ORIGINAL RESEARCH

Aerobic Exercise, Metabolic Syndrome, and Lipid Profiles: Protocol for a Quantitative Review

Gina N Wood, PhD, MEcon[1], Emily Taylor, BBiomedSc(Hons)[2], Anna Murrell, PhD, GradDipSciEd[3], Vanessa Ng, BBiomedSc[2], Aditya Patil[2], Tom van der Touw, PhD[2], Mitch Wolden, PhD, DPT, PT[4], Neil A Smart, PhD, ESSAF[2]

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ABSTRACT

Background: We describe two systematic reviews and univariate meta-analyses of randomized controlled trials to estimate the effect size of aerobic exercise training on the standard lipid profile of adults diagnosed with, and free of, metabolic syndrome; and the determination if study or intervention covariates explain change in lipid outcomes.

Methods: English language searches of online databases from inception to June 2020. Data will be included from (a) randomized controlled trials of sedentary adult humans with intervention and non-exercising control groups of $n \geq 10$; (b) an aerobic exercise training intervention duration ≥12 weeks of at least moderate intensity (>40% VO_{2MAX}); and (c) reporting of pre/post lipid measurements. Subjects with chronic disease (except diabetes mellitus or metabolic syndrome), or pregnant/lactating, or trials testing diet/medication, or resistance/isometric/unconventional training will be excluded.

Results: We will follow the Preferred Reporting Items for Systematic Reviews and Meta-Analysis statement. Univariate meta-analysis will estimate the effect size of aerobic exercise training on the standard lipid profile, using a random raw mean difference, Knapp-Hartung adjusted, 95% confidence interval, model. Statistical tests and precision and standard error funnel plots will evaluate heterogeneity. Multivariate meta-regression will explore whether study or intervention covariates explain change in lipids. Analyses will be performed in Comprehensive Meta-Analysis 3.0. Study quality will be evaluated using TESTEX.

Conclusion: We aim to estimate the effect size of aerobic exercise training on the standard lipid profiles of adults with and free of metabolic syndrome, and establish if these changes result in minimal meaningful change to cardiovascular disease risk. We aim to determine if meta-regression covariates might explain change in lipids. *Journal of Clinical Exercise Physiology*. 2021;10(2):42–50.

Keywords: cholesterol, triglycerides, lipoprotein, physical activity, systematic review

INTRODUCTION

Metabolic syndrome (MetS), defined as the presence or medication of any 3 MetS factors (obesity, dyslipidaemia, elevated blood pressure, and either the presence of insulin resistance or glucose intolerance, or Type 1 or 2 diabetes mellitus) is implicated in cardiovascular disease (CVD) (1). Dyslipidemia, an abnormally elevated or lowered blood lipid profile, is a significant MetS risk factor of CVD (2,3) and ischemic stroke (4). Moderate-intensity and vigorous-intensity aerobic exercise training (AET) positively impacts MetS risk factors, thus lowering CVD risk (5,6).

[1]Faculty of Health Sciences, Curtin University, Bentley, WA6102 Australia
[2]School of Science and Technology in the Faculty of Science, Agriculture, Business and Law, University of New England, Armidale, NSW 2351 Australia
[3]School of Rural Medicine in the Faculty of Medicine and Health, University of New England, Armidale, NSW 2351 Australia
[4]Physical Therapy Program, University of Jamestown, Fargo, ND 58104 USA

Address for correspondence: Gina Wood, Faculty of Health Sciences, Curtin University, Bentley, WA 6102, Australia; +61 8 9266 3970; e-mail: gina.wood@postgrad.curtin.edu.au.

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Moderate intensity aerobic exercise is defined as 3 to 6 metabolic equivalents of task (METs); 40% to 60% of heart rate reserve or maximal oxygen uptake (VO_{2MAX}); 55% to 70% of maximal heart rate; or rate of perceived effort of 11 to 13 on the Borg scale (7). Lack of aerobic physical activity has negative consequences for lipids (8). The standard lipid profile of total cholesterol (TC), triglycerides (TRG), high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C) (9) is positively impacted by AET in subclinical and clinical populations (10–13). The positive influence of AET on the standard lipid profile is associated with a reduction in CVD risk: for every 1% lowering of TC, the incidence of coronary heart disease decreases by 2% (14). CVD risk decreases by 1.7% for every 1% lowering of LDL-C, and CVD risk decreases by 2% in males and ≥3% in females for every 0.026 $mmol \cdot L^{-1}$ increase in HDL-C (15,16).

