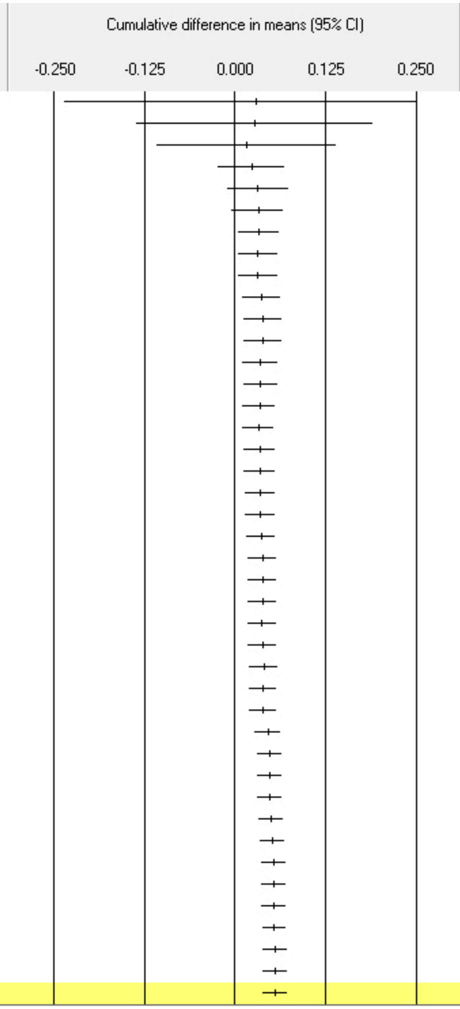


Figure 6.7 Cumulative random effects univariate meta-analysis of HDL-C (K-4: outliers and influencer removed)

Model	Study name	Outcome	Cumulative statistics						Cumulative sample size		Study Quality	Weight (Random)	
			Point	Standard error	Variance	Lower limit	Upper limit	p-Value	Exercise	Control		Weight (Random)	Relative weight
	Ronnemaa 1988	LDL-C	-0.250	0.370	0.137	-0.974	0.474	0.499	13	12	8	7.32	0.25
	Smutok 1993	LDL-C	-0.182	0.244	0.060	-0.661	0.297	0.457	26	22	9	9.42	0.58
	Anderssen 1995	LDL-C	-0.106	0.102	0.010	-0.307	0.094	0.300	75	65	11	78.81	3.31
	Lehmann 1995	LDL-C	-0.146	0.069	0.005	-0.282	-0.011	0.034	91	78	9	114.26	7.27
	Motoyama 1995	LDL-C	-0.141	0.067	0.005	-0.272	-0.009	0.036	106	93	12	12.11	7.69
	Ligtenberg 1997	LDL-C	-0.134	0.065	0.004	-0.262	-0.005	0.041	131	119	11	11.90	8.11
	Stefanick 1998 (females)	LDL-C	-0.117	0.055	0.003	-0.224	-0.010	0.032	174	164	12	101.23	11.62
	Stefanick 1998 (males)	LDL-C	-0.099	0.049	0.002	-0.194	-0.003	0.043	221	210	12	87.17	14.64
	Laaksonen 2000	LDL-C	-0.104	0.047	0.002	-0.197	-0.011	0.029	241	232	11	22.40	15.42
	Lavrencic 2000	LDL-C	-0.104	0.047	0.002	-0.196	-0.011	0.028	255	247	10	8.28	15.70
	Verissimo 2002	LDL-C	-0.121	0.046	0.002	-0.211	-0.031	0.009	286	279	8	21.03	16.43
	Watkins 2003	LDL-C	-0.124	0.046	0.002	-0.214	-0.035	0.006	300	290	10	5.15	16.61
	Sykes 2004	LDL-C	-0.124	0.045	0.002	-0.212	-0.036	0.006	324	302	10	14.39	17.11
	Sigal 2007	LDL-C	-0.124	0.043	0.002	-0.207	-0.040	0.004	379	363	15	57.57	19.11
	Slentz 2007 (high vol VICT)	LDL-C	-0.130	0.041	0.002	-0.209	-0.050	0.001	443	382	10	55.98	21.05
	Slentz 2007 (low vol MICT)	LDL-C	-0.135	0.039	0.002	-0.212	-0.058	0.001	494	399	10	45.22	22.61
	Slentz 2007 (low vol VICT)	LDL-C	-0.149	0.037	0.001	-0.222	-0.076	0.000	555	417	10	68.17	24.98
	Kadoglou 2009	LDL-C	-0.156	0.037	0.001	-0.228	-0.084	0.000	578	441	11	18.54	25.62
	Gram 2010	LDL-C	-0.155	0.036	0.001	-0.226	-0.084	0.000	600	463	13	18.97	26.28
	Choi 2012	LDL-C	-0.157	0.036	0.001	-0.228	-0.086	0.000	638	500	10	5.52	26.47
	Kim 2012	LDL-C	-0.167	0.036	0.001	-0.237	-0.097	0.000	653	515	11	21.88	27.23
	Labrunée 2012	LDL-C	-0.166	0.035	0.001	-0.236	-0.096	0.000	664	527	9	8.57	27.53
	Yavari 2012	LDL-C	-0.167	0.035	0.001	-0.237	-0.098	0.000	679	542	12	8.14	27.81
	Madden 2013	LDL-C	-0.168	0.035	0.001	-0.236	-0.099	0.000	704	569	13	12.46	28.24
	Venojärvi 2013	LDL-C	-0.175	0.034	0.001	-0.242	-0.109	0.000	743	609	11	49.98	29.97
	Dogan Dede 2015	LDL-C	-0.176	0.034	0.001	-0.242	-0.110	0.000	773	639	12	15.47	30.51
	Vinetti 2015	LDL-C	-0.178	0.034	0.001	-0.244	-0.112	0.000	783	649	9	2.06	30.58
	Alvarez 2016	LDL-C	-0.176	0.033	0.001	-0.241	-0.111	0.000	796	659	12	32.12	31.70
	Farinatti 2016	LDL-C	-0.099	0.021	0.000	-0.139	-0.058	0.000	825	673	10	1416.30	80.80
	Arija 2017	LDL-C	-0.106	0.020	0.000	-0.146	-0.067	0.000	1085	777	15	138.35	85.60
	Paolillo 2017	LDL-C	-0.106	0.020	0.000	-0.146	-0.067	0.000	1095	787	9	6.17	85.81
	Shakil-ur-Rehman 2017	LDL-C	-0.113	0.020	0.000	-0.151	-0.074	0.000	1146	838	9	125.55	90.17
	Chan 2018	LDL-C	-0.111	0.019	0.000	-0.149	-0.073	0.000	1228	920	13	48.44	91.85
	Wedell-Neergaard 2018	LDL-C	-0.114	0.019	0.000	-0.152	-0.077	0.000	1242	933	9	46.68	93.47
	Cao 2019	LDL-C	-0.114	0.019	0.000	-0.152	-0.077	0.000	1255	948	10	11.43	93.86
	Conners 2019	LDL-C	-0.114	0.019	0.000	-0.151	-0.077	0.000	1268	961	14	65.78	96.14
	Dai 2019	LDL-C	-0.116	0.019	0.000	-0.153	-0.079	0.000	1302	996	11	19.84	96.83
	Fang 2019	LDL-C	-0.124	0.019	0.000	-0.162	-0.086	0.000	1339	1034	9	16.95	97.42
	Farag 2019	LDL-C	-0.121	0.019	0.000	-0.158	-0.084	0.000	1369	1064	10	15.92	97.97
	Jiang 2019 (female)	LDL-C	-0.123	0.019	0.000	-0.160	-0.086	0.000	1380	1077	10	11.83	98.38
	Jiang 2019 (male)	LDL-C	-0.122	0.019	0.000	-0.159	-0.086	0.000	1394	1088	10	12.15	98.80
	Van den Eynde 2020	LDL-C	-0.123	0.019	0.000	-0.160	-0.087	0.000	1438	1128	9	34.53	100.00
Random			-0.123	0.019	0.000	-0.160	-0.087	0.000					

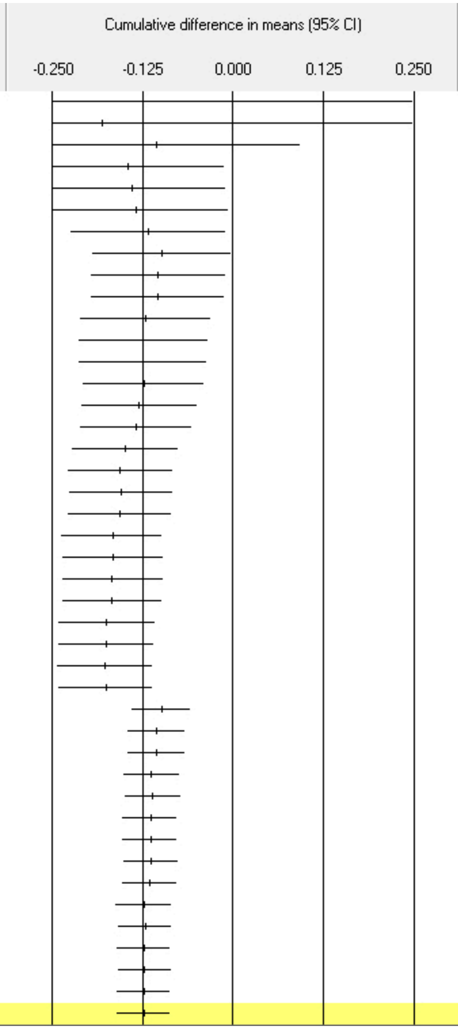


Figure 6.8 Cumulative random effects univariate meta-analysis of LDL-C (K-0: all RCTs)

Model	Study name	Outcome	Cumulative statistics						Cumulative sample size		Study Quality	Weight (Random)	
			Point	Standard error	Variance	Lower limit	Upper limit	p-Value	Exercise	Control		Weight (Random)	Relative weight
	Ronnemaa 1988	LDL-C	-0.250	0.370	0.137	-0.974	0.474	0.499	13	12	8	7.32	0.50
	Smutok 1993	LDL-C	-0.182	0.244	0.060	-0.661	0.297	0.457	26	22	9	9.42	1.14
	Anderssen 1995	LDL-C	-0.106	0.102	0.010	-0.307	0.094	0.300	75	65	11	78.81	6.51
	Lehmann 1995	LDL-C	-0.146	0.069	0.005	-0.282	-0.011	0.034	91	78	9	114.26	14.29
	Motoyama 1995	LDL-C	-0.141	0.067	0.005	-0.272	-0.009	0.036	106	93	12	12.11	15.12
	Ligtenberg 1997	LDL-C	-0.134	0.065	0.004	-0.262	-0.005	0.041	131	119	11	11.90	15.93
	Stefanick 1998 (females)	LDL-C	-0.117	0.055	0.003	-0.224	-0.010	0.032	174	164	12	101.23	22.83
	Stefanick 1998 (males)	LDL-C	-0.099	0.049	0.002	-0.194	-0.003	0.043	221	210	12	87.17	28.77
	Laaksonen 2000	LDL-C	-0.104	0.047	0.002	-0.197	-0.011	0.029	241	232	11	22.40	30.29
	Lavrencic 2000	LDL-C	-0.104	0.047	0.002	-0.196	-0.011	0.028	255	247	10	8.28	30.86
	Verissimo 2002	LDL-C	-0.121	0.046	0.002	-0.211	-0.031	0.009	286	279	8	21.03	32.29
	Watkins 2003	LDL-C	-0.124	0.046	0.002	-0.214	-0.035	0.006	300	290	10	5.15	32.64
	Sykes 2004	LDL-C	-0.124	0.045	0.002	-0.212	-0.036	0.006	324	302	10	14.39	33.62
	Sigal 2007	LDL-C	-0.124	0.043	0.002	-0.207	-0.040	0.004	379	363	15	57.57	37.54
	Slentz 2007 (high vol VICT)	LDL-C	-0.130	0.041	0.002	-0.209	-0.050	0.001	443	382	10	55.98	41.36
	Slentz 2007 (low vol MICT)	LDL-C	-0.135	0.039	0.002	-0.212	-0.058	0.001	494	399	10	45.22	44.44
	Slentz 2007 (low vol VICT)	LDL-C	-0.149	0.037	0.001	-0.222	-0.076	0.000	555	417	10	68.17	49.08
	Kadoglou 2009	LDL-C	-0.156	0.037	0.001	-0.228	-0.084	0.000	578	441	11	18.54	50.35
	Gram 2010	LDL-C	-0.155	0.036	0.001	-0.226	-0.084	0.000	600	463	13	18.97	51.64
	Choi 2012	LDL-C	-0.157	0.036	0.001	-0.228	-0.086	0.000	638	500	10	5.52	52.01
	Kim 2012	LDL-C	-0.167	0.036	0.001	-0.237	-0.097	0.000	653	515	11	21.88	53.50
	Labrunée 2012	LDL-C	-0.166	0.035	0.001	-0.236	-0.096	0.000	664	527	9	8.57	54.09
	Yavari 2012	LDL-C	-0.167	0.035	0.001	-0.237	-0.098	0.000	679	542	12	8.14	54.64
	Madden 2013	LDL-C	-0.168	0.035	0.001	-0.236	-0.099	0.000	704	569	13	12.46	55.49
	Venojärvi 2013	LDL-C	-0.175	0.034	0.001	-0.242	-0.109	0.000	743	609	11	49.98	58.90
	Dogan Dede 2015	LDL-C	-0.176	0.034	0.001	-0.242	-0.110	0.000	773	639	12	15.47	59.95
	Vinetti 2015	LDL-C	-0.178	0.034	0.001	-0.244	-0.112	0.000	783	649	9	2.06	60.09
	Alvarez 2016	LDL-C	-0.176	0.033	0.001	-0.241	-0.111	0.000	796	659	12	32.12	62.28
	Arija 2017	LDL-C	-0.183	0.031	0.001	-0.244	-0.123	0.000	1056	763	15	138.35	71.71
	Paolillo 2017	LDL-C	-0.183	0.031	0.001	-0.243	-0.123	0.000	1066	773	9	6.17	72.13
	Shakil-ur-Rehman 2017	LDL-C	-0.189	0.029	0.001	-0.246	-0.132	0.000	1117	824	9	125.55	80.68
	Chan 2018	LDL-C	-0.183	0.028	0.001	-0.239	-0.127	0.000	1199	906	13	48.44	83.98
	Wedell-Neergaard 2018	LDL-C	-0.187	0.028	0.001	-0.241	-0.132	0.000	1213	919	9	46.68	87.16
	Cao 2019	LDL-C	-0.186	0.028	0.001	-0.241	-0.132	0.000	1226	934	10	11.43	87.94
	Conners 2019	LDL-C	-0.182	0.027	0.001	-0.235	-0.129	0.000	1239	947	14	65.78	92.42
	Dai 2019	LDL-C	-0.185	0.027	0.001	-0.238	-0.132	0.000	1273	982	11	19.84	93.77
	Fang 2019	LDL-C	-0.192	0.027	0.001	-0.244	-0.139	0.000	1310	1020	9	16.95	94.93
	Farag 2019	LDL-C	-0.193	0.027	0.001	-0.245	-0.141	0.000	1340	1050	10	15.92	96.01
	Jiang 2019 (female)	LDL-C	-0.195	0.027	0.001	-0.247	-0.143	0.000	1351	1063	10	11.83	96.82
	Jiang 2019 (male)	LDL-C	-0.195	0.026	0.001	-0.246	-0.143	0.000	1365	1074	10	12.15	97.65
	Van den Eynde 2020	LDL-C	-0.195	0.026	0.001	-0.246	-0.144	0.000	1409	1114	9	34.53	100.00
Random			-0.195	0.026	0.001	-0.246	-0.144	0.000					

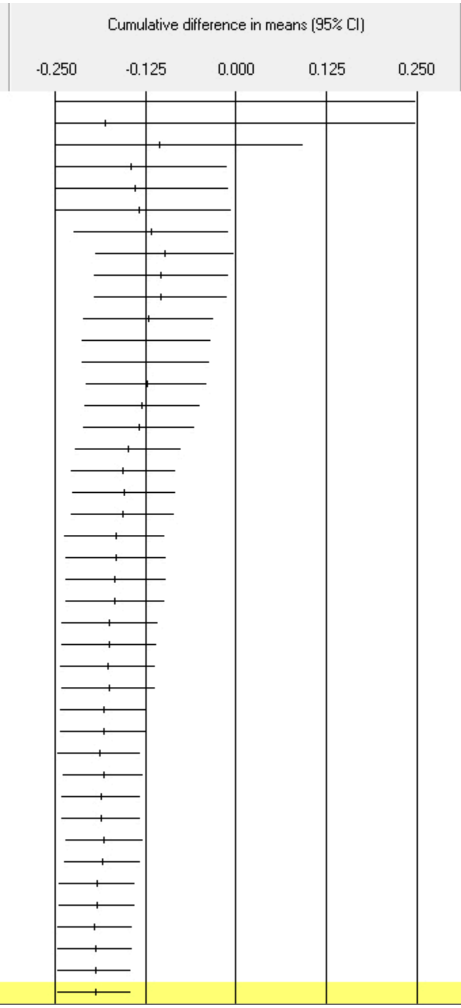


Figure 6.9 Cumulative random effects univariate meta-analysis of LDL-C (K-4: outliers and influencer removed)

3.5 Small-study Effects Included RCTs exceeded the minimum number of required reported ES.[114] Two sets of small study effects analyses were performed: the first for all studies included ie K-0, and the second for K-1 (TRG, LDL-C) and K-4 (TC, HDL-C) studies ie influencer and respective outlier studies excluded, see Table 6.4. Small study effects analyses in the presence of between study heterogeneity may yield inconsistent results such as seen in the K-0 (all studies) small study effects analysis. Using Duval and Tweedie’s trim and fill, the influencer and outlier effects are demonstrated by the imputation of missing studies for TC, see SM Figures 6.14-6.15, and an increase in ES for TC, see Table 6.4, but small study effects are not present in the other analysis types for TC. Removing the influencer and outliers for TC extinguishes the imputed trim and fill small study effects as shown by the K-4 small study effects analysis for TC, see Table 6.4 and SM Figures 6.22-6.23. This pattern of inconsistent results for small study effects analysis is generally repeated for the remaining lipids with the exception of HDL-C, see Table 6.4 and SM Figures 6.16-6.17, 6.24-6.25 for TRG, SM Figures 6.18-6.19, 6.26-6.27 for HDL-C, and SM Figures 6.29-6.21, 6.28-6.29 for LDL-C. The evidence of potential small study effects for the SLP, particularly for ES with influencer and outliers removed, suggests small study effects are trivial and do not invalidate the results of the univariate MA. In addition, small study effects tests suggest a greater precision of ES and 95% CI is achieved with influencer and outliers removed for the univariate MA of each outcome.

Small-study Effects			
K-0 All studies			
Lipid	Small study effects analysis type	Results	
TC	Classic Failsafe N	42 studies z-value=-11.06 2-tailed *P*<.001	Fail-safe N =1295 studies required for combined 2-tailed *P*>.05
	Begg & Mezumdar rank correlation test*	Kendall's τb=-0.056	2-tailed *P*=.60
	Egger's regression intercept	intercept (B0) =0.16 95% CI -0.28, 0.61 t=0.74, df=40	2-tailed *P*=.47
	Duval & Tweedie's trim and fill (mmol/L)	Imputed ES=-0.34 Imputed 95% CI -0.42, -0.28	9 imputed missing studies, ES increased by 0.05 mmol/L, 95% CI width did not change.
TRG	Classic Failsafe N	40 studies z-value=-8.13 2-tailed *P*<.001	Fail-safe N =648 studies required for combined 2-tailed *P*>.05
	Begg & Mezumdar rank correlation test	Kendall's τb=-0.12	2-tailed *P*=.28
	Egger's regression intercept	intercept (B0) =0.-28 (95% CI -0.62, 0.05) t=1.71, df=38	2-tailed *P*=.10
	Duval & Tweedie's trim and fill (mmol/L)	Imputed ES=-0.16 Imputed 95% CI -0.22, -0.11	4 imputed missing studies, ES decreased by 0.01 mmol/L, 95% CI widened by 0.06 mmol/L.
HDL-C	Classic Failsafe N	45 studies z-value=9.81 2-tailed *P*<.001	Fail-safe N =1083 studies required for combined 2-tailed *P*>.05
	Begg & Mezumdar rank correlation test	Kendall's τb=0.33	2-tailed *P*=.001
	Egger's regression intercept	intercept (B0) =0.66 95% CI 0.07, 1.25 t=2.25, df=43	2-tailed *P*=.03
	Duval & Tweedie's trim and fill (mmol/L)	imputed ES=0.06 imputed 95% CI 0.03, 0.08	6 imputed missing studies, ES decreased by 0.02, 95% CI width did not change.
LDL-C	Classic Failsafe N	42 studies z-value=-7.53 2-tailed *P*<.001	Fail-safe N =578 studies required for combined 2-tailed *P*>.05
	Begg & Mezumdar rank correlation test	Kendall's τb=-0.007	2-tailed *P*=.95
	Egger's regression intercept	intercept (B0) =-0.90 95% CI -1.25, -0.54 t=5.07, df=40	2-tailed *P*<.001
	Duval & Tweedie's trim and fill (mmol/L)	imputed ES=-0.09 imputed 95% CI -0.14, -0.03	19 imputed missing studies, ES decreased by 0.03, 95% CI widened by 0.11.

* (2 tailed *P* value calculated based on continuity-corrected normal approximation)

Table 6.4 Results of small studies effects for each grouping of RCTs (K-0 ie all studies, and K-4 ie outliers and influencer removed) by analysis type and lipid

Small-study Effects (Table 6.4 continued)			
Studies remaining after exclusion of outliers and influencer			
Lipid	Small study effects analysis type	Results	
TC (K-4) Outliers and influencer removed	Classic Failsafe N	38 studies z-value=-5.89 2-tailed *P*<.001	Fail-safe N =305 studies required for combined 2-tailed *P*>.05
	Begg & Mezumdar rank correlation test*	Kendall's τb=0.003	2-tailed *P*=.98
	Egger's regression intercept	intercept (B0) =0.25 95% CI -0.77, 0.28 t=0.95, df=36	2-tailed *P*=.35
	Duval & Tweedie's trim and fill mmol/L	Imputed ES=-0.21 Imputed 95% CI -0.28, -0.15	No imputed missing studies, no change to ES or CI
TRG (K-1) Influencer removed	Classic Failsafe N	39 studies z-value=-6.43 2-tailed *P*<.001	Failsafe N = 381
	Begg & Mezumdar rank correlation test	Kendall's τb=-0.15	2-tailed *P*=.17
	Egger's regression intercept	intercept (B0) =-0.55 95% CI -1.12, 0.01 t=2.00, df=37	2-tailed *P*=.05
	Duval & Tweedie's trim and fill mmol/L	imputed ES=-0.17 imputed 95% CI -0.23, -0.10	5 imputed missing studies, ES decreased by 0.01, 95% CI narrowed by 0.01.
HDL-C (K-4) Outliers and influencer removed	Classic Failsafe N	41 studies z-value=6.86 2-tailed *P*<.001	Fail-safe N =462 studies required for combined 2-tailed *P*>.05
	Begg & Mezumdar rank correlation test	Kendall's τb=0.31	2-tailed *P*=.01
	Egger's regression intercept	intercept (B0) =0.77405 95% CI 0.15, 1.40 t=2.50, df=39.	2-tailed *P*=.02
	Duval & Tweedie's trim and fill mmol/L	imputed ES =0.05 imputed 95% CI 0.02, 0.07	7 imputed missing studies, ES decreased by 0.01 mmol/L, 95% CI widened by 0.02 mmol/L
LDL-C (K-1) Influencer removed	Classic Failsafe N	41 studies z-value= -7.33 2-tailed *P*<.001	Fail-safe N =533 studies required for combined 2-tailed *P*>.05
	Begg & Mezumdar rank correlation test	Kendall's τb=-0.12561	2-tailed *P*=.25
	Egger's regression intercept	intercept (B0) =-0.51 95% CI -1.04, 0.02 t=1.10, df=39	2-tailed *P*=.06
	Duval & Tweedie's trim and fill mmol/L	imputed ES =-0.18 imputed 95% CI -0.23, -0.13	5 imputed missing studies, ES decreased by 0.02 mmol/L, 95% CI width did not change.

* (2 tailed *P* value calculated based on continuity-corrected normal approximation)

Table 6.4 Results of small studies' effects for each grouping of RCTs (K-0 ie all studies, and K-4 ie outliers and influencer removed) by analysis type and lipid

3.6 Meta-regression Exploratory meta-regression modelling of *a priori* study (year of publication, total number of participants, and TESTEX score) and intervention (intensity VO_{2MAX} %, minutes per session, sessions per week, duration of intervention) covariates was undertaken for the K-0 set of RCTs, and K-1 (TRG, LDL-C) and K-4 (TC, HDL-C) sets of RCTs for all lipids. With the exception of LDL-C, AET intervention covariates were not found to explain the change in any lipids in the K-0 set of RCTs. Change in LDL-C using the K-0 set of RCTs was approximately 50% explained mainly by volume, see SM Table 6.11. Using the sets of RCTs with influencer removed for TRG, intensity explained approximately 50% of the change in lipids as a result of AET, see SM Table 6.12. With influencer and outliers removed for HDL-C, volume was principally responsible for change in lipids as a result of AET, see SM Table 6.13. Examining study covariates for K-0 studies, year of publication, number of total participants, and TESTEX score explained some of the ES for TC, TRG and HDL-C as a result of intervention, see SM Tables 6.14-6.16. The same result occurred for HDL-C using the set of RCTs with influencer and outliers removed, see SM Table 6.17.

4.0 DISCUSSION

This SR and MA, of 48 data sets from 44 RCTs of 2990 participants, compared the effects of ≥12 weeks of AET performed at ≥40% VO_{2MAX}, against non-exercising control groups, on the lipid profile of sedentary adults with MetS and/or T1DM/T2DM. Unlike some of the findings of others,[4 115-117] our work shows both significance and clinically important change in lipids, with a narrower 95% CI for each lipid in comparison with 95% CIs estimated by previous works. The range of reduction we found in TC, whether using the smallest number of RCTs (restricted by study quality, and removal of influencer and outlier) or including all RCTs, exceeds the ES reported as an insignificant change in the only study reporting TC for this population.[116] Given that a 1% reduction in TC is associated with a 2% decrease in the incidence of coronary heart disease,[12] the estimated reduction in TC that we found suggests a possible CVD risk reduction of 10-15%.

With respect to TRG, our results confirm those of previous significant findings reporting an effect size for TRG after an AET intervention for similar populations.[4 115] Moreover, our estimated ES for TRG is close to the lower range of the reported estimated ES of statin interventions for TRG in clinical and dyslipidaemic populations.[118] Effective changes in TRG with statin treatment are significantly dependent on a high TRG baseline level.[119] AET, as a prescription for MetS populations with lower-risk baseline TRG values such as those included in our analysis, is a viable alternative to statin therapy, based on our estimated ES. Our meta-regression results suggest that AET of an increased intensity may also be an effective therapeutic tool to reduce TRG for populations with higher baseline TRG values.

Our results regarding HDL-C do not agree with previous findings, which found no significance in HDL-C levels raised as a result of an AET intervention in populations of similar health status.[4 115-117 120] At the most restricted level of study inclusion (no influencer, no outliers, and only including RCTs with study quality score ≥10), our most conservative estimated ES was greater than that found by all other SRs with MA bar one.[116] The presence of small study effects neither altered the significance nor reduced our estimated ES below that found using the most restricted pool of RCTs. Our results suggest that an AET intervention raises HDL-C by a clinically important amount, potentially leading to a decrease in CVD risk of 4-9%, given that an increase of 0.02586 mmol/L represents a decrease in CVD risk of 2% for men and ≥3% for women.[11] Our exploratory meta-regression suggests that an increase in volume of AET has the potential to further improve HDL-C, unlike increasing the dosages of statins, which either achieve no statistically significant increase in HDL-C in populations similar to those included in our analysis, or tend to decrease HDL-C in normolipidaemic populations.[121]

The range of our estimated ES for LDL-C exceeded the ES computed in previous works which found no significance in LDL-C levels lowered as a result of an AET intervention in populations of similar health status,[115-117 120] and exceeded the estimated ES of a previous work which found the impact of AET to be significant.[4] Our estimated ES represents a clinically important change: CVD risk decreases 1.7% for each 1% drop in LDL-C,[10] suggesting that our estimated ES of AET on MetS/T1DM and T2DM populations leads to a decrease in CVD risk of between 7-11%. Our exploratory meta-regression analysis proposes that increasing the volume of AET undertaken may lead to larger reductions in LDL-C, similar to the optimal therapeutic response of LDL-C to statins also being dependent on greater dosage.[122]

The estimated ES of statins appears to be significantly related to baseline lipid levels[121 123] and population characteristics (CVD risk, CVD patients),[118] as well as genetic risk.[124] Few of the RCTs included in our meta-analysis reported baseline lipid levels elevated (or in the case of HDL-C, depressed) to CVD-associated risk levels. The magnitude of difference between the reported estimated ES of statins and our estimated ES of AET may be contingent upon the duration of the studies undertaken. In our meta-analysis, the longest duration of a single RCT was 2 years, and most of the RCTs we included were of much shorter duration. In contrast, statin study data is collated over periods up to 5 years. Increasing statin dosages increases lipid-improving ES,[56 122] and may increase costs[25-27] and adverse effects.[28 29 125] Increasing AET volume to recommended minimums in MetS populations is not generally associated with increases in costs or adverse effects.[20-24 126 127] Aerobic physical activity has been shown to positively impact a range of health biomarkers upon which statins appear to have minimal effect, such as blood pressure,[128] or dubious effect, such as waist circumference and BMI,[129 130] or a potential for adverse effect, such as glycaemic control,[131 132] and cardiovascular fitness via decreased physical activity and mitochondrial dysfunction.[133]

4.4 Clinical Significance and Future Research

We recommend that clinicians encourage MetS and T1DM/T2DM populations to meet nationally recommended AET volumes (>150 minutes per week at moderate intensity or >75 minutes per week at vigorous intensity)[134-136] as a CVD risk management strategy. Our exploratory meta-regression results are broadly sympathetic to previous works investigating AET intervention covariates impacting change in the SLP,[16 17 31 39] which suggest that manipulating intervention covariates to optimise AET dosage may lead to greater improvements in the SLP. Others have found AET of doses above amounts indicated by national guidelines, of at least 180 minutes per week at >40% VO_{2MAX} or >1200kcal/week[30-33] or 200 minutes per week at >65% VO_{2MAX} for >26 weeks,[16] significantly and positively impact lipids. Therefore we encourage clinicians to use these reported AET prescriptions as lipid management strategies, and to consider adjusting intervention covariates to match patient preferences while achieving these volumes and intensities.

Our meta-regression analysis of study covariates suggests that study quality explains ES for at least TC, TRG, and HDL-C. Our study quality TESTEX and within-study risk of bias analyses indicated that included RCTs failed to specify the method of randomisation and allocation concealment; report medication use, drop-out reasons, or adverse events; report monitoring of the non-exercising group or adherence to either the exercising or non-exercising protocol; set a minimum compliance level; use objective measuring devices; and report post-intervention exercise volume (total sessions attended, total minutes per session, achieved intensity). Timing of post-intervention blood analyses was not always reported. Patient data, such as pre-post body weight, body fat or lean mass, waist circumference or BMI, systolic and diastolic blood pressure, and fasting blood glucose, were often missing. Researchers conducting RCTs can better report their findings by including quantitative data for these variables. Although we did not set out *a priori* to pool lipid ratios or non-HDL-C outcomes, we note that few studies included these outcomes as results. TRG better predicts CVD risk in women[137] and we recommend trials report non-HDL-C and lipid ratios.

We propose that future trials compare AET interventions of sufficient duration, volume and intensity known to positively affect lipid levels with tolerated dosages of statins against control groups (placebo and no exercise) in MetS and T1DM/T2DM populations. Since ≈50% of patients adhere to medication,[138] future research should investigate levels of adherence to AET interventions and assess motivation for adherence and reasons for non-compliance. The results from such research may inform how to better promote prescriptive AET adoption.

4.5 Strengths and Limitations in this Systematic Review and Meta-analysis Our work has a number of strengths. To our knowledge, this SR and MA has pooled the largest-to-date set of RCT data for AET protocols investigating change in the SLP of sedentary populations diagnosed only with MetS and T1DM/T2DM.

Previous SRs did not use TESTEX[64] to measure the quality of included studies. We followed a rigorous inclusion/exclusion protocol to ensure minimisation of confounding factors amongst the RCT populations.[139]

We relied on aggregated RCT data, a possible limitation.[140 141] We searched using English language terms, potentially introducing publication bias. We excluded studies with intervention and comparison group N<10, possibly reducing ES. The number of RCTs included with longer durations were few; perhaps negatively impacting ES. The inclusion of AET protocols with minimum moderate intensity (≥40% VO_{2MAX}) may have elicited very small changes in lipids,[16] thus understating ES. Because reporting of protocol adherence and intensity varied, potential biases in the measurement of data reported in the included RCTs may have skewed our results. A small number of RCTs noted that control groups increased physical activity levels during interventions, and this may have altered ES. Our meta-regression results should be considered as exploratory only.

With respect to data pooling, where the SD of the MD, exact *P* values within groups, or 95% CIs were not available, statistical analyses depended on extrapolated data. Our imputation of the SD of the MD was conservative and we conducted sensitivity analyses (leave-one-out); this approach may have weakened results.

5.0 CONCLUSION

Pooled RCT data indicated AET programs of moderate intensity with a minimum 12 week duration significantly and clinically improved the SLP in MetS and T1DM/T2DM populations with normal-risk baseline lipid levels. Our results suggest that AET outperforms statins for improving HDL-C in this population. Given that AET positively impacts not only lipids but other MetS factors, AET should be a principal treatment for minimising CVD risk.

Supplementary Materials

Example Search

EBSCO example search	"(aerobic exercise OR physical activity OR moderate intensity continuous training OR high intensity interval training OR aerobic exercise or aerobic training or endurance training) AND (lipids or lipoprotein or apolipoprotein or triglycerides) NOT (postprandial or post-prandial or lifestyle intervention or HIV or human immunodeficiency or prostrate or alzheimer or cardiovascular rehabilitation or cognitive disorder or claudication or spinal cord or cancer or stroke or ischaemic or ischemic or renal failure or kidney disease or NAFLD or polycystic or pregnant or lactating or child or adolescent or juvenile or athlete) AND (randomised controlled trial or randomized controlled trial or rct) NOT (rats or mice or rodents or animals) NOT systematic review Scholarly (Peer Reviewed) Journals; Randomized Controlled Trials; Age Groups: Adult: 19-44 years, Middle Aged: 45-64 years, Aged: 65+ years, Aged, 80 and over AND Apply equivalent subjects

SM Table 6.5 Search Strategy example

Author Year	Eligibility criteria specified	Randomisation specified	Allocation concealment	Groups similar at baseline	Blinding of assessor	Outcomes measures assessed in 85% patients	Adverse events reported	Exercise adherence reported	Intention -to-treat analysis	Between-group statistical comparisons reported for primary outcome reported	Between-group statistical comparisons reported for secondary outcome reported	Point measures and measures of variability for all outcome measures reported	Activity monitoring in control groups reported	Relative exercise intensity remained constant	Exercise volume and energy expenditure reported	Overall TESTEX (/15)
Alvarez 2016	1	1	1	1	1	0	1	1	0	1	1	1	0	1	1	12
Anderssen 1995	1	0	0	1	1	1	1	1	0	1	1	1	0	1	1	11
Arija 2017	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	15
Cao 2019	1	1	0	1	1	1	0	1	0	1	1	1	0	1	0	10
Chan 2018	1	1	1	1	1	0	1	1	1	1	1	1	0	1	1	13
Choi 2012	1	1	0	1	1	1	0	0	0	1	0	1	1	1	1	10
Conners 2019	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	14
Dai 2019	1	1	0	1	1	1	1	0	0	1	1	1	0	1	1	11
Doğan Dede 2015	1	0	1	1	1	1	1	1	0	1	1	1	0	1	1	12
Fang 2019	1	0	0	1	1	1	0	0	0	1	1	1	0	1	1	9
Farag 2019	1	0	0	1	1	1	0	1	1	1	1	1	0	1	0	10
Farinatti 2016	1	0	0	1	1	0	1	1	0	1	1	1	0	1	1	10
Gordon 2008	1	0	0	1	1	1	0	1	0	1	1	1	0	1	1	10
Gram 2010	1	1	0	1	1	1	1	1	1	1	1	1	0	1	1	13
Jiang 2019 (female)	1	0	0	1	1	1	1	0	0	1	1	1	0	1	1	10
Jiang 2019 (male)	1	0	0	1	1	1	1	0	0	1	1	1	0	1	1	10
Kadoglou 2009	1	0	0	1	1	1	1	1	0	1	1	1	0	1	1	11
Kang 2016	1	0	0	0	1	1	0	0	1	0	0	1	0	1	1	7
Kim 2012	1	0	1	1	1	1	0	0	1	1	1	1	0	1	1	11
Laaksonen 2000	1	1	1	1	1	0	0	1	0	1	1	1	0	1	1	11
Labrunée 2012	1	0	0	1	1	1	0	0	0	1	1	1	0	1	1	9
Lambers 2008	1	1	1	1	1	0	1	1	0	1	1	1	0	1	1	12
Lavrencic 2000	1	0	0	1	1	1	0	1	0	1	1	1	0	1	1	10
Lehmann 1995	1	0	0	1	1	1	0	0	0	1	1	1	0	1	1	9
Ligtenberg 1997	1	0	0	1	1	1	1	1	0	1	1	1	0	1	1	11

Author Year	Eligibility criteria specified	Randomisation specified	Allocation concealment	Groups similar at baseline	Blinding of assessor	Outcomes measures assessed in 85% patients	Adverse events reported	Exercise adherence reported	Intention -to-treat analysis	Between-group statistical comparisons reported for primary outcome reported	Between-group statistical comparisons reported for secondary outcome reported	Point measures and measures of variability for all outcome measures reported	Activity monitoring in control groups reported	Relative exercise intensity remained constant	Exercise volume and energy expenditure reported	Overall TESTEX (/15)
Madden 2013	1	1	0	1	1	1	0	1	1	1	1	1	1	1	1	13
Motoyama 1995	1	1	0	1	1	1	0	1	1	1	1	1	0	1	1	12
Paolillo 2017	1	0	0	1	1	0	0	0	0	1	1	1	1	1	1	9
Phing 2017	1	1	0	1	1	0	0	1	0	1	1	1	0	1	1	10
Raz 1994	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	14
Ronnemaa 1988	1	0	0	1	1	1	0	0	0	1	0	1	0	1	1	8
Shakil-ur-Rehman 2017	1	0	0	1	1	1	0	0	0	1	1	1	0	1	1	9
Sigal 2007	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	15
Slentz 2007 (high vol VICT)	1	0	1	1	1	1	0	1	0	1	0	1	0	1	1	10
Slentz 2007 (low vol MICT)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Slentz 2007 (low vol VICT)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Smutok 1993	1	0	0	1	1	0	0	0	0	1	1	1	1	1	1	9
Stefanick 1998 (females)	1	1	1	1	1	1	0	1	0	1	1	1	0	1	1	12
Stefanick 1998 (males)	1	1	1	1	1	1	0	1	0	1	1	1	0	1	1	12
Sykes 2004	1	0	0	1	1	1	0	1	0	1	1	1	0	1	1	10
Thompson 2010	1	1	1	1	1	0	0	1	1	1	1	1	0	1	1	12
Van den Eynde 2020	1	0	0	1	1	1	0	0	0	1	1	1	0	1	1	9
Venojärvi 2013	1	0	0	1	1	0	1	1	0	1	1	1	1	1	1	11
Verissimo 2002	1	0	0	1	1	1	1	0	0	1	0	0	0	1	1	8
Vinetti 2015	1	0	0	1	1	1	0	0	0	1	1	1	1	1	0	9
Watkins 2003	1	0	0	1	1	0	0	1	0	1	1	1	1	1	1	10
Wedell-Neergaard 2018	1	1	0	1	1	0	1	0	0	1	1	1	0	0	1	9
Yavari 2012	1	0	0	1	1	0	1	1	1	1	1	1	1	1	1	12

SM Table 6.6 TESTEX Assessment of Study Quality

Within-Study Risk of Bias Factors and Method

We awarded either of low or high for the following factors:

1. Study non-randomised or randomised – low if randomised, high if non-randomised;[1]
2. For intervention groups, a minimum level of compliance to be counted as having participated in the intervention group or control group – low if a minimum level of compliance was set, high if there was no minimum compliance level;
3. Habitual medication use reported – low if reported, high if not reported;
4. Drop-out reasons given – low if reported, high if not reported;
5. Baseline fitness and effort determined – low if baseline fitness and effort was measured, high if not determined;
6. > 50% of sessions supervised – low if > 50% of sessions were supervised, high if not; and
7. Effort monitoring and measurement devices – low if digital recording devices were used, high if analog or no device.

Studies were scored overall low, medium, or high risk of bias according to the number of times either "low" or "high" was accorded. A low risk of bias was awarded for 0-2 instances of "high", a medium risk of bias was awarded for 3-4 instances of "high", and a high risk of bias was awarded for 5-7 instances of "high". All factors were equally weighted. All researchers scored each paper and disputes were resolved by GW and NS.

[1] All studies were randomised

Author Year	Study non-randomised or randomised[1]	Minimum compliance level set	Habitual medication use reported	Dropout reason reported	Baseline fitness and effort determined	> 50% sessions supervised	Effort monitoring and measurement device	Risk of bias assesment low, medium, or high
Alvarez 2016	low	low	low	low	low	low	low	low
Anderssen 1995	low	low	high	low	low	low	low	low
Arija 2017	low	high	high	low	high	low	high	medium
Cao 2019	low	high	high	low	low	low	low	low
Chan 2018	low	low	low	low	low	high	low	low
Choi 2012	low	high	low	high	low	high	low	medium
Conners 2019	low	low	low	low	low	low	low	low
Dai 2019	low	low	high	low	low	low	high	low
Doğan Dede 2015	low	low	low	low	high	low	low	low
Fang 2019	low	high	low	low	low	low	high	low
Farag 2019	low	high	high	low	high	high	high	high
Farinatti 2016	low	low	high	low	low	high	high	medium
Gordon 2008	low	low	high	high	low	high	high	medium
Gram 2010	low	low	high	low	low	low	high	low
Jiang 2019 (female)	low	high	high	low	low	low	low	low
Jiang 2019 (male)	low	high	high	low	low	low	low	low
Kadoglou 2009	low	low	low	low	low	high	high	low
Kang 2016	low	high	high	high	low	low	low	medium
Kim 2012	low	high	high	low	low	low	low	low
Laaksonen 2000	low	high	low	low	low	low	high	low
Labrunée 2012	low	low	high	low	low	low	low	low
Lambers 2008	low	low	low	low	low	low	low	low
Lavrencic 2000	low	high	low	low	low	low	high	low
Lehmann 1995	low	low	high	low	low	high	low	low
Ligtenberg 1997	low	low	low	low	low	high	high	low
Madden 2013	low	low	high	low	low	low	low	low
Motoyama 1995	low	high	low	low	low	low	high	low
Paolillo 2017	low	low	high	low	low	low	low	low

Author Year	Study non-randomised or randomised[1]	Minimum compliance level set	Habitual medication use reported	Dropout reason reported	Baseline fitness and effort determined	> 50% sessions supervised	Effort monitoring and measurement device	Risk of bias assesment low, medium, or high
Phing 2017	low	low	high	high	low	low	high	**medium**
Raz 1994	low	low	high	low	low	low	high	**low**
Ronnemaa 1988	low	high	low	high	low	low	high	**medium**
Shakil-ur-Rehman 2017	low	high	high	high	low	low	high	**medium**
Sigal 2007	low	low	low	low	low	low	low	**low**
Slentz 2007 (high vol VICT)	low	low	high	high	low	low	low	**low**
Slentz 2007 (low vol MICT)	high	high	high	high	high	high	high	**high**
Slentz 2007 (low vol VICT)	high	high	high	high	high	high	high	**high**
Smutok 1993	low	high	high	low	low	low	high	**medium**
Stefanick 1998 (females)	low	high	high	high	low	low	high	**medium**
Stefanick 1998 (males)	low	high	high	high	low	low	high	**medium**
Sykes 2004	low	high	high	low	low	low	low	**low**
Thompson 2010	low	high	high	low	low	high	low	**medium**
Van den Eynde 2020	low	high	high	high	low	low	low	**medium**
Venojärvi 2013	low	high	low	low	low	low	low	**low**
Verissimo 2002	low	high	high	low	low	low	high	**medium**
Vinetti 2015	low	high	low	low	low	low	low	**low**
Watkins 2003	low	high	high	high	low	low	high	**medium**
Wedell-Neergaard 2018	low	high	high	high	low	low	low	**medium**
Yavari 2012	low	low	high	low	low	low	low	**low**

SM Table 6.7 Assessed Within-Study Risk of Bias Factors

Leave-one-out (K-1) analysis and relative weight rankings

SM Table 6.8 shows all studies ranked by random relative weight according to outcome; univariate random meta-analysis (raw mean difference, Knapp-Hartung adjustment, 95% confidence intervals) of the standard lipid profile. Highlighted studies are influencer studies.

		Statistics for each study							Sample size				Weight (Random)		Residual (Random)
RCT NAME	Outcome	Difference in means	Standard error	Variance	Lower CI limit	Upper CI limit	P Value	Exercise	Control	Total	Study Quality - TESTEX	Weight (Random)	Relative weight	Std Residual
Farinatti 2016	TC	-0.33	0.02	0.00	-0.36	-0.29	0.00	29	14	43	10	85.27	11.46	-0.39
Arija 2017	TC	-0.28	0.10	0.01	-0.47	-0.09	0.00	260	104	364	15	48.10	6.46	0.05
Stefanick 1998 (males)	TC	-0.03	0.11	0.01	-0.25	0.19	0.77	47	46	93	12	41.25	5.54	1.67
Stefanick 1998 (females)	TC	-0.12	0.12	0.01	-0.35	0.11	0.30	43	45	88	12	39.68	5.33	1.07
Anderssen 1995	TC	-0.04	0.12	0.01	-0.28	0.20	0.74	49	43	92	11	38.62	5.19	1.57
Venojärvi 2013	TC	-0.30	0.14	0.02	-0.58	-0.02	0.03	39	40	79	11	31.75	4.27	-0.08
Kadoglou 2009	TC	-0.46	0.15	0.02	-0.75	-0.17	0.00	23	24	47	11	30.18	4.06	-0.97
Slentz 2007 (low vol VICT)	TC	-0.25	0.16	0.03	-0.56	0.06	0.12	61	18	79	10	27.07	3.64	0.20
Sigal 2007	TC	-0.05	0.16	0.03	-0.37	0.27	0.76	60	63	123	15	26.38	3.55	1.23
Kim 2012	TC	-0.69	0.16	0.03	-1.01	-0.36	0.00	15	15	30	11	25.98	3.49	-2.07
Slentz 2007 (high vol VICT)	TC	-0.19	0.17	0.03	-0.51	0.14	0.26	64	19	83	10	25.61	3.44	0.50
Slentz 2007 (low vol MICT)	TC	-0.23	0.17	0.03	-0.55	0.10	0.17	51	17	68	10	25.48	3.43	0.30
Alvarez 2016	TC	-0.16	0.18	0.03	-0.51	0.20	0.39	13	10	23	12	22.82	3.07	0.63
Gordon 2008	TC	-0.79	0.19	0.04	-1.16	-0.42	0.00	77	77	154	10	21.42	2.88	-2.37
Wedell-Neergaard 2018	TC	-0.28	0.19	0.04	-0.65	0.09	0.14	14	13	27	9	21.25	2.86	0.03
Chan 2018	TC	-0.32	0.21	0.04	-0.73	0.09	0.13	82	82	164	13	18.06	2.43	-0.15
Dogan Dede 2015	TC	-0.25	0.23	0.05	-0.71	0.20	0.27	30	30	60	12	15.38	2.07	0.13
Verissimo 2002	TC	-0.49	0.24	0.06	-0.96	-0.03	0.04	31	32	63	8	14.72	1.98	-0.80
Dai 2019	TC	-1.38	0.24	0.06	-1.85	-0.91	0.00	34	35	69	11	14.54	1.95	-4.23
Farag 2019	TC	-0.41	0.24	0.06	-0.89	0.07	0.09	30	30	60	10	14.01	1.88	-0.47
Fang 2019	TC	-0.61	0.25	0.06	-1.09	-0.12	0.01	37	38	75	9	13.64	1.83	-1.20
Laaksonen 2000	TC	-0.18	0.26	0.07	-0.69	0.33	0.49	20	22	42	11	12.65	1.70	0.38
Thompson 2010	TC	-0.01	0.27	0.07	-0.55	0.53	0.97	20	21	41	12	11.58	1.56	0.95
Ligtenberg 1997	TC	-0.20	0.31	0.10	-0.81	0.41	0.52	25	26	51	11	9.36	1.26	0.26
Gram 2010	TC	-0.26	0.33	0.11	-0.90	0.38	0.43	22	22	44	13	8.47	1.14	0.07
Motoyama 1995	TC	-0.26	0.33	0.11	-0.91	0.39	0.43	15	15	30	12	8.26	1.11	0.08
Raz 1994	TC	-0.10	0.33	0.11	-0.75	0.55	0.76	19	19	38	14	8.16	1.10	0.53
Sykes 2004	TC	-0.09	0.33	0.11	-0.74	0.56	0.79	24	12	36	10	8.16	1.10	0.56
Cao 2019	TC	-0.15	0.34	0.11	-0.81	0.51	0.66	13	15	28	10	8.00	1.08	0.39
Madden 2013	TC	-0.20	0.37	0.13	-0.92	0.52	0.59	25	27	52	13	6.86	0.92	0.23
Jiang 2019 (female)	TC	-0.01	0.38	0.14	-0.75	0.73	0.98	11	13	24	10	6.45	0.87	0.70
Lavrencic 2000	TC	-0.10	0.39	0.15	-0.86	0.66	0.80	14	15	29	10	6.11	0.82	0.46
Smutok 1993	TC	0.00	0.40	0.16	-0.78	0.78	1.00	13	10	23	9	5.95	0.80	0.70
Yavari 2012	TC	-0.56	0.40	0.16	-1.34	0.22	0.16	15	15	30	12	5.88	0.79	-0.68

RCT NAME	Outcome	Difference in means	Standard error	Variance	Lower CI limit	Upper CI limit	*P* Value	Exercise	Control	Total	Study Quality - TESTEX	Weight (Random)	Relative weight	Std Residual
		Statistics for each study						Sample size				Weight (Random)		Residual (Random)
Lambers 2008	TC	-0.30	0.40	0.16	-1.08	0.48	0.45	18	11	29	12	5.85	0.79	-0.03
Jiang 2019 (male)	TC	-0.11	0.40	0.16	-0.90	0.68	0.78	14	11	25	10	5.79	0.78	0.42
Ronnemaa 1988	TC	-0.27	0.42	0.18	-1.10	0.56	0.52	13	12	25	8	5.27	0.71	0.04
Paolillo 2017	TC	-0.03	0.43	0.18	-0.87	0.82	0.95	10	10	20	9	5.11	0.69	0.59
Labrunée 2012	TC	-0.10	0.46	0.21	-1.00	0.80	0.83	11	12	23	9	4.54	0.61	0.40
Vinetti 2015	TC	-0.84	0.48	0.23	-1.78	0.09	0.08	10	10	20	9	4.16	0.56	-1.14
Watkins 2003	TC	-0.16	0.55	0.31	-1.24	0.93	0.78	14	11	25	10	3.14	0.42	0.23
Choi 2012	TC	-0.44	0.56	0.31	-1.53	0.65	0.43	38	37	75	10	3.12	0.42	-0.27
	Total	**-0.29**	**0.04**	**0.00**	**-0.36**	**-0.21**	**<.001**	**1453**	**1141**	**2594**				
Farinatti 2016	TRG	-0.16	0.01	0.00	-0.19	-0.14	0.00	29	14	43	10	4694.33	79.13	0.59
Arija 2017	TRG	0.00	0.08	0.01	-0.16	0.15	0.98	260	104	364	15	160.40	2.70	2.13
Choi 2012	TRG	-0.15	0.09	0.01	-0.32	0.03	0.10	38	37	75	10	125.68	2.12	0.24
Conners 2019	TRG	-0.14	0.09	0.01	-0.32	0.04	0.14	13	13	26	14	115.15	1.94	0.31
Kim 2012	TRG	-0.16	0.10	0.01	-0.35	0.04	0.12	15	15	30	11	100.33	1.69	0.12
Stefanick 1998 (females)	TRG	-0.16	0.11	0.01	-0.37	0.04	0.12	45	43	88	12	90.56	1.53	0.06
Slentz 2007 (high vol VICT)	TRG	-0.16	0.14	0.02	-0.43	0.11	0.24	64	19	83	10	53.27	0.90	0.06
Slentz 2007 (low vol VICT)	TRG	-0.14	0.15	0.02	-0.43	0.15	0.35	61	18	79	10	45.83	0.77	0.20
Farag 2019	TRG	-0.16	0.15	0.02	-0.45	0.14	0.30	30	30	60	10	43.49	0.73	0.08
Laaksonen 2000	TRG	-0.29	0.16	0.03	-0.60	0.02	0.07	20	22	42	11	39.35	0.66	-0.77
Stefanick 1998 (males)	TRG	-0.25	0.16	0.03	-0.56	0.07	0.12	47	46	93	12	38.51	0.65	-0.50
Fang 2019	TRG	-0.22	0.17	0.03	-0.55	0.11	0.19	37	38	75	9	36.01	0.61	-0.31
Chan 2018	TRG	-0.10	0.17	0.03	-0.43	0.23	0.55	82	82	164	13	35.22	0.59	0.40
Anderssen 1995	TRG	-0.41	0.17	0.03	-0.74	-0.08	0.02	49	43	92	11	34.99	0.59	-1.44
Verissimo 2002	TRG	-0.42	0.17	0.03	-0.76	-0.08	0.02	31	32	63	8	33.53	0.57	-1.45
Vinetti 2015	TRG	-0.46	0.19	0.04	-0.83	-0.09	0.01	10	10	20	9	28.46	0.48	-1.56
Phing 2017	TRG	-0.66	0.19	0.04	-1.04	-0.28	0.00	35	88	123	10	26.97	0.45	-2.56
Slentz 2007 (low vol MICT)	TRG	-0.32	0.20	0.04	-0.70	0.07	0.10	51	17	68	10	25.93	0.44	-0.77
Sigal 2007	TRG	-0.05	0.20	0.04	-0.44	0.34	0.80	60	63	123	15	25.30	0.43	0.59
Raz 1994	TRG	-0.20	0.21	0.04	-0.61	0.21	0.33	19	19	38	14	23.24	0.39	-0.15
Thompson 2010	TRG	-0.20	0.23	0.05	-0.64	0.24	0.37	20	21	41	12	19.73	0.33	-0.14
Wedell-Neergaard 2018	TRG	-0.04	0.25	0.06	-0.53	0.45	0.87	14	13	27	9	15.97	0.27	0.51
Motoyama 1995	TRG	-0.08	0.26	0.07	-0.60	0.43	0.76	15	15	30	12	14.44	0.24	0.33
Kadoglou 2009	TRG	-0.13	0.27	0.07	-0.66	0.40	0.63	23	24	47	11	13.59	0.23	0.14
Venojärvi 2013	TRG	-0.20	0.28	0.08	-0.75	0.35	0.48	39	40	79	11	12.50	0.21	-0.11
Kang 2016	TRG	-0.08	0.31	0.10	-0.70	0.53	0.79	12	11	23	7	10.20	0.17	0.27
Yavari 2012	TRG	-1.23	0.33	0.11	-1.87	-0.58	0.00	15	15	30	12	9.36	0.16	-3.24
Dai 2019	TRG	-0.13	0.33	0.11	-0.78	0.52	0.69	34	35	69	11	9.11	0.15	0.11

RCT NAME	Outcome	Statistics for each study: Difference in means	Standard error	Variance	Lower CI limit	Upper CI limit	*P* Value	Sample size: Exercise	Control	Total	Study Quality - TESTEX	Weight (Random): Weight (Random)	Relative weight	Residual (Random): Std Residual
Ronnemaa 1988	TRG	-0.09	0.39	0.15	-0.86	0.68	0.82	13	12	25	8	6.46	0.11	0.20
Labrunée 2012	TRG	-0.20	0.40	0.16	-0.98	0.58	0.62	11	12	23	9	6.27	0.11	-0.08
Paolillo 2017	TRG	-0.07	0.40	0.16	-0.85	0.72	0.86	10	10	20	9	6.26	0.11	0.25
Lambers 2008	TRG	-0.10	0.43	0.18	-0.94	0.74	0.82	18	11	29	12	5.42	0.09	0.16
Watkins 2003	TRG	-0.05	0.47	0.22	-0.97	0.88	0.92	14	11	25	10	4.49	0.08	0.26
Jiang 2019 (male)	TRG	-0.36	0.48	0.23	-1.29	0.57	0.45	14	11	25	10	4.41	0.07	-0.40
Jiang 2019 (female)	TRG	-0.41	0.52	0.27	-1.42	0.60	0.43	11	13	24	10	3.75	0.06	-0.47
Ligtenberg 1997	TRG	-0.10	0.52	0.27	-1.11	0.91	0.85	25	26	51	11	3.74	0.06	0.13
Cao 2019	TRG	-0.54	0.52	0.27	-1.56	0.48	0.30	13	15	28	10	3.66	0.06	-0.71
Sykes 2004	TRG	-0.42	0.55	0.30	-1.49	0.65	0.44	24	12	36	10	3.34	0.06	-0.46
Smutok 1993	TRG	-0.03	0.64	0.41	-1.29	1.22	0.96	13	10	23	9	2.45	0.04	0.21
Gordon 2008	TRG	-0.22	1.58	2.50	-3.32	2.88	0.89	77	77	154	10	0.40	0.01	-0.03
	Total	**-0.17**	**0.01**	**0.00**	**-0.19**	**-0.14**	**<.001**	**1411**	**1147**	**2558**				
Farinatti 2016	HDL-C	0.06	0.01	0.00	0.04	0.07	0.00	29	14	43	10	438.44	6.13	-0.41
Stefanick 1998 (males)	HDL-C	0.04	0.02	0.00	-0.01	0.08	0.12	47	46	93	12	361.28	5.05	-0.78
Anderssen 1995	HDL-C	0.03	0.03	0.00	-0.03	0.08	0.33	49	43	92	11	347.58	4.86	-0.98
Phing 2017	HDL-C	0.12	0.03	0.00	0.06	0.18	0.00	35	88	123	10	318.51	4.46	0.80
Stefanick 1998 (females)	HDL-C	0.03	0.04	0.00	-0.04	0.10	0.35	43	45	88	12	288.27	4.03	-0.75
Arija 2017	HDL-C	0.03	0.04	0.00	-0.04	0.10	0.41	260	104	364	15	287.48	4.02	-0.81
Choi 2012	HDL-C	0.05	0.04	0.00	-0.02	0.12	0.15	38	37	75	10	285.94	4.00	-0.43
Sigal 2007	HDL-C	0.00	0.04	0.00	-0.07	0.07	1.00	60	63	123	15	283.70	3.97	-1.31
Shakil-ur-Rehman 2017	HDL-C	0.10	0.04	0.00	0.02	0.17	0.02	51	51	102	9	260.67	3.65	0.33
Slentz 2007 (low vol MICT)	HDL-C	0.02	0.04	0.00	-0.06	0.10	0.66	51	17	68	10	256.57	3.59	-0.95
Slentz 2007 (high vol VICT)	HDL-C	0.05	0.04	0.00	-0.04	0.14	0.27	64	19	83	10	238.38	3.34	-0.43
Slentz 2007 (low vol VICT)	HDL-C	0.02	0.05	0.00	-0.07	0.11	0.61	61	18	79	10	232.44	3.25	-0.82
Kadoglou 2009	HDL-C	0.04	0.05	0.00	-0.06	0.14	0.42	23	24	47	11	206.79	2.89	-0.51
Wedell-Neergaard 2018	HDL-C	0.04	0.05	0.00	-0.06	0.14	0.44	14	13	27	9	203.14	2.84	-0.52
Ligtenberg 1997	HDL-C	0.07	0.05	0.00	-0.03	0.17	0.18	25	26	51	11	201.56	2.82	-0.09
Laaksonen 2000	HDL-C	0.01	0.05	0.00	-0.09	0.11	0.85	20	22	42	11	197.50	2.76	-0.94
Gram 2010	HDL-C	0.05	0.06	0.00	-0.07	0.16	0.44	22	22	44	13	176.49	2.47	-0.42
Conners 2019	HDL-C	0.20	0.06	0.00	0.08	0.32	0.00	13	13	26	14	165.70	2.32	1.57
Thompson 2010	HDL-C	0.07	0.07	0.00	-0.06	0.20	0.30	20	21	41	12	149.06	2.09	-0.08
Alvarez 2016	HDL-C	0.29	0.07	0.00	0.15	0.42	0.00	13	10	23	12	145.15	2.03	2.54
Verissimo 2002	HDL-C	0.19	0.07	0.01	0.05	0.33	0.01	31	32	63	8	136.38	1.91	1.39
Van den Eynde 2020	HDL-C	0.00	0.07	0.01	-0.14	0.14	1.00	44	40	84	9	134.64	1.88	-0.89
Chan 2018	HDL-C	0.03	0.07	0.01	-0.12	0.18	0.69	82	82	164	13	127.60	1.79	-0.53
Motoyama 1995	HDL-C	0.32	0.08	0.01	0.17	0.46	0.00	15	15	30	12	126.09	1.76	2.72

RCT NAME	Outcome	Statistics for each study: Difference in means	Standard error	Variance	Lower CI limit	Upper CI limit	P Value	Sample size: Exercise	Control	Total	Study Quality - TESTEX	Weight (Random): Weight (Random)	Relative weight	Residual (Random): Std Residual
Dogan Dede 2015	HDL-C	0.00	0.08	0.01	-0.15	0.15	1.00	30	30	60	12	123.21	1.72	-0.85
Fang 2019	HDL-C	0.01	0.08	0.01	-0.15	0.17	0.92	37	38	75	9	113.68	1.59	-0.73
Kang 2016	HDL-C	0.15	0.08	0.01	-0.01	0.31	0.07	12	11	23	7	112.31	1.57	0.76
Cao 2019	HDL-C	0.18	0.08	0.01	0.02	0.34	0.03	13	15	28	10	109.26	1.53	1.09
Yavari 2012	HDL-C	0.03	0.09	0.01	-0.14	0.20	0.74	15	15	30	12	103.85	1.45	-0.49
Dai 2019	HDL-C	0.24	0.09	0.01	0.05	0.42	0.01	34	35	69	11	90.75	1.27	1.53
Kim 2012	HDL-C	0.14	0.10	0.01	-0.04	0.33	0.13	15	15	30	11	88.18	1.23	0.64
Raz 1994	HDL-C	0.00	0.10	0.01	-0.19	0.19	1.00	19	19	38	14	85.49	1.20	-0.71
Lavrencic 2000	HDL-C	0.00	0.10	0.01	-0.20	0.20	1.00	14	15	29	10	78.06	1.09	-0.68
Smutok 1993	HDL-C	0.03	0.11	0.01	-0.18	0.23	0.81	13	10	23	9	74.09	1.04	-0.43
Farag 2019	HDL-C	0.08	0.11	0.01	-0.14	0.29	0.48	30	30	60	10	72.89	1.02	-0.01
Sykes 2004	HDL-C	0.10	0.11	0.01	-0.12	0.32	0.38	24	12	36	10	66.80	0.93	0.20
Paolillo 2017	HDL-C	0.03	0.11	0.01	-0.20	0.25	0.82	10	10	20	9	66.38	0.93	-0.41
Lambers 2008	HDL-C	0.11	0.11	0.01	-0.11	0.33	0.34	18	11	29	12	65.32	0.91	0.28
Vinetti 2015	HDL-C	0.09	0.12	0.01	-0.14	0.31	0.47	10	10	20	9	63.22	0.88	0.07
Labrunée 2012	HDL-C	0.70	0.12	0.01	0.47	0.93	0.00	11	12	23	9	63.17	0.88	4.98
Watkins 2003	HDL-C	0.10	0.12	0.01	-0.14	0.34	0.40	14	11	25	10	58.28	0.82	0.21
Ronnemaa 1988	HDL-C	0.03	0.14	0.02	-0.24	0.30	0.82	13	12	25	8	48.67	0.68	-0.32
Jiang 2019 (female)	HDL-C	0.35	0.14	0.02	0.07	0.63	0.01	11	13	24	10	44.88	0.63	1.84
Jiang 2019 (male)	HDL-C	0.35	0.17	0.03	0.01	0.69	0.04	14	11	25	10	31.78	0.44	1.55
Madden 2013	HDL-C	0.20	0.23	0.05	-0.25	0.65	0.38	25	27	52	13	18.27	0.26	0.53
	Total	**0.08**	**0.01**	**0.00**	**0.05**	**0.10**	**<.001**	**1492**	**1227**	**2719**				
Farinatti 2016	LDL-C	-0.05	0.03	0.00	-0.10	0.00	0.07	29	14	43	10	1416.30	49.11	3.92
Arija 2017	LDL-C	-0.23	0.09	0.01	-0.40	-0.07	0.01	260	104	364	15	138.35	4.80	-1.32
Shakil-ur-Rehman 2017	LDL-C	-0.24	0.09	0.01	-0.42	-0.07	0.01	51	51	102	9	125.55	4.35	-1.35
Lehmann 1995	LDL-C	-0.18	0.09	0.01	-0.36	0.00	0.05	16	13	29	9	114.26	3.96	-0.62
Stefanick 1998 (females)	LDL-C	-0.08	0.10	0.01	-0.27	0.11	0.42	43	45	88	12	101.23	3.51	0.44
Stefanick 1998 (males)	LDL-C	-0.03	0.11	0.01	-0.24	0.18	0.81	47	46	93	12	87.17	3.02	0.92
Anderssen 1995	LDL-C	-0.09	0.11	0.01	-0.31	0.13	0.42	49	43	92	11	78.81	2.73	0.30
Slentz 2007 (low vol VICT)	LDL-C	-0.28	0.12	0.01	-0.52	-0.04	0.02	61	18	79	10	68.17	2.36	-1.31
Conners 2019	LDL-C	-0.10	0.12	0.02	-0.34	0.14	0.41	13	13	26	14	65.78	2.28	0.17
Sigal 2007	LDL-C	-0.12	0.13	0.02	-0.38	0.14	0.36	55	61	116	15	57.57	2.00	0.02
Slentz 2007 (high vol VICT)	LDL-C	-0.19	0.13	0.02	-0.45	0.07	0.16	64	19	83	10	55.98	1.94	-0.50
Venojärvi 2013	LDL-C	-0.30	0.14	0.02	-0.58	-0.02	0.03	39	40	79	11	49.98	1.73	-1.26
Chan 2018	LDL-C	-0.03	0.14	0.02	-0.31	0.25	0.83	82	82	164	13	48.44	1.68	0.65
Wedell-Neergaard 2018	LDL-C	-0.29	0.15	0.02	-0.58	0.00	0.05	14	13	27	9	46.68	1.62	-1.15
Slentz 2007 (low vol MICT)	LDL-C	-0.21	0.15	0.02	-0.50	0.08	0.16	51	17	68	10	45.22	1.57	-0.57

		Statistics for each study						Sample size				Weight (Random)		Residual (Random)
RCT NAME	Outcome	Difference in means	Standard error	Variance	Lower CI limit	Upper CI limit	*P* Value	Exercise	Control	Total	Study Quality - TESTEX	Weight (Random)	Relative weight	Std Residual
Van den Eynde 2020	LDL-C	-0.20	0.17	0.03	-0.53	0.13	0.24	44	40	84	9	34.53	1.20	-0.45
Alvarez 2016	LDL-C	-0.13	0.18	0.03	-0.48	0.22	0.46	13	10	23	12	32.12	1.11	-0.04
Laaksonen 2000	LDL-C	-0.20	0.21	0.04	-0.61	0.21	0.34	20	22	42	11	22.40	0.78	-0.36
Kim 2012	LDL-C	-0.50	0.21	0.05	-0.92	-0.08	0.02	15	15	30	11	21.88	0.76	-1.76
Verissimo 2002	LDL-C	-0.49	0.22	0.05	-0.92	-0.06	0.02	31	32	63	8	21.03	0.73	-1.69
Dai 2019	LDL-C	-0.38	0.22	0.05	-0.82	0.06	0.09	34	35	69	11	19.84	0.69	-1.17
Gram 2010	LDL-C	-0.10	0.23	0.05	-0.55	0.35	0.66	22	22	44	13	18.97	0.66	0.10
Kadoglou 2009	LDL-C	-0.45	0.23	0.05	-0.90	0.01	0.05	23	24	47	11	18.54	0.64	-1.40
Fang 2019	LDL-C	-0.73	0.24	0.06	-1.20	-0.25	0.00	37	38	75	9	16.95	0.59	-2.48
Farag 2019	LDL-C	-0.32	0.25	0.06	-0.81	0.17	0.20	30	30	60	10	15.92	0.55	-0.80
Dogan Dede 2015	LDL-C	-0.20	0.25	0.06	-0.70	0.30	0.43	30	30	60	12	15.47	0.54	-0.30
Sykes 2004	LDL-C	-0.11	0.26	0.07	-0.63	0.41	0.68	24	12	36	10	14.39	0.50	0.05
Madden 2013	LDL-C	-0.20	0.28	0.08	-0.76	0.36	0.48	25	27	52	13	12.46	0.43	-0.27
Jiang 2019 (male)	LDL-C	-0.13	0.29	0.08	-0.69	0.43	0.65	14	11	25	10	12.15	0.42	-0.02
Motoyama 1995	LDL-C	-0.04	0.29	0.08	-0.61	0.52	0.88	15	15	30	12	12.11	0.42	0.28
Ligtenberg 1997	LDL-C	0.00	0.29	0.08	-0.57	0.57	1.00	25	26	51	11	11.90	0.41	0.43
Jiang 2019 (female)	LDL-C	-0.44	0.29	0.08	-1.01	0.13	0.13	11	13	24	10	11.83	0.41	-1.09
Cao 2019	LDL-C	-0.15	0.30	0.09	-0.73	0.43	0.61	13	15	28	10	11.43	0.40	-0.09
Smutok 1993	LDL-C	-0.13	0.33	0.11	-0.77	0.51	0.69	13	10	23	9	9.42	0.33	-0.02
Labrunée 2012	LDL-C	-0.10	0.34	0.12	-0.77	0.57	0.77	11	12	23	9	8.57	0.30	0.07
Lavrencic 2000	LDL-C	-0.10	0.35	0.12	-0.78	0.58	0.77	14	15	29	10	8.28	0.29	0.07
Yavari 2012	LDL-C	-0.30	0.35	0.12	-0.98	0.39	0.40	15	15	30	12	8.14	0.28	-0.50
Ronnemaa 1988	LDL-C	-0.25	0.37	0.14	-0.97	0.47	0.50	13	12	25	8	7.32	0.25	-0.34
Paolillo 2017	LDL-C	-0.08	0.40	0.16	-0.87	0.71	0.85	10	10	20	9	6.17	0.21	0.11
Choi 2012	LDL-C	-0.49	0.43	0.18	-1.33	0.34	0.25	38	37	75	10	5.52	0.19	-0.87
Watkins 2003	LDL-C	-0.47	0.44	0.19	-1.33	0.40	0.29	14	11	25	10	5.15	0.18	-0.78
Vinetti 2015	LDL-C	-0.93	0.70	0.49	-2.30	0.43	0.18	10	10	20	9	2.06	0.07	-1.16
	Total	**-0.12**	**0.02**	**0.00**	**-0.16**	**-0.09**	**<.001**	**1438**	**1128**	**2566**				

CI: confidence intervals; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; TC: total cholesterol; TRG: triglycerides

SM Table 6.8 Studies ranked by random relative weight for each outcome

SM Table 6.9 shows K-1 analysis of all studies for each outcome, with the studies ranked by random relative weight. The per line statistics shown in SM Table 5 are the pooled values when the study is removed, per study.

Study name	Outcome	Statistics for each study					*P value*
		Difference in means	Standard error	Variance	Lower CI limit	Upper CI limit	
Farinatti 2016	TC	-0.28	0.04	0.00	-0.37	-0.20	<.001
Kim 2012	TC	-0.27	0.04	0.00	-0.34	-0.20	<.001
Slentz 2007 (high vol VICT)	TC	-0.29	0.04	0.00	-0.36	-0.22	<.001
Slentz 2007 (low vol MICT)	TC	-0.29	0.04	0.00	-0.36	-0.21	<.001
Alvarez 2016	TC	-0.29	0.04	0.00	-0.36	-0.22	<.001
Gordon 2008	TC	-0.27	0.04	0.00	-0.34	-0.20	<.001
Wedell-Neergaard 2018	TC	-0.29	0.04	0.00	-0.36	-0.21	<.001
Chan 2018	TC	-0.29	0.04	0.00	-0.36	-0.21	<.001
Dogan Dede 2015	TC	-0.29	0.04	0.00	-0.36	-0.21	<.001
Verissimo 2002	TC	-0.28	0.04	0.00	-0.35	-0.21	<.001
Dai 2019	TC	-0.29	0.02	0.00	-0.33	-0.25	<.001
Arija 2017	TC	-0.29	0.04	0.00	-0.36	-0.21	<.001
Farag 2019	TC	-0.28	0.04	0.00	-0.36	-0.21	<.001
Fang 2019	TC	-0.28	0.04	0.00	-0.35	-0.21	<.001
Laaksonen 2000	TC	-0.29	0.04	0.00	-0.36	-0.21	<.001
Thompson 2010	TC	-0.29	0.04	0.00	-0.36	-0.22	<.001
Ligtenberg 1997	TC	-0.29	0.04	0.00	-0.36	-0.21	<.001
Gram 2010	TC	-0.29	0.04	0.00	-0.36	-0.21	<.001
Motoyama 1995	TC	-0.29	0.04	0.00	-0.36	-0.21	<.001
Raz 1994	TC	-0.29	0.04	0.00	-0.36	-0.22	<.001
Sykes 2004	TC	-0.29	0.04	0.00	-0.36	-0.22	<.001
Cao 2019	TC	-0.29	0.04	0.00	-0.36	-0.21	<.001
Stefanick 1998 (males)	TC	-0.30	0.04	0.00	-0.37	-0.23	<.001
Madden 2013	TC	-0.29	0.04	0.00	-0.36	-0.21	<.001
Jiang 2019 (female)	TC	-0.29	0.04	0.00	-0.36	-0.22	<.001
Lavrencic 2000	TC	-0.29	0.04	0.00	-0.36	-0.21	<.001
Smutok 1993	TC	-0.29	0.04	0.00	-0.36	-0.22	<.001
Yavari 2012	TC	-0.28	0.04	0.00	-0.36	-0.21	<.001
Lambers 2008	TC	-0.29	0.04	0.00	-0.36	-0.21	<.001
Jiang 2019 (male)	TC	-0.29	0.04	0.00	-0.36	-0.21	<.001
Ronnemaa 1988	TC	-0.29	0.04	0.00	-0.36	-0.21	<.001
Paolillo 2017	TC	-0.29	0.04	0.00	-0.36	-0.22	<.001
Labrunée 2012	TC	-0.29	0.04	0.00	-0.36	-0.21	<.001
Stefanick 1998 (females)	TC	-0.29	0.04	0.00	-0.37	-0.22	<.001
Vinetti 2015	TC	-0.28	0.04	0.00	-0.35	-0.21	<.001
Watkins 2003	TC	-0.29	0.04	0.00	-0.36	-0.21	<.001
Choi 2012	TC	-0.29	0.04	0.00	-0.36	-0.21	<.001
Anderssen 1995	TC	-0.30	0.04	0.00	-0.37	-0.23	<.001
Venojärvi 2013	TC	-0.29	0.04	0.00	-0.36	-0.21	<.001
Kadoglou 2009	TC	-0.28	0.04	0.00	-0.35	-0.20	<.001
Slentz 2007 (low vol VICT)	TC	-0.29	0.04	0.00	-0.36	-0.21	<.001
Sigal 2007	TC	-0.29	0.04	0.00	-0.37	-0.22	<.001
	Total	**-0.29**	**0.04**	**0.00**	**-0.36**	**-0.21**	**<.001**
Farinatti 2016	TRG	-0.18	0.03	0.00	-0.24	-0.13	<.001
Laaksonen 2000	TRG	-0.17	0.01	0.00	-0.19	-0.14	<.001
Stefanick 1998 (males)	TRG	-0.17	0.01	0.00	-0.19	-0.14	<.001
Fang 2019	TRG	-0.17	0.01	0.00	-0.19	-0.14	<.001
Chan 2018	TRG	-0.17	0.01	0.00	-0.19	-0.14	<.001
Anderssen 1995	TRG	-0.17	0.01	0.00	-0.19	-0.14	<.001
Verissimo 2002	TRG	-0.17	0.01	0.00	-0.19	-0.14	<.001
Vinetti 2015	TRG	-0.17	0.01	0.00	-0.19	-0.14	<.001
Phing 2017	TRG	-0.17	0.01	0.00	-0.19	-0.14	<.001
Slentz 2007 (low vol MICT)	TRG	-0.17	0.01	0.00	-0.19	-0.14	<.001
Sigal 2007	TRG	-0.17	0.01	0.00	-0.19	-0.14	<.001
Arija 2017	TRG	-0.17	0.01	0.00	-0.20	-0.15	<.001
Raz 1994	TRG	-0.17	0.01	0.00	-0.19	-0.14	<.001
Thompson 2010	TRG	-0.17	0.01	0.00	-0.19	-0.14	<.001

Study name	Outcome	Statistics for each study					*P value*
		Difference in means	Standard error	Variance	Lower CI limit	Upper CI limit	
Wedell-Neergaard 2018	TRG	-0.17	0.01	0.00	-0.19	-0.14	<.001
Motoyama 1995	TRG	-0.17	0.01	0.00	-0.19	-0.14	<.001
Kadoglou 2009	TRG	-0.17	0.01	0.00	-0.19	-0.14	<.001
Venojärvi 2013	TRG	-0.17	0.01	0.00	-0.19	-0.14	<.001
Kang 2016	TRG	-0.17	0.01	0.00	-0.19	-0.14	<.001
Yavari 2012	TRG	-0.17	0.01	0.00	-0.19	-0.14	<.001
Dai 2019	TRG	-0.17	0.01	0.00	-0.19	-0.14	<.001
Ronnemaa 1988	TRG	-0.17	0.01	0.00	-0.19	-0.14	<.001
Choi 2012	TRG	-0.17	0.01	0.00	-0.19	-0.14	<.001
Labrunée 2012	TRG	-0.17	0.01	0.00	-0.19	-0.14	<.001
Paolillo 2017	TRG	-0.17	0.01	0.00	-0.19	-0.14	<.001
Lambers 2008	TRG	-0.17	0.01	0.00	-0.19	-0.14	<.001
Watkins 2003	TRG	-0.17	0.01	0.00	-0.19	-0.14	<.001
Jiang 2019 (male)	TRG	-0.17	0.01	0.00	-0.19	-0.14	<.001
Jiang 2019 (female)	TRG	-0.17	0.01	0.00	-0.19	-0.14	<.001
Ligtenberg 1997	TRG	-0.17	0.01	0.00	-0.19	-0.14	<.001
Cao 2019	TRG	-0.17	0.01	0.00	-0.19	-0.14	<.001
Sykes 2004	TRG	-0.17	0.01	0.00	-0.19	-0.14	<.001
Smutok 1993	TRG	-0.17	0.01	0.00	-0.19	-0.14	<.001
Conners 2019	TRG	-0.17	0.01	0.00	-0.19	-0.14	<.001
Gordon 2008	TRG	-0.17	0.01	0.00	-0.19	-0.14	<.001
Kim 2012	TRG	-0.17	0.01	0.00	-0.19	-0.14	<.001
Stefanick 1998 (females)	TRG	-0.17	0.01	0.00	-0.19	-0.14	<.001
Slentz 2007 (high vol VICT)	TRG	-0.17	0.01	0.00	-0.19	-0.14	<.001
Slentz 2007 (low vol VICT)	TRG	-0.17	0.01	0.00	-0.19	-0.14	<.001
Farag 2019	TRG	-0.17	0.01	0.00	-0.19	-0.14	<.001
	Total	**-0.17**	**0.01**	**0.00**	**-0.19**	**-0.14**	**<.001**
Farinatti 2016	HDL-C	0.08	0.01	0.00	0.05	0.11	<.001
Slentz 2007 (low vol MICT)	HDL-C	0.08	0.01	0.00	0.05	0.10	<.001
Slentz 2007 (high vol VICT)	HDL-C	0.08	0.01	0.00	0.05	0.10	<.001
Slentz 2007 (low vol VICT)	HDL-C	0.08	0.01	0.00	0.05	0.10	<.001
Kadoglou 2009	HDL-C	0.08	0.01	0.00	0.05	0.10	<.001
Wedell-Neergaard 2018	HDL-C	0.08	0.01	0.00	0.05	0.10	<.001
Ligtenberg 1997	HDL-C	0.08	0.01	0.00	0.05	0.10	<.001
Laaksonen 2000	HDL-C	0.08	0.01	0.00	0.05	0.10	<.001
Gram 2010	HDL-C	0.08	0.01	0.00	0.05	0.10	<.001
Conners 2019	HDL-C	0.07	0.01	0.00	0.05	0.10	<.001
Thompson 2010	HDL-C	0.08	0.01	0.00	0.05	0.10	<.001
Stefanick 1998 (males)	HDL-C	0.08	0.01	0.00	0.05	0.10	<.001
Alvarez 2016	HDL-C	0.07	0.01	0.00	0.05	0.09	<.001
Verissimo 2002	HDL-C	0.07	0.01	0.00	0.05	0.10	<.001
Van den Eynde 2020	HDL-C	0.08	0.01	0.00	0.05	0.10	<.001
Chan 2018	HDL-C	0.08	0.01	0.00	0.05	0.10	<.001
Motoyama 1995	HDL-C	0.07	0.01	0.00	0.05	0.09	<.001
Dogan Dede 2015	HDL-C	0.08	0.01	0.00	0.05	0.10	<.001
Fang 2019	HDL-C	0.08	0.01	0.00	0.05	0.10	<.001
Kang 2016	HDL-C	0.07	0.01	0.00	0.05	0.10	<.001
Cao 2019	HDL-C	0.07	0.01	0.00	0.05	0.10	<.001
Yavari 2012	HDL-C	0.08	0.01	0.00	0.05	0.10	<.001
Anderssen 1995	HDL-C	0.08	0.01	0.00	0.06	0.10	<.001
Dai 2019	HDL-C	0.07	0.01	0.00	0.05	0.10	<.001
Kim 2012	HDL-C	0.08	0.01	0.00	0.05	0.10	<.001
Raz 1994	HDL-C	0.08	0.01	0.00	0.05	0.10	<.001
Lavrencic 2000	HDL-C	0.08	0.01	0.00	0.05	0.10	<.001
Smutok 1993	HDL-C	0.08	0.01	0.00	0.05	0.10	<.001
Farag 2019	HDL-C	0.08	0.01	0.00	0.05	0.10	<.001
Sykes 2004	HDL-C	0.08	0.01	0.00	0.05	0.10	<.001
Paolillo 2017	HDL-C	0.08	0.01	0.00	0.05	0.10	<.001
Lambers 2008	HDL-C	0.08	0.01	0.00	0.05	0.10	<.001
Vinetti 2015	HDL-C	0.08	0.01	0.00	0.05	0.10	<.001
Phing 2017	HDL-C	0.07	0.01	0.00	0.05	0.10	<.001