Various systematic reviews have examined the impact of AET on the standard lipid profile, however, without conducting meta-analyses (13,16–23) Quantitative reviews investigating how AET affects lipids have focused on single lipids (24), a specific sex (25–27), change in baseline body weight (28), mixed health status (25,26,29,30), intensity effectiveness (12), modalities of AET (running (31), walking (32), high intensity intervals versus moderate intensity steady state (29,30,33), and comparison of lipid levels (34). A Cochrane Review reported lipids as a secondary outcome using only 3 studies (35). The results of these systematic reviews reveal a range of estimated effect sizes varying according to participant and intervention characteristics, which lack agreement as to magnitude of effect, direction of change, or significance (see Table 1). Hence a minimal meaningful change in the standard lipid profile as the result of prescribed AET volumes (dosages) has yet to be determined.

Cholesterol-lowering medication dosages when steadily increased, result in greater effects on lowering targeted lipids or raising HDL-C than fixed dosages (47–49). The full reduction in risk of ischaemic heart disease is achieved within 5 years of lowering TC by 0.6 $mmol \cdot L^{-1}$ (50). Both cholesterol-lowering medication and AET require a minimum period to elicit positive changes, however trials of pharmacological intervention are generally conducted for longer periods (51) than trials of AET intervention (52).

A recent meta-epidemological review of randomized controlled trials (RCTs) found physical activity interventions to have equal or greater beneficial effects on mortality outcomes compared with pharmaceutical interventions (53). Aerobic physical activity, rather than pharmacotherapy, is generally encouraged as a first treatment option for dyslipidaemia in subclinical populations and as a concurrent treatment in clinical populations (49,54–57) because pharmacotherapy is not without side effects (58,59) and represents a financial cost to health systems (60–62). However, pharmacotherapy dosages may be more easily prescribed and monitored than aerobic physical activity, which is more commonly preferred as a preventative treatment (63–65).

To the best of our knowledge, no comprehensive systematic review and meta-analysis has been conducted that pools the outcomes of RCTs that compare the effects of various AET dosages (AET modes of at least moderate intensity and at least 12 weeks' duration) with no exercise, on the standard lipid profile of otherwise healthy adults diagnosed with, and free of, MetS. Further, to the best of our knowledge, no quantitative review has estimated these specific effect sizes and determined the resulting minimal meaningful change in cardiovascular risk.

We aim to conduct and publish one systematic review and meta-analysis to estimate the effect size of AET on TC, TRG, HDL-C, and LDL-C in a nonMetS cohort, and another for a MetS cohort, with both cohorts free of symptomatic disease (other than diabetes). We further aim to conduct exploratory meta-regression to investigate whether study or intervention covariates might explain changes in lipids. We also wish to discuss our findings in the context of statin therapy, since statins represent 98% of the cholesterol lowering medication prescribed (66).

METHODS

These 2 quantitative reviews have been designed by authors GNW and NS and registered in the International Prospective Register of Systematic Reviews (PROSPERO) (67): CRD42019145560 (non MetS); CRD42020151925 (MetS). Our results will be presented according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (68).

Study Eligibility

Only RCTs of humans ≥18 years comparing an AET intervention of ≥12 weeks with an intended minimum moderate intensity effort (>40% VO_{2MAX}) (7) against a nonexercising control group will be included. Trials of participants with symptomatic disease, other than Type 1 or 2 diabetes mellitus or MetS, or of pregnant or lactating females, or elite athletes, will be excluded. Trials using a nonAET physical activity intervention, or a dietary or pharmaceutical intervention, will be excluded. Trials failing to provide details of the AET protocol sufficient to estimate AET dosage (volume of AET) will be excluded.

Study Selection

Four researchers will conduct online database searches and collate title and abstract results using Microsoft Excel; v 16.31; Redmond, WA. Full PDF texts of potentially eligible RCTs will be independently assessed by these researchers. In the event of disagreement over inclusion of RCTs in the final list, a fifth researcher will be consulted. Endnote v X.9 (or later); Clarivate, Philadelphia, PA, will be used as the citation management software.