Study name	Outcome	Statistics for each study					*P value*
		Difference in means	Standard error	Variance	Lower CI limit	Upper CI limit	
Labrunée 2012	HDL-C	0.07	0.01	0.00	0.05	0.09	<.001
Watkins 2003	HDL-C	0.08	0.01	0.00	0.05	0.10	<.001
Ronnemaa 1988	HDL-C	0.08	0.01	0.00	0.05	0.10	<.001
Jiang 2019 (female)	HDL-C	0.07	0.01	0.00	0.05	0.10	<.001
Jiang 2019 (male)	HDL-C	0.07	0.01	0.00	0.05	0.10	<.001
Madden 2013	HDL-C	0.08	0.01	0.00	0.05	0.10	<.001
Stefanick 1998 (females)	HDL-C	0.08	0.01	0.00	0.05	0.10	<.001
Arija 2017	HDL-C	0.08	0.01	0.00	0.05	0.10	<.001
Choi 2012	HDL-C	0.08	0.01	0.00	0.05	0.10	<.001
Sigal 2007	HDL-C	0.08	0.01	0.00	0.06	0.10	<.001
Shakil-ur-Rehman 2017	HDL-C	0.08	0.01	0.00	0.05	0.10	<.001
	Total	**0.08**	**0.01**	**0.00**	**0.05**	**0.10**	**<.001**
Farinatti 2016	LDL-C	-0.19	0.03	0.00	-0.25	-0.14	<.001
Sigal 2007	LDL-C	-0.12	0.02	0.00	-0.16	-0.09	<.001
Slentz 2007 (high vol VICT)	LDL-C	-0.12	0.02	0.00	-0.16	-0.09	<.001
Venojärvi 2013	LDL-C	-0.12	0.02	0.00	-0.16	-0.08	<.001
Chan 2018	LDL-C	-0.12	0.02	0.00	-0.16	-0.09	<.001
Wedell-Neergaard 2018	LDL-C	-0.12	0.02	0.00	-0.16	-0.08	<.001
Slentz 2007 (low vol MICT)	LDL-C	-0.12	0.02	0.00	-0.16	-0.09	<.001
Van den Eynde 2020	LDL-C	-0.12	0.02	0.00	-0.16	-0.09	<.001
Alvarez 2016	LDL-C	-0.12	0.02	0.00	-0.16	-0.09	<.001
Laaksonen 2000	LDL-C	-0.12	0.02	0.00	-0.16	-0.09	<.001
Kim 2012	LDL-C	-0.12	0.02	0.00	-0.16	-0.08	<.001
Arija 2017	LDL-C	-0.12	0.02	0.00	-0.16	-0.08	<.001
Verissimo 2002	LDL-C	-0.12	0.02	0.00	-0.16	-0.08	<.001
Dai 2019	LDL-C	-0.12	0.02	0.00	-0.16	-0.08	<.001
Gram 2010	LDL-C	-0.12	0.02	0.00	-0.16	-0.09	<.001
Kadoglou 2009	LDL-C	-0.12	0.02	0.00	-0.16	-0.08	<.001
Fang 2019	LDL-C	-0.12	0.02	0.00	-0.16	-0.08	<.001
Farag 2019	LDL-C	-0.12	0.02	0.00	-0.16	-0.09	<.001
Dogan Dede 2015	LDL-C	-0.12	0.02	0.00	-0.16	-0.09	<.001
Sykes 2004	LDL-C	-0.12	0.02	0.00	-0.16	-0.09	<.001
Madden 2013	LDL-C	-0.12	0.02	0.00	-0.16	-0.09	<.001
Jiang 2019 (male)	LDL-C	-0.12	0.02	0.00	-0.16	-0.09	<.001
Shakil-ur-Rehman 2017	LDL-C	-0.12	0.02	0.00	-0.16	-0.08	<.001
Motoyama 1995	LDL-C	-0.12	0.02	0.00	-0.16	-0.09	<.001
Ligtenberg 1997	LDL-C	-0.12	0.02	0.00	-0.16	-0.09	<.001
Jiang 2019 (female)	LDL-C	-0.12	0.02	0.00	-0.16	-0.09	<.001
Cao 2019	LDL-C	-0.12	0.02	0.00	-0.16	-0.09	<.001
Smutok 1993	LDL-C	-0.12	0.02	0.00	-0.16	-0.09	<.001
Labrunée 2012	LDL-C	-0.12	0.02	0.00	-0.16	-0.09	<.001
Lavrencic 2000	LDL-C	-0.12	0.02	0.00	-0.16	-0.09	<.001
Yavari 2012	LDL-C	-0.12	0.02	0.00	-0.16	-0.09	<.001
Ronnemaa 1988	LDL-C	-0.12	0.02	0.00	-0.16	-0.09	<.001
Paolillo 2017	LDL-C	-0.12	0.02	0.00	-0.16	-0.09	<.001
Lehmann 1995	LDL-C	-0.12	0.02	0.00	-0.16	-0.08	<.001
Choi 2012	LDL-C	-0.12	0.02	0.00	-0.16	-0.09	<.001
Watkins 2003	LDL-C	-0.12	0.02	0.00	-0.16	-0.09	<.001
Vinetti 2015	LDL-C	-0.12	0.02	0.00	-0.16	-0.09	<.001
Stefanick 1998 (females)	LDL-C	-0.12	0.02	0.00	-0.16	-0.09	<.001
Stefanick 1998 (males)	LDL-C	-0.13	0.02	0.00	-0.16	-0.09	<.001
Anderssen 1995	LDL-C	-0.12	0.02	0.00	-0.16	-0.09	<.001
Slentz 2007 (low vol VICT)	LDL-C	-0.12	0.02	0.00	-0.16	-0.08	<.001
Conners 2019	LDL-C	-0.12	0.02	0.00	-0.16	-0.09	<.001
	Total	**-0.12**	**0.02**	**0.00**	**-0.16**	**-0.09**	**<.001**

CI: confidence intervals; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; TC: total cholesterol; TRG: triglycerides

SM Table 6.9 Leave-one-out (K-1) analysis of studies ranked by random relative weight for each outcome

Pooled analysis 95% confidence interval boundaries: detection of outliers

The upper and lower confidence interval (CI) limits of each study was compared to the pooled analysis CI boundaries. SM Table 6.10 shows the studies revealed to be outliers; the upper CI limit of a study was less than the pooled CI lower limit, or the lower CI limit of a study was larger than pooled CI upper limit.

Study name	Outcome	Lower CI limit	Upper CI limit	Sample size Exercise	Control	Total	Study Quality
Dai 2019	TC	-1.852	-0.914	34	35	69	11
Gordon 2008	TC	-1.158	-0.422	77	77	154	10
Kim 2012	TC	-1.007	-0.363	15	15	30	11
Pooled statistics		**-0.357**	**-0.214**				
Alvarez 2016	HDL-C	0.151	0.419	13	10	23	12
Motoyama 1995	HDL-C	0.168	0.464	15	15	30	12
Labrunée 2012	HDL-C	0.471	0.929	11	12	23	9
Pooled statistics		**0.053**	**0.099**				

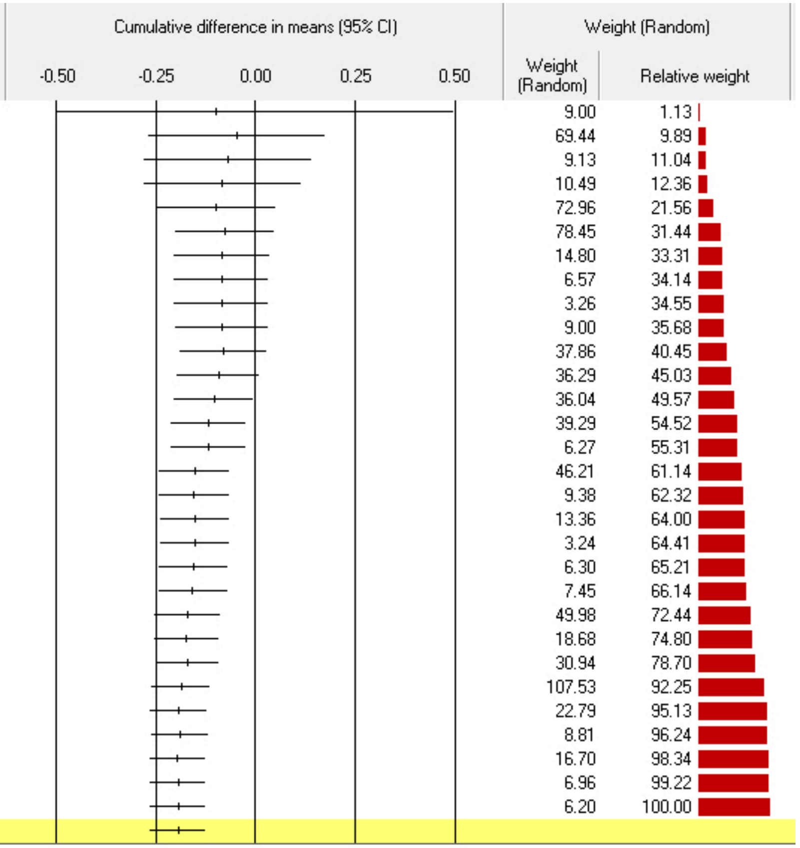
CI: confidence intervals; HDL-C: high-density lipoprotein cholesterol; TC: total cholesterol

SM Table 6.10 Pooled 95% confidence interval boundary detection of outliers

TESTEX Forest plots

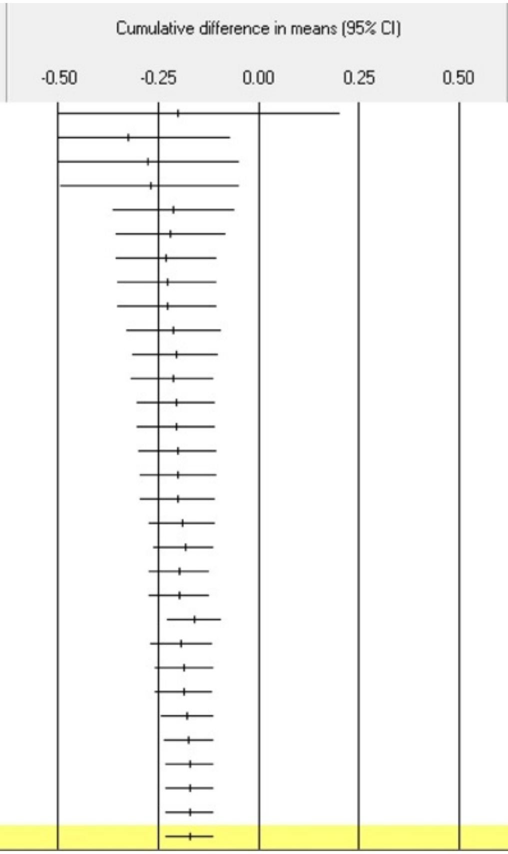
Cumulative random univariate meta-analysis of the SLP (raw mean difference, K-H adjustment, 95% confidence intervals)

Model	Study name	Outcome	Cumulative statistics						Cumulative sample size		Study Quality	Weight (Random)	
			Point	Standard error	Variance	Lower limit	Upper limit	p-Value	Exercise	Control		Weight (Random)	Relative weight
	Raz 1994	TC	-0.100	0.333	0.111	-0.753	0.553	0.764	19	19	14	9.00	1.13
	Anderssen 1995	TC	-0.047	0.113	0.013	-0.268	0.174	0.678	68	62	11	69.44	9.89
	Motoyama 1995	TC	-0.069	0.107	0.011	-0.278	0.140	0.519	83	77	12	9.13	11.04
	Ligtenberg 1997	TC	-0.083	0.101	0.010	-0.281	0.115	0.411	108	103	11	10.49	12.36
	Stefanick 1998 (females)	TC	-0.099	0.076	0.006	-0.249	0.051	0.194	151	148	12	72.96	21.56
	Stefanick 1998 (males)	TC	-0.078	0.063	0.004	-0.202	0.046	0.216	198	194	12	78.45	31.44
	Laaksonen 2000	TC	-0.084	0.062	0.004	-0.205	0.036	0.172	218	216	11	14.80	33.31
	Lavrencic 2000	TC	-0.084	0.061	0.004	-0.204	0.035	0.164	232	231	10	6.57	34.14
	Watkins 2003	TC	-0.085	0.060	0.004	-0.204	0.033	0.158	246	242	10	3.26	34.55
	Sykes 2004	TC	-0.085	0.059	0.004	-0.202	0.031	0.150	270	254	10	9.00	35.68
	Sigal 2007	TC	-0.081	0.056	0.003	-0.191	0.028	0.145	330	317	15	37.86	40.45
	Slentz 2007 (high vol VICT)	TC	-0.092	0.053	0.003	-0.196	0.012	0.082	394	336	10	36.29	45.03
	Slentz 2007 (low vol MICT)	TC	-0.104	0.050	0.003	-0.203	-0.006	0.038	445	353	10	36.04	49.57
	Slentz 2007 (low vol VICT)	TC	-0.118	0.048	0.002	-0.212	-0.023	0.015	506	371	10	39.29	54.52
	Lambers 2008	TC	-0.120	0.048	0.002	-0.214	-0.027	0.012	524	382	12	6.27	55.31
	Kadoglou 2009	TC	-0.152	0.045	0.002	-0.241	-0.063	0.001	547	406	11	46.21	61.14
	Gram 2010	TC	-0.154	0.045	0.002	-0.242	-0.066	0.001	569	428	13	9.38	62.32
	Thompson 2010	TC	-0.151	0.044	0.002	-0.238	-0.064	0.001	589	449	12	13.36	64.00
	Choi 2012	TC	-0.152	0.044	0.002	-0.239	-0.066	0.001	627	486	10	3.24	64.41
	Yavari 2012	TC	-0.157	0.044	0.002	-0.244	-0.071	0.000	642	501	12	6.30	65.21
	Madden 2013	TC	-0.158	0.044	0.002	-0.244	-0.072	0.000	667	528	13	7.45	66.14
	Venojärvi 2013	TC	-0.170	0.042	0.002	-0.252	-0.089	0.000	706	568	11	49.98	72.44
	Dogan Dede 2015	TC	-0.173	0.041	0.002	-0.253	-0.092	0.000	736	598	12	18.68	74.80
	Alvarez 2016	TC	-0.172	0.040	0.002	-0.250	-0.094	0.000	749	608	12	30.94	78.70
	Arija 2017	TC	-0.188	0.037	0.001	-0.260	-0.115	0.000	1009	712	15	107.53	92.25
	Chan 2018	TC	-0.192	0.036	0.001	-0.263	-0.120	0.000	1091	794	13	22.79	95.13
	Cao 2019	TC	-0.191	0.036	0.001	-0.262	-0.120	0.000	1104	809	10	8.81	96.24
	Farag 2019	TC	-0.196	0.036	0.001	-0.266	-0.126	0.000	1134	839	10	16.70	98.34
	Jiang 2019 (female)	TC	-0.194	0.036	0.001	-0.264	-0.124	0.000	1145	852	10	6.96	99.22
	Jiang 2019 (male)	TC	-0.194	0.036	0.001	-0.263	-0.124	0.000	1159	863	10	6.20	100.00
Random			-0.194	0.036	0.001	-0.263	-0.124	0.000					



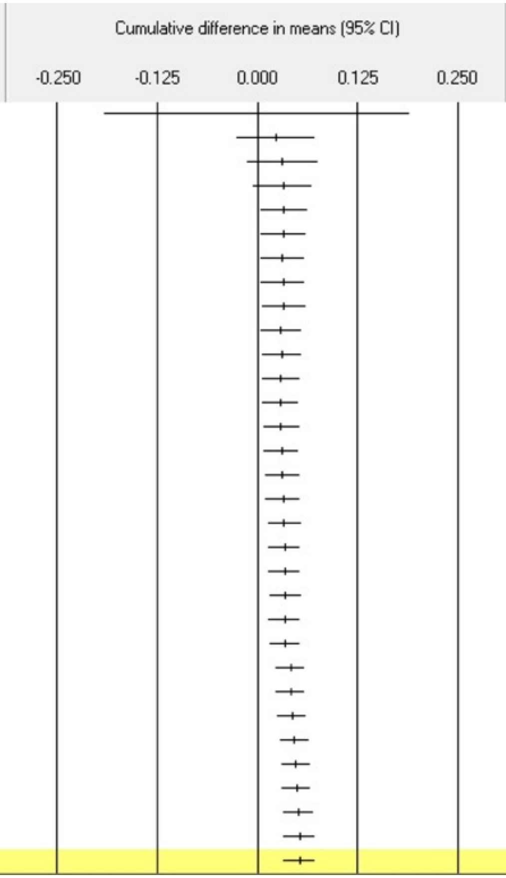
SM Figure 6.10 TC TESTEX score ≥10 (outliers and influencer removed) forest plot with statistics

Model	Study name	Outcome	Cumulative statistics						Cumulative sample size		Study Quality	Weight (Random)	
			Point	Standard error	Variance	Lower limit	Upper limit	p-Value	Exercise	Control		Weight (Random)	Relative weight
	Raz 1994	TRG	-0.200	0.207	0.043	-0.607	0.207	0.335	19	19	14	23.24	2.13
	Anderssen 1995	TRG	-0.326	0.131	0.017	-0.583	-0.069	0.013	68	62	11	34.99	5.33
	Motoyama 1995	TRG	-0.277	0.117	0.014	-0.507	-0.048	0.018	83	77	12	14.44	6.65
	Ligtenberg 1997	TRG	-0.269	0.114	0.013	-0.493	-0.045	0.019	108	103	11	3.74	7.00
	Stefanick 1998 (females)	TRG	-0.211	0.077	0.006	-0.363	-0.059	0.006	153	146	12	90.56	15.29
	Stefanick 1998 (males)	TRG	-0.218	0.070	0.005	-0.355	-0.081	0.002	200	192	12	38.51	18.81
	Laaksonen 2000	TRG	-0.230	0.064	0.004	-0.355	-0.104	0.000	220	214	11	39.35	22.42
	Watkins 2003	TRG	-0.226	0.063	0.004	-0.350	-0.102	0.000	234	225	10	4.49	22.83
	Sykes 2004	TRG	-0.229	0.063	0.004	-0.352	-0.106	0.000	258	237	10	3.34	23.13
	Sigal 2007	TRG	-0.213	0.060	0.004	-0.330	-0.095	0.000	318	300	15	25.30	25.45
	Slentz 2007 (high vol VICT)	TRG	-0.204	0.055	0.003	-0.312	-0.096	0.000	382	319	10	53.27	30.33
	Slentz 2007 (low vol MICT)	TRG	-0.212	0.053	0.003	-0.316	-0.109	0.000	433	336	10	25.93	32.70
	Slentz 2007 (low vol VICT)	TRG	-0.204	0.050	0.002	-0.302	-0.106	0.000	494	354	10	45.83	36.90
	Gordon 2008	TRG	-0.204	0.050	0.002	-0.302	-0.106	0.000	571	431	10	0.40	36.94
	Lambers 2008	TRG	-0.203	0.049	0.002	-0.300	-0.106	0.000	589	442	12	5.42	37.43
	Kadoglou 2009	TRG	-0.200	0.049	0.002	-0.296	-0.105	0.000	612	466	11	13.59	38.68
	Thompson 2010	TRG	-0.200	0.048	0.002	-0.293	-0.107	0.000	632	487	12	19.73	40.48
	Choi 2012	TRG	-0.188	0.042	0.002	-0.271	-0.106	0.000	670	524	10	125.68	51.99
	Kim 2012	TRG	-0.184	0.039	0.001	-0.259	-0.108	0.000	685	539	11	100.33	61.18
	Yavari 2012	TRG	-0.198	0.038	0.001	-0.273	-0.123	0.000	700	554	12	9.36	62.03
	Venojärvi 2013	TRG	-0.198	0.038	0.001	-0.273	-0.123	0.000	739	594	11	12.50	63.18
	Arija 2017	TRG	-0.161	0.034	0.001	-0.228	-0.094	0.000	999	698	15	160.40	77.86
	Phing 2017	TRG	-0.193	0.039	0.002	-0.270	-0.116	0.000	1034	786	10	26.97	80.33
	Chan 2018	TRG	-0.186	0.037	0.001	-0.259	-0.113	0.000	1116	868	13	35.22	83.56
	Cao 2019	TRG	-0.186	0.037	0.001	-0.258	-0.114	0.000	1129	883	10	3.66	83.89
	Conners 2019	TRG	-0.177	0.033	0.001	-0.242	-0.112	0.000	1142	896	14	115.15	94.44
	Dai 2019	TRG	-0.173	0.032	0.001	-0.236	-0.111	0.000	1176	931	11	9.11	95.27
	Farag 2019	TRG	-0.170	0.030	0.001	-0.229	-0.110	0.000	1206	961	10	43.49	99.25
	Jiang 2019 (female)	TRG	-0.171	0.030	0.001	-0.230	-0.111	0.000	1217	974	10	3.75	99.60
	Jiang 2019 (male)	TRG	-0.172	0.030	0.001	-0.231	-0.112	0.000	1231	985	10	4.41	100.00
Random			-0.172	0.030	0.001	-0.231	-0.112	0.000					



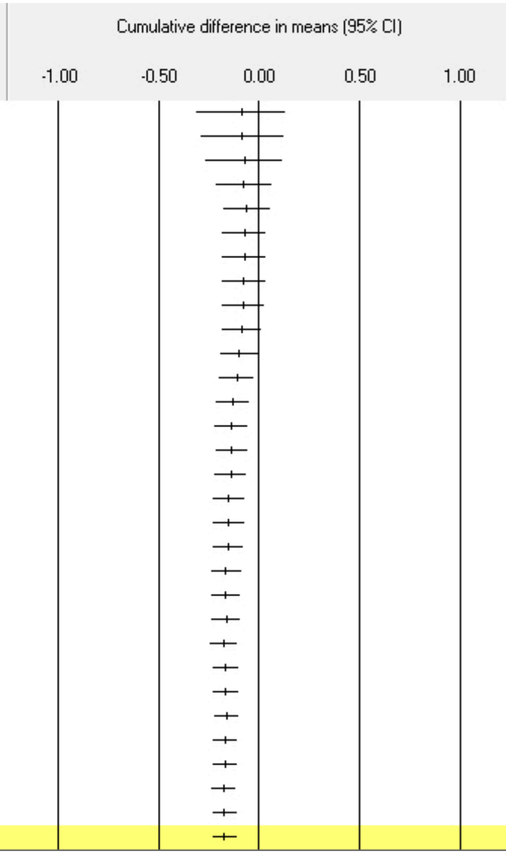
SM Figure 6.11 TRG TESTEX score ≥10 (influencer removed) forest plot with statistics

Model	Study name	Outcome	Cumulative statistics						Cumulative sample size		Study Quality	Weight (Random)	
			Point	Standard error	Variance	Lower limit	Upper limit	p-Value	Exercise	Control		Weight (Random)	Relative weight
	Raz 1994	HDL-C	0.000	0.097	0.009	-0.191	0.191	1.000	19	19	14	102.10	1.02
	Anderssen 1995	HDL-C	0.023	0.025	0.001	-0.025	0.072	0.344	68	62	11	1026.29	11.32
	Ligtenberg 1997	HDL-C	0.032	0.022	0.000	-0.012	0.076	0.154	93	88	11	326.93	14.60
	Stefanick 1998 (females)	HDL-C	0.032	0.019	0.000	-0.005	0.069	0.088	136	133	12	638.43	21.00
	Stefanick 1998 (males)	HDL-C	0.034	0.015	0.000	0.005	0.062	0.022	183	179	12	1155.69	32.59
	Laaksonen 2000	HDL-C	0.032	0.014	0.000	0.004	0.060	0.024	203	201	11	316.40	35.76
	Lavrencic 2000	HDL-C	0.031	0.014	0.000	0.004	0.059	0.025	217	216	10	91.68	36.68
	Watkins 2003	HDL-C	0.032	0.014	0.000	0.005	0.060	0.020	231	227	10	65.55	37.34
	Sykes 2004	HDL-C	0.033	0.014	0.000	0.006	0.060	0.016	255	239	10	76.52	38.11
	Sigal 2007	HDL-C	0.029	0.013	0.000	0.004	0.054	0.024	315	302	15	616.43	44.29
	Slentz 2007 (high vol VICT)	HDL-C	0.031	0.012	0.000	0.006	0.055	0.013	379	321	10	436.25	48.67
	Slentz 2007 (low vol MICT)	HDL-C	0.030	0.012	0.000	0.006	0.053	0.013	430	338	10	501.26	53.69
	Slentz 2007 (low vol VICT)	HDL-C	0.029	0.011	0.000	0.007	0.052	0.011	491	356	10	416.76	57.87
	Lambers 2008	HDL-C	0.030	0.011	0.000	0.008	0.052	0.009	509	367	12	74.59	58.62
	Kadoglou 2009	HDL-C	0.031	0.011	0.000	0.009	0.052	0.006	532	391	11	340.92	62.04
	Gram 2010	HDL-C	0.031	0.011	0.000	0.010	0.052	0.005	554	413	13	265.72	64.71
	Thompson 2010	HDL-C	0.032	0.011	0.000	0.011	0.053	0.003	574	434	12	208.07	66.79
	Choi 2012	HDL-C	0.034	0.010	0.000	0.013	0.054	0.001	612	471	10	627.12	73.08
	Kim 2012	HDL-C	0.035	0.010	0.000	0.015	0.055	0.001	627	486	11	105.96	74.14
	Yavari 2012	HDL-C	0.035	0.010	0.000	0.015	0.055	0.001	642	501	12	129.43	75.44
	Madden 2013	HDL-C	0.035	0.010	0.000	0.015	0.055	0.001	667	528	13	18.93	75.63
	Dogan Dede 2015	HDL-C	0.035	0.010	0.000	0.015	0.054	0.001	697	558	12	160.94	77.25
	Arija 2017	HDL-C	0.034	0.010	0.000	0.015	0.053	0.000	957	662	15	634.57	83.61
	Phing 2017	HDL-C	0.042	0.009	0.000	0.024	0.060	0.000	992	750	10	808.41	91.72
	Chan 2018	HDL-C	0.042	0.009	0.000	0.024	0.060	0.000	1074	832	13	168.52	93.41
	Cao 2019	HDL-C	0.044	0.009	0.000	0.026	0.062	0.000	1087	847	10	137.93	94.79
	Conners 2019	HDL-C	0.047	0.009	0.000	0.029	0.065	0.000	1100	860	14	242.00	97.22
	Dai 2019	HDL-C	0.049	0.009	0.000	0.031	0.066	0.000	1134	895	11	109.70	98.32
	Farag 2019	HDL-C	0.049	0.009	0.000	0.031	0.066	0.000	1164	925	10	84.62	99.17
	Jiang 2019 (female)	HDL-C	0.051	0.009	0.000	0.032	0.069	0.000	1175	938	10	49.07	99.66
	Jiang 2019 (male)	HDL-C	0.053	0.010	0.000	0.033	0.072	0.000	1189	949	10	33.83	100.00
Random			0.053	0.010	0.000	0.033	0.072	0.000					



SM Figure 6.12 HDL-C TESTEX score ≥10 (outliers and influencer removed) forest plot with statistics

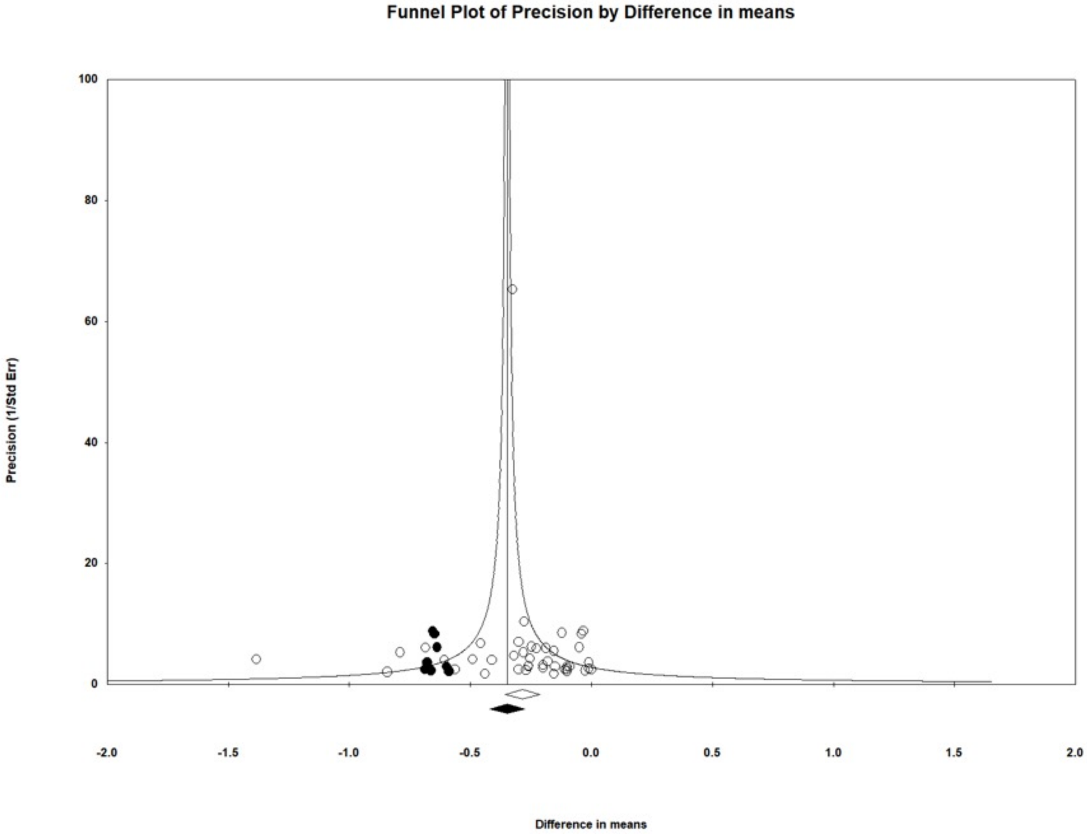
Model	Study name	Outcome	Cumulative statistics						Cumulative sample size		Study Quality	Weight (Random)	
			Point	Standard error	Variance	Lower limit	Upper limit	p-Value	Exercise	Control		Weight (Random)	Relative weight
	Anderssen 1995	LDL-C	-0.090	0.113	0.013	-0.311	0.131	0.424	49	43	11	78.81	7.33
	Motoyama 1995	LDL-C	-0.084	0.105	0.011	-0.289	0.122	0.424	64	58	12	12.11	8.46
	Ligtenberg 1997	LDL-C	-0.074	0.099	0.010	-0.267	0.119	0.452	89	84	11	11.90	9.56
	Stefanick 1998 (females)	LDL-C	-0.077	0.070	0.005	-0.214	0.060	0.271	132	129	12	101.23	18.98
	Stefanick 1998 (males)	LDL-C	-0.062	0.059	0.003	-0.177	0.053	0.292	179	175	12	87.17	27.08
	Laaksonen 2000	LDL-C	-0.072	0.056	0.003	-0.182	0.039	0.205	199	197	11	22.40	29.17
	Lavrencic 2000	LDL-C	-0.072	0.056	0.003	-0.182	0.037	0.194	213	212	10	8.28	29.94
	Watkins 2003	LDL-C	-0.079	0.055	0.003	-0.187	0.030	0.155	227	223	10	5.15	30.42
	Sykes 2004	LDL-C	-0.080	0.054	0.003	-0.186	0.026	0.140	251	235	10	14.39	31.75
	Sigal 2007	LDL-C	-0.086	0.050	0.003	-0.184	0.012	0.087	306	296	15	57.57	37.11
	Slentz 2007 (high vol VICT)	LDL-C	-0.098	0.047	0.002	-0.190	-0.006	0.036	370	315	10	55.98	42.32
	Slentz 2007 (low vol MICT)	LDL-C	-0.108	0.045	0.002	-0.196	-0.021	0.016	421	332	10	45.22	46.52
	Slentz 2007 (low vol VICT)	LDL-C	-0.129	0.042	0.002	-0.211	-0.047	0.002	482	350	10	68.17	52.86
	Kadoglou 2009	LDL-C	-0.139	0.041	0.002	-0.220	-0.058	0.001	505	374	11	18.54	54.59
	Gram 2010	LDL-C	-0.138	0.041	0.002	-0.217	-0.058	0.001	527	396	13	18.97	56.35
	Choi 2012	LDL-C	-0.141	0.040	0.002	-0.220	-0.062	0.000	565	433	10	5.52	56.86
	Kim 2012	LDL-C	-0.153	0.040	0.002	-0.231	-0.075	0.000	580	448	11	21.88	58.90
	Yavari 2012	LDL-C	-0.155	0.039	0.002	-0.232	-0.078	0.000	595	463	12	8.14	59.66
	Madden 2013	LDL-C	-0.156	0.039	0.002	-0.232	-0.079	0.000	620	490	13	12.46	60.82
	Venojärvi 2013	LDL-C	-0.166	0.038	0.001	-0.240	-0.092	0.000	659	530	11	49.98	65.46
	Dogan Dede 2015	LDL-C	-0.167	0.037	0.001	-0.240	-0.094	0.000	689	560	12	15.47	66.90
	Alvarez 2016	LDL-C	-0.165	0.036	0.001	-0.237	-0.094	0.000	702	570	12	32.12	69.89
	Arija 2017	LDL-C	-0.176	0.034	0.001	-0.241	-0.110	0.000	962	674	15	138.35	82.76
	Chan 2018	LDL-C	-0.168	0.033	0.001	-0.232	-0.104	0.000	1044	756	13	48.44	87.26
	Cao 2019	LDL-C	-0.168	0.032	0.001	-0.232	-0.104	0.000	1057	771	10	11.43	88.33
	Conners 2019	LDL-C	-0.164	0.031	0.001	-0.225	-0.102	0.000	1070	784	14	65.78	94.44
	Dai 2019	LDL-C	-0.168	0.031	0.001	-0.229	-0.107	0.000	1104	819	11	19.84	96.29
	Farag 2019	LDL-C	-0.170	0.031	0.001	-0.231	-0.110	0.000	1134	849	10	15.92	97.77
	Jiang 2019 (female)	LDL-C	-0.173	0.031	0.001	-0.233	-0.113	0.000	1145	862	10	11.83	98.87
	Jiang 2019 (male)	LDL-C	-0.173	0.030	0.001	-0.233	-0.113	0.000	1159	873	10	12.15	100.00
Random			-0.173	0.030	0.001	-0.233	-0.113	0.000					



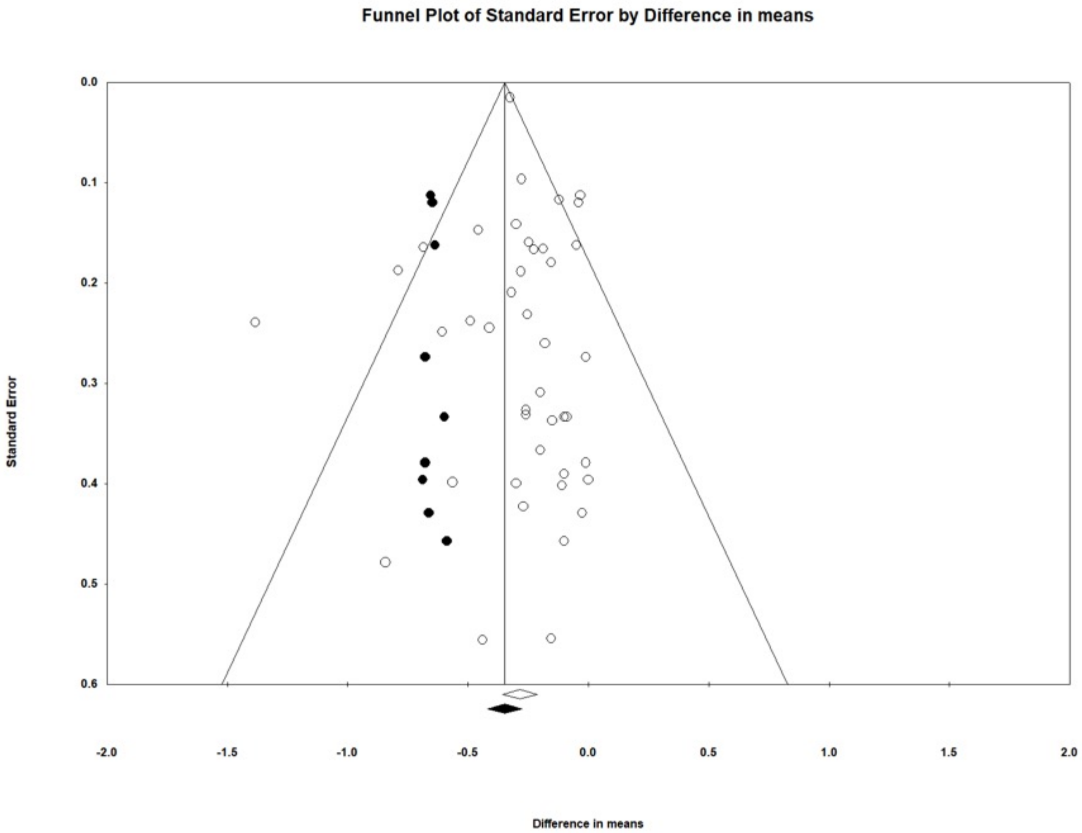
SM Figure 6.13 LDL-C TESTEX score ≥10 (influencer removed) forest plot with statistics