Data Sources

Online searches of English or bilingual journals indexed in PubMed, EMBASE, all Web of Science and EBSCO health

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TABLE 1. Findings and characteristics of previous systematic reviews with meta-analysis.

Cohort	Hypothesis Being Tested	Findings	Systematic Review with Meta-Analysis
Mixed healthy, subclinical, and clinical	AET affects lipids	AET significantly affects TG only	Chudyk 2011 (36)
		AET significantly affects LDL-C only	Kelley 2007 (37)
		AET does not significantly affect lipids	Hwang 2011 (30), Qui 2014 (38)
	AET affects lipids by gender (M; F)	AET significantly affects lipids by gender	Kelley 2006a (26); Kelley 2004 (25)
	AET affects lipids by gender (F)	AET significantly affects TC and TRG, but not HDL-C and LDL-C, in females	Lokey 1989 (27)
		No clear result whether AET affects lipids in females	Zhang 2016 (39)
	AET affects non-HDL-C	AET significantly affects non-HDL-C	Kelley 2005b (32)
	AET affects antiatherogenic lipoproteins	AET does not significantly affect antiatherogenic lipoproteins except for HDL-C2	Kelley 2006b (40)
	AET affects lipoproteins	The significant effect of AET on lipoprotein depends on particle size and lipoprotein (inconsistent)	Sarzynski 2015 (41)
AET covariates	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 (42)
Mixed healthy, subclinical, and clinical	AET intervention variables influence the effect of AET on lipids	Above a prespecified threshold, AET intervention variables significantly influence the effect of AET on lipids;	Fikenzer 2018 (12);
		AET intervention variables significantly influence the effect of AET on TRG and HDL-C, but not TC and LDL-C	Hespanhol Junior 2015 (31)
	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 (41)
Subclinical	AET affects lipids	AET significantly affects HDL-C only	Fagard 2006 (43)
		AET significantly affects TRG only	Kelley 2012 (44)
		AET significantly affects lipids, but not LDL-C	Halbert 1999 (34)
		AET does not significantly affect lipids	Ruppar 2014 (45)
	AET affects HDL-C only	AET significantly affects HDL-C only	Kodama 2007 (24)
MetS, clinical	AET affects lipids	AET significantly affects lipids	Kelley 2005a (46)
		AET significantly affects lipids, but not HDL-C	Ostman 2017 (5)
		AET significantly affects lipids, but not TC	Shaw 2006 (35)
Weight change	Nonspecific exercise affects lipids with weight change	Nonspecific exercise significantly affects lipids in the presence of weight loss or weight stability but not weight gain	Tran 1985 (28)

AET = aerobic exercise training; HDL = high-density lipoprotein; HIIT = high-intensity interval training; LDL = low-density lipoprotein; MetS = metabolic syndrome; MICT = moderate intensity continuous training; TC = total cholesterol; TRG = triglyceride

and medical databases from inception of the database until June 30, 2020, will be conducted. Searches will include a mix of Medical Subject Headings (MeSH) and free text terms (Box 1). Other reviews and reference lists of papers will be hand searched for additional RCTs.

Outcomes

Preintervention and postintervention measurements or equivalent, in mass ($mg \cdot dL^{-1}$) or molar ($mmol \cdot L^{-1}$) units for the standard lipid profile, for each of intervention and non-exercising control groups, must be reported. Measurements

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BOX 1: FREE TEXT SEARCH TERMS USED FOR ONLINE DATABASE SEARCHES

- aerobic exercise training
- physical activity
- endurance exercise
- lipids
- lipoproteins
- triglycerides
- cholesterol
- moderate intensity
- high-intensity intervals

reported in conventional units ($mg \cdot dL^{-1}$) will be multiplied by 0.02586 to convert to the International System (SI) molar unit $mmol \cdot L^{-1}$ (69). Lead authors will be contacted via email regarding missing data or outcome measurement scales as necessary. Outcome data presented graphically will be converted to numerical values using WebPlotDigitzer, v 4.2, 2019; Pacifica, CA, by 2 researchers independently.