Small Study Effects

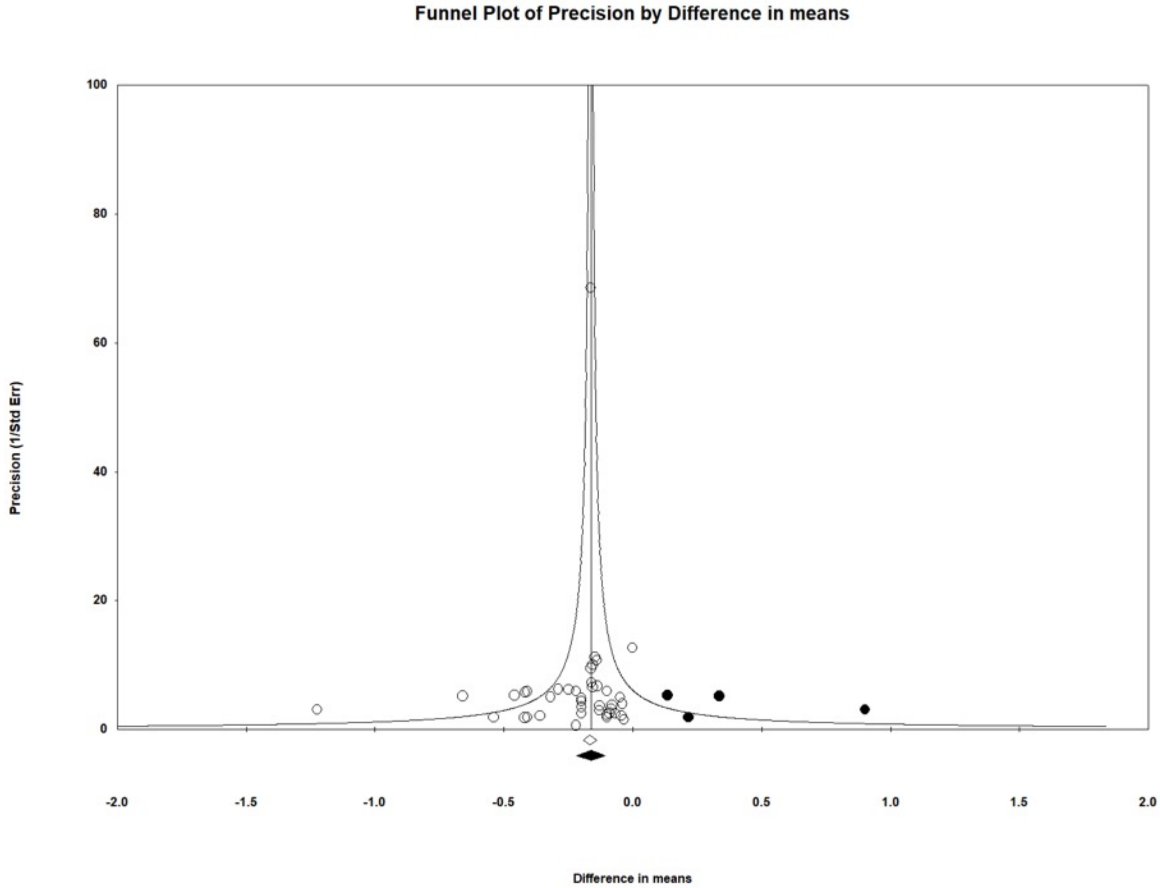
Funnel Plots for K-0 (all studies)



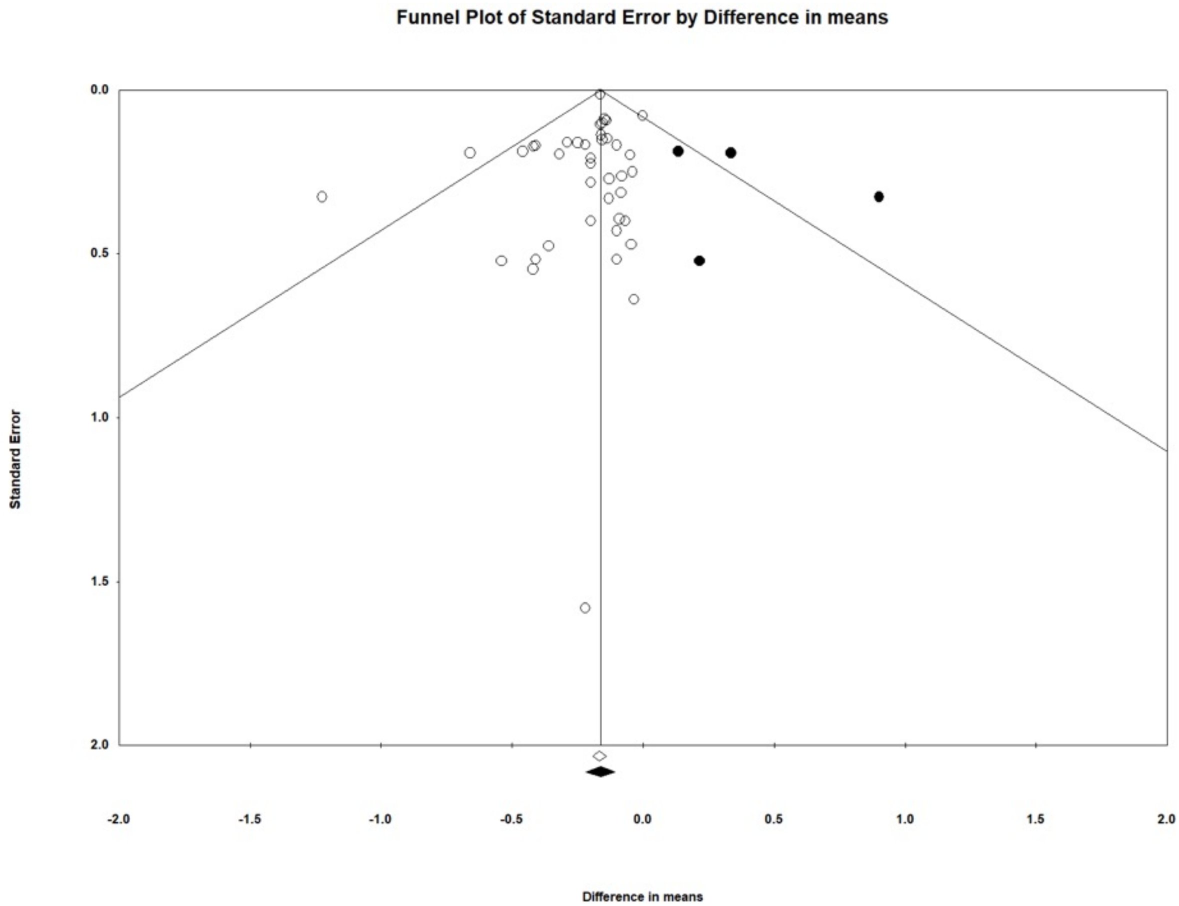
SM Figure 6.14 Funnel Plot TC K-0 Precision



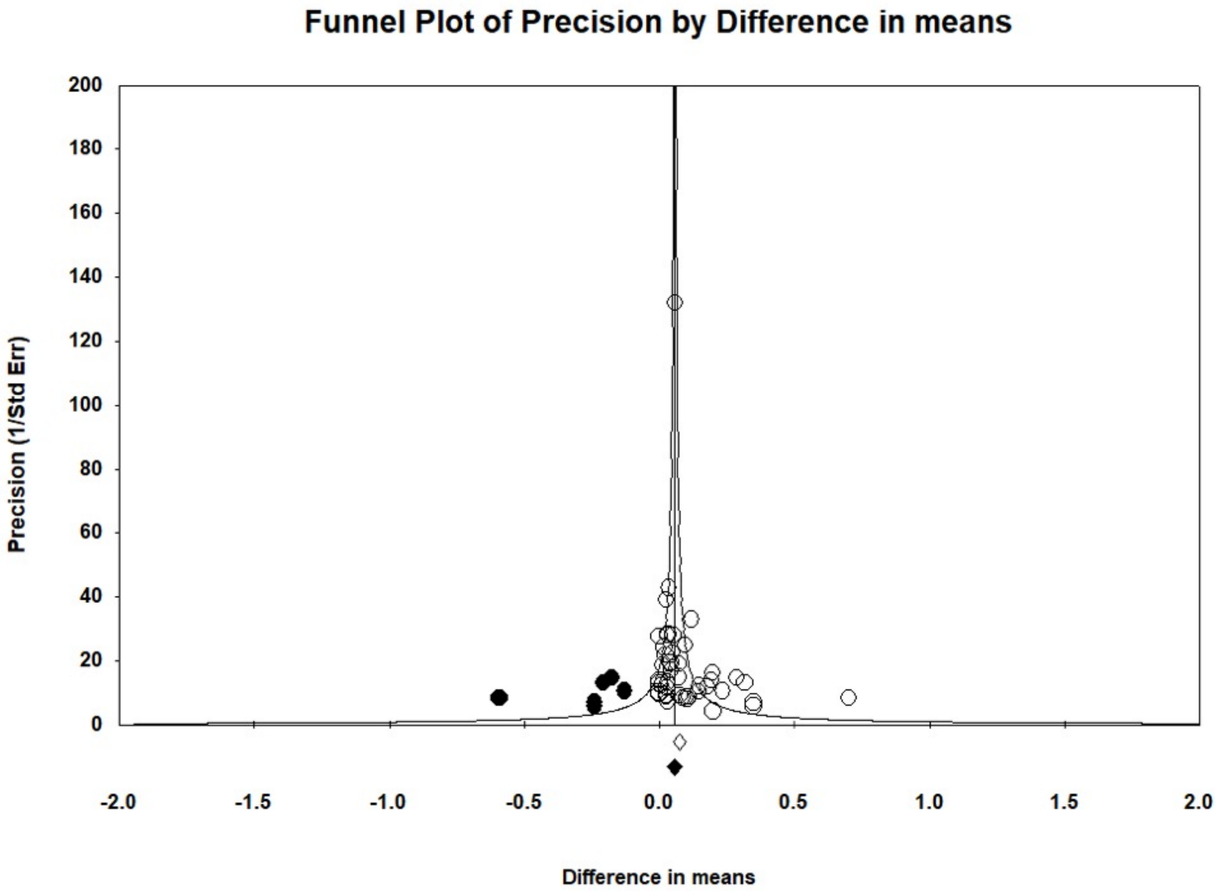
SM Figure 6.15 Funnel Plot TC K-0 Standard Error



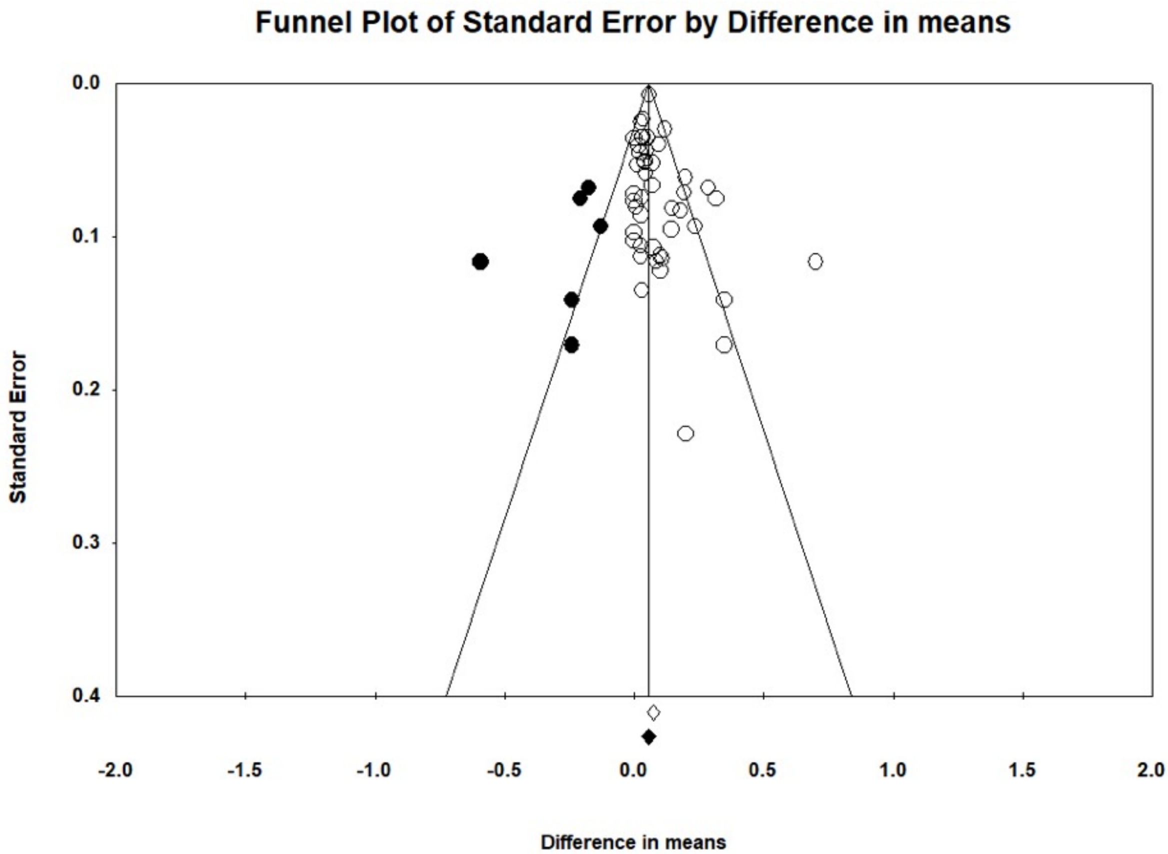
SM Figure 6.16 Funnel Plot TRG K-0 Precision



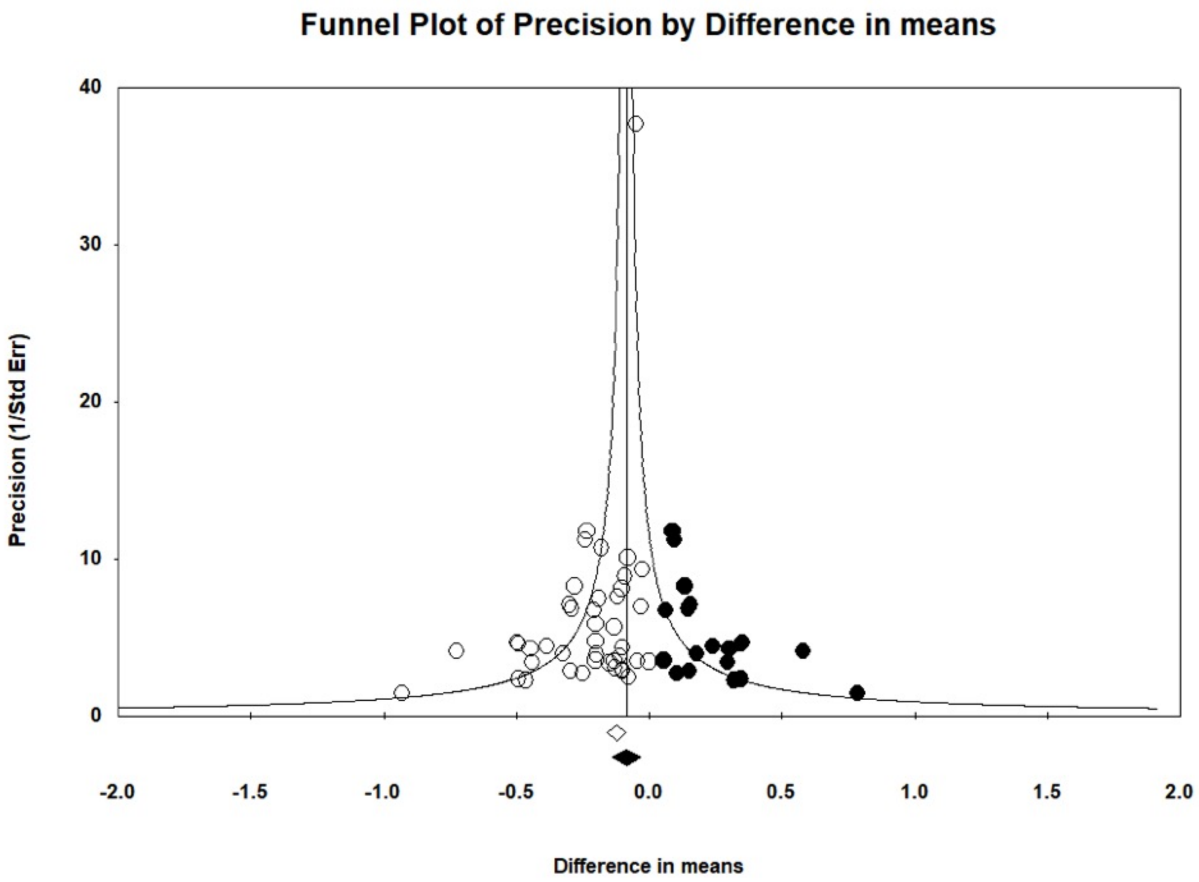
SM Figure 6.17 Funnel Plot TRG K-0 Standard Error



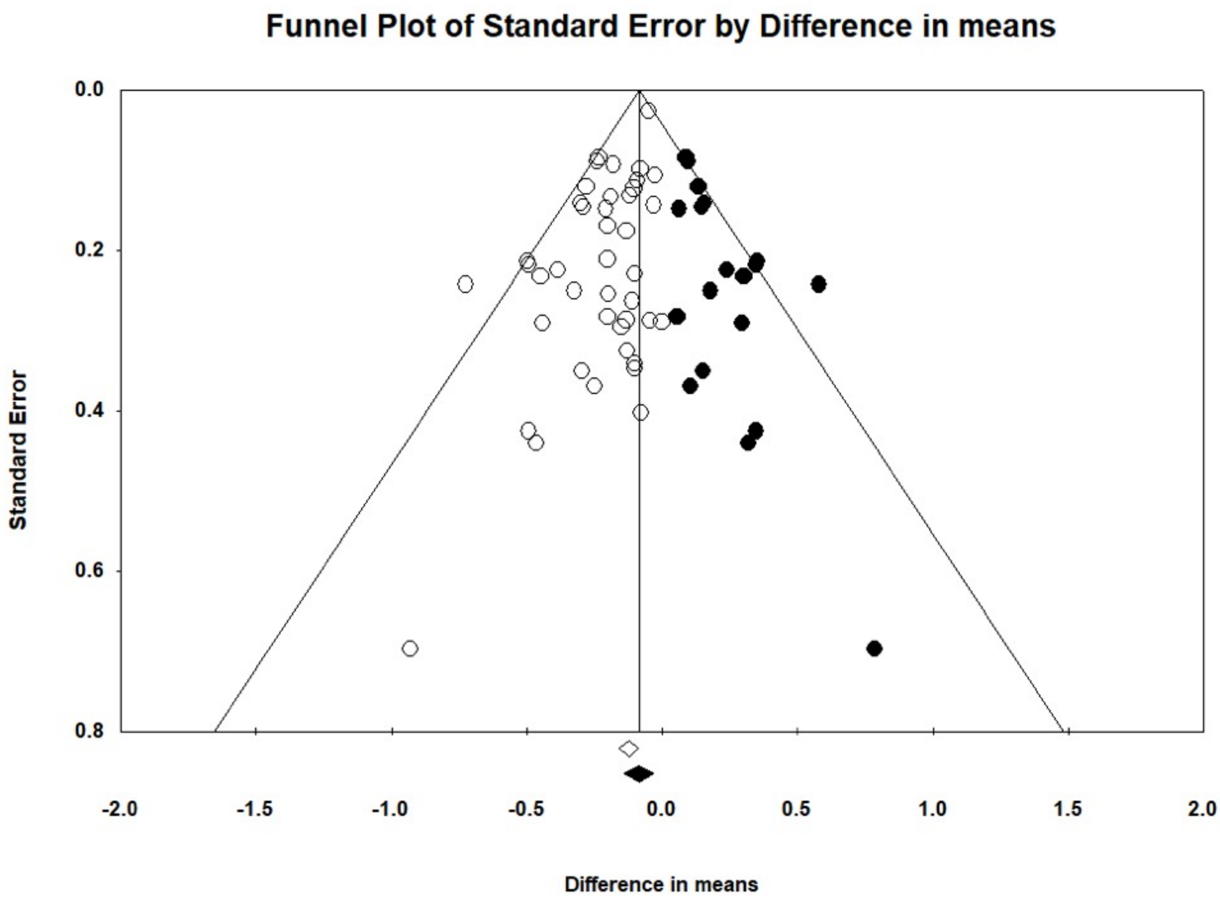
SM Figure 6.18 Funnel Plot HDL-C K-0 Precision



SM Figure 6.19 Funnel Plot HDL-C K-0 Standard Error

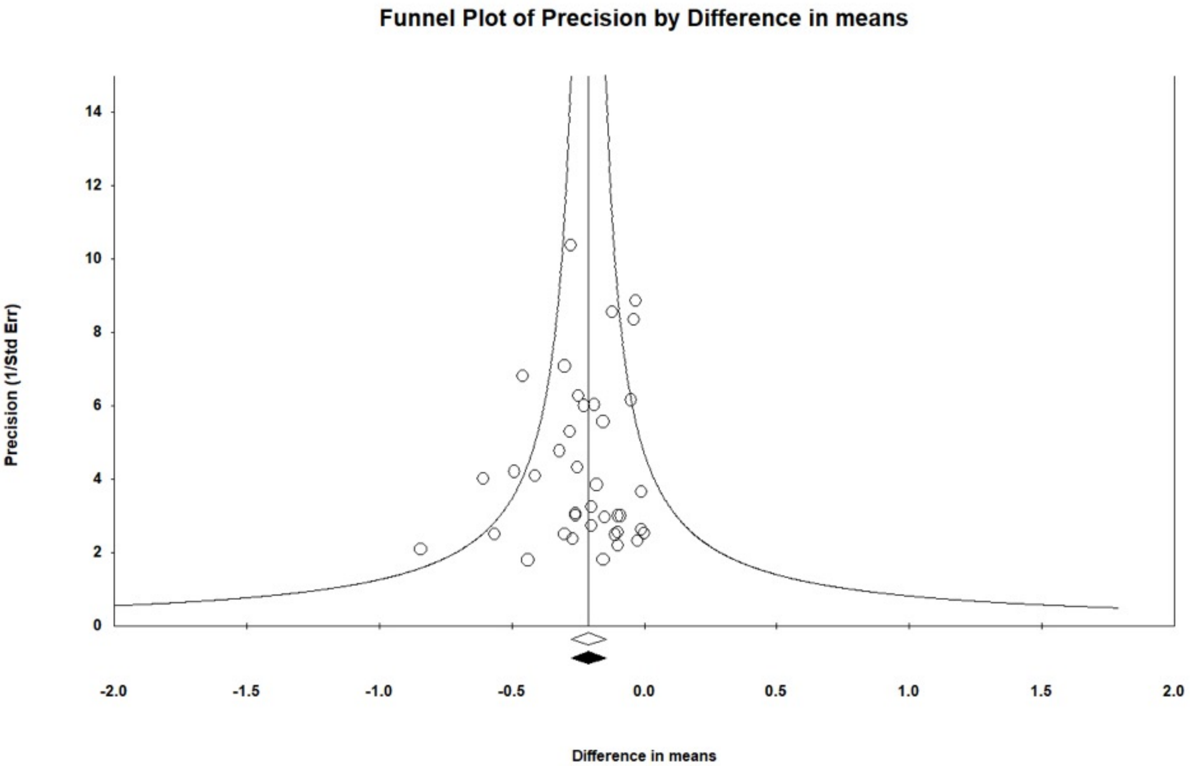


SM Figure 6.20 Funnel Plot LDL-C K-0 Precision

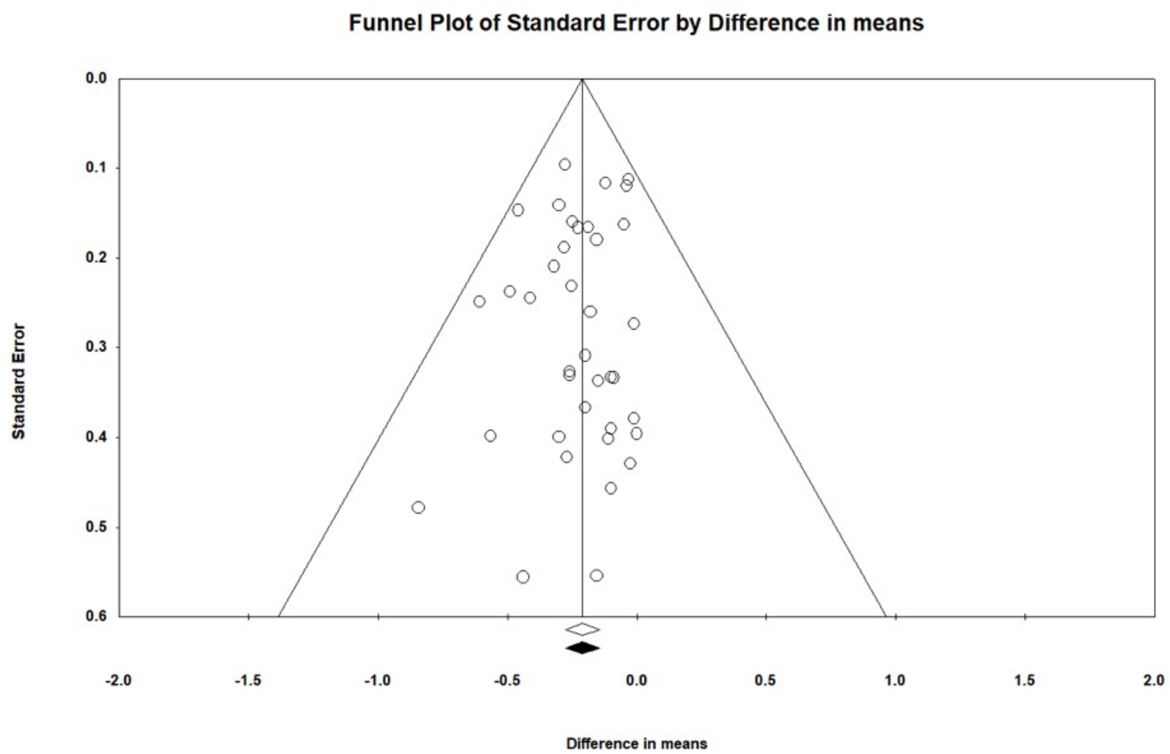


SM Figure 6.21 Funnel Plot LDL-C K-0 Standard Error

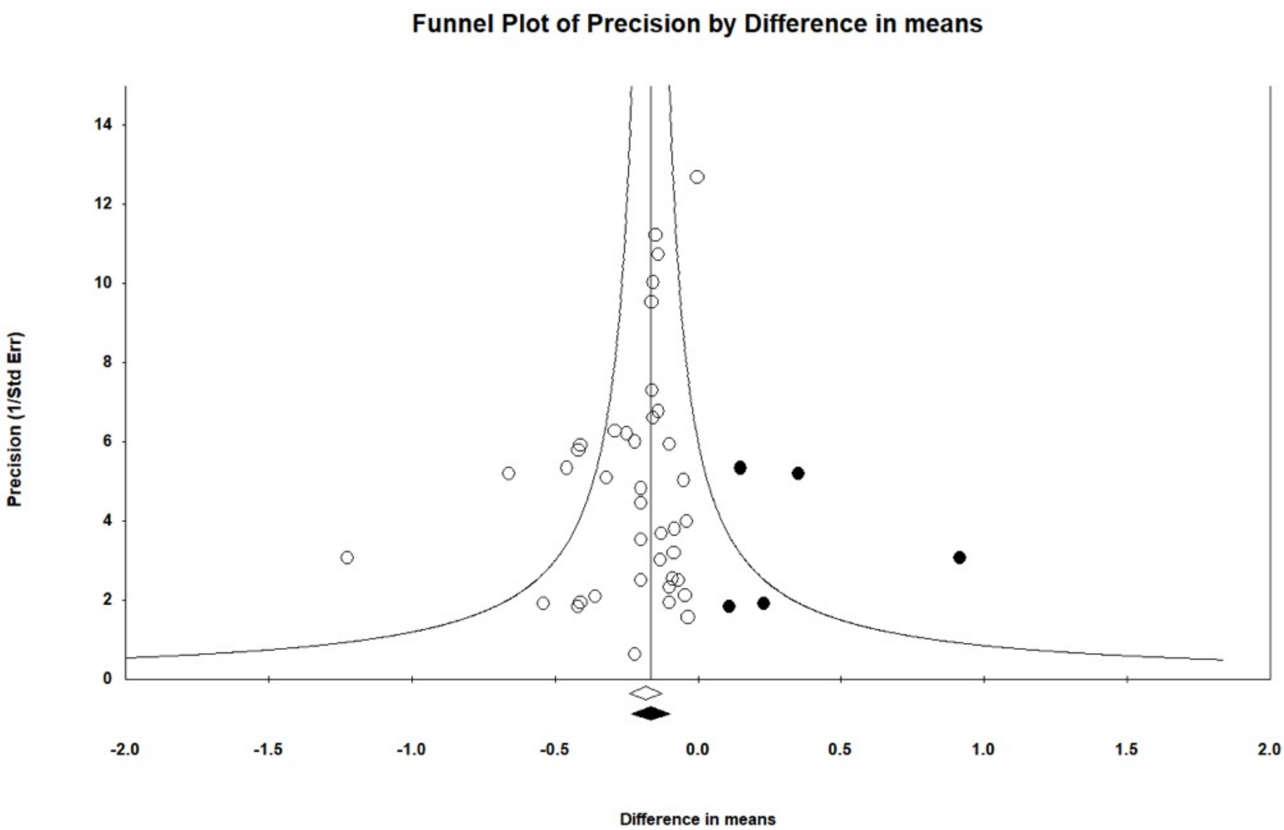
Funnel Plots for K-4 (studies remaining after exclusion of outliers and influencer)



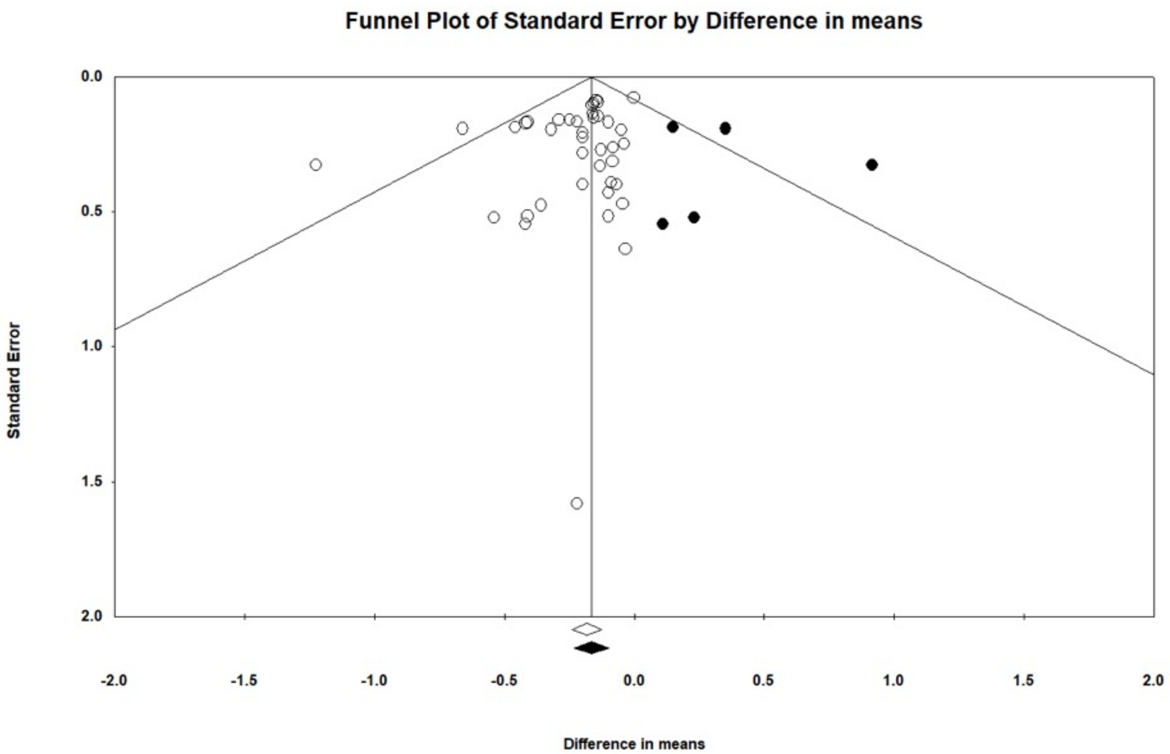
SM Figure 6.22 Funnel Plot TC K-4 Precision



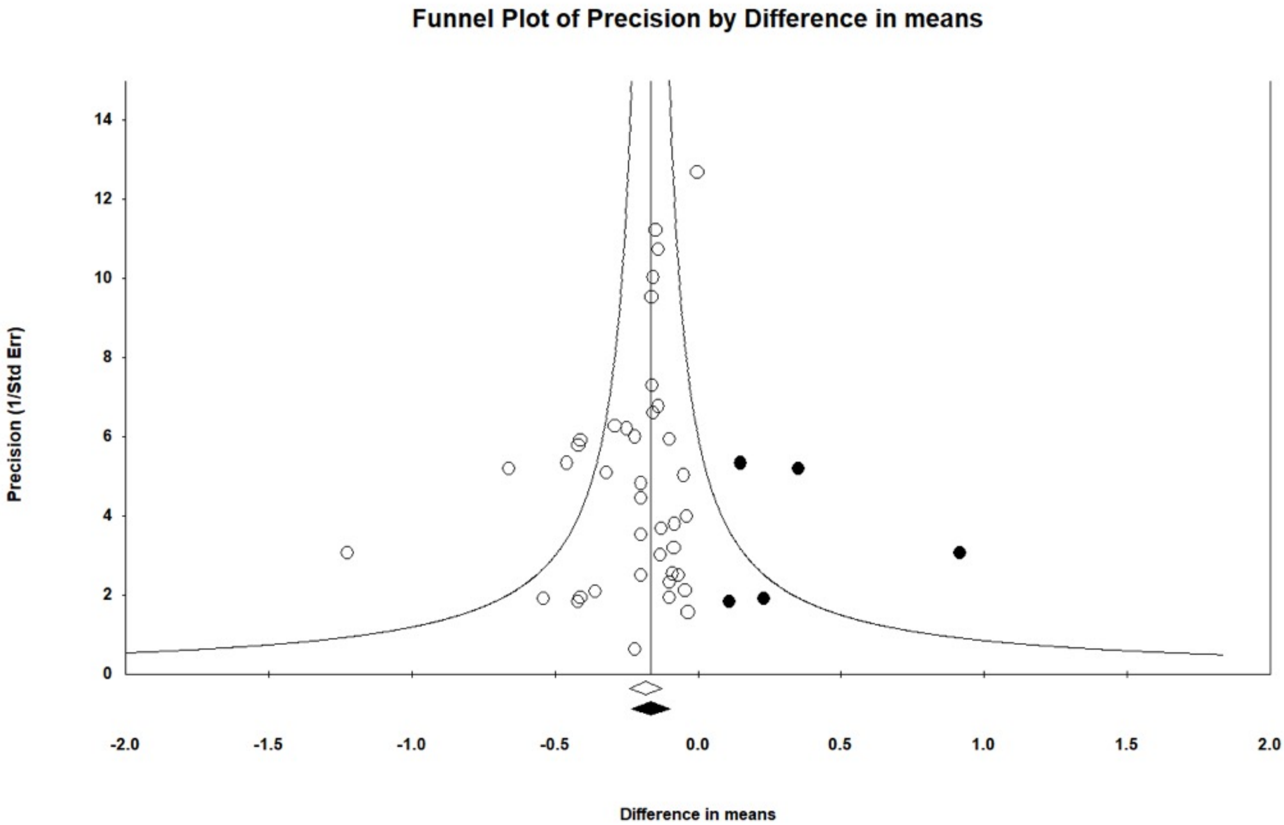
SM Figure 6.23 Funnel Plot TC K-4 Standard Error



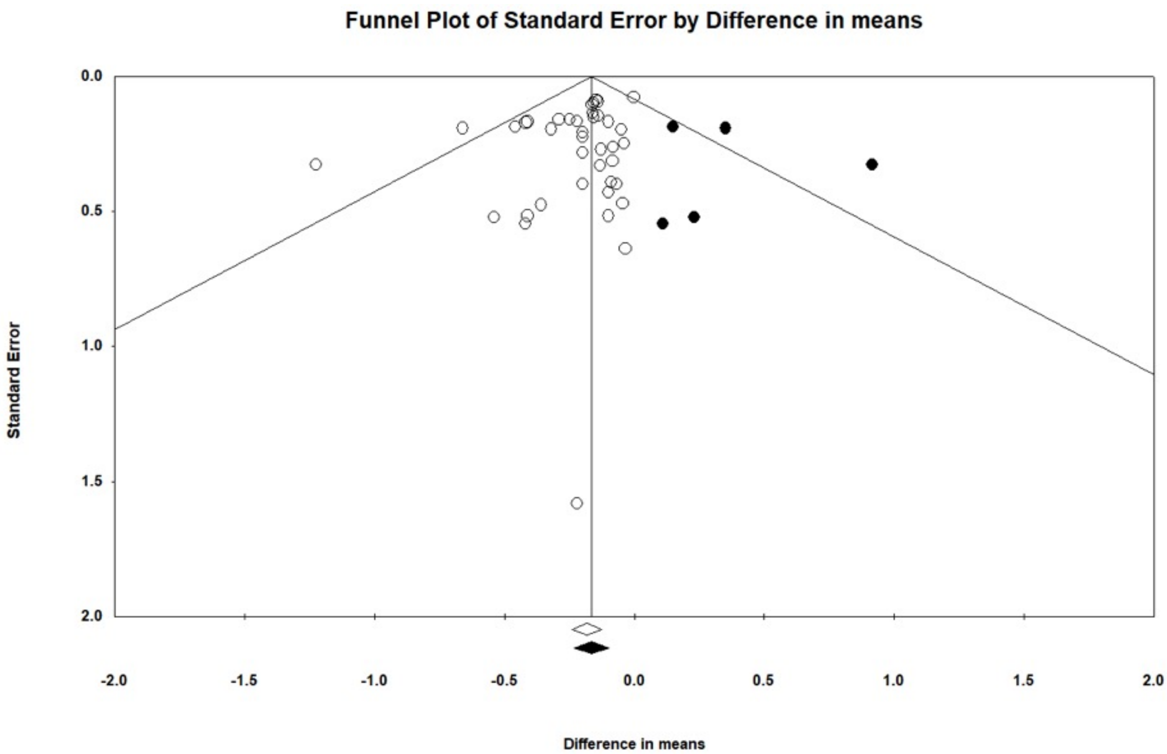
SM Figure 6.24 Funnel Plot TRG K-4 Precision



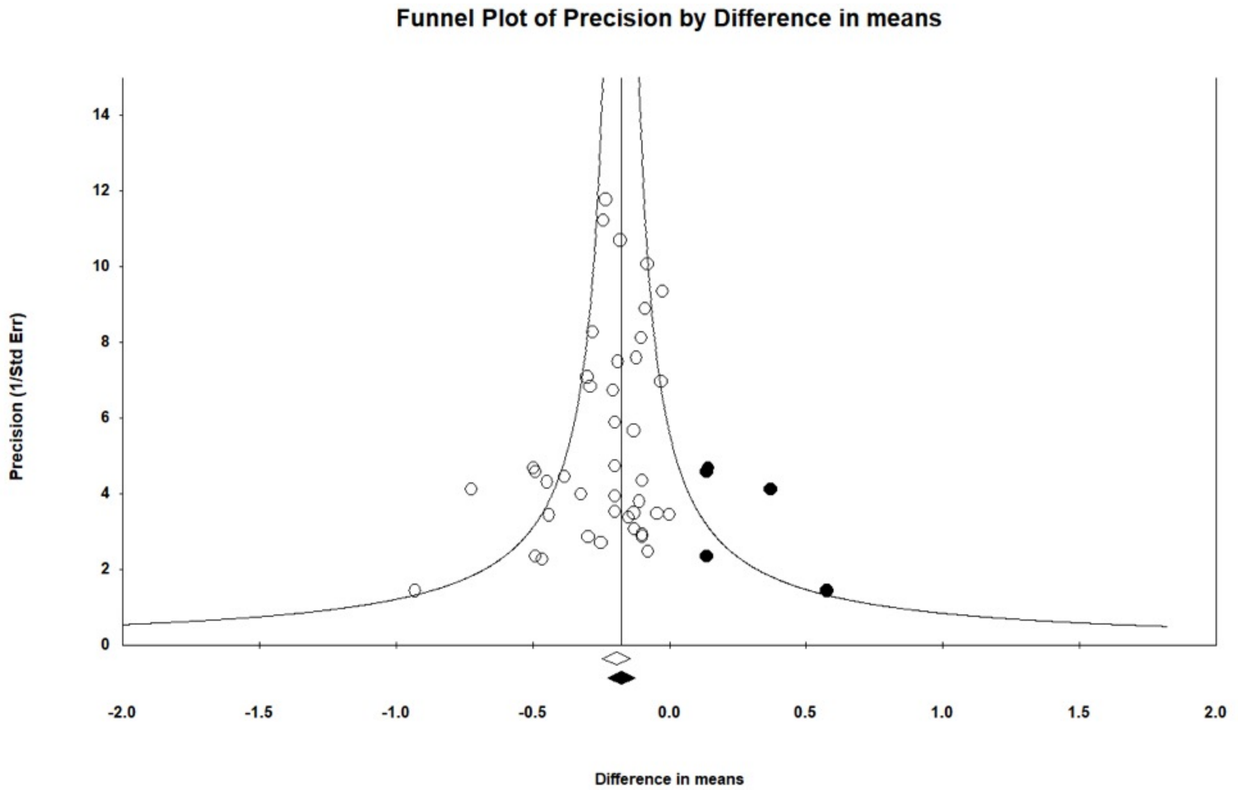
SM Figure 6.25 Funnel Plot TRG K-4 Standard Error