Data Extraction

Preestablished data extraction sheets using Microsoft Excel will be populated with extracted data for each RCT (Box 2). The list of included RCTs will be divided among and randomly distributed to 3 teams. 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, the lead author will be consulted.

Study Quality

Each RCT will be assessed using the validated Tool for the Assessment of Study Quality and Reporting in Exercise (TESTEX) (70), a 15-point scale specific to exercise training studies for determining study quality and bias. A score of ≥ 10 is deemed good study quality and reporting (71). Within-study risk of bias will be determined by evaluating an additional 7 factors (Box 3). Either low, medium, or high within-study risk of bias scores will be awarded. The RCTs will be divided between and randomly distributed to 3 researchers. Relevant data will be extracted independently according to the TESTEX criteria. Data sheets of the extracted TESTEX variables will be cross-checked for accuracy. Disputes will be mediated by NS. A study quality subanalysis of RCTs grouped according to a TESTEX score ≥10 and a within-study risk evaluation of low-to-medium will be conducted.

BOX 2: EXTRACTED DATA

- General trial information
  - Author(s), year of publication and study design
  - Demographic and clinical characteristics
  - AET intervention and control protocols
  - Intervention and control group values before and after intervention for the standard lipid profile
- Specific numerical data
  - 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 for within or between group *P* values or change in *P* values,
  - 95% within- or between group confidence intervals (CI) or change in CIs for each found outcome

BOX 3: WITHIN-STUDY RISK OF BIAS FACTORS AND METHOD

We award either low or high for the following factors:

- Study nonrandomized or randomized: low if randomized, high if nonrandomized (all studies to be included must be randomized)
- Minimum compliance level set for participation in intervention or control groups: low if a minimum level of compliance is set, high if no minimum compliance level is set
- Habitual medication use reported: low if reported, high if not reported
- Dropout reasons reported: low if reported, high if not reported
- Baseline fitness and effort determined: low if baseline fitness and effort is measured, high if not determined
- >50% of sessions supervised: low if >50% of sessions are supervised, high if not >50% sessions supervised
- Effort monitoring and measurement device: low if digital recording devices are used, high if analog or no device

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

Data Synthesis

Statistical analyses will be performed using Comprehensive Meta-Analysis v 3.0; Biostat, Inc., Englewood, NJ. A continuous univariate random effects model (72) with Hartung-Knapp-Sidik-Jonkman adjustment (73) will use the raw mean difference, a 5% level of significance, and a 95% confidence interval, to estimate effect sizes. A description of the lipid outcome measures to be pooled and the method for dealing with missing data is provided in Table 2. The data sets will be divided equally between 2 researchers who will independently enter the data in Comprehensive Meta-Analysis, and review each other's entry files for accuracy prior to performing analyses.

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TABLE 2. Description of measures to be pooled and method for handling missing data.

Measures to be Pooled
Reported raw mean difference (MD), standard deviation (SD), and sample size (N) for each of the intervention and control groups. Per group outcome data, whether reported for intention-to-treat (ITT) or for non-ITT analysis
Calculation of Missing Data Where Possible
MD will be calculated by subtracting $M_{pretreatment}$ from $M_{posttreatment}$. The SD of the MD will be calculated as follows: $$SD = \sqrt{\left[\left(SD_{pretreatment}\right)^2 + \left(SD_{posttreatment}\right)^2 - \left(2r \times SD_{pretreatment} \times SD_{posttreatment}\right)\right]},$$ assuming a correlation coefficient $r = 0.5$, which is considered a conservative estimate (74).

Meta-analysis and Subanalyses

A cumulative random meta-analysis will report the effect size of AET on the standard lipid profile, and RCTs will be sorted chronologically to show the cumulative effect of each. Subanalyses of study quality will use TESTEX scores (RCTs with a score ≥10) and within-study bias analysis 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 will also be performed to evaluate the influence of each RCT on the effect size of pooled data (75).

Small-Study Effects

Analysis of small study effects will be conducted (Table 3), with 2 researchers entering and cross-checking data and a third research performing the analysis.