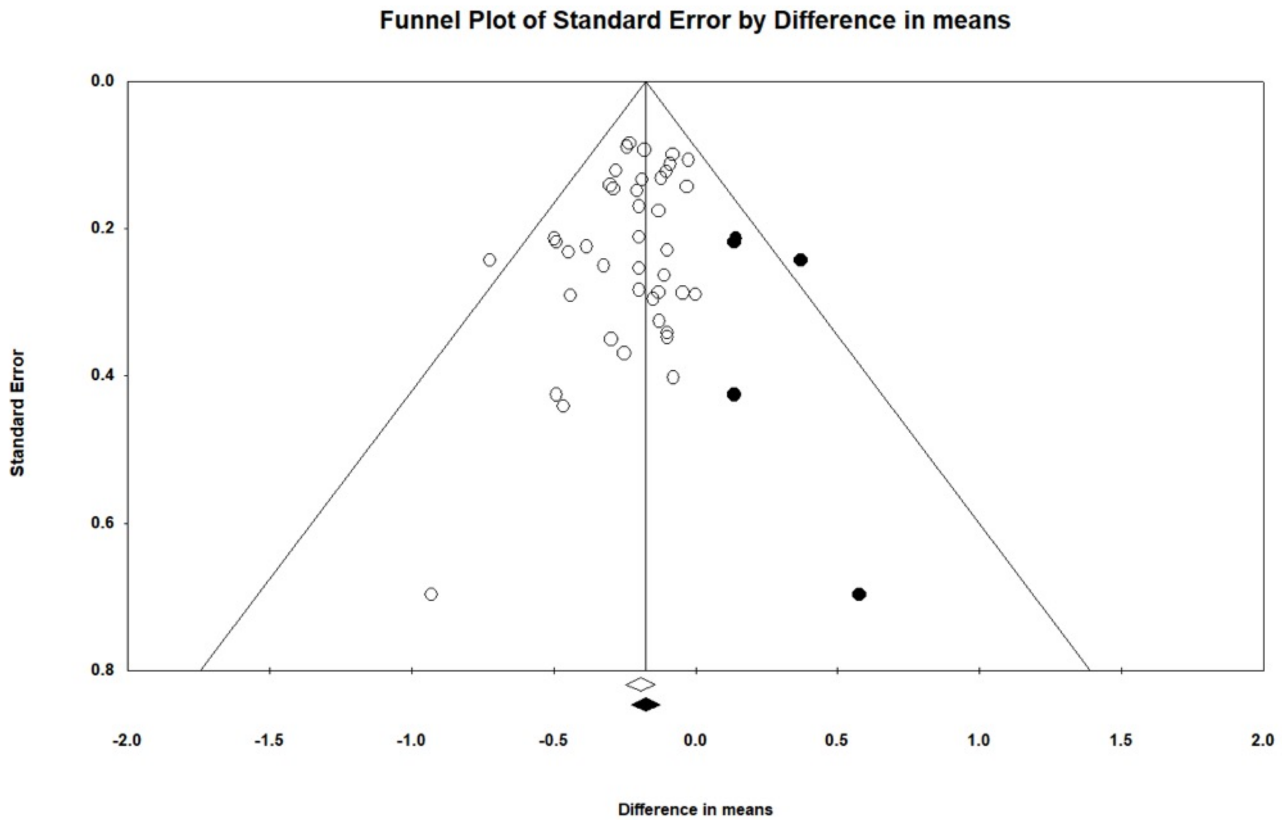
SM Figure 6.26 Funnel Plot HDL-C K-4 Precision



SM Figure 6.27 Funnel Plot HDL-C K-4 Standard Error



SM Figure 6.28 Funnel Plot LDL-C K-4 Precision



SM Figure Figure 6.29 Funnel Plot LDL-C K-4 Standard Error

Meta-regression

Incremental Meta-regression, Random effects (REML), Knapp Hartung, Difference in means, LDL-C, K-0 Studies

	Current Model		Test of Model (a)				Goodness of fit (b)			Change from prior (c)(d)		Test of change (c)			
Covariate	Tau²	R²	F	df1	df2	P-value	Q	df	P-value	Tau²	R²	F	df1	df2	P-value
Intercept	0.004	0.00													
Intensity	0.004	0.06	0.68	1	40	0.414	37.05	40	0.604	0.000	0.06	0.68	1	40	0.414
Mins/Session	0.002	0.53	2.32	2	39	0.112	27.97	39	0.905	-0.002	0.47	3.66	1	39	0.063
Sessions/week	0.002	0.48	1.59	3	38	0.208	27.67	38	0.892	0.000	-0.05	0.39	1	38	0.535
Duration weeks	0.000	1.00	4.52	4	37	0.005	21.15	37	0.983	-0.002	0.52	6.52	1	37	0.015

SM Table 6.11 Meta-regression of intervention covariates for LDL-C, K-0 studies

Incremental Meta-regression, Random effects (REML), Knapp Hartung, Difference in means, TRG, K-1 (no influencer) Studies

	Current Model		Test of Model (a)				Goodness of fit (b)			Change from prior (c)(d)		Test of change (c)			
Covariate	Tau²	R²	F	df1	df2	P-value	Q	df	P-value	Tau²	R²	F	df1	df2	P-value
Intercept	0.002	0													
Intensity	0.001	0.49	1.00	1	37	0.325	30	37	0.759	-0.001	0.49	1.00	1	37	0.325

SM Table 6.12 Meta-regression of intervention covariates for TRG, K-1 (no influencer) studies

Incremental Meta-regression, Random effects (ML), Knapp Hartung, Difference in means, HDL-C, K-4 (no outlier, no influencer) Studies

	Current Model		Test of Model (a)				Goodness of fit (b)			Change from prior (c)(d)		Test of change (c)			
Covariate	Tau²	R²	F	df1	df2	P-value	Q	df	P-value	Tau²	R²	F	df1	df2	P-value
Intercept	0.0002	0								0	0.01	0.01	1	39	0.9158
Intensity	0.0002	0.01	0.01	1	39	0.916	41.26	39	0.372	0	0.06	0.11	1	38	0.7465
Mins/Session	0.0001	0.07	0.06	2	38	0.943	41.13	38	0.335	-0.0001	0.37	0.21	1	37	0.6489
Sessions/week	0.0001	0.45	0.11	3	37	0.954	40.85	37	0.305	-0.0001	0.55	1.06	1	36	0.3094
Duration weeks	0	1	0.36	4	36	0.834	39.68	36	0.309	0	0.01	0.01	1	39	0.9158

SM Table 6.13 Meta-regression of intervention covariates for HDL-C, K-4 (no outlier, no influencer) studies

Incremental Meta-regression, Random effects (REML), Knapp Hartung, Difference in means, TC, K-0 Studies

	Current Model		Test of Model (a)				Goodness of fit (b)			Change from prior (c)(d)		Test of change (c)			
Covariate	Tau²	R²	F	df1	df2	P-value	Q	df	P-value	Tau²	R²	F	df1	df2	P-value
Intercept	0.024	0													
Year	0.009	0.62	8.67	1	40	0.005	47.26	40	0.200	-0.015	0.62	8.67	1	40	0.005
Total Study N	0.011	0.52	4.1	2	39	0.024	47.16	39	0.173	0.003	-0.10	0.2	1	39	0.658
TESTEX score	0.01	0.58	3.84	3	38	0.017	44.63	38	0.213	-0.002	0.06	2.88	1	38	0.098

SM Table 6.14 Meta-regression of study covariates for TC, K-0 studies

Incremental Meta-regression, Random effects (REML), Knapp Hartung, Difference in means, TRG, K-0 Studies

	Current Model		Test of Model (a)				Goodness of fit (b)			Change from prior (c)(d)		Test of change (c)			
Covariate	Tau²	R²	F	df1	df2	P-value	Q	df	P-value	Tau²	R²	F	df1	df2	P-value
Intercept	0.002	0													
Year	0.001	0.69	1.16	1	37	0.289	30.54	37	0.766	-0.002	0.69	1.16	1	37	0.2885
Total Study N	0	1	2.83	2	36	0.072	26.19	36	0.885	-0.001	0.31	4.35	1	36	0.0442
TESTEX score	0	1	2.45	3	35	0.078	24.51	35	0.908	0	0	1.68	1	35	0.2029

SM Table 6.15 Meta-regression of study covariates for TRG, K-0 studies

Incremental Meta-regression, Random effects (REML), Knapp Hartung, Difference in means, HDL-C, K-0 Studies

	Current Model		Test of Model (a)				Goodness of fit (b)			Change from prior (c)(d)		Test of change (c)			
Covariate	Tau²	R²	F	df1	df2	P-value	Q	df	P-value	Tau²	R²	F	df1	df2	P-value
Intercept	0.0029	0													
Year	0.0021	0.29	1.71	1	43	0.197	90.96	43	0	-0.0008	0.29	1.71	1	43	0.197
Total Study N	0.0015	0.48	2.76	2	42	0.075	88.6	42	0	-0.0006	0.19	3.59	1	42	0.065
TESTEX score	0.0015	0.48	1.8	3	41	0.163	88.59	41	0	0	0	0.01	1	41	0.931

SM Table 6.16 Meta-regression of study covariates for HDL-C, K-0 studies

Incremental Meta-regression, Random effects (REML), Knapp Hartung, Difference in means, HDL-C, K-4 (no outliers, no influencer) Studies

	Current Model		Test of Model (a)				Goodness of fit (b)			Change from prior (c)(d)		Test of change (c)			
Covariate	Tau²	R^2	F	df1	df2	P-value	Q	df	P-value	Tau²	R^2	F	df1	df2	P-value
Intercept	0.0002	0													
Year	0	1	7.26	1	39	0.0103	34.01	39	0.6966	-0.0002	1	7.26	1	39	0.0103
Total Study N	0	1	5.31	2	38	0.0093	30.66	38	0.7954	0	0	3.35	1	38	0.0751
TESTEX score	0	1	3.72	3	37	0.0197	30.12	37	0.7812	0	0	0.54	1	37	0.4674

SM Table 6.17 Meta-regression of study covariates for HDL-C, K-4 (no outliers, no influencer) studies

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7 Chapter 7 – The Effects of Aerobic Exercise Training on Lipoprotein Sub-fractions, Apolipoproteins, and Associated Ratios: A Systematic Review with Multivariate Meta-analysis and Meta-regression of Randomised Controlled Trials

7.1 Manuscript information – submitted 24th August 2020

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An author's role in a research output must be sufficient for that person to take public responsibility for at least part of the output in that person's area of expertise. No person who is an author, consistent with this definition, must be excluded as an author without their permission in writing.

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7.2 Statement of authors' contribution

Higher Degree Research Thesis by Publication
University of New England

STATEMENT OF AUTHORS' CONTRIBUTION

We, the PhD candidate and the candidate's Principal Supervisor, certify that all co-authors have consented to their work being included in the thesis and they have accepted the candidate's contribution as indicated in the *Statement of Originality*.

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7.3 Statement of originality

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STATEMENT OF ORIGINALITY

We, the PhD candidate and the candidate's Principal Supervisor, certify that the following text, figures, diagrams, tables, labels, keys and legends are the candidate' original work.

Type of work	Page numbers
All text, figures, diagrams, tables, labels, keys and legends in the Chapter **except** the referenced PRISMA diagram.	pp 318-333 pp 335-383

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7.4 Full manuscript as submitted

The effects of aerobic exercise training on lipoprotein sub-fractions, apolipoproteins, and lipid ratios: A systematic review and multivariate meta-analysis and meta-regression of randomised controlled trials.

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Declarations

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The authors report no relationships that could be construed as a conflict of interest and take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

The authors report that no data privacy statement is applicable to this systematic review.

The authors report that no data sharing statement is applicable to this systematic review.

The authors report that no data consent statement is applicable to this systematic review.

The authors report that no ethics approval is applicable to this systematic review.

The authors report that no code availability statement is applicable to this systematic review.

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All authors consent to the publication of this systematic review.

Data is available on request.

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ABSTRACT

Background Compared with the standard lipid profile, lipid and apolipoprotein (Apo) ratios and lipoprotein sub-fractions more effectively predict cardiovascular disease risk.

Objectives We conducted a systematic review with multivariate meta-analysis/meta-regression of randomised controlled trials (RCTs) to 1) determine the effects of aerobic exercise training (AET) on lipoprotein sub-fractions, apolipoproteins, and relevant ratios; and 2) identify variables associated with change in these outcomes.

Methods We searched English language searches of online databases from inception to June 2020. We included published RCTs of adult humans with ≥10 per group participants; an AET intervention duration ≥12 weeks of at least moderate intensity (>40% VO_{2MAX}); and reporting pre/post measurements. Non-sedentary subjects, those with chronic disease (except diabetes mellitus Type 1-2), or pregnant/lactating, as well as trials testing diet/medications, or resistance/isometric/unconventional training interventions, were excluded.

Results Fifty-seven RCTs totalling 3194 participants were analysed. Multivariate meta-analysis showed AET significantly raised joined Apo A1, A2, high-density lipoprotein 2 (HDL2) and HDL3 mmol/L (raw mean difference (MD) 0.047 [95% confidence intervals 0.011, 0.082], P=.01); lowered joined Apo B100 and very low-density lipoprotein mmol/L (MD -0.08 [-0.161, 0.0003], P=.05); and lowered the joined ratios total cholesterol (TC)/HDL-C, LDL-C/HDL-C, and Apo B100/Apo A1 (MD -0.201 [-0.291, -0.111], P<.001). Multivariate meta-regression showed intervention variables contributed to positive change in joined lipid and Apo ratios, and joined antiatherogenic apolipoprotein and HDL sub-fractions.

Conclusion Joined atherogenic lipid and apo ratios, and joined atherogenic apolipoproteins and lipoprotein sub-fractions, were lowered by AET. Joined antiatherogenic apolipoproteins and lipoprotein sub-fractions were raised by AET.

PROSPERO ID CRD42020151925.

Keywords Lipids, Cholesterol, Triglycerides, Lipoprotein, Apolipoprotein, Aerobic Exercise

Word count: 4149 excluding abstract, tables, labels, reference list and perspectives

Perspectives

1. Aerobic exercise training (AET) lowers atherogenic apolipoprotein and lipoprotein sub-fractions and lipid ratios, and raises antiatherogenic apolipoproteins and lipoprotein sub-fractions, in sedentary adults.

2. AET volume (session minutes, sessions per week, aerobic training intensity, and intervention duration) explained positive change in antiatherogenic apolipoproteins and HDL sub-fractions, as well as joined atherogenic lipid and apolipoprotein ratios.

3. Reporting of apolipoprotein ratios is less common than standard lipid outcomes. Future AET trials should report apolipoproteins as cardiovascular disease risk biomarkers.

1.0 INTRODUCTION

The standard lipid profile (SLP) biomarkers used to evaluate cardiovascular (CVD) risk comprise total cholesterol (TC), triglycerides (TRG), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C).(1) Dyslipidaemia, an abnormally elevated or lowered lipid profile, is a risk factor of CVD.(2,3) A recent 17-year follow-up study of females concluded TC/HDL-C was a potent predictor of CVD events.(4) A systematic review (SR) collating data from several large observational studies found TC/HDL-C and LDL-C/HDL-C ratios better predicted CVD risk was than SLP biomarkers.(5)

Apolipoproteins (Apo) A1 and A2 are the largest protein constituent of HDL.(6) The Apo B100 contains an LDL-receptor responsible for the uptake of LDL, and serves to assemble and secrete VLDL.(7) Raised levels of Apo A1 and A2 are considered to be antiatherogenic, while increased levels of Apo B100 and VLDL are atherogenic.(8) Apolipoproteins and the Apo B100/Apo A1 ratio have been investigated as biomarkers more sensitive to identifying CVD risk than TC, TRG, and LDL-C.(9-11) Systematic reviews have examined the risk prediction power of Apo A1, A2, and B100 for cardiovascular risk and found Apo B100 and the Apo B100/Apo A1 ratio improved prediction.(12-14) Lowered levels of lipoprotein sub-fractions HDL2 and HDL3 are considered to increase CVD risk, although HDL3 may be less protective in the presence of Metabolic Syndrome (MetS).(15) Sub-fractions of HDL-C may be more relevant in identifying CVD risk than HDL-C.(11)

Lack of aerobic physical activity has negative consequences for lipids.(16) Aerobic exercise training (AET) positively impacts dyslipidaemia,(17-20) thus lowering CVD risk.(21,22) Aerobic or moderate intensity training is defined as >40% of heart rate reserve (HRR) or maximal oxygen uptake (VO_{2MAX}); 55-70% of maximal heart rate (MHR); or rate of perceived effort (RPE) of 11-13 on the Borg scale.(23)

Various SRs, with and without meta-analysis (MA), have examined the impact of AET on lipids and lipoproteins. (19,20,24-42) Studies have shown AET of at least 180 minutes per week at >40% VO_{2MAX} or >1200 kcal/week is necessary to induce positive changes to TC, TRG, HDL-C, LDL-C.(43,44) Quantitative SRs have established longer AET intervention and session duration results in greater effects,(29,34) and a minimum effective AET volume (>45 minutes per session for 3-4 sessions per week for duration >26 weeks at >65% VO_{2MAX}) results in significant changes to the SLP.(19)

To the best of our knowledge, no comprehensive SR with MA and meta-regression (MR) has investigated the effects of AET on lipoprotein sub-fractions, Apo A1, A2, and B100, and lipid and Apo ratios in adults. This may be a result of the under-reporting of apolipoproteins, or reporting in differing units of measurement, thus limiting the number of pooled analyses. A meta-analytical technique appropriate for large numbers of studies with missing or multiple correlated and non-independent outcomes, such lipid ratios, lipoprotein sub-fractions, and apolipoproteins, is multivariate (MV) MA.(45,46)

We aimed to conduct an SR and multivariate meta-analysis/meta-regression (MVMAMR) comparing the effects of AET achieving a minimum aerobic intensity (>40% VO_{2MAX}) or equivalent, against non-exercising control groups on lipoprotein sub-fractions, apolipoproteins, associated ratios, and lipid ratios. Further, we wanted to investigate whether RCT study covariates such as year of publication, participant number, study quality score, and number of extracted outcomes, and AET intervention covariates such as volume, intensity, frequency, session duration and intervention duration, explained change in outcome measures.

2.0 METHODS

This SR and MVMAMR was designed by GNW and NS and registered in the International Prospective Register of Systematic Reviews (PROSPERO)(47) CRD42020151925. The results are presented according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.(48)

2.1 Study Eligibility Studies were eligible for inclusion if the study design was an RCT comparing an AET intervention against a non-exercising control group, and reporting pre-post intervention and control measurements of ratios, lipoprotein sub-fractions, and apolipoproteins as primary or secondary outcomes in humans ≥18 years.

2.2 Data Sources Potential studies were identified by systematic online searches of PubMed, EMBASE, all Web of Science and EBSCO health and medical databases from inception to June 30, 2020, for RCTs published in English or bilingual journals. Searches included a mix of MeSH and free text terms such as aerobic exercise training, physical activity, endurance exercise, lipids, lipoproteins, apolipoproteins, triglycerides, and cholesterol. Searches excluded studies of pregnant or lactating females; elite athletes; juveniles; current or previous incidence of CVD, stroke, cancer, and NAFLD populations; and dietary and pharmaceutical interventions (see SM Table 7.5 – example search strategy). Other SRs and reference lists of papers were hand searched for additional RCTs.

2.3 Study Selection GNW, ET, AP, and VN conducted online database searches and reviewed search results on the basis of title and abstract independently, using Microsoft Excel (Version 16.31 2019). GNW, ET, AP and VN assessed and reviewed the full PDF texts of potentially eligible RCTs independently. NS was consulted to resolve disagreement over the final list of studies for inclusion. Studies of intervention and control group population sample sizes (N) <10 were excluded.(49)

2.3.1 Participants Studies of adult participants with no chronic disease, other than Type 1 or 2 diabetes mellitus, were included. Participants taking medication for any MetS factors were included.

2.3.2 Intervention An AET intervention ≥12 weeks was considered the minimum time to affect lipid profiles.(28) RCTs of either prescribed steady state or interval AET which employed a reported moderate intensity effort (≥40% VO_{2MAX}) were included. No restrictions were placed on AET session time or type. Studies including either an isometric, unconventional, resistance- or combined-training intervention, or lifestyle, dietary or pharmaceutical interventions, without separate AET interventions as comparators against a non-exercising control group, were excluded. Studies comparing multiple AET protocols without a non-exercising control group as comparator were excluded. Studies which did not provide details of the AET protocol, such as session duration, intensity, number of sessions in the intervention, or other details which allowed estimation of volume of exercise if not reported, were excluded.

2.3.3 Comparator An AET intervention was required to be compared to a non-exercising control group.

2.3.4 Outcomes Pre- and post-intervention measurements in mass (mg/dL) or molar (mmol/L) units of measurement of lipoprotein sub-fractions, apolipoproteins, or associated ratios and lipid ratios, for each of intervention and non-exercising control groups, were required to be reported. Lipid sub-fractions measurements given in mg/dL were multiplied by 0.02586 to convert to mmol/L.(50) All Apo measurements, whether reported as mass or molar, remained unconverted. Lead authors of included studies were contacted via electronic correspondence for missing values of outcomes. Any outcome data presented graphically were converted to numerical values using WebPlotDigitzer (Version 4.2, 2019).

2.4 Data extraction Pre-established data extraction sheets designed by GNW, using Microsoft Excel (Version 16.31 2019), were populated with extracted data. The list of included RCTs were divided between and randomly distributed to 3 teams comprising AP and TvdT, AM and GNW, and ET and NS. Each team member extracted data independently. Each set of extracted data were reviewed by the other team member and agreement was reached by consulting GNW in the case of discrepancies. The following data were extracted: 1) author(s), year of publication and study design; 2) demographic and clinical characteristics; 3) AET intervention and control protocols; 4) intervention and control group values before and after intervention for any Apo or lipoprotein sub-fractions, and lipid ratios, lipoprotein ratios, or Apo ratios. Values extracted included any of pre- and post mean (M) or mean difference (MD), pre- and post standard deviation (SD) or change in SD, standard error (SE) or change in SE, pre- and post within- or between group *P* values or change in *P* values, and 95% within- or between group confidence intervals (CI) or change in CIs.

2.5 Study Quality Study quality was determined using the validated Tool for the Assessment of Study Quality and Reporting in Exercise (TESTEX),(51) a 15-point scale specific to exercise training studies. A score ≥10 is considered good study quality and reporting.(52) Within-study risk of bias was determined by evaluating 7 factors (see SM Table 7.7), and awarding either low, medium or high within-study risk of bias scores. The RCTs were divided between and randomly distributed to ET and GNW, who extracted the relevant data independently according to the TESTEX criteria. Data sheets were cross-checked between ET and GNW for accuracy, and the results reviewed by AM. Disagreement was mediated by NS. A study quality sub-analysis of RCTs grouped according to a TESTEX score ≥10 and a within-study risk evaluation of low-to-medium was conducted.

2.6 Data Synthesis Statistical analyses were performed using Comprehensive Meta-Analysis (CMA) 3.0 (Biostat, Inc., New Jersey, USA). To allow for multiple missing and correlated outcomes,(45,46) a continuous multivariate random effects model(53) with Hartung-Knapp-Sidik-Jonkman adjustment(54) was used with the effects measure of raw MD, a 5% level of significance, and a 95% CI to report change in outcome measures. Outcomes were joined according to atherogenicity, change of effect size (ES) direction, and unit of measurement (mmol/L or mg/dL). Outcomes which could not be joined were analysed with a univariate model as described above. Reported raw MD, SD, and N for each of intervention and control groups were pooled when at least two outcomes were provided. When these values were not explicitly reported, required data were calculated where possible. As necessary, the MD was calculated by subtracting $M_{\text{pre-treatment}}$ from $M_{\text{post-treatment}}$. The SD of the MD was calculated as follows: SD = square root $[(SD_{\text{pre-treatment}})^2 + (SD_{\text{post-treatment}})^2 - (2r \times SD_{\text{pre-treatment}} \times SD_{\text{post-treatment}})]$, assuming a correlation coefficient r = 0.5, considered a conservative estimate.(55) Per group outcome data, whether reported for intention-to-treat (ITT) or for non-ITT analysis, were pooled. The data sets were divided equally between GNW and NS who independently entered the data in CMA. GNW and NS then reviewed each data set entered in CMA for accuracy prior to performing analyses.

2.6.1 Meta-analysis and Sub-analyses Comprehensive Meta-Analysis offers the choice of using the mean of joined outcomes, or the largest outcome reported per study. The former aids in avoiding Type 1 errors and increases the potential accuracy of estimated ES and CIs, although may under-estimate ES and significance. A cumulative random MVMA was conducted in CMA. Outcomes were joined, using the mean of multiple per-study outcomes, to assess the impact of AET over time. In each cumulative random MVMA, RCTs were sorted chronologically. For outcomes unable to be joined (eg ES direction, unit of measurement), a cumulative random univariate MA assessed the impact of AET over time with RCTs sorted chronologically.

Sub-analyses were conducted in CMA for study quality using TESTEX scores (RCTs with a score ≥10) and within-study bias analysis (low to medium). Data was entered by GNW and reviewed by NS for accuracy. A leave-one-out (K-1, where K = total number of pooled RCTs, and each RCT is excluded once) sensitivity analysis was also performed to evaluate the influence of each RCT on the ES of pooled data.(56)

2.6.2 Small-Study Effects Comprehensive Meta-Analysis was used to examine small-study effects and determine the likelihood of missing studies. We used each of Rosenthal's failsafe N, Orwin's failsafe N, Duval and Tweedie's trim-and-fill, Egger's regression test, Begg and Mezumdar's rank correlation test, and precision and standard error funnel plots, to test for possible small-study effects. Data was entered into CMA by GNW and NS independently and cross-checked for accuracy. MW conducted the analyses.

2.6.3 Meta-regression Meta-regression was conducted in CMA without adjustment for *P* values to determine whether any *a priori* covariates explained a change in statistically significant outcomes. *A priori* AET intervention covariates included intensity (percentage of VO_{2MAX}), minutes per session, sessions per week, and duration (weeks). These variables have been shown to influence lipid outcomes.(19,29,34) Other *a priori* covariates were year of publication (potential for improved laboratory testing in recent RCTs), total study participants

N (potential for under-powered studies to influence outcomes), extracted relevant outcomes N (changes in similar outcomes are correlated), and TESTEX study quality score (potential for better quality RCTs to influence outcomes). Data was entered in CMA by GNW and validated by NS and MW. Using a random effects maximum likelihood model with a Hartung-Knapp adjustment, the intercept and each AET covariate, singly and cumulatively, were regressed against the dependent variable MD. The same regression was repeated for study covariates.

2.6.4 Heterogeneity Heterogeneity was quantified using the Q statistic, and the corresponding *P* value, τ^2, τ, and I^2.(53) The Q statistic, and the corresponding *P* value, compared the differences among the calculated ES; τ^2 measured absolute between-study heterogeneity and the estimated SD (τ).(53) The relative measure of heterogeneity I^2 ranges from 0% (complete homogeneity) to 100% (complete heterogeneity).(57)

3.0 RESULTS

The search and inclusion process is presented in the PRISMA flow diagram(48) Figure 7.1.

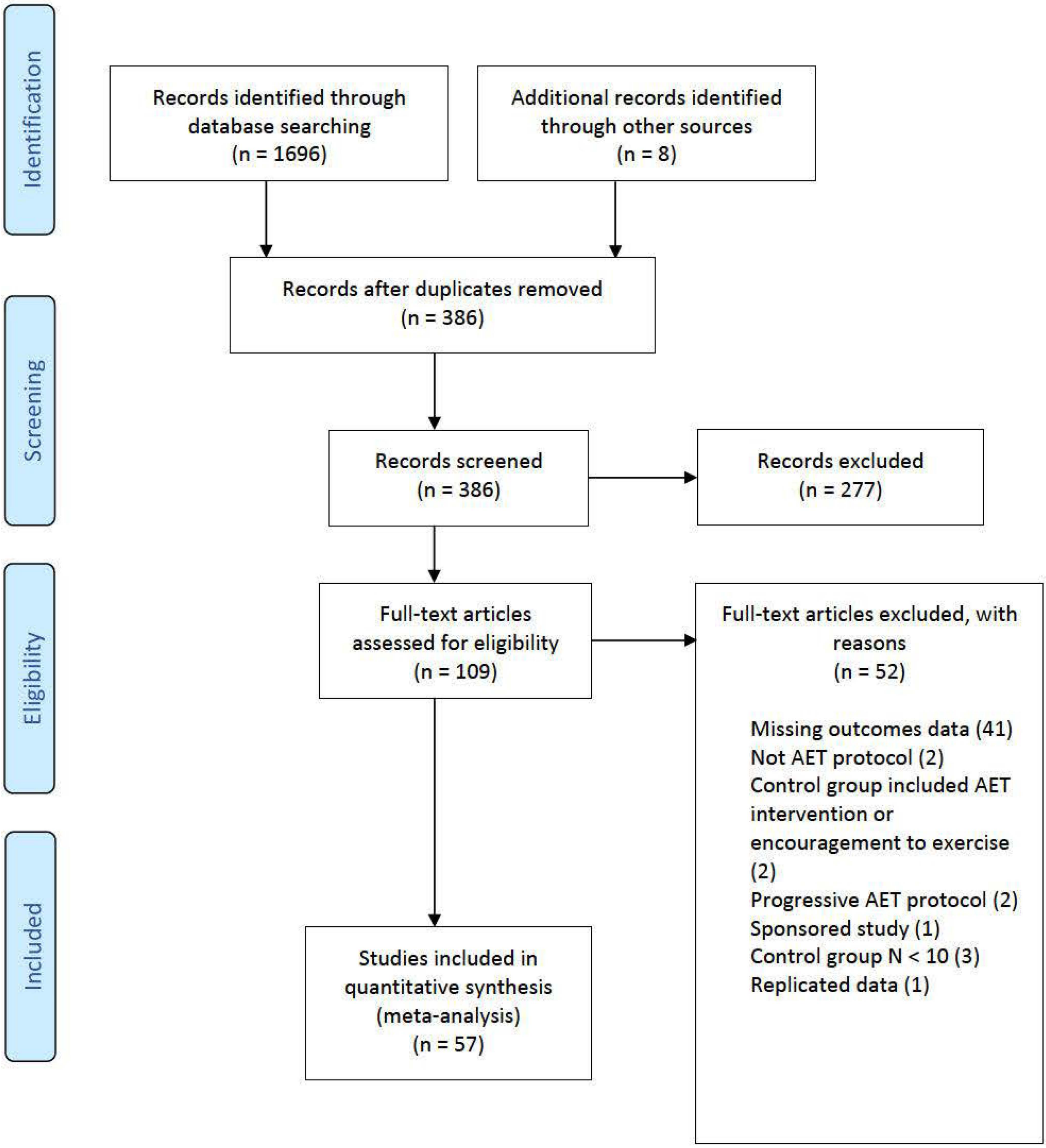


Figure 7.1 PRISMA flow diagram showing flow of papers.

Combined searches generated a total of 1436 potential papers. After removal of duplicates and exclusion of articles based on abstract and title, 109 full-text articles remained for screening against inclusion and exclusion criteria. Screening resulted in the inclusion of 57 RCTs (16,58-108) for data extraction, pooling, and analysis. We contacted 3 lead authors. One lead author provided data as requested. Two papers presented data graphically which was converted using WebPlotDigitzer (Version 4.2, 2019).

3.1 Study, Participant, and Intervention Characteristics Participant and intervention details of included RCTs are indicated in Table 7.1.

	Total N	Age	Gender	Number of extracted outcomes	Study Quality Score (/15)	Intensity VO_{2MAX} %	Intervention Duration (Weeks)	Sessions per week	Minutes per session
Aldred 1995 (58)	22	35 - 55	F	2	10	59	12	4.6	29
Baker 1986 (59)	34	> 55	M	1	9	72	20	3	48
Bell 2010 MICT (60)	85	35 - 55	Mx	1	11	63	24	2.8	29
Boardley 2007 (61)	68	> 55	Mx	1	9	65	16	3	35
Choi 2012(62)	75	35 - 55	F	2	10	50	12	5	60
Connolly 2020 (63)	24	35 - 55	F	1	12	60	12	2.9	15
Costa 2018 (64)	40	35 - 55	F	1	10	60	12	2	30
Finucane 2010 (65)	87	> 55	Mx	1	12	60	12	3	60
Furukawa 2003 (66)	45	35 - 55	F	2	12	50	12	2.5	30
Gahreman 2016 (67)	24	< 35	M	1	13	75	12	3	20
Gordon 2008 (68)	154	> 55	Mx	1	10	40	24	5	60
Grandjean 1996(69)	37	35 - 55	F	1	11	70	24	3	40
Hagan 1986 a (70)	24	< 35	F	2	10	59	12	5	30
Hagan 1986 b (70)	24	< 35	M	2	10	47	12	5	30
Hespel 1988 (71)	27	35 - 55	M	4	9	80	16	3	40
Hinkleman 1993 (72)	36	35 - 55	F	1	12	62	15	5	45
Huttunen 1979 (73)	90	35 - 55	M	2	11	50	16	3.5	30
Kiens 1980 (74)	37	35 - 55	M	1	8	80	12	2.6	45
Knoepfli-Lenzin 2010 (75)	32	35 - 55	M	1	8	67	12	2.5	58
Korshøj 2016 (76)	116	35 - 55	Mx	1	9	60	16	2	30
Krustrup 2010 (77)	31	35 - 55	F	1	10	70	16	1.8	52
Kukkonen-Harjula 1998 (78)	108	35 - 55	Mx	2	12	70	15	3.8	45
Laaksonen 2000 (79)	42	< 35	M	2	11	70	12	4	40
Lehmann 1995 (80)	29	35 - 55	Mx	2	8	50	12	4	38
LeMura 2000 (81)	22	< 35	F	1	9	59	16	3	30
Ligtenberg 1997 (82)	51	> 55	Mx	3	11	70	26	3	50
Lindheim 1994 (83)	45	35 - 55	F	4	9	52	26	3	30
Martins 2010 (84)	63	> 55	Mx	1	6	60	16	3	45
Mohanka 2006 (85)	173	> 55	F	2	12	57	52	3	45
Motoyama 1995 (86)	30	> 55	Mx	1	12	50	39	5.2	30
Niederseer 2011 (87)	34	> 55	Mx	2	10	55	12	2.4	210
Nieman 1993 (72)	30	> 55	F	1	13	55	12	5	38
Nieman 2002 (89)	43	35 - 55	F	1	13	65	12	4.8	45
Paolillo 2017 (90)	20	35 - 55	F	2	12	79	52	2	45
Ready 1995 (91)	25	> 55	F	3	8	54	26	4.9	54
Ring-Dimitriou 2007 (92)	30	35 - 55	Mx	2	9	75	39	1	80
Rosenkilde 2018 (93)	24	35 - 55	M	3	11	75	12	3	60
Rossi 2016 (94)	33	> 55	F	1	7	70	16	2	52
Ruangthai 2019 (95)	25	> 55	Mx	2	11	48	24	3	40
Shearman 2010 (96)	37	35 - 55	M	3	10	44	12	4.3	34
Sigal 2007 (97)	123	35 - 55	Mx	2	15	75	22	2.4	45
Slentz 2007 hvVICT (16)	84	35 - 55	Mx	1	10	73	26	3.6	58
Slentz 2007 lvMICT (16)	72	35 - 55	Mx	1	10	48	26	3.5	58
Slentz 2007 lvVICT (16)	83	35 - 55	Mx	1	10	73	26	2.9	43
Stefanick 1998 a (98)	88	> 55	F	3	12	50	52	3	53
Stefanick 1998 b (98)	93	35 - 55	M	3	12	50	52	3	53
Stensel 1993 (99)	65	35 - 55	M	3	11	60	52	7	28
Sunami 1999 (100)	40	> 55	Mx	3	10	50	22	3	60
Suter 1990 (101)	61	35 - 55	M	1	9	77	16	3	30
Suter 1992 (102)	32	35 - 55	F	5	9	80	16	3	45
Tully 2007 (=) (103)	52	35 - 55	Mx	1	13	53	12	4.2	26
Tully 2007 (<) (103)	54	35 - 55	Mx	1	13	53	12	4.2	29
Verissimo 2002 (104)	63	> 55	Mx	7	8	55	35	3	50
von Thiele Schwarz 2008 (105)	118	35 - 55	F	1	8	49	52	3	60
Wirth 1985 (106)	21	35 - 55	M	1	8	60	17	3	60
Wood 1983 (107)	81	35 - 55	M	6	9	80	12	3	25
Wood 1988 (108)	88	35 - 55	M	1	9	80	52	4	45
Total	**3194**		**Median**	**1**	**10**	**60**	**16**	**3**	**45**

Age: in years; F: females; M: males; Mx: mixed genders; N: number; a: females; b: males; hv: high volume; lv: low volume; MICT: moderate intensity continuous training; VICT: vigorous intensity continuous training; (=): equals recommended; (<): less than recommended

Table 7.1 Study, Participant, Intervention, and Outcomes Attributes

Total participants numbered 3194 (exercise: 1721; control: 1473). Of these, 963 participants were female, 780 were male, and 1451 participants included both genders. Participants under 35 years numbered 136, between 35 – 55 years there were 2060 participants, and 998 participants were over 55 years. All participants were stated as being sedentary before the start of trials.

Intervention AET included weight-bearing activities such as running or walking on treadmills or outdoors, circuit training with no or minimal resistance components, and non-weight-bearing activities such as swimming, cycling, and ergocycle. Aerobic exercise intensity ranged from 40-80% VO_{2MAX}. Studies included supervised and unsupervised training sessions, with unchanged or progressive effort increments in response to training adaptations, as well as measures of effort clinically- or self-monitored, and reported via training logs, see SM Tables 7.6-7.7. Studies stated that control groups were instructed not to exercise and not to change daily habits.

3.2 Comparative Outcomes The ratio outcomes extracted from included RCTs were TC/HDL-C, LDL-C/HDL-C, HDL-C/TC, HDL-C/LDL-C, Apo B100/A1, and Apo A1/Apo B100. Sub-fractions extracted (mmol/L and mg/dL) were VLDL, HDL2 and HDL3. Apolipoproteins extracted (mmol/L and mg/dL) were Apo A1, Apo A2, Apo B100.

Outcomes were joined according to antiatherogenicity, atherogenicity, ES direction, and reporting measurement. The TC/HDL-C, LDL-C/HDL-C, and Apo B100/A1 ratios were joined (negative ES direction) and analysed. The Apo A1/Apo B100, HDL-C/TC and HDL-C/LDL-C ratios were joined (positive ES direction) and analysed. Apolipoprotein A1 and A2 mmol/L were joined with HDL2 and HDL3 mmol/L (antiatherogenic) and analysed. Apolipoprotein B100 mmol/L were joined with VLDL mmol/L (atherogenic) and analysed. Apolipoprotein A1 and

A2 reported as mg/dL were joined (antiatherogenic) and analysed. Apolipoprotein B100 reported as mg/dL (atherogenic) was analysed separately.

Apolipoproteins A1 and A2, with or without the inclusion of HDL2 and HDL3, and independent of unit of measurement, were significantly raised by AET as shown in Table 7.2. The joined TC/HDL-C, LDL-C-HDL-C and Apo B100/Apo A1 ratios significantly fell with AET as shown in Table 7.2. Sub-analyses using K-1 sensitivity analysis for statistically significant outcomes did not change results, see SM Figures 7.6-7.8.

Multivariate Analysis Model	Random, 95% CI, Maximum Likelihood, Knapp-Hartung, Mean Difference				Population N		
Apolipoprotein, sub-fraction, ratio Mean of combined outcomes	**Point Estimate**	**Lower Limit**	**Upper Limit**	***P* value**	**Exercise**	**No Exercise**	**Total**
Apo A1 + Apo A2 + HDL2 + HDL3 mmol/L	0.047	0.011	0.082	**.010**	260	235	495
Apo A1 + Apo A2 mg/dL	2.297	0.441	4.153	**.015**	403	370	773
Apo B100 + VLDL mmol/L	-0.053	-0.114	0.008	.087	535	360	895
TC/HDL-C + LDL-C/HDL-C + Apo B100/Apo A1	-0.201	-0.291	-0.111	**<.000**	974	934	1908
HDL-C/TC + HDL-C/LDL-C + Apo A1/Apo B100	0.022	-0.002	0.046	0.077	121	97	218

Univariate Analysis Model	Random, 95% CI, Maximum Likelihood, Knapp-Hartung, Mean Difference				Population N		
Apolipoprotein, sub-fraction, ratio	**Point Estimate**	**Lower Limit**	**Upper Limit**	***P* value**	**Exercise**	**No Exercise**	**Total**
Apo B100 mg/dL	-0.953	-2.616	0.710	.261	369	335	704

CI: confidence interval; N: number; Apo: apolipoprotein; HDL-C: high-density lipoprotein cholesterol; mmol/L: millimoles per litre; SQ study quality TESTEX sub-analysis; mg/dL: milligram per decilitre; VLDL: very low-density lipoprotein cholesterol; TC: total cholesterol; bolded *P* values indicate significance.

Table 7.2 Multivariate and Univariate Analysis Results of Joined and Separate Outcomes

The chronological positive impact of AET is shown in the cumulative random MVMA of included RCTS for each of 1) Apo A1 + Apo A2 + HDL2 + HDL3 mmol/L in Figure 7.2; 2) Apo A1 + Apo A2 mg/dL in Figure 7.3; and TC/HDL-C + LDL-C/HDL-C + Apo B100/Apo A1 in Figure 7.4.

Model	Study name	Outcome	Cumulative statistics: Point	Lower limit	Upper limit	p-Value	Cumulative sample size: Exercise	No exercise	TESTEX Score	Weight (Random): Weight (Random)	Relative weight
	Kiens 1980	Apo A1	0.130	-0.012	0.272	0.073	24	13	8	190.51	6.18
	Wood 1983	Combined	0.144	0.007	0.281	0.039	72	46	9	14.31	6.65
	Suter 1992	Combined	0.093	-0.012	0.198	0.083	88	62	9	143.44	11.31
	Aldred 1995	HDL-C2	0.082	-0.009	0.172	0.076	99	73	10	125.00	15.36
	Ligtenberg 1997	Apo A1	0.049	-0.021	0.118	0.170	124	99	11	318.63	25.71
	Sunami 1999	HDL-C2	0.066	0.002	0.131	0.043	144	119	10	134.87	30.09
	Verissimo 2002	Combined	0.076	0.025	0.126	0.003	175	152	8	589.01	49.21
	Kukkonen-Harjula	Combined	0.052	0.009	0.094	0.017	228	206	12	1347.39	92.95
	Shearman 2010	Apo A1	0.047	0.011	0.082	0.009	248	223	10	216.22	99.97
	Rosenkilde 2018	Apo A1	0.047	0.011	0.082	0.010	260	235	11	1.06	100.00
Random			0.047	0.011	0.082	0.010					

Figure 7.2 Cumulative random multivariate meta-analysis of the impact of AET on Apo A1 + Apo A2 + HDL2 + HDL3 mmol/L

Model	Study name	Outcome	Cumulative statistics: Point	Lower limit	Upper limit	p-Value	Cumulative sample size: Exercise	No exercise	TESTEX Score	Weight (Random): Weight (Random)	Relative weight
	Huttunen 1979	Combined	1.650	-4.871	8.171	0.620	44	46	11	0.09	8.10
	Wood 1983	Combined	1.244	-1.590	4.079	0.390	92	79	9	0.39	42.86
	Hespel 1988	Combined	1.522	-1.157	4.201	0.266	105	93	9	0.06	47.97
	Stensel 1993	Apo A1	1.501	-1.123	4.125	0.262	147	116	11	0.02	50.01
	Lindheim 1994	Apo A1	1.629	-0.977	4.235	0.220	167	141	9	0.01	50.71
	Lehmann 1995	Apo A1	1.968	-0.615	4.551	0.135	183	154	8	0.01	51.61
	Stefanick 1998 (females)	Apo A1	1.930	-0.463	4.324	0.114	226	199	12	0.09	60.09
	Stefanick 1998 (males)	Apo A1	1.787	-0.258	3.832	0.087	273	245	12	0.25	82.37
	Laaksonen 2000	Apo A1	1.789	-0.244	3.823	0.085	293	267	11	0.01	83.30
	Verissimo 2002	Apo A1	2.150	0.153	4.147	0.035	324	299	8	0.03	86.35
	Furukawa 2003	Apo A1	2.396	0.446	4.347	0.016	345	323	12	0.05	90.51
	Ring-Dimitriou 2007	Apo A1	2.607	0.552	4.662	0.013	365	333	9	0.00	90.91
	Choi 2012	Apo A1	2.297	0.441	4.153	0.015	403	370	10	0.10	100.00
Random			2.297	0.441	4.153	0.015					

Figure 7.3 Cumulative random multivariate meta-analysis of the impact of AET on Apo A1 + Apo A2 mg/dL

Model	Study name	Outcome	Cumulative statistics				Cumulative sample size		TESTEX Score	Weight (Random)	
			Point	Lower limit	Upper limit	p-Value	Exercise	No exercise		Weight (Random)	Relative weight
	Hagan 1986 females	TC/HDL-C	0.000	-1.140	1.140	1.000	12	12	10	2.84	0.60
	Hagan 1986 males	TC/HDL-C	0.043	-0.818	0.904	0.922	24	24	10	2.16	1.06
	Wood 1988	TC/HDL-C	-0.419	-0.856	0.018	0.060	71	65	9	12.31	3.66
	Suter 1992	Apo B/Apo	-0.157	-0.442	0.128	0.280	87	81	9	61.53	16.66
	Hinkleman 1993	TC/HDL-C	-0.104	-0.315	0.107	0.334	105	99	12	4.68	17.65
	Nieman 1993	TC/HDL-C	-0.060	-0.149	0.028	0.181	119	115	13	2.89	18.26
	Lindheim 1994	TC/HDL-C	-0.067	-0.154	0.021	0.134	139	140	9	9.45	20.26
	Ready 1995	TC/HDL-C	-0.070	-0.157	0.017	0.115	154	150	8	3.45	20.99
	Aldred 1995	TC/HDL-C	-0.074	-0.161	0.012	0.092	165	161	10	6.52	22.36
	Motoyama 1995	TC/HDL-C	-0.189	-0.378	-0.001	0.049	180	176	12	6.49	23.74
	Stefanick 1998 (females)	TC/HDL-C	-0.249	-0.441	-0.057	0.011	223	221	12	25.18	29.06
	Stefanick 1998 (males)	TC/HDL-C	-0.228	-0.391	-0.065	0.006	270	267	12	17.51	32.76
	Sunami 1999	Combined	-0.241	-0.397	-0.084	0.003	290	287	10	10.51	34.98
	LeMura 2000	TC/HDL-C	-0.229	-0.376	-0.082	0.002	300	299	9	0.21	35.03
	Verissimo 2002	Combined	-0.310	-0.494	-0.126	0.001	331	331	8	6.01	36.30
	Nieman 2002	TC/HDL-C	-0.293	-0.467	-0.118	0.001	352	353	13	5.30	37.42
	Mohanka 2006	Combined	-0.261	-0.416	-0.105	0.001	439	439	12	19.47	41.53
	Boardley 2007	TC/HDL-C	-0.239	-0.387	-0.091	0.002	472	474	9	9.00	43.43
	Tully 2007 a (=)	TC/HDL-C	-0.229	-0.377	-0.082	0.002	514	484	13	2.11	43.88
	Tully 2007 b (<)	TC/HDL-C	-0.227	-0.369	-0.084	0.002	558	494	13	1.96	44.29
	Sigal 2007	Combined	-0.210	-0.338	-0.081	0.001	616	556	15	18.90	48.29
	von Thiele Schwarz 2008	LDL-C/HDL	-0.171	-0.280	-0.062	0.002	674	616	8	41.34	57.03
	Martins 2010	TC/HDL-C	-0.192	-0.303	-0.082	0.001	706	647	6	15.47	60.30
	Knoepfli-Lenzin 2010	TC/HDL-C	-0.184	-0.291	-0.076	0.001	721	664	8	4.55	61.26
	Krustrup 2010 MICT	LDL-C/HDL	-0.172	-0.273	-0.071	0.001	738	678	10	12.62	63.93
	Bell 2010 MICT	TC/HDL-C	-0.159	-0.256	-0.061	0.001	778	723	11	15.52	67.21
	Finucane 2010	TC/HDL-C	-0.147	-0.239	-0.055	0.002	815	773	12	14.03	70.17
	Niederseer 2011	Combined	-0.138	-0.224	-0.053	0.002	833	789	10	9.44	72.17
	Rossi 2016	TC/HDL-C	-0.142	-0.224	-0.060	0.001	848	807	7	21.25	76.66
	Korshøj 2016	LDL-C/HDL	-0.166	-0.248	-0.084	0.000	905	866	9	40.09	85.13
	Gahreman 2016	TC/HDL-C	-0.161	-0.240	-0.083	0.000	917	878	13	5.07	86.20
	Costa 2018	TC/HDL-C	-0.214	-0.315	-0.114	0.000	937	898	10	13.72	89.10
	Rosenkilde 2018	Apo B/Apo	-0.200	-0.293	-0.107	0.000	949	910	11	37.75	97.08
	Ruangthai 2019	Combined	-0.198	-0.289	-0.106	0.000	962	922	11	7.30	98.62
	Connolly 2020	TC/HDL-C	-0.201	-0.291	-0.111	0.000	974	934	12	6.52	100.00
Random			-0.201	-0.291	-0.111	0.000					

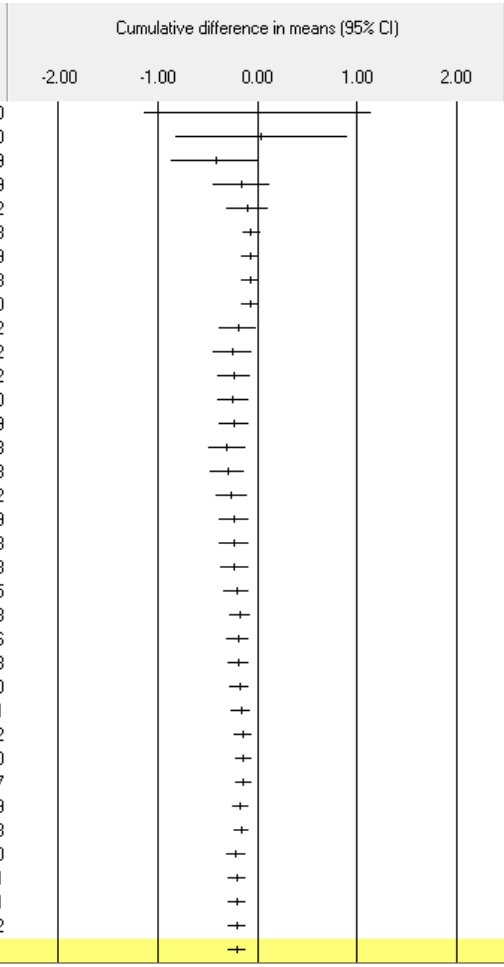


Figure 7.4 Cumulative random multivariate meta-analysis of the impact of AET on TC/HDL-C + LDL-C/HDL-C + Apo B100/Apo A1

3.3 Study Quality and Reporting The median TESTEX score was 10 (from a maximum score of 15; range 6 to 15), see SM Table 7.6. Within-study risk of bias was mainly low or medium, see SM Table 7.7. No RCT receiving a TESTEX score ≥10 was awarded a within-study risk of bias score of high. Sub-analyses using TESTEX scores ≥10 resulted in significance for Apo B100 combined with VLDL, see Figure 7.5, and the TC/HDL-C + LDL-C/HDL-C + Apo B100/Apo A1 ratio remained significant, see Table 7.3. Better quality studies increased the ES for Apo B100 reported in mg/dL but did not attain significance.

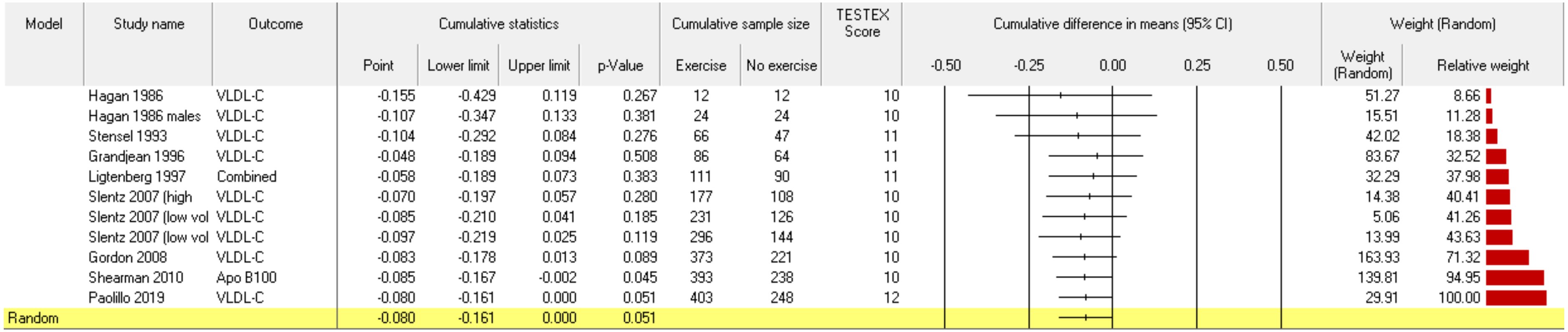
Multivariate Analysis Model	Random, 95% CI, Maximum Likelihood, Knapp-Hartung, Mean Difference				Population N		
Apolipoprotein, sub-fraction, ratio Mean of combined outcomes	**Point Estimate**	**Lower Limit**	**Upper Limit**	***P* value**	**Exercise**	**No Exercise**	**Total**
Apo A1 + Apo A2 + HDL2 + HDL3 mmol/L SQ	0.027	-0.015	0.070	.208	141	140	281
Apo A1 + Apo A2 mg/dL SQ	1.775	-0.725	4.275	.164	255	243	498
Apo B100 + VLDL mmol/L SQ	-0.080	-0.161	0.000	**.051**	403	248	651
TC/HDL-C + LDL-C/HDL-C + Apo B100/Apo A1 SQ	-0.192	-0.310	-0.075	**.001**	625	578	1203
HDL-C/TC + HDL-C/LDL-C + Apo A1/Apo B100 SQ (only(96))	0.100	-0.145	0.345	.423	20	17	37

Univariate Analysis Model	Random, 95% CI, Maximum Likelihood, Knapp-Hartung, Mean Difference				Population N		
Apolipoprotein, sub-fraction, ratio	**Point Estimate**	**Lower Limit**	**Upper Limit**	***P* value**	**Exercise**	**No Exercise**	**Total**
Apo B100 mg/dL SQ	-2.073	-4.896	0.750	.150	211	197	408

CI: confidence interval; Apo: apolipoprotein; HDL-C: high-density lipoprotein cholesterol; mmol/L: millimoles per litre; SQ study quality TESTEX sub-analysis; mg/dL: milligram per decilitre; VLDL: very low-density lipoprotein cholesterol; TC: total cholesterol; bolded *P* values indicate significance.

Table 7.3 Multivariate and Univariate Sub-analysis Results of Combined and Separated Outcomes using TESTEX scores

The chronological positive impact of AET, adjusted for study quality, is shown in the cumulative random MVMA of included RCTs for Apo B100 + VLDL mmol/L SQ in Figure 7.5.



Model	Study name	Outcome	Cumulative statistics				Cumulative sample size		TESTEX Score	Cumulative difference in means (95% CI)	Weight (Random)	
			Point	Lower limit	Upper limit	p-Value	Exercise	No exercise		-0.50 -0.25 0.00 0.25 0.50	Weight (Random)	Relative weight
	Hagan 1986	VLDL-C	-0.155	-0.429	0.119	0.267	12	12	10		51.27	8.66
	Hagan 1986 males	VLDL-C	-0.107	-0.347	0.133	0.381	24	24	10		15.51	11.28
	Stensel 1993	VLDL-C	-0.104	-0.292	0.084	0.276	66	47	11		42.02	18.38
	Grandjean 1996	VLDL-C	-0.048	-0.189	0.094	0.508	86	64	11		83.67	32.52
	Ligtenberg 1997	Combined	-0.058	-0.189	0.073	0.383	111	90	11		32.29	37.98
	Slentz 2007 (high	VLDL-C	-0.070	-0.197	0.057	0.280	177	108	10		14.38	40.41
	Slentz 2007 (low vol	VLDL-C	-0.085	-0.210	0.041	0.185	231	126	10		5.06	41.26
	Slentz 2007 (low vol	VLDL-C	-0.097	-0.219	0.025	0.119	296	144	10		13.99	43.63
	Gordon 2008	VLDL-C	-0.083	-0.178	0.013	0.089	373	221	10		163.93	71.32
	Shearman 2010	Apo B100	-0.085	-0.167	-0.002	0.045	393	238	10		139.81	94.95
	Paolillo 2019	VLDL-C	-0.080	-0.161	0.000	0.051	403	248	12		29.91	100.00
Random			-0.080	-0.161	0.000	0.051						

Figure 7.5 Cumulative random multivariate meta-analysis of Apo B100 + VLDL SQ mmol/L

3.4 Lipid Extraction Methodology The included RCTs extracted blood from individuals in fasted states and in seated or supine positions thus no RCT was excluded (data not shown).

3.5 Small Study Effects Included studies exceeded the minimum number of ES.(109) There was minimal to no evidence of potential small study effects for each of the statistically significant outcomes after analysis with Classic fail-safe N, Orwin's fail-safe N, Duval and Tweedie's trim-and-fill, Egger's regression test, and Begg and Mezumdar's rank correlation test, nor following inspection of precision and standard error funnel plots. Given the minimal evidence, the impact of the potential small study effects is trivial, which suggests validation of the results of the corresponding MVMAs, see SM Tables 7.8-7.23, SM Figures 7.9-7.16.

3.6 Meta-regression Multivariate MR modelling of significant results suggested that the improvement in Apo A1 + Apo A2 + HDL2 + HDL3 mmol/L was fully explained by all study covariates (publication year, participant number, number of extracted outcomes, and study quality score), τ^2 = 0.0000, R^2 = 1.00. The intervention covariate minutes per session accounted for some improvement in this outcome, τ^2 = 0.0001, R^2 = 0.57. The other intervention covariates (intensity, sessions per week, and intervention duration), singly or combined, fully explained the improvement in this outcome (τ^2 = 0.0000, R^2 = 1.00), see SM Tables 7.24-7.25.

The study covariate publication year was minimally associated with improvement in the TC/HDL-C + LDL-C/HDL-C + Apo B100/Apo A1 ratio (τ^2 = 0.0134, R^2 = 0.07). Combined intervention covariates (intensity, minutes per session, sessions per week, and intervention duration) also explained improvement for this outcome (τ^2 = 0.0023, R^2 = 0.84), see SM Tables 7.26-7.27.

Neither study nor intervention covariates explained change in Apo A1 + Apo A2 mg/dL or Apo B100 + VLDL SQ mmol/L (data not shown).

3.7 Heterogeneity Neither the degree of absolute between-study heterogeneity (τ^2) or the relative heterogeneity (I^2) for each analysed outcome indicated that studies should not be pooled, or that significance testing should not be undertaken, see Table 7.4.

Outcome	Heterogeneity				τ^2			
	Q-value	Df [Q]	*P* value	I^2 %	τ^2	Standard Error	Variance	τ
Apo A1 + Apo A2 + HDL2 + HDL3 mmol/L	7.96	9	.54	0.00	0.00	0.00	0.00	0.01
Apo A1 + Apo A2 mg/dL	11.82	12	.46	0.00	0.00	5.48	30.01	0.00
TC/HDLC + LDL-C/HDL-C + Apo B100/ Apo A1	46.39	34	.08	26.71	0.01	0.01	0.00	0.12
HDL-C/TC + HDL-C/LDL-C + Apo A1/Apo B100	1.6	4	.81	0.00	0.00	0.00	0.00	0.00
Apo B100 + VLDL mmol/L	7.42	16	.96	0.00	0.00	0.01	0.00	0.00
Apo B100 mg/dL	9.92	12	.62	0.00	0.00	4.99	24.89	0.00

Apo: apolipoprotein; HDL-C: high-density lipoprotein cholesterol; mmol/L: millimoles per litre; mg/dL: milligram per decilitre; VLDL: very low-density lipoprotein; TC: total cholesterol.

Table 7.4 Heterogeneity values reporting I^2 and τ^2

4.0 DISCUSSION

This SR and MVMAMR, of 57 RCTs of 3194 participants, compared the effects of at least 12 weeks of AET performed at ≥40% VO_{2MAX}, against non-exercising control groups on lipoprotein sub-fractions, apolipoproteins, associated ratios, and lipid ratios. Previous findings examining the effect of AET on the standard lipid profile have shown that AET improves TC, TRG, HDL-C and LDL-C. Despite the potential for smaller ES and statistical insignificance by adopting a MVMAMR approach, we have shown that AET at ≥40% VO_{2MAX}

for ≥12 weeks achieved better outcomes than no exercise for TC/HDL-C + LDL-C/HDL-C + Apo B100/apo A1, Apo A1 + Apo A2 + HDL2 + HDL3 mmol/L, Apo A1 + Apo A2 mg/dL, and Apo B100 + VLDL mmol/L. Lipoprotein sub-fractions, lipid and Apo ratios, and Apo A1, A2, B100 are better predictors of CVD risk.(4,5,9-14) Our results suggest AET improves these CVD risk biomarkers, which could potentially be prioritised for measurement over the standard lipid profile, when AET is prescribed to reduce CVD risk.

Our work extends that of others investigating whether AET covariates explain change in standard lipid profile biomarkers.(19,29,34) We found that AET intervention covariates explained positive change in antiatherogenic apolipoproteins and lipoprotein sub-fractions. Our recent comparison of AET protocols suggested that antiatherogenic HDL-C is positively affected by AET intensity.(41)

4.1 Clinical Significance and Future Research Our SR and MVMA results indicated AET programs of ≥40% VO_{2MAX} undertaken for ≥12 weeks positively affect lipid ratios, apolipoproteins, and lipoprotein sub-fraction class of CVD risk biomarkers. Our work indicated that intervention volume variables (intensity, session minutes, sessions per week, and intervention duration) explain positive change in these outcomes. The findings of others suggest an AET protocol of >180 minutes per week at >40% VO_{2MAX} or >1200 kcal/week, (29,34,43,44) or a minimum effective AET volume (>45 minutes per session for 3-4 sessions per week for duration >26 weeks at >65% VO_{2MAX}),(19) is necessary to effect positive change in the standard lipid profile. To obtain larger effects on the lipid CVD risk biomarkers we measured, and given that intervention variables predict ES, the volume and intensity of weekly AET may need to be increased above national guidelines of 150 minutes of moderate intensity AET or 75 minutes of vigorous intensity AET per week.

Given the paucity of reported apolipoprotein, sub-fraction, and ratio data, we propose that future research should compare AET protocols of appropriate volume against non-exercising interventions and report apolipoproteins, lipoprotein sub-fractions, and relevant ratios. Since TRG better predicts CVD risk in women,(110) we recommend trials also record non-HDL-C, TRG/HDL-C and non-HDL-C/HDL-C, as these ratios were under-reported in our included RCTs.

Our study quality TESTEX and within-study risk of bias analyses indicated that many included RCTs failed to specify the method of randomisation and allocation concealment; report medication use, drop-out reasons, or adverse events; report monitoring of the non-exercising group or adherence to either the exercising or non-exercising protocol; set a minimum compliance level; use objective measuring devices; and report post-intervention exercise volume (total sessions attended, total minutes per session, achieved intensity). Timing of post-intervention blood analyses was not always recorded. Patient data, such as pre-post body weight, body fat or lean mass, waist circumference or BMI, systolic and diastolic blood pressure, and fasting blood glucose, were also often missing. Researchers conducting RCTs can better report their findings by including quantitative data for these variables.

4.2 Strengths and Limitations in this Systematic Review and Meta-analysis/Meta-regression

Our work has a number of strengths. To the best of our knowledge, this SR and MVMAMR is the first to have compared the effects of AET against no exercise on lipid sub-fractions, ratios, and apolipoproteins.

We used the validated study quality evaluation tool TESTEX(51) to measure the quality of included studies. We followed a rigorous inclusion/exclusion protocol to ensure minimisation of confounding factors amongst the RCT populations.(111)

A potential limitation of our work is the use of aggregated RCT data and not individual subject data,(112,113) with the exception of one study.(97) We searched using English language terms only, reducing the pool of available studies for selection and possibly introducing small study effects. We excluded studies with intervention and comparison group N < 10, and this may have reduced estimated ES. The number of RCTs included with longer durations were few, and this may have been a source of bias that negatively impacted ES. Despite the potential for bias, our small study effects analyses indicated that the potential change in the calculated ES due to bias was trivial and should not influence the interpretation of our results. We also included AET protocols starting from the minimum of moderate intensity (≥40% VO_{2MAX}). Such a low intensity may elicit very small changes in lipids,(19) and the inclusion of these protocols may have understated ES. Additionally, reporting of protocol adherence and intensity varied. Some studies used objective measures such as electronic devices. Other studies used subjective measures eg Borg scale, self-reported HR, log books, denoted by different indices of intensity (energy expenditure, VO_{2MAX}, MHR, METs, Borg scale). This may have introduced bias in the measurement of data reported in the included RCTs. Little information regarding the AET protocol or energy expenditure was provided in some included RCTs, thus we estimated intensity as a percent of VO_{2MAX}. Protocols consisted of conventional AET, potentially influencing ES. A very small number of RCTs noted that control groups increased physical activity levels during the duration of the study, and this may have reduced ES. Our meta-regression covariates were not randomised at study level and thus our meta-regression findings should be considered as exploratory.

With respect to data pooling, where the SD of the MD, exact *P* values within groups, or 95% CIs were not available, statistical analyses depended on extrapolated data. Our imputation of the SD of the MD was conservative and this approach may have weakened results.

5.0 CONCLUSION

This MVMAMR of pooled data indicated AET programs of moderate intensity with a minimum 12 week duration significantly reduced the joint TC/HDL-C, LDL-C/HDL-C, and Apo B100/Apo A1 ratio, as well as Apo B100 and VLDL values, while significantly raising Apo A1 and A2 and the sub-fractions HDL2 and HDL3, in sedentary adults. Our results mimic the results of previous SRs and MAs examining standard lipid CVD risk biomarkers. Meta-regression suggested intervention variables explained change in outcomes lipid ratios and antiatherogenic apolipoproteins and lipoprotein sub-fractions. We were unable to estimate effect measures for non-HDL-C owing to lack of reported data. Importantly, few studies reported the Apo B100/Apo A1 ratio, which is considered an equivalent if not more accurate lipid CVD risk biomarker in comparison to standard lipid CVD risk biomarkers. Future trials should endeavour to focus on measuring and reporting Apo B100/Apo A1 ratios, apolipoproteins and lipoprotein sub-fractions when examining the effect of aerobic exercise training.

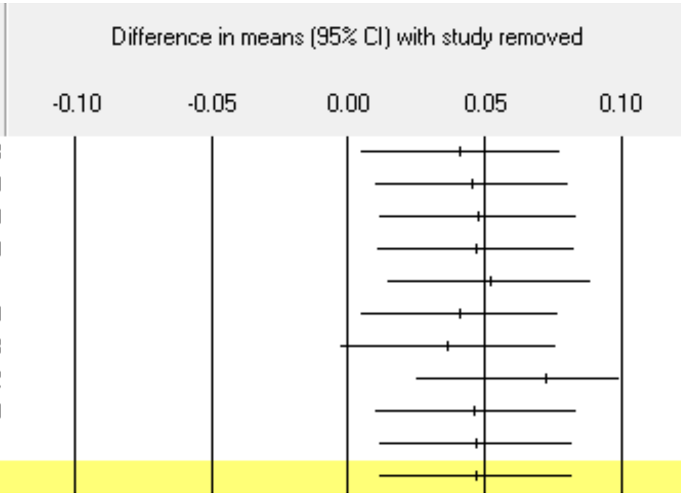
Supplementary Materials

Web of Science example search	TOPIC:(random* control* trial*) *AND* TOPIC:(*cholesterol* OR *lipoprotein* OR triglycer* OR lipid*) *AND* TOPIC:(exercise OR physical activity OR aerobic training OR moderate intensity OR high intensity OR HIIT OR MICT OR endurance) *NOT* TOPIC: (heart failure OR belief* OR *statin* OR diet* OR HIV OR cardiac rehabilitation OR NAFLD OR *Alzheimer* OR *stroke OR cancer OR athlete OR child* OR pregna n* or lactat* or adolescent OR juvenile OR bariatric OR renal failure OR polycystic OR depression) *NOT* TOPIC:(systematic review* OR meta-analys*) Timespan: All years. Databases: WOS, CABI, CCC, KJD, MEDLINE, RSCI, SCIELO. Search language=Auto

SM Table 7.5 Search Strategy example

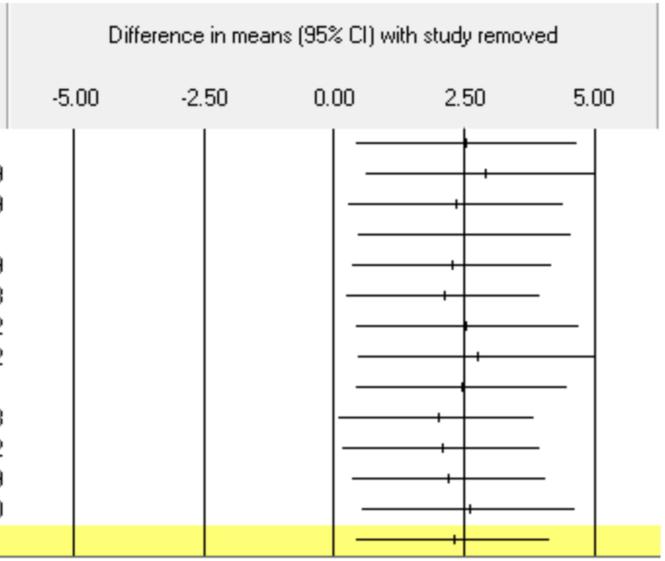
Sensitivity Analyses (K-1 sub-analysis)

Model	Study name	Outcome	Statistics with study removed				TESTEX Score
			Point	Lower limit	Upper limit	p-Value	
	Kiens 1980	Apo A1	0.041	0.005	0.078	0.027	8
	Wood 1983	Combined	0.045	0.010	0.081	0.012	9
	Suter 1992	Combined	0.048	0.012	0.084	0.009	9
	Aldred 1995	HDL-C2	0.047	0.011	0.083	0.011	10
	Ligtenberg 1997	Apo A1	0.052	0.015	0.089	0.006	11
	Sunami 1999	HDL-C2	0.041	0.005	0.077	0.026	10
	Verissimo 2002	Combined	0.036	-0.003	0.076	0.069	8
	Kukkonen-Harjula	Combined	0.073	0.025	0.120	0.003	12
	Shearman 2010	Apo A1	0.046	0.010	0.083	0.013	10
	Rosenkilde 2018	Apo A1	0.047	0.011	0.082	0.009	11
Random			0.047	0.011	0.082	0.010	



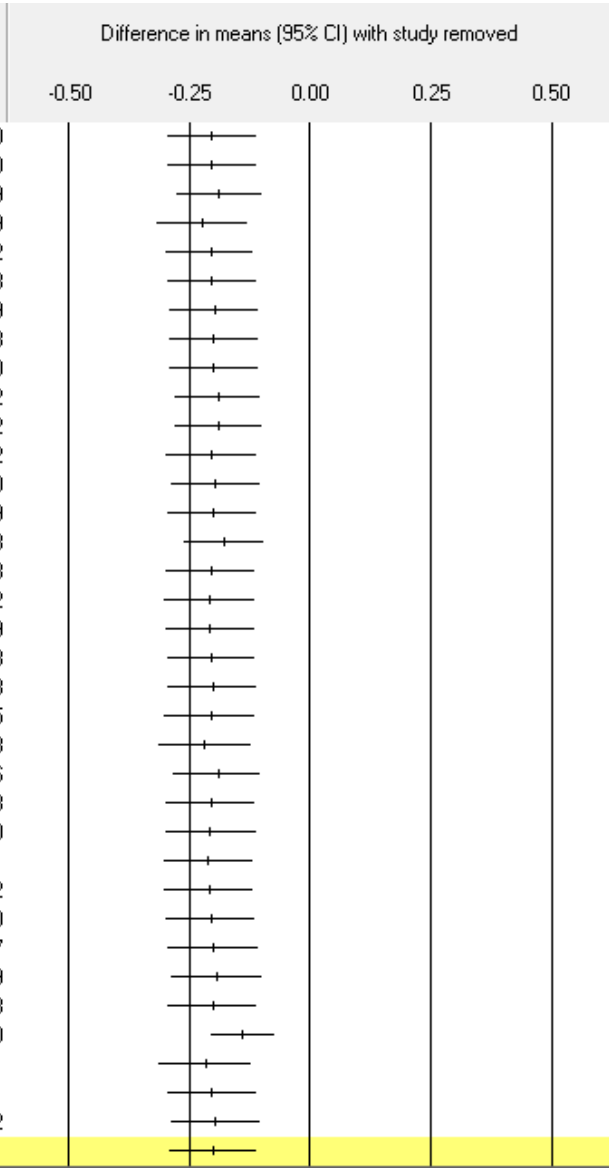
SM Figure 7.6 Cumulative random multivariate meta-analysis of joined outcomes Apo A1 + Apo A2 + HDL2 + HDL3 mmol/L with one study removed per line

Model	Study name	Outcome	Statistics with study removed				TESTEX Score
			Point	Lower limit	Upper limit	p-Value	
	Huttunen 1979	Combined	2.552	0.424	4.680	0.019	11
	Wood 1983	Combined	2.914	0.611	5.216	0.013	9
	Hespel 1988	Combined	2.359	0.297	4.422	0.025	9
	Stensel 1993	Apo A1	2.494	0.452	4.536	0.017	11
	Lindheim 1994	Apo A1	2.286	0.371	4.201	0.019	9
	Lehmann 1995	Apo A1	2.127	0.262	3.991	0.025	8
	Stefanick 1998 (females)	Apo A1	2.553	0.419	4.687	0.019	12
	Stefanick 1998 (males)	Apo A1	2.741	0.471	5.011	0.018	12
	Laaksonen 2000	Apo A1	2.468	0.435	4.502	0.017	11
	Verissimo 2002	Apo A1	1.992	0.107	3.876	0.038	8
	Furukawa 2003	Apo A1	2.071	0.175	3.966	0.032	12
	Ring-Dimitriou 2007	Apo A1	2.214	0.355	4.073	0.020	9
	Choi 2012	Apo A1	2.607	0.552	4.662	0.013	10
Random			2.297	0.441	4.153	0.015	



SM Figure 7.7 Cumulative random multivariate meta-analysis of joined outcomes Apo A1 + Apo A2 mg/dL with one study removed per line

Model	Study name	Outcome	Statistics with study removed				TESTEX Score
			Point	Lower limit	Upper limit	p-Value	
	Hagan 1986	TC/HDL-C ratio	-0.204	-0.296	-0.112	0.000	10
	Hagan 1986 males	TC/HDL-C ratio	-0.204	-0.295	-0.112	0.000	10
	Wood 1988	TC/HDL-C ratio	-0.188	-0.277	-0.100	0.000	9
	Suter 1992	Apo B/Apo A1	-0.222	-0.316	-0.128	0.000	9
	Hinkleman 1993	TC/HDL-C ratio	-0.206	-0.297	-0.115	0.000	12
	Nieman 1993	TC/HDL-C ratio	-0.205	-0.296	-0.113	0.000	13
	Lindheim 1994	TC/HDL-C ratio	-0.199	-0.291	-0.107	0.000	9
	Ready 1995	TC/HDL-C ratio	-0.200	-0.291	-0.108	0.000	8
	Aldred 1995	TC/HDL-C ratio	-0.200	-0.291	-0.108	0.000	10
	Motoyama 1995	TC/HDL-C ratio	-0.191	-0.279	-0.102	0.000	12
	Stefanick 1998	TC/HDL-C ratio	-0.188	-0.279	-0.097	0.000	12
	Stefanick 1998	TC/HDL-C ratio	-0.203	-0.297	-0.109	0.000	12
	Sunami 1999	Combined	-0.196	-0.287	-0.105	0.000	10
	LeMura 2000	TC/HDL-C ratio	-0.202	-0.293	-0.111	0.000	9
	Verissimo 2002	Combined	-0.179	-0.261	-0.097	0.000	8
	Nieman 2002	TC/HDL-C ratio	-0.205	-0.297	-0.113	0.000	13
	Mohanka 2006	Combined	-0.209	-0.303	-0.115	0.000	12
	Boardley 2007	TC/HDL-C ratio	-0.208	-0.300	-0.116	0.000	9
	Tully 2007 a (=)	TC/HDL-C ratio	-0.204	-0.294	-0.114	0.000	13
	Tully 2007 b (<)	TC/HDL-C ratio	-0.202	-0.293	-0.110	0.000	13
	Sigal 2007	Combined	-0.206	-0.300	-0.113	0.000	15
	von Thiele Schwarz	LDL-C/HDL-C ratio	-0.219	-0.315	-0.122	0.000	8
	Martins 2010	TC/HDL-C ratio	-0.191	-0.282	-0.101	0.000	6
	Knoepfli-Lenzin	TC/HDL-C ratio	-0.206	-0.297	-0.115	0.000	8
	Krustrup 2010	LDL-C/HDL-C ratio	-0.207	-0.300	-0.114	0.000	10
	Bell 2010 MICT	TC/HDL-C ratio	-0.212	-0.303	-0.120	0.000	11
	Finucane 2010	TC/HDL-C ratio	-0.209	-0.302	-0.116	0.000	12
	Niederseer 2011	Combined	-0.205	-0.298	-0.112	0.000	10
	Rossi 2016	TC/HDL-C ratio	-0.199	-0.293	-0.106	0.000	7
	Korshøj 2016	LDL-C/HDL-C ratio	-0.193	-0.288	-0.099	0.000	9
	Gahreman 2016	TC/HDL-C ratio	-0.202	-0.294	-0.110	0.000	13
	Costa 2018	TC/HDL-C ratio	-0.140	-0.206	-0.075	0.000	10
	Rosenkilde 2018	Apo B/Apo A1	-0.216	-0.312	-0.119	0.000	11
	Ruangthai 2019	Combined	-0.204	-0.296	-0.111	0.000	11
	Connolly 2020	TC/HDL-C ratio	-0.198	-0.289	-0.106	0.000	12
Random			-0.201	-0.291	-0.111	0.000	



SM Figure 7.8 Random multivariate meta-analysis of joined outcomes TC/HDL-C + LDL-C/HDL-C + Apo B100/Apo A1 with one study removed per line

TESTEX Data Table Scoring

Author Year	Eligibility criteria specified	Random-isation specified	Allocation conceal-ment	Groups similar at baseline	Blinding of assessor	Outcomes measures assessed in 85% patients	Adverse events reported	Exercise adherence reported	Intention-to-treat analysis	Between-group statistical comparisons reported for primary outcome	Between-group statistical comparisons reported for secondary outcome	Point measures and measures of variability for all outcome measures	Activity monitoring in control groups	Relative exercise intensity remained constant	Exercise volume and energy expenditure given	Overall TESTEX (/15)
Aldred 1995	1	0	0	1	1	1	0	1	0	1	1	1	0	1	1	**10**
Baker 1986	1	0	0	1	1	1	0	1	0	1	1	1	0	1	0	**9**
Bell 2010	1	0	1	1	1	0	0	1	0	1	1	1	1	1	1	**11**
Boardley 2007	1	0	0	1	1	1	0	1	0	1	1	1	0	1	0	**9**
Choi 2012	1	1	0	1	1	1	0	0	0	1	0	1	1	1	1	**10**
Connolly 2020	1	1	1	1	1	0	1	1	0	1	1	1	0	1	1	**12**
Costa 2018	1	1	1	1	1	0	0	1	1	1	1	1	0	0	0	10
Finucane 2010	1	1	0	1	1	1	1	1	0	1	1	1	0	1	1	**12**
Furukawa 2010	1	1	1	0	1	1	0	1	1	1	1	1	1	0	1	**12**
Gahreman 2016	1	1	1	1	1	1	1	1	0	1	1	1	0	1	1	**13**
Gordon 2008	1	0	0	1	1	1	0	1	0	1	1	1	0	1	1	**10**
Grandjean 1996	1	0	1	1	1	1	0	0	1	1	1	1	0	1	1	**11**
Hagan 1986	1	0	0	1	1	1	0	1	0	1	1	1	0	1	1	**10**
Hespel 1988	1	0	0	1	1	1	0	1	1	1	1	1	0	0	0	**9**
Hinkleman 1993	1	1	1	0	1	1	1	0	0	1	1	1	1	1	1	**12**
Huttunen 1979	1	0	1	1	1	1	0	1	0	1	1	1	0	1	1	**11**
Kiens 1980	1	1	0	0	1	0	0	1	0	1	1	1	0	0	1	**8**
Knoepfli-Lenzin 2010	1	0	0	0	1	0	1	1	0	1	1	1	0	0	1	**8**
Korshøj 2016	1	1	0	1	1	0	0	0	1	1	1	1	0	0	1	**9**
Krustrup 2010	1	0	0	1	1	0	1	1	0	1	1	1	0	1	1	**10**
Kukkonen-Harjula 1998	1	1	0	1	1	1	1	1	1	1	1	0	0	1	1	**12**
Laaksonen 2000	1	1	1	1	1	0	0	1	0	1	1	1	0	1	1	**11**
Lehmann 1995	1	0	0	1	1	1	0	0	0	0	1	1	0	1	1	**8**
LeMura 2000	0	1	0	0	1	1	0	0	0	1	1	1	1	1	1	**9**
Ligtenberg 1997	1	0	0	1	1	1	1	1	0	1	1	1	0	1	1	**11**
Lindheim 1994	1	0	0	0	1	1	0	0	1	0	1	1	1	1	1	**9**
Martins 2010	1	0	0	0	1	0	0	0	0	1	1	1	0	0	1	**6**
Mohanka 2006	1	1	0	1	1	1	0	1	1	1	1	1	1	0	1	**12**
Motoyama 1995	1	1	0	1	1	1	0	1	1	1	1	1	0	1	1	**12**
Niederseer 2011	1	0	0	1	1	0	1	1	0	1	1	1	0	1	1	**10**
Nieman 1993	1	0	0	1	1	1	1	1	1	1	1	1	1	1	1	**13**
Nieman 2002	1	0	1	1	1	1	0	1	1	1	1	1	1	1	1	**13**

Paolillo 2017	1	1	1	1	1	0	1	0	0	1	1	1	1	1	1	**12**
Ready 1995	1	0	0	0	1	0	0	1	0	1	1	1	0	1	1	**8**
Ring-Dimitriou 2007	1	0	0	1	1	0	1	1	0	1	1	1	0	1	0	**9**
Rosenkilde 2018	1	1	0	1	1	0	1	1	0	1	1	1	0	1	1	**11**
Rossi 2016	1	0	0	0	1	0	0	0	0	1	1	1	0	1	1	**7**
Ruangthai 2019	1	0	1	1	1	0	1	1	0	1	1	1	0	1	1	**11**
Shearman 2010	1	0	0	1	1	1	0	0	0	1	1	1	1	1	1	**10**
Sigal 2007	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	**15**
Slentz 2007	1	0	1	1	1	1	0	1	0	1	0	1	0	1	1	**10**
Stefanick 1998	1	1	1	1	1	1	0	1	0	1	1	1	0	1	1	**12**
Stensel 1993	1	0	1	0	1	1	1	1	0	1	1	1	0	1	1	**11**
Sunami 1999	1	0	0	1	1	1	0	1	0	1	1	1	0	1	1	**10**
Suter 1990	1	0	0	1	1	1	0	1	0	1	1	0	0	1	1	**9**
Suter 1992	1	0	0	1	1	1	0	1	0	1	1	0	0	1	1	**9**
Tully 2007 a (=)	1	1	0	1	1	1	1	1	1	1	1	1	1	0	1	**13**
Verissimo 2002	1	0	0	1	1	1	1	0	0	1	0	0	0	1	1	**8**
Von Thiele Schwarz 2008	1	0	0	1	1	1	0	0	0	1	1	0	0	1	1	**8**
Wirth 1985	1	0	0	1	1	1	1	0	0	1	1	1	0	0	0	**8**
Wood 1983	1	1	0	1	1	1	0	0	0	1	1	1	0	0	1	**9**
Wood 1988	1	0	0	1	1	0	0	0	0	1	1	1	1	1	1	**9**

SM Table 7.6 TESTEX Assessment of Study Quality

Within-Study Risk of Bias

We awarded either of low or high for the following factors:

1. Study non-randomised or randomised – low if randomised, high if non-randomised;[1]
2. For intervention groups, a minimum level of compliance to be counted as having participated in the intervention group or control group – low if a minimum level of compliance was set or reported, high if there was no minimum compliance level;
3. Habitual medication use reported – low if reported, high if not reported;
4. Drop-out reasons given – low if reported, high if not reported;
5. Baseline fitness and effort determined – low if baseline fitness and effort was measured, high if not determined;
6. 50% of sessions supervised – low if >50% of sessions were supervised, high if not; and
7. Effort monitoring and measurement devices – low if digital recording devices were used, high if analog or no device.