Meta-regression

Multivariate meta-regression without adjustment for P values will be conducted to determine whether any a priori covariates might explain a change in statistically significant point estimates. Intervention a priori covariates comprise intensity (percentage of VO_{2MAX}); minutes per session; sessions per week; and duration in weeks. Study covariates comprise year of publication (potential for improved laboratory testing in recent RCTs); total study participants N (potential for underpowered studies to influence outcomes); and TESTEX study quality and risk of bias scores (potential for better quality RCTs to influence outcomes). Using a random effects maximum likelihood model with a Hartung-Knapp adjustment, the intercept and each covariate will be regressed against the dependent variable.

TABLE 3. Small study effects tests.

Statistical Test
Rosenthal fail-safe N
Duval and Tweedie trim-and-fill
Egger regression test
Begg and Mezumdar rank correlation test
Graphical Test
Precision and standard error funnel plots

Heterogeneity

Heterogeneity will be quantified using the Q statistic, and the corresponding P value, τ^2, τ, and I^2 (72). The Q statistic, and the corresponding P value, compares the differences among the calculated effect sizes; τ^2 measures absolute between-study heterogeneity and the estimated SD (τ) (72). The relative measure of heterogeneity I^2 ranges from 0% (complete homogeneity) to 100% (complete heterogeneity) (76). If necessary, a further sensitivity analysis, using pooled analysis 95% confidence interval boundaries, will be conducted (77).

RESULTS

The search and inclusion process will presented using a PRISMA flow diagram (68). Data will be extracted, pooled and analysed from the final list of RCTs.

Study, Participant, and Intervention Characteristics

Extracted participant and intervention details of included RCTs will be given. 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 (e.g., walking, swimming, etc.).

Small Study Effects

The number of included studies will be compared to the minimum number required to perform small study effect analyses (78). Effects measures will be evaluated to determine whether meta-analysis should be conducted.

Study Quality and Reporting

The TESTEX analysis will be reported, with the cumulative random meta-analysis of each outcome that remains (or attains significance) from subanalysis.

Comparative Outcomes

The changes in TC, TRG, HDL-C, and LDL-C will be reported as point estimates with relevant statistical measures and cohort sizes. Sensitivity analyses ($K - 1$) for statistically significant outcomes will also be reported. The cumulative

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random meta-analysis of each outcome will be presented chronologically.

Lipid Extraction Methodology

The lipid extraction method (how blood is drawn from trial participants) will be assessed for adherence to standard accepted methods (fasted, rested, seated or supine position during the blood draw) of lipid extraction. Sensitivity analyses will be conducted where trials report nonconventional lipid extraction methods as these may influence the estimated effect size.

Meta-regression

Exploratory meta-regression R^2 values will indicate any study or intervention likely contributing to the estimated effect size.

Heterogeneity

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

DISCUSSION

AET results in changes in the standard lipid profile, or no change, depending on the cohort studied. We will compare our analysis of changes in the standard lipid profile of homogenous cohorts, with previous work analysing the effect of AET in heterogenous cohorts. We aim to determine if our estimated effect sizes produce a reduction of CVD risk (i.e., whether these represent minimal meaningful changes in the standard lipid profile), and CVD risk. Meta-regression may indicate if intervention covariates contribute to a change in outcomes, as others suggest (12,24,31,79,80), or if study covariates also influence change. The TESTEX analysis of study quality will indicate how researchers might better present their findings.

To the best of our knowledge, these 2 quantitative reviews are the first that seek to compare the effects of AET against no exercise on the standard lipid profile of separate nonMetS and MetS cohorts, and to determine whether a minimal meaningful change in the standard lipid profile results in a corresponding change to CVD risk. We will follow a rigorous inclusion/exclusion protocol to ensure minimisation of confounding factors amongst the RCT populations (81). A potential limitation of our work is the reliance on aggregated RCT data and not individual subject data (82,83). Secondly, using English language search terms may reduce the pool of available studies for selection and possibly introduce small study effects. The exclusion of studies with, respectively, intervention and comparison groups of $N < 10$ may decrease effect size. 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. A measurement bias (digital vs analog) of achieved AET volume in the included RCTs and the exclusion of unconventional AET protocols such as yoga may impact effect size.

CONCLUSION

Using two quantitative reviews, we hope to augment the evidence suggesting AET mitigates CVD risk through minimal meaningful changes to the standard lipid profile.

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