Studies were scored overall low, medium, or high risk of bias according to the number of times either "low" or "high" was awarded. A low risk of bias was scored for 0-2 instances of "high", a medium risk of bias was scored for 3-4 instances of "high", and a high risk of bias was scored for 5-7 instances of "high". All factors were equally weighted.

[1] All studies were randomised

Within-Study Risk of Bias Data Table Scoring

Author Year	Study non-randomised or randomised	Minimum compliance level set	Habitual medication use reported	Dropout reason reported	Baseline fitness and effort determined	>50% sessions supervised	Effort monitoring and measurement device	Risk of bias assesment low, medium, or high
Aldred 1995	low	low	low	low	low	high	high	**low**
Baker 1986	low	low	low	low	low	low	high	**low**
Bell 2010	low	low	low	low	low	low	low	**low**
Boardley 2007	low	low	low	high	high	low	high	**medium**
Choi 2012	low	high	low	high	low	high	low	**medium**
Connolly 2020	low	low	low	low	low	high	low	**low**
Costa 2018	low	high	low	low	low	high	high	**medium**
Finucane 2010	low	low	low	low	low	low	low	**low**
Furukawa 2003	low	high	high	low	low	high	low	**medium**
Gahreman 2016	low	high	low	low	low	low	low	**low**
Gordon 2008	low	low	high	high	low	high	high	**medium**
Grandjean 1996	low	low	high	high	low	high	high	**medium**
Hagan 1986	low	low	high	high	low	low	high	**medium**
Hespel 1988	low	low	low	low	low	low	high	**low**
Hinkleman 1993	low	high	low	low	low	low	low	**low**
Huttunen 1979	low	high	low	low	low	high	high	**medium**
Kiens 1980	low	high	high	high	high	high	low	**high**
Knoepfli-Lenzin 2010	low	low	high	low	low	low	low	**low**
Korshøj 2016	low	high	high	high	low	low	low	**medium**
Krustrup 2010	low	low	low	low	low	low	low	**low**
Kukkonen-Harjula 1998	low	low	low	low	low	low	low	**low**
Laaksonen 2000	low	high	low	low	low	low	high	**low**
Lehmann 1995	low	low	low	low	low	high	high	**low**
LeMura 2000	low	low	high	high	low	high	low	**medium**
Ligtenberg 1997	low	low	low	low	low	high	high	**low**
Mohanka 2006	low	low	low	high	low	high	low	**low**
Motoyama 1995	low	high	low	low	low	low	high	**low**
Niederseer 2011	low	high	low	high	low	low	low	**low**
Nieman 1993	low	low	low	low	low	low	low	**low**
Nieman 2002	low	low	high	low	low	low	low	**low**
Paolillo 2017	low	high	high	low	low	low	low	**low**
Ready 1995	low	low	high	low	low	high	high	**medium**
Ring-Dimitriou 2007	low	high	high	low	low	low	high	**medium**
Rosenkilde 2018	low	low	high	low	low	low	low	**low**
Rossi 2016	low	low	high	low	high	high	high	**medium**
Ruangthai 2019	low	low	low	low	low	low	low	**low**
Shearman 2010	low	high	low	low	low	high	high	**medium**
Sigal 2007	low	low	low	low	low	low	low	**low**
Slentz 2007	low	low	high	high	low	low	low	**low**
Stefanick 1998	low	high	high	high	low	low	high	**medium**
Stensel 1995	low	high	low	low	low	high	low	**low**
Sunami 1999	low	low	high	high	low	low	high	**medium**
Suter 1990	low	low	high	high	low	high	low	**medium**
Suter 1992	low	low	high	high	low	high	low	**medium**
Tully 2007	low	high	high	low	low	high	high	**medium**
Verissimo 2002	low	high	high	low	low	low	high	**medium**
von Thiele Schwarz 2008	low	low	high	low	low	low	high	**low**
Wirth 1985	low	high	high	low	low	low	high	**medium**
Wood 1983	low	low	high	low	low	low	high	**low**
Wood 1988	low	low	high	low	low	high	high	**medium**

SM Table 7.7 Assessed Within-Study Risk of Bias Factors

Small Study Effects

Apo A1 + Apo A2 + HDL2 + HDL3 mmol/L

Classic fail-safe N

Z-value for observed studies	2.92577
P-value for observed studies	0.00344
Alpha	0.05000
Tails	2.00000
Z for alpha	1.95996
Number of observed studies	10.00000
Number of missing studies that would bring p-value to > alpha	13.00000

Orwin's fail-safe N

Difference in means in observed studies	0.04673
Criterion for a 'trivial' difference in means	0.02336
Mean difference in means in missing studies	0.00000
Number missing studies needed to bring difference in means under 0.(	11.00000

SM Table 7.8. Classic fail-safe N and Orwin's fail-safe N

Begg and Mazumdar rank correlation

Kendall's S statistic (P-Q)	9.00000
Kendall's tau without continuity correction	
Tau	0.20000
z-value for tau	0.80498
P-value (1-tailed)	0.21041
P-value (2-tailed)	0.42083
Kendall's tau with continuity correction	
Tau	0.17778
z-value for tau	0.71554
P-value (1-tailed)	0.23714
P-value (2-tailed)	0.47427

SM Table 7.9. Begg and Mazumdar rank correlation

Apo A1 + Apo A2 + HDL2 + HDL3 mmol/L continued

Egger's regression intercept

Intercept	0.79760
Standard error	0.50289
95% lower limit (2-tailed)	-0.36207
95% upper limit (2-tailed)	1.95728
t-value	1.58603
df	8.00000
P-value (1-tailed)	0.07570
P-value (2-tailed)	0.15139

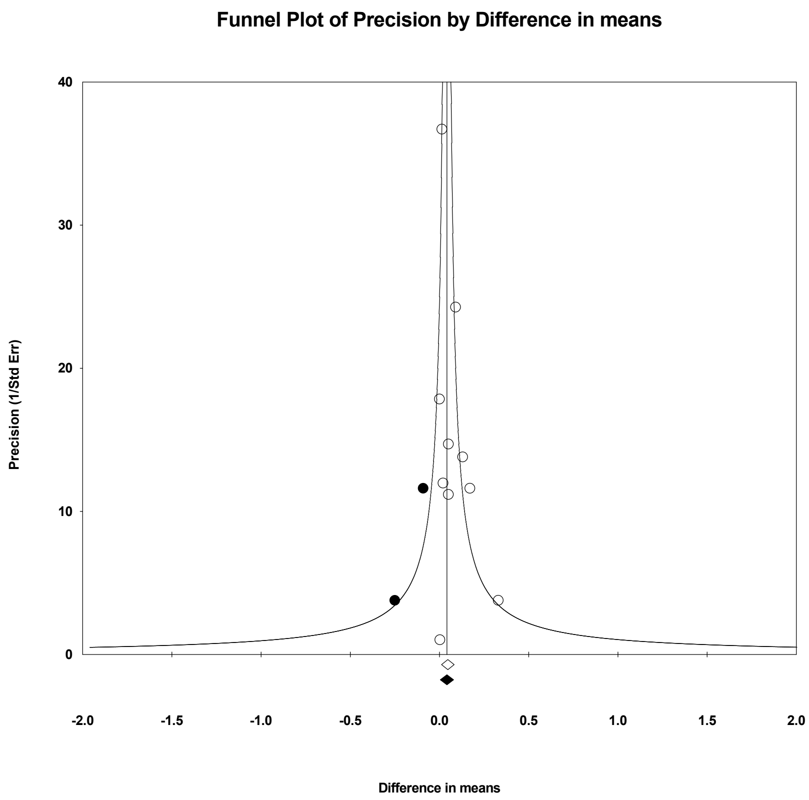
SM Table 7.10. Egger's regression intercept

Duval and Tweedie's trim and fill

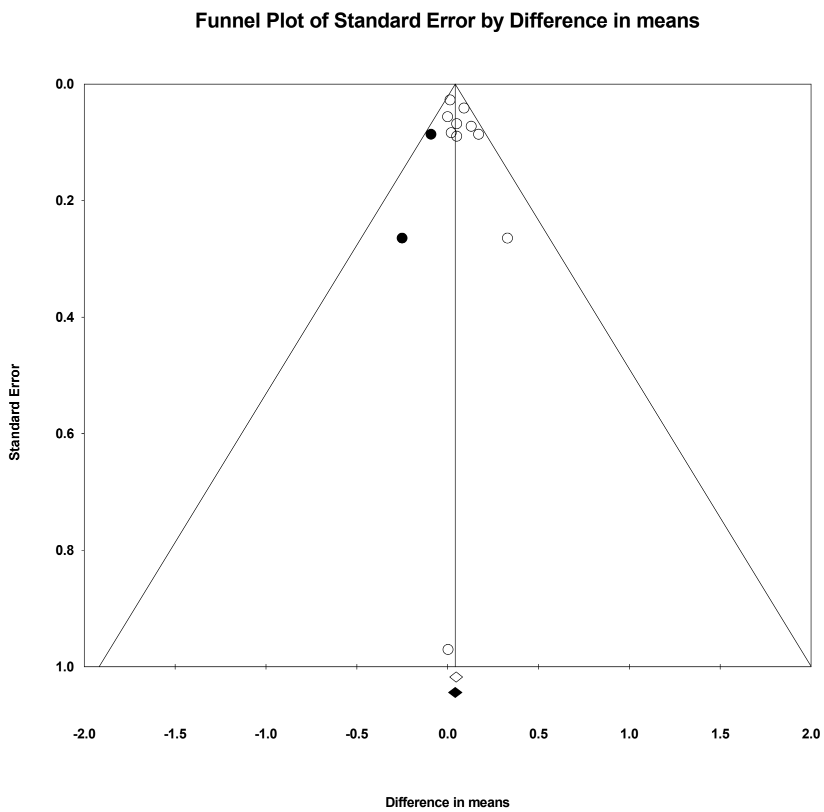
		Fixed Effects			Random Effects			Q Value
	Studies Trimmed	Point Estimate	Lower Limit	Upper Limit	Point Estimate	Lower Limit	Upper Limit	
Observed values		0.04673	0.01141	0.08204	0.04673	0.01141	0.08204	7.95961
Adjusted values	2	0.03964	0.00515	0.07413	0.04153	0.00413	0.07894	11.63400

SM Table 7.11. Duval and Tweedie's trim and fill

Apo A1 + Apo A2 + HDL2 + HDL3 mmol/L continued



SM Figure 7.9 Funnel Plot of Precision by Difference in Means (random effects)



SM Figure 7.10 Funnel Plot of Standard Error by Difference in Means (random effects)

Apo A1 + Apo A2 mg/dL

Classic fail-safe N

Z-value for observed studies	3.40258
P-value for observed studies	0.00067
Alpha	0.05000
Tails	2.00000
Z for alpha	1.95996
Number of observed studies	13.00000
Number of missing studies that would bring p-value to > alpha	27.00000

Orwin's fail-safe N

Difference in means in observed studies	2.29709
Criterion for a 'trivial' difference in means	1.25000
Mean difference in means in missing studies	0.00000
Number missing studies needed to bring difference in means under 1.:	11.00000

SM Table 7.12 Classic fail-safe N and Orwin's fail-safe N

Begg and Mazumdar rank correlation

Kendall's S statistic (P-Q)	50.00000
Kendall's tau without continuity correction	
Tau	0.64103
z-value for tau	3.05044
P-value (1-tailed)	0.00114
P-value (2-tailed)	0.00229
Kendall's tau with continuity correction	
Tau	[redacted]
z-value for tau	
P-value (1-tailed)	
P-value (2-tailed)	

SM Table 7.13 Begg and Mazumdar rank correlation

Apo A1 + Apo A2 mg/dL continued

Egger's regression intercept

Intercept	1.27984
Standard error	0.36004
95% lower limit (2-tailed)	0.48739
95% upper limit (2-tailed)	2.07229
t-value	3.55467
df	11.00000
P-value (1-tailed)	0.00226
P-value (2-tailed)	0.00451

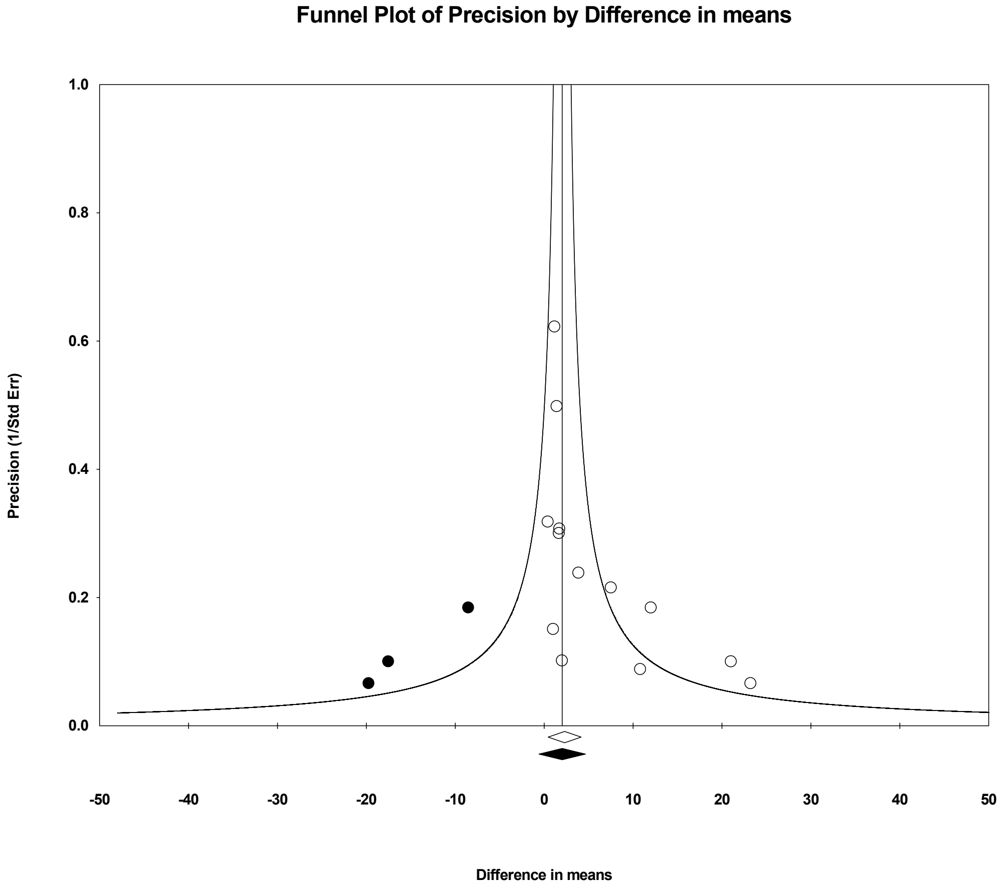
SM Table 7.14 Egger's regression intercept

Duval and Tweedie's trim and fill

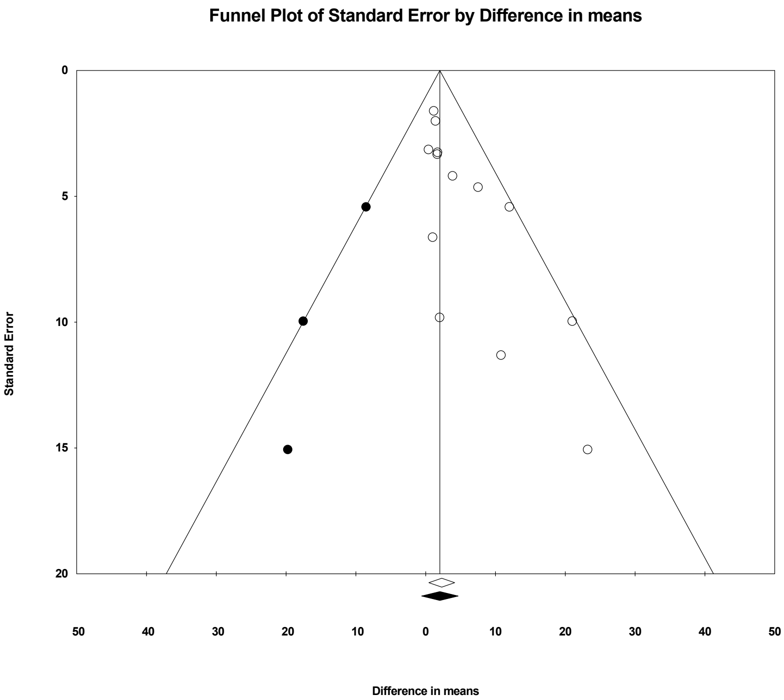
		Fixed Effects			**Random Effects**			**Q Value**
	Studies Trimmed	Point Estimate	Lower Limit	Upper Limit	Point Estimate	Lower Limit	Upper Limit	
Observed values		2.29709	0.44141	4.15277	2.29709	0.44141	4.15277	11.80224
Adjusted values	3	1.72473	-0.09188	3.54133	2.02680	-0.57877	4.63237	21.53754

SM Table 7.15 Duval and Tweedie's trim and fill

Apo A1 + Apo A2 mg/dL continued



SM Figure 7.11 Funnel Plot of Precision by Difference in Means (random effects)



SM Figure 7.12 Funnel Plot of Standard Error by Difference in Means (random effects)

Apo B100 + VLDL-C mmol/L SQ

Classic fail-safe N

Z-value for observed studies	-2.33333
P-value for observed studies	0.01963
Alpha	0.05000
Tails	2.00000
Z for alpha	1.95996
Number of observed studies	11.00000
Number of missing studies that would bring p-value to > alpha	5.00000

Orwin's fail-safe N

Difference in means in observed studies	-0.08025
Criterion for a 'trivial' difference in means	-0.04012
Mean difference in means in missing studies	0.00000
Number missing studies needed to bring difference in means over -0.0	12.00000

SM Table 7.16 Classic fail-safe N and Orwin's failsafe N

Begg and Mazumdar rank correlation

Kendall's S statistic (P-Q)	-25.00000
Kendall's tau without continuity correction	
Tau	-0.45455
z-value for tau	1.94625
P-value (1-tailed)	0.02581
P-value (2-tailed)	0.05163
Kendall's tau with continuity correction	
Tau	-0.43636
z-value for tau	1.86840
P-value (1-tailed)	0.03085
P-value (2-tailed)	0.06171

SM Table 7.17 Begg and Mazumdar rank correlation

Apo B100 + VLDL-C mmol/L SQ continued

Egger's regression intercept

Intercept	-0.89258
Standard error	0.44331
95% lower limit (2-tailed)	-1.89542
95% upper limit (2-tailed)	0.11026
t-value	2.01343
df	9.00000
P-value (1-tailed)	0.03746
P-value (2-tailed)	0.07491

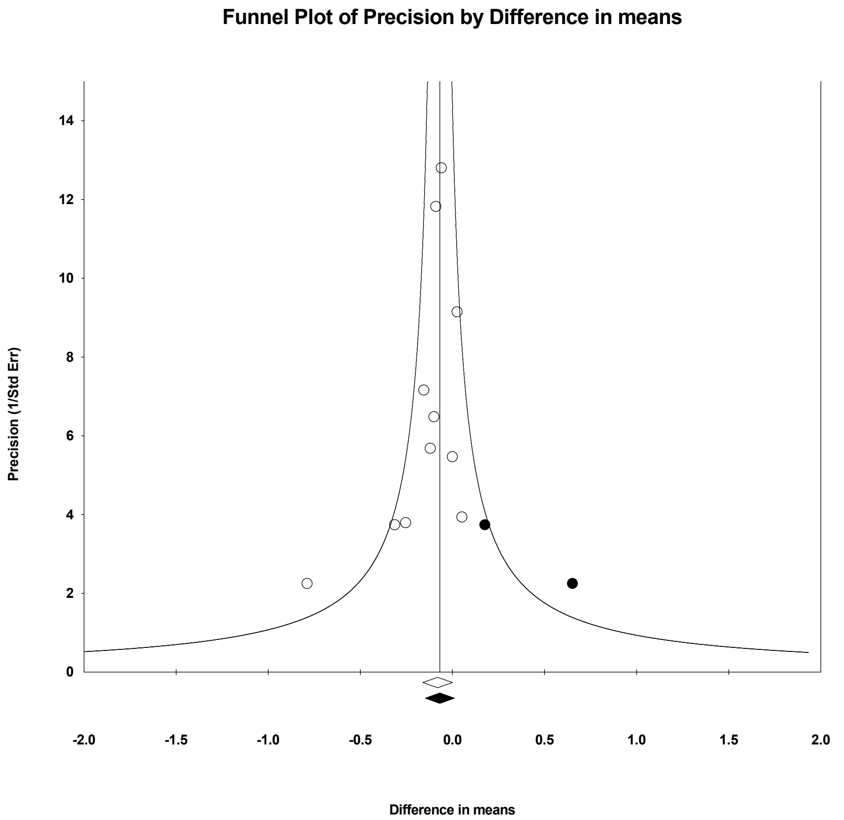
SM Table 7.18 Egger's regression intercept

Duval and Tweedie's trim and fill

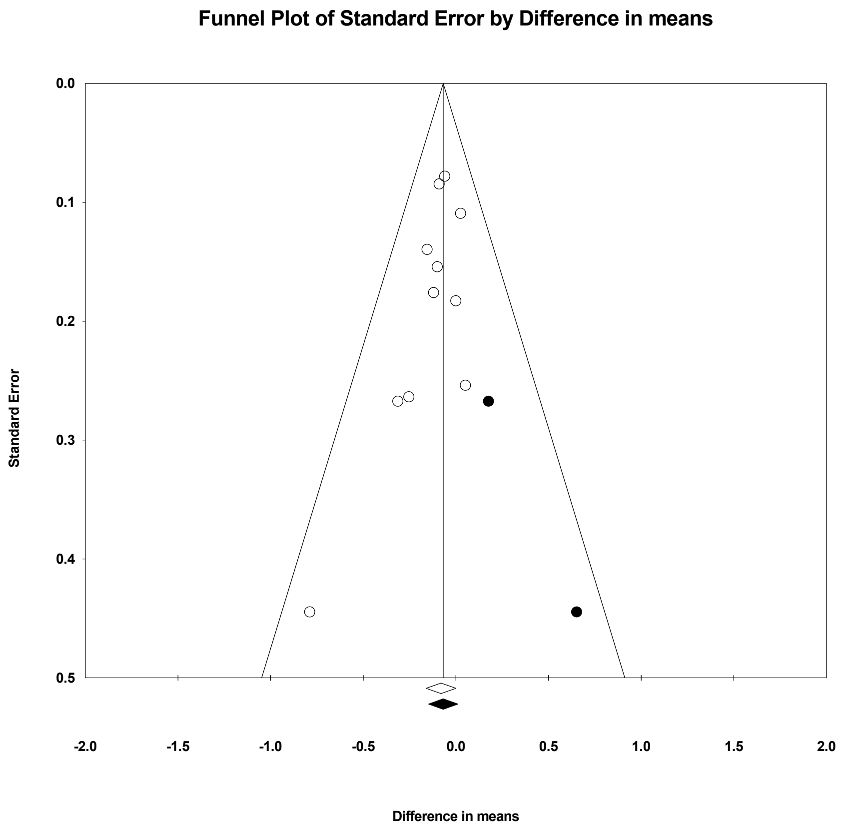
		Fixed Effects			Random Effects			Q Value
	Studies Trimmed	Point Estimate	Lower Limit	Upper Limit	Point Estimate	Lower Limit	Upper Limit	
Observed values		-0.08025	-0.16082	0.00031	-0.08025	-0.16082	0.00031	5.56817
Adjusted values	2	-0.06831	-0.14761	0.01099	-0.06831	-0.14761	0.01099	9.11478

SM Table 7.19 Duval and Tweedie's trim and fill

Apo B100 + VLDL-C mmol/L SQ continued



SM Figure 7.13 Funnel Plot of Precision by Difference in Means (random effects)



SM Figure 7.14 Funnel Plot of Standard Error by Difference in Means (random effects)

TC/HDL-C + LDL-C/HDL-C + Apo B100/Apo A1

Classic fail-safe N

Z-value for observed studies	-4.96983
P-value for observed studies	0.00000
Alpha	0.05000
Tails	2.00000
Z for alpha	1.95996
Number of observed studies	35.00000
Number of missing studies that would bring p-value to > alpha	191.00000

Orwin's fail-safe N

Difference in means in observed studies	-0.14106
Criterion for a 'trivial' difference in means	-0.07053
Mean difference in means in missing studies	0.00000
Number missing studies needed to bring difference in means over -0.0	36.00000

SM Table 7.20 Classic fail-safe N and Orwin's fail-safe N

Begg and Mazumdar rank correlation

Kendall's S statistic (P-Q)	13.00000
Kendall's tau without continuity correction	
Tau	0.02185
z-value for tau	0.18462
P-value (1-tailed)	0.42676
P-value (2-tailed)	0.85353
Kendall's tau with continuity correction	
Tau	0.02017
z-value for tau	0.17042
P-value (1-tailed)	0.43234
P-value (2-tailed)	0.86468

SM Table 7.21 Begg and Mazumdar rank correlation

TC/HDL-C + LDL-C/HDL-C + Apo B100/Apo A1 continued

Egger's regression intercept

Intercept	-0.56311
Standard error	0.28865
95% lower limit (2-tailed)	-1.15037
95% upper limit (2-tailed)	0.02416
t-value	1.95082
df	33.00000
P-value (1-tailed)	0.02981
P-value (2-tailed)	0.05961

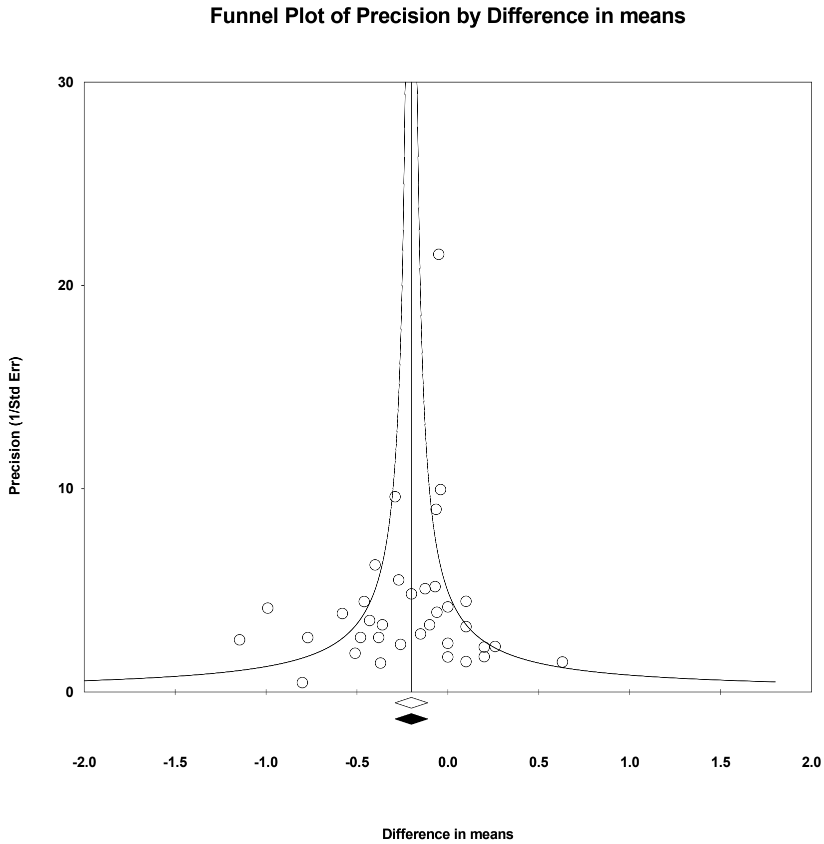
SM Table 7.22 Egger's regression intercept

Duval and Tweedie's trim and fill

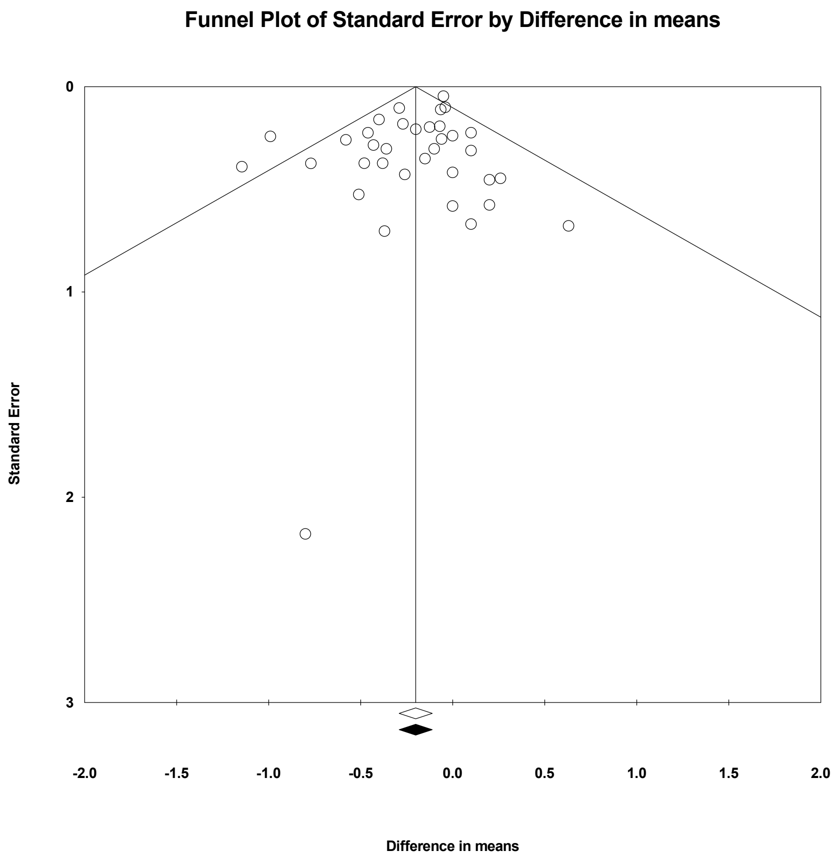
		Fixed Effects			Random Effects			Q Value
	Studies Trimmed	Point Estimate	Lower Limit	Upper Limit	Point Estimate	Lower Limit	Upper Limit	
Observed values		-0.14106	-0.20008	-0.08204	-0.20110	-0.29121	-0.11100	46.39249
Adjusted values	0	-0.14106	-0.20008	-0.08204	-0.20110	-0.29121	-0.11100	46.39249

SM Table 7.23 Duval and Tweedie's trim and fill

TC/HDL-C + LDL-C/HDL-C + Apo B100/Apo A1 continued



SM Figure 7.15 Funnel Plot of Precision by Difference in Means (random effects)



SM Figure 7.16 Funnel Plot of Standard Error by Difference in Means (random effects)

Meta-regression Analyses

Increments for Model 1, Random effects (ML), Knapp Hartung, Difference in means
Apo A1 + Apo A2 + HDL2 + HDL3 mmol/L
Study variables

	Current Model		Test of Model (a)				Goodness of fit (b)			Change from prior (c)		Test of change (c)				
Covariate	**Tau²**	**R²**	**F**	**df1**	**df2**	**P-value**	**Q**	**df**	**P-value**	**Tau²**	**R²**	**F**	**df1**	**df2**	**P-value**	
Intercept	0.0002	0														
Year	0	1.00	1.96	1	8	0.1992	6	8	0.6471	-0.0002	1.00	1.96	1	8	0.1992	
Total Number of Participants	0	1.00	1.34	2	7	0.3225	5.29	7	0.625	0	0	0.71	1	7	0.4262	F=1.14, df=4, df Err=5, p=.4329
Number of extracted outcomes	0	1.00	1.11	3	6	0.4153	4.63	6	0.5927	0	0	0.66	1	6	0.447	
TESTEX Score	0	1.00	1.14	4	5	0.4329	3.39	5	0.6401	0	0	1.24	1	5	0.317	

SM Table 7.24 Apo A1 + Apo A2 + HDL2 + HDL3 mmol/L (study variables)

Increments for Model 1, Random effects (ML), Knapp Hartung, Difference in means
Apo A1 + Apo A2 + HDL2 + HDL3 mmol/L
Intervention variables

	Current Model		Test of Model (a)				Goodness of fit (b)			Change from prior (c)		Test of change (c)				
Covariate	**Tau²**	**R²**	**F**	**df1**	**df2**	**P-value**	**Q**	**df**	**P-value**	**Tau²**	**R²**	**F**	**df1**	**df2**	**P-value**	
Intercept	0.0002	0														
Intensity VO2max %	0	1.00	1.1	1	8	0.325	6.86	8	0.5518	-0.0002	1.00	1.1	1	8	0.325	
Intervention Duration (Weeks)	0	1.00	0.66	2	7	0.5458	6.64	7	0.4676	0	0	0.22	1	7	0.6514	F=1.24, df=4, df Err=5, p=.4024
Sessions per week	0	1.00	1.65	3	6	0.2759	3.02	6	0.8062	0	0	3.62	1	6	0.1059	
Minutes per session	0	1.00	1.24	4	5	0.4024	3.02	5	0.6971	0	0	0	1	5	0.9676	

SM Table 7.25 Table 18b Apo A1 + Apo A2 + HDL2 + HDL3 mmol/L (intervention variables)

Increments for Model 1, Random effects (ML), Knapp Hartung, Difference in means
TC/HDL-C + LDL-C/HDL-C + Ao B100/Apo A1
<u>Study variables</u>

	Current Model		Test of Model (a)				Goodness of fit (b)			Change from prior (c)(d)		Test of change (c)				
Covariate	**Tau²**	**R²**	**F**	**df1**	**df2**	**P-value**	**Q**	**df**	**P-value**	**Tau²**	**R²**	**F**	**df1**	**df2**	**P-value**	
Intercept	0.0144	0														
Year	0.0134	0.07	0.05	1	33	0.8214	43.82	33	0.0987	-0.001	0.07	0.05	1	33	0.8214	
Total Number of Participants	0.0141	0.02	0.26	2	32	0.774	43.69	32	0.0815	0.0007	-0.05	0.47	1	32	0.4969	F=0.29, df=4, df Err=30, p=.8795
Number of extracted outcomes	0.015	0	0.17	3	31	0.9145	42.67	31	0.0791	0.0009	-0.02	0.01	1	31	0.9143	
TESTEX Score	0.0174	0	0.29	4	30	0.8795	42.58	30	0.0638	0.0025	0	0.63	1	30	0.4348	

SM Table 7.26 TC/HDL-C + LDL-C/HDL-C + Apo B100/Apo A1 (study variables)

Increments for Model 1, Random effects (ML), Knapp Hartung, Difference in means
TC/HDL-C + LDL-C/HDL-C + Apo B100/Apo A1
<u>Intervention variables</u>

	Current Model		Test of Model (a)				Goodness of fit (b)			Change from prior (c)		Test of change (c)				
Covariate	**Tau²**	**R²**	**F**	**df1**	**df2**	**P-value**	**Q**	**df**	**P-value**	**Tau²**	**R²**	**F**	**df1**	**df2**	**P-value**	
Intercept	0.0144	0														
Intensity VO2max %	0.0084	0.41	1.62	1	33	0.2126	41.45	33	0.1485	-0.006	0.41	1.62	1	33	0.2126	
Intervention Duration (Weeks)	0.0069	0.52	0.87	2	32	0.4286	40.92	32	0.134	-0.0015	0.1	0.05	1	32	0.8297	F=1.00, df=4, df Err=30, p=.4213
Sessions per week	0.0038	0.74	0.88	3	31	0.4602	40.24	31	0.1238	-0.0032	0.22	0.42	1	31	0.5222	
Minutes per session	0.0023	0.84	1	4	30	0.4213	39.18	30	0.1217	-0.0015	0.11	0.87	1	30	0.3587	

SM Table 7.27 TC/HDL-C + LDL-C/HDL-C + Apo B100/Apo A1 (intervention variables)

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8 Chapter 8 – Conclusion

The incidence of cardiovascular disease (CVD) represents a major global burden, both financially and socially. The most common forms of CVD, ischaemic heart disease and stroke, are principally caused by atherosclerosis, a condition arising from dyslipidaemia, or elevated levels of the atherogenic total cholesterol (TC), triglycerides (TRG), and low-density lipoprotein cholesterol (LDL-C), and lowered levels of the antiatherogenic high-density lipoprotein cholesterol (HDL-C). Dyslipidaemia has a range of known contributory factors as detailed in Chapter 1, all of which, except for those relating to various genetic disorders, are positively impacted by aerobic exercise training (AET) or by behavioural change such as cessation of smoking and reduced intake of saturated fat, alcohol and anabolic steroids.

Aerobic exercise training comprises any structured physical activity achieving a minimum 40% VO_{2MAX}, or moderate intensity, whether in the form of steady state uninterrupted exercise, or repeated short intervals of higher intensity interspersed with periods of respite. Weight-bearing modes of AET include walking, running, team games, dancing, circuit training, and the indoor equivalent of these, while non-weight bearing modes of AET include swimming, cycling, rowing and their indoor equivalents. A minimum amount of weekly physical activity, 150 minutes of moderate intensity or 75 minutes of vigorous intensity, is recommended globally by government health authorities as protective of health. However, around the world physical inactivity remains prevalent; in Australia the contributory cost of physical inactivity to the financial burden of CVD is at least AUS$2.2 billion, in 2016 terms. Amongst self-reporting adults younger than 65 years in Australia, <50% report sufficient activity levels as per recommended guidelines. The situation is even more dire amongst Australian aged 65 years and above, indicating the importance and necessity of measuring lipids to assess CVD risk.

Lipids are measured as a means to quantify CVD risk, and lowering atherogenic lipids (TC, TRG, LDL-C) and raising the antiatherogenic lipid HDL-C are health-care treatment goals. Cited evidence suggests that in comparison with pharmacotherapy, AET confers similar benefits in reduction of mortality. Aerobic exercise training is most effective, compared to other forms of exercise training, in positively changing lipids. Globally, government health authority guidelines recommend minimum levels of physical activity necessary to promote general good health. The quantitative reviews undertaken as part of this thesis confirm that these health authority recommended minimum levels of AET positively impact the standard lipid profile (SLP) comprising TC, TRG, HDL-C, and LDL-C in heterogenous populations free of chronic disease such as CVD and cancer. Aerobic exercise training thus lowers CVD risk and the incidence of CVD.

The aims of this thesis were as follows:

1. to determine the current state of quantitative research, ie systematic review with meta-analysis, that has examined the impact of AET on the SLP and emerging lipid biomarkers of populations free of chronic disease other than cardiometabolic conditions such as Metabolic Syndrome (MetS) and Type 1 or 2 diabetes mellitus;
2. after surveying the current state of knowledge in this area, to identify knowledge gaps and research synthesis opportunities;

3. to develop robust protocols, which sought to minimise the intrusion of confounding factors, for conducting quantitative systematic reviews (SRs) of the effects of AET on the SLP and emerging lipid biomarkers of these populations;
4. to undertake quantitative synthesis (meta-analysis), as the research methodology, of randomised controlled trials (RCTs) investigating the impact of AET on the SLP and emerging lipid biomarkers of these populations;
5. to quantitatively estimate the change in lipids ie the effect size (ES), resulting from AET interventions, on lipid indices relevant to the prediction of CVD risk for these populations;
6. to identify factors likely to impact the ES of AET on lipids in these populations; and
7. to indicate whether an AET protocol, optimised for the AET variables intensity, minutes per session, sessions per week, and duration, can be formulated, for the purpose of managing the lipids in these populations.

Chapter 1 reviewed the existing quantitative literature: SRs with meta-analysis (MA) which have synthesised trials testing and measuring the effect of AET on the SLP and emerging lipid biomarkers, in diverse adult populations free of chronic disease (except MetS and Type 1 or 2 diabetes mellitus). In several of these SRs with MAs reviewed in Chapter 1, the effect measures of trials of participants with CVD were pooled with outcomes of trials of sub-clinical and healthy participants. The literature review undertaken in Chapter 1 identified several research gaps, as at 31st March, 2018:

1. existing SRs with MAs pooled heterogenous trials, populations and AET protocols, and reported a wide range of estimated effects measures and 95% confidence intervals

(CIs); many of the reported CIs crossed the line of null effect. The resulting inference is that no improvement in lipids could be expected from AET interventions;

2. the statistical heterogeneity reported in these quantitative reviews suggested that the clinical status of participants, and the AET protocols used as interventions, varied substantially between the studies included for quantitative analysis;
3. a large number of existing SRs and MAs only conducted or reported minimal study quality analysis;
4. no previous works had synthesised data on the effect of AET on the emerging lipid biomarkers of apolipoproteins (Apo A1, Apo A2, Apo B100), lipoprotein sub-fractions (HDL sub-classes and particle size and density), or ratios (TC/HDL-C, LDL-C/HDL-C, Apo B100/Apo A1), other than a) two reviews which included an effect measurement for TC/HDL-C, one of which also included an effect measurement for non-HDL-C (HDL-C subtracted from TC); b) one review which reported on the HDL sub-class HDL-C2; and c) one review of only six related RCTs which investigated the effect of AET and AET intervention covariates on various atherogenic and antiatherogenic lipoprotein particles' size and density. These four quantitative reviews reported inconsistent results with regard to the significance of AET effect on these emerging lipid biomarkers; and
5. some SRs with MAs selectively reported change in individual lipids rather than the full SLP; some quantitative reviews examined changes in lipids in either male or female mixed health populations. A SR with MA comparing AET protocols used the outcome measures of only three studies of mixed health status populations, and found no difference between high-intensity intervals and moderate-intensity steady state in affecting lipids.

A subsequent search of quantitative reviews published from 1st April 2018 to 31st July, 2019 found 3 further reviews. One compared supervised AET against unsupervised AET in diabetic participants and found no significant difference in impact on lipids of supervision status. Two reviews compared AET intervention variables (intensity and interval duration) in mixed health populations: one found no significant impact on lipids of these intervention variables, the other found that HIIT raised HDL-C more than MICT in this population.

The literature review thus revealed three areas of research opportunity: 1) re-appraising whether AET protocols differentiated by intensity and interval duration changed lipids equally; 2) quantifying the change in the SLP, as a result of AET interventions, of homogenous populations differentiated by health status; and 3) quantifying the change in emerging lipid biomarkers as a result of AET interventions.

After undertaking the review in Chapter 1, two SR with MA protocols were developed. The first protocol, detailed in Chapter 2, described a methodology for SRs with univariate meta-analysis and meta-regression to quantitatively determine the effect measures (ES of mean differences and 95% CIs) of the impact of AET on the standard lipid profile of two relatively homogenous populations, each classified according to the presence or absence of MetS, and both free of chronic disease such as cancer and CVD. The protocol also described a means to identify any study covariates (year of publication, total number of participants, and study quality score) or intervention covariates (intensity, minutes per session, sessions per week, total duration of intervention) which could explain changes in the SLP.

The second protocol, detailed in Chapter 3, described a methodology for a SR with multivariate meta-analysis and meta-regression to examine the effect of AET on emerging lipid biomarkers in populations free of chronic disease other than MetS and Type 1 or 2 diabetes mellitus, and to quantitatively determine the associated effect measures (ES of mean differences and 95% CIs) of the impact of AET. A multivariate meta-analysis approach was chosen to allow for the paucity of reported data for some of the lipid biomarkers, as well as to account for correlation of pooled outcomes, with a view to reducing Type 1 errors. Meta-regression was employed to identify any study or intervention covariates which might explain changes in lipids.

Chapter 4 investigated the hypothesis that AET protocols of 1) repeated short active (high intensity) and passive (low intensity) intervals (HIIT) or 2) moderate intensity combined with a single steady state interval (MICT) are unequal in effect on the SLP and TC/HDL-C ratio. The results of the SR and MA showed that neither HIIT nor MICT was superior in affecting TC, TRG, and LDL-C, or the TC/HDL-C ratio, suggesting that change in these lipids occurs independently of training intensity and duration of interval effort. Few trials meeting inclusion criteria reported lipids as the primary outcome, reflecting a possible lack of statistical power in the included trials. One possible explanation for the equivocal findings was the number of included trials with fewer HIIT sessions per week than MICT sessions: total HIIT weekly minutes were less than the comparable total MICT weekly minutes, as well as being less than the prescribed >75 minutes per week of vigorous intensity activity recommended by government health authorities.

The trials included in the SR and MA of Chapter 4 reported testing the twin hypotheses that HIIT requires less time to perform and is more enjoyable than MICT, while achieving the same effect as MICT on various health biomarkers. Additionally, the achieved intensities in the HIIT protocols of some included trials overlapped with the intensity of the comparable MICT protocol, and are thus unlikely to have been sufficiently differentiated to demonstrate or detect a measurable difference. However, HIIT did have a significant and greater effect on HDL-C than MICT. As a consequence of this finding, meta-regression of study and AET intervention covariates was included in the SRs and MAs estimating the ES of AET on lipids in subsequent chapters of this thesis. The presence or absence of MetS appeared to influence the effect of HIIT and MICT on lipids: in sub-analyses, HIIT significantly lowered TRG more than MICT for participants diagnosed with MetS or MetS factors, and MICT significantly raised HDL-C more than MICT for the same populations. These results suggested that the separation of populations according to the presence or absence of cardiometabolic factors (as investigated in the SRs and MAs of Chapters 5-6) may lead to a greater precision of estimation of ES. Future trials comparing protocol intensity and variety may consider using AET protocols of >180 minutes per week at >40% VO_{2MAX} (increased volume of AET) or 135-180 minutes per week at >65% VO_{2MAX} (increased intensity of AET) depending on population status and lipid to be tested. These volumes and intensities have been shown (as cited evidence) as being necessary to positively impact lipids, even though the findings of these trials and reviews suggest that government health authority physical activity recommendations (of 150 minutes per week at moderate intensity or 75 minutes per week of vigorous intensity) are insufficient to positively influence lipids. Future trials comparing protocol intensity and variety should adequately distinguish AET intervention covariates between HIIT and MICT protocols, such that the HIIT protocol achieves an aggregated (work and rest) AET intensity of vigorous ie

>65% VO_{2MAX} for 75, 135, and 180 minutes per week, and the MICT protocol should achieve a moderate AET intensity ie 40-60% VO_{2MAX} for >180 minutes per week. Future trials should also explore, via follow up, whether participants are more likely to continue to adhere to HIIT or MICT, or both protocols, at the end of an intervention period, and which social, physiological, and psychological factors support adherence to AET or lead to previous levels of sedentariness. Future trials should also aim to better report trial parameters that could impact the size of changes in lipids eg number of achieved interval minutes and achieved aggregated intensity, amount of time spent in warm up and cool down, adherence to protocol, and compliance levels.

Chapter 5 presented the results of the SR and random effects MA conducted according to the protocol described in Chapter 2. This quantitative review estimated the change in lipids, due to AET, in adults free of chronic disease such as CVD and not diagnosed with MetS. Despite constraining per-group participant sizes of the included RCTs to ≥10 and excluding RCTs of intervention duration <12 weeks, the results of the quantitative review demonstrated that AET compared to no exercise significantly lowers the atherogenic lipids TC, TRG, and LDL-C, and significantly raises antiatherogenic HDL-C. These significant estimated effect measures of AET on TC, TRG, and HDL-C were sparsely confirmed by previous works examining the effect of AET on these lipids in this population. Most previous works either found no significance, or estimated a smaller ES of AET for these lipids. This is the first SR and MA examining similar populations to find that AET significantly lowered LDL-C. Previous works reported estimated 95% CIs which crossed the line of null effect (no significance), and if indicated, reported moderate levels of heterogeneity.

Unsurprisingly, the estimated ES of AET on TC, TRG, and LDL-C for non-MetS populations in the quantitative review conducted in Chapter 5 are lower than the estimated ES of statin interventions reported in pharmacotherapy literature for TC, TRG, and LDL-C in clinical populations. The meta-regression which used the estimated effect size of AET for non-MetS populations did not find that intervention covariates explained changes in TC or TRG for this population, but the number of AET sessions per week was found to influence change in LDL-C. Pharmacotherapy literature (to date) reports that increases in statin dosages in clinical populations lead to larger reductions in atherogenic lipids. A quantitative analysis of the effects of AET in clinical populations might reveal that steadily increasing the dosage of AET results in larger improvements to lipids, in particular in LDL-C. Pharmacotherapy trial literature (to date) also reports that larger positive changes in lipids arising from statin interventions are significantly correlated with higher baseline lipid levels ie baseline lipid levels that are associated with increased CVD risk. The baseline TC, TRG and LDL-C lipid levels of the included RCT populations analysed in Chapter 5 were not categorised as being at the level associated with increased CVD risk. A quantitative analysis of the effects of AET on lipids in populations with baseline CVD-risk level lipids may reveal results similar to that of statin interventions in this cohort.

The significant ES of AET on the standard lipid profile which were estimated in Chapter 5 suggest that AET interventions compared to no exercise lead to modest decreases in CVD risk, since cited evidence indicates that every 1% reduction in atherogenic LDL-C represents a 1.7% decrease in CVD risk, and every 1% decrease in antiatherogenic HDL-C represents a 3% increase in CVD risk (or a 0.026 mmol/L increase in HDL-C is equivalent to 3% decrease for females and 2% decrease for males in CVD risk). The quantitative review undertaken in

Chapter 5 showed that AET raises HDL-C in non-MetS populations free of CVD and other chronic disease, whereas the reported estimated effect of statin interventions is to decrease HDL-C in the same population. A paradox appears to exist between the effects of AET and statins on HDL-C. Future research possibilities are discussed below.

Chapter 6 presented the results of the SR and random effects MA, conducted according to the protocol described in Chapter 2. This quantitative review was designed to estimate the ES of AET on the standard lipid profile of adults free of chronic disease, but otherwise diagnosed with MetS or Type 1 or 2 diabetes mellitus. Although segmenting for health status, constraining the per-group population size of included RCTs to ≥10, and requiring a minimum intervention duration of 12 weeks, the results of the quantitative review showed that AET compared to no exercise significantly lowers atherogenic TC, TRG, and LDL-C, and significantly raises antiatherogenic HDL-C. The estimated numerical range of effect of AET on the SLP represents a clinically important change in lipids, unlike previous works, which estimated 95% CIs that crossed the line of null effect for TC, HDL-C and LDL-C, estimated smaller ES of AET, and reported varying levels of heterogeneity. The results of Chapter 6 suggest possible CVD risk reductions of 4-15%, depending on which lipid is to be affected, with the inclusion of AET as an efficacious treatment option.

The exploratory meta-regression undertaken in Chapter 6 inferred that the AET intervention covariate intensity may predict change in TRG. The estimated numerical range of effect of AET on TRG in this population was close to the lower range of the reported estimated ES of statin interventions for TRG in clinical (CVD) and dyslipidaemic populations. Increased intensity of AET protocols may effectively reduce TRG for populations with higher baseline TRG values, as do higher dosages used in statin interventions for this population, according to the evidence of pharmacotherapy literature as cited.

The exploratory meta-regression of Chapter 6 found that an increase in volume (session time, number of sessions in a given period, and total duration of session programme) of AET has the potential to further improve HDL-C. This finding of potentially improving HDL-C by increasing AET dosage contrasts with increasing the dosages of statins, which according to cited evidence, achieve no statistically significant increase in HDL-C in populations similar to those included in the RCTs pooled for the SR and MA conducted in Chapter 6. Meta-regression also indicated that a small amount of change in LDL-C is explained by volume of AET.

Chapter 6 found that the ES (range or point estimate) of AET upon TC and LDL-C was lower than the quantitatively derived ranges for these lipids as reported in pharmacotherapy literature for statin interventions (common statins are usually prescribed for at risk or CVD-affected populations). However, AET positively affects a range of biomarkers, and populations should be encouraged to undertake exercise equivalent to the minimum national recommended guidelines of >150 minutes per week at moderate intensity, or >75 minutes per week at vigorous intensity. Given that the meta-regression analysis of pooled outcome lipid data of MetS populations undertaken in Chapter 6 suggests that AET intervention covariates explain change in three of the four standard lipid profile components, clinicians can accommodate patient preferences for increasing either of intensity or volume of AET to manage and improve lipid profiles more efficaciously. Future research possibilities are discussed below.

Chapter 7 presented novel work examining the effects of AET on a range of emerging lipid biomarkers (lipid ratios, apolipoproteins, apolipoprotein ratios, and lipoproteins, described in Chapter 1 and Chapter 3). This novel work was a systematic review with a multivariate random effects meta-analysis and meta-regression conducted according to the protocol described in Chapter 3. The results of this quantitative review showed these lipid indices to be sensitive to AET. Aerobic exercise training compared to no exercise was found to significantly lower combined atherogenic ratios, such as TC/HDL-C + LDL-C/HDL-C + Apo B100/apo A1, as well as increase combined antiatherogenic apolipoproteins and lipoproteins Apo A1 + Apo A2 + HDL2 + HDL3 mmol/L and Apo A1 + Apo A2 mg/dL, and lower atherogenic apolipoproteins and lipoproteins Apo B100 + VLDL mmol/L.

Meta-regression indicated change in these outcomes was explained by study covariates, suggesting a progression in study quality over time: the better the study quality the greater the estimated ES of AET. Intervention covariates were also found to explain change in these emerging lipid biomarkers, suggesting that AET protocols can be manipulated to induce greater effects in these indices of CVD risk. Thus AET is proposed to have a significant role to in therapeutic strategies for managing CVD risk factors, as these emerging lipid biomarkers appear to be more effective in predicting CVD risk. Future trials should report these emerging lipid biomarkers, in both concentration and particle size, as well as non-HDL-C, which could not be included for quantitative analysis in this thesis because data for non-HDL-C was under-reported. Cited evidence reports that TRG are effective for predicting CVD risk in women, therefore non-HDL-C, whose core lipid is TRG, should be included in reported trial results. Future trials should also seek to test AET protocols with greater volumes and intensities than are currently recommended by government health authorities of >150 minutes per week at moderate intensity or >75 minutes per week at vigorous intensity. Previous trials suggest greater volumes and intensities (>180 minutes per week at moderate intensity or 135-180 minutes per week at vigorous intensity) are necessary to positively impact lipids, and Chapter 6 indicates that outcomes may be sensitive to changes in intervention covariates.

Having established the positive effects of AET on lipids, and given the current and increasing financial and social costs of CVD, future research should focus on:

1. identifying the most effective social, physiological, and psychological means of increasing population participation rates in AET;
2. identifying social, physiological, and psychological barriers to participating in and continuing to maintain adequate levels of AET;
3. identifying opportunities to apply digital technology to encourage greater AET participation rates;
4. determining via sub-analysis whether population characteristics influence the effects of AET on the standard lipid profile and emerging lipid biomarkers;
5. determining whether other forms of exercise training, such as resistance, isometric, strength and combined AET deliver greater increases in antiatherogenic apolipoproteins and lipoproteins and decreases in non-HDL-C and atherogenic apolipoproteins and lipoproteins than AET alone, using a network multivariate meta-analysis and meta-regression as the quantitative approach;

6. conducting a network multivariate meta-analysis and meta-regression to compare the effects of AET and other forms of exercise with the effects of pharmacotherapy on the SLP and emerging lipid biomarkers in populations segmented by health status; and
7. conducting randomised controlled trials in homogenous sub-clinical and clinical populations with emerging lipid biomarkers as the primary outcome, using AET protocols which conform to the minimum thresholds of energy expenditure cited as evidence from previous trials.

This original body of work was designed to identify and address gaps in quantitative research synthesis of the effects of AET on the SLP and emerging lipid biomarkers in populations free of chronic disease and diagnosed either with or without MetS or Type 1 or 2 diabetes mellitus. This thesis contributes to the current body of evidence-based research related to exercise and CVD, and has suggested future research paths. The analyses of pooled outcome data found that AET covariates may explain change in the SLP in populations diagnosed with MetS or Type 1 or 2 diabetes mellitus, suggesting that an optimal AET prescription for this population can be formulated. Moreover, atherogenic and antiatherogenic apolipoproteins, lipoprotein fractions, and lipid ratios, which predict CVD risk with greater precision than the SLP, are sensitive to AET. Aerobic exercise training covariates appear to explain change in these emerging lipid biomarkers, which have been shown to be under-reported, despite being identified as having equivalent or better accuracy in predicting CVD risk. It is possible that AET protocols can be optimised to positively impact atherogenic and antiatherogenic apolipoproteins, lipoprotein fractions, and ratios. More data is required to concretely identify the effect of AET and AET intervention covariates on lipid particle size and concentration.

In summary, although this research has not identified the perfect combination of AET covariates to positively impact lipid profiles, it has found that AET achieves a clinically important and positive change in lipids. This research suggests that a dose-response relationship between AET and changes in lipids exists. Increasing the AET dose results in more favourable lipid profiles for populations with higher levels of CVD risk. The resulting decline in CVD risk reduces the social and financial burden of this disease.

Appendix 1 – Chapter 1 Supplementary Material

Question being asked/answered	Systematic review with meta-analysis (year, reported measures and intervention)	Pooled effect size of interventions for lipid outcomes	Population (health status, age, gender)	RCTs only (Yes/No) Number of studies (S) Total population (N) Study quality (SQ) evaluation (Yes/No) Sensitivity analysis (SA) using study quality (SA, No SA)
Q: Did AET affect lipids in mixed populations? A: Only significantly in TG	**Chudyk 2011**(144) mmol/L WMD, 95% CI (P>.05) Aerobic exercise training vs no exercise	TG: -0.30 (-0.48, -0.11) P<.05 HDL-C: 0.00 (-0.05, 0.05) LDL-C: -0.10 (-0.44, 0.24) No data on heterogeneity	Health status: T2DM, MetS factors, MetS Age: not indicated Gender: not indicated	RCT only: Yes S: 21 N: not indicated SQ: No, No SA
Q: Did intensity influence the effect of AET on lipids in mixed populations? A: Not significantly	**De Nardi 2018**(141) mmol/L WMD, 95% CI (P>.05) Experimental: HIIT Control: MICT No non exercising control group included.	TC: -0.16 (-0.68, 0.35) TRG: 0.14 (-0.26, 0.55) HDL-C: 0.07 (-0.06, 0.19) LDL-C: -0.06 (-0.41, 0.28) Moderate i^2 heterogeneity for all lipids	Health status: T2DM, prediabetes only (no MetS diagnosis), overweight, obese Age: mean range 51-70 years Gender: F, Mx	RCT only: Yes S: 4 N: 83 SQ: Yes, no SA
Q: Did AET affect lipids in sub-clinical populations? A: Not significantly except for HDL-C	**Fagard 2006** (157) mmol/L WMD, 95% CI (P>.05) Aerobic exercise training vs no exercise	TC: -0.04 (-0.13, 0.05) TRG: -0.11 (-0.24, 0.01) HDL-C: 0.03 (0.01, 0.06) (P<.05) LDL-C: -0.08 (-0.30, 0.15) No data on heterogeneity	Health status: healthy sedentary, hypertensive, other MetS factors Age: 21-83 years Gender: Mx	RCT only: Yes S: not specified N: 31-39 study groups SQ: No, No SA
Q: Did AET intervention variables influence the effect of AET on lipids in mixed populations? A: Above a pre-specified threshold, significantly	**Fikenzer 2018(155)** (mmol/L) (only data (M, SD) for studies rated "effective" was reported) Aerobic exercise training	TC: decrease 3.7% from 5.49 ± 0.40 to 5.28 ± 0.40 TRG: decrease 8.2% from 1.58 ± 0.29 to 1.45 ± 0.35 HDL-C: increase 4.4% from 1.17 ± 0.17 to 1.22 ± 0.17 LDL: decrease 4.8% from 3.58 ± 0.33 to 3.41 ± 0.27 No data on heterogeneity	Health status: healthy, MetS, T2D, CVD, sedentary, active, highly active Age: not aggregated Gender: F, M, Mx	RCT only: No S: 10 (for studies meeting "effective" criteria) N: 373 SQ: No, no SA
Q: Did AET affect lipids in sub-clinical populations? A: Significantly except for LDL-C	**Halbert 1999(159)** (mmol/L) MD, 95% CI (P<.05) (data for aerobic studies only) Aerobic exercise training	TC: -0.10 (-0.18, -0.02) TRG: -0.08 (-0.14, -0.02) HDL-C: 0.05 (0.02, 0.08) LDL-C: -0.10 (-0.19, -0.02) (P>.05) No data on heterogeneity	Health status: healthy, sedentary, no CVD, normolipidaemic, hyperlipidaemic Age: 19-83 years Gender: F, M, Mx	RCT only: No S: 31 N: 1328 SQ: Yes, no SA

Question being asked/answered	**Systematic review with meta-analysis (year, reported measures and intervention)**	**Pooled effect size of interventions for lipid outcomes**	**Population (health status, age, gender)**	**RCTs only (Yes/No)** **Number of studies (S)** **Total population (N)** **Study quality (SQ) evaluation (Yes/No)** **Sensitivity analysis (SA) using study quality (SA, No SA)**
Q: Did AET intervention variables influence the effect of AET on lipids in healthy populations? A: Above a pre-specified threshold, significantly for TRG and HDL-C	**Hespanhol Junior 2015(**156**)** (mmol/L)* WMD, 95% CI (data for running studies only) Aerobic exercise training vs no exercise	TC: -0.06 (-0.15, 0.03) (P>.05) TRG: -0.15 (-0.24, -0.07) HDL-C: 0.07 (0.03, 0.10) LDL-C: -0.02 (-0.13, 0.09) (P>.05) Duration sub-analysis data showed moderate i^2 heterogeneity for HDL-C	Health status: healthy, sedentary Age: 33.8 (10.2) years Gender: F, M, Mx	RCT only: Yes S: 6-8 N: unspecified SQ: Yes, no SA
Q: Did AET affect lipids in mixed populations? A: Not significantly	**Hwang 2011**(146) mmol/L WMD, 95% CI (P>.05) Experiment: HIIT Control: MICT No non-exercising group as control	TRG: -0.20 (-0.50, 0.10) HDL-C: 0.0 (–0.1, 0.2) No data on heterogeneity	Health status: overweight, obese, CVD Age: 40-60 years Gender: Mx	RCT only: Yes S: 3 N: 91 SQ: Yes, no SA
Q: Did AET affect lipids in mixed population females? A: Significantly	**Kelley 2004(**149**)** (mmol/L)* M, SE, 95% CI Aerobic exercise training vs no exercise	TC: -0.11 ± 0.03 (-0.18, -0.04) TRG: -0.05 ± 0.02 (-0.09, 0.00) HDL-C: 0.05 ± 0.02 (0.00, 0.09) LDL-C: -0.11 ± 0.03 (-0.17, -0.06) Moderate i^2 heterogeneity: TC, LDL-C High i^2 heterogeneity: TRG, HDL-C	Health status: overweight, obese, sedentary, T2DM, CVD, dyslipidaemic Age: 20-76 years Gender: F	RCT only: Yes S: 41 N: 1715 SQ: Yes, no SA
Q: Did AET affect lipids in MetS populations? A: Significantly	**Kelley 2005a(**161**)** mmol/L* M, SE, 95% CI Aerobic exercise training vs no exercise	TC: -0.09 (-0.17, 0.00) TRG: -0.18 (-0.34, -0.02) HDL-C: 0.04 (0.00, 0.08) LDL-C: -0.01 (-0.08, 0.05) Low i^2 heterogeneity: TC, LDL-C High i^2 heterogeneity: TRG, HDL-C	Health status: overweight, obese, sedentary, T2D, dyslipidaemic Age: 30-63 years Gender: F, M, Mx	RCT only: Yes S: 13 N: 613 SQ: Yes, no SA
Q: Did AET affect non-HDL-C in mixed populations? A: Significantly	**Kelley 2005b(**152**)** mmol/L* M, SE, 95% CI Aerobic exercise training vs no exercise	Non-HDL-C: -0.15 (-0.23, -0.06) No data on heterogeneity	Health status: overweight, obese, sedentary, T2DM, CVD, MetS, dyslipidaemic Age: 30-76 years Gender: F, M, Mx	RCT only: Yes S: 22 N: 948 SQ: Yes, no SA

Question being asked/answered	Systematic review with meta-analysis (year, reported measures and intervention)	Pooled effect size of interventions for lipid outcomes	Population (health status, age, gender)	RCTs only (Yes/No) Number of studies (S) Total population (N) Study quality (SQ) evaluation (Yes/No) Sensitivity analysis (SA) using study quality (SA, No SA)
Q: Did AET affect lipids in mixed population males? A: Significantly	**Kelley 2006a(148)** (mmol/L)* M, SE, 95% CI Aerobic exercise training vs no exercise	TC: −0.13 ± 0.03 (−0.19,−0.07) TRG: −0.14 ± 0.02 (−0.18, −0.09) HDL-C: 0.03 ± 0.01 (0.01, 0.06) LDL-C: −0.08 ± 0.05 (-0.17, 0.01) Moderate i^2 heterogeneity: TC, TRG High i^2 heterogeneity: HDL-C, LDL-C	Health status: overweight, obese, active, sedentary, CVD, MetS, T2DM Age: 20-63 years Gender: M	RCT only: Yes S: 49 N: 2990 SQ: No, no SA
Q: Did AET affect antiatherogenic lipoprotein in mixed populations? A: Not significantly except for HDL-C2	**Kelley 2006b**(153) mmol/L* M, SE, bootstrap 95% CI (P>.05) Aerobic exercise training vs no exercise	HDL-C: 0.04 ± 0.03 (-0.05, 0.09) HDL-C2: 0.08 ± 0.02 (0.03, 0.11) (P>.05) HDL-C3: -0.02 ±0.02 (-0.06, 0.02) Zero heterogeneity	Health status: overweight, obese, T1DM, T2DM, CVD, MetS factors Age: 25-94 years Gender: F, M, Mx	RCT only: Yes S: 19 N: 984 SQ: Yes, no SA
Q: Did AET affect lipids in mixed populations? A: Not significantly except for LDL-C	**Kelley 2007**(145) mmol/L M, SE, 95% CI (P>.05) Aerobic exercise training vs no exercise	TC: -0.10 (-0.23,0.03) TRG: -0.11 (-0.30, 0.08) HDL-C: 0.02 (-0.05, 0.09) LDL:C -0.17 (-0.31, -0.03) (P<.05) TC/HDL-C: -0.03 (-0.07, 0.01) Low i^2 heterogeneity for TRG High i^2 heterogeneity: HDL-C, TC/HDL-C	Health status: overweight, obese, T2DM, active Age: 46-63 years Gender: F, M, Mx	RCT only: Yes S: 7 N:220 SQ: Yes, no SA
Q: Did AET affect lipids in sub-clinical populations? A: Not significantly except for TRG	**Kelley 2012** 157 mmol/L* M, 95% CI (P>.05) Aerobic exercise training vs no exercise	TC: 0.02 (0.08, 0.13) TRG: -0.07 (-0.13, -0.00) (P<.05) HDL-C: 0.03 (-0.01, 0.05) LDL-C: 0.05 (-0.04, 0.15) Zero heterogeneity	Health status: overweight, obese, MetS factors Age: 20-75 years Gender: F, M, Mx	RCT only: Yes S: 6 N: 387 SQ: Yes, no SA
Q: Did AET affect HDL-C in sub-clinical populations? A: Significantly	**Kodama 2007(160)** (mmol/L) MD, 95% CI Aerobic exercise training vs no exercise	HDL-C: 0.07 (0.04-0.10) Heterogeneity: $\chi^2 = 38.7$	Health status: overweight, obese, no CHD, cancer, or haemodialysis Age: 23-75 years Gender: F, M, Mx	RCT only: Yes S: 25 N: 1404 SQ: Yes, no SA

Question being asked/answered	Systematic review with meta-analysis (year, reported measures and intervention)	Pooled effect size of interventions for lipid outcomes	Population (health status, age, gender)	RCTs only (Yes/No) Number of studies (S) Total population (N) Study quality (SQ) evaluation (Yes/No) Sensitivity analysis (SA) using study quality (SA, No SA)
Q: Did AET affect lipids in females? A: Significant except for HDL-C and LDL-C	**Lokey 1989(150)** (mmol/L)* MD (P<.05) Aerobic exercise training	TC: −0.10 TRG: −0.10 HDL-C: −0.04 (P>.05) LDL-C: 0.005 (P>.05) TC/HDL-C: -0.12 No data on heterogeneity	Health status: not indicated Age: 20-56 years Gender: F	RCT only: No S: 27 N: 460 SQ: No, no SA
Q: Did AET affect lipids in clinical populations? A: Significantly except for HDL-C	**Ostman 2017**(162) mmol/L MD, 95% CI Aerobic exercise training vs no exercise	TG: -0.21 (-0.29, 0.13) HDL-C: 0.03 (-0.01, 0.08) P>.05 LDL-C: -0.03 (-0.05, -0.00) Heterogeneity i^2 medium for HDL-C, low for LDL-C	Health status: MetS, T2DM Age: not indicated Gender: not indicated	RCT only: Yes S: 13/15/2 N: 308/265/44 SQ: Yes, no SA
Q: Did AET affect lipids in mixed populations? A: Not significantly	**Qui 2014(147)**mmol/L WMD, 95% CI (P>.05) Aerobic exercise training vs no exercise	HDL-C: 0.02 (-0.06, 0.10) LDL-C: 0.04 (-0.07, 0.16) Heterogeneity i^2 medium for TRG, high for HDL-C, low for LDL-C	Health status: T2DM, MetS factors, MetS Age: mean range 43-70 years Gender: F, M, Mx	RCT only: Yes S: 9 N: 290 SQ: Yes, no SA
Q: Did AET affect lipids in sub-clinical populations? A: Significantly pre-post within group	**Ruppar 2014**(143) mmol/L* MD, SE (indirectly derived from an overall lipid outcome) Aerobic exercise training	TC: -0.22 ± 0.03 HDL-C: 0.04 ± 0.006 LDL-C: -0.20 ± 0.03 TC/HDL-C: -0.34 ± 0.05	Health status: healthy, MetS factors (no chronic disease) Age: 18-80 years Gender, F, M, Mx	RCT only: No S: 87 treatment vs control, 149 single group pre/post N: 444 SQ: No, no SA
Q: Did AET and AET interventional variables affect lipoproteins in mixed populations? A: Insignificance and significance for AET and AET variables	**Sarzynski 2015**(154) (nmol/L, nm) MD, 95% CI Aerobic exercise training Aerobic intensity types compared	Multiple results for changes in lipoprotein sub-fraction concentration and particle size (VLDL-P, LDL-P, HDL-P) from a collaboration of studies on the genetics of lipid response to AET and other exercise modes. Heterogeneity i^2 low to high across all outcomes	Health status: MetS factors, MetS Age: 17-75 years Gender: F, Mx	RCT only: No S: 6 N: 1555 SQ: No, no SA
Q: Did AET affect lipids in clinical populations? A: Significantly except for TC	**Shaw 2006** (142) MD, 95% CI (P<.05) Aerobic exercise training vs no exercise	TC: 0.03 (-0.09, 0.15) (P>.05) TRG: -0.18 (-0.31, -0.05) HDL-C: 0.06 (0.03, 0.09) Zero heterogeneity: TC, TRG High i^2 heterogeneity: HDL-C	Health status: overweight, obese Age: 30-64 Gender: M, Mx	RCT only: Yes S: 3 N: 172 SQ: Yes, no SA

Question being asked/answered	Systematic review with meta-analysis (year, reported measures and intervention)	Pooled effect size of interventions for lipid outcomes	Population (health status, age, gender)	RCTs only (Yes/No) Number of studies (S) Total population (N) Study quality (SQ) evaluation (Yes/No) Sensitivity analysis (SA) using study quality (SA, No SA)
Q: Did exercise affect lipids according to baseline weight and post weight changes? A: Significant except for weight gain	**Tran 1985(163)** (mmol/L)* MD (SD) (P<.05) Exercise training and type not indicated	No Change in weight: TC: −0.19 (0.55) TRG: −0.16 (0.34) HDL-C: 0.04 (0.13) LDL-C: −0.09 (0.34) Weight Loss: TC: −0.34 (0.44) TRG: −0.24 (0.37) HDL-C: 0.06 (0.16) LDL-C: −0.29 (0.53) Weight gain: (P>.05) TC: 0.08 (0.18) TRG: 0.11 (0.24) HDL-C: 0.04 (0.10) LDL-C: 0.08 (0.14) No data on heterogeneity	Health status: not indicated Age: not indicated Gender: not indicated	RCT only: No S: 95 N: not indicated SQ; No, no SA
Q: Did AET affect lipids in mixed population females? A: Unclear	**Zhang 2016**(151) Unit of measurement not indicated (assumed mmol/L) MD, 95% CI Aerobic exercise training vs no exercise	TC: 0.12 (0.07, 0.16)† HDL-C: -0.08 (-0.10, -0.06)† LDL-C: 0.12 (0.07, 0.16)† Low to moderate i^2 heterogeneity for all lipids †Data and significance appear to be contradicted in the text.	Health status: T2DM, obese, overweight, MetS factors, healthy sedentary Age: 18-60 years Gender: F	RCT only: Yes S: 12 N: 254 SQ: Yes, no SA

Appendix 1 Table 1 Characteristics of systematic reviews and meta-analyses searched to 31st March 2018.

Systematic review with meta-analysis (year, reported measures and intervention)	Pooled effect size of interventions for lipid outcomes	Population (health status, age, gender)	RCTs only (Yes/No) Number of studies (S) Total population (N) Study quality (SQ) evaluation (Yes/No) Sensitivity analysis (SA) using study quality (SA, No SA)
Pan 2018(165) mmol/L* univariate and network meta-analysis MD, 95% CI for supervised AET (P>.05) Ratio of mean for unsupervised AET (P>.05) Aerobic exercise training vs no exercise	Supervised AET TC: -0.52 (-0.71, -0.29) TRG: -0.22 (-0.34, -0.07) HDL-C: -0.10 (-0.13, -0.05) LDL: -0.31, (-0.56, -0.03) Unsupervised AET: TC: 0.96 (0.90, 1.02) TRG: 0.95 (0.86, 1.05) HDL-C: 0.99 (0.87; 1.12) LDL: 1.08 (0.88; 1.33) Statistically significant heterogeneity	Health status: T2DM Age: not indicated Gender: Mx	RCT only: Yes S: 1-6 N: not indicated SQ: Yes, no SA
Su 2019(166) SMD, 95% CI (P>.05) Experiment: HIIT Control: MICT No non-exercising control group included	TC: 0.11(-0.20, 0.45) TRG: 0.01(-0.49, 0.29) HDL-C: 0.09(-0.51, 0.33) LDL-C: -0.10(-0.37, 0.17) No data on heterogeneity	Health status: overweight, obese Age: not indicated Gender: not indicated	RCT only: S: 12/12/8/19 N: ≈120 SQ: Yes, no SA
Wood 2019(167) (mmol/L) MD, 95% CI (P>.05) Experiment: HIIT Control: MICT No non-exercising control group included	TC: 0.10 (−0.03, 0.22) TRG: −0.05 (−0.11, 0.01) HDL-C: 0.07 (0.04, 0.11) (P<.05) LDL-C: 0.05 (−0.06, 0.17) TC/HDL-C: -0.03 (-0.36, 0.29) Zero to low i^2 heterogeneity for all lipids	Health status: overweight, obese, MetS factors, MetS, T2DM, active, sedentary, no chronic disease Age: 18-80 years Gender: F, M, Mx	RCT only: Yes S: 26 N: 823 SQ: Yes, SA

Appendix 1 Table 2 Characteristics of systematic reviews and meta-analyses published from 1st April 2018 to July 31st 2020